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Design, synthesis and antiproliferative activities of diaryl urea derivatives bearing *N*-acylhydrazone moiety

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Abstract

A new series of diaryl urea derivatives bearing *N*-acylhydrazone moiety were designed and synthesized. All the target compounds were evaluated for their antiproliferative activities against human leukemia cell line (HL-60), human lung adenocarcinoma epithelial cell line (A549) and human breast cancer cell line (MDA-MB-231) *in vitro* by standard MTT assay. The pharmacological results indicated that some compounds exhibited promising antitumor activities. Compound **1j** showed the most potent antiproliferative activity against the tested three cell lines with IC_{50} values of 0.13 μmol/L, 0.7 μmol/L and 0.5 μmol/L, respectively.

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Keywords: Diaryl ureas; *N*-acylhydrazone; Antiproliferative activities

In recent years, medicinal chemists paid much attention to the design and discovery of multi-targeted anti-cancer drugs, with an aim of enhancing the efficacy and safety relative to drugs that modulate only a single target [1–4]. Sorafenib (Fig. 1), the first bioavailable multiple kinase inhibitor, is reported to have a reasonable enzyme potency against both Raf and VEGF and PDGF receptor tyrosine kinases [5] and pathway inhibition in cells (IC_{50} values of 40–1200 nmol/L depending on the cell line) [6,7]. PAC-1 (Fig. 1) is the first small molecular procaspase-3 activator [8], which induces apoptotic death in tumor cell lines and retards tumor growth *in vivo* [9].

Inspired by the structures of sorafenib and PAC-1, we retained the pharmacophoric domains (diaryl urea from sorafenib and *N*-acylhydrazone from PAC-1) and fused them through a thiazole ring as the linker. Thus we designed and synthesized a series of diaryl urea derivatives bearing *N*-acylhydrazone moiety (Fig. 1). Various ureido-linked phenyl (Ar^1) and hydrazone-linked phenyl (Ar^2) groups were introduced to explore the influence of electronic and steric effects on the antitumor activity (structure **1**). Since the PAC-1 derivatives without the hydroxyl group displayed no anti-cancer activity *in vitro* [9], 2-hydroxy substitution was retained for the phenyl ring Ar^2. Furthermore, an imidazolindione fragment was inserted between the hydrazone and Ar^2 to investigate the influence of the alteration of the hydrazone scaffold on the antiproliferative activity (structure **2**).

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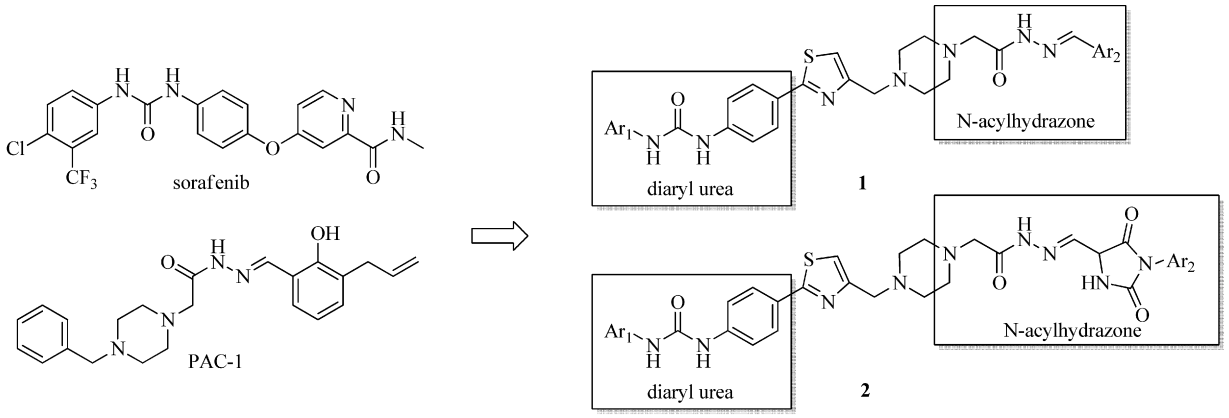
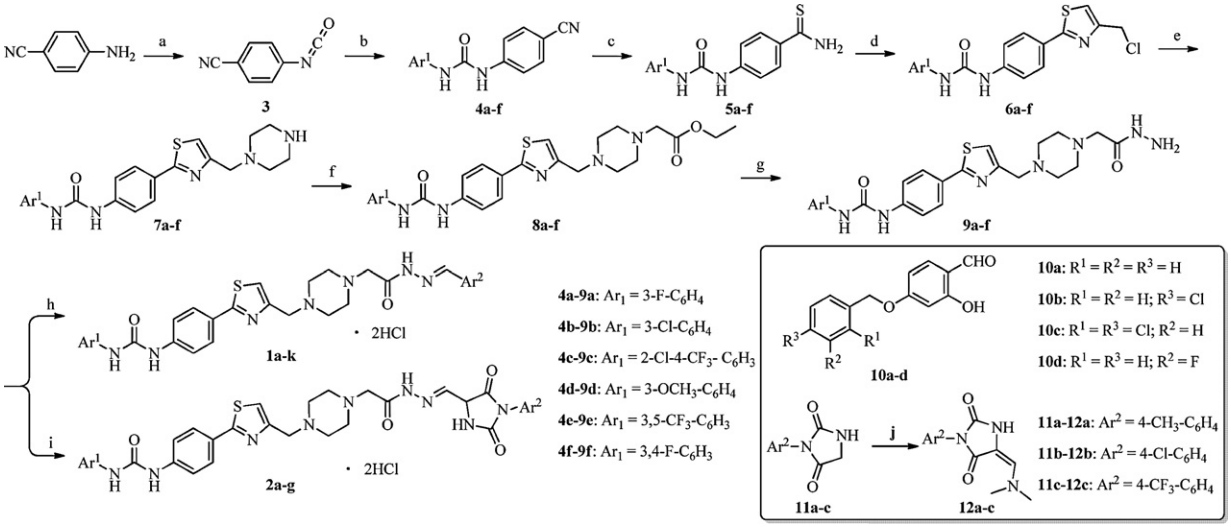


Fig. 1. Structures of sorafenib, PAC-1 and target compounds.

A general synthesis of target compounds is described in Scheme 1. The commercially available 4-aminobezo-nitrile reacted with triphosgene in dioxane to obtain 4-isocyanatobenzonitrile **3**. Subsequent treatment of **3** with different substituted anilines afforded diaryl ureas **4a–f**, which were then turned into thioamides **5a–f** under the condition of magnesium chloride and sodium bisulfide in *N*,*N*-dimethylformamide. Cyclization of **5a–f** with 1,3-dichloroacetone in tetrahydrofuran readily afforded thiozoles **6a–f**, which was subjected to a three-step nucleophilic substitution reaction to obtain acylhydrazines **9a–f**. Finally, target compounds **1a–k** and **2a–g** were prepared *via* condensation of **9a–f** with various benzaldehydes, benzyloxybenzaldehydes **10a–d** and imidazolindiones **12a–c**, respectively. **10a–d** were readily prepared according to the reported procedure [10] and **12a–c** were obtained from the condensation reactions of *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) with intermediates **11a–c** which were synthesized according to the reported procedure [11]. All the structures of target compounds were confirmed by MS and ^{1}H NMR [12].

All the target compounds were evaluated for their antiproliferative activities against human leukemia cell line (HL-60), human lung adenocarcinoma epithelial cell line (A549) and human breast cancer cell line (MDA-MB-231) with sorafenib and PAC-1 as the positive controls. As listed in Table 1, most of the target compounds exhibited moderate to strong activities to the tested cell lines. Compound **1j** showed the most potent antiproliferative activity



Scheme 1. Synthesis of target compounds. Reactions and conditions: (a) triphosgene, dioxane, 80 °C, 24 h, 84%; (b) Ar^1NH_2, THF, r.t., 1 h; (c) $MgCl_2$, NaSH, DMF, overnight; (d) 1,3-dichloroacetone, THF, 50 °C, 7 h; (e) piperazine, ethanol, r.t., 2 h; (f) ethyl chloroacetate, K_2CO_3, NaI, ethanol, 50 °C, 2 h; (g) 80% hydrazine hydrate, ethanol, 50 °C, 48 h; (h) Ar^2CHO or **10a–d**, ethanol; then HCl–ethanol; (i) **12a–c**, ethanol; then HCl–ethanol; (j) DMF-DMA, CH_3CN, r.f., 4 h.

Table 1
Structures and antiproliferative activities of compounds **1a–k** and **2a–g** against HL-60, A549 and MDA-MB-231 cell lines.

Compd.	Ar^1	Ar^2	IC_{50} (μmol/L)		
			HL-60	A549	MDA-MB-231
1a	3-F-C_6H_4	5-Br-2-OH-C_6H_3	7.1	2.3	1.4
1b	3-F-C_6H_4	3,4-F-2-OH-C_6H_2	6.2	1.9	1.1
1c	3-F-C_6H_4	2-OH-3,5-t-butyl-C_6H_2	1.1	NA	23
1d	2-Cl-4-CF_3-C_6H_3	2-OH-C_6H_4	9.9	2.0	1.4
1e	3-Cl-C_6H_4	5-Cl-2-OH-C_6H_3	6	4.4	1.6
1f	3-Cl-C_6H_4	2-OH-3,5-t-butyl-C_6H_2	2.7	0.7	1.0
1g	3-Cl-C_6H_4	2-OH-4-CH_3-C_6H_3	1.2	NA	NA
1h	3-F-C_6H_4	2-OH-4-(C_6H_5-CH_2O)-C_6H_3	1.1	1.1	1.0
1i	3-F-C_6H_4	2-OH-4-(4-Cl-C_6H_4-CH_2O)-C_6H_3	2.8	0.8	0.8
1j	3-F-C_6H_4	2-OH-4-(2,4-Cl-C_6H_3-CH_2O)-C_6H_3	0.13	0.7	0.5
1k	3-F-C_6H_4	2-OH-4-(3-F-C_6H_4-CH_2O)-C_6H_3	1.6	0.9	0.7
2a	3-F-C_6H_4	4-CH_3-C_6H_4	32	18	93
2b	3-F-C_6H_4	4-Cl-C_6H_4	22	12	31
2c	3-Cl-C_6H_4	4-CH_3-C6H$_4$	24	73	14
2d	3-OCH_3-C_6H_4	4-CF_3-C6H$_4$	NA	NA	NA
2e	2-Cl-4-CF_3-C_6H_3	4-CF_3-C_6H_4	30	NA	NA
2f	3,5-CF_3-C_6H_3	4-CF_3-C_6H_4	12	12	31
2g	3,4-F-C_6H_3	4-CF_3-C_6H_4	6.2	3.5	3.0
Sorafenib			ND	2.6	5.4
PAC-1			9.1	5.6	4.1

NA, no activity; ND, not determined.

against HL-60, A549 and MDA-MB-231 cell lines with IC_{50} values of 0.13 μmol/L, 0.7 μmol/L and 0.5 μmol/L, which were 3.7- to 70-fold higher than sorafenib and PAC-1.

The phenylhydrazones **1a–k** were more potent than the imidazolidinylhydrazones **2a–f** with the exception of compound **2g**, which suggested that the directly linked phenyl group Ar^2 to the hydrazone is essential for the activity. As for substituents on the hydrazone-linked phenyl ring Ar^2, compounds **1a**, **1b**, **1e** and **1c** with bromo, fluoro, chloro and *tert*-butyl groups, respectively, showed comparable inhibitory activities against the three cell lines to compound **1d** with only *ortho*-hydroxyl group. It suggested that the electronic effects of substituents on Ar^2 make few contributions to the activity. Interestingly, compounds **1h–k** with the benzyloxy group at the *para*-position of Ar^2 displayed a remarkable enhanced activity against the three tested cell lines. These investigations prompt us to carry on further studies on their mechanisms of action.

Acknowledgments

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[11] X.Y. He, P. Zhou, J. Qiu, et al. Bioorg. Med. Chem. 19 (2011) 6726.
[12] **1a**: mp: 199–201 °C. ESI-MS *m/z*: 666.3 $(M+H)^+$. HRMS-ESI: calcd. for $C_{30}H_{30}BrFN_7O_3S$ $(M+H)^+$ 666.1293, found 666.1303. IR (KBr, cm^{-1}): 3398.5, 1669.1, 1600.1, 1544.0, 1457.5, 1313.5, 1207.8, 1144.0, 1003.4, 970.5, 838.3. ^1H NMR (300 MHz, DMSO-d_6) δ: 11.13 (s, 1H), 10.49 (s, 1H), 9.51 (s, 1H), 9.48 (s, 1H), 8.46 (s, 1H), 7.90–7.88 (m, 3H), 7.73 (s, 1H), 7.61 (d, 3H, J = 7.1 Hz), 7.51 (d, 2H, J = 11.9 Hz), 7.43–7.35 (m, 1H), 7.32 (d, 1H, J = 7.1 Hz), 7.13 (d, 1H, J = 8.3 Hz), 6.90 (d, 1H, J = 8.3 Hz), 6.80 (t, 1H, J = 8.6 Hz), 4.51 (s, 1H), 3.77 (s, 2H), 2.73 (brs, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.48, 161.29, 156.82, 156.26, 152.84, 145.55, 142.17, 141.91, 134.04, 130.87, 130.74, 130.62, 127.58, 122.72, 121.76, 119.22, 118.60, 114.28, 111.21, 110.90, 108.83, 108.54, 105.38, 105.02, 83.71, 72.35, 51.47, 51.43. **1b**: mp: 207–210 °C. ESI-MS *m/z*: 624.3 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 11.50 (s, 1H), 9.04 (s, 1H), 8.98 (s, 1H), 8.47 (s, 1H), 7.85 (d, 2H, J = 8.7 Hz), 7.62–7.57 (m, 3H), 7.50 (d, 2H, J = 12.0 Hz), 7.41 (s, 1H), 7.32 (q, 1H, J = 8.1 Hz), 7.14 (d, 1H, J = 8.1 Hz), 6.95 (dd, 1H, J_1 = 6.9 Hz, J_2 = 12.0 Hz), 6.81 (t, 1H, J = 8.7 Hz), 3.66 (s, 1H), 3.64 (s, 1H), 3.32 (s, 1H), 3.10 (s, 1H), 2.53 (brs, 8H). **1c**: mp: 215–217 °C. ESI-MS *m/z*: 700.6 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 12.10 (s, 1H), 11.41 (s, 1H), 9.02 (s, 1H), 8.97 (s, 1H), 8.49 (s, 1H), 7.85 (d, 3H, J = 8.7 Hz), 7.58 (d, 2H, J = 8.7 Hz), 7.50 (d, 1H, J = 11.9 Hz), 7.41 (s, 1H), 7.33–7.28 (m, 2H), 7.18 (d, 1H, J = 2.3 Hz), 7.14 (d, 1H, J = 8.1 Hz), 6.82 (t, 1H, J = 8.4 Hz), 3.67 (s, 1H), 3.64 (s, 1H), 3.30 (s, 1H), 3.14 (s, 1H), 2.56 (brs, 8H), 1.39 (s, 9H), 1.27 (s, 9H). **1d**: mp: 267–269 °C. ESI-MS *m/z*: 672.3 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 11.96 (s, 1H), 10.57 (s, 1H), 10.15 (s, 1H), 9.00 (s, 1H), 8.61 (s, 1H), 8.37 (s, 1H), 7.96 (d, 1H, J = 1.6 Hz), 7.94 (d, 2H, J = 2.2 Hz), 7.75 (d, 1H, J = 9.2 Hz), 7.69 (d, 3H, J = 9.0 Hz), 7.39 (d, 1H, J = 8.3 Hz), 7.32–7.23 (m, 1H), 6.96–6.84 (m, 2H), 4.59 (s, 2H), 4.50 (s, 2H), 3.84 (brs, 8H). **1e**: mp: 234–235 °C. ESI-MS *m/z*: 637.8 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 11.12 (s, 1H), 10.48 (s, 1H), 9.66–9.60 (m, 2H), 7.92–7.87 (m, 3H), 7.72 (s, 2H), 7.64–7.60 (m, 3H), 7.32 (s, 1H), 7.30 (s, 2H), 7.04–7.01 (m, 1H), 6.95 (d, 1H, J = 8.8 Hz), 4.49 (s, 2H), 3.76 (brs, 2H), 3.25 (brs, 8H). **1f**: mp: 240–242 °C. ESI-MS *m/z*: 716.5 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 12.10 (s, 1H), 11.43 (s, 1H), 9.07 (s, 1H), 8.98 (s, 1H), 8.49 (s, 1H), 7.86 (d, 2H, J = 8.6 Hz), 7.72 (s, 1H), 7.59 (d, 2H, J = 8.6 Hz), 7.43 (s, 1H), 7.31 (s, 1H), 7.30 (s, 2H), 7.18 (d, 1H, J = 2.2 Hz), 7.05–7.02 (m, 1H), 3.71 (s, 2H), 3.30 (s, 1H), 3.15 (s, 1H), 2.58 (brs, 8H), 1.39 (s, 9H), 1.27 (s, 9H). **1g**: mp: 222–224 °C. ESI-MS *m/z*: 618.3 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 11.45 (s, 1H), 11.16 (s, 1H), 9.53 (s, 2H), 8.47 (s, 1H), 7.86 (d, 2H, J = 8.6 Hz), 7.72 (s, 1H), 7.59 (d, 2H, J = 8.6 Hz), 7.50 (s, 1H), 7.35 (s, 1H), 7.30 (d, 2H, J = 4.8 Hz), 7.04–7.00 (m, 1H), 6.74 (s, 1H), 6.71 (s, 1H), 3.78 (s, 2H), 3.30 (s, 1H), 3.16 (s, 1H), 2.62 (brs, 6H), 2.38 (s, 2H), 2.27 (s, 3H). **1h**: mp: 207–209 °C. ESI-MS *m/z*: 694.0 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 11.76 (s, 1H), 10.21 (s, 1H), 9.55–9.47 (m, 2H), 8.40 (s, 1H), 8.25 (s, 1H), 7.91 (d, 2H, J = 8.6 Hz), 7.62 (d, 3H, J = 8.6 Hz), 7.52–7.30 (m, 8H), 7.13 (d, 1H, J = 9.3 Hz), 6.80 (t, 1H, J = 8.7 Hz), 6.59 (d, 1H, J = 8.7 Hz), 6.54 (s, 1H), 5.12 (s, 1H), 5.09 (s, 1H), 4.42 (brs, 2H), 4.32 (s, 2H), 3.53 (brs, 8H). **1i**: mp: 222–224 °C. ESI-MS *m/z*: 728.3 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 11.80 (s, 1H), 10.23 (s, 1H), 9.67 (t, 2H, J = 12.2 Hz), 8.41 (s, 1H), 8.26 (s, 1H), 7.93–7.90 (m, 3H), 7.64 (t, 3H, J = 8.6 Hz), 7.52 (s, 1H), 7.46 (brs, 5H), 7.31 (q, 1H, J = 8.2 Hz), 7.13 (d, 1H, J = 8.0 Hz), 6.79 (t, 1H, J = 8.6 Hz), 6.59–6.54 (m, 2H), 5.12 (s, 1H), 5.09 (s, 1H), 4.51 (s, 1H), 4.44 (s, 2H), 3.67 (s, 1H), 3.54 (brs, 8H). **1j**: mp: 215–217 °C. ESI-MS *m/z*: 762.1 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 11.79 (s, 1H), 10.25 (s, 1H), 9.60 (t, 2H, J = 12.8 Hz), 8.42 (s, 1H), 8.26 (s, 1H), 7.91 (d, 2H, J = 8.6 Hz), 7.90–7.59 (m, 4H), 7.52–7.44 (m, 3H), 7.31 (q, 1H, J = 7.2 Hz), 7.13 (d, 1H, J = 8.7 Hz), 6.78 (t, 1H, J = 8.9 Hz), 6.61–6.55 (m, 2H), 5.16 (s, 1H), 5.14 (s, 1H), 4.48 (s, 2H), 4.43 (s, 2H), 3.50 (brs, 8H). **1k**: mp: 220–222 °C. ESI-MS *m/z*: 712.1 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 11.82 (s, 1H), 10.24 (s, 1H), 9.76 (s, 1H), 9.70 (d, 1H, J = 12.2 Hz), 8.42 (s, 1H), 8.26 (s, 1H), 7.92 (d, 3H, J = 10.6 Hz), 7.63 (d, 3H, J = 8.7 Hz), 7.53–7.41 (m, 2H), 7.35–7.27 (m, 3H), 7.20–7.12 (m, 2H), 6.79 (t, 1H, J = 8.4 Hz), 6.61–6.55 (m, 3H), 5.15 (s, 1H), 5.12 (s, 1H), 4.53 (s, 1H), 4.46 (s, 2H), 3.73 (s, 1H), 3.59(brs, 8H). **2a**: mp: 210–212 °C. ESI-MS *m/z*: 683.9 $(M+H)^+$. HRMS-ESI: calcd. for $C_{34}H_{35}FN_9O_4S$ $(M+H)^+$ 684.2511, found 684.2510. IR (KBr, cm^{-1}): 3270.5, 1725.0, 1597.8, 1540.3, 1408.1, 1313.4, 1209.5, 1143.6, 1003.9, 969.7, 840.2. ^1H NMR (300 MHz, DMSO-d_6) δ: 11.38 (s, 1H), 10.20 (s, 1H), 9.46–9.26 (m, 3H), 8.20 (s, 1H), 7.87 (d, 3H, J = 8.4 Hz), 7.61 (d, 3H, J = 8.6 Hz), 7.51 (d, 2H, J = 12.0 Hz), 7.35–7.14 (m, 6H), 6.79 (t, 1H, J = 8.3 Hz), 3.94 (s, 2H), 3.17 (s, 2H), 2.86 (s, 4H), 2.69 (s, 4H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.50, 161.27, 160.15, 156.54, 154.66, 152.74, 145.33, 142.92, 142.15, 142.01, 141.86, 130.87, 130.74, 129.84, 129.59, 127.47, 127.11, 126.98, 126.87, 126.77, 118.78, 114.47, 108.95, 108.64, 105.57, 105.22, 99.98, 83.27, 73.36, 51.87, 51.61, 21.16. **2b**: mp: 233–235 °C. ESI-MS *m/z*: 704.3 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.58 (s, 1H), 9.88 (s, 1H), 9.65 (d, 2H, J = 12.8 Hz), 8.63 (d, 1H, J = 8.6 Hz), 7.91 (d, 3H, J = 8.0 Hz) 7.62 (d, 2H, J = 8.6 Hz), 7.52 (d, 3H, J = 8.5 Hz), 7.44 (d, 2H, J = 8.7 Hz), 7.31 (q, 1H, J = 7.9 Hz), 7.13 (d, 1H, J = 7.9 Hz), 6.78 (t, 1H, J = 8.5 Hz), 6.68 (d, 1H, J = 8.8 Hz), 4.47 (s, 2H), 3.68 (s, 2H), 3.46 (brs, 8H). **2c**: mp: 230–231 °C. ESI-MS *m/z*: 700.3 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 12.06 (s, 1H), 10.57 (s, 1H), 9.77–9.66 (m, 3H), 8.55 (d, 1H, J = 7.4 Hz), 7.92 (d, 4H, J = 8.0 Hz), 7.71 (s, 1H), 7.62 (d, 2H, J = 8.5 Hz), 7.30–7.24 (m, 6H), 7.03 (s, 1H), 6.63 (d, 1H, J = 8.4 Hz), 4.48 (s, 2H), 3.70 (s, 2H), 3.45 (s, 8H), 2.33 (s, 3H). **2d**: mp: 199–200 °C. ESI-MS *m/z*: 749.9 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.17 (s, 1H), 9.32–9.26 (m, 1H), 9.00–8.71 (m, 1H), 8.02–7.87 (m, 5H), 7.70–7.59 (m, 5H), 7.37 (d, 3H, J = 8.8 Hz), 6.88 (d, 3H, J = 8.8 Hz), 4.27 (s, 2H), 3.72 (s, 3H), 3.26 (brs, 10H). **2e**: mp: 213–215 °C. ESI-MS *m/z*: 822.1 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.67 (s, 1H), 10.43 (s, 1H), 10.05 (s, 1H), 8.94 (s, 1H), 8.80 (d, 1H, J = 9.1 Hz), 8.63 (s, 1H), 7.95 (d, 2H, J = 8.5 Hz), 7.94 (s, 1H), 7.84 (d, 2H, J = 8.6 Hz), 7.73 (d, 2H, J = 8.8 Hz), 7.69 (dd, 3H, J_1 = 2.5 Hz, J_2 = 8.6 Hz), 7.40 (d, 1H, J = 8.3 Hz), 6.73 (d, 1H, J = 9.1 Hz), 4.50 (s, 2H), 3.73 (s, 2H), 3.48–3.41 (m, 8H). **2f**: mp: 194–196 °C. ESI-MS *m/z*: 856.1 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.35 (s, 1H), 10.15 (s, 1H), 9.83 (s, 1H), 9.77 (s, 1H), 8.53 (s, 1H), 8.14 (s, 2H), 7.94–7.83 (m, 5H), 7.70–7.64 (m, 7H), 6.72 (d, 1H, J = 9.3 Hz), 4.41 (s, 2H), 3.48–3.41 (m, 2H), 3.24 (brs, 8H). **2g**: mp: 211–213 °C. ESI-MS *m/z*: 756.1 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.91 (s, 1H), 10.40 (s, 1H), 10.29 (s, 1H), 10.11 (s, 1H), 8.91 (d, 1H, J = 8.6 Hz), 8.06 (d, 2H, J = 8.1 Hz), 7.85 (d, 2H, J = 8.5 Hz), 7.69 (d, 2H, J = 8.6 Hz), 7.65 (d, 3H, J = 8.2 Hz), 7.38 (q, 1H, J = 9.6 Hz), 7.23–7.16 (m, 1H), 6.89–6.87 (m, 1H), 6.75 (d, 1H, J = 9.1 Hz), 4.14 (s, 2H), 4.03 (s, 1H), 3.42 (brs, 3H), 3.27 (brs, 2H), 3.05 (brs, 2H), 2.81 (brs, 2H).