Design and synthesis of novel molecular tweezer anion receptors based on diphenic acid carbonyl thiosemicarbazide

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Ten novel molecular tweezer anion receptors based on diphenic acid carbonyl thiosemicarbazide have been designed and synthesised in high yield and their binding properties were examined by UV-Vis spectra titration. Their structures were characterised by ^{1}H NMR, IR, MS spectra and elemental analysis.

Keywords: molecular tweezer, thiosemicarbazide, molecular recognition

Molecular recognition is one of the most fundamental processes in many chemical and biochemical systems. Anions play an important role in biology, pharmacy, catalysis and environmental science.[1] The study of artificial receptors for the detection of biologically relevant anions is an important challenge in modern bioorganic chemistry.[2–6] Among the various types of artificial receptors which have been synthesised, molecular tweezers containing two arms connected by a spacer are an increasingly interesting class of receptors.[7–11] The natural occurring cavities of these molecular tweezers receptors can provide appropriate microenvironment for substrates.[12,13] Hydrogen-bonding is one of the major driving forces for molecular recognition. Although the energy of a single hydrogen-bond is weak, the coordination of multiple hydrogen-bonding will result in high selectivity in combining with substrates. We have reported that arylhydrazide molecular tweezer receptors which contain four NH bond have good recognition properties for anions.[14] On the basis of this fact, we designed and synthesised 10 novel carbonyl thiosemicarbazide type molecular tweezer artificial receptors **7a–j**, which contain six NH bonds. These receptors based on carbonyl thiosemicarbazide as arms, have the NH groups directed towards the centre of the cavity resulting in a high selectivity in combining with the substrates. The recognition properties of the receptors have been examined by UV-Vis spectra titration. The preliminary results indicate that this kind of molecular tweezer shows good recognition properties for NO_3^- and $H_2PO_4^-$. The synthesis shown in Scheme 1.

Results and discussion

In searching for the best reaction conditions of the synthesis of molecular tweezer artificial receptors, we examined the preparation of **7a–c.** A series of experiments were carried out to investigate the effect of temperature and solvent on synthesis. The results are shown in the following tables.

As shown in Table 1, different temperatures were employed under the similar reaction conditions. Although the results were different: 40 °C was the best temperature to obtain a good yield.

As shown in Table 2, the effect of CH_2Cl_2, $CHCl_3$ and CH_3COCH_3 on the reaction was investigated. This showed that although different solvents were employed under similar reaction conditions, the results did not differ much. When CH_2Cl_2 was used, the yield was a little higher and hence CH_2Cl_2 was the best solvent for the reaction.

This provided an easy and effective method for the preparation of carbonyl thiosemicarbazide type molecular anion receptors. This method possesses the advantages of a high yield, easy manipulation and easy purification of the products.

The variations in the UV-Vis absorption of these complexing system has been used as an effective and simple method to measure for the association constants of complexes in supramolecular systems.

Titration experiments for the anion recognition of receptors **7a**, **7b** were performed using UV-Vis spectroscopy in $CHCl_3$ at 25 °C. Using the linear fitting method, we obtained the association constants of the complex. The preliminary results showed that these molecular tweezers possessed the ability to form complexes with the guest anions which were examined as shown Fig. 1. The supramolecular complexes consisted of 1:1 host and guest molecules. The association constants of the molecular tweezer **7a**, for example, is 638, 5345, 12124 L mol^{-1} for CH_3COO^-, $H_2PO_4^-$, NO_3^- anions respectively. The main driving forces are the multiple hydrogen bonds in molecular recognition. The UV-Vis plot of **7a** for NO_3^- is shown in Fig. 2.

The main reason is that when the host **7a** is at minimum energy, its conformation is a cleft, which has the ability to form complex with guest molecules. The minimum energy conformation of **7a** has been investigated by computer-aided molecular modelling using a Chem 3D program. This is shown in Fig. 3 and the minimum energy conformation for the inclusion complex of molecular tweezer **7a** with NO_3^- as shown in Fig. 4. The details of molecular recognition of compounds **7a–j** are under further studies.

Experimental

Melting points were determined on a micro-melting point apparatus and were uncorrected. IR spectra were obtained on 1700 Perkin-Elmer FTIR using KBr disks. ^{1}H NMR spectra were recorded on a Varian INOVA 400 MHz spectrometer using TMS as internal standard. Mass spectra were determined on FinniganLCQ^{DECA} instrument. Elemental analysis was performed on a Carlo-Erba-1106 autoanalyzer. Microwave irradiation was carried out with a MCL-3 microwave oven which was modified from domestic microwave oven and tested at full power (700 W) to conform to the performance index before use. All the solvents were purified before use.

Preparation of **3a–j***; general procedure*

The aromatic acid (5 mmol), thionyl chloride (0.2 mL) and ethanol (15 mL) were placed in a dried round-bottomed flask and the mixture was irradiated by microwaves (75 W) for 4 min. On completion of the reaction, the mixture was cooled to room temperature. The excess thionyl chloride was removed. Then the reaction mixture was added to 85% hydrazine hydrate (2 mL) and subjected to microwave irradiation (75 W) for 3 min. The mixture was evaporated to give the crude product. The crude product was recrystallised from ethanol to give a pure sample. The melting points of the hydrazides **3a–j** are shown in Table 3.

Preparation of **7a–j***; general procedure*

NH_4SCN (0.2300 g, 3 mmol), PEG-400 (0.0360 g, 3% with respect to ammonium thiocyanate) and dichloromethane (10 mL) were added in a dried round-bottomed flask and strirred at 40 °C. A solution of compound **5** (1 mmol) in dichloromethane (5 mL) slowly added to the mixture. After the addition was finished, the reaction was continued

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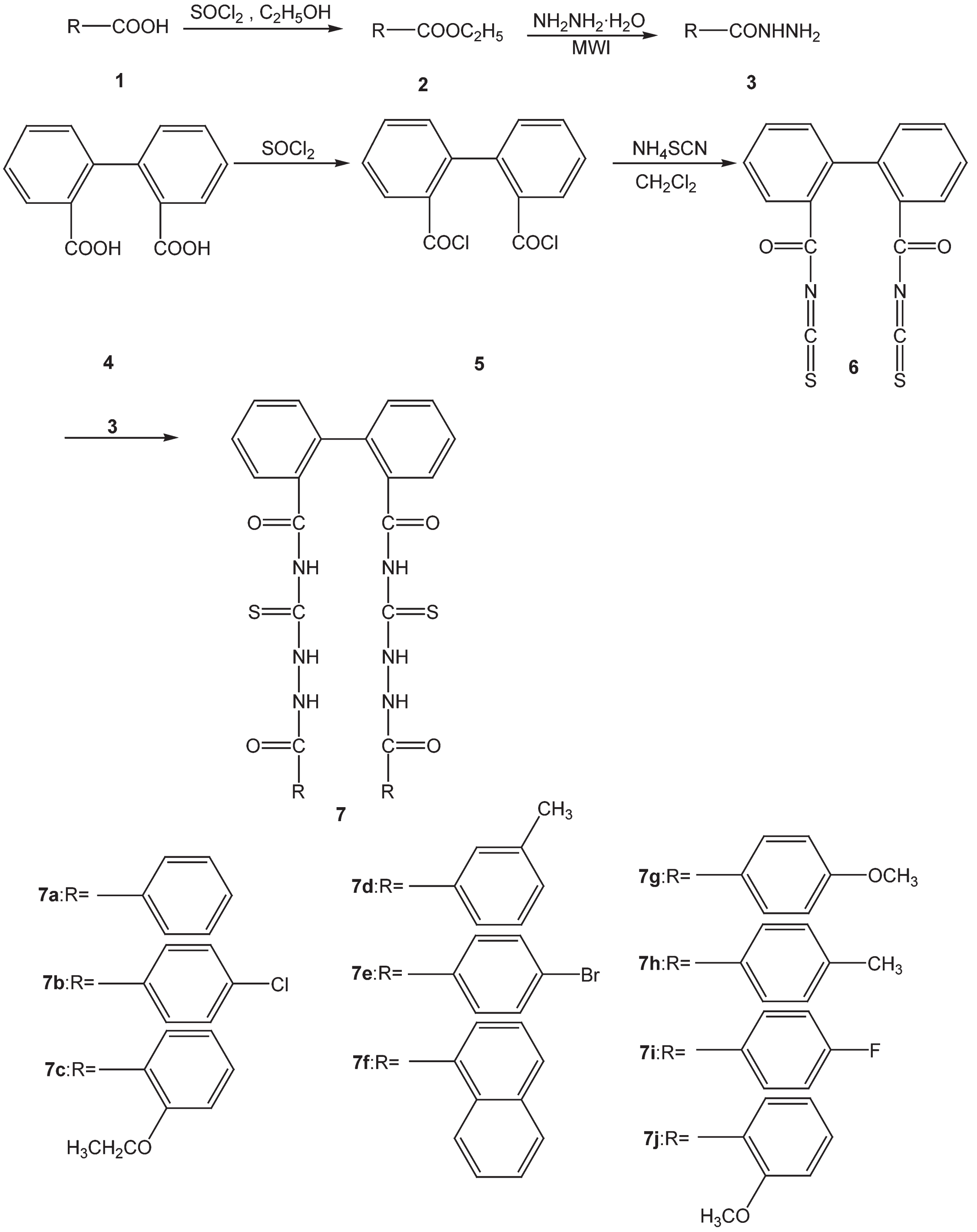

Scheme 1 The synthetic route of molecular tweezers **7a–j**.

Table 1 The effect of reaction temperature on the yield of compounds **7a–c**

Entry	temperature	Yield of **7a** /%	Yield of **7b** /%	Yield of **7c** /%
1	0 °C	30	28	33
2	20 °C	52	47	53
3	40 °C	78	85	83

Table 2 The effect of solvent on the yield of compounds **7a–c**

Entry	Solvent	Yield of **7a** /%	Yield of **7b** /%	Yield of **7c** /%
1	CH_3COCH_3	73	81	71
2	CH_2Cl_2	81	86	80
3	$CHCl_3$	75	72	75

for 1 h, and then, compound **3** (3 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 0.5 h, and the whole process was monitored by TLC. The mixture was evaporated to give the crude product. The crude product was washed with cold ethanol and recrystallised from ethanol to give a pure sample. The physical and spectra data of the compounds **7a–j** are as follows.

7a: White crystal; yield 81%, m.p. 215–216 °C; IR (KBr, cm^{-1}): 3248, 3086, 2919, 1672, 1523, 1433, 1244, 1171, 1064, 778, 710; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.82 (s, 2H, SCNHCO), 11.51 (s, 2H, NH), 11.03 (s, 2H, NHCO), 7.87 (d, $J = 7.2$ Hz, 4H, ArH), 7.79 (d, $J = 7.2$ Hz, 2H, ArH), 7.64–7.48 (m, 10H, ArH), 7.27 (d, $J = 6.8$ Hz, 2H, ArH); ESI-MS *m/z* (%): 597.10 ([M+1]$^+$, 100). Anal. Calcd for

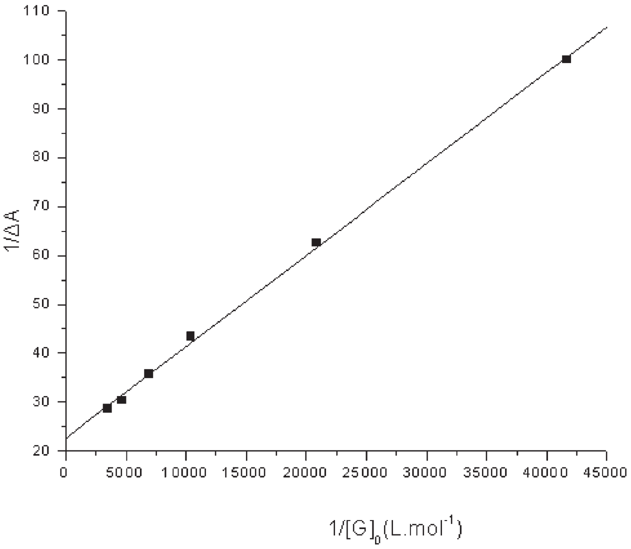

Fig. 1 Typical plot of 1/ΔA versus $1/[G]_0$ for the inclusion complex of molecular tweezer **7a** with NO_3^- in $CHCl_3$ at 25 °C.

$C_{30}H_{24}N_6O_4S_2$: C, 60.39; H, 4.05; N, 14.08. Found: C, 60.21; H, 4.06; N, 14.06%.

7b: Pale yellow crystal; yield 86%, m.p. 158–160 °C; IR (KBr, cm^{-1}): 3234, 3059, 2982, 1676, 1519, 1436, 1277, 1094, 750; ^1H NMR (DMSO-d_6, 400 MHz) δ: 11.81 (s, 2H, SCNHCO), 11.51 (s, 2H, NH), 11.14 (s, 2H, NHCO), 7.88 (d, $J = 8.4$ Hz, 4H, ArH), 7.79 (d, $J = 7.6$ Hz, 2H, ArH), 7.64–7.58 (m, 8H, ArH), 7.27 (d, $J = 7.6$ Hz, 2H, ArH); ESI-MS *m/z* (%): 1352.73 ($[2M+Na]^+$, 100). Anal. Calcd for $C_{30}H_{22}Cl_2N_6O_4S_2$: C, 54.14; H, 3.33; N, 12.63. Found: C, 54.09; H, 3.32; N, 12.66%.

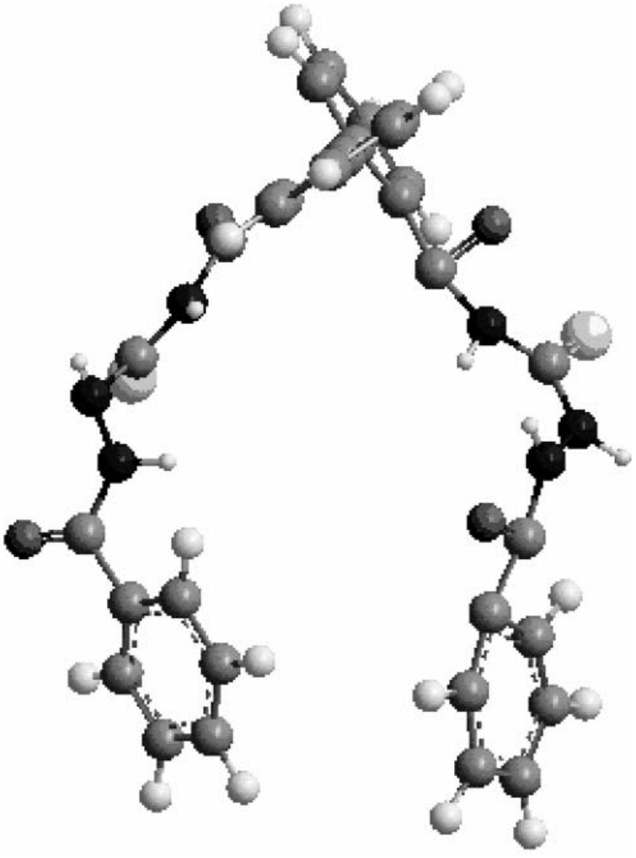

Fig. 3 Minimum energy conformation of molecular tweezer **7a.**

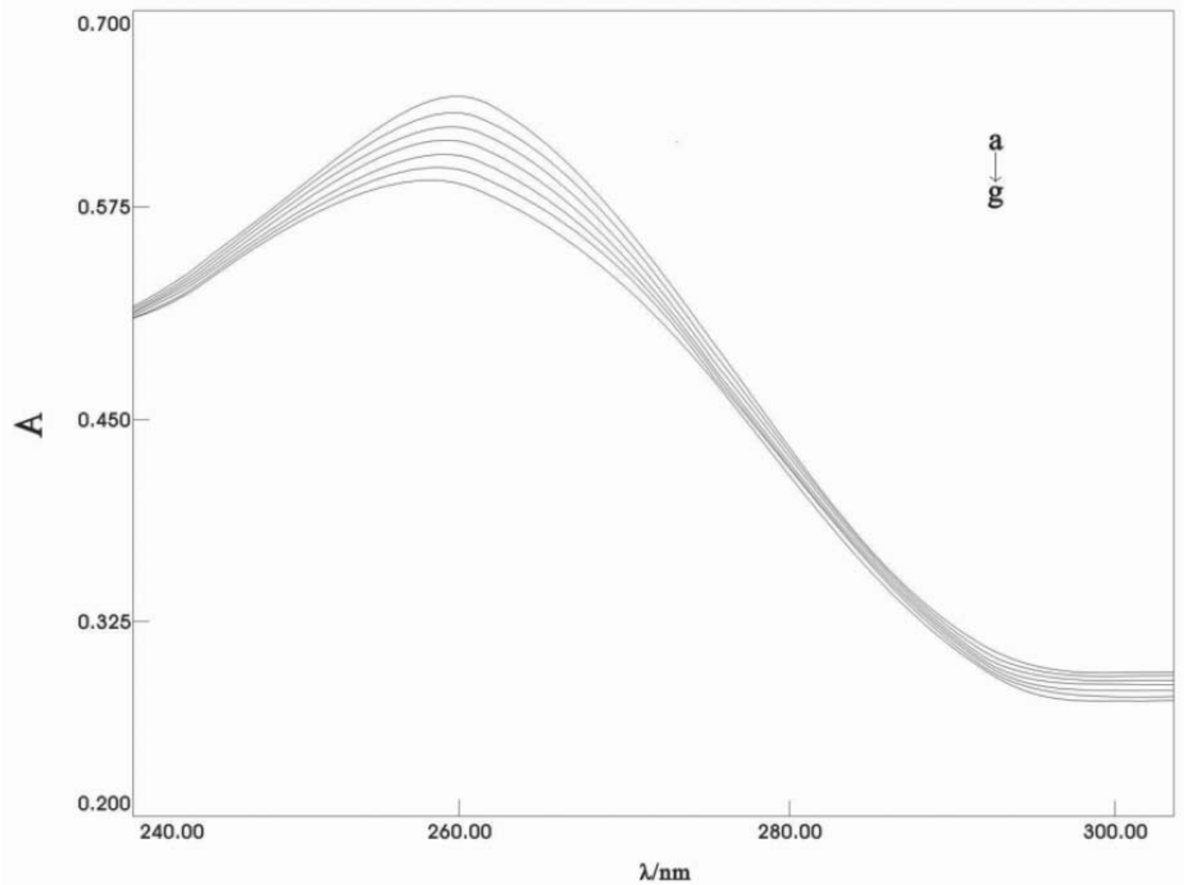

Fig. 2 UV-Vis spectra of molecular tweezers **7a** (3×10^{-4} mol L^{-1}) in the presence of NO_3^-. (a) 0 mol L^{-1}; (b) 0.024×10^{-3} mol L^{-1}; (c) 0.024×10^{-3} mol L^{-1}; (d) 0.048×10^{-3} mol L^{-1}; (e) 0.048×10^{-3} mol L^{-1}; (f) 0.072×10^{-3} mol L^{-1}; (g) 0.072×10^{-3} mol L^{-1} with λ_{max} at 262.6 nm.

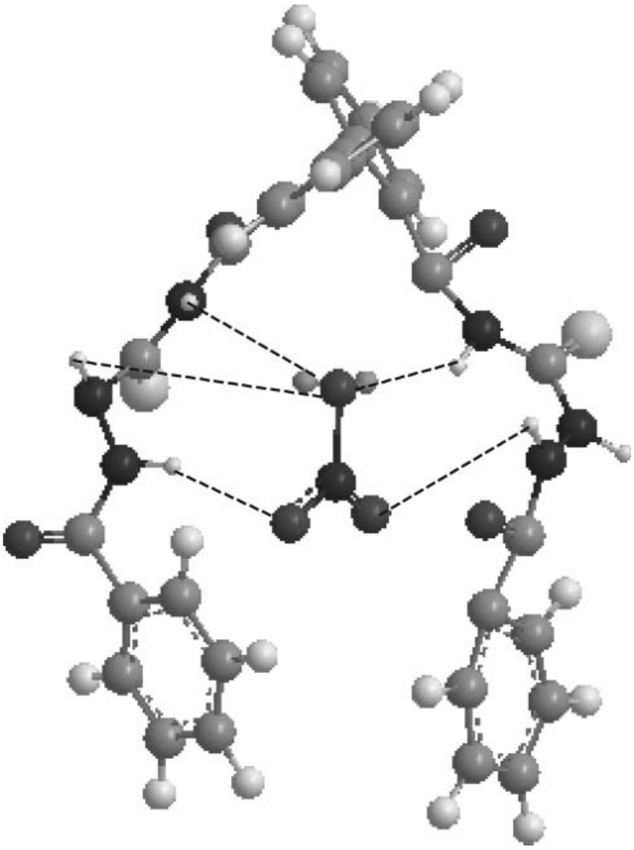

Fig. 4 Minimum energy conformation for the complex of molecular tweezer **7a** with NO_3^-.

Table 3 The melting points of hydrazides **3a–j**

Entry	Compound	Yield/%	M.p. / °C	Lit. m.p. / °C
1	**3a**	85	112–114	112.5[15]
2	**3b**	78	117–118	118–120[15]
3	**3c**	85	63–65	62–64[15]
4	**3d**	88	98–100	101–103[15]
5	**3e**	80	249–251	251–253[15]
6	**3f**	83	160–163	160–162.5[15]
7	**3g**	82	135–137	137–139[15]
8	**3h**	78	116–118	115[15]
9	**3i**	80	160–163	162–166[15]
10	**3j**	83	78–80	78–80[15]

7c: Yellow crystal; yield 80%, m.p. 210–213 °C; IR (KBr, cm^{-1}): 3162, 3067, 2983, 1672, 1527, 1462, 1243, 1179, 1038, 750; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.24 (d, J = 8.4 Hz, 2H, SCNHCO), 11.80 (s, 2H, NH), 11.44 (d, J = 8.0 Hz, 2H, NHCO), 8.02 (dd, J = 1.8 Hz, 7.8 Hz, 2H, ArH), 7.78 (d, J = 6.8 Hz, 2H, ArH), 7.66–7.54 (m, 6H, ArH), 7.29 (t, J = 6.6 Hz, 4H, ArH), 7.15 (t, J = 7.4 Hz, 2H, ArH), 4.33 (q, J = 7.0 Hz, 4H, OCH_2), 1.54 (t, J = 7.0 Hz, 6H, CH_3); ESI-MS m/z (%): 685.32 ([M+1]$^+$, 100). Anal. Calcd for $C_{34}H_{32}N_6O_6S_2$: C, 59.63; H, 4.71; N, 12.27. Found: C, 59.70; H, 4.59; N, 12.25%.

7d: White crystal; yield 80%, m.p. 183–185 °C; IR (KBr, cm^{-1}): 3261, 3054, 2922, 1670, 1524, 1438, 1247, 1198, 1168, 1059, 732; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 13.00 (s, 2H, SCNHCO), 9.82 (s, 2H, NH), 9.50 (s, 2H, NHCO), 7.80–7.78 (m, 2H, ArH), 7.63–7.54 (m, 8H, ArH), 7.39–7.34 (m, 4H, ArH), 7.26–7.22 (m, 2H, ArH), 2.42 (s, 6H, CH_3); ESI-MS m/z (%): 625.15 ([M+1]$^+$, 100). Anal. Calcd for $C_{32}H_{28}N_6O_4S_2$: C, 61.52; H, 4.52; N, 13.45. Found: C, 61.62; H, 4.51; N, 13.41%.

7e: Pale yellow crystal; yield 87%, m.p. 237–240 °C; IR (KBr, cm^{-1}): 3253, 3075, 2922, 1672, 1520, 1453, 1242, 1167, 1053, 710; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.81 (s, 2H, SCNHCO), 11.50 (s, 2H, NH), 11.14 (s, 2H, NHCO), 7.80–7.72 (m, 12H, ArH), 7.63–7.57 (m, 4H, ArH); ESI-MS m/z (%): 755.12 ([M+1]$^+$, 100). Anal. Calcd for $C_{30}H_{22}Br_2N_6O_4S_2$: C, 47.76; H, 2.94; N, 11.14. Found: C, 47.70; H, 2.94; N, 11.17%.

7f: Pale crystal; yield 72%, m.p. 230–231 °C; IR (KBr, cm^{-1}): 3258, 3054,2975, 1672, 1507, 1469, 1249, 1169, 1082, 777; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.86 (s, 2H, SCNHCO), 11.57 (s, 2H, NH), 11.07 (s, 2H, NHCO), 8.39 (dd, J = 3.8 Hz, 6.2 Hz, 2H, ArH), 8.08 (d, J = 8.4 Hz, 2H, ArH), 8.01 (dd, J = 3.2 Hz, 6.4 Hz, 2H, ArH), 7.83–7.77 (m, 4H, ArH), 7.68–7.65 (m, 2H, ArH), 7.61–7.56 (m, 8H, ArH), 7.31 (d, J = 7.2 Hz, 2H, ArH); ESI-MS m/z (%): 1431.46 ([2M+K]$^+$, 100). Anal. Calcd for $C_{38}H_{28}N_6O_4S_2$: C, 65.50; H, 4.05; N, 12.06. Found: C, 65.39; H, 4.06; N, 12.03%.

7g: Pale crystal; yield 85%, m.p. 204–207 °C; IR (KBr, cm^{-1}): 3245, 3067, 2971, 1671, 1522, 1434, 1255, 1173, 1025, 757; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.84 (s, 2H, SCNHCO), 11.49 (s, 2H, NH), 10.89 (s, 2H, NHCO), 7.85 (d, J = 8.8 Hz, 4H, ArH), 7.78 (d, J = 7.2 Hz, 2H, ArH), 7.65–7.56 (m, 4H, ArH), 7.27 (d, J = 7.6 Hz, 2H, ArH), 7.04 (d, J = 8.8 Hz, 4H, ArH), 3.82 (s, 6H, OCH_3); ESI-MS m/z (%): 1334.96 ([2M+Na]$^+$, 100). Anal. Calcd for $C_{32}H_{28}N_6O_6S_2$: C, 58.52; H, 4.30; N, 12.80. Found: C, 58.47; H, 4.31; N, 12.77%.

7h: White crystal; yield 80%, m.p. 226–228 °C; IR (KBr, cm^{-1}): 3239, 3045, 2983, 1672, 1532, 1438, 1245, 1182, 1064, 746; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.83 (s, 2H, SCNHCO), 11.50 (s, 2H, NH), 10.96 (s, 2H, NHCO), 7.77 (d, J = 7.2 Hz, 6H, ArH), 7.64–7.57 (m, 4H, ArH), 7.31–7.27 (m, 6H, ArH), 2.36 (s, 6H, CH_3); ESI-MS m/z (%): 1271.27 ([2M+Na]$^+$, 100). Anal. Calcd for $C_{32}H_{28}N_6O_4S_2$: C, 61.52; H, 4.52; N, 13.45. Found: C, 61.42; H, 4.51; N, 13.43%.

7i: White crystal; yield 78%, m.p. 207–208 °C; IR (KBr, cm^{-1}): 3246, 3067, 2981, 1671, 1525, 1441, 1240, 1161, 1065, 756; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.80 (s, 2H, SCNHCO), 11.50 (s, 2H, NH), 11.07 (s, 2H, NHCO), 7.95–7.91 (m, 4H, ArH), 7.79 (d, J = 7.2 Hz, 2H, ArH), 7.66–7.56 (m, 4H, ArH), 7.37 (t, J = 9.0 Hz, 4H, ArH), 7.27 (d, J = 6.8 Hz, 2H, ArH); ESI-MS m/z (%): 1303.19 ([2M+K]$^+$, 100). Anal. Calcd for $C_{30}H_{22}F_2N_6O_4S_2$: C, 56.95; H, 3.50; N, 13.28. Found: C, 57.04; H, 3.51; N, 13.24%.

7j: Pale yellow crystal; yield 83%, m.p. 252–256 °C; IR (KBr, cm^{-1}): 3159, 3017, 2934, 1655, 1528, 1446, 1246, 1182, 1044, 754, 652; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.08 (d, J = 7.2 Hz, 2H, SCNHCO), 11.81 (s, 2H, NH), 11.59 (d, J = 6.8 Hz, 2H, NHCO), 7.99 (dd, J = 1.6 Hz, 8.0 Hz, 2H, ArH), 7.77 (d, J = 7.2 Hz, 2H, ArH), 7.66–7.54 (m, 6H, ArH), 7.30 (t, J = 8 Hz, 4H, ArH), 7.17 (t, J = 7.6 Hz, 2H, ArH), 4.03 (s, 6H, OCH_3); ESI-MS m/z (%): 657.15 ([M+1]$^+$, 100). Anal. Calcd for $C_{32}H_{28}N_6O_6S_2$: C, 58.52; H, 4.30; N, 12.80. Found: C, 58.55; H, 4.29; N, 12.83%.

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