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An Efficient Synthesis of Heterocyclic Analogues of Thioflavones from Haloheteroaromatic Acids

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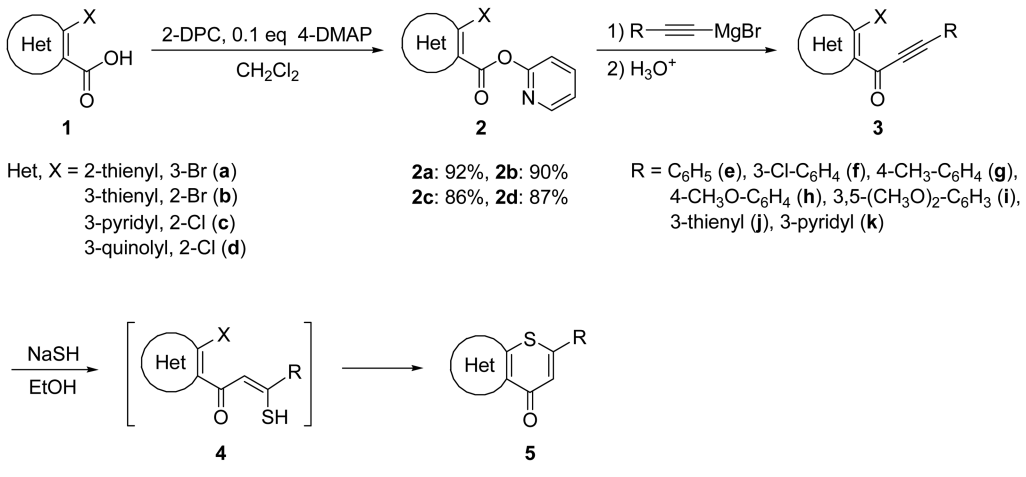
The thioflavones (2-phenyl-4*H*-1-benzothiopyran-4-ones), thio analogues of flavones, exhibit various pharmacological activities[1] such as antimalarial, gastroprotective, antiviral, and antitumor effects, and serve as potent inhibitors of steroid sulfatase (STS).[2] Recently, heterocyclic analogues of thioflavones in which the condensed benzene ring is replaced by a heteroaromatic moiety have attracted notable interest due to their potential for bioisosterism.[3]

Thioflavones have been synthesized by the condensation of substituted phenols with ethyl benzoylacetates in hot polyphosphoric acid, but yields are generally low.[4] Similar cyclization of β-(arylthio)cinnamates, derived from the 1,4-addition of arylthiolates to arylpropiolates, with P_2O_5/CH_3SO_3H afforded thioflavones, but competitive cyclization into the methoxy-substituted cinnamyl ring became troublesome.[5] Although the condensation of β-keto sulfoxides, derived from methyl 2-mercaptobenzoates and sodium methylsulphinylmethides, with benzaldehydes followed by the thermal elimination of sulfoxide and subsequent cyclization can circumvent this drawback, the reaction proceeds in multiple steps and overall yields are low to moderate.[1d,6] Another condensation of dilithiated *N*-benzoylhydrazones[7] and trilithiated acetoanilides[8] using excess lithium diisopropylamide with methyl thiosalicylates affords C-acylated intermediates *via* a Claisen-type reaction that undergo hydrolysis and cyclodehydration to produce thioflavones in moderate to high yields.

Alternatively, the reaction of *S*-aroylthiosalicylic acids with highly reactive *N*-phenyl(triphenylphosphoranylidene)-ethenimine[9] or (trimethylsilyl)methylene triphenylphosphorane[10] and 2-(acylmercapto)phenacyl bromides[11] with triphenylphosphine leads to the corresponding acylphosphoranes, which undergo intramolecular Wittig cyclization on the thiolester's carbonyl to afford thioflavones in multiple steps. The elimination of thioflavanone derivatives such as their 1-oxides[12] and spirothiadiazolines[13] with Ac_2O/TsOH and ceric ammonium nitrate, respectively, also affords thioflavones at high temperature.

However, only a few methods[3,14] for the synthesis of heterocylic analogues of thioflavones have been reported despite the biological significance of their heteroaromatic structures. In a short preliminary screening test, a thioflavone containing the condensed 3-thienyl moiety exhibited a potent vasorelaxant effect mediated by the NO/cGMP pathway. Furthermore, there have been no reports on the synthesis of heterocyclic analogues of various 2-aryl substituted thioflavones including heteroaromatic groups. As an extension of our search for thioflavonoids,[15] we describe an efficient synthesis method for heterocyclic analogues of thioflavones as potential drug candidates from haloheteroaromatic acids with high yields.

2-Pyridyl haloheteroaroates (**2**) were readily prepared by



1 **2** **3**

Het, X = 2-thienyl, 3-Br (**a**)
3-thienyl, 2-Br (**b**)
3-pyridyl, 2-Cl (**c**)
3-quinolyl, 2-Cl (**d**)

2a: 92%, **2b**: 90%
2c: 86%, **2d**: 87%

R = C_6H_5 (**e**), 3-Cl-C_6H_4 (**f**), 4-CH_3-C_6H_4 (**g**), 4-CH_3O-C_6H_4 (**h**), 3,5-$(CH_3O)_2$-C_6H_3 (**i**), 3-thienyl (**j**), 3-pyridyl (**k**)

4 **5**

Scheme 1

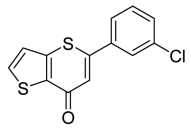
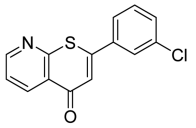
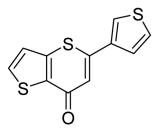
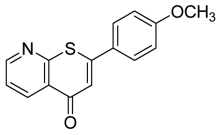
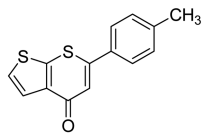
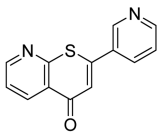
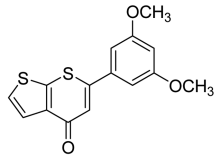
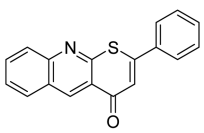
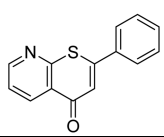
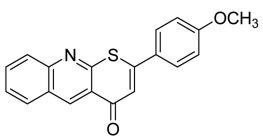
the addition of 0.1 equiv of 4-(dimethylamino)pyridine (4-DMAP) to a solution of haloheteroaromatic acids (**1**) and di-2-pyridyl carbonate (2-DPC)[16] in methylene chloride (Scheme 1). The reaction proceeded by the nucleophilic attack of 4-DMAP on the acyl group of mixed carboxylic anhydrides to form *N*-acylpyridinium salts, with the evolution of carbon dioxide, which were then converted to the corresponding 2-pyridyl esters. After being stirred for 3.5 h at room temperature, the mixture was separated by the usual workup and **2a-d** were obtained after short-pathway silica gel column chromatography using 50% EtOAc/*n*-hexane in 86-92% yields.

The synthesis of alkynones (**3**) was successfully accomplished by the nucleophilic acyl substitution of **2** with alkynylmagnesium bromides in tetrahydrofuran (THF) at 0 °C. The addition of (hetero)arylethynylmagnesium bromides, which were prepared from (hetero)arylacetylenes and ethylmagnesium bromide for 0.5 h between 0 °C and room temperature, to a solution of **2** in THF at 0 °C led to the formation of precipitates. After the completion of the reaction, the mixture was hydrolyzed with a saturated NH_4Cl solution and separated by aqueous workup. The purification of the residue by silica gel column chromatography using 30% EtOAc/*n*-hexane afforded **3** in 82-93% yields. There were no observable side products, such as the corresponding tertiary alcohols, due to the subsequent addition of (hetero)-arylethynylmagnesium bromides to the desired alkynones.

The construction of the benzothiopyran ring from **3** was achieved *via* the 1,4-addition of sodium hydrosulfide and a one-pot sequence of intramolecular substitution. Thus, the addition of **3** in EtOH to a suspended solution of a slight excess of sodium hydrosulfide in EtOH at ~40 °C prompted the rapid 1,4-addition of the hydrosulfide ion to yield unsaturated thiolate adducts (**4**), detected by TLC as yellow spots, which underwent intramolecular nucleophilic aromatic substitution at reflux to yield the heterocyclic analogues of thioflavones (**5**) with the formation of sodium halide precipitates. After the completion of the reaction, the mixture was separated by acidic workup and the residue was recrystallized twice in 10% EtOAc/*n*-hexane to give **5** as pale yellow solids in 84-95% yields. The ^{1}H NMR absorptions of **5** comprised sharp singlets for the characteristic C_3 vinyl proton signals from δ 7.19 to δ 7.26 ppm.

As shown in Table 1, various heterocyclic thioflavone analogues were synthesized with overall high yields (60-79%) from the starting material **1**. The reaction worked equally well with 2-bromothiophene (**5bg**, **5bi**) and 3-bromothiophene groups (**5af**, **5aj**) regardless of the 2- or 3-position of the bromo group in thiophenecarboxylic acid. The reaction also proceeded well both for the electron-withdrawing substituents such as chloro groups (**5af**, **5cf**) and electron-donating substituents such as methyl (**5bg**) and methoxy groups (**5bi**, **5ch**, **5dh**) of the 2-substituted phenyl rings. Furthermore, this method was applicable to the synthesis of **5** containing a heteroaromatic ring, such as 3-thienyl (**5aj**) and 3-pyridyl groups (**5ck**), in place of aryl

Table 1. Preparation of alkynones **3** and heterocyclic thioflavone analogues **5** from haloheteroaromatic acids **1**

Entry	Product	Isolated yields, %[a]		Entry	Product	Isolated yields, %[a]	
		3[b]	**5**[c]			**3**[b]	**5**[c]
af		91	93 (78)	**cf**		82	92 (65)
aj		86	85 (67)	**ch**		91	86 (67)
bg		92	95 (79)	**ck**		90	87 (67)
bi		93	90 (75)	**de**		83	88 (64)
ce		83	84 (60)	**dh**		90	87 (68)

[a]The numbers in parentheses indicate the overall yields of three steps from haloheteroaromatic acids **1**. [b]Chromatographic yields. [c]Recrystallized yields.

groups with high yields.

In conclusion, this method provides an efficient means of synthesizing heterocyclic analogues of thioflavones from the readily available starting material **1**. This procedure has the advantage of providing high yields at each step as well as the rapidity and the versatility of the reaction. Thus, it may be widely utilized for the synthesis of heterocyclic thioflavone analogues.

Experimental Section

General Procedure for the Synthesis of 2-Pyridyl 2-Chloropyridine-3-carboxylate (2c). 4-DMAP (61 mg, 0.5 mmol) was added to a solution of 2-chloropyridine-3-carboxylic acid (788 mg, 5.0 mmol) and di-2-pyridyl carbonate (1.08 g, 5.0 mmol) in methylene chloride (25 mL) at room temperature. After being stirred for 3.5 h at this temperature, the mixture was poured into a saturated $NaHCO_3$ solution (30 mL) and extracted with methylene chloride (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The residue was subjected to short-pathway silica gel column chromatography using 50% EtOAc/*n*-hexane as an eluent to yield **2c** (1.01 g, 86%). mp 70-71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58-8.62 (m, 1H), 8.43-8.49 (m, 2H), 7.84-7.91 (m, 1H), 7.38-7.43 (m, 1H), 7.28-7.34 (m, 1H), 7.25 (dd, J_1 = 8.1 Hz, J_2 = 0.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 157.9, 153.1, 151.3, 149.2, 141.5, 140.2, 126.0, 123.0, 122.6, 116.8; FT-IR (KBr) 3026, 1749 (C=O), 1601, 1582, 1493, 1452, 1207, 1031, 753, 697 cm^{-1}; Ms *m/z* (%) 199 (M^+-35, 100), 142 (30), 140 (91), 114 (14), 112 (42).

General Procedure for the Synthesis of 1-(2-Chloropyridin-3-yl)-3-phenylprop-2-yn-1-one (3ce). Ethylmagnesium bromide (1.0 M, 4.0 mL, 4.0 mmol) was added to a solution of phenylacetylene (409 mg, 4.0 mmol) in THF (10 mL) at 0 °C under an argon atmosphere. After being stirred for 0.5 h between 0 °C and room temperature, the resulting phenylethynylmagnesium bromide was added to a solution of **2c** (939 mg, 4.0 mmol) in THF (10 mL). The mixture was stirred for 0.5 h at 0 °C and then quenched with a saturated NH_4Cl solution (5 mL). After the evaporation of THF, the mixture was poured into a saturated NH_4Cl solution (30 mL), extracted with methylene chloride (3 × 20 mL), and washed with a saturated $NaHCO_3$ solution (30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using 30% EtOAc/*n*-hexane as an eluent to yield **3ce** (802 mg, 83%). mp 70-72 °C (lit.[3] 69-71 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (dd, J_1 = 4.7 Hz, J_2 = 2.0 Hz, 1H), 8.35 (dd, J_1 = 7.7 Hz, J_2 = 2.0 Hz, 1H), 7.63-7.68 (m, 2H), 7.46-7.54 (m, 1H), 7.38-7.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 152.8, 149.9, 141.1, 133.6, 133.0, 131.8, 129.2, 122.8, 120.0, 96.1, 88.4; FT-IR (KBr) 3048, 2199 (C≡C), 1637 (C=O), 1573, 1402, 1313, 1090, 1015, 752, 682 cm^{-1}; Ms *m/z* (%) 243 (M^++2, 19), 241 (M^+, 57), 215 (15), 213 (43), 129 (100).

General Procedure for the Synthesis of 2-Phenyl-4*H*-thiopyrano[2,3-*b*]pyridin-4-one (5ce). A solution of **3ce** (725 mg, 3.0 mmol) in EtOH (15 mL) was added to a suspended solution of sodium hydrosulfide hydrate (~60%, 420 mg, 4.5 mmol) in EtOH (15 mL) at ~40 °C. The resulting tan solution was refluxed for 1.5 h. After the evaporation of EtOH, the mixture was poured into a solution of 0.5 N HCl (30 mL), extracted with methylene chloride (3 × 20 mL), and washed with a saturated $NaHCO_3$ solution (30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The residue was recrystallized twice in 10% EtOAc/*n*-hexane to yield **5ce** (603 mg, 84%) as a pale yellow solid. mp 120-121 °C (lit.[3] 114-117 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (dd, J_1 = 4.4 Hz, J_2 = 1.9 Hz, 1H), 8.76 (dd, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1H), 7.67-7.72 (m, 2H), 7.46-7.54 (m, 4H), 7.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.7, 159.4, 155.1, 153.2, 137.1, 136.7, 131.5, 129.8, 128.4, 127.4, 123.9, 123.3; FT-IR (KBr) 3022, 1633 (C=O), 1579, 1451, 1337, 1128, 758, 686 cm^{-1}; Ms *m/z* (%) 239 (M^+, 100), 238 (33), 211 (92), 210 (34), 109 (16).

2-(3-Chlorophenyl)-7*H*-thieno[3,2-*b*]thiopyran-4-one (5af): mp 128-129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 5.3 Hz, 1H), 7.64 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 7.50-7.56 (m, 1H), 7.46-7.49 (m, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.36 (d, J = 5.3 Hz, 1H), 7.19 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 151.0, 138.7, 138.2, 137.3, 135.4, 133.5, 130.7, 130.6, 127.4, 125.4, 125.3, 124.2; FT-IR (KBr) 3054, 1620 (C=O), 1471, 1435, 1095, 884, 739, 711 cm^{-1}; Ms *m/z* (%) 280 (M^++2, 37), 278 (M^+, 87), 252 (43), 250 (100), 142 (34).

2-Thienyl-7*H*-thieno[3,2-*b*]thiopyran-4-one (5aj): mp 138-139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 5.3 Hz, 1H), 7.72 (dd, J_1 = 2.9 Hz, J_2 = 1.4 Hz, 1H), 7.48 (dd, J_1 = 5.1 Hz, J_2 = 3.0 Hz, 1H), 7.41 (dd, J_1 = 5.1 Hz, J_2 = 1.4 Hz, 1H), 7.32 (d, J = 5.3 Hz, 1H), 7.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 146.6, 138.3, 137.5, 137.2, 133.2, 127.8, 125.6, 125.2, 124.8, 122.2; FT-IR (KBr) 3072, 1591 (C=O), 1575, 1435, 1065, 924, 773 cm^{-1}; Ms *m/z* (%) 252 (M^++2, 17), 250 (M^+, 100), 222 (91), 142 (41), 114 (16).

6-(4-Methylphenyl)-4*H*-thieno[2,3-*b*]thiopyran-4-one (5bg): mp 151-152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 5.4 Hz, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 5.4 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.19 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 151.7, 144.4, 141.3, 137.6, 133.4, 130.1, 126.9, 125.5, 125.2, 124.5, 21.4; FT-IR (KBr) 3081, 1610 (C=O), 1594, 1426, 1277, 1130, 811, 771 cm^{-1}; Ms *m/z* (%) 258 (M^+, 100), 257 (42), 243 (30), 230 (37), 142 (80), 114 (22).

6-(3,5-Dimethoxyphenyl)-4*H*-thieno[2,3-*b*]thiopyran-4-one (5bi): mp 116-118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 5.4 Hz, 1H), 7.46 (d, J = 5.4 Hz, 1H), 7.22 (s, 1H), 6.76 (d, J = 2.2 Hz, 2H), 6.58 (t, J = 2.2 Hz, 1H), 3.85 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 161.3, 151.5, 144.4, 138.1, 137.7, 125.5, 125.4, 125.0, 105.2, 102.6, 55.6; FT-IR (KBr) 3087, 2949, 1628 (C=O), 1603, 1423, 1325, 1161, 1063, 843, 681 cm^{-1}; Ms *m/z* (%) 304 (M^+, 100), 303 (15), 276 (16), 142 (24).

2-(3-Chlorophenyl)-4*H*-thiopyrano[2,3-*b*]pyridin-4-one (5cf): mp 188-189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (dd, J_1 = 4.5 Hz, J_2 = 1.9 Hz, 1H), 8.77 (dd, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1H), 7.67-7.71 (m, 1H), 7.56-7.61 (m, 1H), 7.45-7.55 (m, 3H), 7.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.2, 158.8, 153.1, 153.0, 138.0, 136.8, 135.5, 131.1, 130.7, 128.1, 127.1, 125.2, 124.1, 123.1; FT-IR (KBr) 3052, 1633 (C=O), 1578, 1452, 1331, 1130, 779, 748, 682 cm^{-1}; Ms *m/z* (%) 275 (M^++2, 39), 273 (M^+, 100), 247 (30), 245 (79), 137 (18), 109 (15).

2-(4-Methoxyphenyl)-4*H*-thiopyrano[2,3-*b*]pyridin-4-one (5ch): mp 160-161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (dd, J_1 = 4.5 Hz, J_2 = 1.9 Hz, 1H), 8.75 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 7.68 (d, J = 8.9 Hz, 2H), 7.49 (dd, J_1 = 8.0 Hz, J_2 = 4.5 Hz, 1H), 7.22 (s, 1H), 7.03 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3, 162.1, 159.0, 154.4, 152.7, 136.7, 128.5, 128.4, 128.0, 122.8, 122.2, 114.8, 55.5; FT-IR (KBr) 3007, 2838, 1614 (C=O), 1599, 1507, 1455, 1347, 1266, 1182, 1027, 814 cm^{-1}; Ms *m/z* (%) 269 (M^+, 100), 241 (41), 226 (44), 132 (32).

2-(3-Pyridyl)-4*H*-thiopyrano[2,3-*b*]pyridin-4-one (5ck): mp 191-192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (d, J = 2.4 Hz, 1H), 8.84 (dd, J_1 = 4.5 Hz, J_2 = 1.9 Hz, 1H), 8.78 (dd, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1H), 8.76-8.81 (m, 1H), 8.01 (ddd, J_1 = 9.2 Hz, J_2 = 2.4 Hz, J_3 = 1.7 Hz, 1H), 7.55 (dd, J_1 = 8.1 Hz, J_2 = 4.5 Hz, 1H), 7.49 (ddd, J_1 = 8.0 Hz, J_2 = 4.9 Hz, J_3 = 0.7 Hz, 1H), 7.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0, 158.6, 153.0, 152.0, 151.2, 147.7, 136.9, 134.4, 132.3, 128.0, 124.4, 124.0, 123.3; FT-IR (KBr) 3073, 3018, 1630 (C=O), 1582, 1399, 1336, 1128, 700 cm^{-1}; Ms *m/z* (%) 240 (M^+, 100), 239 (22), 212 (74), 137 (20), 109 (18).

2-Phenyl-4*H*-thiopyrano[2,3-*b*]quinolin-4-one (5de): mp 208-210 °C (lit.[3] 208-210 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.11 (d, J = 8.6 Hz, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.87-7.93 (m, 1H), 7.73-7.78 (m, 2H), 7.61-7.67 (m, 1H), 7.51-7.57 (m, 3H), 7.24 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.1, 157.1, 155.1, 149.3, 138.7, 136.5, 133.2, 131.2, 129.7, 129.4, 128.1, 127.3, 127.0, 126.9, 125.1, 122.2; FT-IR (KBr) 3041, 1631 (C=O), 1613, 1450, 1376, 1209, 861, 755, 696 cm^{-1}; Ms *m/z* (%) 289 (M^+, 100), 288 (16), 261 (66), 260 (21), 159 (12).

2-(4-Methoxyphenyl)-4*H*-thiopyrano[2,3-*b*]quinolin-4-one (5dh): mp 200-202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.10 (d, J = 8.6 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.85-7.92 (m, 1H), 7.72 (d, J = 8.9 Hz, 2H), 7.59-7.66 (m, 1H), 7.20 (s, 1H), 7.04 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.1, 162.2, 157.2, 154.7, 149.2, 138.5, 133.0, 129.7, 128.6, 128.4, 128.1, 127.2, 126.9, 125.2, 120.8, 114.8, 55.6; FT-IR (KBr) 3033, 2850, 1630 (C=O), 1604, 1508, 1446, 1376, 1253, 1183, 825 cm^{-1}; Ms *m/z* (%) 319 (M^+, 100), 291 (26), 276 (21), 132 (18).

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