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$AlCl_3$–NaI assisted cleavage of polymer-bound esters with concomitant amine coupling and azido-reductive cyclization: synthesis of pyrrolobenzodiazepine derivatives

Ahmed Kamal [a,*], S. Prabhakar [a], Nagula Shankaraiah [b], Nagula Markandeya [a], P. Venkat Reddy [a], Vunnam Srinivasulu [a], Manda Sathish [a]

[a] Medicinal Chemistry & Pharmacology, CSIR–Indian Institute of Chemical Technology, Hyderabad 500007, India
[b] Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad 500037, India

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ABSTRACT

A practical one-pot solid-phase parallel diversity-oriented synthesis (DOS) strategy has been successfully applied for the construction of scaffolds embedded with privileged pyrrolo [2,1-*c*][1,4]benzodiazepines (PBDs) and their dilactams. The synthetic approach involves $AlCl_3$–NaI assisted cleavage of resin-bound ester, with amine coupling and tandem azido-reductive cyclization as the key step. The maximum skeletal diversity has been expanded through the introduction of different linkers at A-C8-position of PBD with various substituents from a single key intermediate. Gratifyingly, the final compounds have been purified by the solid-supported liquid–liquid extraction (SLE) technique. Interestingly, some of these molecules have shown enhanced DNA-binding affinity in comparison with naturally occurring DC-81. This novel approach is acquiescent for the construction of new pharmaceutical drug candidates for the evaluation of biological profile in drug discovery.

Combinatorial chemistry plays a key role in drug discovery for the lead identification of new chemical entities (NCEs) containing heterocyclic scaffold, which continues to be an essential component in exploring the biological activity.[1] The solid-phase organic synthesis (SPOS) has emerged as a powerful tool in the production of small molecules intending to exploit combinatorial chemistry towards the potential drug candidates.[2] The core components of chemical biology are the identification of novel small-molecule modulators as perturbing agents in biological systems and the application of these small bioactive molecules to pinpoint on the development of specific DNA-interactive agents.[3] In this scenario, there is a great demand for drug-like small molecules with wider biological applications in identifying specific small molecule modulators. To address this issue, the organic chemistry community has investigated diversity-oriented synthesis (DOS) as a new strategy to efficiently populate the chemical space with skeletally diverse molecules through complexity generating reactions.[4]

Of particular importance for the lead identification is the incorporation of novel heterocyclic cores into library design and production. Recently, there has been an increasing interest in the synthesis of DNA sequence selective binding agents, particularly low molecular weight antitumor antibiotics. A good example is the PBD ring system, which represents a currently well-known privileged structural motif observed in various natural products, such as DC-81 and anthramycin (Fig. 1), derived from various *Streptomyces* species.[5,6] The mechanism of action of these PBDs has been extensively investigated and their interaction with duplex DNA has been rationalized.[7] PBD-5,11-diones have also been employed as interesting intermediates in the synthesis of naturally occurring and synthetically modified PBD imines, such

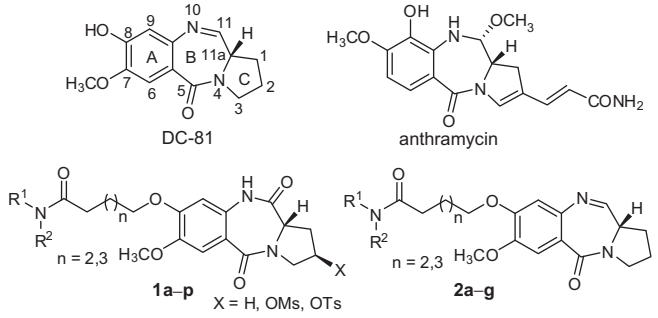

Figure 1. A library of pyrrolobenzodiazepine derivatives (**1a**–**p** and **2a**–**g**) and their natural products DC-81 and anthramycin.

* Corresponding author. Tel.: +91 40 27193157; fax: +91 40 27193189.
E-mail address: ahmedkamal@iict.res.in (A. Kamal).

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Table 1
Synthesis of a library of substituted pyrrolo [2,1-c][1,4]benzodiazepine-5,11-diones (**1a**–**p**)

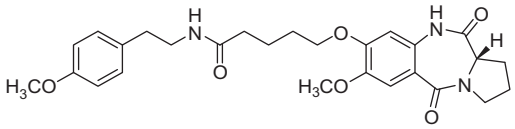
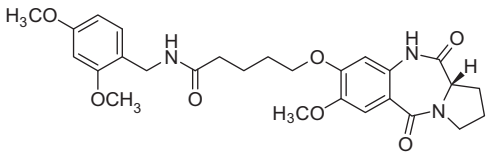
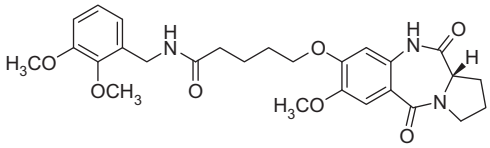
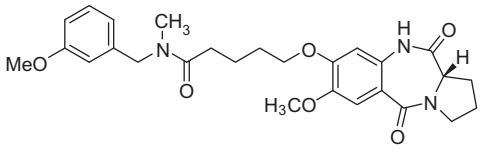
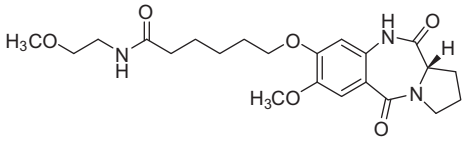
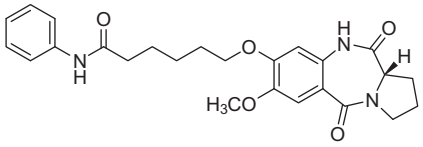
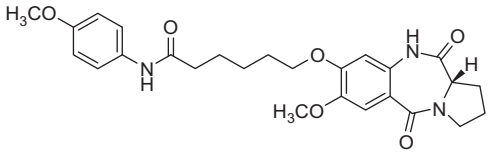
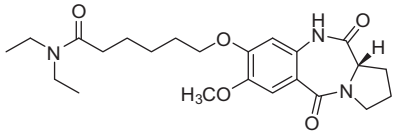
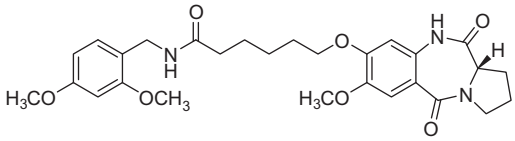
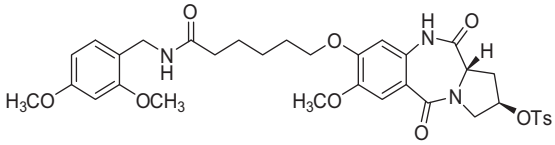
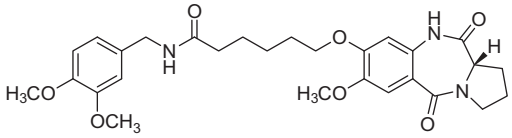
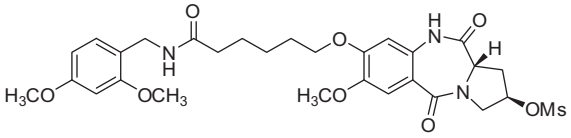
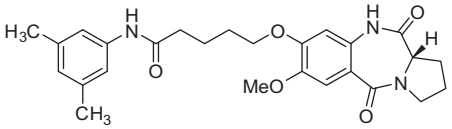
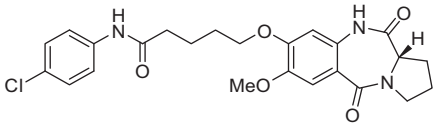
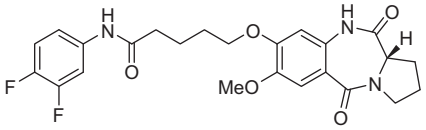
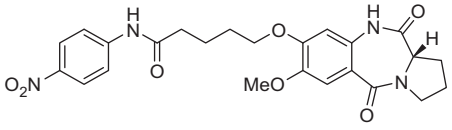
Entry	Product	Yields[a] (%)	HRMS (calcd)	HRMS (found)
1a		56, 25[b]	518.2267	518.2257
1b		60	534.2216	534.2182
1c		50	534.2179	534.2185
1d		50	518.2267	518.2263
1e		54	456.2110	456.2101
1f		52	474.2004	474.1980
1g		60	504.2110	504.2104
1h		50	454.2210	454.2202
1i		62	548.2372	548.2364
1j		58	718.2410	718.2390
1k		55	548.2372	548.2376

Table 1 (*continued*)

Entry	Product	Yields[a] (%)	HRMS (calcd)	HRMS (found)
1l		62	642.2097	642.2080
1m		53	488.2155	488.2153
1n		57	494.1453	494.1451
1o		54	496.1654	496.1658
1p		60	505.1693	505.1691

[a] Yields were obtained based on preparative thin layer chromatography.
[b] $AlCl_3$ alone used as reagent.

as tomaymycin and chicamycin.[8] Moreover, this tricyclic ring system has been used for a number of pharmaceutical applications.[9–12] Our research group has been extensively involved in the development of new solid-phase[13] and solution-phase[14] synthetic strategies, and thus includes the library generation techniques. Earlier, we have developed the solid-phase combinatorial approaches for the construction of privileged pyrrolo [2,1-*c*][1,4]benzodiazepines (PBDs) and imidazo-pyridines.[15] In continuation of the efforts, we report herein the use of DOS strategy and the solid-phase parallel synthetic approach to construct a library of natural product-like small molecules that contain PBD with maximum skeletal diversity. In this context, we have developed and focused our attention on the generation of DNA-interactive PBDs (**1a**–**p** and **2a**–**g**, Fig. 1) as an attractive core structure that we envisaged and derivatized to produce a DNA-binding targeted compound library.

In the present investigation, we have extensively demonstrated the $AlCl_3$–NaI assisted cleavage of resin-bound esters with amine coupling and tandem azido-reductive cyclization approach in a one-pot manner. Over the past few years, the aluminium based catalysts or reagents have been found to be more efficient in the pharmaceutical applications. Anhydrous $AlCl_3$ is a typical strong Lewis acid. Recently, the aluminium containing reagents or catalysts have been reported for the aromatic azido reductions in combination with other metals like Fe, Ni and Zn.[14d,16] In this protocol, we have employed the $AlCl_3$ and NaI reagent system for aromatic azido reduction apart from resin-bound ester cleavage and amine coupling. Similarly, Morphy and co-workers[17] have examined a variety of reagents for the conversion of esters to amides,[18–22] among them $A1Cl_3$ was selected as the best reagent of choice for this transformation. Moreover, we have explored a direct reaction and release cleavage concept using Wang resin as linker. Also we employed a solid-supported liquid–liquid extraction (SLE)[23] technique that is more effective in the removal of excess amine and excess reagent ($AlCl_3$–NaI) residues from the final products in a high-throughput format. More precisely, our core aim is to display the diversity at A-C8/C-C2 and C10–C11-position (imine/amide) of the PBD ring system, by changing the chain length of resin-bound esters with a variety of primary or secondary amines, resulting in a generation of a library of new PBDs.

A number of methodologies have been developed for the solution-phase synthesis of tricyclic PBD-5,11-diones employing different types of approaches ranging from deprotective to reductive cyclizations.[24] However, there are very few reports on the solid-phase synthesis of these biologically important compounds.[16] In the literature, not much attention has been given to PBD-5,11-diones with diversity at the A-C8/C-C2-position.

Our synthetic strategy started from the preparation of methyl 2-azido-4-hydroxy-5-methoxybenzoate (**5**),[26] which could be envisaged directly from the reported method.[13c] Next, the Wang resin (**3**) was coupled to the bromo acids **4a**,**b** with DIC and DMAP. This chemical transformation was confirmed by the IR stretching vibration of resin-bound ester at 1745 cm^{-1}. Etherification was successfully performed with intermediate **5** and resin-bound bromo ester using K_2CO_3 as base to provide the desired polymer-supported precursors **6a**,**b**. This was indicated by IR spectra that show a strong azide stretching at 2110 cm^{-1}. Hydrolysis of polymer-bound aromatic methyl esters by careful addition of 1 N NaOH,[13d,25] was carried out and this was subsequently coupled with substituted L-proline esters **7a**–**c** in the presence of EDCI and HOBt to provide the key resin-bound intermediates **8a**–**f**. This step was confirmed by IR spectra, as the new amide bond stretching peak appeared at 1635 cm^{-1}. After establishment of the key intermediates **8a**–**f**, we attempted a Lewis acid-assisted one-pot model experiments with $AlCl_3$ alone and in combination with NaI. It has been shown that the later reagent system was effective and useful (Table 1, entry 1). This reaction was carried out at room temperature by using CH_2Cl_2 as the solvent. Herein, we employed a set of amine building blocks **9a**–**o** for the library generation as shown in Fig. 2.

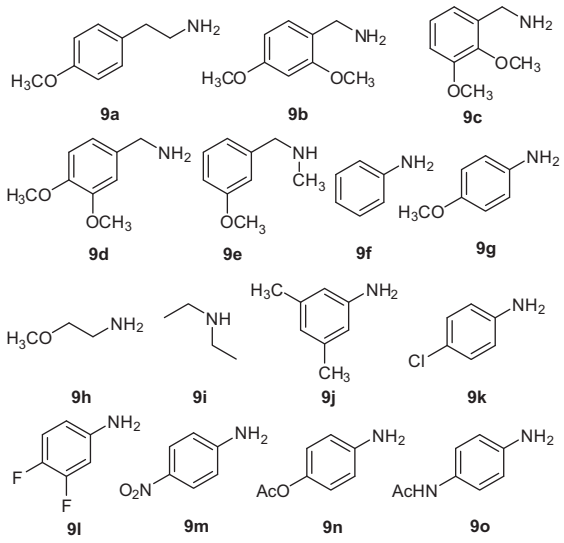
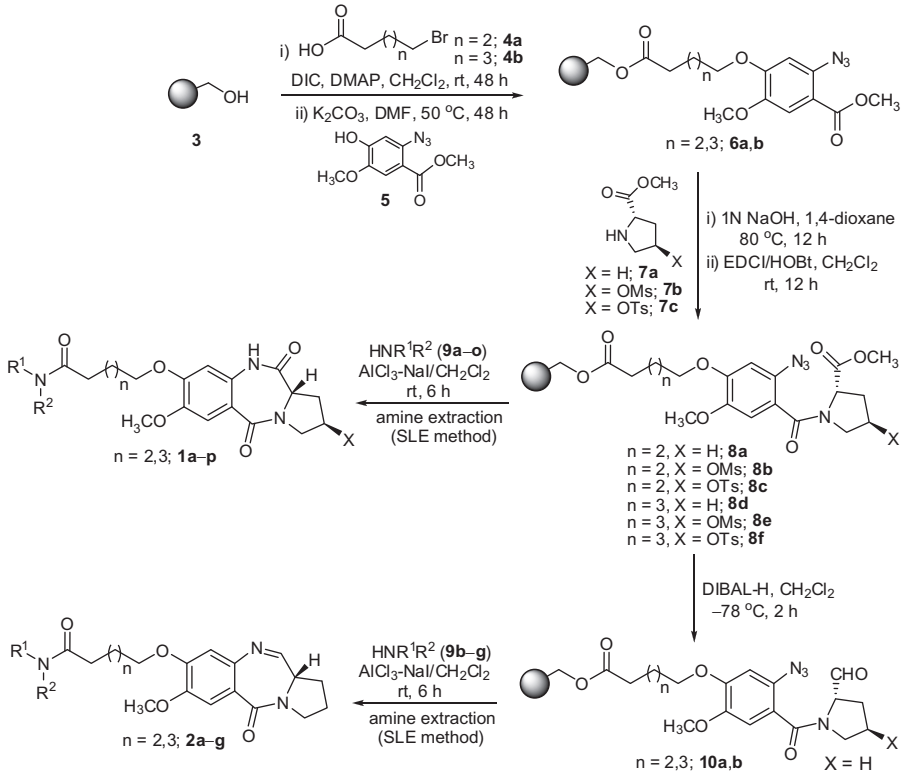


Figure 2. A set of amine building blocks **9a–o** (R^1 and R^2) for the library generation.

Finally, the resin-bound 2-azido-5-methoxybenzoyl proline esters (**8a–f**) were treated with $AlCl_3$–NaI followed by the addition of excess amines **9a–o**, and thus purified by employing the SLE technique to afford the desired C8-linked PBD-5,11-diones **1a–p** in 50–62% yields as shown in Table 1 (Scheme 1).[27] We have investigated the functional group scope of this method by using a variety of substituted amino building blocks **9a–o**. It was found that this method is tolerable to many functionalities such as chloro, fluoro, methyl, methoxy and nitro groups including some sensitive functional groups such as mesyl and tosyl (**1j** and **1l**, Table 1). However, the reaction did not proceed well and obtained the complex reaction products with *p*-amino acetoxy (**9n**) and *p*-amino acetanilide (**9o**) as substrates by employing $AlCl_3$–NaI reagent system. Next, the removal of excess amine was accomplished by using SLE with diatomaceous earth as the support. In this respect, we have utilized Varian's Hydromatrix (diatomaceous earth) for the amine extraction. The choice of aqueous buffer for extraction depended on the physical properties of the amine to be extracted. This extraction was found to be an effective method for the removal of water-soluble impurities in a high throughput format. In general, 2 N aqueous hydrochloric acid was employed for hydrophobic amines, and water was the preferred media for removal of hydrophilic amines. The organic material passed through the Hydromatrix support into a collection plate below, while the amine salts were retained by the solid matrix, resulting in the effective removal of the amine impurities. The removal of the amine depends upon its *C* log *P* value.[23f] Further, it has been observed from the SLE method that the purity of the corresponding product depends on its solubility in respective solvent used for the purification and also depends on their substitution pattern at the C8/C2-position of the PBDs.

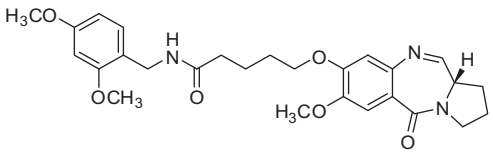
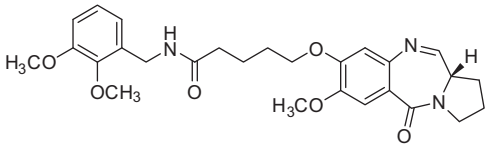
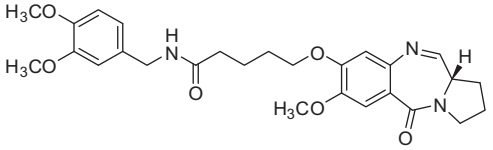
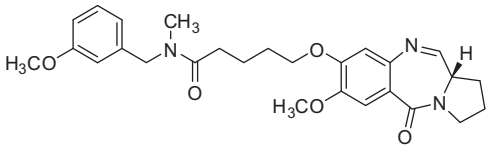
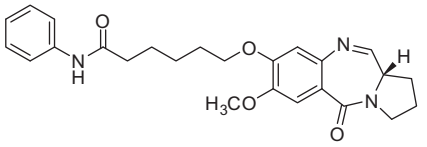
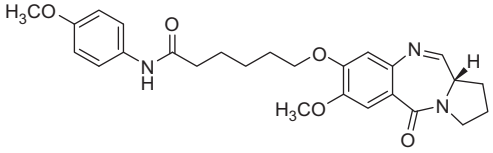
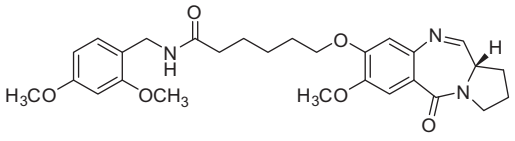
In continuation of these efforts, we turned our attention for the construction of the core DNA-interactive PBD-imines by changing the functionality at C10–C11-position of the central ring system. The resin-bound 2-azido-5-methoxybenzoyl proline esters (**8a–f**) were selectively reduced to their corresponding resin-bound 2-azido-5-methoxybenzoyl prolinaldehyde (**10a**,**b**) with DIBAL-H[13b] which was confirmed by IR spectra and a strong aldehyde stretching vibration was observed at 1744 cm^{-1} and carbonyl hydrogen (O=**C**–**H**) stretching was also observed at 2758 cm^{-1}. Similarly, the resin-bound aldehydes **10a**,**b** were treated with excess amount of amines **9b–g** in the presence of $AlCl_3$–NaI to afford the desired final products **2a–g** (Scheme 1) in 52–66% yields as shown in Table 2.

Next, the DNA-binding ability of substituted PBD-5,11-diones **1a–p** and their imines **2a–g** was examined by thermal denaturation



Scheme 1. Solid-phase synthetic strategy for the generation of a library of substituted PBD-5,11-diones (**1a–p**) and their imines (**2a–g**) via azido-reductive cyclization approach employing $AlCl_3$–NaI.

Table 2
Synthesis of a library of substituted pyrrolo [2,1-*c*][1,4]benzodiazepines (**2a–g**)

Entry	Product	Yields[a] (%)	HRMS (calcd)	HRMS (found)
2a		55	496.244	496.2459
2b		55	496.2454	496.2460
2c		54	496.2457	496.2465
2d		62	480.2498	480.2517
2e		55	436.2224	436.2236
2f		66	466.2346	466.2341
2g		52	510.2604	510.2590

[a] Yields were obtained based on preparative thin layer chromatography.

studies using calfthymus (CT) DNA. These studies show the melting stabilization (ΔT_m) for the CT–DNA duplex at pH 7.0, incubated at 37 °C, where PBD/DNA molar ratio is 1:5. In this assay, the helix melting temperature changes (ΔT_m) for each compound were studied at 0 and after 18 h of incubation at 37 °C. In this study, the first series of non-covalent DNA-interactive PBD dilactams **1b**, **1e–g** and **1i–o** have shown helix melting temperature ranging from 0.5 to 1.8 °C (Table 3). Interestingly, the ΔT_m of compound **1j** and **1o** have shown significant melting temperature (ΔT_m 1.7 °C and 1.8 °C) in comparison with DC-81 (ΔT_m 0.7 °C, Table 3) for 18 h incubation at 37 °C. However, some of the compounds (**1a**, **1c**, **1d**, **1h** and **1p**) have not shown any elevated temperature even at 0 h and 18 h. Similarly, the DNA interactive PBD imines **2a–g** were evaluated for their DNA-binding affinity by thermal denaturation studies. Interestingly, the ΔT_m of compound **2a** have shown remarkable DNA-binding affinity at 2.9 °C at 0 h, while the melting temperature increases to 4.2 °C up on incubation for 18 h at 37 °C. Next, the compounds **2c** and **2e** were also shown significant helix melting temperature ranging from 2.1 to 3.7 °C. In the same experiment the naturally occurring DC-81 elevates the helix melting temperature of CT-DNA by 0.7 °C after incubation for 18 h. It is interesting to observe that some of these PBD dilactams and their imine derivative ΔT_m values are significant by changing the alkyl chain length, probably as they have a better fit in the minor groove of duplex DNA.

In conclusion, we have developed a convenient solid-phase protocol for the synthesis of C8-linked PBD-5,11-diones and their PBD-imines employing azido-reductive cyclization approach by using $AlCl_3$ in combination with NaI. These PBD-5,11-diones and their imines have shown potential DNA-binding affinity. In this protocol, the key step is the resin cleavage, amine coupling with concomitant azido reductive-cyclization followed by the SLE purification technique to provide the scaffolds in a one-pot manner. The products have been obtained in modest to good yields and purity. This strategy provides an efficient way to access PBDs that are of pharmaceutical interest. More importantly, this type of strategies enables rapid validation of synthetic sequences and building blocks for library synthesis, which often represents the bottleneck in the process of generating new chemical libraries.

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The authors S.P., N.M.K., P.V.R., V.S. and M.S. are thankful to CSIR, New Delhi, for providing the fellowships.

Table 3
Thermal denaturation data for substituted pyrrolo [2,1-*c*][1,4]benzodiazepine-5,11-diones (**1a**–**p**) and their imines (**2a**–**g**) with calfthymus CT–DNA

Compounds (PBD)	[PBD]/[DNA] molar ratio[a]	ΔT_m[b] (°C) After incubation at 37 °C for	
		0 h	18 h
1a	1:5	–[c]	–
1b	1:5	0.5	0.9
1c	1:5	–	–
1d	1:5	–	–
1e	1:5	0.7	0.9
1f	1:5	1.0	1.1
1g	1:5	0.9	1.3
1h	1:5	–	–
1i	1:5	0.9	1.1
1j	1:5	1.2	1.7
1k	1:5	1.0	1.1
1l	1:5	0.7	0.9
1m	1:5	0.6	0.6
1n	1:5	1.0	1.1
1o	1:5	1.3	1.7
1p	1:5	–	–
2a	1:5	2.9	4.2
2b	1:5	2.2	2.9
2c	1:5	2.8	3.7
2d	1:5	0.5	0.7
2e	1:5	2.1	3.1
2f	1:5	2.3	2.7
2g	1:5	1.9	2.2
DC-81	1:5	0.3	0.7

[a] For CT–DNA alone at pH 7.00 ± 0.01, T_m = 69.6 °C ± 0.01 (mean value from 8 separate determinations), all T_m values are ±0.05 – 0.15 °C.
[b] For a 1:5 M ratio of [PBD]/[DNA], where CT–DNA concentration = 100 μM and ligand concentration = 20 μM in aqueous sodium phosphate buffer [10 mM sodium phosphate + 1 mM EDTA, pH 7.00 ± 0.01].
[c] Not shown any DNA-binding affinity.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.033.

References and notes

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26. Diazotization reaction followed by reaction with sodium azide was handled with care for the preparation of methyl 2-azido-4-hydroxy-5-methoxybenzoate (**5**) by wearing safety glasses, face mask, and gloves, and reaction is performed in a well equipped fume hood (see detailed safety precautions of handling organic azides and their toxicity in the supporting information).
27. In a typical reaction, the Wang resin (**3**, 2.0 g, 1.2 mmol/g, 100–200 mesh and 1% DVB) was swollen in CH_2Cl_2 (20 mL). 5-Bromopentanoic acid (**4**, 2.15 g, 12.0 mmol) and DIC (1.51 g, 12.0 mmol) were dissolved in the minimum volume of CH_2Cl_2/DMF (1:1) required for complete dissolution. The activated scaffold solution was added to the resin, followed by the addition of slurry of

DMAP (4 mg, 10 mol %) in CH_2Cl_2 (0.5 mL). The reaction vessel was shaken at room temperature for 48 h. The resin was washed with CH_2Cl_2 (2 × 25 mL), DMF (2 × 25 mL), MeOH (2 × 25 mL) again followed by DMF (2 × 25 mL), CH_2Cl_2 (3 × 25 mL), and then further dried in vacuo overnight to afford the resin-bound 5-bromopentanoic acid in good yield (2.73 g, 81%). Next, to the resin-bound 5-bromopentanoic acid (2.70 g, 3.9 mmol), swelled in DMF (10 mL), K_2CO_3 (2.13 g, 15.6 mmol) was added at ambient temperature, and the reaction suspension was stirred for another 30 min. Later, methyl 2-azido-4-hydroxy-5-methoxybenzoate (**5**, 1.73 g, 7.8 mmol) was added to the resin. The reaction suspension was stirred at 50 °C for 48 h. The solid-support was washed with water (3 × 20 mL), CH_2Cl_2 (2 × 20 mL), MeOH (3 × 15 mL), and then dried in vacuo to afford the resin-bound precursor **6a** (3.07 g, 75%). To a suspension of this resin-bound ester in 1,4-dioxane (10 mL) was added 1 N NaOH solution (2.5 mL) and the reaction mixture was heated at 80 °C for 12 h. On cooling, the resin was filtered and rinsed with water (2 × 15 mL), water/dioxane (1:9, 2 × 15 mL), MeOH (2 × 15 mL), CH_2Cl_2 (2 × 15 mL), Et_2O (2 × 15 mL) and dried in vacuo to afford the resin-bound acid. Next, to the resin-bound 2-azido-4-(5-ethoxy-5-oxopentyloxy)-benzoic acid (2.81 g, 2.6 mmol) swelled in CH_2Cl_2 (10 mL), EDCI (0.99 g, 5.2 mmol), HOBt (0.71 g, 5.2 mmol) and L-proline methyl ester (**7a**, 0.84 g, 6.5 mmol) were added. This reaction mixture was stirred for 12 h at room temperature, then resin was filtered and washed with H_2O (3 × 10 mL), CH_2Cl_2 (2 × 10 mL), MeOH (3 × 10 mL) and Et_2O (3 × 10 mL) to afford the resin bound methyl 5-(5-azido-4-(2-formylpyrrolidine-1-carbonyl)-2-methoxyphenoxy) pentanoate **8a** in good yield (2.89 g, 71%). To a suspension of this resin (0.110 g, 1.2 mmol) in CH_2Cl_2 (5 mL), $AlCl_3$ (0.79 g, 6 mmol), NaI (0.22 g, 2 mmol) and 2-(4-methoxyphenyl)ethanamine (**9a**, 0.35 mL, 2.4 mmol) were added at room temperature and stirred for 6 h. Aqueous 1 M potassium carbonate solution (2 mL) was added to the reaction mixture followed by excess of NaI, quenched with saturated sodium thiosulfate ($Na_2S_2O_3$), and then resin was separated by simple filtration and washed with CH_2Cl_2 (10 mL). The removal of excess amine impurities from the final resin cleaved crude product was achieved by solid-supported liquid–liquid extraction (SLE) with a fritted vessel previously packed with 'Varian's Hydromatrix'. The crude compound **1a** which contains excess of amine was passed through the Hydromatrix support into a collection plate below, while the amine salts were retained by the solid matrix, resulting in the effective removal of the amine impurities. This filtrate and washings were evaporated to dryness under reduced pressure. Finally, it was further purified by the preparative thin layer chromatography by using ethyl acetate:methanol (98:2) as eluent to afford the corresponding compound **1a** in high purity (brown solid, 0.013 g, 56%).