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Synthesis of Tyramine-Derived Aromatic Amides as Building Blocks for Tripodal Phosphorothioates and Star-Shaped Hexakis(aryloxy)cyclotriphosphazenes

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Abstract: Tyramine combines a nucleophilic primary amine and a phenolic hydroxyl group in one small molecule, which makes it a convenient bifunctional building block. In this work, four aromatic carboxylic acids (benzoic, 2-naphthoic, indole-2-carboxylic and nicotinic acid) were coupled chemoselectively with tyramine using EDC/HOBt in DMF at room temperature. The coupling gave the N-(4-hydroxyphenethyl)amides **1a–1d** in 86–90% yield with the phenolic OH left free. The phenol was then used as a nucleophile towards two phosphorus cores in dry THF with anhydrous cesium carbonate as the base. With phosphorothioyl trichloride, substitution of all three P–Cl bonds gave the tripodal phosphorothioate triesters **2a–2d** (85–89%). With hexachlorocyclotriphosphazene, replacement of all six chlorine atoms gave the star-shaped hexakis(aryloxy)cyclotriphosphazenes **3a–3d** (84–86%). Both phosphorylation steps proceeded at room temperature, and the products were purified by simple precipitation from dichloromethane into pentane, without chromatography. All twelve compounds were characterized by FT-IR, ^{1}H and ^{13}C NMR spectroscopy, HRMS and elemental analysis. The mild, modular route gives access to multivalent molecules that display three or six identical aryl amide units on a central phosphorus scaffold, and these compounds are now available for biological and materials evaluation.

Keywords: tyramine; amide coupling; EDC/HOBt; phosphorothioate; cyclotriphosphazene; nucleophilic substitution; cesium carbonate; multivalent scaffolds

1. Introduction

The amide bond is one of the most common linkages in drugs and natural products, and the coupling of a carboxylic acid with an amine is among the most frequently used reactions in medicinal chemistry [1–3]. Carbodiimide reagents, especially water-soluble 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) used together with 1-hydroxybenzotriazole (HOBt), remain popular because they work under mild conditions, tolerate many functional groups, and give a urea by-product that is easily removed with water [1,2,4].

Tyramine, 4-(2-aminoethyl)phenol, is a biogenic amine that occurs widely in plants and foods. Its N-acyl derivatives, such as the cinnamoyltyramine alkylamides, form a family of natural products with reported antimicrobial, antioxidant and immunomodulatory properties [5,6]. From a synthetic point of view, tyramine is attractive because its primary amine and its phenol differ strongly in nucleophilicity. The amine can therefore be acylated selectively, and the phenol stays available for a second, independent transformation. The aromatic acids chosen here bring in different pharmacophoric units. Indole-2-carboxamides, for example, are well-studied enzyme inhibitor scaffolds [7,8], and the pyridine ring of nicotinic acid adds a basic, hydrogen-bond-accepting site.

Cyclotriphosphazenes, $(NPX_2)_3$, are inorganic six-membered rings of alternating phosphorus and nitrogen atoms. Hexachlorocyclotriphosphazene ($N_3P_3Cl_6$) is a common starting material, because its six P–Cl bonds can be replaced by alkoxides, aryloxides or amines [9–14]. Fully substituted derivatives place six identical groups around

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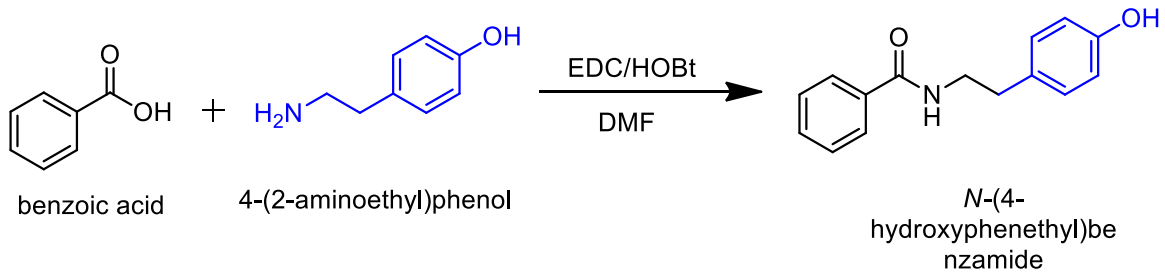
a compact, rigid core, and such multivalent cyclophosphazenes have been explored as antimicrobial and anticancer agents, drug carriers and biomaterials [9,10,15–17]. Aryloxy substitution is usually carried out with preformed sodium aryloxides, often prepared with sodium hydride, sometimes under reflux [18]. Phosphorothioyl trichloride ($PSCl_3$) offers a smaller, tripodal analogue of the same idea: replacement of its three chlorine atoms by phenoxides gives triaryl phosphorothioates with three arms on a single P=S centre.

In this work, we combined these two ideas. We first prepared four N-(4-hydroxyphenethyl)amides (**1a–1d**) by EDC/HOBt coupling, and then used their free phenol groups to build tripodal phosphorothioates (**2a–2d**) and star-shaped hexakis(aryloxy)cyclotriphosphazenes (**3a–3d**). Both phosphorylation steps were carried out at room temperature with cesium carbonate as a mild base, which avoids sodium hydride and heating [19]. Here we report the synthesis and full characterization of these twelve compounds.

2. Results and Discussion

2.1. Synthesis of the N-(4-Hydroxyphenethyl)amides 1a–1d

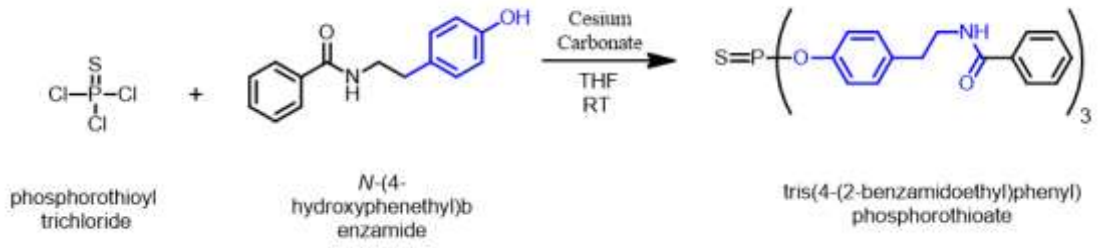
The amides **1a–1d** were prepared by coupling benzoic acid, 2-naphthoic acid, indole-2-carboxylic acid and nicotinic acid with an equimolar amount of tyramine in DMF, using EDC (1.2 equiv.) and HOBt (1.2 equiv.) at room temperature (Scheme 1). EDC activates the acid as an O-acylisourea. HOBt converts this intermediate into a benzotriazolyl active ester, which suppresses the rearrangement to the unreactive N-acylurea [1,2]. The aliphatic primary amine of tyramine reacts with the active ester much faster than the phenol does, so acylation took place only at nitrogen and the phenolic OH remained free. The reactions were complete within 3–4 h (TLC). After an aqueous work-up, which removed DMF, the water-soluble urea and excess HOBt, the amides were obtained as solids in 86–90% yield (Table 1).



Scheme **1.** Synthesis of the N-(4-hydroxyphenethyl)amides **1a–1d**, shown for **1a**. Reagents and conditions: ArCOOH (1.0 mmol), tyramine (1.0 mmol), EDC (1.2 mmol), HOBt (1.2 mmol), DMF, rt, 3–4 h. Ar = phenyl (**1a**), 2-naphthyl (**1b**), 1H-indol-2-yl (**1c**), pyridin-3-yl (**1d**).

2.2. Synthesis of the Tripodal Phosphorothioates 2a–2d

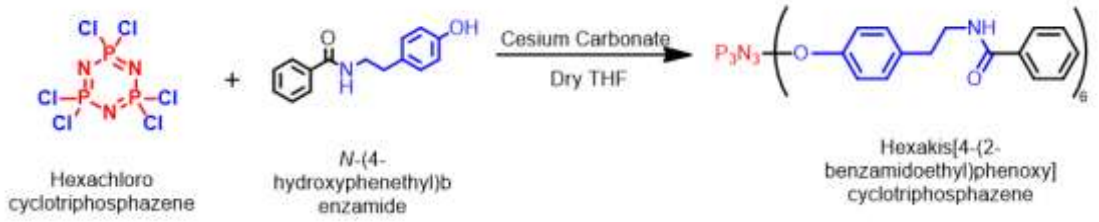
The phosphorothioates **2a–2d** were obtained by treating the amides with $PSCl_3$ in dry THF in the presence of anhydrous Cs_2CO_3 (Scheme 2). The amide (3.2 equiv.) was first stirred with Cs_2CO_3 (5.0 equiv.) for 30 min to generate the cesium phenoxide, and a THF solution of $PSCl_3$ (1.0 equiv.) was then added dropwise. The slight excess of phenol helped drive the third, slowest substitution to completion, and the excess of base neutralized the HCl released at each step. Slow addition of the electrophile kept its local concentration low and limited the formation of mono- and di-substituted chlorophosphorothioates. The cesium phenoxides are more soluble and more reactive in THF than the corresponding sodium or potassium salts [19], so the substitution went to completion at room temperature within 2–4 h. After removal of THF, an aqueous/dichloromethane work-up and precipitation of the crude product from dichloromethane into pentane gave **2a–2d** in 85–89% yield.



Scheme 2. Synthesis of the tripodal phosphorothioates **2a–2d**, shown for **2a**. Reagents and conditions: amide **1** (3.2 mmol), Cs_2CO_3 (5.0 mmol), dry THF, rt, 30 min; then $PSCl_3$ (1.0 mmol) in THF, dropwise, rt, 2–4 h.

2.3. Synthesis of the Hexakis(aryloxy)cyclotriphosphazenes 3a–3d

The same phenoxide chemistry was applied to $N_3P_3Cl_6$ (Scheme 3). Here 6.5 equiv. of amide and 8.0 equiv. of Cs_2CO_3 were used for each equivalent of the phosphazene. Substitution of the P–Cl bonds of cyclotriphosphazenes by aryloxides proceeds stepwise [11,12]. The first replacements are fast, but the later ones become slower, because each new aryloxy group reduces the electrophilicity of the phosphorus centres and increases steric crowding around the ring. In line with this, the reactions needed longer times (7 h) than the $PSCl_3$ reactions. Completion was judged by the disappearance of the intermediate spots on TLC. Earlier syntheses of hexakis(aryloxy)cyclotriphosphazenes typically use sodium aryloxides generated with NaH, in some cases at reflux in dioxane [18]. In the present case, full substitution was achieved at room temperature with Cs_2CO_3, and the products **3a–3d** were isolated in 84–86% yield after the same precipitation work-up.



Scheme 3. Synthesis of the hexakis(aryloxy)cyclotriphosphazenes **3a–3d**, shown for **3a**. Reagents and conditions: amide **1** (6.5 mmol), Cs_2CO_3 (8.0 mmol), dry THF, rt, 30 min; then $N_3P_3Cl_6$ (1.0 mmol) in THF, dropwise, rt, 7 h.

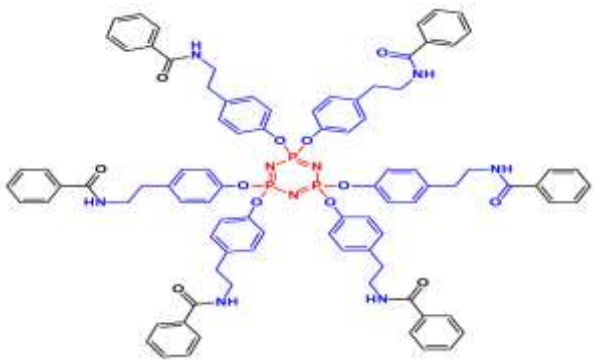


Figure 1. Structure of hexakis[4-(2-benzamidoethyl)phenoxy]cyclotriphosphazene (3a), showing six identical tyramine-derived benzamide arms arranged around the central P_3N_3 ring (red).

The yields and melting points of all compounds are collected in Table 1. Across the series, the yields hardly depend on the aryl group. This indicates that the electronic nature of the acyl unit, from the electron-rich indole to the electron-poor pyridine, has little effect on either the coupling or the phosphorylation steps. The melting points of the amides (171–178 °C) fall to 124–131 °C in the phosphorothioates. This is consistent with the loss of the phenolic OH group, which in the amides can act as an intermolecular hydrogen-bond donor. The hexakis derivatives melt at somewhat higher temperatures (141–155 °C) than the tripodal compounds, as expected for their larger size and more rigid central core.

Table 1. Yields and melting points of compounds 1a–1d, 2a–2d and 3a–3d.

Compound	Ar	Core	Molecular formula	M_r	Time (h)	Yield (%)	m.p. (°C)
1a	Phenyl	–	$C_{15}H_{15}NO_2$	241.29	3	88	176
1b	2-Naphthyl	–	$C_{19}H_{17}NO_2$	291.35	3	90	171
1c	1H-Indol-2-yl	–	$C_{17}H_{16}N_2O_2$	280.33	4	86	174
1d	Pyridin-3-yl	–	$C_{14}H_{14}N_2O_2$	242.28	4	87	178
2a	Phenyl	P=S	$C_{45}H_{42}N_3O_6PS$	783.88	2	86	125
2b	2-Naphthyl	P=S	$C_{57}H_{48}N_3O_6PS$	934.06	2	88	128
2c	1H-Indol-2-yl	P=S	$C_{51}H_{45}N_6O_6PS$	900.99	4	85	131
2d	Pyridin-3-yl	P=S	$C_{42}H_{39}N_6O_6PS$	786.84	4	89	124
3a	Phenyl	P_3N_3	$C_{90}H_{84}N_9O_{12}P_3$	1576.64	7	86	143
3b	2-Naphthyl	P_3N_3	$C_{114}H_{96}N_9O_{12}P_3$	1877.00	7	84	146
3c	1H-Indol-2-yl	P_3N_3	$C_{102}H_{90}N_{15}O_{12}P_3$	1810.86	7	86	141
3d	Pyridin-3-yl	P_3N_3	$C_{84}H_{78}N_{15}O_{12}P_3$	1582.56	7	84	155

3. Materials and Methods

3.1. General Information

Benzoic acid, 2-naphthoic acid, indole-2-carboxylic acid, nicotinic acid, tyramine, EDC, HOBt, $PSCl_3$, $N_3P_3Cl_6$ and anhydrous Cs_2CO_3 were purchased from TCI and Avra and used as received. Solvents of analytical grade were obtained from Merck. THF for the phosphorylation reactions was freshly distilled over benzophenone. Reactions involving $PSCl_3$ and $N_3P_3Cl_6$ were carried out in oven-dried glassware under a dry nitrogen atmosphere. TLC was performed on silica gel 60 F_{254} aluminium plates (Merck), with visualization under UV light (254 nm). Melting points were determined in open capillaries. FT-IR spectra were recorded on a Schimadzu spectrophotometer (KBr pellets, 4000–400 cm^{-1}). ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded

on a Bruker spectrometer in DMSO-d_6. Chemical shifts (δ) are given in ppm relative to TMS, and coupling constants (J) in Hz. Elemental analyses were carried out on a CHNS analyser.

3.2. General Procedure A: Synthesis of Amides 1a–1d

The aromatic carboxylic acid (1.0 mmol) and tyramine (137.2 mg, 1.0 mmol) were dissolved in DMF (15 mL) and stirred at room temperature. EDC (186.3 mg, 1.2 mmol) and HOBt (162.1 mg, 1.2 mmol) were added, and stirring was continued at room temperature until the acid was consumed (TLC, $CHCl_3$–MeOH 9:1). The mixture was diluted with water and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the amide.

N-(4-Hydroxyphenethyl)benzamide (1a). Prepared from benzoic acid (122.1 mg, 1.0 mmol) by General Procedure A (3 h). Off-white solid; yield 212.3 mg (88%); m.p. 176 °C;. IR (KBr) ν_{max} 3310, 3030, 2930, 2860, 1635, 1545, 1515 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ δ 9.15 (s, 1H, OH), 8.50 (t, J = 5.6 Hz, 1H, NH), 7.80 (d, J = 7.2 Hz, 2H, ArH), 7.52–7.40 (m, 3H, ArH), 7.02 (d, J = 8.4 Hz, 2H, ArH), 6.68 (d, J = 8.4 Hz, 2H, ArH), 3.42 (q, J = 6.8 Hz, 2H, NCH_2), 2.72 (t, J = 7.4 Hz, 2H, $ArCH_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 155.6, 134.7, 131.0, 129.6, 129.4, 128.2, 127.1, 115.1, 41.2, 34.4. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{16}NO_2$ 242.1176, found 242.1164. Anal. calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.65; H, 6.28; N, 5.80%.

N-(4-Hydroxyphenethyl)-2-naphthamide (1b). Prepared from 2-naphthoic acid (172.2 mg, 1.0 mmol) by General Procedure A (3 h). white solid; yield 262.2 mg (90%); m.p. 171 °C; IR (KBr) ν 3305, 3055, 2935, 1632 cm^{-1}]. ^1H NMR (400 MHz, DMSO-d_6) δ δ 9.17 (s, 1H, OH), 8.65 (t, J = 5.6 Hz, 1H, NH), 8.42 (s, 1H, ArH), 8.02–7.95 (m, 3H, ArH), 7.90 (dd, J = 8.6, 1.7 Hz, 1H, ArH), 7.62–7.55 (m, 2H, ArH), 7.06 (d, J = 8.4 Hz, 2H, ArH), 6.69 (d, J = 8.4 Hz, 2H, ArH), 3.49 (q, J = 6.8 Hz, 2H, NCH_2), 2.77 (t, J = 7.4 Hz, 2H, $ArCH_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ δ 166.3, 155.6, 134.1, 132.2, 132.0, 129.6, 129.4, 128.9, 127.9, 127.7, 127.5, 127.4, 126.7, 124.3, 115.1, 41.3, 34.4. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{18}NO_2$ 292.1332, found 292.1321. Anal. calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.31; H, 5.89; N, 4.83%..

N-(4-Hydroxyphenethyl)-1H-indole-2-carboxamide (1c). Prepared from indole-2-carboxylic acid (161.2 mg, 1.0 mmol) by General Procedure A (4 h). off white solid; yield 241.1 mg (86%); m.p. 174 °C. IR (KBr) ν_{max} 3400, 3290, 3050, 1625. ^1H NMR (400 MHz, DMSO-d_6) δ δ 11.55 (s, 1H, indole NH), 9.18 (s, 1H, OH), 8.52 (t, J = 5.6 Hz, 1H, CONH), 7.60 (d, J = 8.0 Hz, 1H, ArH), 7.42 (d, J = 8.2 Hz, 1H, ArH), 7.17 (t, J = 7.6 Hz, 1H, ArH), 7.08 (s, 1H, indole H-3), 7.06 (d, J = 8.4 Hz, 2H, ArH), 7.02 (t, J = 7.5 Hz, 1H, ArH), 6.69 (d, J = 8.4 Hz, 2H, ArH), 3.47 (q, J = 6.8 Hz, 2H, NCH_2), 2.76 (t, J = 7.4 Hz, 2H, $ArCH_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.2, 155.7, 136.4, 132.0, 129.6, 129.5, 127.1, 123.3, 121.4, 119.7, 115.1, 112.3, 102.4, 40.9, 34.6. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_2$ 281.1285, found 281.1272. Anal. calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.82; H, 5.73; N, 9.98%.

N-(4-Hydroxyphenethyl)nicotinamide (1d). Prepared from nicotinic acid (123.1 mg, 1.0 mmol) by General Procedure A (4 h). off white solid; yield 210.8 mg (87%); m.p. 178 °C. IR (KBr) ν_{max} 3300, 3041, 2935, 1590 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ [observed peak list: δ δ 9.17 (s, 1H, OH), 8.97 (d, J = 1.8 Hz, 1H, PyH), 8.68 (dd, J = 4.8, 1.6 Hz, 1H, PyH), 8.66 (t, J = 5.6 Hz, 1H, NH), 8.14 (dt, J = 7.9, 2.0 Hz, 1H, PyH), 7.48 (dd, J = 7.9, 4.8 Hz, 1H, PyH), 7.03 (d, J = 8.4 Hz, 2H, ArH), 6.68 (d, J = 8.4 Hz, 2H, ArH), 3.44 (q, J = 6.8 Hz, 2H, NCH_2), 2.73 (t, J = 7.4 Hz, 2H, $ArCH_2$). ^{13}C NMR (100 MHz, DMSO-d_6) 164.6, 155.7, 151.7, 148.4, 134.9, 130.2, 129.6, 129.3, 123.4, 115.1, 41.3, 34.3. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2$ 243.1128, found 243.1116. Anal. calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.38; H, 5.80; N, 11.57%.

3.3. General Procedure B: Synthesis of Phosphorothioates 2a–2d

Under nitrogen, the amide **1** (3.2 mmol) was dissolved in dry THF (15 mL) in a 100 mL round-bottom flask. Anhydrous Cs_2CO_3 (1.629 g, 5.0 mmol) was added, and the suspension was stirred at room temperature for 30 min. A solution of $PSCl_3$ (169.4 mg, 1.0 mmol) in dry THF (15 mL) was added dropwise, and the mixture was stirred at room temperature until completion (TLC, CH_2Cl_2–hexane 1:1). The solvent was evaporated, and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in a minimum volume of CH_2Cl_2 and poured into pentane with stirring, and the precipitate was collected by filtration and dried under vacuum.

Tris(4-(2-benzamidoethyl)phenyl) phosphorothioate (2a). Prepared from **1a** (772.1 mg, 3.2 mmol) by General Procedure B (2 h). white solid; yield 674.1 mg (86%); m.p. 125 °C. IR (KBr) ν_{max} 33060, 2934, 2862 cm^{-1}]. ^1H NMR (400 MHz, DMSO-d_6) δ 8.55 (t, J = 5.6 Hz, 3H, NH), 7.80 (d, J = 7.2 Hz, 6H, ArH), 7.53–7.42 (m, 9H, ArH), 7.28 (d, J = 8.5 Hz, 6H, ArH), 7.15 (d, J = 8.5 Hz, 6H, ArH), 3.50 (q, J = 6.8 Hz, 6H, NCH_2), 2.86 (t, J = 7.2 Hz, 6H, $ArCH_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.3, 148.6 (d, $^2J_{PC}$ = 7.5 Hz), 137.5, 134.6, 131.1, 130.3, 128.2, 127.1, 120.9 (d, $^3J_{PC}$ = 5.0 Hz), 40.7, 34.5.. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{45}H_{43}N_3O_6PS$ 784.2605, found 784.2592. Anal. calcd for $C_{45}H_{42}N_3O_6PS$: C, 68.95; H, 5.40; N, 5.36; S, 4.09. Found: C, 68.94; H, 5.34; N, 5.34%.

Tris(4-(2-(2-naphthamido)ethyl)phenyl) phosphorothioate (2b). Prepared from **1b** (932.3 mg, 3.2 mmol) by General Procedure B (2 h). white solid; yield 822.0 mg (88%); m.p. 128 °C. IR (KBr) ν_{max} [3310, 3056, 2930, 1638, cm^{-1}]. ^1H NMR (400 MHz, DMSO-d_6) δ 8.70 (t, J = 5.6 Hz, 3H, NH), 8.45 (s, 3H, ArH), 8.02–7.95 (m, 9H, ArH), 7.91 (dd, J = 8.6, 1.7 Hz, 3H, ArH), 7.63–7.55 (m, 6H, ArH), 7.31 (d, J = 8.5 Hz, 6H, ArH), 7.16 (d, J = 8.5 Hz, 6H, ArH), 3.57 (q, J = 6.8 Hz, 6H, NCH_2), 2.91 (t, J = 7.2 Hz, 6H, $ArCH_2$).. ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.4, 148.6 (d, $^2J_{PC}$ = 7.5 Hz), 137.6, 134.1, 132.2, 131.9, 130.3, 128.9, 127.9, 127.7, 127.6, 127.4, 126.8, 124.3, 120.9 (d, $^3J_{PC}$ = 5.0 Hz), 40.8, 34.5.. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{57}H_{49}N_3O_6PS$ 934.3074, found 934.3061. Anal. calcd for $C_{57}H_{48}N_3O_6PS$: C, 73.30; H, 5.18; N, 4.50; S, 3.43. Found: C, 73.28; H, 5.17; N, 4.52%.

Tris(4-(2-(1H-indole-2-carboxamido)ethyl)phenyl) phosphorothioate (2c). Prepared from **1c** (897.0 mg, 3.2 mmol) by General Procedure B (4 h). white solid; yield 765.8 mg (85%); m.p. 131 °C. IR (KBr) ν_{max} 3310, 3068, 2945, 1639, cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 3H, indole NH), 8.58 (t, J = 5.6 Hz, 3H, CONH), 7.61 (d, J = 8.0 Hz, 3H, ArH), 7.42 (d, J = 8.2 Hz, 3H, ArH), 7.30 (d, J = 8.5 Hz, 6H, ArH), 7.18 (t, J = 7.6 Hz, 3H, ArH), 7.16 (d, J = 8.5 Hz, 6H, ArH), 7.10 (s, 3H, indole H-3), 7.02 (t, J = 7.5 Hz, 3H, ArH), 3.55 (q, J = 6.8 Hz, 6H, NCH_2), 2.90 (t, J = 7.2 Hz, 6H, $ArCH_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.3, 148.6 (d, $^2J_{PC}$ = 7.5 Hz), 137.6, 136.5, 131.9, 130.3, 127.1, 123.4, 121.5, 120.9 (d, $^3J_{PC}$ = 5.0 Hz), 119.8, 112.3, 102.6, 40.6, 34.6. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{51}H_{46}N_6O_6PS$ 901.2932, found 901.2921. Anal. calcd for $C_{51}H_{45}N_6O_6PS$: C, 67.99; H, 5.03; N, 9.33; S, 3.56. Found: C, 67.97; H, 5.05; N, 9.35%.

Tris(4-(2-(nicotinamido)ethyl)phenyl) phosphorothioate (2d). Prepared from **1d** (775.3 mg, 3.2 mmol) by General Procedure B (4 h). white solid; yield 700.3 mg (89%); m.p. 124 °C. IR (KBr) ν_{max} 3316, 3023, 2932, 1638, cm^{-1}]. ^1H NMR (400 MHz, DMSO-d_6) δ 8.98 (d, J = 1.8 Hz, 3H, PyH), 8.72 (t, J = 5.6 Hz, 3H, NH), 8.69 (dd, J = 4.8, 1.6 Hz, 3H, PyH), 8.15 (dt, J = 7.9, 2.0 Hz, 3H, PyH), 7.49 (dd, J = 7.9, 4.8 Hz, 3H, PyH), 7.29 (d, J = 8.5 Hz, 6H, ArH), 7.16 (d, J = 8.5 Hz, 6H, ArH), 3.52 (q, J = 6.8 Hz, 6H, NCH_2), 2.88 (t, J = 7.2 Hz, 6H, $ArCH_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ C, 64.09; H, 5.02; N, 10.67%. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{42}H_{40}N_6O_6PS$ 787.2462, found 787.2450. Anal. calcd for $C_{42}H_{39}N_6O_6PS$: C, 64.11; H, 5.00; N, 10.68; S, 4.07. Found: C, 64.09; H, 5.02; N, 10.67%.

3.4. General Procedure C: Synthesis of Cyclotriphosphazenes 3a–3d

Under nitrogen, the amide **1** (6.5 mmol) was dissolved in dry THF (25 mL) in a 250 mL round-bottom flask. Anhydrous Cs_2CO_3 (2.607 g, 8.0 mmol) was added, and the suspension was stirred at room temperature for 30

min. A solution of $N_3P_3Cl_6$ (347.6 mg, 1.0 mmol) in dry THF (15 mL) was added dropwise, and stirring was continued at room temperature until the partially substituted intermediates were no longer detected (TLC, CH_2Cl_2–hexane 1:1). Work-up and precipitation were carried out as described in General Procedure B.

Hexakis[4-(2-benzamidoethyl)phenoxy]cyclotriphosphazene (3a). Prepared from **1a** (1.568 g, 6.5 mmol) by General Procedure C (7 h). white solid; yield 1.356 g (86%); m.p. 143 °C. IR (KBr) ν_{max} [3310, 3064, 2936, 1638, cm^{-1}]. ^1H NMR (400 MHz, DMSO-d_6) δ 8.52 (t, J = 5.6 Hz, 6H, NH), 7.80 (d, J = 7.2 Hz, 12H, ArH), 7.52–7.42 (m, 18H, ArH), 7.08 (d, J = 8.5 Hz, 12H, ArH), 6.86 (d, J = 8.5 Hz, 12H, ArH), 3.44 (q, J = 6.8 Hz, 12H, NCH_2), 2.80 (t, J = 7.2 Hz, 12H, $ArCH_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 148.7 (m), 136.8, 134.6, 131.1, 129.9, 128.2, 127.1, 120.8, 40.8, 34.5.. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{90}H_{85}N_9O_{12}P_3$ 1576.5525, found 1576.5512. Anal. calcd for $C_{90}H_{84}N_9O_{12}P_3$: C, 68.56; H, 5.37; N, 8.00. Found: C, 68.54; H, 5.25; N, 8.02%.

Hexakis[4-(2-(2-naphthamido)ethyl)phenoxy]cyclotriphosphazene (3b). Prepared from **1b** (1.894 g, 6.5 mmol) by General Procedure C (7 h). white solid; yield 1.577 g (84%); m.p. 146 °C. IR (KBr) ν_{max} [3312, 3048, 2934, 1635, cm^{-1}]. ^1H NMR (400 MHz, DMSO-d_6) δ 8.67 (t, J = 5.6 Hz, 6H, NH), 8.43 (s, 6H, ArH), 8.02–7.95 (m, 18H, ArH), 7.90 (dd, J = 8.6, 1.7 Hz, 6H, ArH), 7.62–7.55 (m, 12H, ArH), 7.11 (d, J = 8.5 Hz, 12H, ArH), 6.88 (d, J = 8.5 Hz, 12H, ArH), 3.51 (q, J = 6.8 Hz, 12H, NCH_2), 2.85 (t, J = 7.2 Hz, 12H, $ArCH_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.3, 148.7 (m), 136.9, 134.1, 132.2, 131.9, 129.9, 128.9, 127.9, 127.7, 127.5, 127.4, 126.7, 124.3, 120.8, 40.9, 34.5.. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{114}H_{97}N_9O_{12}P_3$ 1876.6464, found 1876.6453. Anal. calcd for $C_{114}H_{96}N_9O_{12}P_3$: C, 72.95; H, 5.16; N, 6.72. Found C, 75.93; H, 5.15; N, 6.70%.

Hexakis[4-(2-(1H-indole-2-carboxamido)ethyl)phenoxy]cyclotriphosphazene (3c). Prepared from **1c** (1.822 g, 6.5 mmol) by General Procedure C (7 h). white solid; yield 1.557 g (86%); m.p. 141 °C. IR (KBr) ν_{max} [3312, 3056, 2937, 1635, cm^{-1}]. ^1H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 6H, indole NH), 8.55 (t, J = 5.6 Hz, 6H, CONH), 7.60 (d, J = 8.0 Hz, 6H, ArH), 7.41 (d, J = 8.2 Hz, 6H, ArH), 7.17 (t, J = 7.6 Hz, 6H, ArH), 7.11 (d, J = 8.5 Hz, 12H, ArH), 7.07 (s, 6H, indole H-3), 7.02 (t, J = 7.5 Hz, 6H, ArH), 6.89 (d, J = 8.5 Hz, 12H, ArH), 3.50 (q, J = 6.8 Hz, 12H, NCH_2), 2.84 (t, J = 7.2 Hz, 12H, $ArCH_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.2, 148.7 (m), 136.9, 136.4, 131.9, 129.9, 127.1, 123.3, 121.5, 120.8, 119.8, 112.3, 102.5, 40.7, 34.6. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{102}H_{91}N_{15}O_{12}P_3$ 1810.6179, found 1810.6165. Anal. calcd for $C_{102}H_{90}N_{15}O_{12}P_3$: C, 67.65; H, 5.01; N, 11.60. Found: C, 67.64; H, 5.03; N, 11.62%.

Hexakis[4-(2-(nicotinamido)ethyl)phenoxy]cyclotriphosphazene (3d). Prepared from **1d** (1.575 g, 6.5 mmol) by General Procedure C (7 h). white solid; yield 1.329 g (84%); m.p. 155 °C. IR (KBr) ν_{max} [3310, 3055, 2938, 1634, cm^{-1}]. ^1H NMR (400 MHz, DMSO-d_6) δ [observed peak list: δ (multiplicity, J in Hz, integration, assignment)]. ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 151.8, 148.7 (m), 148.4, 136.7, 135.0, 130.1, 129.9, 123.5, 120.8, 40.9, 34.4. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{84}H_{79}N_{15}O_{12}P_3$ 1582.5240, found 1582.5228. Anal. calcd for $C_{84}H_{78}N_{15}O_{12}P_3$: C, 63.75; H, 4.97; N, 13.28. Found: C, 63.73; H, 4.96; N, 13.26%.

4. Conclusions

Four tyramine-derived aromatic amides were prepared by chemoselective EDC/HOBt coupling, with the phenolic hydroxyl group left free. They were then used as nucleophiles to build two families of multivalent phosphorus compounds. With $PSCl_3$, the reaction gave tripodal phosphorothioates bearing three amide arms, and with $N_3P_3Cl_6$ it gave star-shaped cyclotriphosphazenes bearing six. Both phosphorylations proceeded completely at room temperature with Cs_2CO_3 in THF, gave good yields (84–89%), and required only precipitation for purification. The route is short and modular. In principle, any aromatic acid that couples with tyramine can be placed on a P=S or P_3N_3 core in two steps.

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