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Stereoselective Synthesis of (2E) 3-Amino-2-(1*H*-benzimidazol-2-yl)acrylate and Symmetric Bisacrylates by Transamination Reactions

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ABSTRACT: *A range of various amines* **2***(***a–i***) was tested in transamination reactions using ethyl 2-(1H-benzimidazol-2-yl)-3-dimethylamino-acrylate* **1a***. The (E)-s-cis/trans conformation of some representative products* **4** *was analyzed by* ^{1}H *and* ^{13}C *NMR spectra. The C-2/C-3 bond of the compounds* **3***(***a–i***) is strongly polarized by a push-pull effect. In the same manner, reactions of ethyl 2-(benzoxazol-2-yl)-3-dimethylamino-acrylate* **1c** *with 1,4-diaminobenzene* **2i***, ethylenediamine* **2i***, and 1,5-diaminomaphthalene* **2k** *have been investigated and gave directly the corresponding symmetric bis-acrylates* **4***(***a–c***) in good yields.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 446–454, 1999

INTRODUCTION

The benzimidazole derivatives are used extensively in medicinal chemistry [1]; the antihistamine Astemizole [2] and the antiulcerative Omeprazole [3] are notable clinical examples. Additionally, the 2-alkylthiobenzimidazoles [4] and their corresponding derivatives have been shown to be proton-pump inhibitors [5], and anti-ulcer [6] and anti-virals agents [7].

Recently, we have reported that the ambident synthon derived from ethyl 2-(1*H*-benzimidazol-2-yl)-3-dimethylamino-acrylate **1a** [8, 9a] was used for the synthesis of 1-oxo-1,2-dihydropyrimido-[1,6-*a*]-benzimidazole-4-carboxylate [8,9a], according to a regioselective aza-annulation with good yields. Encouraged by these primary results, we have explored the reactivity of acrylate **1a** in transamination reactions [10] with various primary amines, amino alcohols, and methyl glycinate. In the same manner, reactions of ethylenediamine and aromatic diamines with ethyl 2-(benzoxazol-2-yl)-3-dimethylamino-acrylate **1b** [8,9a] and ethyl 2-(benzothiazol-2-yl)-3-dimethylamino-acrylate **1c** [8,9a], respectively, were also examined (See Figure 1). We now report preparative procedures including full characterization of new acrylates derived from benzimidazole and NMR (^{1}H, ^{13}C) structure studies.

RESULTS AND DISCUSSION

Transamination Reactions of Ethyl 2-(1H-benzimidazol-2-yl)-3-dimethylamino Acrylate **1a** *with a Range of Amines* **2(a–i)**

The starting acrylate **1a** was readily obtained as previously described [9a] using solvent-free conditions assisted by focused microwave irradiations [9b].

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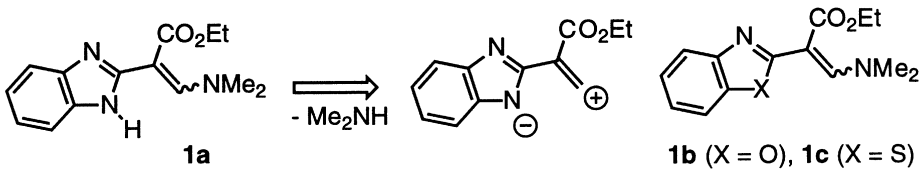


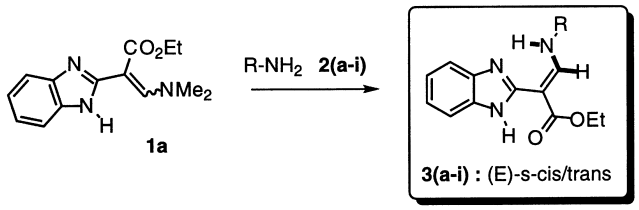
FIGURE 1

Synthesis of functionalized acrylates **3**(**a–f**) was easily achieved according to the following procedure (Scheme 1). A mixture of **1a** and each amine **2**(**a–f**) in methylene chloride was refluxed with vigorous stirring for 48 hours. After filtration of the reaction mixture through silica gel 60 F-254 (Merck) and removal of solvent in vacuo, the new acrylates **3**(**a–f**) were isolated in good yields (Table 1) after purification by recrystallization. For cyanamide **2g**, the reaction was carried out in refluxing ethanol and **3g** was also formed with the same reaction time (48 hours). Next, compound **3h** was prepared in the following way: addition of **1a** in one portion into a suspension of methyl glycinate hydrochloride and dry triethylamine [11] at 0°C in CH_2Cl_2; this mixture was also heated at 41°C over 48 hours and gave **3h** in good yield after work-up (Table 1). Finally, when **1a** was heated in chloroform with 1,4-diaminobenzene **2i**, it was possible to obtain selectively the monotransaminated product **3i** in 90% yield. Attempts to obtain directly the corresponding bistransaminated compound in the same conditions by reaction of **1a** (2 equivalents) with **2i** were unsuccessful; this can be explained by the low reactivity of the 4-amino group of **3i** for the second transamination reaction.

The assigned structures of acrylates **3**(**a–i**) were substantiated by the ^{1}H and ^{13}C NMR (Table 2), IR, and MS analyses. A characteristic feature of the ^{1}H NMR spectra of acrylates **3**(**a–i**) is the considerable downfield shift of the H-3 doublet ($\delta_{H\text{-}3}$ = 7.89–8.35 ppm). The coupling constant ^3J = 12.5–14.4 Hz between the amino proton and H-3 strongly suggests the trans (antiperiplanar) orientation [12] of these hydrogens. Furthermore, the separated downfield shift of NH signals (**3a**: δ_{NH} = 10.97 and 11.04 ppm) is due to an intramolecular hydrogen bond [13] that stabilizes the (E)-s-cis/trans conformation.

In the ^{13}C NMR spectrum, the upfield shift of C-2 ($\delta_{C\text{-}2}$ = 86.41–88.71 ppm, except for **3g**) indicates a high electron density, and the shift of C-3 is located downfield ($\delta_{C\text{-}3}$ = 147.88–154.26 ppm). In fact, the C-2/C-3 bond is highly polarized as a consequence of a push-pull effect [14].

The quaternary carbon atoms are also readily assigned: C-3a′, C-7a′ (formally ipso carbon atoms)



SCHEME 1

and C-2′ gave downfield shifts ($\delta_{C\text{-}2'}$ = 147.6–152.8 ppm). The ^{1}H resonance-coupled ^{13}C NMR spectra showed the presence of the C-2 doublet with a coupling constant J = 9.7 Hz for compound **3a** in agreement with our previous observations [9].

Preparation of symmetric bisacrylates **4**(**a–e**) *derived from benzoxazole and benzothiazole with diamines* **2**(**i–k**)

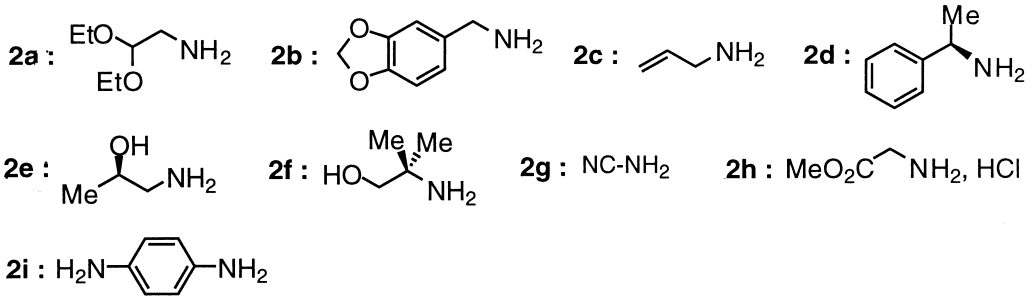
We found it interesting to extend this process to aliphatic and aromatic diamines **2**(**i–k**) *(Scheme 2). The 3-dimethylamino acrylates* **1b** (X = O) and **1c** (X = S) reacted smoothly with 1,4-diaminobenzene **2i** in refluxing dry chloroform (**4a**~ 240 hours and **4c**~ 96 hours). Treatment of the crude reaction mixture with diethyl ether afforded the respective insoluble symmetric bisacrylates **4a,c** in yields ranging from 80 to 85%. The low reactivity of the aromatic diamine **2i** in the transamination reaction was also observed under the same conditions by reaction of 1,5-diaminonaphthalene **2k** with ethyl 2-(benzothiazol-2-yl)-3-dimethylamino acrylate **1c**: after an optimum reaction time of ~168 hours, compound **4e** was obtained in moderate yield (58%).

From the standard 3-dimethylamino acrylates **1b** and **1c**, the transamination efficiency was better with ethylenediamine **2j**. The corresponding bisacrylates **4b** and **4d** required a reaction time of 48 hours.

The symmetric structure of the bisacrylates **4**(**a–e**) derived from benzoxazole, benzothiazole, and the respective aliphatic and aromatic diamines was confirmed by the presence of only one set of signals in each of the ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR

TABLE 1 Synthesis of Ethyl 3-amino-2-(1*H*-benzimidazol-2-yl)acrylates **3(a–i)** by Transamination Reactions.

Amine	*Reaction conditions*	*Product* **3**	*Yield of* **3** *(%)*[a]	*M.p. of* **3** *(°C)*
2a	*b*	**3a**	78	84–85
2b	*b*	**3b**	90	141–142
2c	*b*	**3c**	90	103–104
2d	*b*	**3d**	90	117–118
2e	*b*	**3e**	80	165–166
2f	*b*	**3f**	80	—[f]
2g	*c*	**3g**	61	257–258
2h	*d*	**3h**	86	163–164
2i	*e*	**3i**	90	216–218



[a]Yield of isolated product.
[b]Dry CH_2Cl_2, Δ, 48 h.
[c]Dry EtOH, Δ, 48 h.
[d]CH_2Cl_2, Et_3N, O°C, 2 h then Δ, 48 h.
[e]Dry $CHCl_3$, Δ, 110 h.
[f]Viscous oil.

TABLE 2 Selected ^1H and ^{13}C NMR Data (δ values) of **3(a–i)** with TMS as an Internal Standard

Product	*H-3*	*NH*		*C-2*	*C-3*	*C-2′*
3a[a]	8.05	10.97	11.04	87.2	154.3	152.6
3b[a]	8.03	11.14	11.44	87.3	153.5	152.6
3c[a]	8.00	10.99	11.15	87.2	153.6	152.7
3d[a]	8.03	11.14	11.44	87.2	152.2	152.8
3e[a]	7.89	10.72	11.19	86.8	154.3	152.7
3f[a]	8.10	10.98	11.10	86.6	149.7	152.8
3g[a]	8.35	11.25	11.48	100.0	153.6	151.1
3h[a]	7.91	11.12	–	88.7	153.6	152.1
3i[b]	8.41	10.59	–	86.4	153.6	152.1

[a]$CDCl_3$ solvent.
[b]C_6D_6/CF_3CO_2H solvent (1:4).

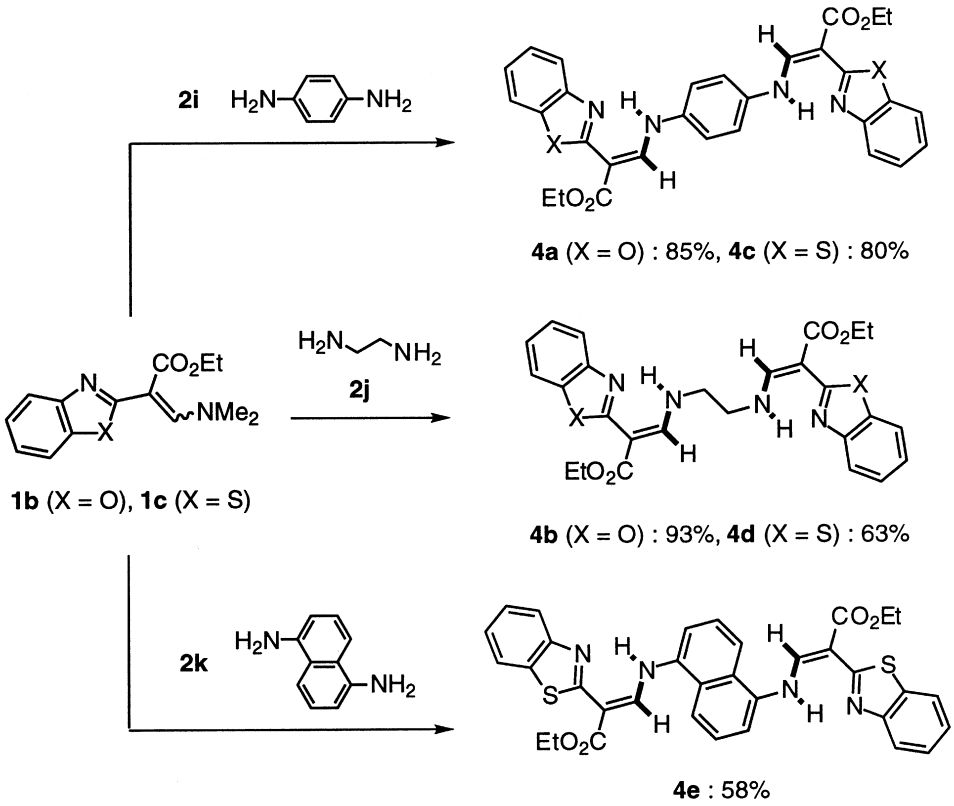
spectra of the bisacrylates **4(a–e)** (Table 3), we observed only a single doublet at δ = 8.37–8.90 ppm for the olefinic proton H-3. The presence of a coupling constant (^3J = 12–14 Hz) between the amino proton and H-3 indicates a trans relationship. Furthermore, it is interesting to notice that the ethylene segment of the bisacrylate **4b** appears as a broad singlet at $\delta(CH_2)$ = 4.10 ppm, accounting for four protons. This was also observed for **4d** ($\delta(CH_2)$ = 4.01 ppm) and was in agreement with a symmetric geometry. We have also found that the C-2/C-3 bond revealed a strong polarization (**4b**: $\delta_{C\text{-}2}$ = 83.4 ppm and $\delta_{C\text{-}3}$ = 160.1 ppm) that is attributed to the push-pull double bond structure.

CONCLUSION

From the above results it can be concluded that the transamination reactions of ethyl 2-(1*H*-benzimidazol-2-yl)-3-dimethylamino-acrylate **1a** with various primary amines **2(a–i)** was stereoselective and afforded the new acrylates **3(a–i)** with an (E)-s-cis/trans conformation. ^1H and ^{13}C NMR spectra of these compounds were assigned. From the spectral characteristics, the C-2/C-3 bond exhibits a strong polarization as a consequence of a push-pull effect. This process was also extended to the preparation of symmetric bisacrylates **4(a–e)** in good yields.

EXPERIMENTAL

Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck). For preparative column chromatog-



SCHEME 2

TABLE 3 Selected ^1H and ^{13}C NMR Data (δ Values) of Bisacrylates **4(a–e)** with TMS as an Internal Standard

Compound	*H-3*	*NH*	*C-2*	*C-3*	*C-2′*
4a[a]	8.56	12.00	90.8	146.4	162.7
4b[a]	8.50	9.90	83.4	160.1	163.5
4c[a]	8.80	9.85	92.8	150.4	165.5
4d[a]	8.37	9.80	90.6	159.0	166.0
4e[a]	8.90	11.40	93.3	153.1	165.9

[a]$CDCl_3/CF_3CO_2H$ solvent (95/5).

raphy, silica gel 60F 254 Merck (230–240 Mesh ASTM) was used. Melting points were determined on a Kofler melting point apparatus and are uncorrected.

IR spectra were taken with a PERKIN-ELMER 157G spectrometer. ^1H NMR spectra were recorded on a BRUKER AC 300 P (300 MHz) spectrometer, and ^{13}C NMR spectra were recorded on a BRUKER AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra (HRMS) were taken on a VARIAN MAT 311 at a ionizing potential of 70 eV in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes).

Methylene chloride was distilled over calcium chloride after standing overnight and stored over molecular sieves (3Å). Ethyl 2-(1*H*-benzimidazol-2-yl)-3-dimethylamino acrylate **1a**, ethyl 2-(benzoxazol-2-yl)-3-dimethylamino acrylate **1b**, and ethyl 2-(benzothiazol-2-yl)-3-dimethylamino acrylate **1c** were synthesized in large scale, according to our previous method, [9a], from commercial *N*,*N*-dimethylformamide diethylacetal and ethyl 2-(1*H*-benzimidazol-2-yl)acetate [15], ethyl 2-(benzoxazol-2-yl)acetate [16], and ethyl 2-(benzothiazol-2-yl)acetate [16], respectively.

General Procedures for the Preparation of α-Hetero-β-enamino Esters **3(a–g)**

A mixture of ethyl 2-(1*H*-benzimidazol-2-yl)-3-dimethylamino acrylate **1a** (1.0 g, 3.86 mmol) and each commercial amine **2**(**a–g**) (3.86 mmol) in dry methylene chloride (20 mL) was heated at 41°C during 48 hours (monitored by TLC with the appropriate eluent) with vigorous magnetic stirring. Then, the reaction mixture was allowed to cool and was rapidly filtered through a column of silica gel 60F 254 Merck (3 g, Ø 3 cm). Removal of the solvent in vacuo gave an oil which crystallized on standing. Recrystallization from ethyl alcohol denatured with up to

5% v/v of ether gave pure compounds **3**(**a–f**) as colorless needles.

Ethyl 2-(1H-benzimidazol-2-yl)-3-(2,2-diethoxyethyl)amino Acrylate (**3a**)

The crude product **3a** was obtained from **1a** (1.0 g, 3.86 mmol) and 2,2-diethoxyethylamine **2a** (0.51 g, 3.86 mmol). Purification by recrystallization from ethanol gave pure **3a** (1.04 g, 78%) as needles (m.p. = 84–85°C); IR (nujol) 3380, 1620, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 6 H, J = 7.1 Hz), 1.35 (t, 3 H, J = 7.1 Hz), 3.50–3.65 (m, 2 H, J = 5.3 Hz), 3.70–3.85 (ddd, J = 7.1, 5.3 Hz), 4.28 (q, 2 H, J = 7.1 Hz), 4.60 (t, 1 H, J = 5.3 Hz), 7.15 (m, 2 H, H-5′, H-6′), 7.38 (m, 1 H, H-4′, H-7′), 7.59 (m, 1 H, H-4′, H-7′), 8.05 (d, 1 H, J = 12.3 Hz, H-3), 10.97 (br s, 1 H, NH), 11.14 (br s, 1 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (qt, J = 127, 2.7 Hz), 15.4 (qt, J = 129, 2.9 Hz), 52.1 (td, J = 139, 4.8 Hz), 59.8 (tq, J = 151, 4.4 Hz), 63.7 (tq, J = 142, 4.4 Hz), 87.2 (d, J = 2.1 Hz, C-2), 102.0 (dt, J = 160 Hz), 110.2 (dd, J = 160, 4.6 Hz, C-5′, C-6′), 117.3 (dd, J = 158, 4.4 Hz, C-5′, C-6′), 121.4 (dd, J = 161, 7.7 Hz, C-4′, C-7′), 121.5 (dd, J = 160, 7.6 Hz, C-4′, C-7′), 131.8 (sm, C-3a′, C-7a′), 142.5 (sm, C-3a′, C-7a′), 152.6 (d, J = 9.7 Hz, C-2′), 154.3 (dt, J = 139, 2.8 Hz, C-3), 168.1 (sm, C-1); HRMS, *m/z*: 347.1842 found for $M^{\cdot+}$ (calc for $C_{18}H_{25}N_3O_4$: 347.1845). Anal. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.25; H, 7.20; N, 12.10; O, 18.44. Found: C, 62.18; H, 7.29; N, 12.17; O, 18.36.

Ethyl 2-(1H-benzimidazol-2-yl)-3-(3,4-(methylenedioxy)phenylmethyl)amino Acrylate (**3b**)

The crude product **3b** was obtained from **1a** (1.0 g, 3.86 mmol) and piperonylamine **2b** (0.58 g, 3.86 mmol). Purification by recrystallization from ethanol gave pure **3b** (1.26 g, 90%) as needles (m.p. = 141–142°C); IR (nujol) 2985, 1600, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, 3 H, J = 7.1 Hz), 4.26 (q, 2 H, J = 7.1 Hz), 4.46 (s, 2 H), 5.9 (s, 2 H), 6.74 (s, 3 H, Ar), 7.09–7.18 (m, 2 H, H-5′, H-6′), 7.32–7.38 (m, 1 H, H-4′, H-7′), 7.55–7.60 (m, 1 H, H-4′, H-7′), 8.03 (d, 1 H, J = 12.9 Hz, H-3), 11.14 (br s, 1 H, NH), 11.44 (br s, 1 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (qt, J = 127, 2.5 Hz), 52.9 (t, J = 134 Hz), 59.8 (tq, J = 147, 4.5 Hz), 87.3 (d, J = 1.6 Hz, C-2), 101.2 (t, J = 169 Hz), 107.7 (dd, J = 146, 4.9 Hz, Ar), 108.4 (d, J = 164 Hz, Ar), 110.2 (dd, J = 160, 6.4 Hz, C-5′, C-6′), 117.4 (dd, J = 159, 6.7 Hz, C-5′, C-6′), 120.5 (dt, J = 159, 4.5 Hz, Ar), 121.4 (dd, J = 159, 7.6 Hz, Ar), 121.6 (dd, J = 160, 7.7 Hz, C-4′, C-7′), 131.5 (sm, C_{ipso}, Ar), 131.8 (sm, C-3a′, C-7a′), 142.2 (sm, C-3a′, C-7a′), 147.3 (sm, Ar), 148.1 (sm, Ar), 152.6 (dd, J = 9.5, 2.8 Hz, C-2′), 153.5 (dd, J = 169, 5.2 Hz, C-3), 168.0 (sm, C-1); HRMS, *m/z*: 365.1364 found for $M^{\cdot+}$ (calc for $C_{20}H_{19}N_3O_4$: 365.1376). Anal. Calcd for $C_{20}H_{19}N_3O_4$: C, 65.76; H, 5.21; N, 11.51; O, 17.53. Found: C, 65.99; H, 5.26; N, 11.48; O, 17.27.

Ethyl 2-(1H-benzimidazol-2-yl)-3-(prop-2-enyl)amino Acrylate (**3c**)

The crude product **3c** was obtained from **1a** (1.0 g, 3.86 mmol) and allylamine **2c** (0.22 g, 3.86 mmol). Purification by recrystallization from ethanol gave pure **3c** (0.94 g, 90%) as needles (m.p. = 103–104°C); IR (nujol) 3350, 2985, 1620, 1600, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, 3 H, J = 7.1 Hz), 4.07 (dd, 2 H, J = 5.1 Hz), 4.28 (q, 2 H, J = 7.1 Hz), 5.29 (ddd, 2 H, J = 17.4, 11.8, 1.3 Hz), 5.99 (m, 1 H, =CH), 7.14–7.19 (m, 2 H, H-5′, H-6′), 7.37–7.41 (m, 1 H, H-4′, H-7′), 7.59–7.63 (m, 1 H, H-4′, H-7′), 8.00 (d, 1 H, J = 12.4 Hz, H-3), 10.99 (br s, 1 H, NH), 11.15 (br s, 1 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (qt, J = 127, 2.4 Hz), 51.4 (tm, J = 135 Hz, $\underline{CH_2}$–CH;=), 59.8 (tq, J = 147, 4.4 Hz), 87.2 (d, J = 1.7 Hz, C-2), 110.4 (dd, J = 160, 4.5 Hz, C-5′, C-6′), 117.3 (tt, J = 160, 5.5 Hz, H_2C=), 117.4 (dd, J = 160, 4.8 Hz, C-5′, C-6′), 121.4 (dd, J = 160, 7.6 Hz, C-4′, C-7′), 121.6 (dd, J = 160, 7.5 Hz, C-4′, C-7′), 131.9 (sm, C-3a′, C-7a′), 134.1 (dm, J = 157 Hz, $\underline{C}$H=), 142.1 (sm, C-3a′, C-7a′), 152.7 (dd, J = 9.1, 2.5 Hz, C-2′), 153.6 (dd, J = 168, 3.9 Hz, C-3), 168.1 (sm, C-1); HRMS, *m/z*: 271.1321 found for $M^{\cdot+}$ (calc for $C_{15}H_{17}N_3O_2$: 271.1316). Anal. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.42; H, 6.27; N, 15.50; O, 11.81. Found: C, 65.61; H, 6.25; N, 15.24; O, 12.90.

Ethyl 2-(1H-benzimidazol-2-yl)-3-[(R)-2-phenylethyl)]amino Acrylate (**3d**)

The crude product **3d** was obtained from **1a** (1.0 g, 3.86 mmol) and *d*-(+)-α-methylbenzylamine **2d** (0.47 g, 3.86 mmol). Purification by recrystallization from ethanol gave pure **3d** (1.16 g, 90%) as needles (m.p. = 117–118°C); IR (nujol) 3390, 2885, 1630, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3 H, J = 7.1 Hz), 1.69 (d, 3 H, J = 6.9 Hz), 4.23 (2 × q, 3 H, J = 7.1 Hz), 4.64 (m, 1 H, J = 6.9 Hz), 7.12–7.21 (m, 1 H, Ar, H-5′, H-6′), 7.34 (s, 5 H, Ar), 7.35–7.39 (m, 1 H, Ar, H-4′, H-7′), 7.59–7.69 (m, 1 H, Ar, H-4′, H-7′), 8.03 (d, 1H, f = 13.5 Hz, H-3), 11.14 (br s, 1 H, NH), 11.44 (br s, 1 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (qt, J = 127, 2.6 Hz), 24.0 (qd, J = 128, 4.0 Hz), 58.6 (dm, J = 136 Hz), 59.8 (tq, J = 143, 4.4 Hz), 87.2 (d, J = 1.5 Hz, C-2), 110.3 (dd, J = 160, 4.6 Hz, C-5′, C-6′), 117.6 (dd, J = 161, 4.8 Hz, C-5′,

C-6′), 121.5 (dd, J = 160, 7.6 Hz, C-4′, C-7′), 121.7 (dd, J = 161, 7.7 Hz, C-4′, C-7′), 126.1 (dm, J = 161, 4.2 Hz, Ar, C-3), 127.7 (dm, J = 160 Hz, Ar, C-4), 129.0 (dd, J = 160, 6.1 Hz, Ar, C-2), 131.9 (sm, Ar, C_{ipso}), 142.36 (sm, C-3a′, C-7a′), 143.3 (sm, C-3a′, C-7a′), 152.2 (dd, J = 168, 3.8 Hz, C-3), 152.8 (dd, J = 9.5, 2.5 Hz, C-2′), 168.2 (sm, C-1); HRMS, *m/z*: 335.1628 found for M^+ (calc for $C_{20}H_{21}N_3O_2$: 335.1633). Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.64; H, 6.27; N, 12.54; O, 9.55. Found: C, 71.45; H, 6.26; N, 12.33; O, 9.96.

(*2R*) *Ethyl 2-*(*1H-benzimidazol-2-yl*)*-3-*(*2-hydroxypropyl*)*amino Acrylate* (**3e**)

The crude product **3e** was obtained from **1a** (1.0 g, 3.86 mmol) and R-(−)-1-amino-2-propanol **2e** (0.29 g, 3.86 mmol). Purification by recrystallization from ethanol gave pure **3e** (0.89 g, 80%) as needles (m.p. = 165–166°C); IR (nujol) 3380, 2880, 1730, 1620, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, 3 H, J = 6.3 Hz), 1.29 (t, 3 H, J = 7.1 Hz), 3.20 (dd, 1 H, J = 8.7, 6.5 Hz), 3.35 (dd, 1 H, J = 9.3, 8.7 Hz), 3.94 (m, 1 H), 4.20 (q, 1 H, J = 7.1 Hz), 7.06–7.17 (m, 2 H, Ar, H-5′, H-6′), 7.28–7.35 (m, 1 H, Ar, H-4′, H-7′), 7.51–7.58 (m, 1 H, Ar, H-4′, H-7′), 7.89 (d, 1 H, J = 12.6 Hz, H-3), 10.72 (br s, 1 H, NH), 11.19 (br s, 1 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5 (qt, J = 127, 2.5 Hz), 20.2 (qd, J = 128, 2.8 Hz), 57.0 (tt, J = 145, 4.3 Hz), 59.8 (tq, J = 147, 4.3 Hz), 67.1 (dm, J = 140, 4.1 Hz), 86.7 (d, J = 2.2 Hz, C-2), 110.3 (dd J = 150, 4.8 Hz, C-5′, C-6′), 117.3 (dd, J = 150, 4.8 Hz, C-5′, C-6′), 121.5 (dd, J = 161, 8 Hz, C-4′, C-7′), 121.6 (dd, J = 161, 8 Hz, C-4′, C-7′), 131.7 (sm, C-3a′, C-7a′), 142.1 (sm, C-3a′, C-7a′), 152.7 (dd, J = 9.4, 2.8 Hz, C-2′), 154.3 (dt, J = 169, 5 Hz, C-3), 168.0 (sm, C-1); HRMS, *m/z*: 289.1426 found for M^+ (calc for $C_{15}H_{19}N_3O_3$: 289.1426). Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.28; H, 6.57; N, 14.53; O, 16.61. Found: C, 62.14; H, 6.48; N, 14.59; O, 16.79.

Ethyl 2-(*1H-benzimidazol-2-yl*)*-3-*(*2-hydroxy-1,1-dimethylpropyl*)*amino Acrylate* (**3f**)

The crude product **3f** was obtained in 80% yield (0.81 g) from **1a** (1.0 g, 3.86 mmol) and 2-amino-2-methyl-1-propanol **2f** (0.34 g, 3.86 mmol) as a colorless viscous oil; IR (nujol) 3385, 2980, 1740, 1620, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3 H, J = 7.1 Hz), 1.36 (s, 6 H), 3.55 (s, 2 H), 4.23 (q, 2 H, J = 7.1 Hz), 7.09–7.12 (m, 2 H, H-5′, H-6′), 7.30–7.38 (m, 1 H, H-4′, H-7′), 7.53–7.61 (m, 1 H, H-4′, H-7′), 8.10 (d, 1 H, J = 12.9 Hz, H-3), 10.98 (br s, 1 H, NH), 11.10 (br s, 1 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (qt, J = 127, 2.4 Hz), 24.3 (qm, J = 131 Hz), 56.8 (sm), 59.8 (tq, J = 143, 4.3 Hz), 70.7 (tt, J = 142, 4.8 Hz), 86.6 (d, J = 1.68 Hz, C-2), 110.2 (dd, J = 150, 4.8 Hz, C-5′, C-6′), 117.3 (dd, J = 150, 4.8 Hz, C-5′, C-6′), 121.4 (dd, J = 161, 8.1 Hz, C-4′, C-7′), 121.6 (dd, J = 161, 7.9 Hz, C-4′, C-7′), 131.7 (sm, C-3a′, C-7a′), 142.2 (sm, C-3a′, C-7a′), 149.7 (d, J = 168 Hz, C-3), 152.8 (d, J = 9 Hz, C-2′), 168.2 (sm, C-1); HRMS, *m/z*: 303.1544 found for M^+ (calc for $C_{16}H_{21}N_3O_3$: 303.1583).

Ethyl 2-(*1H-benzimidazol-2-yl*)*-3-cyanoamino Acrylate* (**3g**)

The crude product **3f** was obtained from **1a** (1.0 g, 3.86 mmol) and cyanamide **2g** (0.16 g, 3.86 mmol) after refluxing in 15 mL of dry ethanol. Purification by recrystallization from ethanol gave pure **3g** (0.60 g, 61%) as brown needles (m.p. = 257–258°C); IR (nujol) 3400, 2880, 1730, 1620, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (t, 3 H, J = 6.9 Hz), 4.58 (q, 2 H, J = 6.9 Hz), 7.84–7.94 (m, 2 H, H-5′, H-6′), 8.08 (m, 1 H, H-4′, H-7′), 8.15 (m, 1 H, H-4′, H-7′), 8.35 (d, 1 H, J = 13.5 Hz, H-3), 11.24 (br s, 1 H, NH) 11.48 (br s, 1 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0 (qt, J = 128, 2.4 Hz), 64.3 (tq, J = 128, 4.3 Hz), 100.0 (d, J = 1.4 Hz, C-2), 114.3 (dd, J = 168, 5.1 Hz, C-5′, C-6′), 115.1 (dd, J = 173, 8.5 Hz, C-5′, C-6′), 124.3 (sm, C-3a′, C-7a′), 127.7 (dd, J = 168, 7.9 Hz, C-4′, C-7′), 131.0 (sm, C-3a′, C-7a′), 131.1 (dd, J = 168, 6.2 Hz, C-4′, C-7′), 151.1 (d, J = 10.8 Hz, C-2′), 153.6 (dd, J = 162, 4.8 Hz, C-3), 163.1 (sm, C-1); HRMS, *m/z*: 256.0960 found for M^+ (calc for $C_{13}H_{12}N_4O_2$: 256.0948). Anal. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.94; H, 4.69; N, 21.87; O, 12.50. Found: C, 60.91; H, 4.71; N, 21.92; O, 12.46.

Ethyl 2-(*1H-benzimidazol-2-yl*)*-3-*(*methoxycarbonylmethyl*)*amino Acrylate* (**3h**)

To a suspension of methylglycinate hydrochloride **2h** (0.96 g, 7.72 mmol) in 15 mL of dry methylene chloride cooled to 0°C with vigorous stirring, a solution of dry ethylamine (0.84 g, 8.3 mmol) in 10 mL of dry CH_2Cl_2 was added dropwise over 30 minutes. After stirring for 1.5 hour, **1a** (2.0 g, 7.72 mmol) was added at 0°C in one portion to the reaction mixture, then the resulting suspension was refluxed for 48 hours (monitored by TLC, Rf = 0.63 with CH_2Cl_2 as an eluent). The reaction mixture was allowed to cool. The organic solution was treated three times with water (10 mL), twice with brine (10 mL), dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo lead to a viscous oil (2.10 g, 90%) that crystallized on standing. This was dissolved in methylene chloride (40 mL) that was submitted to filtration through

a column of silica gel 60F 254 Merck (3 g, Ø 3 cm). Solvent evaporation by rotary evaporation afforded the desired compound **3h**. Recrystallization from ethanol gave **3h** (2.0 g, 86%) as white needles (m.p. = 163–164°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, 3 H, J = 7.1 Hz), 3.76 (s, 3 H), 4.14 (s, 2 H), 4.26 (q, 2 H, J = 7.1 Hz), 7.11–7.20 (m, 2 H, Ar, H-4′, H-6′), 7.34–7.39 (m, 1 H, Ar, H-4′, H-7′), 7.57–7.63 (m, 1 H, Ar, H-4′, H-7′), 7.91 (br s, 1 H, H-3), 11.12 (br s, 2 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5 (qt, J = 127, 2.5 Hz), 49.8 (td, J = 139, 5.6 Hz), 52.3 (q, J = 148 Hz), 60.0 (tq, J = 147, 4.5 Hz), 88.7 (d, J = 1.6 Hz, C-2), 110.3 (dd, J = 159, 6.7 Hz, C-5′, C-6′), 117.6 (dd, J = 159, 6.7 Hz, C-5′, C-6′), 121.5 (dd, J = 159, 7.7 Hz, C-4′, C-7′), 121.8 (dd, J = 161, 7.9 Hz, C-4′, C-7′), 131.8 (sm, C-3a′, C-7a′), 142.1 (sm, C-3a′, C-7a′), 152.1 (dd, J = 9.7, 3.0 Hz, C-2′), 153.6 (dt, J = 169, 5.2 Hz, C-3), 167.1 (sq, J = 3.2 Hz, CO), 169.8 (sm, C-1); HRMS, *m/z*: 303.1223 found for $M^{\cdot+}$ (calc for $C_{15}H_{17}N_3O_4$: 303.1219). Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.61; N, 13.86; O, 21.12. Found: C, 59.82; H, 5.82; N, 13.82; O, 21.17.

Ethyl 2-(1H-benzimidazol-2-yl)-3-(4-aminophenyl)amino Acrylate (**3i**)

A mixture of **1a** (0.96 g, 3.7 mmol) and 1,4-diaminobenzene **2i** (0.2 g, 1.86 mmol) in dry chloroform (15 mL) was refluxed for ~110 hours (monitored by TLC) with vigorous magnetic stirring. After elimination of the solvent in vacuo, the crude reaction mixture was triturated with ether (30 mL). After standing for 2 hours, the precipitated product **3i** was filtered off, washed twice successively with ether (10 mL) and acetone (5 mL), and dried in a dessicator over $CaCl_2$. Purification by recrystallization from acetone gave **3i** in 90% yield (0.54 g) as yellow needles (m.p. = 216–218°C); IR (nujol) 3360, 1625, 1610, 1505 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6/CF_3CO_2H: 1/4) δ 1.39 (q, 3 H, J = 7 Hz), 4.38 (q, 2 H, J = 7 Hz), 7.30–7.33 (m, 4 H, Ar), 7.43–7.46 (m, 3 H, Ar), 7.50–7.53 (d, J = 8.5 Hz, H-4′, H-7′), 8.41 (d, 1 H, J = 14.4 Hz, H-3), 10.59 (br s, 4H, NH); ^{13}C NMR (75 MHz, C_6D_6/CF_3CO_2H: 1/4) δ 12.8 (qt, J = 128, 2.8 Hz), 63.6 (tq, J = 155, 4.3 Hz), 86.4 (d, J = 1.8 Hz, C-2), 112.6 (dd, J = 160 Hz, C-5′, C-6′), 116.4 (dd, J = 158 Hz, C-5′, C-6′), 120.2–124.8–126.2–126.3–129.5 (Ar), 136.4 (sm, C-3a′, C-7a′), 139.5 (sm, C-3a′, C-7a′), 147.6 (d, J = 8 Hz, C-2′), 147.9 (dm, J = 140 Hz, C-3), 166.4 (sm, C-1); HRMS, *m/z*: 322.1428 found for $M^{\cdot+}$ (calc for $C_{18}H_{18}N_4O_2$: 322.1430). Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.59; N, 17.39; O, 9.93. Found: C, 67.10; H, 5.62; N, 17.34; O, 9.94.

1,4-Bis(2-(benzoxazol-2′-yl)-2-ethoxycarbonylethenyl)aminobenzene (**4a**)

This compound was prepared according to the method used for the synthesis of **3i** from the respective ethyl 2-(benzoxazol-2-yl)-3-dimethylamino acrylate **1b** (1.0 g, 3.84 mmol) and 1,4-diaminobenzene **2i** (0.21 g, 1.92 mmol), with a reaction time of ~240 hours in 85% yield (0.87 g) as pale yellow needles (m.p. = 242–244°C from acetone); IR (nujol) 3365, 1680, 1600, 1505 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/CF_3CO_2H: 95/5) δ 1.42 (2 × t, 6 H, J = 7 Hz), 4.39 (2 × q, 4 H, J = 7 Hz), 7.29–7.50 (m, 8 H, Ar), 7.55–7.62 (m, 4 H, Ar), 8.56 (d, 2 H, J = 12 Hz, H-3), 12.00 (br s, 2 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$/CF_3CO_2H: 95/5) δ 14.6 (qt, J = 128, 2.4 Hz), 60.5 (tq, J = 147, 3.6 Hz), 90.8 (C-2), 110.7 (ddm, J = 170, 8.2 Hz, C-5′, C-6′), 118.0 (ddm, J = 164, 6.5 Hz, C-5′, C-6′), 118.8 (d, J = 162 Hz, Ar), 123.7 (dd, J = 167, 7.8 Hz, C-4′, C-7′), 124.1 (dd, J = 162, 7.5 Hz, C-4′, C-7′), 136.5 (sm, C_{ipso}, Ar), 140.3 (sm, C-3a′), 146.4 (d, J = 172 Hz, C-3), 149.0 (d, J = 7.2 Hz, C-7a′), 162.7 (d, J = 10.9 Hz, C-2′), 165.2 (sm, C-1); HRMS, *m/z*: 538.1858 found for $M^{\cdot+}$ (calc for $C_{30}H_{26}N_4O_6$: 538.1852). Anal. Calcd for $C_{30}H_{26}N_4O_6$: C, 66.91; H, 4.83; N, 10.40; O, 17.84. Found: C, 66.63; H, 4.90; N, 10.38; O, 18.09.

1,2-Bis(2-(benzoxazol-2′-yl)-2-ethoxycarbonylethenyl)amino Ethane (**4b**)

This compound was prepared in the same way from ethyl 2-(benzoxazol-2-yl)-3-dimethylamino acrylate **1b** (1.0 g, 3.84 mmol) and ethylenediamine **2j** (0.12 g, 1.92 mmol) with a reaction time of 48 hours in 93% yield (0.87 g) as white needles (m.p. = 208–210°C from chloroform); IR (nujol) 3370, 1680, 1620, 1610, 1510 cm^{-1}; H NMR (300 MHz, $CDCl_3$/CF_3CO_2H: 95/5) δ 1.20 (t, 6 H, J = 7 Hz), 4.10 (br s, 4 H), 4.34 (q, 4 H, J = 7 Hz), 7.10–7.40 (m, 4 H, Ar), 7.40–7.47 (m, 4 H, Ar), 8.5 (br d, 2 H, J = 12.8 Hz, H-3), 9.9 (br s, 2 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$/CF_3CO_2H: 95/5) δ 13.7 (qt, J = 128 Hz), 50.4 (t, J = 138 Hz), 62.8 (tq, J = 154 Hz), 83.4 (C-2), 111.1 (dm, J = 176 Hz, C-5′, C-6′), 113.8 (dm, J = 164 Hz, C-5′, C-6′), 127.0 (dd, J = 186 Hz, C-4′, C-7′), 127.2 (dd, J = 180 Hz, C-4′, C-7′), 128.2 (sm, C-3a′), 146.6 (sm, C-7a′), 160.0 (d, J = 171 Hz, C-3), 163.5 (C-2′), 165.1 (sm, C-1); HRMS, *m/z*: 490.1856 found for $M^{\cdot+}$ (calc for $C_{26}H_{26}N_4O_6$ 490.1822). Anal. Calcd for $C_{26}H_{26}N_4O_6$: C, 63.67; H, 5.30; N, 11.42; O, 19.59. Found: C, 63.77; H, 5.28; N, 11.62; O, 19.33.

1,4-Bis(2-(benzothiazol-2′-yl)-2-ethoxycarbonylethenyl)amino Benzene (**4c**)

This compound was prepared according to the above method from ethyl 2-(benzothiazol-2-yl)-3-dimeth-

ylamino acrylate **1c** (1.06 g, 3.84 mmol) and 1,4-diaminobenzene **2i** (0.21 g, 1.92 mmol) with a reaction time of 96 hours in 80% yield (0.88 g) as pale yellow needles (m.p. > 260°C from acetone); IR (nujol) 3360, 1660, 1620, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CF_3CO_2H$: 95/5) δ 1.55 (t, 6 H, J = 7 Hz), 4.60 (q, 4 H, J = 7 Hz), 7.52 (s, 4 H, Ar), 7.55–7.64 (dd, 2 H, J = 7.8 Hz, H-5′, H-6′), 7.65–7.72 (dd, 2 H, J = 7.9 Hz, H-5′, H-6′), 7.80–7.84 (d, 2 H, J = 8.1 Hz, H-4′, H-7′), 7.88–7.92 (d, 2 H, J = 8.1 Hz, H-4′, H-7′), 8.8 (d, 2 H, J = 14 Hz, H-3), 9.85 (br s, 2 H, NH); ^{13}C NMR (75 MHz, $CDCl_3/CF_3CO_2H$: 95/5) δ 13.8 (qt, J = 128 Hz), 63.8 (tq, J = 148, 5 Hz), 92.8 (C-2), 115.9 (dd, J = 170, 7.5 Hz, C-5′, C-6′), 122.2 (dd, J = 165, 8.1 Hz, C-5′, C-6′), 120.5 (d, J = 165 Hz, Ar), 127.2 (sm, C-3a′, C-7a′), 127.4 (dd, J = 155, 7.5 Hz, C-4′, C-7′), 129.5 (dd, J = 159, 7.9 Hz, C-4′, C-7′), 136.5 (sm, C_{ipso}, Ar), 138.9 (sm, C-3a′, C-7a′), 150.4 (d, J = 168 Hz, C-3), 165.5 (d, J = 10 Hz, C-2′), 170.5 (sm, C-1); HRMS, *m/z*: 570.1419 found for $M^{+\cdot}$ (calc for $C_{30}H_{26}N_4O_4S_2$: 570.1395). Anal. Calcd for $C_{30}H_{26}N_4O_4S_2$: C, 63.15; H, 4.56; N, 9.82; O, 11.22; S, 11.22. Found: C, 63.11; H, 4.56; N, 9.77; O, 11.18; S, 11.38.

1,2-Bis-(2-(benzothiazol-2′-yl)-2-ethoxycarbonyl-ethenyl)amino Ethane (**4d**)

This compound was prepared in the same way from ethyl 2-(benzothiazol-2-yl)-3-dimethylamino acrylate **1c** (1.06 g, 3.84 mmol) and ethylenediamine **2j** (0.12 g, 1.92 mmol) with a reaction time of 48 hours in 63% yield (0.63 g) as white needles (m.p. = 200–202°C from acetone); IR (nujol) 3350, 1660, 1620, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CF_3CO_2H$: 95/5) δ 1.43 (t, 6 H, J = 7 Hz), 4.01 (br s, 4 H), 4.48 (q, 4 H, J = 7 Hz), 7.52–7.57 (dd, 4 H, J = 7.4 Hz, H-5′, H-6′), 7.62–7.67 (dd, 4 H, J = 7.8 Hz, H-5′, H-6′), 7.77–7.80 (d, 2 H, J = 8.1 Hz, H-4′, H-7′), 7.83–7.87 (d, 2 H, J = 7.9 Hz, H-4′, H-7′), 8.37 (d, 2 H, J = 14.3 Hz, H-3), 9.80 (br s, 2 H, NH); ^{13}C NMR (75 MHz, $CDCl_3/CF_3CO_2H$: 95/5) δ 13.6 (qt, J = 128 Hz), 50.5 (t, J = 145 Hz), 63.6 (tq, J = 150 Hz), 90.6 (C-2), 115.6 (dd, J = 169, 7.8 Hz, C-5′, C-6′), 122.1 (dd, J = 167, 9 Hz, C-5′, C-6′), 126.8 (dd, J = 163 Hz, C-4′, C-7′), 129.1 (dd, J = 163 Hz, C-4′, C-7′), 127.3 (sm, C-3a′, C-7a′), 138.7 (sm, C-3a′, C-7a′), 156.0 (d, J = 161 Hz, C-3), 166.0 (d, J = 9.6 Hz, C-2′), 171.3 (sm, C-1); HRMS, *m/z*: 522.1371 found for $M^{+\cdot}$ (calc for $C_{26}H_{26}N_4O_4S_2$: 522.1395). Anal. Calcd for $C_{26}H_{26}N_4O_4S_2$: C, 59.77; H, 4.98; N, 10.72; O, 12.26; S, 12.26. Found: C, 59.83; H, 5.03; N, 10.77; O, 12.30; S, 12.07.

1,5-Bis(2-(benzothiazol-2′-yl)-2-ethoxycarbonyl-ethenyl)amino Napththalene (**4e**)

This compound was prepared according to the same method from ethyl 2-(benzothiazol-2-yl)-3-dimethylamino acrylate **1c** (1.06 g, 3.84 mmol) and 1,5-diaminonaphthalene **2k** (0.30 g, 1.92 mmol) with a reaction time of ~168 hours in 58% yield (0.69 g) as yellow needles (m.p. = 257–259°C from acetone); IR (nujol) 3360, 1670, 1600, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CF_3CO_2H$: 95/5) δ 1.61 (t, 6 H, J = 7.1 Hz), 4.67 (q, 4 H, J = 7.1 Hz), 7.55–7.60 (dd, 2 H, J = 7.8 Hz, H-5′, H-6′), 7.64–7.70 (dd, 2 H, J = 7.8 Hz, H-5′, H-6′), 7.73–7.84 (m, 6 H, Ar), 7.89–7.92 (d, 2 H, J = 7.9 Hz, H-4′, H-7′), 8.01–8.04 (d, 2 H, J = 7.6 Hz, H-4′, H-7′), 8.90 (d, 2 H, J = 13.4 Hz, H-3), 11.4 (br s, 2 H, NH); ^{13}C NMR (75 MHz, $CDCl_3/CF_3CO_2H$: 95/5) δ 14.0 (qt, J = 129, 2.5 Hz), 66.3 (tq, J = 193, 4.5 Hz), 93.3 (t, J = 1.5 Hz, C-2), 116.0–117.9–120.4–122.2–126.8–127.3–127.4–127.8–129.5–134.9–139.0 (Ar), 153.1 (d, J = 169 Hz, C-3), 165.9 (d, J = 8.7 Hz, C-2′), 170.4 (sm, C-1); HRMS, *m/z*: 620.1570 found for $M^{+\cdot}$ (calc for $C_{34}H_{28}N_4O_4S_2$: 620.1552). Anal. Calcd for $C_{34}H_{28}N_4O_4S_2$: C, 65.80; H, 4.51; N, 9.03; O, 10.32; S, 10.32. Found: C, 65.86; H, 4.32; N, 9.09; O, 10.39; S, 10.34.

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