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SYNTHESIS AND EVALUATION OF NOVEL 3,4-EPOXYPIPERIDINES AS EFFICIENT DNA ALKYLATING AGENTS

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Abstract – 3,4-Epoxypiperidine derivatives are novel DNA alkylating agents based on an active site of the antitumor antibiotics azinomycins A and B. A 3,4-epoxypiperidine library was constructed containing derivatives with a variety of functional groups at C5 *via* Huisgen reaction, and DNA cleavage activity was examined. Results revealed a more active derivative than any 3,4-epoxypiperidines previously reported.

INTRODUCTION

Azinomycins A and B are antitumor antibiotics which were isolated from *Streptomyces griseofuscus* S42227 in 1986 (Figure 1).[1,2] Azinomycins possess potent *in vitro* cell cytotoxicity and greater *in vivo* antitumor activity than mitomycin C.[3,4] This bioactivity is derived from a 4-hydroxy-1-azabicyclo[3.1.0]hexane structure inherent in azinomycins.[5,6] Therefore, compounds containing the 4-hydroxy-1-azabicyclo[3.1.0]hexane structure are predicted to function as a DNA alkylating agents. However, this structure is unstable, which makes synthesis of 4-hydroxy-1-azabicyclo[3.1.0]hexane derivatives difficult.[7,8,9,10]

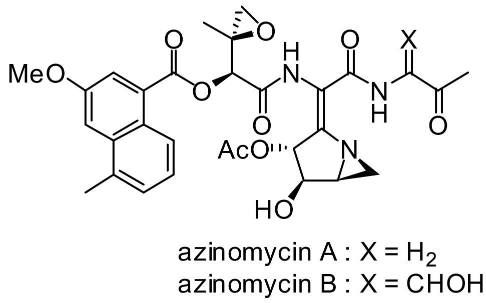


Figure 1. Structure of azinomycin A and B

A previously proposed hypothesis suggests that interconversion between the 4-hydroxy-1-azabicyclo[3.1.0]hexane structure and the 3,4-epoxypiperidine structure is possible (Figure 2). Based on this hypothesis, several 3,4-epoxypiperidine derivatives were synthesized, and some possessed significant DNA cleavage activity.[11] A relation between structure and DNA-cleavage activity also confirmed that a

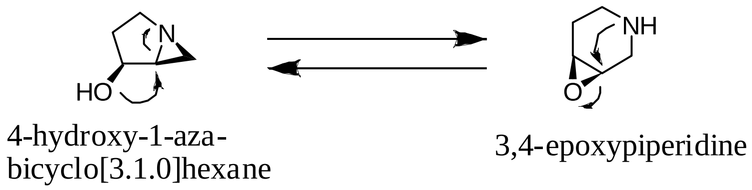


Figure 2. Hypothetical interconversion between azabicyclohexane and 3,4-epoxypiperidine

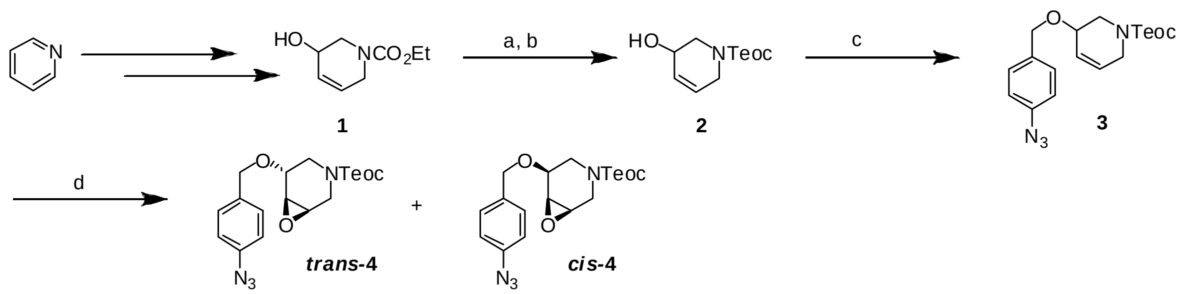
nitrogen atom and epoxide group are essential for DNA cleavage. These results supported the hypothesis and revealed the utility of 3,4-epoxypiperidine derivatives as DNA alkylating agents.

A previous report clarified that an aromatic substituent group at C5 played a significant role in DNA cleavage activity.[11] Thus, the present study describes the construction of a library of 3,4-epoxypiperidine derivatives with various functional groups at C5 to determine if a more active compound can be synthesized.

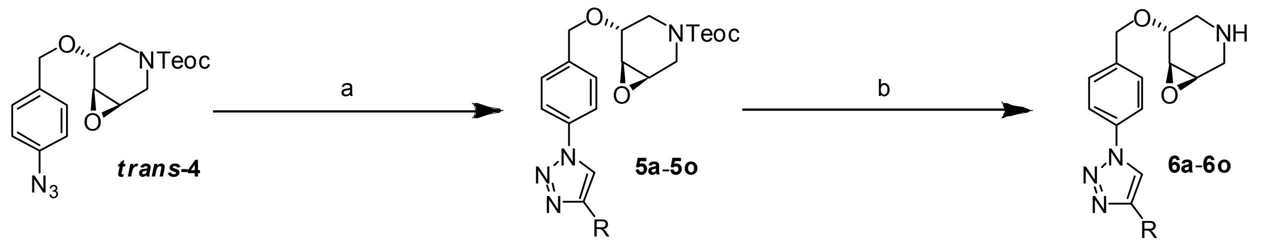
RESULTS AND DISCUSSION

The Huisgen reaction, a 1,3-dipolar cycloaddition between an azide and alkyne, was chosen for synthesis of the 3,4-epoxypiperidine derivatives. The Huisgen reaction is a representative reaction of "click chemistry" as proposed by Sharpless *et al.*[12] As azido and alkynyl groups are insensitive to several conditions, the Huisgen reaction is suitable for introduction of a functional group in the final stage of synthesis. In addition, a number of alkynes are commercially available. Therefore, the synthesis of a 3,4-epoxypiperidine derivative containing an azido group was planned for application of the Huisgen reaction.

Initially, an ethoxycarbonyl group of tetrahydropyridine **1**, prepared from pyridine according to a method previously reported[13], was exchanged for a 2-trimethylsilylethoxycarbonyl (Teoc) group, which can be easily removed under mild conditions. Introduction of an azido group into compound **2** was achieved using 4-azidobenzyl bromide prepared from 4-iodobenzyl alcohol *via* two steps.[14,15] Finally,



Scheme 1. Synthesis of 3,4-epoxypiperidine derivative **4**. *Reagents and conditions*: a) 5 N KOH, EtOH, reflux; b) Teoc-OSu, CH_2Cl_2, rt, 83%; c) NaH, 4-azidobenzyl bromide, DMF, rt; d) MCPBA, CH_2Cl_2, ***trans*-4**: 40% from **2**; ***cis*-4**: 15% from **2**.



Scheme 2. Huisgen reaction and deprotection of Teoc group. *Reagents and conditions*: a) R-C≡CH, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, *t*-BuOH : H_2O = 1 : 1, rt; b) TBAF, neat, rt.

Table 1. Construction of a 3,4-epoxypiperidine library using various alkynes.

		Huisgen reaction[a]			removal of Teoc group[b]		
entry	R	product	reaction time (h)	yield (%)[c]	product	reaction time (h)	yield (%)[c]
a	trimethylsilyl	**5a**	27	85	**6a**	2	82
b	methoxymethyl	**5b**	2	72	**6b**	1	quant.
c	ethoxycarbonyl	**5c**	1	64	**6c**	2	96
d	cyclopropyl	**5d**	1	87	**6d**	1	82
e	cyclohexyl	**5e**	1	quant.	**6e**	1.5	quant.
f	phenyl	**5f**	1	85	**6f**	1	76
g	benzyl	**5g**	1	85	**6g**	1	94
h	2-phenylethyl	**5h**	2	82	**6h**	1	83
i	2-pyridyl	**5i**	1	71	**6i**	2	quant.
j	4-fluorophenyl	**5j**	5	75	**6j**	1	quant.
k	1-naphthyl	**5k**	4	94	**6k**	1	quant.
l	2-naphthyl	**5l**	0.5	93	**6l**	0.5	quant.
m	1-anthracenyl	**5m**	24	58	**6m**	1	quant.
n	2-anthracenyl	**5n**	24	84	**6n**	2	72
o	9-anthracenyl	**5o**	24	66	**6o**	1.5	95

[a]Condition (entries a–l): alkyne (2 equiv.), $CuSO_4 \cdot 5H_2O$ (1 equiv.), sodium ascorbate (2 equiv.), *t*-BuOH : H_2O = 1 : 1, rt; condition (entries m–o): alkyne (1.3 equiv.), $CuSO_4 \cdot 5H_2O$ (1 equiv.), sodium ascorbate (2 equiv.), *t*-BuOH : H_2O = 1 : 1, rt. [b]Conditions: TBAF (1.5 equiv.), neat, rt. [c]Yield of isolated product.

epoxidation with MCPBA and separation of two diastereomers by silica gel column chromatography gave ***trans*-4** and ***cis*-4** as racemates in 40% and 15% yield, respectively. Determination of relative configuration was accomplished by comparison of ^{1}H NMR spectra of ***trans*-4** and ***cis*-4** with that of the compounds previously reported.[11]

A previous report revealed that the *trans* isomer was more active than the *cis* isomer. Therefore, ***trans*-4** was selected for reaction with several alkynes (Scheme 2, Table 1). In general, reactions of ***trans*-4** with alkynes occurred smoothly with good yields as shown in Table 1. When trimethylsilyl acetylene was employed, elimination of a trimethylsilyl group was also observed to give the corresponding non-substituted triazole (Table 1, entry a). Because some aromatic alkynes, such as 1-, 2- and 9-ethynylanthracenes, are not soluble in the reaction media (*t*-BuOH : H_2O = 1 : 1), reaction time was extended and product yields were moderate (Table 1, entries m, n, and o). The resulting triazoles **5** were transformed into 3,4-epoxypiperidine derivatives **6** in good yields upon removal of the Teoc group.

DNA cleavage activity of the 3,4-epoxypiperidines was examined using a relaxation assay of supercoiled plasmid DNA.[11] DNA damage transforms a supercoiled plasmid DNA (form I) into an open circular DNA (form II), which can be analyzed by agarose gel electrophoresis; a change in form alters the mobility on the agarose gel. The 3,4-epoxypiperidines **6a** to **6o** possessed several degrees of DNA cleavage activity. In particular, the derivatives containing aromatic rings at the C5 position showed significant improvement in DNA cleavage activity. These results indicate that the aromatic rings

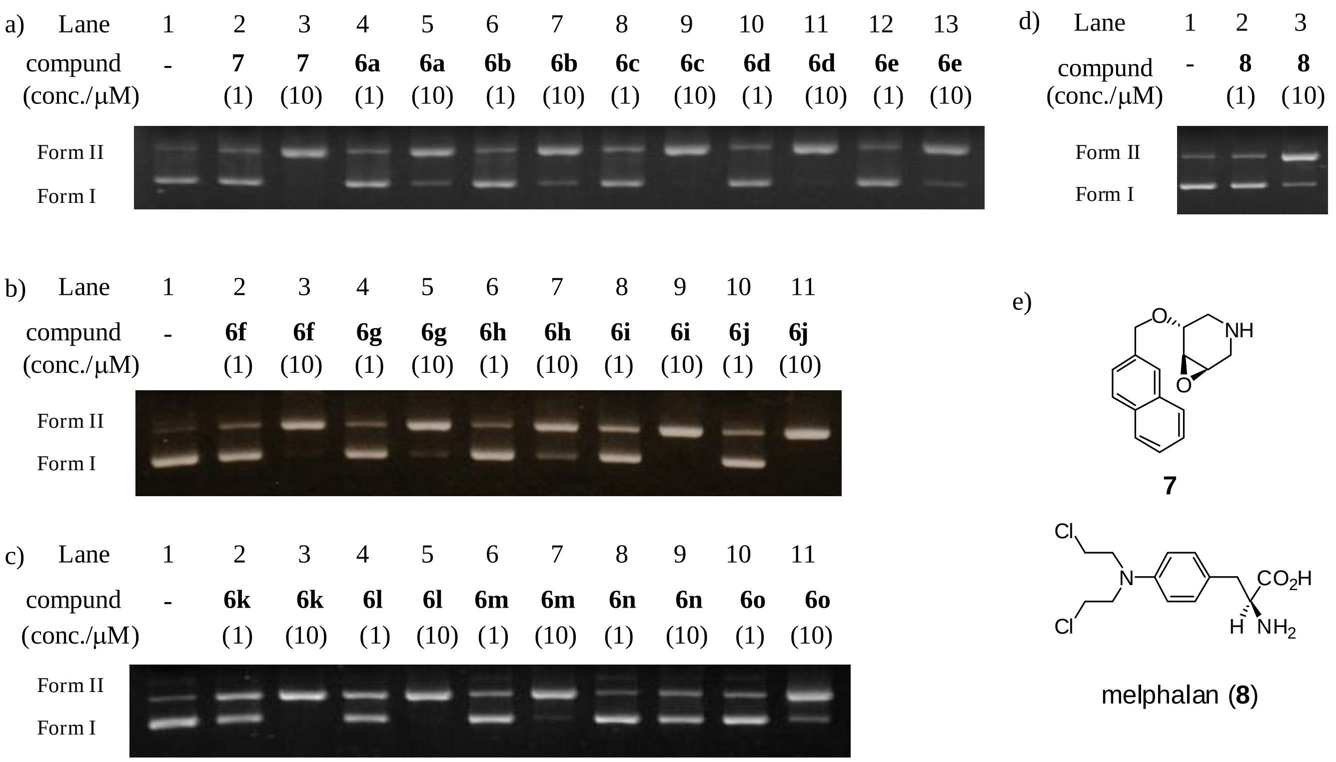


Figure 3. DNA cleavage activity of a) epoxypiperidine **7** and **6a**–**6e**, b) epoxypiperidine **6f**–**6j**, c) epoxypiperidine **6k**–**6o** and d) melphalan (**8**) as a positive control. e) Structures of **7** and melphalan (**8**).

functionas intercalators and enhance the affinity toward DNA. Interestingly, DNA cleavage of the benzyl derivative with the benzene ring connected to the triazole ring *via* a methylene bridge was not as great as that of derivatives with aromatic rings connected directly to the triazole ring (**6f** *vs*. **6g**). This fact was more dramatic for **6h**, *i.e.*, the activity of **6h** with an ethylene bridge was much weaker. These results demonstrate that the relative position of the aromatic ring and triazole structure is important for expression of activity. In compound **6f**, the benzene ring and triazole ring may work cooperatively to intercalate into the DNA strand. In addition, the size of aromatic ring obviously affected the activity. The activities of the naphthyl derivatives **6k** and **6l** were greater than those of the phenyl derivative **6f**, which acts at several μM, and melphalan (**8**), a clinically employed DNA alkylating agent.[16] Anthracenyltriazoles **6m**, **6n** and **6o** were less active than naphthyl triazoles **6k** and **6l**, indicating that the naphthyltriazolyl group is the best choice as the C5-substituent of the 3,4-epoxypiperidine derivative.

In conclusion, a 3,4-epoxypiperidine library **6a**–**6o** was constructed *via* a Huisgen reaction and the DNA alkylating activity of the derivatives was evaluated. Results of relaxation assay of plasmid DNA revealed that naphthyl triazole derivatives **6k** and **6l** possessed more potent activity than previously reported 3,4-epoxypiperidine derivative **7** and the DNA alkylating agent, melphalan, used for cancer treatment. This result indicates that 3,4-epoxypiperidine derivatives show promise as anticancer therapy drugs.

EXPERIMENTAL

Unless otherwise mentioned, all chemicals from commercial sources were used without further purification. CH_2Cl_2 and triethylamine were distilled over calcium hydride. All reactions were conducted under a nitrogen atmosphere. Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on JEOL EX-270 (^1H, 270 MHz; ^{13}C, 67.8 MHz), AL-300 (^1H, 300 MHz; ^{13}C, 75.5 MHz), ECS-400 (^1H, 400 MHz; ^{13}C, 100 MHz) instruments. Values of δ are in ppm relative to tetramethylsilane (0.00 ppm) or $CDCl_3$ (7.26 ppm) as internal standards. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. FAB-mass or EI-mass were measured on a JEOL JMS-600 or JMS-700 mass spectrometer. NALDI-mass was measured on Bruker Daitonics® Autoflex II TOF/TOF. Column chromatography was conducted using Fuji Silysia FL-100D, PSQ-100B silica gel.

4-Azidobenzyl bromide: 4-Iodobenzyl alcohol was converted to 4-azidobenzyl alcohol according to a previously reported method.[14] To a solution of 4-iodobenzyl alcohol (5.0 g, 21 mmol) in DMSO (35 mL) and water (7 mL) was added CuI (410 mg, 2.1 mmol), sodium ascorbate (640 mg, 3.2 mmol), NaN_3 (1.7 g, 26 mmol), and *N*,*N*-dimethylethylenediamine (94 mg, 120 μL, 1.1 mmol) at rt, and the resulting mixture stirred at the same temperature for 12 h. The reaction mixture was diluted with AcOEt and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give 4-azidobenzyl alcohol (3.1 g) as a yellow oil. To a stirred solution of 4-azidobenzyl alcohol (3.1 g) in CH_2Cl_2 (150 mL) was added phosphorus tribromide (2.8 g, 1.0 mL, 10 mmol) at 0°C, and the reaction mixture stirred for 20 min at the same temperature. After addition of ice water and extraction twice with CH_2Cl_2, the combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford 4-azidobenzyl bromide (3.7 g) as a brown oil, which was employed for the next reaction without purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.48 (2H, s), 7.00 (2H, dt, *J* = 2.0, 8.5 Hz), 7.38 (2H, dt, *J* = 2.0, 8.5 Hz).[15]

(5*RS*)-5-Hydroxy-*N*-(2-trimethylsilyl)ethoxycarbonyl-1,2,5,6-tetrahydropyridine (2): A solution of compound **1** (5.0 g, 29.2 mmol) in EtOH (20 mL) and 5 N KOH solution (20 mL) was refluxed for 19 h, and the reaction solvent concentrated under reduced pressure. CH_2Cl_2 (30 mL) and *N*-[2-(trimethylsilyl)ethoxycarbonyloxy]succinimide (8.3 g, 32.1 mmol) was added to the residue. The reaction mixture was stirred for 45 min at room temperature, diluted with Et_2O, and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 2) to give **2** (4.9 g, 83%) as a pale yellow oil; IR ν_{max} (KBr): 3414, 2953, 2896, 1700, 1433, 1356, 1234, 1178, 1159, 1113, 1063 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.39 (9H, s), 1.01 (2H, t, *J* = 7.5 Hz), 3.60 (2H, brs), 3.83 (1H, dd, *J* = 2.0, 16.0 Hz), 4.01–4.23 (2H, m), 4.20 (2H, t, *J* = 7.5 Hz), 5.85–5.94 (2H, m); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80°C) δ: –1.9, 17.0, 42.4, 47.0, 61.9, 62.2, 124.4, 129.8, 154.5; Mass (FAB) m/z 244 (M+H$^+$); HRMS (FAB) calcd for $C_{11}H_{22}N_1O_3Si$: 244.1369. Found: 244.1353.

(5*RS*)-5-(4-Azidobenzyloxy)-*N*-(2-trimethylsilyl)ethoxycarbonyl-1,2,5,6-tetrahydropyridine (3): To a stirred solution of **2** (4.2 g, 17.5 mmol) in DMF (60 mL) was added NaH (60% in oil, 1.40 g, 35 mmol) at 0°C and the mixture was stirred at the same temperature for 20 min. 4-Azidobenzyl bromide (3.7 g, 17.5 mmol) in DMF (60 mL) was added dropwise to the reaction mixture at 0°C, and stirred at rt for 1 h. After addition of water at 0°C, the resulting mixture was extracted twice with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give **3** (6.5 g) as a brown oil, which was used for the next reaction without further purification; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.05 (9H, s), 1.01 (2H, t, *J* = 8.0), 3.58 (1H, brs), 3.77 (1H, brs), 3.96 (3H, brs), 4.20 (2H, t, *J* = 8.0 Hz), 4,51–4.64 (2H, m), 5.90 (2H, s), 7.00 (2H, d, *J* = 8.5 Hz), 7.35 (2H, d, *J* = 8.5 Hz); Mass (FAB) m/z 375 (M+H$^+$); HRMS (FAB) calcd for $C_{18}H_{27}N_4O_3Si$: 375.1852. Found: 375.1830.

(3*RS*,4*RS*,5*RS*)-5-(4-Azidobenzyloxy)-3,4-epoxy-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (*tnans*-4): To a solution of **3** (6.6 g, 17.5 mmol) in CH_2Cl_2 (170 mL) was added MCPBA (9.1 g, 52.5 mmol) at rt and the resulting mixture stirred at the same temperature for 84 h. After addition of a mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (*ca*. 120 mL, 1 : 1), the reaction mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ solution, water, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 4) to give ***trans*-4** (2.9 g, 40% from **2**) and ***cis*-4** (1.1 g, 15% from **2**) as pale yellow oils; ***trans*-4**; IR ν_{max} (KBr): 2953, 2898, 2112, 1698, 1507, 1462, 1424, 1358, 1284, 1248, 1178, 1126, 1089 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.04 (9H, s), 1.01 (2H, t, *J* = 8.0 Hz), 3.27 (2H, s), 3.44–3.56 (2H, m), 3.86 (3H, brs), 4.18 (2H, t, *J* = 8 Hz), 4.56 (1H, d, *J* = 11.0 Hz), 4.70 (1H, d, *J* = 11.0 Hz), 7.02 (2H, d, *J* = 8.0 Hz), 7.36 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80 °C) δ: –1.9, 16.8, 41.3, 41.4, 49.3, 51.2, 62.4, 69.6, 69.7, 118.6, 128.9, 134.9, 138.4, 154.9; Mass (FAB) m/z 391 ($M+H^+$); HRMS (FAB) calcd for $C_{18}H_{27}N_4O_4Si$: 391.1802. Found: 391.1775.

1-(3-Hydroxy-3-methyl-1-butynyl)anthracene: To a solution of 1-bromoanthracene (500 mg, 1.9 mmol) and 2-methyl-3-butyn-2-ol (330 mg, 0.38 mL, 3.9 mmol) in triethylamine (10 mL) were added CuI (3.7 mg, 19 μmol) and $Pd(PPh_3)_2Cl_2$ (6.8 mg, 9.7 μmol), and the reaction mixture stirred at 80°C for 10 h. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel column chromatography ($CHCl_3$: *n*-hexane = 1 : 1) to give 1-(3-hydroxy-3-methyl-1-butynyl)anthracene (380 mg, 75%) as a yellow oil; IR ν_{max} (KBr): 3347, 3050, 2980, 2928, 1613, 1456, 1373, 1314, 1268, 1225, 1163 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.82 (6H, s), 2.19 (1H, s), 7.38 (1H, t, *J* = 7.0 Hz), 7.49–7.52 (2H, m), 7.67 (1H, d, *J* = 7.0 Hz), 7.95 (1H, d, *J* = 8.0 Hz), 7.98–8.01 (1H, m), 8.07–8.09 (1H, m), 8.40 (1H, s), 8.84 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.7, 65.9, 80.4, 99.1, 120.3, 124.4, 124.8, 125.7, 126.8, 127.9, 128.5, 129.1, 130.2, 130.9, 131.1, 131.8, 132.0; Mass (EI) m/z 260 (M^+, 100), 245 (50), 242 (29), 202 (29); HRMS (EI) calcd for $C_{19}H_{16}O$: 260.1201. Found: 260.1211.

1-Ethynylanthracene: A mixture of 1-(3-hydroxy-3-methyl-1-butynyl)anthracene (380 mg, 1.4 mmol) and KOH (120 mg, 2.1 mmol) in toluene (15 mL) was heated under reflux for 1 h. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel column chromatography ($CHCl_3$: *n*-hexane = 1 : 1) to give 1-ethynylanthracene (225 mg, 78%) as a yellow solid; mp 68–70°C (EtOH); IR ν_{max} (KBr): 3284, 3051, 1611, 1537, 1452, 1371, 1309 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.60 (1H,s), 7.41 (1H, dd, *J* = 7.0, 9.0 Hz), 7.49-7.53 (2H, m), 7.76 (1H, d, *J* = 6.5 Hz), 8.03 (2H, d, *J* = 9.0 Hz), 8.09–8.11 (1H, m), 8.45 (1H, s), 8.93 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 82.0, 82.4, 119.8, 124.4, 124.9, 125.9, 125.9, 126.9, 128.0, 128.5, 129.7, 131.0, 131.1, 131.9, 132.2; Mass (EI) m/z 202 (M^+, 100); HRMS (EI) calcd for $C_{16}H_{10}$: 202.0782. Found: 202.0783.

2-(3-Hydroxy-3-methyl-1-butynyl)anthracene: To a solution of 2-bromoanthracene (500 mg, 1.9 mmol) and 2-methyl-3-butyn-2-ol (330 mg, 0.38 mL, 3.9 mmol) in triethylamine (10 mL) were added CuI (3.7 mg, 19 μmol) and $Pd(PPh_3)_2Cl_2$ (6.8 mg, 9.7 μmol), and the reaction mixture was stirred at 80°C for 10 h. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel column chromatography ($CHCl_3$) to give 2-(3-hydroxy-3-methyl-1-butynyl)anthracene (175 mg, 35%) as a yellow solid; mp 188°C (EtOH); IR ν_{max} (KBr): 3347, 2982, 2929, 1623, 1457, 1362, 1272, 1242, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.67 (6H, s), 2.06 (1H, s), 7.33 (1H, d, *J* = 9.0 Hz), 7.39 (2H, dd, *J* = 3.0, 6.5 Hz), 7.84 (1H, d, *J* = 9.0 Hz), 7.90 (1H, brs), 8.03 (1H, s), 8.28 (2H, d, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.5, 65.8, 82.7, 94.5, 119.4, 125.7, 125.8, 126.2, 126.2, 127.6, 128.1, 128.2, 128.2, 130.6, 130.9, 131.9, 132.0, 132.1; Mass (EI) m/z 260 (M^+, 100), 245 (69), 202 (56); HRMS (EI) calcd for $C_{19}H_{16}O$: 260.1201. Found: 260.1208.

2-Ethynylanthracene: A mixture of 2-(3-hydroxy-3-methyl-1-butynyl)anthracene (135 mg, 0.52 mmol) and KOH (43 mg, 0.77 mmol) in toluene (5 mL) was heated under reflux for 1 h. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel column chromatography ($CHCl_3$) to give 1-ethynylanthracene (96 mg, 92%) as a yellow solid; mp 175–176°C (EtOH); IR ν_{max} (KBr): 3290, 3053, 1621, 1456, 1304, 1270, 1155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.21 (1H,s),7.46–7.51 (3H, m), 7.96 (1H, d, *J* = 9.0 Hz), 8.00 (2H, brs), 8.21 (1H, s), 8.40 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 77.9, 84.2, 118.7, 125.8, 125.9, 126.2, 126.4, 127.5, 128.1, 128.3, 128.3, 130.8, 132.0, 132.2, 132.9;Mass (EI) m/z 202 (M^+, 100); HRMS (EI) calcd for $C_{16}H_{10}$: 202.0782. Found: 202.0785.

Typical procedure for preparation of 5

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-[4-(1*H*-1,2,3-triazol-1-yl)benzyloxy]-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5a): To a solution of ***trans*-4** (75 mg, 0.19 mmol) in *t*-BuOH (1.0 mL) and water (1.0 mL) were added $CuSO_4 \cdot 5H_2O$ (48 mg, 0.19 mmol), sodium ascorbate (76 mg, 0.38 mmol), and trimethylsilylacetylene (39 mg, 55 μL, 0.38 mmol) at rt, and the reaction mixture stirred at the same temperature for 27 h. The reaction mixture was extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 1) to give **5a** (68 mg, 85%) as a white paste; IR ν_{max} (KBr): 2953, 1696, 1522, 1463, 1420, 1359, 1321, 1281, 1250, 1177, 1127, 1092, 1030 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.07 (9H, s), 1.01 (2H, t, *J* = 8.0 Hz), 3.31 (2H, brs), 3.48–3.60 (2H, m), 3.87 (3H, brs), 4.18 (2H, t, *J* = 8.0 Hz), 4.64 (1H, d, *J* = 11.5 Hz), 4.80 (1H, d, *J* = 11.5 Hz), 7.53 (2H, d, *J* = 7.5 Hz), 7.74 (2H, d, *J* = 7.5 Hz), 7.86 (1H, s), 7.99 (1H, s); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80°C) δ: –1.0, 18.0, 42.3, 42.4, 50.3, 52.2, 63.4, 70.5, 70.8, 69.7, 120.8, 123.6, 129.4, 134.7, 136.8, 139.4, 155.8; Mass (FAB) m/z 417 ($M+H^+$); HRMS (FAB) calcd for $C_{20}H_{29}N_4O_4Si$: 417.1958. Found: 417.1960.

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-[4-(4-methoxymethyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]-

***N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5b)**: a colorless oil; IR ν_{max} (KBr): 2952, 1696, 1521, 1463, 1421, 1281, 1249, 1094, 1044, 1024 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.04 (9H, s), 1.00 (2H, t, *J* = 8.0 Hz), 3.31 (2H, brs), 3.47 (3H, s), 3.47–3.60 (2H, m), 3.87 (3H, brs), 4.18 (2H, t, *J* = 8.0 Hz), 4.63 (1H, d, *J* = 11.5 Hz), 4.82 (1H, d, *J* = 11.5 Hz), 7.52 (2H, d, *J* = 8.0 Hz), 7.73 (2H, d, *J* = 8.0 Hz), 7.97 (1H, s); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80°C) δ: –1.0, 18.0, 42.3, 42.4, 50.3, 52.2, 58.0, 63.4, 65.7, 70.5, 70.8, 120.6, 122.5, 129.4, 136.7, 139.4, 145.7, 155.9; Mass (FAB) m/z 489 ($M+H^+$); HRMS (FAB) calcd for $C_{23}H_{33}N_4O_6Si$: 489.2169. Found: 489.2168.

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-[4-(4-ethoxycarbonyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5c): a yellow oil; IR ν_{max} (KBr): 2953, 2898, 1733, 1697, 1541, 1521, 1463, 1422, 1372, 1339, 1250, 1174, 1149, 1127, 1092 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.04 (9H, s), 1.01 (2H, t, *J* = 8.0 Hz), 1.45 (3H, t, *J* = 7.0 Hz), 3.31 (2H, brs), 3.43–3.65 (2H, m), 3.87 (3H, brs), 4.18 (2H, t, *J* = 8.0 Hz), 4.48 (2H, q, *J* = 7.0 Hz), 4.65 (1H, d, *J* = 11.0 Hz), 4.83 (1H, d, *J* = 11.0 Hz), 7.56 (2H, d, *J* = 8.0 Hz), 7.75 (2H, d, *J* = 8.0 Hz), 8.50 (1H, s); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80°C) δ: –1.0, 14.7, 18.0, 42.3, 42.4, 50.3, 52.2, 61.2, 63.5, 70.5, 70.9, 121.2, 127.6, 129.4, 136.1, 140.2, 140.5, 155.9, 160.7; Mass (FAB) m/z 461 ($M+H^+$); HRMS (FAB) calcd for $C_{22}H_{33}N_4O_5Si$: 461.2220. Found: 461.2225.

(3*RS*,4*RS*,5*RS*)-5-[4-(4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]-3,4-epoxy-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5d): a colorless oil; IR ν_{max} (KBr) : 2952, 1695, 1521, 1463, 1420, 1338, 1281, 1249, 1126, 1091, 1039 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.04 (9H, s), 0.93–1.03 (6H, m), 1.98–2.08 (1H, m), 3.30 (2H, brs), 3.48–3.63 (2H, m), 3.86 (3H, brs), 4.18 (2H, t, *J* = 8.0 Hz), 4.62 (1H, d, *J* = 11.5 Hz), 4.79 (1H, d, *J* = 11.5 Hz), 7.50 (2H, d, *J* = 8.0 Hz), 7.66 (1H, s), 7.69 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80°C) δ: –1.0, 7.0, 8.0, 18.0, 42.3, 42.4, 50.3, 52.2, 63.4, 70.6, 70.8, 119.4, 120.3, 129.3, 136.8, 139.0, 150.7, 156.0; Mass (FAB) m/z 457 ($M+H^+$); HRMS (FAB) calcd for $C_{23}H_{33}N_4O_4Si$: 457.2271. Found: 457.2272.

(3*RS*,4*RS*,5*RS*)-5-[4-(4-Cyclohexyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]-3,4-epoxy-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5e)

a colorless oil; IR ν_{max} (KBr) : 2926, 2853, 1697, 1519, 1449, 1420, 1280, 1249, 1126, 1091, 1047 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.04 (9H, s), 1.00 (2H, t, *J* = 8.0 Hz), 1.37–1.51 (6H, m), 1.74–1.86 (2H, m), 2.11 (2H, brs), 2.86 (1H, brs), 3.30 (2H, brs), 3.44–3.59 (2H, m), 3.87 (3H, brs), 4.18 (2H, t, *J* = 8 Hz), 4.62 (1H, d, *J* = 11.0 Hz), 4.80 (1H, d, *J* = 11.0 Hz), 7.50 (2H, d, *J* = 8.0 Hz), 7.68 (2H, d, *J* = 8.0 Hz), 7.73 (1H, s); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80°C) δ: –1.0, 18.0, 26.0, 26.2, 33.0, 35.3, 42.3, 42.4, 50.3, 52.2, 63.4, 70.6, 70.8, 119.3, 120.3, 129.3, 137.0, 139.0, 153.8, 155.9; Mass (FAB) m/z 499 ($M+H^+$); HRMS (FAB) calcd for $C_{26}H_{30}N_4O_4Si$: 499.2741. Found: 499.2733.

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-[4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5f): a white solid; mp 58–60°C (toluene : *n*-hexane = 1 : 3); IR ν_{max} (KBr): 2953, 1697, 1522, 1460, 1419, 1281, 1250, 1124, 1090, 1042 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.05 (9H, s), 1.01 (2H, t, *J* = 8.0 Hz), 3.32 (2H, brs), 3.49–3.66 (2H, m), 3.87 (3H, brs), 4.20 (2H, t, *J* = 8 Hz), 4.65 (1H, d, *J* = 11.5 Hz), 4.70 (1H, d, *J* = 11.5 Hz), 7.31–7.56 (5H, m), 7.79 (2H, d, *J* = 8.0 Hz), 7.92 (2H, d, *J* = 8.0 Hz), 8.20 (1H, s); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80°C) δ: –1.0, 18.0, 42.4, 42.4, 50.3, 52.2, 63.5, 70.6, 70.8, 120.0, 120.6, 126.1, 128.7, 129.4, 131.0, 136.0, 136.7, 139.5, 148.0, 155.9; Mass (FAB) m/z 493 (M+H$^+$); HRMS (FAB) calcd for $C_{26}H_{33}N_4O_4Si$: 493.2271. Found: 493.2261; *Anal*. Calcd for $C_{26}H_{32}N_4O_4Si$: C, 63.39; H, 6.55; N, 11.37. Found: C, 63.16; H, 6.48; N, 11.35.

(3*RS*,4*RS*,5*RS*)-5-[4-(4-Benzyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]-3,4-epoxy-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5g): a white paste; IR ν_{max} (KBr): 2952, 1697, 1520, 1456, 1419, 1359, 1282, 1250, 1124, 1090, 1043, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.03 (9H, s), 1.00 (2H, t, *J* = 8.0 Hz), 3.29 (2H, brs), 3.44–3.61 (2H, m), 3.84–3.88 (3H, m), 4.17 (2H, t, *J* = 8 Hz), 4.18 (2H, s), 4.61 (1H, d, *J* = 12.0 Hz), 4.79 (1H, d, *J* = 12.0 Hz), 7.24–7.28 (1H, m), 7.32–7.34 (4H, m), 7.47 (2H, d, *J* = 8.0 Hz), 7.58 (1H, s), 7.68 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (75.45 MHz, DMSO-d_6, 80°C) δ: –2.0, 17.0, 30.9, 41.3, 41.4, 49.3, 51.2, 62.4, 69.6, 69.8, 119.5, 120.2, 125.7, 127.9, 128.1, 128.3, 135.8, 138.2, 138.8, 146.7, 154.9; Mass (FAB) m/z 507 (M+H$^+$); HRMS (FAB) calcd for $C_{27}H_{35}N_4O_4Si$: 507.2428. Found: 507.2426.

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-[4-(4-phenethyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5h): a colorless oil; IR ν_{max} (KBr): 2952, 1696, 1520, 1455, 1420, 1281, 1249, 1126, 1091, 1045 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.04 (9H, s), 1.01 (2H, t, *J* = 8.0 Hz), 3.09 (2H, t, *J* = 5.5 Hz), 3.11 (2H, t, *J* = 5.5 Hz), 3.30 (2H, brs), 3.48–3.63 (2H, m), 3.87 (3H, brs), 4.18 (2H, t, *J* = 8.0 Hz), 4.62 (1H, d, *J* = 11.5 Hz), 4.80 (1H, d, *J* = 11.5 Hz), 7.21–7.30 (5H, m), 7.49–7.54 (3H, m), 7.67 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80°C) δ: –1.9, 17.1, 26.5, 34.3, 41.5, 41.5, 549.4, 51.3, 62.6, 69.7, 69.9, 119.5, 119.8, 125.6, 127.9, 127.9, 128.5, 136.0, 138.2, 140.8, 147.1, 155.0; Mass (FAB) m/z 521 (M+H$^+$); HRMS (FAB) calcd for $C_{28}H_{37}N_4O_4Si$: 521.1584. Found: 521.2581.

(3*RS*, 4*RS*,5*RS*)-3,4-Epoxy-5-{4-[4-(2-pyridinyl) -1*H*-1,2,3-triazol-1-yl]benzyloxy}-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5i): colorless crystals; mp 110–111°C (toluene : *n*-hexane = 1 : 2); IR ν_{max} (KBr): 2952, 1695, 1602, 1521, 1468, 1412, 1357, 1279, 1249, 1126, 1091, 1029 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.07 (9H, s), 1.00 (2H, t, *J* = 7.5 Hz), 3.30 (2H, brs), 3.43–3.60 (2H, m), 3.87 (3H, brs), 4.18 (2H, t, *J* = 7.5 Hz), 4.64 (1H, d, *J* = 10.0 Hz), 4.81 (1H, d, *J* =

10.0 Hz), 7.26 (1H, t, J = 7.0 Hz), 7.54 (2H, d, J = 6.5 Hz), 7.79–7.81 (2H, m), 8.25 (1H, d, J = 7.0 Hz), 8.59 (1H, s), 8.61 (1H, d, J = 7.0 Hz); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80°C) δ: –1.0, 17.9, 42.3, 42.4, 50.3, 52.2, 63.4, 70.5, 70.8, 120.4, 120.8, 121.7, 123.7, 129.3, 136.6, 137.6, 139.6, 148.8, 150.1, 150.2, 155.8; Mass (FAB) m/z 494 (M+H$^+$); *Anal*. Calcd for $C_{25}H_{31}N_5O_4Si$: C, 60.83; H, 6.33; N, 14.19. Found: C, 60.97; H, 6.28; N, 14.13.

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-{4-[4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl]benzyloxy}-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5j): a white solid; mp 97–99°C (toluene : *n*-hexane = 1 : 2); IR ν_{max} (KBr): 2953, 1698, 1495, 1465, 1423, 1280, 1250, 1093, 1043 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.04 (9H, s), 1.01 (2H, t, J = 7.5 Hz), 3.31 (2H, brs), 3.48–3.59 (2H, m), 3.87 (3H, brs), 4.18 (2H, t, J = 7.5 Hz), 4.65 (1H, d, J= 11.5 Hz), 4.84 (1H, d, J = 11.5 Hz), 7.16 (2H, t, J = 8.5 Hz), 7.55 (2H, d, J = 8.0 Hz), 7.78 (2H, d, J = 8.0 Hz), 7.89 (2H, dd, J = 5.5, 8.5 Hz), 8.14 (1H, s); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80°C) δ: –1.0, 18.0, 42.4, 42.4, 50.3, 52.2, 63.5, 70.6, 70.8, 116.4 (d, J = 22.0 Hz), 112.0, 120.6, 127.6 (d, J = 3.0 Hz), 128.1 (d, J = 8.5 Hz), 129.4, 136.7, 139.6, 147.1, 155.9, 162.7 (d, J = 245.0 Hz); Mass (FAB) m/z 511 (M+H$^+$); HRMS (FAB) calcd for $C_{26}H_{32}FN_4O_4Si$: 511.2177. Found: 511.2171.

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-{4-[4-(1-naphthyl) -1*H*-1,2,3-triazol-1-yl]benzyloxy}-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5k): a pale yellow foam; IR ν_{max} (KBr): 2952, 1695, 1520, 1462, 1423, 1356, 1248, 1126, 1091, 1045 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.05 (9H, s), 1.02 (2H, t, J = 8.0 Hz), 3.30 (2H, brs), 3.50–3.65 (2H, m), 3.88 (3H, brs), 4.19 (2H, t, J = 8.0 Hz), 4.67 (1H, d, J = 12.0 Hz), 4.86 (1H, d, J = 12.0 Hz), 7.51–7.59 (5H, m), 7.92–7.95 (5H, m), 8.25 (1H, s), 8.44 (1H, t, J = 5.0 Hz); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80 °C) δ: –1.0, 18.0, 42.4, 42.5, 50.3, 52.2, 63.5, 70.6, 70.8, 120.8, 122.6, 126.0, 126.1, 126.6, 127.2, 127.7, 128.2, 128.9, 129.4, 129.4, 131.2, 134.3, 136.8, 139.5, 147.3, 155.9; Mass (FAB) m/z 543 (M+H$^+$); HRMS (FAB) calcd for $C_{30}H_{35}N_4O_4Si$: 543.2428. Found: 543.2429.

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-{4-[4-(2-naphthyl) -1*H*-1,2,3-triazol-1-yl]benzyloxy}-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5l) a white solid; mp. 113–114°C (toluene : *n*-hexane = 1 : 3); IR ν_{max} (KBr): 2953, 1698, 1520, 1464, 1418, 1250, 1117, 1042, 951 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.05 (9H, s), 1.02 (2H, t, J = 8.0 Hz), 3.31 (2H, brs), 3.45–3.61 (2H, m), 3.88 (3H, brs), 4.20 (2H, t, J = 8.0 Hz), 4.66 (1H, d, J = 11.5 Hz), 4.84 (1H, d, J = 11.5 Hz), 7.49–7.58 (4H, m), 7.81–8.00 (6H, m), 8.31 (1H, s), 8.43 (1H, s); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80°C) δ: –1.0, 18.0, 42.4, 42.5, 50.3, 52.2, 63.5, 70.6, 70.9, 120.4, 120.6, 124.4, 124.5, 126.7, 127.1, 128.3, 128.5, 128.5, 129.1, 129.4, 133.4, 133.8, 136.7, 139.5, 148.0, 155.9; Mass (FAB) m/z 543 (M+H$^+$); *Anal*. Calcd for $C_{30}H_{34}N_4O_4Si$: C, 66.39; H, 6.31; N, 10.32. Found: C, 66.11; H, 6.29; N, 10.29.

(3*RS*,4*RS*,5*RS*)-5-{4-[4-(1-Anthracenyl)-1*H*-1,2,3-triazol-1-yl]benzyloxy}-3,4-epoxy-*N*-

(2-trimethylsilyl)ethoxycarbonylpiperidine (5m): a yellow foam; IR ν_{max} (KBr): 2952, 2898, 2109, 1694, 1519, 1462, 1418, 1312, 1281, 1250, 1125, 1092, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.05 (9H, s), 1.02 (2H, t, *J* = 8.0 Hz), 3.34 (2H, brs), 3.51–3.67 (2H, m), 3.89–3.97 (3H, m), 4.20 (2H, t, *J* = 8.0 Hz), 4.71 (1H, d, *J* = 12.0 Hz), 4.87 (1H, d, *J* = 12.0 Hz), 7.46–7.62 (5H, m), 7.77 (1H, d, *J* = 6.5 Hz), 7.90 (2H, d, *J* = 8.0 Hz), 8.03 (2H, d, *J* = 8.0 Hz), 8.10 (1H, d, *J* = 8.0 Hz) 8.34 (1H, s), 8.52 (1H, s), 9.06 (1H, s); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80 °C) δ: –1.9, 17.0, 41.4, 41.5, 49.3, 51.3, 62.5, 69.6, 69.8, 119.9, 121.8, 124.0, 124.4, 125.2, 125.5, 126.2, 126.3, 127.3, 127.3, 128.2, 128.4, 128.4, 128.7, 130.8, 131.3, 131.3, 135.8, 138.6, 146.4, 154.9; Mass (FAB) m/z 593 $(M+H^+)$; HRMS (FAB) calcd for $C_{34}H_{37}N_4O_4Si$: 593.2584. Found: 593.2584.

(3*RS*,4*RS*,5*RS*)-5-{4-[4-(2-Anthracenyl)-1*H*-1,2,3-triazol-1-yl]benzyloxy}-3,4-epoxy-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5n): a yellow solid; mp 155–156°C (toluene : *n*-hexane = 1 : 3); IR ν_{max} (KBr): 2954, 1698, 1520, 1464, 1418, 1281, 1251, 1231, 1092, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.05 (9H, s), 1.02 (2H, t, *J* = 8.0 Hz), 3.32 (2H, brs), 3.50–3.65 (2H, m), 3.88–3.90 (3H, m), 4.20 (2H, t, *J* = 8.0 Hz), 4.63 (1H, d, *J* = 11.5 Hz), 4.82 (1H, d, *J* = 11.5 Hz), 7.45–7.55 (4H, m), 7.80 (1H, d, *J* = 7.5 Hz), 7.94–8.09 (4H, m), 8.30 (1H, s), 8.41 (1H, s), 8.46 (1H, s), 8.58 (1H, s); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80°C) δ: –1.9, 17.0, 41.4, 41.5, 49.3, 51.2, 62.5, 69.6, 69.9, 119.5, 119.6, 123.3, 123.4, 125.2, 125.3, 125.7, 125.9, 126.9, 127.6, 127.6, 128.4, 128.5, 130.5, 130.8, 131.2, 131.4, 135.7, 138.6, 147.0, 154.9; Mass (FAB) m/z 593 $(M+H^+)$; HRMS (FAB) calcd for $C_{34}H_{37}N_4O_4Si$: 593.2584. Found: 593.2595.

(3*RS*,4*RS*,5*RS*)-5-{4-[4-(9-Anthracenyl)-1*H*-1,2,3-triazol-1-yl]benzyloxy}-3,4-epoxy-*N*-(2-trimethylsilyl)ethoxycarbonylpiperidine (5o): a white foam; IR ν_{max} (KBr): 2952, 1694, 1519, 1462, 1421, 1357, 1313, 1279, 1249, 1126, 1091, 1047, 1026 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.06 (9H, s), 1.02 (2H, t, *J* = 8.0 Hz), 3.34 (2H, brs), 3.51–3.62 (2H, m), 3.91 (3H, brs), 4.20 (2H, t, *J* = 8.0 Hz), 4.69 (1H, d, *J* = 12.0 Hz), 4.87 (1H, d, *J* = 12.0 Hz), 7.42–7.52 (4H, m), 7.61 (2H, d, *J* = 7.5 Hz), 7.92 (2H, d, *J* = 8.0 Hz), 7.93 (2H, d, *J* = 8.0 Hz), 8.07 (2H, d, *J* = 7.5 Hz), 8.25 (1H, s), 8.59 (1H, s); ^{13}C NMR (67.8 MHz, DMSO-d_6, 80°C) δ: –1.9, 17.0, 14.4, 41.5, 49.3, 51.3, 62.5, 69.6, 69.8, 123.7, 124.1, 124.9, 125.4, 125.9, 127.7, 128.0, 128.5, 130.3, 130.6, 135.8, 138.6, 143.1, 154.9; Mass (FAB) m/z 593 $(M+H^+)$; HRMS (FAB) calcd for $C_{34}H_{37}N_4O_4Si$: 593.2584. Found: 593.2584.

Typical procedure of preparation of 6

(3*RS*,4*RS*,5*RS*)-3,4-epoxy-5-[4-(1*H*-1,2,3-triazol-1-yl)benzyloxy]piperidine (6a): Tetra-*n*-butylammonium fluoride (1.0 M THF solution, 36 μmol, 36 μL) was added to **5a** (10 mg, 24 μmol) and the solvent was concentrated under reduced pressure. The reaction mixture was left at rt for 2 h and purified by silica gel column chromatography ($CHCl_3$: MeOH = 25 : 1) to give **6a** (5.3 mg, 82%) as a colorless oil. This compound was immediately dissolved in DMSO to prevent polymerization, ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.51 (1H, dd, *J* = 7.5, 13.5 Hz), 3.06 (1H, dd, *J* = 5.0, 13.5 Hz), 3.14–3.25 (3H, m), 3.29 (1H, d, *J* = 4.0 Hz), 3.65 (1H, dd, *J* = 5.5, 7.5 Hz), 4.69 (1H, d, *J* = 12.0 Hz), 4.75 (1H, d, *J* = 12.0 Hz), 7.53 (2H, d, *J* = 8.5 Hz), 7.75 (2H, dt, *J* = 2.0, 8.5 Hz), 7.85 (1H, d, *J* = 1.0 Hz), 7.99 (1H, d, *J* = 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.9, 45.2, 50.9, 52.8, 70.6, 70.7, 120.7, 121.7, 128.9, 134.5, 136.5, 138.7.

(3*RS*,4*RS*,5*RS*)-3,4-epoxy-5-[4-(4-methoxymethyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]piperidine (6b): a colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.51 (1H, dd, *J* = 7.5, 13.5 Hz), 3.06 (1H, dd, *J* = 5.5, 13.5 Hz), 3.14–3.25 (3H, m), 3.29 (1H, d, *J* = 3.5 Hz), 3.48 (3H, s), 3.65 (1H, dd, *J* = 5.5, 7.5 Hz),4.68 (2H, s), 4.67 (1H, d, *J* = 12.0 Hz), 4.74 (1H, d, *J* = 12.0 Hz), 7.52 (2H, d, *J* = 8.5 Hz), 7.73 (2H, d, *J* = 8.5 Hz), 7.98 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.8, 45.2, 50.9, 52.8, 58.5, 66.0, 70.6, 70.7, 120.5, 120.6, 128.8, 136.5, 138.7, 145.9.

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-[4-(4-ethoxycarbonyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]piperidine (6c): a colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.44 (3H, t, *J* = 7.5 Hz), 2.50 (1H, dd, *J* = 7.5, 13.5 Hz), 3.06 (1H, dd, *J* = 5.0, 13.5 Hz), 3.14–3.25 (3H, m), 3.29 (1H, d, *J* = 4.0 Hz), 3.65 (1H, dd, *J* = 5.5, 7.0 Hz), 4.47 (2H, q, *J* = 7.5 Hz), 4.70 (1H, d, *J* = 12.0 Hz), 4.75 (1H, d, *J* = 12.0), 7.55 (2H, d, *J* = 8.5 Hz), 7.76 (2H, dt, *J* = 2.0, 8.5 Hz), 8.50 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 43.8, 45.2, 50.9, 52.8, 61.5, 70.6, 70.7, 120.9, 125.4, 128.9, 135.8, 139.6, 140.89 160.6.

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-[4-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]piperidine (6d): a colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.90–1.05 (4H, m), 1.98–2.08 (1H, m), 2.50 (1H, dd, *J* = 7.5, 13.5 Hz), 3.05 (1H, dd, *J* = 5.0, 13.5 Hz), 3.10–3.21 (3H, m), 3.29 (1H, d, *J* = 3.5 Hz), 3.64 (1H, t, *J* = 6.0 Hz), 4.67 (1H, d, *J* = 12.0 Hz), 4.72 (1H, d, *J* = 12.0 Hz), 7.49 (2H, d, *J* = 8.5 Hz), 7.67 (1H, s), 7.71 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 6.7, 7.9, 43.9, 45.2, 51.0, 52.9, 70.6, 70.8, 117.8, 120.4, 128.8, 136.8, 138.3, 151.0; Mass (NALDI) m/z 413 ($M+H^+$).

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-[4-(4-cyclohexyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]piperidine (6e): a colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.20–1.52 (5H, m), 1.69–1.78 (3H, m), 2.08–2.11 (2H, m), 2.47 (1H, dd, *J* = 7.5, 13.5 Hz), 2.76–2.84 (1H, m), 3.01 (1H, dd, *J* = 5.0, 13.5 Hz), 3.10–3.21 (3H, m), 3.25 (1H, d, *J* = 4.0 Hz), 3.60 (1H, dd, *J* = 5.5, 7.5 Hz), 4.64 (1H, d, *J* = 12.0 Hz), 4.69 (1H, d, *J* = 12.0 Hz), 7.46 (2H, d, *J* = 8.5 Hz), 7.63 (1H, s), 7.75 (2H, dt, *J* = 2.0, 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.0, 26.1, 33.0, 35.3, 43.8, 45.1, 50.9, 52.8, 70.5, 70.8, 117.4, 120.4, 128.8, 136.9, 138.2, 154.5; Mass (NALDI) m/z 355 ($M+H^+$).

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-[4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]piperidine (6f): a white solid; mp 129–131°C (toluene : *n*-hexane = 2 : 1); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.51 (1H, dd, *J* = 7.5, 13.5 Hz), 3.07 (1H, dd, *J* = 5.0, 13.5 Hz), 3.14-3.25 (3H, m), 3.30 (1H, d, *J* = 3.5 Hz), 3.65 (1H, dd, *J* = 5.5, 7.5 Hz), 4.70 (1H, d, *J* = 12.0 Hz), 4.76 (1H, d, *J* = 12.0 Hz), 7.37-7.56 (5H, m), 7.81 (2H, d, *J* = 8.5 Hz), 7.93 (2H, d, *J* = 8.5 Hz), 8.19 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.8, 45.1, 50.9, 52.8, 70.6, 70.7, 117.5, 120.5, 125.8, 128.4, 128.9, 128.9, 130.1, 136.5, 138.7, 148.4.

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-[4-(4-benzyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]piperidine (6g): a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.43 (1H, dd, *J* = 7.0, 13.5 Hz), 2.97 (1H, dd, *J* = 4.0, 13.5 Hz), 3.04 (1H, dd, *J* = 2.0, 15.0 Hz), 3.08–3.10 (1H, m), 3.14 (1H, d, *J* = 15.0 Hz), 3.21 (1H, d, *J* = 4.0 Hz), 3.56 (1H, dd, *J* = 5.0, 7.0 Hz), 4.11 (2H, s), 4.60 (1H, d, *J* = 12.5 Hz), 4.64 (1H, d, *J* = 12.5 Hz), 7.17–7.21 (1H, m), 7.26–7.27 (4H, m), 7.41 (2H, d, *J* = 8.0 Hz), 7.52 (1H, s), 7.62 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 32.3, 43.8, 45.2, 50.9, 52.8, 70.5, 70.7, 119.5, 120.4, 126.6, 128.7, 128.7, 136.6, 138.4, 138.7, 148.5; Mass (NALDI) m/z 363 ($M+H^+$).

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-[4-(4-phenethyl-1*H*-1,2,3-triazol-1-yl)benzyloxy]piperidine (6h): a colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.50 (1H, dd, *J* = 7.5, 13.5 Hz), 3.02–3.19 (8H, m), 3.29 (1H, d, *J* = 4.0 Hz), 3.63 (1H, dd, *J* = 5.5, 7.5 Hz), 4.67 (1H, d, *J* = 12.0 Hz), 4.73 (1H, d, *J* = 12.0 Hz), 7.19-7.33 (5H, m), 7.49 (2H, d, *J* = 8.5 Hz), 7.54 (1H, s), 7.68 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.5, 35.4, 43.8, 45.2, 50.9, 52.8, 70.5, 70.7, 119.1, 120.4, 126.2, 128.4, 128.5, 128.8, 136.7, 138.3, 141.0, 148.1; Mass (NALDI) m/z 377 ($M+H^+$).

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-{4-[4-(2-pyridinyl)-1*H*-1,2,3-triazol-1-yl]benzyloxy}piperidine (6i): a white solid; mp 115–118°C (toluene : *n*-hexane = 2 : 1); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.51 (1H, dd, *J* = 7.5, 13.5 Hz), 3.07 (1H, dd, *J* = 5.5, 13.5 Hz), 3.14-3.24 (3H, m), 3.30 (1H, d, *J* = 3.5 Hz), 3.66 (1H, dd, *J* = 5.5, 7.5 Hz), 4.70 (1H, d, *J* = 12.0 Hz), 4.75 (1H, d, *J* = 12.0 Hz), 7.29 (1H, dd, J = 1.0, 5.0 Hz), 7.54 (2H, d, *J* = 8.5 Hz),7.79–7.85 (3H, m), 8.25 (1H, dt, J = 1.0, 8.0 Hz), 8.61 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.8, 45.2, 50.9, 52.8, 70.6, 70.7, 119.9, 120.4, 120.5, 123.1, 128.9, 136.5, 137.0, 138.8, 149.0, 149.5, 149.9; Mass (NALDI) m/z 372 ($M+Na^+$).

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-{4-[4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl]benzyloxy}piperidine (6j): a white solid; mp 179°C (toluene : *n*-hexane = 2 : 1); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.52 (1H, dd, *J* = 7.5, 13.5 Hz), 3.07 (1H, dd, *J* = 5.5, 13.5 Hz), 3.14-3.25 (3H, m), 3.30 (1H, d, *J* = 3.5 Hz), 3.65 (1H, dd, *J* = 5.5, 7.5 Hz), 4.70 (1H, d, *J* = 12.0 Hz), 4.76 (1H, d, *J* = 12 Hz), 7.16 (2H, t, *J* = 8.5 Hz), 7.55 (2H, d, *J* = 8.5 Hz), 7.79 (2H, d, *J* = 8.5 Hz), 8.89 (2H, dd, *J* = 5.5, 8.5 Hz), 8.15 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.9, 45.2, 51.0, 52.8, 70.6, 70.7, 115.9 (d, *J* = 22.0 Hz), 117.3, 120.6, 126.4 (d, *J* = 3.0 Hz), 127.6 (d, *J* = 8.0 Hz), 128.9, 136.5, 138.8, 147.6, 162.8 (d, *J* = 247.0 Hz).

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-{4-[4-(1-naphthyl)-1*H*-1,2,3-triazol-1-yl]benzyloxy}piperidine (6k): a yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.53 (1H, dd, *J* = 7.5, 13.5 Hz), 3.07 (1H, dd, *J* = 5.0, 13.5 Hz), 3.15-3.26 (3H, m), 3.31 (1H, d, *J* = 3.5 Hz), 3.67 (1H, dd, *J* = 5.5, 7.5 Hz), 4.72 (1H, d, *J* = 12.0 Hz), 4.78 (1H, d, *J* = 12.0 Hz), 7.52–7.65 (5H, m), 7.80 (1H, dd, *J* = 1.5, 7.5 Hz), 7.86 (2H, dt, *J* = 2.0, 8.5 Hz), 7.91–8.00 (2H, m), 8.25 (1H, s), 8.42–8.46 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.9, 45.2, 51.0, 52.9, 70.6, 70.8, 120.5, 120.6, 125.4, 126.1, 126.8, 127.4, 127.6, 128.5, 128.9, 129.2, 131.1, 133.9, 136.6, 138.8, 147.6; Mass (NALDI) m/z 399 ($M+H^+$).

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-{4-[4-(2-naphthyl)-1*H*-1,2,3-triazol-1-yl]benzyloxy}piperidine (6l): a colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.52 (1H, dd, *J* = 7.5, 13.5 Hz), 3.07 (1H, dd, *J* = 5.0, 13.5 Hz), 3.14–3.25 (3H, m), 3.31 (1H, d, *J* = 3.5 Hz), 3.66 (1H, dd, *J* = 5.5, 7.5 Hz), 4.71 (1H, d, *J* = 12.0 Hz), 4.76 (1H, d, *J* = 12.0 Hz),7.47–7.57 (4H, m), 7.81–8.03 (6H, m), 8.31 (1H, s), 8.43 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.9, 45.2, 51.0, 52.9, 70.6, 70.7, 117.8, 120.6, 123.8, 124.7, 126.3, 126.5, 127.5, 127.8, 128.2, 128.7, 128.9, 133.3, 133.5, 136.6, 138.8, 148.5; Mass (NALDI) m/z 399 ($M+H^+$).

(3*RS*,4*RS*,5*RS*)-5-{4-[4-(1-Anthracenyl)-1*H*-1,2,3-triazol-1-yl]benzyloxy}-3,4-epoxypiperidine (6m): a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.55 (1H, dd, *J* = 7.5, 13.5 Hz), 3.09 (1H, dd, *J* = 5.0, 13.5 Hz), 3.14 (1H, dd, *J* = 1.5, 15.0 Hz), 3.18–3.19 (1H, m), 3.23 (1H, d, *J* = 15.0 Hz), 3.33 (1H, d, *J* = 3.5 Hz), 3.68 (1H, dd, *J* = 5.0, 7.5 Hz), 4.74 (1H, d, *J* = 12.0 Hz), 4.78 (1H, d, *J* = 12.0 Hz), 7.46–7.56 (4H, m), 7.60 (2H, d, *J* = 8.0 Hz), 7.77 (1H, d, *J* = 7.0 Hz), 7.91 (2H, d, *J* = 8.0 Hz), 8.02–8.04 (2H, m), 8.10 (1H, d, *J* = 8.0 Hz), 8.35 (1H, s), 8.52 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.8, 45.2, 50.9, 52.8, 70.6, 70.7, 120.6, 120.6, 120.7, 124.5, 124.6, 125.6, 125.8, 126.9, 127.0, 127.8, 128.7, 128.9, 129.4, 129.6, 131.6, 131.9, 132.1, 136.6, 138.8, 147.9; Mass (NALDI) m/z 449 ($M+H^+$).

(3*RS*,4*RS*,5*RS*)-5-{4-[4-(2-Anthracenyl)-1*H*-1,2,3-triazol-1-yl]benzyloxy}-3,4-epoxypiperidine (6n): a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.53 (1H, dd, *J* = 7.0, 13.5 Hz), 3.08 (1H, dd, *J* = 5.0, 13.5 Hz), 3.13 (1H, dd, *J* = 1.5, 15.0 Hz), 3.18–3.19 (1H, m), 3.23 (1H, d, *J* = 15.0 Hz), 3.32 (1H, d, *J* = 4.0 Hz), 3.67 (1H, dd, *J* = 5.0, 7.0 Hz), 4.72 (1H, d, *J* = 12.0 Hz), 4.76 (1H, d, *J* = 12.0 Hz), 7.48–7.52 (2H, m), 7.57 (2H, d, *J* = 8.0 Hz), 7.85 (2H, d, *J* = 8.0 Hz), 7.97–8.04 (3H, m), 8.11 (1H, d, *J* = 8.0 Hz), 8.35 (1H, s), 8.45 (1H, s), 8.50 (1H, s), 8.61 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.9, 45.2, 51.0, 52.9, 70.6, 70.8, 117.8, 120.6, 123.6, 124.7, 125.6, 125.7, 126.3, 126.7, 126.8, 128.2, 128.2, 128.9, 129.1, 131.3, 131.5, 132.0, 132.1, 136.6, 138.8, 148.5, 154.5; Mass (NALDI) m/z 449 ($M+H^+$).

(3*RS*,4*RS*,5*RS*)-5-{4-[4-(9-Anthracenyl)-1*H*-1,2,3-triazol-1-yl]benzyloxy}-3,4-epoxypiperidine (6o): a yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.49 (1H, dd, *J* = 7.0, 13.5 Hz), 2.98–3.05 (2H, m), 3.10–3.14 (2H, m), 3.26 (1H, d, *J* = 3.5 Hz), 3.63 (1H, dd, *J* = 5.0, 7.0 Hz), 4.69 (2H, s), 7.34–7.45 (4H, m), 7.53 (2H, d, *J* = 8.0 Hz), 7.82–7.88 (4H, m), 8.00 (2H, d, *J* = 8.0 Hz), 8.18 (1H, s), 8.35 (1H, s), 8.51 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.8, 45.2, 50.9, 52.8, 70.6, 70.7, 120.5, 122.6, 123.9, 125.3, 125.8, 126.2, 128.5, 128.5, 128.9, 131.3, 136.5, 138.8, 144.7; Mass (NALDI) m/z 449 ($M+H^+$).

Examination of relaxation assay of supercoiled plasmid DNA: To a solution of supercoiled pBR 322 DNA (0.15 μg) in pH 7.0 TE buffer (9 μL) was added a DMSO solution of the compounds (1 μL, 10 μM and 100 μM), and the mixture was incubated for 24 h at 37°C. The resulting DNA analysis was conducted using electrophoresis (tris-acetate-EDTA buffer, ethidium bromide 1.3 μM solution) on 0.7% native agarose gel at 7.4 v/cm for 30 min.

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