Synthesis of 3-Aminoalkyl-2-arylaminoquiazolin-4(3*H*)-ones and 3,3'-Disubstituted Bis-2-arylaminoquinazolin-4(3*H*)-ones *via* Reactions of 1-Aryl-3-(2-ethoxycarbonylphenyl)carbodiimides with Diamines

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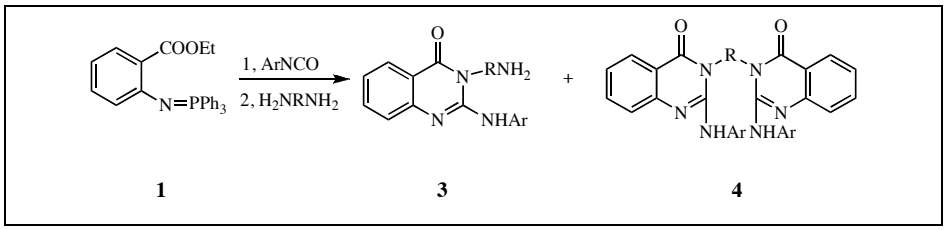

1-Aryl-3-(2-ethoxycarbonylphenyl)carbodiimides **2**, obtained from aza-Wittig reactions of iminophosphorane **1** with aryl isocyanates, reacted with primary diamines in 1:1 and 2:1 molar ratio under mild conditions to give selectively the regioisomers 3-aminoalkyl-2-arylaminoquinazolin-4(3*H*)-ones **3** and 3,3'-disubstituted bis-2-arylaminoquinazolin-4(3*H*)-ones **4** in good yields, respectively. To fully characterize the regioselectivity of aza-Wittig reactions of 1-aryl-3-(2-ethoxycarbonylphenyl)carbo-diimides with primary diamines, crystals of **4e** were obtained, and its structure was determined by X-ray crystallography.

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INTRODUCTION

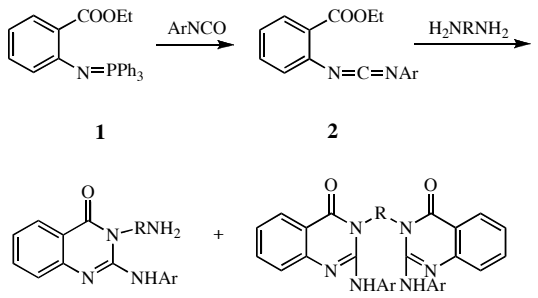
The synthesis of quinazoline-4(3*H*)-one derivatives has been the focus of great interest recently [1-4]. This is due, in part, to the broad spectrum of their biological properties. Some of these activities include antimicrobial [5,6], anti-inflammatory [7,8], antifungal [9], anticancer [10], antidiabetic [11], anticonvulsant [12], analgesic [13], antibacterial [14], protein tyrosine kinase inhibitors [15], EGFR inhibitors [16], PDGFR phosphorylation inhibitors [17], CNS depressants [18], antitumor activity [19] and AMPA receptor-antagonistic properties [20,21]. Furthermore, the heterocyclic core constitutes more than 40 alkaloids [22] isolated from natural products, and some show interesting biological profiles such as antimalarial [23] and diuretic [24] properties. The ranges of biological activities, the extensive existence in nature products and characteristic chemical structures have made synthetic studies of quinazoline-4(3*H*)-one very attractive.

In accordance with the significance of quinazolin-4(3*H*)-ones, numerous synthetic methods have been developed for the construction of these kinds of fused heterocycles: (a) The most common synthetic method to 2,3-substituted quinazolin-4(3*H*)-ones are based on the acylation-cyclisation of anthranilic acid or its derivative and proceed usually *via* an *o*-aminobenzamide intermediate [25]; (b) Usually, 4*H*-benzo[*d*][1,3]oxazin-4-ones are valuable starting materials for the synthesis of variety of 2,3-disubstituted quinazolin-4(3*H*)-ones [26]; (c) Initial synthesis of 3-substituted 2-thio-2,3-dihydro-quinazolin-4(1*H*)-one from methoxyaniline or methyl-anthranilate *via* thiourea intermediate followed by hydrazinolysis or aminolysis affords 2,3-substituted quinazolin-4(3*H*)-one [27]; (d) Recently, synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones *via* a one-pot, three component reaction of isatoic anhydride and an orthoester with ammonium acetate or a primary amine catalyzed by silica sulfuric acid under solvent-free conditions have been developed [28]. Unfortunately, some of these reported methods suffer from drawbacks like forcing conditions, long reaction times, unsatisfactory yields, cumbersome product isolation procedures and synthesis in multi-step synthetic programs.

Keeping in view the potential biological activities of 2,3-disubstituted quinazolin-4(3*H*)-ones, many of them have been synthesized. Over the past 20 years, the aza-Wittig reactions of iminophosphoranes have attracted increasing interest in view of their utility in the synthesis of nitrogen-containing heterocyclic compounds [29]. Annelation of ring systems with N-heterocycles by means of an aza-Wittig reaction has been widely utilized because

of the availability of functionalized iminophosphoranes. However, the chemistry of tandem aza-Wittig reactions of iminophosphorane with aryl isocyanates, and primary diamines has received less attention. Although there are numerous methods available for the synthesis of quinazolinones and their derivatives, until now, no general and simple approach to the synthesis of 3-aminoalkyl-2-arylaminoquinazolin-4(3*H*)-one **3** and 3,3'-disubstituted bis-2-arylaminoquinazolin-4(3*H*)-one **4**.

Scheme 1



In connection with our ongoing heterocyclic synthesis and drug discovery project [30], we have focused on the synthesis of quinazolinones, thienopyrimidinones and imidazaolinones by employing aza-Wittig reaction of α or β-ethoxycarbonyl iminophosphorane with aromatic isocyanate and subsequent reaction with various nucleophiles under mild conditions. Herein, we wish to report a fundamental approach to the synthesis of novel 3-aminoalkyl-2-arylaminoquinazolin-4(3*H*)-one **3** and 3,3'-disubstituted bis-2-arylaminoquinazolin-4(3*H*)-ones **4** (Scheme 1).

RESULTS AND DISCUSSION

Iminophosphorane **1**, easily prepared from ethyl β-aminobenzoate according to the method described in our previous work [31], reacted with aromatic isocyanates to give 1-aryl-3-(2-ethoxycarbonylphenyl) carbodiimides **2** without needing to remove the byproduct Ph_3PO. 1-Aryl-3-(2-ethoxycarbonylphenyl) carbodiimides **2** were allowed to react with primary diamines in 1:1 and 2:1 molar ratio, either in absent of or in the presence of sodium ethoxide, to generate selectively the regioisomers 3-aminoalkyl-2-arylaminoquinazolin-4(3*H*)-ones **3** and 3,3'-disubstituted bis-2-arylaminoquinazolin-4(3*H*)-ones **4** in same satisfactory yields, respectively. The results are listed in Table 1.

The solitary formation of **3** and **4** can be rationalized in terms of an initial nucleophilic addition in 1:1 and 2:1 molar ratio to give the guanidine intermediate **5** and **6** respectively, which cyclized to give **3** and **4** across the alkylamino group rather than arylamino one. This is probably due to the geometry of intermediates **5** and **6** that are mainly in the *E*-form, which is suitable for the alkylamino group to cyclize (Figure 1).

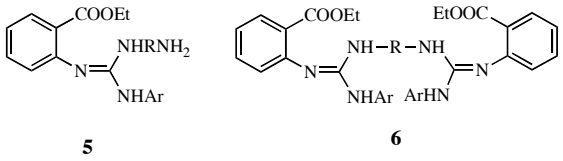


Figure 1

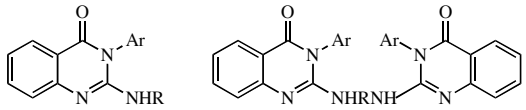


Figure 2

The fact that base catalyst has no influence on the reaction selectivity is perhaps attributed to the higher nucleophilic activity of alkylamino group than the arylamino one in the intermediates **5** and **6** for which there would not be time for base catalyst to react with the arylamino group followed by nucleophilic addition to the carbonyl group to give the regioisomers **7** and **8** (Figure 2).

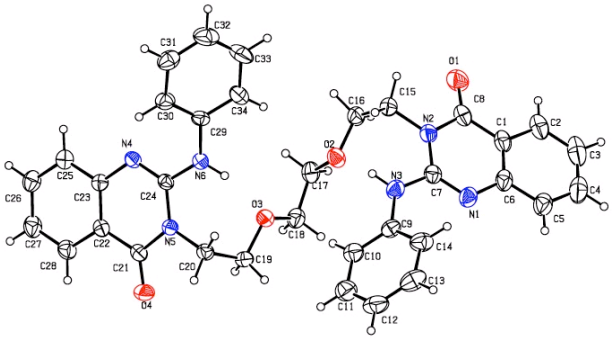


Figure 3. X-ray molecular structure of **4e**.

The structures of **3** and **4** are deduced from their ^{1}H NMR and IR data and/or X-ray analysis. For example, the ^{1}H NMR analysis in **3e** shows the signals of NH at 11.02 ppm as a sharp absorption, NH_2 at 1.84 ppm as wide absorption, NCH_2 at 4.29 ppm as triplet and CH_2N at 3.29 ppm as triplet, which strongly suggests the existence of NH and $NCH_2CH_2NH_2$ groups in **3e**. The ^{1}H NMR analyses in **4e** shows signals of NCH_2 at 4.28 ppm as triplet, 3.92 ppm as triplet and 3.78 ppm as singlet, which strongly suggests the existence of the $NCH_2CH_2OCH_2$-

$CH_2OCH_2CH_2N$ group in **4e**. It should also be noted here that NH signals or NH_2 signals were only observed in the ^1H NMR spectra of some of **3** and **4** whereas others missed their NH signals or NH_2 signals in ^1H NMR spectra. Such cases occur in of the analogous heterocycles and other hetercycles bearing phenol moieties [32]. The IR analysis of **3** and **4** all shows strange absorption bands in the range of 1650–1686 cm^{-1} belonging to C=O stretching vibration. The MS of **3** and **4** all show M^+ peaks with low to moderate abundance. Moreover, the structure of 3,3'-disubstituted bis-2-arylamino quinazolin-4(3*H*)-one **4e** was also confirmed by X-ray diffraction analysis (Figure 3) [33].

Table 1

Preparation of 3-aminoalkyl-2-arylaminoquinazolin-4(3*H*)-one **3** and 3,3'-disubstituted bis-2-arylaminoquinazolin-4(3*H*)-ones **4**[a].

Entry	Ar	R	Time (h)	Yield (%)[b]
3a	Ph	$-CH_2CH_2-$	6	80
3b	Ph	$-CH_2CH_2CH_2-$	8	65
3c	4-Cl-Ph	$-CH_2CH_2-$	6	82
3d	Cl-Ph	$-CH_2CH(CH_3)-$	10	80
3e	4-F-Ph	$-CH_2CH_2-$	6	85
4a	Ph	$-CH_2CH_2-$	6	85
4b	Ph	$-CH_2CH(CH_3)-$	10	78
4c	Ph	$-CH_2CH_2CH_2-$	8	80
4d	Ph	$-CH_2CH_2CH_2CH_2-$	12	55
4e	Ph		12	75
4f	4-Cl-Ph	$-CH_2CH_2-$	6	88
4g	4-Cl-Ph	$-CH_2CH_2CH_2-$	8	82
4h	4-Cl-Ph		12	78
4i	4-F-Ph	$-CH_2CH_2-$	6	89
4j	4-F-Ph	$-CH_2CH(CH_3)-$	10	78
4k	4-F-Ph	$-CH_2CH_2CH_2-$	8	85
4l	4-F-Ph		12	80

[a]The reaction was carried out according to general experimental procedure. [b]Isolated yields based on iminophosphorane **1**.

In conclusion, we have developed an efficient synthesis of novel 3,3'-disubstituted bis-2-arylaminoquinazolin-4(3*H*)-ones *via* a tandem aza-Wittig reaction of 1-aryl-3-(2-ethoxycarbonylphenyl)carbodiimides with primary diamines. Due to the mild reaction conditions, high selectivity, good yields, easily accessible starting materials and straightforward product isolation, we think that this synthetic method discussed here provided us a efficient approach to synthesize 3-aminoalkyl-2-aryl-aminoquinazolin-4(3*H*)-ones and 3,3'-disubstituted bis-2-arylaminoquinazolin-4(3*H*)-ones.

EXPERIMENTAL

Melting points were recorded on X-4 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer Spectrum One spectrophotometer using KBr optics. ^1H NMR spectra were recorded with a Varian mercury 400 spectrometer using TMS as internal standard. Mass spectra were recorded on a Finnigan Trace mass spectrometer. Elemental analyses were performed on a Perkin-Elmer CHN 2400 elementary analysis instrument. X-ray data for **4e** were collected using a Bruker Smart Apex CCD area detector diffractometer and Mo-Ka radiation.

Synthesis of 3-Aminoalkyl-2-arylaminoquinazolin-4(3*H*)-one 3; General Procedure. To a solution of iminophosphorane 1 (1.28 g, 3.0 mmol) in anhydrous THF (10 mL) was added aromatic isocyanate (3 mmol) at room temperature. The reaction mixture was left unstirred for 6-12 h at 0-5 °C to generate carbodiimides **2**, which were used directly without further purification.

To a solution of primary diamines (3 mmol) in THF (10 mL) was dropwise added above prepared solution of **2**. After the reaction mixture was stirred for 6–12h at room temperature, the solvent was removed under reduced pressure and the residue was recrystallized from CH_2Cl_2/CH_3OH (1:1/v:v) to give 3-aminoalkyl-2-arylaminoquinazolin-4(3*H*)-one **3**.

Synthesis of 3,3'-Disubstituted Bis-2-arylaminoquinazolin-4(3*H*)-one 4; General Procedure. To the solution of **2** prepared above was added a solution of primary diamines (1.5 mmol) in THF (10 mL). After the reaction mixture was stirred 6–12h at room temperature, the solvent was removed under reduced pressure and the residue was recrystallized from CH_2Cl_2/CH_3OH (1:1/v:v) to give 3, 3'-disubstituted bis-2-arylaminoquinazolin-4(3*H*)-one **4**.

3a: White crystals; mp 160–161 °C. IR (KBr): 3379 (N–H), 1665 (C=O), 1603 (C=N), 1345 (C–N) cm^{-1}. ^1HNMR (400 MHz, $CDCl_3$): δ = 11.12 (s, 1H, NH), 7.02–8.13 (m, 9H, Ar-H), 4.23 (t, 2H, J = 5.6 Hz, NCH_2), 3.20 (m, 2H, CH_2N), 1.79 (s, 2H, NH_2). MS: m/z (%) = 280.4 (25) [M^+], 262.6 (20), 236.5 (100), 144.9 (29), 119.1 (22), 89.9 (51), 77.1 (84), 65.2 (25). *Anal*. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.68; H, 5.73; N, 20.02.

3b: White crystals; mp 143–145 °C. IR (KBr): 3366 (N–H), 1664 (C=O), 1609 (C=N), 1345 (C–N) cm^{-1}. ^1HNMR (400 MHz, $CDCl_3$): δ = 7.03–8.15 (m,9H, Ar–H), 4.30 (t, J = 4.1Hz, 2H, NCH_2), 2.84 (m, 2H, CH_2N), 2.09 (m, 2H, CCH_2C), 1.56 (s, 2H, NH_2). MS: m/z (%) = 294.0 (51) [M^+], 276.1 (30), 250.0 (55), 235.6 (100), 220.6 (85), 201.8 (88), 144.9 (28), 118.9 (28), 92.9 (35), 76.6 (47), 64.9 (13). *Anal*. Calcd for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.17; H, 6.20; N, 19.08.

3c: White crystals; mp 151–153 °C. IR (KBr): 3384 (N–H), 1667 (C=O), 1602 (C=N), 1343 (C–N) cm^{-1}. ^1HNMR (400 MHz, $CDCl_3$): δ = 7.18–8.12 (m, 8H, Ar–H), 4.23 (t, J = 3.6 Hz, 2H, NCH_2), 3.23 (m, 2H, CH_2N), 1.86 (s, 2H, NH_2). MS: m/z (%) = 313.8 (18) [M^+], 297.0 (40), 272.3 (100), 255.0 (17), 235.1 (8), 145.2 (14), 118.8 (14), 91.1 (13). *Anal*. Calcd for $C_{16}H_{15}N_4OCl$: C, 61.05; H, 4.80; N, 17.80. Found: C, 61.23; H, 4.80; N, 17.74.

3d: White crystals; mp 137–139 °C. IR (KBr): 3452 (N–H), 1666 (C=O), 1604 (C=N), 1344 (C–N) cm^{-1}. ^1HNMR (400 MHz, $CDCl_3$): δ = 7.14–7.98 (m, 8H, Ar–H), 4.38(d, J = 6.4 Hz, 2H, NCH_2), 2.34 (m, 1H, CH), 1.77 (d, J = 3.5 Hz 3H, CH_3). MS: m/z (%) = 327.3 (7) [M^+], 309.6 (30), 297.7 (13), 269.7 (89), 254.4 (55), 235.2 (26), 220.3 (22), 143.6 (39), 118.8 (45), 92.6 (97), 75.8 (36), 62.3 (100). *Anal*. Calcd for $C_{17}H_{17}N_4OCl$: C, 62.10; H, 5.21; N, 17.04. Found: C, 62.21; H, 5.21; N, 16.99.

3e: White crystals; mp 164–165 °C. IR (KBr): 3387 (N–H), 1666 (C=O), 1607 (C=N), 1346 (C–N) cm^{-1}. ^1HNMR (400 MHz, $CDCl_3$): δ = 11.02 (s, 1H, NH), 7.01–8.14 (m, 8H, Ar–H), 4.29 (t, J = 4.4 H, NCH_2), 3.29 (m, 2H, CH_2N), 1.84 (s, 2H, NH_2). MS: m/z (%) = 298.2 (29) [M^+], 280.1 (37), 256.4 (100), 239.2

(84), 183.9 (19), 144.9 (25), 109.0 (31), 89.9 (28), 75.1 (7). *Anal*. Calcd for $C_{16}H_{15}N_4OF$: C, 64.42; H, 5.07; N, 18.78. Found: C, 64.50; H, 5.08; N, 18.73.

4a: White crystals; mp 249–250 °C. IR(KBr): 3425 (N–H), 1664 (C=O), 1609 (C=N), 1343 (C–N) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.97 (s, 2H, NH), 6.75–8.20 (m, 18H, Ar–H), 4.56 (s, 4H, 2×NCH_2CH_2N). MS: m/z (%) = 500.3 (53) [M^+], 262.0 (100), 238.4 (42), 221.0 (51), 165.7 (9), 144.9 (8), 118.9 (11), 89.6 (28), 76.9 (23), 62.8 (11). *Anal*. Calcd for $C_{30}H_{24}N_6O_2$: C, 71.99; H, 4.83; N, 16.79. Found: C, 72.07; H, 4.82; N, 16.81.

4b: White crystals; mp 160–162 °C. IR (KBr): 3442 (N–H), 1682 (C=O), 1607 (C=N), 1364 (C–N) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 9.23 (s, 2H, NH), 6.80–8.14 (m, 18H, Ar–H), 4.78 (m, 1H, CHN), 4.36 (d, J = 13.2 Hz, 2H, CH_2), 1.67 (d, J = 3.3 Hz, 3H, CH_3). MS: m/z (%) = 514 (31) [M^+], 275 (100), 237 (79), 220 (23), 144 (6), 117 (14), 91 (16), 77 (17). *Anal*. Calcd for $C_{31}H_{26}N_6O_2$: C, 72.36; H, 5.09; N, 16.33. Found: C, 72.34; H, 5.11; N, 16.33.

4c: White crystals; mp 229–231 °C. IR (KBr): 3329 (N–H), 1650 (C=O), 1610 (C=N), 1345 (C–N) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.67 (s, 2H, NH), 7.14–7.98 (m,18H, Ar–H), 4.41 (t, J = 7.2 Hz, 4H, 2×NCH_2), 2.12 (m, 2H, CCH_2C). MS: m/z (%) = 514 (63) [M^+], 352 (27), 276 (80), 265 (54), 237 (100), 145 (13), 117 (18), 91 (14), 76 (7). *Anal*. Calcd for $C_{31}H_{26}N_6O_2$: C, 72.36; H, 5.09; N, 16.33. Found: C, 72.26; H, 5.10; N, 16.37.

4d: White crystals; mp 194–196 °C. IR (KBr): 3343 (N–H), 1668 (C=O), 1608 (C=N), 1343 (C–N) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 6.67–8.12 (m, 18H, Ar–H), 4.47 (t, J = 4.4 Hz, 4H, NCH_2), 2.03 (t, J = 3.6 Hz, 4H, CCH_2CH_2C). MS: m/z (%) = 528.2 (65) [M^+], 366.9 (16), 278.2 (38), 235.9 (100), 90.0 (15), 77.2 (16), 65.2 (4). *Anal*. Calcd for $C_{32}H_{28}N_6O_2$: C, 72.71; H, 5.34; N, 15.90. Found: C, 72.85; H, 5.33; N, 15.94.

4e: White crystals; mp 132–133 °C. IR (KBr): 3349 (N–H), 1683 (C=O), 1608 (C=N), 1360 (C–N) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 6.91–8.12 (18H, Ar–H), 4.28 (t, J = 4.4 Hz, 4H, N-CH_2), 3.92 (t, J = 4.0 Hz, 4H, 2×CH_2O), 3.78 (s, 4H, OCH_2CH_2O). MS: m/z (%) = 588 (20) [M^+], 352 (4), 297 (7), 238 (100), 221 (24), 145 (12), 118 (21), 77 (15), 64 (11). *Anal*. Calcd for $C_{34}H_{32}N_6O_4$: C, 69.37; H, 5.48; N, 14.28. Found: C, 69.46; H, 5.49; N, 14.22.

4f: White crystals; mp 240–242 °C. IR (KBr): 3327 (N–H), 1655 (C=O), 1605 (C=N), 1365 (C–N) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 9.64 (s, 2H, NH), 6.59–7.77 (m, 16H, Ar–H), 4.68 (s, 4H, 2×NCH_2). MS: m/z (%) = 569.7 (24) [M^+], 320.2 (92), 295.6 (83), 271.2 (100), 235.3 (21), 146.5 (35), 90.8 (20), 77.0 (9). *Anal*. Calcd for $C_{30}H_{22}N_6O_2Cl_2$: C, 63.28; H, 3.89; N, 14.76. Found: C, 63.37; H, 3.88; N, 14.80.

4g: White crystals; mp 225–227 °C. IR (KBr): 3399 (N–H), 1667 (C=O), 1613 (C=N), 1359 (C–N) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.17–8.10 (m, 16H, Ar–H), 4.36 (t, J = 7.0 Hz, 4H, 2×NCH_2), 2.34 (m, 2H, CCH_2C). MS: m/z (%) = 583.0 (27) [M^+], 420.2 (18), 346.5 (20), 297.4 (59), 270.4 (100), 254.7 (43), 235.3 (15), 144.6 (18), 120.0 (17), 91.9 (16). *Anal*. Calcd for $C_{31}H_{24}N_6O_2Cl_2$: C, 63.81; H, 4.15; N, 14.40. Found: C, 64.01; H, 4.14; N, 14.43.

4h: White crystals; mp 149–151 °C. IR (KBr): 3325 (N–H), 1681 (C=O), 1606 (C=N), 1339(C–N) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.08–8.20 (m, 16H, Ar–H), 4.25 (t, J = 4.4 Hz, 4H, 2×NCH_2), 3.90 (t, J = 4.5 Hz, 4H, 2×CH_2O), 3.80 (s, 4H, OCH_2CH_2O). MS: m/z (%) = 657 (22) [M^+], 353 (15), 296 (52), 271 (100), 236 (59), 221 (23), 146 (11), 118 (14), 91 (13), 76 (8). *Anal*. Calcd for $C_{34}H_{30}N_6O_4Cl_2$: C, 62.10; H, 4.60; N, 12.78. Found: C, 62.01; H, 4.61; N, 12.75.

4i: White crystals; mp 235–237 °C. IR (KBr): 3207 (N–H), 1686 (C=O), 1612 (C=N), 1358 (C–N) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 9.06 (s, 2H, NH), 6.81–8.18 (m, 16H, Ar–H), 4.53 (s, 4H, 2×NCH_2). MS: m/z (%) = 536.6 (25) [M^+], 279.7 (100), 255.3 (95), 238.8 (17), 145.0 (10), 118.9 (18), 91.0 (14), 69.8 (6). *Anal*. Calcd for $C_{30}H_{22}N_6O_2F_2$: C, 67.16; H, 4.13; N, 15.66. Found: C, 67.33; H, 4.12; N, 15.70.

4j: White crystals; mp 215–217 °C. IR (KBr): 3345 (N–H), 1668 (C=O), 1608 (C=N), 1346 (C–N) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 9.22 (s, 2H, NH), 6.75–8.13 (m, 16H, Ar–H), 4.78 (m, 1H, CH), 4.29 (d, J = 1.2 Hz, 2H, NCH_2), 1.27 (d, J = 9.6 Hz, 3H, CH_3). MS: m/z (%) = 550.2 (26) [M^+], 389.1 (20), 294.0 (39), 279.9 (57), 255.5 (92), 238.7 (100), 200.0 (17), 144.8 (26), 118.8 (14), 89.5 (59), 74.1 (14), 62.9 (9). *Anal*. Calcd for $C_{31}H_{24}N_6O_2F_2$: C, 67.63; H, 4.39; N, 15.26. Found: C, 67.47; H, 4.40; N, 15.31.

4k: White crystals; mp 239–241 °C. IR (KBr): 3338 (N–H), 1668 (C=O), 1610 (C=N), 1348 (C–N) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ =: 6.84–8.10 (m, 16H, Ar–H), 4.39 (t, J = 8.0 Hz, 4H, 2×NCH_2), 2.35 (m, 2H, CCH_2C). MS: m/z (%) = 550.0 (25) [M^+], 389.4 (20), 294.2 (100), 281.6 (65), 253.3 (96), 239.6 (95), 119.4 (65), 91.6 (89), 77.0 (33), 63.7 (26). *Anal*. Calcd for $C_{31}H_{24}N_6O_2F_2$: C, 67.63; H, 4.39; N, 15.26. Found: C, 67.45; H, 4.39; N, 15.30.

4l: White crystals; mp 141–143 °C. IR (KBr): 3390 (N–H), 1665 (C=O), 1610 (C=N), 1345 (C–N) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 6.85–8.12 (m, 16H, Ar–H), 4.25 (t, J = 4.4 Hz, 4H, 2×NCH_2), 3.90 (t, J = 4.4 Hz, 4H, 2×CH_2O), 3.80 (s, 4H, OCH_2CH_2O). MS: m/z (%) = 624.8 (25) [M^+], 298.5 (7), 280.1 (51), 256.2 (100), 239.0 (90), 213.0 (29), 145.1 (15), 120.1 (19), 89.7 (28), 74.9 (17). *Anal*. Calcd for $C_{34}H_{30}N_6O_4F$: C, 65.38; H, 4.84; N, 13.45. Found: C, 65.18; H, 4.85; N, 13.47.

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[33] The structure of **4e,** which was recrystallized from MeOH, was determined by single-crystal X-ray diffraction analysis. Data collection: SMART (Bruker, **2001**); cell refinement: SAINT (Bruker, **2001**); data reduction: SAINT; program(s) used to solve structure: SHELXS97 (Sheldrick, **1997**); program(s) used to refine structure: SHELXL97 (Sheldrick, **1997**); molecular graphics: PLATON (Spek, **2003**). Crystal data: C34H32N6O4, M = 558.66, Monoclinic, P2 (1)/c, a = 15.822(2) Å, b = 8.0024(7) Å, c = 23.7333(14) Å, α = 90°, β = 93.993(1) °, γ = 90°, V = 2997.6(5) Å3, Z = 4, Dcalcd = 1.304 g/cm3, 13493 collected reflections, 6514 independent (Rint = 0.0617), R1 = 0.0564, wR2 = 0.1171. The crystal data has been deposited in the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 668066. Copies of the data can be obtained, free of charge, via the internet (http://www.ccdc.cam. ac.uk/data_request /cif), by e-mail (data_request@ccdc.cam.ac.uk), or by fax (+44-1223-336033).