Electronic Supplementary Information

**Synthesis and Biological Evaluation of N-(4-phenylthiazol-2-yl)cinnamamide Derivatives as Potential Antitumor Agents**

Yong Luo, ‡ a Yongxia Zhu, ‡ a Kai Ran, a Zhihao Liu, a Ningyu Wang, a Qiang Feng, a c Jun Zeng, a Lidan Zhang, b Bing He, a c Tinghong Ye, a Shirui Zhu, d Xiaolong Qiu e and Luoting Yu a *

a Sichuan University, State Key Laboratory of Biotherapy/Collaborative Innovation Center of Biotherapy and Cancer Center, West China Hospital, West China Medical School, Sichuan University, Chengdu 610041, China. b Department of Pharmaceutical and Bioengineering, School of Chemical Engineering, Sichuan University, Chengdu, Sichuan 610065, China. c College of Chemistry and Life Science, Chengdu Normal University, Chengdu 611130, China. d Department of Encephalopathy, The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Henan University of Traditional Chinese Medicine, Zhengzhou, 450004, China. e Wisdom Pharmaceutical Co., Ltd, Haimen, 226123, China.

*Author to whom correspondence should be addressed; E-Mail: yuluot@scu.edu.cn; Tel.: +86-28-8516-4063; Fax: +86-28-8516-4060.

‡ These authors contributed equally to this work.

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1. Reagents and general methods

Unless otherwise noted, all reagents were purchased from commercial suppliers and without further purification. The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AVANCEIII 400 spectrometer. $^1$H NMR spectra were recorded at 400 MHz, $^{13}$C NMR spectra were recorded at 101 MHz, $^{19}$F NMR spectra were recorded at 376 MHz. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are showed in (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. High-resolution mass spectra (HRMS) were recorded on a Micromass Quattro Micro mass spectrometer (Waters). Column chromatography and thin layer chromatography (TLC) were performed using Haiyang Silica gel (60H 300-400 mesh, Qingdao Marine Chemical Ltd., Qingdao, China) and Haiyang silica gel GF254 plates (0.20-0.25mm), respectively. HPLC analysis was performed on an UltiMate 3000 HPLC system (Dionex, USA): Venusil XBP 5 µm, 150 Å, C18 column (4.6 mm×150 mm); mobile phase: 70% Acetonitrile and 30% water in 20 min; flow rate: 1.0 mL min$^{-1}$; injection volume: 20 µL. All tested compound were purified until the purity was $\geq$ 95%, detected by HPLC under UV 254nm wavelength. Melting points were determined on WRS-1B digital melting-point apparatus.

General procedure for step (i) – (v)

Step (i)

(i) To a solution of 2a–2m,2o (4 mmol, 1.0 equiv) in acetonitrile (50 mL) was added tetrabutylammoniumtribromide (1.93 g, 4 mmol, 1.0 equiv). The reaction mixture was stirred under room temperature for overnight, until the solution turned to light yellow or colorless. The solution was removed in vacuo and extracted with saturated aqueous NaHCO$_3$ and CH$_2$Cl$_2$; the organic layers were combined and concentrated under reduced pressure to give the crude product 2-bromo-1-aryl ethanone 3a-3m,3o, which directly using for next step.

Step (ii)

(ii) To a stirred solution of AlCl$_3$ (16 g, 120 mmol, 3.0 equiv) in dichloromethane (100 mL) was added 2n or 2p (40 mmol, 1.0 equiv) at 0°C. Then a solution of 2-bromoacetyl bromide (6.95 mL, 80 mmol, 2.0 equiv) in CH$_2$Cl$_2$ (10 mL) was added wisely in a period of 20 min. The reaction was stirred at 0–5 °C for additional 15~30 min. After that, carefully added the NaHCO$_3$ until pH>7 and extracted with CH$_2$Cl$_2$ (3×30mL). The combined the organic layers were dried over Na$_2$SO$_4$
and concentrated in vacuo to afford crude product 2-bromo-1-arylethanone 3n, 3p as yellow solid, which directly using for next step.

**Step (iii)**

![chemical structure](image)

(iii) A mixture of 2-bromo-1-arylethanone (40 mmol, 1.0 equiv) and thiourea (3.35 g, 44 mmol, 1.1 equiv) in anhydrous ethanol (50 mL) was refluxed for 3 h. After that, the solvent was removed in vacuo washed with cold ether. Then the mixture was extracted with saturated aqueous NaHCO₃ and CH₂Cl₂ (3*30 mL). The combined organic phases were dried with anhydrous Na₂SO₄. Then removed the solvent, the residue was purified by silica gel column (hexane/EtOAc=8:1 to 4:1) and dried under vacuum to give 4-arylthiazol-2-amine 4a-4p, yield was 50~90%.

**Step (iv)**

![chemical structure](image)

(iv) A mixture of 5a to 5p (2.4 mol, 1.0 equiv), malonic acid (500 mg, 4.8 mol, 2.0 equiv), catalytic amount of piperidin (22 µL, 0.24 mol, 0.1 equiv) and pyridine (20 mL) was refluxed under 115°C for overnight. After cooling to room temperature, the solution was poured into 500 mL ice water and acidified to pH 3~4 with 2N HCl. The precipitate was collected by filtration and recrystallized from anhydrous ethanol to afford product 6a-6p. Yield was 60~97%.

**Step (v)**

![chemical structure](image)

(v) 6a-6o (2mmol, 1.5 equiv), EDCI (383 mg, 2 mmol, 1.5 equiv) and DMAP (162 mg, 1.33 mmol, 1.0 equiv) were added to dichloromethane (50 mL), the reaction was allowed to stirred for 30 minutes, then 4a-4p (290 mg, 1.33 mmol, 1.0 equiv) was added. The mixture was stirred at room temperature for 1d. Then quenched with H₂O (10 mL) and extracted with CH₂Cl₂ (3*30 mL), the organic layer was collected, dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc=8:1 to 4:1) to provide 1,7a to 7p, 8a to 8o. The yield was 29~80%.

**Step (vi-x)**
(vi) 5-Dimethylaniline (10 mL, 0.082 mol, 1.0 equiv) was dissolved in DCM, followed by adding K$_2$CO$_3$ (22.1 g, 0.164 mol, 2.0 equiv), keep it under ice cold for 30 min, dropwise the acetyl chloride (11.34 mL, 0.164 mmol, 2.0 equiv) by constant pressure dropping funnel, then keep it under r.t. for 2h. Then quenched with H$_2$O (10 mL) and extracted with CH$_2$Cl$_2$ (3×30 mL), the organic layer was collected and concentrated the organic phase to get the crude white flaky crystal product N-(3,5-dimethylphenyl) acetamide (13.30 g, 98.8%);

(vii) To a stirred solution of anhydrous aluminum chloride (50.38 g, 369.09 mmol, 4.5 equiv) and N-(3,5-dimethylphenyl) acetamide (13.39 g, 82.02 mmol, 1.0 equiv) in dichloromethane under ice-water bath, followed by dropwise the acetyl chloride (17.50 mL, 246.06 mmol, 3.0 equiv), The reaction was stirred at 0~5 ℃ for additional 3 h. After that, diluted with 600 mL ice water and 20 mL conc. HCl, extracted with CH$_2$Cl$_2$ (3×30 mL). The combined the organic layers was concentrated to get the crude product N-(4-acetyl-3, 5-dimethylphenyl) acetamide, used for next step without further purification.

(viii) N-(4-acetyl-3, 5-dimethylphenyl) acetamide was added in the solution containing 60 mL 2N HCl and 60 mL water, hydrolysis under 80-100 ℃ for 2h. After that, the saturated aqueous NaHCO$_3$ was added to make the mixture basic (pH=8-9). A lot of solid was precipitated, then the solid was filtered and dried overnight in vacuo to give 1-(4-amino-2, 6-dimethylphenyl) ethanone as a pale yellow powder solid, (13.04 g, yield is 97.5%).

(ix) 1-(4-amino-2, 6-dimethylphenyl) ethanone (3.5 g, 21 mmol, 1.0 equiv) was dissolved in a solution of water (47 mL) and conc. HCl (6.6 mL). A solution of NaNO$_2$ (1.84 g, 27 mmol, 1.3 equiv) in water (6 mL) was dropwise added and at 0 to 5 ℃ over 5min. The mixture was boiled for additional one-half hour then ice cold overnight. The white crystals was precipitated and filtration purified by chromatograph (hexanes/EtOAc=4:1) and dried overnight in vacuo to give 1-(4-hydroxy-2, 6-dimethylphenyl) ethanone (1.15 g, the yield is 33%).

(x) 1-(4-hydroxy-2, 6-dimethylphenyl) ethanone (493 mg, 3mmol, 1.0 equiv) and K$_2$CO$_3$ (498mg, 3.6mmol, 1.2 equiv) were added in the acetone (50 mL), one hour later, the mixture was cooled to 0 ℃ and Iodomethane (224 µL, 3.6mmol, 1.2 equiv) or Iodoethane (288 µL, 3.6 mmol, 1.2 equiv) was added dropwise, stirred under reflux overnight. Then the mixture was extracted with H$_2$O (50 mL) CH$_2$Cl$_2$ (3×30 mL). After removal the solvent, the residue was purified by chromatograph (hexanes/EtOAc=20:1) to afford the 2l or 2n as dark oil, and yield is 99.6%~99.8%.

2. Spectral data of compounds 1, 7a~7p and 8a~8o.

1.1 (E)-3-(4-morpholinophenyl)-N-(4-phenylthiazol-2-yl)acrylamide (1):
A yellow solid, mp 251-252 °C, yield 32%, \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 12.36 (s, 1H, NH), 7.92 (d, 2H, \(J=8.0\) Hz, ArH), 7.65 (d, 1H, \(J=16.0\) Hz, ethylene-H), 7.51 (d, 2H, \(J=8.0\) Hz, ArH), 7.44 (t, 2H, \(J=8.0\) Hz, ArH), 7.34 (m, 1H, ArH), 7.01 (d, 2H, \(J=8.0\) Hz, ArH), 6.74 (d, 1H, \(J=16.0\) Hz, ethylene-H), 3.74 (t, 4H, \(J=4.0\) Hz, morpholine-H). \(^13\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 163.92, 158.93, 158.05, 152.33, 148.88, 142.51, 129.38, 127.18, 126.97, 124.39, 115.12, 114.35, 114.07, 106.20, 65.87, 55.11, 47.24. HRMS (ESI): For \(\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_5\text{S} (\text{M}+\text{H})^+\) \(m/z\) calcd., 422.1462, found 422.1547.

1.2 \((E)-N-(4-(4-methoxyphenyl)thiazol-2-yl)-3-(4-morphinophenyl)acrylamide (7a):

An orange solid, mp 240-241 °C, yield 54%, \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 12.31 (s, 1H, NH), 7.84 (d, 2H, \(J=8.0\) Hz, ArH), 7.63 (d, 1H, \(J=16.0\) Hz, ethylene-H), 7.47-7.51 (m, 3H, ArH), 7.01 (m, 4H, ArH), 6.73 (d, 1H, \(J=16.0\) Hz, ethylene-H), 3.79 (s, 3H, OCH\(_3\)), 3.74 (s, 4H, morpholine-H), 3.23 (s, 4H, morpholine-H). \(^13\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 163.83, 158.93, 158.05, 152.33, 148.88, 142.51, 129.38, 127.18, 126.97, 124.39, 115.12, 114.35, 114.07, 106.20, 65.87, 55.11, 47.24. HRMS (ESI): For \(\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_5\text{S} (\text{M}+\text{H})^+\) \(m/z\) calcd., 422.1462, found 422.1547.

1.3 \((E)-N-(4-(3-methoxyphenyl)thiazol-2-yl)-3-(4-morphinophenyl)acrylamide (7b):

A bright yellow solid, mp 189-190 °C, yield 37%. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 12.34 (s, 1H, NH), 7.66 (d, 1H, \(J=16.0\) Hz, ethylene-H), 7.64 (d, 2H, \(J=8.0\) Hz, ArH), 7.47-7.52 (m, 3H, ArH), 7.35 (t, 1H, \(J=8.0\) Hz, ArH), 7.01 (d, 2H, \(J=8.0\) Hz, ArH), 6.91 (dd, 1H, \(J=8.0\) Hz, 4.0 Hz ArH), 6.74 (d, 1H, \(J=16.0\) Hz, ethylene-H), 3.82 (s, 3H, OCH\(_3\)), 3.75 (t, 4H, \(J=4.0\) Hz, morpholine-H), 3.24 (t, 4H, \(J=4.0\) Hz, morpholine-H). \(^13\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 163.93, 159.59, 158.10, 152.35, 148.83, 142.61, 135.71, 129.77, 129.40, 124.37, 118.04, 115.06, 114.34, 113.59, 110.84, 108.61, 65.86, 55.07, 47.24. HRMS (ESI): For \(\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_5\text{S} (\text{M}+\text{H})^+\) \(m/z\) calcd., 422.1462, found 422.1560.

1.4 \((E)-N-(4-(2-methoxyphenyl)thiazol-2-yl)-3-(4-morphinophenyl)acrylamide (7c):
A yellow solid, mp 215–216 °C, yield 24%, $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.47 (s, 1H, NH), 8.09 (d, 1H, J=8.0Hz, ArH), 7.62 (d, 1H, J=16.0Hz, ethylene-H), 7.61 (d, 1H, J=8.0Hz, ArH), 7.51 (d, 2H, J=8.0Hz, ArH), 7.30 (t, 1H, J=8.0Hz, ArH), 7.13 (t, 1H, J=8.0Hz, ArH), 6.99–7.06 (m, 3H, ArH), 6.75 (d, 1H, J=16.0Hz, ethylene-H), 3.92 (s, 3H, OCH$_3$), 3.74 (t, 4H, J=4.0Hz, morpholine-H), 3.22 (t, 4H, J=4.0Hz, morpholine-H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 164.91, 156.60, 152.09, 144.77, 141.07, 129.13, 128.93, 128.45, 127.91, 124.99, 122.92, 120.38, 114.84, 114.36, 111.53, 65.89, 55.40, 47.38.

HRMS (ESI): For C$_{23}$H$_{23}$N$_3$O$_3$S (M+H)$^+$ m/z calcd., 422.1462, found 422.1570.

1.5 (E)-N-(4-(4-fluorophenyl)thiazol-2-yl)-3-(4-morpholinophenyl)acrylamide (7d):

A yellow solid, mp 277–278 °C, yield 37%, $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.37 (s, 1H, NH), 7.96 (d, 2H, J=8.0Hz, ArH), 7.64 (d, 1H, J=16.0Hz, ethylene-H), 7.62 (s, 1H, ArH), 7.51 (d, 2H, J=8.0Hz, ArH), 7.27 (t, 2H, J=8.0Hz, ArH), 7.01 (d, 2H, J=8.0Hz, ArH), 6.77 (d, 1H, J=16.0Hz, ethylene-H), 3.74 (t, 4H, J=4.0Hz, morpholine-H), 3.22 (t, 4H, J=4.0Hz, morpholine-H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 163.99, 158.27, 152.34, 147.95, 142.55, 130.93, 129.41, 127.69, 127.61, 124.38, 115.65, 115.44, 115.14, 114.34, 108.00, 65.87, 47.25. $^{19}$F NMR (376 MHz, CDCl$_3$) δ -114.38.

HRMS (ESI): For C$_{22}$H$_{20}$F$_3$N$_3$O$_2$S (M+Na)$^+$ m/z calcd., 432.1260, found 432.1170.

1.6 (E)-N-(4-(3-fluorophenyl)thiazol-2-yl)-3-(4-morpholinophenyl)acrylamide (7e):

A orange solid, mp 225–226 °C, yield 36%, $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.36 (s, 1H, NH), 7.78 (d, 2H, J=8.0Hz, ArH), 7.71 (d, 1H, J=12.0Hz, ArH), 7.65 (d, 1H, J=16.0Hz, ethylene-H), 7.46–7.52 (m, 3H, ArH), 7.17 (td, 1H, J=12.0Hz, J=4.0Hz, ArH), 7.01 (d, 2H, J=8.0Hz, ArH), 6.74 (d, 1H, J=16.0Hz, ethylene-H), 3.74 (t, 4H, J=4.0Hz, morpholine-H), 3.23 (t, 4H, J=4.0Hz, morpholine-H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 164.00, 161.35, 158.34, 152.38, 147.66, 142.73, 136.68, 130.80, 129.43, 124.33, 121.67, 114.95, 114.34, 112.05, 109.65, 65.87, 47.23. $^{19}$F NMR (376 MHz, CDCl$_3$) δ -112.98.

HRMS (ESI): For C$_{22}$H$_{20}$F$_3$N$_3$O$_2$S (M+Na)$^+$ m/z calcd., 432.1260, found 432.1211.

1.7 (E)-N-(4-(2-fluorophenyl)thiazol-2-yl)-3-(4-morpholinophenyl)acrylamide (7f):
A dark yellow solid, mp 197–198°C, yield 30%. ¹H NMR (400 MHz, DMSO-d₆) δ 12.38(s, 1H, NH), 8.06(d, 1H, J=8.0Hz, J=4.0Hz, ArH), 7.66(d, 1H, J=16.0Hz, ethylene-H), 7.50–7.55(m, 3H, ArH), 7.30–7.40(m, 3H, ArH), 7.02(d, 2H, J=12.0Hz, ArH), 6.74(d, 1H, J=16.0Hz, ethylene-H), 3.74(t, 4H, J=4.0Hz, morpholine-H). ¹³C NMR (101 MHz, DMSO-d₆) δ 164.00, 160.70, 157.62, 152.38, 142.74, 132.53, 129.43, 129.15, 124.75, 124.34, 121.79, 116.03, 114.98, 114.35, 112.68, 65.87, 47.24. ¹⁹F NMR (376 MHz, DCl3) δ -114.50. HRMS (ESI): For C₂₂H₂₀FN₃O₅S (M+H)⁺ m/z calcd.,410.1260, found 410.1354.

1.8 (E)-3-(4-morpholinophenyl)-N-(4-(p-tolyl)thiazol-2-yl)acrylamide (7g):

A yellow solid, mp 288–289°C, yield 35%. ¹H NMR (400 MHz, DMSO-d₆) δ 12.31(s, 1H, NH), 7.80(d, 2H, J=8.0Hz, ArH), 7.64(d, 1H, J=16.0Hz, ethylene-H), 7.55(s, 1H, ArH), 7.50(d, 2H, J=8.0Hz, ArH), 7.24(d, 2H, J=8.0Hz, ArH), 7.01(d, 2H, J=8.0Hz, ArH), 6.73(d, 1H, J=16.0Hz, ethylene-H), 3.74(t, 4H, J=4.0Hz, morpholine-H), 3.24(t, 4H, J=4.0Hz, morpholine-H), 2.33(s, 3H, ArCH₃). ¹³C NMR (101 MHz, DMSO-d₆) δ 163.81, 157.59, 152.60, 148.72, 142.22, 137.20, 131.64, 129.84, 125.41, 124.20, 115.03, 114.18, 107.11, 99.09, 65.87, 47.25, 20.78. HRMS (ESI): For C₂₃H₂₃N₃O₅S (M+Na)⁺ m/z calcd.,428.1511, found 428.1407.

1.9 (E)-3-(4-morpholinophenyl)-N-(4-(m-tolyl)thiazol-2-yl)acrylamide (7h):

A yellow solid, mp 197–198°C, yield 33%. ¹H NMR (400 MHz, DMSO-d₆) δ 12.35(s, 1H, NH), 7.70–7.76(m, 2H, ArH), 7.65(d, 1H, J=16.0Hz, ethylene-H), 7.61(s, 1H, ArH), 7.51(d, 2H, J=8.0Hz, ArH), 7.32(t, 1H, J=8.0Hz, ArH), 7.15(d, 1H, J=8.0Hz, ArH), 7.02(d, 2H, J=8.0Hz, ArH), 6.73(d, 1H, J=16.0Hz, ethylene-H), 3.75(t, 4H, J=4.0Hz, morpholine-H), 3.24(t, 4H, J=4.0Hz, morpholine-H), 2.33(s, 3H, ArCH₃), 2.37(s, 3H, ArCH₃). ¹³C NMR (101 MHz, DMSO-d₆) δ 163.89, 158.09, 152.36, 149.07, 142.58, 137.76, 134.25, 129.40, 128.61, 128.37, 126.31, 124.36, 122.81, 115.06, 114.36, 108.04, 99.49, 65.87, 47.25, 21.22. HRMS (ESI): For C₂₃H₂₃N₃O₅S (M+Na)⁺ m/z calcd., 428.1511, found 428.1432.

1.10 (E)-3-(4-morpholinophenyl)-N-(4-(o-tolyl)thiazol-2-yl)acrylamide (7i):
A pale yellow solid, mp 205–206°C, yield 27%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.28(s, 1H, NH), 7.59–7.67(m, 2H, ArH, ethylene-H), 7.51(d, 2H, $J$=8.0Hz, ArH), 7.25–7.27(m, 4H, ArH), 7.01(d, 2H, $J$=8.0Hz, ArH), 6.74(d, 1H, $J$=16.0Hz, ethylene-H), 6.72(s, 1H, ArH), 3.74(t, 4H, $J$=4.0Hz, morpholine-H), 3.23(t, 4H, $J$=4.0Hz, morpholine-H), 2.45(s, 3H, ArCH$_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 163.85, 157.19, 152.34, 149.17, 142.51, 135.33, 134.53, 130.78, 129.38, 129.28, 127.64, 125.79, 124.39, 115.13, 114.36, 111.05, 65.87, 47.25, 21.01. HRMS (ESI): For C$_{23}$H$_{23}$N$_3$O$_2$S (M+H)$^+$ m/z calcd., 428.1511, found 428.1412.

1.11 (E)-N-(4-(2,4-dimethylphenyl)thiazol-2-yl)-3-(4-morpholinophenyl)acrylamide (7j):

A yellow solid, mp 186–187°C, yield 31%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.28(s, 1H, NH), 7.64(d, 1H, $J$=16.0Hz, ethylene-H), 7.50(d, 2H, $J$=8.0Hz, ArH), 7.20(s, 1H, ArH), 7.99–7.09(m, 5H, ArH), 7.74(d, 1H, $J$=16.0Hz, ethylene-H), 3.73(t, 4H, $J$=4.0Hz, morpholine-H), 3.22(t, 4H, $J$=4.0Hz, morpholine-H), 2.42(s, 3H, ArCH$_3$), 2.30(s, 3H, ArCH$_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 163.82, 157.08, 152.32, 149.21, 142.46, 136.79, 135.08, 131.74, 131.43, 129.37, 129.25, 126.42, 124.40, 115.17, 114.35, 110.46, 65.87, 47.25, 20.97, 20.63. HRMS (ESI): For C$_{24}$H$_{25}$N$_3$O$_2$S (M+Na)$^+$ m/z calcd., 442.1667, found 442.1608.

1.12 (E)-N-(4-(3,5-dimethylphenyl)thiazol-2-yl)-3-(4-morpholinophenyl)acrylamide (7k):

A yellow solid, mp 196–197°C, yield 24%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.32(s, 1H, NH), 7.64(d, 1H, $J$=16.0Hz, ethylene-H), 7.55(m, 3H, ArH), 7.50(d, 2H, $J$=8.0Hz, ArH), 7.01(d, 2H, $J$=8.0Hz, ArH), 6.96(s, 1H, ArH), 6.72(d, 1H, $J$=16.0Hz, ethylene-H), 3.74(t, 4H, $J$=4.0Hz, morpholine-H), 3.23(t, 4H, $J$=4.0Hz, morpholine-H), 2.32(s, 6H, ArCH$_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 163.86, 157.98, 152.34, 149.17, 142.56, 137.60, 134.18, 129.39, 129.14, 124.37, 123.53, 115.06, 114.34, 107.83, 65.87, 47.24, 21.00. HRMS (ESI): For C$_{24}$H$_{25}$N$_3$O$_2$S (M+Na)$^+$ m/z calcd., 442.1667, found 442.1589.

1.13 (E)-N-(4-(4-methoxy-2,6-dimethylphenyl)thiazol-2-yl)-3-(4-morpholinophenyl)acrylamide (7l):
A feathery bright yellow solid, mp 254–255°C, yield 39%. 1H NMR (400 MHz, DMSO-d6) δ 12.19(s, 1H, NH), 7.64(d, 1H, J=16.0Hz, ethylene-H), 7.50(d, 2H, J=8.0Hz, ArH), 7.00(d, 2H, J=8.0Hz, ArH), 6.97(s, 1H, ArH), 6.70(m, 3H, ArH, ethylene-H), 3.74(m, 7H, OCH3, morpholine-H), 3.23(t, 4H, J=4.0Hz, morpholine-H). 13C NMR (101 MHz, DMSO-d6) δ 163.70, 158.35, 157.25, 152.32, 148.02, 142.37, 138.08, 129.36, 128.03, 115.21, 114.37, 112.57, 111.16, 65.87, 54.88, 47.27, 20.43. HRMS (ESI): For C25H27N3O3S (M+H) + m/z calcd., 450.1773, found 450.1873.

1.14 (E)-N-(4-(4-ethoxy-2,6-dimethylphenyl)thiazol-2-yl)-3-(4-morpholinophenyl)acrylamide (7m):

A pale yellow solid, mp 267–268°C, yield 31%. 1H NMR (400 MHz, DMSO-d6) δ 12.19(s, 1H, NH), 7.64(d, 1H, J=16.0Hz, ethylene-H), 7.51(d, 2H, J=8.0Hz, ArH), 7.01(d, 2H, J=8.0Hz, ArH), 6.97(s, 1H, ArH), 6.71(d, 1H, J=16.0Hz, ethylene-H), 6.67(s, 2H, ArH), 4.02(q, 2H, J=12.0Hz, J=4.0Hz, CH3CH2OAr), 4.16(t, 4H, J=4.0Hz, morpholine-H), 2.06(s, 6H, ArCH3), 1.33(t, 3H, J=8.0Hz, CH3CH2OAr). 13C NMR (101 MHz, DMSO-d6) δ 163.70, 157.63, 157.23, 152.32, 148.07, 142.38, 138.04, 129.37, 127.90, 124.42, 115.20, 114.37, 113.07, 111.13, 65.87, 62.73, 47.27, 20.42, 14.70. HRMS (ESI): For C26H29N3O3S (M+Na) + m/z calcd., 486.1930, found 486.1853.

1.15 (E)-N-(4-(2,6-difluoro-4-methoxyphenyl)thiazol-2-yl)-3-(4-morpholinophenyl)acrylamide (7n):

A orange solid, mp 241–242°C, yield 27%. 1H NMR (400 MHz, DMSO-d6) δ 12.40(s, 1H, NH), 7.64(d, 1H, J=16.0Hz, ethylene-H), 7.51(d, 2H, J=8.0Hz, ArH), 7.33(s, 1H, ArH), 7.01(d, 2H, J=8.0Hz, ArH), 6.86(d, 2H, J=8.0Hz, ArH), 6.73(d, 1H, J=16.0Hz, ethylene-H), 3.83(s, 3H, OCH3), 3.74(t, 4H, J=4.0Hz, morpholine-H), 3.23(t, 4H, J=4.0Hz, morpholine-H). 13C NMR (101 MHz, DMSO-d6) δ 163.97, 161.78, 160.13, 159.19, 157.65, 152.33, 142.49, 137.47, 129.38, 124.40, 115.19, 114.35, 113.90, 98.58, 65.87, 56.16, 47.25. 19F NMR (376 MHz, CDCl3) δ -111.26. HRMS (ESI): For C23H21F2N3O3S (M+Na) + m/z calcd., 480.1272, found 480.1176.
1.16 (E)-3-(4-morpholinophenyl)-N-(4-(2,4,6-trifluorophenyl)thiazol-2-yl)acrylamide (7o):

A pale yellow solid, mp 225~226°C, yield 31%. ¹H NMR (400 MHz, DMSO-<d>6</d>) δ 12.42(s, 1H, NH), 7.65(d, 1H, J=16.0Hz, ethylene-H), 7.50(d, 2H, J=8.0Hz, ArH), 7.46(s, 1H, ArH), 7.33(t, 2H, J=8.0Hz, ArH), 7.01(d, 2H, J=8.0Hz, ArH), 6.71(d, 1H, J=16.0Hz, ethylene-H), 3.74(t, 4H, J=4.0Hz, morpholine-H). ¹³C NMR (101 MHz, DMSO-<d>6</d>) δ 163.96, 157.92, 152.38, 142.77, 136.44, 132.76, 129.43, 124.31, 115.07, 114.89, 114.34, 113.34, 101.10, 65.87, 47.24. ¹⁹F NMR (376 MHz, CDCl₃) δ -107.84, -109.08. HRMS (ESI): For C₂₂H₁₉F₃N₃O₂S (M+Na)⁺ m/z calcd., 468.1072, found 468.0967.

1.17 (E)-N-(4-mesitylthiazol-2-yl)-3-(4-morpholinophenyl)acrylamide (7p):

A yellow solid, mp 227~228°C, yield 47%. ¹H NMR (400 MHz, DMSO-<d>6</d>) δ 12.20(s, 1H, NH), 7.64(d, 1H, J=16.0Hz, ethylene-H), 7.50(d, 2H, J=8.0Hz, ArH), 7.00(d, 2H, J=8.0Hz, ArH), 6.98(s, 1H, ArH), 6.91(s, 2H, ArH), 6.70(d, 1H, J=16.0Hz, ethylene-H), 3.74(t, 4H, J=4.0Hz, morpholine-H), 3.23(t, 4H, J=4.0Hz, morpholine-H). ¹³C NMR (101 MHz, DMSO-<d>6</d>) δ 163.71, 157.37, 152.33, 148.13, 142.39, 136.59, 136.41, 132.66, 129.70, 124.41, 115.19, 114.37, 114.37, 110.99, 65.87, 47.27, 20.64, 20.09. HRMS (ESI): For C₂₅H₂₇N₃O₂S (M+H)⁺ m/z calcd., 434.1824, found 434.1924.

1.18 (E)-N-(4-mesitylthiazol-2-yl)-3-(4-methoxyphenyl)acrylamide (8a):

A white solid, mp 217~218°C, yield 32%. ¹H NMR (400 MHz, DMSO-<d>6</d>) δ 12.29(s, 1H, NH), 7.69(d, 1H, J=16.0Hz, ethylene-H), 7.59(d, 2H, J=8.0Hz, ArH), 7.03(d, 2H, J=8.0Hz, ArH), 7.00(s, 1H, ArH), 6.92(s, 2H, ArH), 6.77(d, 1H, J=16.0Hz, ethylene-H), 3.81(s, 3H, OCH₃), 2.71(s, 3H, ArCH₃), 2.05(s, 6H, ArCH₃). ¹³C NMR (101 MHz, DMSO-<d>6</d>) δ 163.49, 161.00, 157.28, 148.18, 141.99, 136.61, 136.41, 132.66, 129.70, 127.89, 126.89, 116.96, 114.54, 111.12, 55.33, 20.64, 20.09. HRMS (ESI): For C₂₂H₂₂N₂O₂S (M+Na)⁺ m/z calcd., 379.1402, found 379.1454.

1.19 (E)-3-(4-ethoxyphenyl)-N-(4-mesitylthiazol-2-yl)acrylamide (8b):
A white solid, mp 192–193 °C, yield 30%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.29 (s, 1H, NH), 7.69 (d, 1H, $J$=16.0 Hz, ethylene-H), 7.58 (d, 2H, $J$=8.0 Hz, ArH), 7.02 (m, 3H, ArH), 6.92 (s, 2H, ArH), 6.77 (d, 1H, $J$=16.0 Hz, ethylene-H), 4.09 (q, 2H, $J$=12.0 Hz, CH$_2$CH$_3$), 2.27 (s, 3H, ArCH$_3$), 2.05 (s, 6H, ArCH$_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 163.50, 160.30, 157.29, 148.17, 142.03, 136.61, 136.41, 132.66, 129.71, 127.90, 126.73, 116.84, 114.93, 111.12, 63.29, 20.64, 20.09, 14.51. HRMS (ESI): For C$_{23}$H$_{24}$N$_2$O$_2$S (M+H)$^+$ $m/z$ calcld., 393.1558, found 393.1657.

1.20 (E)-N-(4-mesitylthiazol-2-yl)-3-(4-(2-methoxyethoxy)phenyl)acrylamide (8c):

A white solid, mp 198–199 °C, yield 35%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.31 (s, 1H, NH), 7.69 (d, 1H, $J$=15.6 Hz, ethylene-H), 7.58 (d, 2H, $J$=8.0 Hz, ArH), 7.04 (d, 2H, $J$=8.0 Hz, ArH), 7.00 (s, 1H, ArH), 6.92 (s, 2H, ArH), 6.78 (d, 1H, $J$=16.0 Hz, ethylene-H), 4.15 (q, 2H, $J$=6.0 Hz, OCH$_2$CH$_2$OCH$_3$), 3.67 (q, 2H, $J$=6.0 Hz, OCH$_2$CH$_2$OCH$_3$), 3.31 (s, 3H, OCH$_2$CH$_2$OCH$_3$), 2.26 (s, 3H, ArCH$_3$), 2.05 (s, 6H, ArCH$_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 163.50, 160.23, 157.28, 148.18, 141.95, 136.60, 136.41, 132.66, 129.70, 127.89, 126.94, 117.01, 114.99, 111.12, 70.23, 67.08, 58.15, 20.64, 20.09. HRMS (ESI): For C$_{24}$H$_{26}$N$_2$O$_3$S (M+H)$^+$ $m/z$ calcld., 423.1664, found 423.1757.

1.21 (E)-N-(4-mesitylthiazol-2-yl)-3-(3,4,5-trimethoxyphenyl)acrylamide (8d):

A white solid, mp 237–238 °C, yield 45%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.28 (s, 1H, NH), 7.68 (d, 1H, $J$=15.6 Hz, ethylene-H), 6.98–7.02 (m, 3H, ArH), 6.86–6.92 (m, 3H, ArH, ethylene-H), 3.84 (s, 6H, OCH$_3$), 3.71 (s, 3H, OCH$_3$), 2.26 (s, 3H, ArCH$_3$), 2.05 (s, 6H, ArCH$_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 163.28, 157.11, 153.11, 148.22, 142.26, 139.40, 136.64, 136.42, 132.62, 129.92, 127.91, 119.02, 111.24, 105.43, 60.12, 55.90, 20.64, 20.10. HRMS (ESI): For C$_{24}$H$_{26}$N$_2$O$_3$S (M+H)$^+$ $m/z$ calcld., 439.1613, found 439.1695.

1.22 (E)-N-(4-mesitylthiazol-2-yl)-3-(p-tolyl)acrylamide (8e):
A white solid, mp 208–209°C, yield 35%. 1H NMR (400 MHz, DMSO-d6) δ 12.37(s, 1H, NH), 7.70(d, 1H, J=16.0Hz, ethylene-H), 7.53(d, 2H, J=8.0Hz, ArH), 7.28(d, 2H, J=8.0Hz, ArH), 7.01(s, 1H, ArH), 6.92(s, 2H, ArH), 6.86(d, 1H, J=16.0Hz, ethylene-H), 2.35(s, 3H, ArCH3), 2.26(s, 3H, ArCH3), 2.05(s, 6H, ArCH2). 13C NMR (101 MHz, DMSO-d6) δ 164.37, 163.14, 161.90, 157.16, 148.24, 140.97, 136.62, 132.60, 130.97, 130.22, 127.90, 119.51, 115.99, 111.30, 20.64, 20.08. 19F NMR (376 MHz, CDCl3) δ -110.15. HRMS (ESI): For C22H22N2O5 (M+H) + m/z calcd., 405.1922, found 405.2025.

1.23 (E)-3-(4-(tert-butyl)phenyl)-N-(4-mesitylthiazol-2-yI)acrylamide (8f):

A white solid, mp 265–266°C, yield 41%. 1H NMR (400 MHz, DMSO-d6) δ 12.35(s, 1H, NH), 7.71(d, 1H, J=16.0Hz, ethylene-H), 7.57(d, 2H, J=8.0Hz, ArH), 7.49(d, 2H, J=8.0Hz, ArH), 7.02(s, 1H, ArH), 6.92(s, 2H, ArH), 6.88(d, 1H, J=16.0Hz, ethylene-H), 2.26(s, 3H, ArCH3), 2.05(s, 6H, ArCH3). 13C NMR (101 MHz, DMSO-d6) δ 163.33, 157.19, 153.22, 148.22, 142.05, 136.63, 136.42, 132.63, 131.60, 127.90, 127.81, 125.88, 111.98, 111.24, 34.60, 30.88, 20.65, 20.09. HRMS (ESI): For C22H22N2OS (M+H) + m/z calcd., 436.1548, found 436.1548.

1.24 (E)-3-(4-fluorophenyl)-N-(4-mesitylthiazol-2-yI)acrylamide (8g):

A white solid, mp 204–205°C, yield 46%. 1H NMR (400 MHz, DMSO-d6) δ 12.41(s,1H, NH), 7.70–7.77(m,3H, ArH, ethylene-H), 7.31(d, 2H, J=8.0Hz, ArH), 7.03(s, 1H, ArH), 6.92(s, 2H, ArH), 6.87(d, 1H, J=16.0Hz, ethylene-H), 2.26(s, 3H, ArCH3), 2.05(s, 6H, ArCH3). 13C NMR (101 MHz, DMSO-d6) δ 164.37, 163.14, 161.90, 157.16, 148.24, 140.97, 136.62, 132.60, 130.97, 130.22, 127.90, 119.51, 115.99, 111.30, 20.64, 20.08. 19F NMR (376 MHz, CDCl3) δ -110.15. HRMS (ESI): For C22H22N2OS (M+H) + m/z calcd., 367.1202, found 367.1290.

1.25 (E)-3-(4-bromophenyl)-N-(4-mesitylthiazol-2-yI)acrylamide (8h):

A white solid, mp 190–191°C, yield 48%. 1H NMR (400 MHz, DMSO-d6) δ 12.43(s,1H,NH), 7.72(d,1H, J=16.0Hz, ethylene-H), 7.67(d,2H, J=8.0Hz, ArH), 7.59(d,2H, J=8.0Hz, ArH), 7.03(s,1H, ArH), 6.94(d,1H, J=16.0Hz, ethylene-H), 6.92(s,2H, ArH), 2.26(s, 3H, ArCH3), 2.05(s, 6H, ArCH3). 13C NMR (101 MHz, DMSO-d6) δ 163.01, 157.11, 148.26, 140.89, 136.65, 136.41, 133.59, 132.58, 130.12, 129.85, 127.91, 123.54, 120.45, 111.39, 20.65, 20.09. HRMS (ESI): For C22H28Br2N305 (M+H) + m/z calcd., 427.0400, found 427.0499, 429.0483.

1.26 (E)-N-(4-mesitylthiazol-2-yI)-3-(4-nitrophenyl) acrylamide (8i):
A yellow solid, mp 237–238°C, yield 36%. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 12.55 (s, 1H, NH), 8.31 (d, 2H, \(J=8.0\)Hz, ArH), 7.91 (d, 2H, \(J=8.0\)Hz, ArH), 7.85 (d, 1H, \(J=16.0\)Hz, ethylene-H), 7.09 (d, 1H, \(J=16.0\)Hz, ethylene-H), 7.08 (s, 1H, ArH), 6.92 (s, 2H, ArH), 2.26 (s, 3H, ArCH\(_3\)). 13\(^C\) NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 162.57, 156.97, 148.36, 147.91, 140.76, 139.62, 136.68, 136.42, 132.52, 129.00, 127.92, 124.19, 123.84, 111.61, 20.64, 20.08. HRMS (ESI): For C\(_{21}\)H\(_{19}\)N\(_3\)O\(_3\)S (M+H) \(^+\) \(m/z\) calcd., 394.1147, found 394.1216.

1.27 (E)-N-(4-mesitylthiazol-2-yl)-3-(4-(trifluoromethyl)phenyl)acrylamide (8j):

A white solid, mp 225–226°C, yield 49%. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 12.50 (s, 1H, NH), 7.80–7.88 (m, 5H, ArH), 7.04 (d, 1H, \(J=16.0\)Hz, ethylene-H), 7.02 (s, 1H, ArH), 6.93 (s, 2H, ArH), 2.27 (s, 3H, ArCH\(_3\)), 2.05 (s, 6H, ArCH\(_3\)). 13\(^C\) NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 162.77, 157.02, 148.31, 140.36, 138.33, 136.67, 136.42, 132.55, 129.66, 128.56, 127.91, 125.93, 125.36, 122.45, 111.51, 20.64, 20.08. 19\(^F\) NMR (376 MHz, CDCl\(_3\)) \(\delta\) -61.24. HRMS (ESI): For C\(_{22}\)H\(_{19}\)F\(_3\)N\(_2\)OS (M+H) \(^+\) \(m/z\) calcd., 417.1170, found 417.1243.

1.28 (E)-3-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-mesitylthiazol-2-yl)acrylamide (8k):

A pale yellow solid, mp 197–198°C, yield 49%. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 12.45 (s, 1H, NH), 8.12 (s, 1H, ArH), 7.96 (d, 1H, \(J=8.0\)Hz, ArH), 7.81–7.85 (m, 2H, ArH, ethylene-H), 7.05 (s, 1H, ArH), 7.04 (d, 1H, \(J=16.0\)Hz, ethylene-H), 6.93 (s, 2H, ArH), 2.27 (s, 3H, ArCH\(_3\)), 2.05 (s, 6H, ArCH\(_3\)). 13\(^C\) NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 162.69, 156.98, 148.31, 139.26, 136.67, 136.42, 132.55, 129.66, 128.56, 127.91, 125.93, 125.36, 122.45, 111.51, 20.64, 20.08. 19\(^F\) NMR (376 MHz, CDCl\(_3\)) \(\delta\) -61.51. HRMS (ESI): For C\(_{22}\)H\(_{18}\)ClF\(_3\)N\(_2\)OS (M+H) \(^+\) \(m/z\) calcd., 451.0751, found 451.0850, 453.0825.

1.29 (E)-3-(4-cyclopropylphenyl)-N-(4-mesitylthiazol-2-yl)acrylamide (8l):

A white solid, mp 206–207°C, yield 33%. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 12.33 (s, 1H, NH), 7.69 (d, 1H, \(J=16.0\)Hz, ethylene-H), 7.52 (d, 2H, \(J=8.0\)Hz, ArH), 7.17 (d, 2H, \(J=8.0\)Hz, ArH), 7.02 (s, Ethylene-H).
1H, ArH), 6.92(s,2H, ArH), 6.85(d,1H, J=16.0Hz, ethylene-H), 2.05(s, 3H, ArCH3), 1.97(s,6H, ArCH2), 1.24(s,1H, ArCH(CH3)2), 1.02(q,2H, J=12.0Hz, ArCH(CH3)2), 0.74(q, 2H, J=12.0Hz, ArCH(CH3)2). 13C NMR (101 MHz, DMSO-d6) δ 163.37, 157.21, 148.21, 146.80, 142.14, 136.62, 136.41, 132.64, 131.40, 127.99, 127.90, 125.88, 118.25, 111.21, 20.65, 20.09, 15.22, 10.05. HRMS (ESI): For C24H29N2OS (M+H) + m/z calcd., 389.1609, found 389.1703.
1.30 (E)-N-(4-mesitylthiazol-2-yl)-3-(4-(piperidin-1-yl)phenyl)acrylamide (8m):

A bright yellow solid, mp 251–252 °C, yield 33%. 1H NMR (400 MHz, DMSO-d6) δ 9.80(s,1H, NH), 7.69(d,1H, J=16.0Hz, ethylene-H), 7.38(d, 2H, J=8.0Hz, ArH), 6.88(d, 2H, J=8.0Hz, ArH), 6.83(s,2H, ArH), 6.73(s,1H, ArH), 6.08(d,1H, J=16.0Hz, ethylene-H), 3.31(d,4H, J=4.0Hz, N(CH2)2), 2.20(s,3H, ArCH3), 2.09(s,6H, ArCH2), 1.64~1.57(m,6H, (CH2)2CH2). 13C NMR (101 MHz, DMSO-d6) δ 163.77, 157.37, 152.41, 148.11, 142.55, 136.58, 136.41, 132.79, 129.51, 127.89, 123.09, 114.50, 114.38, 110.93, 48.19, 24.87, 23.93, 20.65, 20.09. HRMS (ESI): For C26H33N2OS (M+H) + m/z calcd., 432.2031, found 432.2139.
1.31 (E)-N-(4-mesitylthiazol-2-yl)-3-(pyridin-4-yl)acrylamide (8n):

A pale yellow solid, mp 233–234 °C, yield 49%. 1H NMR (400 MHz, DMSO-d6) δ 12.57(s,1H, NH), 8.68(d, 2H, J=4.0Hz, ArH), 7.72(d, 1H, J=16.0Hz, ethylene-H), 7.59(d,2H, J=4.0Hz, ArH), 7.12(d,1H, J=16.0Hz, ethylene-H), 7.07(s,1H, ArH), 6.92(s,2H, ArH), 2.26(s,3H, ArCH3), 2.05(s, 6H, ArCH2). 13C NMR (101 MHz, DMSO-d6) δ 162.55, 156.94, 150.50, 148.35, 141.44, 139.51, 136.69, 136.42, 132.51, 127.92, 124.14, 121.81, 111.61, 20.64, 20.08. HRMS (ESI): For C28H39N2OS (M+H) + m/z calcd., 350.1249, found 350.1352.
1.32 (E)-N-(4-mesitylthiazol-2-yl) cinnamamide (8o):

A white solid, mp 191–192 °C, yield 47%. 1H NMR (400 MHz, DMSO-d6) δ 12.40(s, 1H, NH), 7.75(d,1H, J=16.0Hz, ethylene-H), 7.65(d,2H, J=8.0Hz, ArH), 7.44~7.49(m,3H, ArH), 7.03(s, 1H, ArH), 6.93(d,1H, J=16.0Hz, ethylene-H), 6.92(s, 2H, ArH), 2.27(s,3H, ArCH3), 2.05(s,6H, ArCH2). 13C-NMR (101 MHz, DMSO-d6) δ 163.20, 157.15, 148.35, 142.20, 136.64, 136.42, 134.30, 132.61, 130.29, 129.07, 127.95, 127.91, 119.63, 111.31, 20.65, 20.09. HRMS (ESI): For C21H20N2OS (M+Na+) + m/z calcd., 371.1296, found 371.1216.