

1 SUPPLEMENTARY MATERIAL

2
3 The analytical and spectral data of the synthesized compounds are available

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5 **Synthesis and antimicrobial activity of new 3,5-diarylidene-4-**
6 **piperidone derivatives**

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8 KULATHOORAN SINGARAM¹, DHAMODARAN MARIMUTHU^{2*}, SELVAKUMAR
9 BASKARAN³ and VENKATARAMAN RAMASWAMY⁴

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11 ¹Research & Development Centre, Bharathiar University, Coimbatore-641046, India,
12 ^{2*}Department of Chemistry, Perunthalaivar Kamarajar Institute of Engineering and Technology,
13 Karaikal-609603, India and ^{3&4}Department of Chemistry, PG and Research Centre,
14 Sriparamakalyani College, Alwarkurichi 627412, India
15 *Corresponding author. E-mail: dhamu_762003@yahoo.co.in

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17 ANALYTICAL AND SPECTRAL DATA OF THE SYNTHESIZED COMPOUNDS

18 *3,5-Bis(4-fluorobenzylidene)piperidin-4-one hydrochloride (3a)*. Yellow crystals; Yield: 94%;
19 m.p. 236-238 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 4.40 (4H, *s*, -NH-CH₂), 7.35 (4H, *m*,
20 aromatic), 7.59 (4H, *dd*, *J* = 8.8 Hz, 5.6 Hz, Ar), 7.84 (2H, *s*, Ar-CH=C), 9.64 (2H, *s*, NH.HCl);
21 ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 44.5 (NCH₂), 116.4 (*d*, *J* = 21.6 Hz), 128.9, 130.9,
22 133.4 (*d*, *J* = 8.6 Hz), 138.0, 162.0 (*d*, *J* = 247.8 Hz), 183.3 (CO); ESI-HRMS (*m/z*): Calcd. for
23 C₁₉H₁₅F₂NO: 311.1. Found: 312.2 (M+H)

24 *3,5-bis(Thiophen-2-ylmethylene)piperidin-4-one hydrochloride (3b)*. Yellow crystals; Yield:
25 96%; m.p. 357-359 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 4.47 (4H, *s*, -NH-CH₂), 7.31
26 (2H, *dd*, *J* = 5.0, 3.8 Hz, Ar), 7.69 (2H, *s*, Ar-CH=C), 8.02 (4H, *m*, Ar), 10.1 (2H, *s*, NH.HCl); ¹³C-
27 NMR (100 MHz, DMSO-*d*₆, δ / ppm): 44.0 (NCH₂), 124.7, 129.3, 131.3, 133.4, 136.0, 137.4, 181.8
28 (CO); ESI-HRMS (*m/z*): Calcd. for C₁₅H₁₃NOS₂:287.4. Found: 288.2 (M+H).

29 *3,5-bis(Benzo[d][1,3]dioxol-5-ylmethylene)piperidin-4-one (3c)*. Yellow powder; Yield: 93%;
30 m.p. 256-258 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 3.95 (4H, *s*, -NH-CH₂), 5.75 (1H, *s*,
31 NH), 6.09 (4H, *s*, OCH₂O), 7.01 (4H, *m*, Ar), 7.05 (2H, *s*, Ar), 7.49 (2H, *s*, Ar-CH=C); ¹³C-NMR
32 (100 MHz, DMSO-*d*₆, δ / ppm): 48.1 (NCH₂), 102.0 (OCH₂O), 109.0, 110.5, 126.2, 129.6, 134.1,
33 134.9, 148.1, 148.5, 187.8 (CO); ESI-HRMS (*m/z*): Calcd. for C₂₁H₁₇NO₅: 363.1. Found: 364.2
34 (M+H).

35 *3,5-bis(Thiophen-3-ylmethylene)piperidin-4-one hydrochloride (3d)*. Yellow powder; Yield:
36 90%; m.p. 348-350 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 4.49 (4H, *s*, -NH-CH₂), 7.40 (2H,
37 *d*, *J* = 5.2 Hz, Ar), 7.76 (2H, *m*, Ar), 7.85 (2H, *s*, Ar), 8.04 (2H, *s*, Ar-CH=C), 9.95 (2H, *s*, NH.HCl);
38 ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 44.3 (NCH₂), 126.4, 128.2, 129.7, 132.0, 132.9, 136.0,
39 182.8 (CO); ESI-HRMS (*m/z*): Calcd. for C₁₅H₁₃NOS₂: 287.0. Found: 287.7 (M).

40 *3,5-Dibenzylidenepiperidin-4-one (3e)*. Yellow powder; Yield: 90%; m.p. 211-213 °C; ¹H-
41 NMR (400 MHz, DMSO-*d*₆, δ / ppm): 4.48 (4H, *s*, -NH-CH₂), 7.52 (6H, *m*, Ar), 7.62 (4H, *m*, Ar),
42 7.68 (2H, *s*, Ar-CH=C), 9.81 (1H, *s*, NH); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 44.6 (NCH₂),
43 129.1, 131.1, 133.7, 138.2, 142.2, 144.7, 184.5 (CO); ESI-HRMS (*m/z*): Calcd.
44 for C₁₉H₁₇NO: 275.3. Found: 275.2 (M).

45 *3,5-bis(3-Chloro-4-hydroxybenzylidene)piperidin-4-one hydrochloride (3f)*. Yellow crystals;
46 Yield: 95%; m.p. 320-322 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 4.46 (4H, *s*, -NH-CH₂),
47 7.15 (2H, *d*, *J* = 8.4 Hz, Ar), 7.34 (2H, *m*, Ar), 7.57 (2H, *d*, *J* = 2.0 Hz, Ar), 7.74 (2H, *s*, Ar-CH=C),
48 9.76 (2H, *s*, NH.HCl), 11.12 (2H, *s*, OH); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 44.3 (NCH₂),
49 117.4, 120.8, 126.3, 126.4, 131.6, 132.9, 138.4, 155.6 (COH), 182.4 (CO); ESI-HRMS (*m/z*):
50 Calcd. for C₁₉H₁₅Cl₂NO₃: 376.2. Found: 375.9 (M).

51 *3,5-bis(4-Fluorobenzylidene)-1-(3,5-dichloro-2-hydroxyphenylsulfonyl)piperidin-4-one (5a)*.
52 Pale yellow solid; Yield: 92%; m.p. 221-223 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 4.73
53 (4H, *s*, -NCH₂), 7.28 (1H, *d*, *J* = 2.8 Hz, -SO₂-Aryl), 7.34 (4H, *t*, *J* = 8.8 Hz, aromatic), 7.52 (4H,
54 *dd*, *J* = 8.4, 5.6 Hz, Ar), 7.57 (2H, *s*, Ar-CH=C), 7.82 (1H, *d*, *J* = 2.8 Hz, -SO₂-Aryl), 11.06 (1H, *s*,
55 OH); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 46.8 (NCH₂), 116.2 (*d*, *J* = 21.5 Hz), 124.7, 128.5,
56 128.8, 131.1, 131.5, 133.2 (*d*, *J* = 8.5 Hz), 134.3, 135.6, 151.7 (COH), 161.7 (*d*, *J* = 247.2 Hz),
57 185.4 (CO); ESI-HRMS (*m/z*): Calcd. for C₂₅H₁₇Cl₂F₂NO₄S: 536.4. Found: 534.0 (M-2).

58 *1-(3,5-Dichloro-2-hydroxyphenylsulfonyl)-3,5-bis(thiophen-2-ylmethylene)piperidin-4-one*
59 (*5b*). Pale yellow solid; Yield: 93.0%; m.p. 219-221 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm):
60 4.77 (4H, *s*, -NCH₂), 7.28 (2H, *dd*, *J* = 5.2, 3.6 Hz, Ar), 7.49 (1H, *d*, *J* = 2.4 Hz, Ar), 7.49 (2H, *d*,
61 *J* = 3.6 Hz, Ar), 7.77 (2H, *s*, Ar-CH=C), 7.82 (1H, *d*, *J* = 2.8 Hz, Ar), 7.98 (2H, *d*, *J* = 4.8 Hz, Ar),
62 11.16 (1H, *s*, OH); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 46.8 (NCH₂), 123.4, 124.6, 127.5,
63 128.8, 129.0, 133.1, 133.9, 134.6, 135.3, 137.9, 138.3, 151.0 (COH), 184.3 (CO); ESI-HRMS
64 (*m/z*): Calcd. for C₂₁H₁₅Cl₂NO₄S₃: 510.9. Found: 509.82. (M-H).

65 *3,5-bis(Benzo[d][1,3]dioxol-5-ylmethylene)-1-(3,5-dichloro-2-hydroxyphenyl-*
66 *sulfonyl)piperidin-4-one (5c)*. Pale yellow solid; Yield: 95.0%; m.p. 242.5-243.4°C; ¹H-NMR (400
67 MHz, DMSO-*d*₆, δ / ppm): 4.70 (4H, *s*, -NCH₂), 6.1 (4H, *s*, OCH₂O), 6.99 (6H, *m*, Ar), 7.34 (1H,
68 *d*, *J* = 2.8 Hz, Ar), 7.57 (2H, *s*, Ar-CH=C), 7.82 (1H, *d*, *J* = 2.4 Hz, Ar), 11.04 (1H, *s*, OH); ¹³C-
69 NMR (100 MHz, DMSO-*d*₆, δ / ppm): 47.0 (NCH₂), 102.2 (OCH₂O), 109.2, 110.5, 126.5, 128.5,
70 128.7, 130.1, 131.1, 133.3, 133.5, 134.4, 136.7, 148.2, 149.0, 151.0 (COH), 185.1 (CO); ESI-
71 HRMS (*m/z*): Calcd. for C₂₇H₁₉Cl₂NO₈S: 587.0. Found: 586.0 (M-2).

72 *1-(3,5-Dichloro-2-hydroxyphenylsulfonyl)-3,5-bis(thiophen-3-ylmethylene)piperidin-4-one*
73 *(5d)*. Pale yellow solid; Yield: 92.0%; m.p. 217-219 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ /
74 ppm): 4.73 (4H, *s*, -NCH₂), 7.34 (2H, *d*, *J* = 4.4 Hz, Ar), 7.47 (1H, *d*, *J* = 5.6 Hz, Ar), 7.60 (2H, *s*,
75 Ar), 7.72 (2H, *dd*, *J* = 5.2, 4.8 Hz, Ar), 7.84 (1H, *d*, *J* = 2.4 Hz, Ar), 7.92 (2H, *s*, Ar-CH=C);
76 11.08(1H, *s*, OH); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 47.3 (NCH₂), 123.4, 124.3, 127.9,
77 128.7, 129.7, 130.0, 130.1, 131.0, 134.4, 136.3, 136.5, 150.8(COH), 185.2 (CO); ESI-HRMS
78 (*m/z*): Calcd. for C₂₁H₁₅Cl₂NO₄S₃: 510.9. Found: 511.9 (M+1).

79 *3,5-Dibenzylidene-1-(3,5-dichloro-2-hydroxyphenylsulfonyl)piperidin-4-one (5e)*. Pale yellow
80 solid; Yield: 98.0%; m.p. 191-193 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 4.75 (4H, *s*, -
81 NCH₂), 7.30 (1H, *d*, *J* = 2.4 Hz, SO₂-aryl), 7.49 (10H, *m*, Ar), 7.61 (2H, *s*, ArCH=C), 7.85 (1H, *d*,
82 *J* = 2.4 Hz, -SO₂-aryl), 11.07 (1H, *s*, OH); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 47.0 (NCH₂),
83 123.3, 124.5, 128.5, 129.2, 129.3, 130.1, 130.9, 131.7, 134.5, 136.9, 150.8 (COH), 185.4 (CO);
84 ESI-HRMS (*m/z*): Calcd. for C₂₅H₁₉Cl₂NO₄S: 499.0. Found: 498.0 (M-1).

85 *3,5-bis(3-Chloro-4-hydroxybenzylidene)-1-(3,5-dichloro-2-hydroxyphenylsulfonyl) piperidin-*
86 *4-one (5f)*. Yellow solid; Yield: 64.0%; m.p. 300-302°C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm):
87 4.69 (4H, *s*, -NCH₂), 7.08 (2H, *d*, *J* = 8.4 Hz, Ar), 7.26 (2H, *dd*, *J* = 8.4, 2.0 Hz, Ar), 7.34 (1H, *d*,
88 *J* = 2.4 Hz, SO₂-aryl), 7.45 (4H, *m*, Ar and Ar-CH=C), 7.82 (1H, *d*, *J* = 2.4 Hz, SO₂-aryl), 10.87
89 (2H, *s*, OH), 10.99 (1H, *s*, OH); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 46.9, 117.3, 120.7,
90 123.4, 124.5, 126.8, 128.6, 129.1, 129.9, 131.2, 132.9, 134.4, 135.7, 150.8 (COH), 155.0 (COH),
91 184.9(CO); ESI-HRMS (*m/z*): Calcd. for C₂₅H₁₇Cl₄NO₆S: 598.9. Found: 599.8 (M+1).

92 *Methyl 2-(3,5-bis(4-fluorobenzylidene)-4-oxopiperidin-1-ylsulfonyl)benzoate (5g)*. Pale yellow
93 solid; Yield: 93.5%; m.p. 187-189 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 3.58 (3H, *s*,
94 COOCH₃), 4.66 (4H, *s*, -NCH₂), 7.35 (4H, *t*, *J* = 8.8 Hz, Ar), 7.60 (5H, *m*, Ar), 7.78 (2H, *s*, Ar-
95 CH=C), 7.99 (3H, *m*, Ar); ¹³C- NMR (100 MHz, DMSO-*d*₆, δ / ppm): 47.0 (NCH₂), 53.2

96 (COOCH₃), 116.3 (*d*, *J* = 28.5 Hz), 128.9, 129.3, 131.1, 131.4, 133.3, 133.5 (*d*, *J* = 8.5 Hz), 134.1,
97 134.8, 136.3, 161.9 (*d*, *J* = 247.6 Hz), 168.1 (COOCH₃), 184.8 (CO); ESI-HRMS (*m/z*): Calcd. for
98 C₂₇H₂₁F₂NO₅S: 509.1. Found: 510.2 (M+H).

99 *3,5-bis(4-Fluorobenzylidene)-1-((E)-styrylsulfonyl)piperidin-4-one (5h)*. Pale yellow solid;
100 Yield: 92%; m.p. 204-206 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 4.64 (4H, *s*, -NCH₂), 7.26
101 (6H, *m*, Ar), 7.48 (3H, *m*, Ar), 7.56 (4H, *m*, Ar& styryl), 7.66 (2H, *m*, Ar& styryl), 7.72 (2H, *s*,
102 ArCH=C); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 47.0 (NCH₂), 116.3 (*d*, *J* = 21.5 Hz), 123.7,
103 129.2, 129.4, 131.1, 131.4, 133.0, 133.4 (*d*, *J* = 8.8 Hz), 136.3, 143.2, 161.9 (*d*, *J* = 247.6 Hz),
104 185.1 (CO); ESI-HRMS (*m/z*): Calcd. for C₂₇H₂₁F₂NO₃S: 477.1. Found: 476.0. (M-H).

105 *Methyl 2-(4-oxo-3,5-bis(thiophen-2-ylmethylene)piperidin-1-ylsulfonyl)benzoate (5i)*. Pale
106 yellow solid; Yield: 91.0%; m.p. 185-187 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 3.72 (3H,
107 *s*, COOCH₃), 4.70 (4H, *s*, -NCH₂), 7.30 (2H, *m*, Ar), 7.63 (3H, *m*, Ar), 7.69 (3H, *m*, Ar), 7.76 (2H,
108 *s*, ArCH=C), 8.01 (2H, *d*, *J* = 5.2 Hz, Ar); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 46.7(NCH₂),
109 53.4 (COOCH₃), 128.0, 129.1, 129.2, 129.3, 129.48, 131.4, 133.2, 133.3, 134.1, 135.0, 135.2, 137.8,
110 168.0 (COOCH₃), 183.8 (CO); ESI-HRMS (*m/z*): Calcd. for C₂₃H₁₉NO₅S₃: 485.0. Found: 486.0
111 (M+H).

112 *1-(Styrylsulfonyl)-3,5-bis(thiophen-2-ylmethylene)piperidin-4-one (5j)*. Pale yellow solid;
113 Yield: 93.0%; m.p. 200-202 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 4.69 (4H, *s*, -NCH₂),
114 7.30 (2H, *m*, Ar), 7.35 (1H, *s*, Ar), 7.43 (4H, *m*, Ar& styryl), 7.63 (4H, *m*, Ar& styryl), 7.90 (2H,
115 *s*, Ar-CH=C), 8.00 (2H, *d*, *J* = 4.8 Hz, Ar); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 46.7(NCH₂),
116 123.6, 128.1, 129.2, 129.2, 129.4, 129.5, 131.5, 133.0, 133.1, 135.3, 137.8, 143.5, 184.0 (CO); ESI-
117 HRMS (*m/z*): Calcd. for C₂₃H₁₉NO₃S₃: 453.0. Found: 453.0 (M).

118 *Methyl 2-(3,5-bis(benzo[d][1,3]dioxol-5-ylmethylene)-4-oxopiperidin-1-ylsulfonyl) benzoate*
119 (*5k*). Pale yellow solid; Yield: 95.0%; m.p. 191-193 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm):
120 3.64 (3H, *s*, -COOCH₃), 4.63 (4H, *s*, -NCH₂), 6.14 (4H, *s*, OCH₂O), 7.08 (4H, *s*, Ar), 7.14 (2H, *s*,
121 Ar), 7.59 (2H, *s*, Ar-CH=C), 7.61 (1H, *m*, Ar), 7.72 (3H, *m*, Ar); ¹³C-NMR (100 MHz, DMSO-*d*₆,
122 δ / ppm): 47.2 (NCH₂), 53.5, 102.0 (OCH₂O), 109.0 (COOCH₃), 109.5, 110.3, 110.8, 126.5, 127.1,
123 128.7, 129.6, 133.4, 134.0, 134.8, 137.3, 148.3, 149.2, 168,1 (COOCH₃), 184.5 (CO); ESI-HRMS
124 (*m/z*): Calcd. for C₂₉H₂₃NO₉S: 561.1. Found: 562.2 (M+H).

125 *3,5-bis(Benzo[d][1,3]dioxol-5-ylmethylene)-1-((E)-styrylsulfonyl)piperidin-4-one (5l)*. Pale
126 yellow solid; Yield: 94.0%; m.p. 211-213 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 4.61 (4H,

127 *s*, -NCH₂), 6.13 (4H, *s*, OCH₂O), 7.03 (6H, *m*, Ar), 7.28 (2H, *m*, Ar), 7.47 (3H, *m*, Ar and styryl),
128 7.64 (2H, *s*, Ar-CH=C), 7.68 (2H, *m*, Ar and styryl); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm):
129 47.2 (NCH₂), 102.2 (OCH₂O), 108.9, 110.2, 123.6, 127.0, 128.7, 129.2, 129.4, 129.9, 131.4, 133.1,
130 137.3, 143.07, 148.3, 149.2, 184.8 (CO); ESI-HRMS (*m/z*): Calcd. for C₂₉H₂₃NO₇S: 529.1. Found:
131 529.9 (M+H).

132 *N*-(4-Methyl-5-(4-oxo-3,5-bis(thiophen-2-ylmethylene)piperidin-1-ylsulfonyl)thiazol-2-
133 yl)acetamide (**5m**). Pale yellow solid; Yield: 93.0%; m.p. 231-233 °C; ¹H-NMR (400 MHz,
134 DMSO-*d*₆, δ / ppm): 2.18 (3H, *s*, CH₃CO), 2.40 (3H, *s*, CH₃), 4.71 (4H, *s*, -NCH₂), 7.31 (2H, *m*,
135 Ar), 7.65 (2H, *d*, *J* = 3.3 Hz, Ar), 7.88 (2H, *s*, Ar-CH=C), 8.03 (2H, *d*, *J* = 5.2 Hz, Ar), 12.65 (1H,
136 *s*, NH); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 17.0 (CH₃), 22.9 (COOCH₃), 47.1 (NCH₂),
137 119.0, 127.5, 129.2, 129.8, 133.4, 135.7, 137.6, 153.8, 160.4, 167.0 (COOCH₃), 183.3 (CO); ESI-
138 HRMS (*m/z*): Calcd. for C₂₁H₁₉N₃O₄S₄: 505.0. Found: 504.0 (M-H).

139 *1*-(1,2-Dimethyl-1H-imidazol-4-ylsulfonyl)-3,5-bis(thiophen-2-ylmethylene)piperidin-4-one
140 (**5n**). Pale yellow solid; Yield: 91.0%; m.p. 231-233 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm):
141 2.28 (3H, *s*, CH₃), 3.58 (3H, *s*, NCH₃), 4.57 (4H, *s*, -NCH₂), 7.29 (2H, *m*, Ar), 7.60 (2H, *d*, *J* = 3.6
142 Hz, Ar), 7.74 (1H *s*, Ar), 7.82 (2H, *s*, Ar-CH=C), 7.98 (2H, *d*, *J* = 5.2 Hz, Ar); ¹³C-NMR (100
143 MHz, DMSO-*d*₆, δ / ppm): 12.9 (CH₃), 33.5 (NCH₃), 47.1 (NCH₂), 127.0, 128.2, 128.9, 129.1,
144 132.9, 134.0, 135.1, 137.9, 147.8, 184.0 (CO); ESI-HRMS (*m/z*): Calcd. for C₂₀H₁₉N₃O₃S₃: 445.0.
145 Found: 446.2 (M+H).

146 *1*-(3,5-Dichlorophenylsulfonyl)-3,5-bis(thiophen-2-ylmethylene)piperidin-4-one (**5o**). Yellow
147 solid; Yield: 94.0%; m.p. 211-213 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 4.8 (4H, *s*, -
148 NCH₂), 7.3(2H, *m*, Ar), 7.51 (2H, *d*, *J* = 2.0 Hz, Ar), 7.64 (2H, *d*, *J* = 3.6 Hz, Ar), 7.76 (2H, *s*,
149 ArCH=C), 7.99 (1H, *s*, Ar), 8.01 (2H, *m*, Ar); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 46.9
150 (NCH₂), 126.1, 126.8, 129.3, 129.9, 133.4, 133.6, 135.7, 135.8, 137.5, 140.9, 183.1 (CO); ESI-
151 HRMS (*m/z*): Calcd. for C₂₁H₁₅Cl₂NO₃S₃: 494.9. Found: 496.8 (M+2)

152 *1*-(6-Chloropyridin-3-ylsulfonyl)-3,5-bis(thiophen-2-ylmethylene)piperidin-4-one (**5p**). Pale
153 yellow solid; Yield: 91.0%; m.p. 234-235 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 4.72 (4H,
154 *s*, -NCH₂), 7.31 (2H, *m*, Ar), 7.67 (2H, *d*, *J* = 3.6 Hz, Ar), 7.77 (1H, *d*, *J* = 3.6 Hz, Ar), 7.79 (2H,
155 *s*, ArCH=C), 8.03 (2H, *d*, *J* = 5.2 Hz, Ar), 8.12 (1H, *m*, Ar), 8.69 (1H, *m*, Ar); ¹³C-NMR (100 MHz,
156 DMSO-*d*₆, δ / ppm): 46.9 (NCH₂), 125.9, 126.9, 129.3, 130.0, 133.5, 135.7, 137.6, 139.1, 143.2,
157 148.7, 155.3, 183.4 (CO); ESI-HRMS (*m/z*): Calcd. for C₂₀H₁₅ClN₂O₃S₃: 462.0. Found: 462.0 (M)

158 *1-(3,5-Dimethylisoxazol-4-ylsulfonyl)-3,5-bis(thiophen-2-ylmethylene)-piperidin-4-one (5q)*.
159 Pale yellow solid; Yield: 92.0%; m.p. 232-233 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 2.21
160 (3H, *s*, CH₃), 2.47 (3H, *s*, CH₃), 4.76 (4H, *s*, -NCH₂), 7.32 (2H, *m*, Ar), 7.70 (2H, *d*, *J* = 3.6 Hz,
161 Ar), 7.92 (2H, *s*, ArCH=C), 8.03 (2H, *d*, *J* = 5.2 Hz, Ar); ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm):
162 11.2 (CH₃), 13.1 (CH₃), 46.7 (NCH₂), 114.8, 127.2, 129.3, 130.0, 133.7, 136.0, 137.5, 157.5, 174.4,
163 183.1 (CO); ESI-HRMS (*m/z*): Calcd. for C₂₀H₁₈N₂O₄S₃: 446.0. Found: *m/z*446.0 (M).

164 *tert-Butyl 2-oxo-2-(4-oxo-3,5-bis(thiophen-2-ylmethylene)piperidin-1-yl)ethylcarbamate (7a)*.
165 Red crystals; Yield: 78.0%; m.p. 301-304 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 1.35
166 (9H,*s,t*-butyl), 3.87 (2H,*d*, *J* = 6.0 Hz, -COCH₂NH), 4.82 (4H, *d*, *J* = 24.8 Hz, -NCH₂), 6.81 (1H,*t*,
167 *J* = 5.6 Hz, -NH), 7.30 (2H,*m*, Ar), 7.67 (2H,*d*, *J* = 8.8 Hz, Ar), 7.89 (2H, *s*, ArCH=C), 7.99 (2H,
168 *d*, *J* = 5.2 Hz, Ar); ¹³C NMR (100 MHz, DMSO-*d*₆, δ / ppm): 28.6 (-C(CH₃)), 40.6 (-
169 COCH₂NH), 47.0 (NCH₂) 78.5 (-C(CH₃)), 129.1, 133.0, 135.2, 138.0, 156.2 (-NCOO), 168.4 (-
170 COCH₂NH), 185.1 (CO); ESI-HRMS (*m/z*): Calcd. for C₂₂H₂₄N₂O₄S₂: 444.1. Found: 345.2 (M-
171 BOC)⁺

172 *tert-Butyl-(S)-3-methyl-1-oxo-1-(2-oxo-2-(4-oxo-3,5-bis(thiophen-2-ylmethylene)piperidin-1-*
173 *yl)ethylamino)butan-2-ylcarbamate (7b)*. Red crystals; 70% yield; m.p. 311-313 °C; ¹H-NMR (400
174 MHz, CD₃OD, δ / ppm): 1.27 (6H,*m*, -CH(CH₃)₂), 1.33 (9H, *s*, C(CH₃)₃), 2.07 (1H,*m*, -CH(CH₃)₂),
175 3.97 (1H, *d*, *J* = 6.0 Hz, -COCHNH), 4.13 (2H,*m*, -COCH₂NH), 4.94 (4H,*d*, *J* = 25.2 Hz, -NCH₂),
176 7.27 (2H,*m*, Ar), 7.28 (2H,*m*,Ar), 7.54 (2H, *d*, *J* = 3.2 Hz, Ar), 7.84 (2H, *m*, ArCH=C); ¹³C NMR
177 (100 MHz, DMSO-*d*₆, δ / ppm): 18.0 (CH(CH₃)₂), 28.8 (C(CH₃)₃), 31.4 (CH(CH₃)₂), 41.8(-
178 COCH₂NH), 46.6 (NCH₂), 59.9(COCHNH), 79.1(C(CH₃)₃), 129.1, 129.4, 129.5, 133.0, 135. 6,
179 139.0, 154.1, 168.9 (-COCH₂NH), 170.1 (COCHNH), 186.4 (CO); ESI-HRMS (*m/z*): Calcd. for
180 C₂₇H₃₃N₃O₅S₂: 543.2. Found: 444.2 (M-BOC)⁺

181 *1-(2-Aminoacetyl)-3,5-bis(thiophen-2-ylmethylene)piperidin-4-one trifluoroacetate (8a)*.
182 Yellow powder; Yield: 93.0%; m.p. 333-335 °C; ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 4.05
183 (2H, *d*, *J* = 5.2 Hz, -COCH₂NH₂), 4.78 (4H,*s*, -NCH₂), 7.30 (2H, *m*, Ar), 7.68 (2H,*dd*, *J* = 9.6, 3.4
184 Hz, Ar), 7.90 (2H,*d*, *J* = 10.8 Hz, ArCH=C), 8.00 (2H, *m*, Ar); ¹³C NMR (100 MHz, DMSO-*d*₆, δ
185 / ppm): 42.6 (-COCH₂NH₂), 45.7 (NCH₂), 128.9, 129.1, 129.2, 133.0, 135.0, 137.9, 165.8 (-
186 COCH₂NH₂), 184.9 (CO); ESI-HRMS (*m/z*): Calcd. for C₁₇H₁₆N₂O₂S₂: 344.1. Found: 345.0(M+1).

187 *(S)-2-Amino-3-methyl-N-(2-oxo-2-(4-oxo-3,5-bis(thiophen-2-ylmethylene)-piperidin-1-*
188 *yl)ethyl)butanamide trifluoroacetate (8b)*. Yellow powder; Yield: 94%; m.p. 341-343 °C; ¹H-NMR

189 (400 MHz, CD₃OD, δ / ppm): 1.09 (6H, *m*, -CH(CH₃)₂), 2.17 (1H, *m*, -CH(CH₃)₂), 3.74 (1H, *d*, *J* =
190 5.6 Hz, -COCHNH), 4.25 (2H, *d*, *J* = 4.4 Hz, -COCH₂NH), 4.95 (4H, *s*, -NCH₂), 7.22 (2H, *s*, Ar),
191 7.46 (2H, *d*, *J* = 4.0 Hz, Ar), 7.79 (2H, *s*, ArCH=C), 7.90 (2H, *d*, *J* = 8.8 Hz, Ar); ¹³C NMR (100
192 MHz, DMSO-*d*₆, δ / ppm): 31.0 (CH(CH₃)₂), 44.9 (-COCH₂NH), 46.6 (NCH₂), 59.9 (COCHNH₂),
193 78.9, 129.1, 129.4, 131.1, 133.0, 135.6, 139.0, 168.8 (-COCH₂NH), 170.0 (COCHNH₂), 186.4
194 (CO); ESI-HRMS (*m/z*): Calcd. for C₂₂H₂₅N₃O₃S₂: 443.13. Found: 444.2 (M+1).

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