TITLE

Discovery of novel orexin receptor antagonists using a 1,3,5-trioxazatriquinans bearing multiple effective residues (TriMER) library

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ABSTRACT

Structurally diverse small compounds are utilized to obtain hit compounds that have suitable pharmacophores in appropriate three-dimensional conformations for the target drug receptors. We have focused on the 1,3,5-trioxazatriquinane skeleton, which has a high degree of three-dimensional properties, leading to a novel small-scale focused library based on 1,3,5-trioxazatriquinane. In the library screening for the orexin receptor, some of the compounds showed orexin receptor antagonistic activity with a high hit rate of 7%. By optimizing the hit compounds, we discovered a potent dual orexin receptor antagonist, **38b**, and a selective orexin 1 receptor antagonist, **41b** carrying the same plane structure. Both compounds showed reasonable brain permeability and beneficial effects when administered intraperitoneally to wild-type mice. Docking simulations of their enantiomers, (–)-**38b** and (+)-**41b**, with orexin receptors suggested that the interaction between the 1,3,5-trioxazatriquinane core structure and the hydrophobic subpocket in orexin receptors enables a U-shape structure, which causes tight van der Waals interactions with the receptors similar to SB-334867, a selective orexin 1 receptor antagonist. These results indicate that the 1,3,5-trioxazatriquinanes bearing multiple effective residues (TriMERs) could serve as a privileged structure for G-protein coupled receptors (GPCRs) and the TriMER library approach might be useful for the hit discovery process targeting other GPCRs not only opioid and orexin receptors.

INTRODUCTION

1,3,5-Trioxazatriquinane is a unique saturated tricyclic heterocyclic scaffold discovered previously by our group (Figure 1) that was synthesized *via* a trimerization of α -hydroxyaldehydes carrying arbitrary substituents in the presence of ammonium chloride.¹ This skeleton has been utilized to synthesize twin and triplet drugs; 1,3,5-trioxazatriquinane derivatives bearing one, two (KNT-123), and three (KNT-93) morphinan residues were synthesized from naltrexone, and each exhibited different opioid receptor type selectivity and activity.²⁻⁷ Inspired by the rigid scaffold of 1,3,5-trioxazatriquinane carrying multiple functional groups, such as three substitutable methylenes, three ether oxygens, and one basic nitrogen on the center, we utilized 1,3,5-trioxazatriquinane derivatives to explore the efficient orientation between a basic nitrogen atom and aromatic rings, which are important pharmacophores for opioid receptor ligands.^{8,9} SYK-146 exhibited potent and selective κ opioid receptor (KOR) agonist activity⁹ in the same range of activity as a representative KOR agonist, U-69,593. Intriguingly, all active compounds in the screening had a phenethylamine substructure, a common structural part of neurotransmitters, such as dopamine and noradrenaline, as well as central nervous system (CNS) drugs, such as morphine and methylphenidate. These results suggest that 1,3,5-trioxazatriquinane bearing multiple effective residues (TriMERs) has potential as a template scaffold for exploring the shape of a drug, including the orientation of pharmacophore units.

During the course of our efforts to obtain selective ligands for orexin receptors (OXRs; OX₁R and OX₂R),^{10, 11} we discovered that the KOR agonist nalfurafine (**1**) exhibits moderate antagonistic activity for OX₁R ($K_i = 250$ nM for OX₁R). Subsequent optimization focused on the removal of opioid activity and the enhancement of OX₁R antagonistic activity afforded potent selective OX₁R antagonists, such as YNT-707 (**2**, $K_i = 8.14$ nM for OX₁R) and YNT-1310 (**3**, $K_i = 1.36$ nM for

OX₁R). OXRs play important roles in the regulation of a variety of physiological events via activation by their endogenous hypothalamic neuropeptide orexin/hypocretin,^{12, 13} including feeding behavior,¹⁴ sleep–wake cycle,¹⁵ reward/addiction,¹⁶ and energy balance.¹⁷ The dual OX_{1/2}R antagonists (DORAs) are useful for the treatment of insomnia,¹⁸ and selective OX₁R antagonists (ISORAs) have been expected as therapeutic agents for anxiety and drug dependence.¹⁹ Especially, since blockage of OX₂R signaling leads to the reduction of wakefulness, the receptor selectivity (OX₂R/OX₁R ratio) is an important focus in the development of ISORA as psychotherapeutic drugs to avoid the accidents caused by sedative effect. JNJ-613393215, a ISORA that entered the first-in-human studies for the treatment of mood and anxiety disorders, still has an affinity against OX₂R at a submicromolar range.^{20, 21} Therefore, the identification of OX₁R specific structure such as YNT-707 and 1310 is still a potential interest to understand the mode of receptor selectivity against orexin receptors. Moreover, selective OX₂R agonists are effective drugs for the treatment of narcolepsy type 1.^{10, 22}

In this context, we postulated that the 1,3,5-trioxazatriquinane derivatives may bind to other drug targets, such as OXRs. Analysis of the diversity level of the simple template with two aromatic rings and one methylene-oxy bridge using a computational method²³ based on the normalized principal moment-of-inertia (PMI) ratios revealed that the molecular shapes of each isomer of **4** are distributed within the left half of the triangular plot, overlapping with the hot spot of distribution of the protein pocket shape²⁴ (Figure 2). This finding suggests that 1,3,5-trioxazatriquinane skeleton has potential as a privileged structure and the introduction of pharmacophore substituents on two phenyl residues would expand the diversity of the molecular shape within good agreement with the protein pocket diversity. In this report, in order to verify the

utility of our approach in the discovery of novel orexin receptor ligands, we designed and synthesized the TriMER-focused library and screened them against orexin receptors.

Figure 1. Structures of the 1,3,5-trioxazatriquinane skeleton, 1,3,5-trioxazatriquinane derivatives KNT-123, -93, and SYK-146, nalfurfine (**1**), and selective OX₁R antagonists YNT-707 (**2**) and YNT-1310 (**3**).

Figure 2. a) Population analysis of (2*aS*, 4*aS*, 6*aS*)-1,3,5-trioxazatriquinane derivatives bearing two phenyl residues, illustrating the geometrical diversity of (4*S*, 6*S*)-*cis* (type-I, blue), (4*S*, 6*R*)-*trans* (type-II, orange), (4*R*, 6*S*)-*trans* (type-III, green), and (4*R*, 6*R*)-*cis* (type-IV, purple) compounds. The populations are superimposed over the diversity area of the protein pocket shape reported by Wirth *et al.*²⁴ highlighted in light blue. The stable structures for each molecule within 7 kcal/mol were calculated using the Conformational Search function in MOE software package ver. 2019.0102 (Chemical Computing Group, Inc., Montreal, Canada) with LowModeMD method, MMFF94x force field, dielectric constant of 80, and no non-bonded interaction cutoff, and the principal moment of inertia (PMI) was calculated. b) Design of TriMER derivatives.

Design and Synthesis

Based on the working hypothesis, we designed a set of TriMER derivatives consisting of 72 compounds with a combination of four relative steric isomers (racemic type-I–IV), three aromatic substitution patterns (*o*-, *m*-, *p*-), and six *N*-substituents (NO₂, NH₂, NMe₂, NHBoc, NHBz, NHSO₂Ph; Figure 2b). The synthesis of TriMER intermediates **12a–15c** carrying nitro groups at the *o*-, *m*-, or *p*-position was accomplished according to our previous report⁹ from the corresponding nitro acetophenones **8a–c** (Scheme 1). A mixture of α -hydroxyaldehyde **9a–c** and its hemiacetal dimer **10a–c** derived from **8a–c** was treated with ammonium chloride and sodium acetate to obtain the corresponding oxazoline **11a–c**. Each oxazoline reacted with glycolaldehyde dimer in the presence of camphorsulfonic acid to provide **12a–15c**. The reduction of nitro groups afforded corresponding anilines **16a–19c**, and each aniline was derivatized *via* dimethylation and condensation to obtain library compounds bearing NMe₂ (**20a–23c**), NHBoc (**24a–27c**), NHBz (**28a–31c**), and NHSO₂Ph (**32a–35c**).

Scheme 1. Synthesis of TriMER derivatives **12a–35c**^a

^a Reagents and Conditions: (a) (methoxymethyl) triphenylphosphonium chloride, *t*-BuOK, THF, 0 °C; (b) *m*CPBA, CH₂Cl₂, 0 °C; (c) 2 M HCl aq., THF, rt; (d) TosMIC, K₂CO₃, MeOH, rt; (e) NH₄Cl, AcONa, MeOH, reflux; (f) glycolaldehyde dimer, CSA, CHCl₃, rt; (g) H₂, 5% Pd/C, EtOAc, rt; (h) 37% CH₂O aq., AcOH, 5% Pd/C, EtOAc, rt; (i) Boc₂O, Et₃N, (CH₂Cl)₂, rt to reflux; (j) BzCl, Et₃N, (CH₂Cl)₂, rt; (k) PhSO₂Cl, Pyr, (CH₂Cl)₂, rt.

Biological Evaluation

Using the synthetic TriMER library, we conducted cell-based calcium assays to evaluate the OX_R agonist/antagonistic activities in a Chinese hamster ovary (CHO) cell line stably expressing OX₁R and OX₂R. Although none of the tested compounds showed substantial agonistic effects, even at 10 μ M, 5 of 72 synthetic compounds exhibited < 50% inhibitory activity against orexin A-induced OX_R activation in the 1.0 μ M hit range. The inhibitory kinetics of these hit compounds are summarized in Table 1. The highest hit-rate was seen in the type-I (concave *cis* configuration of phenyl residues) derivatives bearing *m*-nitrogen substituents. Though the derivatives carrying *m*-*N*-Boc (**24b**; K_i = 34.2 nM for OX₁R, K_i = 180 nM for OX₂R) and *m*-*N*-Bz (**28b**; K_i = 23.4 nM for OX₁R, K_i = 15.1 nM for OX₂R) substituents presented potent dual OX_{1/2}R antagonistic activity, other substituents, with the exception of *m*-NMe₂ (**20b**; K_i = 655 nM for OX₂R), did not show sufficient OX_R antagonistic activities. None of the type-II and -III (*trans* configuration of phenyl residues) derivatives, except **34b** (*m*-*N*-SO₂Ph; K_i = 222 nM for OX₁R), presented potent antagonistic activity. Intriguingly, in the type-IV (convex *cis* configuration of phenyl residues) derivatives, *m*-*N*-Bz derivative **31b** exhibited potent selective OX₁R antagonistic activity (K_i = 25.4 nM for OX₁R). Notably, **28b** and **31b**, which possess the same *m*-*N*-Bz substituents and *cis* configuration of the core unit, had similar antagonist activity for OX₁R but different activities for OX₂R. The structures of each hit compound overlapped each other because of the common skeleton and this structure-activity relationship information suggested that the *cis* configuration of side residues on the bowl-like skeleton plays an important role in the suitable orientation of the terminal lipophilic substituent toward the binding with the receptors.

Table 1. Assay Results of the TriMER Derivatives for Orexin Receptor Antagonism

Compounds	Core type	R	K_i (nM) ^a	
			OX ₁ R	OX ₂ R
20b	I	NMe ₂	– ^b	655 ± 184
24b	I	NHBoc	34.2 ± 8.93	180 ± 43.1
28b	I	NHBz	23.4 ± 0.95	15.1 ± 2.19
31b	IV	NHBz	25.4 ± 3.70	– ^b
34b	III	NHSO ₂ Ph	– ^b	222 ± 70.2

^a K_i values represent the mean ± SEM. These values were calculated using IC₅₀ values of TriMER derivatives and at least three independent calcium assays performed in triplicate (Cheng–Prusoff equation). ^b K_i value was not calculated. IC₅₀ value was over 10 μM (cutoff value) or was not obtain from concentration–response curve.

Optimization of Bz parts

Next, we investigated the substituents (R') on the terminal aromatic rings to enhance the activity of dual OX_{1/2}R antagonist (DORA) **28b** and selective OX₁R antagonist (1-SORA) **31b**. The synthesis of benzamide derivatives (**36b–53b**) was achieved by condensation with the corresponding carboxylic acid from type-I/IV intermediates **16b** and **19b**, and the introduction of substituent R' had a substantial influence on the potency (Table 2). The introduction of methoxy groups on the terminal aromatic rings increased the affinity for each receptor, and 4-methoxy substituents were most effective for both type-I (**38b**: $K_i = 3.99$ nM for OX₁R, $K_i = 6.01$ nM for OX₂R) and type-IV (**41b**: $K_i = 1.87$ nM for OX₁R). Similar substituent effects were observed in type-IV NMe₂ derivatives, and **47b** carrying 4-NMe₂ substituents exhibited potent selective OX₁R affinity ($K_i = 3.88$ nM). Type-I NMe₂ derivatives **42b–44b** showed affinity for both receptors. The 2-pyridine carboxamide derivatives **48b** ($K_i = 14.9$ nM for OX₁R, $K_i = 69.6$ nM for OX₂R) and **51b** ($K_i = 18.3$ nM for OX₁R) showed higher affinity for the corresponding receptors than the 3- and 4-pyridine carboxamide derivatives (**49b**, **50b**, **52b**, and **53b**). The counter screening of **38b** and **41b** for the opioid receptors (μ -, δ -, κ -) exhibited no affinity against each receptor, suggesting that 1,3,5-trioxazatriquinane with *m*-aniline residues is a selective scaffold for orexin receptors (Figure S13).

Table 2. Assay Results of the Benzamide Derivatives for Orexin Receptor Antagonism

Compounds	Core type	R'	K_i (nM) ^a	
			OX ₁ R	OX ₂ R
28b	I	Ph	23.4 ± 0.95	15.1 ± 2.19
31b	IV	Ph	25.4 ± 3.70	— ^b
36b	I	2-MeO-C ₆ H ₄	18.0 ± 3.45	56.0 ± 17.5
37b	I	3-MeO-C ₆ H ₄	7.66 ± 1.50	5.38 ± 0.83
38b	I	4-MeO-C ₆ H ₄	3.99 ± 0.47	6.01 ± 1.52
39b	IV	2-MeO-C ₆ H ₄	32.8 ± 1.43	722 ± 40.3
40b	IV	3-MeO-C ₆ H ₄	2.86 ± 0.27	— ^b
41b	IV	4-MeO-C ₆ H ₄	1.87 ± 0.30	— ^b
42b	I	2-Me ₂ N-C ₆ H ₄	— ^b	— ^b
43b	I	3-Me ₂ N-C ₆ H ₄	— ^b	— ^b
44b	I	4-Me ₂ N-C ₆ H ₄	— ^b	— ^b
45b	IV	2-Me ₂ N-C ₆ H ₄	634 ± 158	— ^b
46b	IV	3-Me ₂ N-C ₆ H ₄	7.85 ± 1.89	— ^b
47b	IV	4-Me ₂ N-C ₆ H ₄	3.88 ± 0.98	— ^b

48b	I	2-pyridine	14.9 ± 3.97	69.6 ± 15.2
49b	I	3-pyridine	691 ± 179	261 ± 58.0
50b	I	4-pyridine	– ^b	179 ± 35.7
51b	IV	2-pyridine	18.3 ± 2.71	– ^b
52b	IV	3-pyridine	52.0 ± 17.2	– ^b
53b	IV	4-pyridine	104 ± 39.2	– ^b

^a K_i values represent the mean $\pm$ SEM. These values were calculated using IC₅₀ values of benzamide derivatives and at least three independent calcium assays performed in triplicate (Cheng–Prusoff equation). ^b K_i value was not calculated. IC₅₀ value was over 10 μ M (cutoff value) or was not obtain from concentration–response curve.

Pharmacokinetics of **38b** and **41b**

Compounds **38b** and **41b** were evaluated *in vitro* drug metabolism and pharmacokinetics (DMPK) parameters (Table 4). Permeability of each molecule was assessed by the Caco-2 assay,²⁵ in both directions (apical to basolateral (A-B) and basolateral to apical (B-A)) at pH 7.4 mimicking plasma pH. **41b** showed reasonable permeability ($P_{app} = 11.9 \times 10^{-6}$ cm/s (A-B) and efflux ratio 1.8). The permeability of **41b** in the A to B direction was slightly increased when the ATP-binding cassette (ABC) transporter inhibitors such as verapamil, a P-glycoproteins (P-gp)/ ABC family B1 (ABCB1) inhibitor, and KO143, a breast cancer resistant protein (BCRP)/ ABC family G2 (ABCG2) inhibitor, were added to the system, yet the efflux ratio (B-A/A-B) was lower than without these inhibitors. On the other hand, intriguingly, **38b** was lower than the limit of quantitation in receiver samples due to the low recovery despite having the same planar structure as **41b**. The addition of 1% bovine cerium albumin (BSA) to the system dramatically improved the recovery and **38b** showed moderate permeability ($P_{app} = 1.4 \times 10^{-6}$ cm/s (A-B) and efflux ratio 0.2), suggesting that the poor recovery of **38b** would be due to the specific absorption on the transwell plate. Then, the metabolic stability of **38b** and **41b** were assessed with *in vitro* metabolism analysis in human liver microsomes (HLMs).²⁶ Each compound exhibited similar moderate clearance within HLMs (apparent $CL_{int} = 183.5$ (**38b**), 182.7 (**41b**) $\mu\text{L}/\text{min}/\text{mg}$) with estimated half-lives of 38 and 39 min, respectively. These data suggested that 1,3,5-trioxazatriquinane derivatives carrying a rigid scaffold have high to moderate permeability with no significant efflux activity, and relatively fast metabolism. In particular, the permeability of **41b** was reasonable as a CNS drug lead compound ($P_{app} > 10$, Pg-p efflux < 2.5)²⁷, and further development is expected by improving clearance depending on the target disease. Full data for *in vitro* permeability and metabolic stability tests are presented in Tables S1–S2.

As compounds **38b** and **41b** showed reasonable *in vitro* permeability and stability, we then evaluate the brain permeability of each compound in mice using LC-MS/MS system. The concentrations in the brain were measured at 0.5, 1, and 3 h after 3 and 10 mg/kg intraperitoneal administration. As shown in Figure 3, compounds **38b** and **41b** exhibited a good concentration in the brain at 10 mg/kg after 0.5 h injection with the value of 54.7 and 33.9 pmol/g brain, respectively, with a brain concentration over those *K_i* values. And the high brain concentration of each compound persisted for more than 1 h. On the other hand, the highest concentrations of each compound in brain at 3 mg/kg injection were slightly higher than their *K_i* values. Based on these observations, compounds **38b** and **41b** were undertaken for further *in vivo* evaluation.

Table 4. *In Vitro* Membrane Permeability and Metabolic Stability of **38b** and **41b**

compd	Membrane permeability ^a $P_{app, A-B}, \times 10^{-6} \text{ cm s}^{-1} [B-A/A-B]$				Metabolic stability (HLM) ^e $CL_{int} (\mu\text{L min}^{-1} \text{ mg}^{-1}) [\text{Half life}]$
	Caco-2	+ BSA ^b	+ verapamil ^c	+ KO143 ^d	
38b	— ^e	1.4 [0.2]	— ^e	— ^e	183.5 [38 min]
41b	11.9 [1.8]	N.T.	19.4 [1.1]	16.6 [1.6]	182.7 [39 min]

^aBidirectional Caco-2 permeability with pH 7.4/7.4 for donor/receiver chambers, respectively. A = apical, B = basolateral. P_{app} is the apparent permeability coefficient (10^{-6} cm/s). For ABC transporter substrate assessment, the assays are run with ^b1% BSA or ^c100 μM verapamil or ^d10 μM KO143 on both the A and B sides. ^eDetection was lower than the limit of quantitation in receiver sample due to low recovery. ^eCompounds were treated in 0.1 mg/mL human liver microsomes (HLMs) at 37 °C. N.T., not tested.

Figure 3. The concentrations of **38b** (A) and **41b** (B) in brain at 0.5, 1 and 3 hours after 10 mg/kg and 3 mg/kg i.p. administration in C57BL/6J mice. Each value represents the mean $\pm$ S.D. (four or three mice for each point). Closed circle, 10 mg/kg; Closed square, 3 mg/kg. The data of **41b** at 3 hours were obtained from two mice and the brain concentrations of other mice were under the limit of quantification.

In Vivo Assays

We evaluated the effects of DORA **38b** and 1-SORA **41b** in mice. Dual antagonism to both OXRs induces an increase in the sleep state, and DORAs suvorexant (MK-4305)²⁸ and lemborexant (E2006)²⁹ have already been approved for the treatment of insomnia. Therefore, we observed the effect of DORA **38b** on the sleep/wake state using electroencephalogram (EEG)/electromyography (EMG) in wild-type mice (Figure 4). We intraperitoneally administered vehicle or **38b** to wild-type mice immediately before the start of the dark period (ZT12). Administration of 10 mg/kg **38b** substantially decreased the total time of wakefulness and increased the total time of NREM sleep during ZT12–18 compared to vehicle administration. Selective inhibition of OX₁R suppresses motivated behaviors.¹⁶ Though intracerebroventricular administration of orexin A caused a significant increase in locomotor activity in wild-type mice through OX₁R activation, intraperitoneal administration of **41b** suppressed the orexin A-induced enhancement of locomotor activity in a dose-dependent manner, which is well supported by a result of brain permeability of **41b** (Figure 5).

Figure 4. Effect of intraperitoneal administration of **38b** (10 mg/kg) on sleep/wake states in wild-type mice. (a) Hourly plots of total time in NREM sleep, (b) REM sleep, and (c) wakefulness. Data are presented as the mean $\pm$ SEM of 8 mice. **** $P < 0.0001$ for vehicle vs. **38b** by two-way ANOVA. Each arrow indicates an injection. (d) Time spent in NREM sleep, REM sleep, and wakefulness during ZT12–18 after vehicle or **38b** administration. Data are presented as the mean $\pm$ SEM of 8 mice. ** $P < 0.01$ for vehicle vs. **38b** by two-tailed Student's *t* test.

Figure 5. Effect of intraperitoneal administration of **41b** on motivated behavior in wild-type mice. Orexin A-induced locomotor activity was suppressed by intraperitoneal pretreatment with **41b** (10 mg/kg) 30 min before intracerebroventricular injection of orexin A. Data are presented as the mean $\pm$ SEM of 5–13 mice. ** $P < 0.01$, # $P < 0.05$, one-way ANOVA followed by Bonferroni test; n.s., not significant.

Optical resolution of **38b** and **41b** and docking study

Finally, to gain structural insights into the differences between **38b** and **41b** in receptor selectivity, we conducted optical resolution of the most potent antagonists, **38b** and **41b**, with a chiral column (see Supporting Information) and compared their activities with racemic compounds in the same evaluation system (Table 3) to determine the eutomers. (–)-**38b** had a 20-times stronger binding affinity for OX₁R (K_i = 5.23 nM) than its enantiomer (+)-**38b** (K_i = 110 nM) and twice the affinity as racemic-**38b** (K_i = 11.7 nM).³⁰ Both (+)-**38b** and (–)-**38b** had similar affinity for OX₂R (K_i = 26.6 nM and 34.8 nM, respectively).²³ On the other hand, (+)-**41b** had a stronger binding affinity for OX₁R (K_i = 2.17 nM) than its (–)-enantiomer (K_i = 161 nM), and neither enantiomers had an affinity for OX₂R. These results revealed that two *cis*-side chains in both eutomers (–)-**38b** and (+)-**41b** had well overlapped each other and the 1,3,5-trioxazatriquinane core skeletons were flipped to orient the heteroatoms in a similar manner.

Table 3. Assay Results of Racemic- and Enantiopure **38b** and **41b** for Orexin Receptor Antagonism

Compounds	$R' = 4\text{-OMe-C}_6\text{H}_4$	
	K_i (nM) ^a	
	OX ₁ R	OX ₂ R
$(\pm)\text{-}\mathbf{38b}$	11.7 ± 2.13	16.7 ± 9.37
$(+)\text{-}\mathbf{38b}$	110 ± 28.1	26.6 ± 6.70
$(-)\text{-}\mathbf{38b}$	5.23 ± 1.02	34.8 ± 9.47
$(\pm)\text{-}\mathbf{41b}$	4.93 ± 1.00	— ^b
$(+)\text{-}\mathbf{41b}$	2.17 ± 0.69	— ^b
$(-)\text{-}\mathbf{41b}$	161 ± 39.2	— ^b

^a K_i values represent the mean $\pm$ SEM. These values were calculated using IC₅₀ values of each isomer and at least three independent calcium assays performed in triplicate (Cheng–Prusoff equation). ^b K_i value was not detected. IC₅₀ value was over 10 μ M (cutoff value) or was not obtain from concentration–response curve.

Then, we carried out molecular docking studies with eutomers (–)-**38b** and (+)-**41b**. We utilized the crystal structures of human OX₁R with diaryl urea-type 1-SORA SB-334867^{31, 32} (PDB ID: 6TQ7, Figure 6a)³³ because the volume of its binding pocket was greater than other crystal structures due to the outward flipping of F219^{5,42}, which enables (–)-**38b** and (+)-**41b** to be confined in the pocket. In addition, the binding pocket of human OX₂R was technically constructed based on the SB-334867/OX₁R crystal structure by threonine substitutions S103^{2,61} and A127^{3,33} to reproduce the corresponding T111^{2,61} and T135^{3,33}, respectively. The speculated binding modes of both eutomers, (–)-**38b** and (+)-**41b**, in the receptors are shown in Figure 6b–d. The binding forms of (–)-**38b** and (+)-**41b** in the receptors have similar orientations of the diaryl amide side chains by flipping the 1,3,5-trioxazatriquinane core structure, which overlaps with the binding form of SB-334867 by the 1,3,5-trioxazatriquinane junction. Each 1,3,5-trioxazatriquinane core structure occupies a hydrophobic subpocket defined by A^{2,60}, S^{2,61} (T^{2,61} in OX₂R), V^{2,64}, I^{3,28} P^{3,29}, Q^{3,32}, and Y^{2,64} covered by the ECL2 twisted β -hairpin structure that is generally occupied by antagonists in each known crystal structure.^{33–36} The ether oxygens of 1,3,5-trioxazatriquinane face the hydroxyl moiety of S^{2,61} (T^{2,61} in OX₂R), implying formation of direct hydrogen or indirect water-mediated bonding. The left aromatic rings on the 1,3,5-trioxazatriquinane core of both compounds locate the cavity occupied by a water molecule in the binding form of SB-334867. Importantly, the *cis*-configurations of aromatic rings enable a similar orientation of terminal arylamide systems as SB-334867 to fill the binding pocket with van der Waals contacts. SB-334867 forms a hydrogen-bonding network between one urea oxygen, water molecule, and the ECL2-stabilizing salt bridge (E204^{45,52}–H216^{5,39}) and the offset π -stacking between heteroaryl group and H334^{7,39} (Figure 6a). Similarly, (–)-**38b** also forms direct hydrogen bonds between the left amide moiety and E^{45,52} and offset π -stacking between right aryl residue and H^{7,39} in each

receptor (Figures 6b and 6c). On the other hand, while the parallel offset π - π stacking with H^{7.39} is seen in the binding mode of (+)-**41b** with OX₁R, the distance between the left amide moiety and E^{45.52} (CO-O⁻...H-N: 3.51 Å) is much longer than that of (-)-**38b** (CO-O⁻...H-N: 2.66 Å for OX₁R and 2.43 Å for OX₂R, respectively), which may be caused by an inward orientation of left side chain due to the tight angle between the two side chains (Figure 6d). The orthosteric sites of OX₁R and OX₂R have high homology and differ in only two residues (S103^{2.61}/T111^{2.61} and A127^{3.33}/T135^{3.33}). The shape and size of the hydrophobic cavity in these receptors where the 1,3,5-trioxazatriquinane core structure is located are slightly different due to these variations. The binding form of (-)-**38b** in OX₂R slightly moves toward the left side of the pocket compared to that of (-)-**38b** in OX₂R to avoid the steric crash with a γ -methyl group of T111^{2.61} (Figure 6e), which also leads to be avoided the steric repulsion between the terminal benzamide unit on the left part and the γ -methyl group of T135^{3.33} (Figure 6f). On the other hand, the right part of (+)-**41b** in OX₁R locates similar region to that of (-)-**38b** in OX₂R but the left terminal aromatic ring of (+)-**41b** would have a steric clash with the γ -methyl group of T135^{3.33} in OX₂R (Figure 6g), suggesting that the rotation of the 1,3,5-trioxazatriquinane core would be necessary to avoid the steric repulsion (Figure 6h). However, the convex methyl group of (+)-**41b** faces the backbone of C^{45.50} on ECL2 that connects with C^{3.25} *via* a disulfide bond, which would limit the movement of 1,3,5-trioxazatriquinane core. Overall, the major differences between the binding modes of (-)-**38b** and (+)-**41b** were observed in the interaction with ECL2 and subsequent salt bridge. The involvement of ECL2 in peptide-mediated agonism and small molecule-mediated antagonism in orexin receptors has been demonstrated by mutagenesis experiments,^{35, 37} suggesting that the hydrogen-bonding network of salt bridge stabilized by ECL2 would be important for the stabilization of the binding complex. Therefore, we postulated that the steric repulsions between the convex methyl

group of (+)-**41b** and ECL2 as well as the hydrogen bonding with E^{45.52} would be mainly involved in receptor selectivity, though it needs further investigations.

Figure 6. Binding modes of (a) SB-334867 in complex with OX₁R (PDB ID: 6TQ7), (b) (-)-38b with OX₁R, (c) (-)-38b with OX₂R, and (d) (+)-41b with OX₁R determined by our docking procedure. Hydrogen-bonding interactions and π -stacking are indicated by dashed lines. Expanded views around the (e) S/T^{2.61} residues and (f) A/T^{3.33} residues in the superimposition of (-)-38b with OX₁R (yellow) and (-)-38b with OX₂R (blue). Expanded views around the (g) ECL2 and hydrophobic pocket and (h) A/T^{3.33} residues in the superimposition of (+)-41b with OX₁R (orange) and (-)-38b with OX₂R (blue). The orange mesh indicates the surface of convex methyl group of (+)-41b.

CONCLUSIONS

In summary, focusing on the high three-dimensional diversity of the 1,3,5-trioxatriquinane derivatives, we designed and synthesized a novel TriMER-focused library consisting of 72 compounds carrying *N*-substituted phenyl residues. Among the synthesized compounds, three (**24b**, **28b**, **31b**) had a potent K_i value > 50 nM for OXRs, and two (**20b**, **34b**) had moderate K_i values $> 1,000$ nM. The hit rate for the screening was approximately 7%. The structure-activity relationship of the library screening results suggests that the *cis*-configuration of a phenyl residue with an *m*-bulkier substituent would be important as a preferred three-dimensional orientation for the tight binding for OXRs. In particular, stereoisomers **28b** and **31b** with *m*-*N*-Bz substituents had similar antagonist activity for OX₁R but different activities for OX₂R. The optimization of substituents on the benzamide portion provided potent dual OX₁R and OX₂R antagonist **38b** and potent selective OX₁R antagonist **41b**, which carry 4-methoxy groups on their terminal aromatic rings. **38b** and **41b** showed reasonable brain permeability and metabolic stability, and intraperitoneal administration of **38b** and **41b** demonstrated a significant sleep-inducing effect and suppressive effect on orexin A-induced locomotor activity, respectively. The docking simulation using these eutomers (–)-**38b** and (+)-**41b** estimated that both compounds take quite similar orientation in the receptor pockets by flipping the 1,3,5-trioxatriquinane core structure. Besides, the differences between the binding structure of (–)-**38b** and (+)-**41b** suggested that the interaction with ECL2 would be important for the receptor selectivity. Though the GPCR family accepts ligands of diverse shapes and sizes, the ligand-binding pockets shows similarity despite the diversity in the ligands.³⁸ The 1,3,5-trioxatriquinane showed high affinity not only for opioid receptors but orexin receptors. This fact suggests that the 1,3,5-trioxatriquinane could serve as a

privileged structure for GPCRs and the TriMER library approach might be useful for the hit discovery process targeting other GPCRs.

EXPERIMENTAL SECTION

All reagents and solvents were purchased from the following commercial suppliers: Tokyo Chemical Industry., Sigma-Aldrich, Inc., Kanto Chemical Co., Inc., Wako Pure Chemical Ind., Ltd. and Nacalai Tesuque. All commercially available chemicals and solvents were used without further purification. In general, reaction mixtures were magnetically stirred at the respective temperature under argon atmosphere. All synthetic compounds described in this study were checked with analytical thin-layer chromatography (TLC, Kieselgel 60 F254, E. Merck AG), visualized under UV light at 254 nm and phosphomolybdic acid in a sulfuric acid aqueous solution, Hanessian stain or *para*-anisaldehyde followed by heating, and purified by flash column chromatography on silica gel (spherical, neutral, 40–50 μm , Kanto Chemical Co., Japan), preparative TLC (Kieselgel 60 F254, E. Merck AG). Gel permeation chromatography (GPC) was performed on SSC-8200-25 recycle HPLC system (Senshu Scientific Co., Ltd) equipped with YMC-GPC T4000 column (10 μm , 600 mm $\times$ 20 mm), with UV detection at 254 nm and RI detection. ^1H and ^{13}C NMR spectra were recorded on a JEOL ECS-400 (^1H : 400 MHz; ^{13}C : 100 MHz). Chemical shifts are reported in ppm with reference to tetramethylsilane (0.00 ppm) and solvent signals [^1H NMR: CDCl_3 (7.26); ^{13}C NMR: CDCl_3 (77.16)]. Mass spectra were recorded with a JEOL JMS-T100LP spectrometer. Infrared spectra were recorded with a JASCO FT/IR 4100 spectrometer. The purity ($\geq 95\%$) of the assayed compounds was determined by analytical HPLC. Analytical HPLC was performed on AQUITY UPLC system (Waters Co., Ltd) equipped with AQUITY (1.7 μm , 50 mm $\times$ 2.1 mm) column, with PDA detection at 254 nm, at column temperature of 40 $^\circ\text{C}$.

The chiral resolution of selected racemic ligands [($\pm$)-**38b** and ($\pm$)- **41b**] was performed using a AQUITY UPLC system (Waters Co., Ltd) with a Chiralpack AD-H (5 μm , 250mm $\times$ 4.6 mm),

with PDA detection at 254 nm (n-hexane/i-propanol = 1/1) at 25 °C. All single stereoisomers were isolated, and their stereochemical purity was analyzed by chiral HPLC (>97% for each stereoisomer) and then characterized by NMR in CDCl₃. Circular dichroism (CD) spectra were recorded on J-820 circular dichroism spectropolarimeter (JASCO Co., Ltd.). Measurements were carried out at 20 °C using a 10 mm quartz cell in a volume of 3.5 mL. Compounds (1.0 mg) were dissolved in MeOH (5.0 mL). The instrument settings were bandwidth, 1.0 nm; data pitch, 0.2 nm; speed, 100 nm/min; accumulation, 16; and wavelengths, 400–220 nm. Chemical names were generated using ChemDraw Professional 15.0 (Perkin-Elmer Informatics). All synthetic derivatives were isolated as enantiomeric mixture and used for biological evaluations.

4,6-Dimethyl-4,6-bis(2-nitrophenyl)hexahydro-1,3,5-trioxa-2a¹-azacyclopenta[cd]pentalene (12a–15a)

To a solution of potassium *tert*-butoxide (1.56 g, 13.93 mmol) in anhydrous THF (20 mL) were added (methoxymethyl)triphenylphosphonium chloride (5.20 g, 15.14 mmol) at 0 °C under nitrogen flow. After stirring for 1 h, the mixture was added a solution of 2'-nitroacetophenone (**8a**) (1.00 g, 6.06 mmol) in 5 mL of anhydrous THF and stirred at room temperature for 8 h. The reaction mixture was poured into water (15mL) and extracted with CHCl₃ (30 mL, 25 mL, 20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was recrystallized twice from Et₂O/hexane, filtrated, and the filtrate was concentrated. The residue was purified by silica gel chromatography (hexane/ethyl acetate = 20/1) to give the *E/Z* mixture of methyl enol ether (976.6 mg, 5.05 mmol) as a yellow oil.

To a solution of the *E/Z* mixture of methyl enol ether in 1,2-dichloromethane (25 mL) was added mCPBA (1.31 g, 7.58 mmol) at 0 °C and stirred for 1 h and then at room temperature for 9.5 h. The reaction mixture was poured into sat Na₂S₂O₃ aq. solution (30 mL) and extracted with CHCl₃ (5 mL, 25 mL, 20 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/ethyl acetate = 5/1) to give the mixture of epoxide (1.68 g) as a white solid.

To a solution of the epoxide mixture in THF (5 mL) was added 2 M HCl aqueous solution (8 mL) at room temperature and the mixture was stirred at 60 °C for 8 h under Ar atmosphere. After cooling to room temperature, the mixture was neutralized with saturated NaHCO₃ aqueous solution (12 mL) and extracted with CHCl₃ (25 mL, 25 mL, 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to obtain the crude mixture of α -hydroxyaldehyde **9a** (1.15 g), which was used in the next reaction without further purification.

To a solution of the crude mixture of α -hydroxyaldehyde **9a** (986.6 mg) in MeOH (20 mL) were added NH₄Cl (1.25 g, 15.17 mmol) and NaOAc (406.5 mg, 7.58 mmol) at room temperature and the mixture was refluxed for 4 h under Ar atmosphere. After cooling to room temperature, MeOH was removed under reduced pressure. The residue was poured into sat. NaHCO₃ aq. solution (10 mL) and extracted with CHCl₃ (30 mL, 25 mL, 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/ethyl acetate = 2/1) to give the isomeric mixture of **11a** (840.3 mg, 2.26 mmol, 37% in 4 steps) as a brown amorphous.

To a solution of isomeric mixture of **11a** (840.3 mg, 2.26 mmol) in CHCl₃ (10 ml) were added glycolaldehyde dimer (273.8 mg, 2.26 mmol) and 10-camphorsulfonic acid (1.05 g, 4.53 mmol) at room temperature and the mixture was stirred at the same temperature for 14 h under Ar atmosphere. The reaction mixture was poured into sat. NaHCO₃ aq. solution (15 mL) and extracted with CHCl₃ (10 mL, 25 mL, 20 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1) and recycle GPC (CHCl₃) to obtain compound **12a** (371.9 mg, 36%), **13a** (222.1 mg, 21%), **14a** (75.7 mg, 7%) and **15a** (35.7 mg, 3%) as a white solid, respectively.

12a: IR (KBr, cm⁻¹) 2952, 1531, 1375, 1106. ¹H NMR (400 MHz, CDCl₃) δ 1.79 (s, 3H), 1.87 (s, 3H), 3.75 (dd, *J* = 3.2, 10.1 Hz, 1H), 4.21 (d, *J* = 10.1 Hz, 1H), 4.89 (d, *J* = 3.2 Hz, 1H), 5.06 (s, 2H), 7.37–7.40 (m, 1H), 7.43–7.61 (m, 7H). ¹³C NMR (100 MHz, CDCl₃) δ 23.4, 23.6, 71.4, 86.9, 87.5, 96.3, 99.6, 100.8, 124.3, 124.6, 127.7, 127.9, 128.9, 129.2, 131.7, 132.0, 134.7, 135.0, 149.3, 149.4. HR-MS (ESI): Calcd for C₂₀H₁₉N₃NaO₇ [M+Na]⁺, 436.1121. Found, 436.1121.

13a: IR (KBr, cm⁻¹) 2939, 1529, 1360, 1111. ¹H NMR (400 MHz, CDCl₃) δ 1.60 (s, 3H), 1.66 (s, 3H), 3.85 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.26 (d, *J* = 10.1 Hz, 1H), 4.96 (s, 1H), 5.09 (s, 1H), 5.22 (d, *J* = 2.8 Hz, 1H), 7.42–7.48 (m, 2H), 7.61–7.64 (m, 1H), 7.68–7.74 (m, 2H), 7.78–7.83 (m, 2H), 7.88–7.90 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 23.16, 23.20, 71.5, 88.1, 88.2, 94.6, 98.7, 100.1, 124.3, 125.7, 128.1, 128.2, 129.0, 129.6, 132.7, 133.6, 136.2, 136.3, 148.0, 148.6. HR-MS (ESI): Calcd for C₂₀H₁₉N₃NaO₇ [M+Na]⁺, 436.1121. Found, 436.1120.

14a: IR (KBr, cm⁻¹) 2943, 1528, 1364, 1108. ¹H NMR (400 MHz, CDCl₃) δ 1.78 (s, 3H), 1.83 (s, 3H), 3.67 (dd, *J* = 2.8, 10.4 Hz, 1H), 3.99 (d, *J* = 10.4 Hz, 1H), 4.90 (d, *J* = 2.8 Hz, 1H), 5.13 (s,

1H), 5.40 (s, 1H), 7.41–7.48 (m, 2H), 7.57–7.66 (m, 4H), 7.76–7.78 (m, 1H), 7.94–7.96 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 23.4, 23.8, 71.7, 87.7, 87.9, 95.7, 98.1, 100.8, 124.5, 124.9, 127.8, 128.4, 129.1, 129.5, 132.1, 132.9, 135.4, 136.4, 147.9, 149.3. HR-MS (ESI): Calcd for C₂₀H₁₉N₃NaO₇ [M+Na]⁺, 436.1121. Found, 436.1136.

15a: IR (KBr, cm⁻¹) 2945, 1525, 1358, 1106. ¹H NMR (400 MHz, CDCl₃) δ 1.70 (s, 3H), 1.79 (s, 3H), 3.75 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.02 (d, *J* = 10.1 Hz, 1H), 5.16 (s, 1H), 5.27 (d, *J* = 2.8 Hz, 1H), 5.43 (s, 1H), 7.21–7.32 (m, 3H), 7.40–7.44 (m, 1H), 7.52–7.56 (m, 1H), 7.65–7.67 (m, 1H), 7.79–7.83 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 23.2, 23.4, 71.8, 88.1, 88.3, 94.4, 97.7, 100.5, 124.2, 124.3, 128.1, 128.2, 129.4, 129.8, 132.9, 136.3, 136.8, 147.5, 148.1. HR-MS (ESI): Calcd for C₂₀H₁₉N₃NaO₇ [M+Na]⁺, 436.1121. Found, 436.1105.

4,6-Dimethyl-4,6-bis(3-nitrophenyl)hexahydro-1,3,5-trioxa-2a¹-azacyclopenta[cd]pentalene (12b–15b)

To a solution of 3'-nitroacetophenone (**8b**) (3.05 g, 18.5 mmol) in MeOH (90 mL) were added *p*-toluenesulfonylmethyl isocyanide (TosMIC, 7.21 g, 36.9 mmol) and K₂CO₃ (5.10 g, 36.9 mmol) at room temperature and the mixture was stirred for 18 h at the same temperature under Ar atmosphere. After removal of MeOH under reduced pressure, the residue was poured into brine (40 mL) and extracted with CHCl₃ (80 mL, 60 mL, 40 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to obtain the crude mixture of oxazoline (5.61 g), which was used in the next reaction without further purification.

To a solution of the crude mixture of oxazoline (5.61 g) in THF (15 mL) was added 2 M HCl (24 mL) at room temperature and the mixture was stirred at 60 °C for 5.5 h under Ar atmosphere. After cooling to room temperature, the mixture was neutralized with saturated NaHCO₃ aqueous solution (30 mL) and extracted with CHCl₃ (85 mL, 80 mL, 60 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to obtain the crude mixture of α -hydroxyaldehyde **9b** (4.37 g), which was used in the next reaction without further purification.

To a solution of the crude mixture of α -hydroxyaldehyde **9b** (4.37 g) in MeOH (30 mL) were added NH₄Cl (1.99 g, 37.3 mmol) and NaOAc (6.12 g, 74.6 mmol) at room temperature and the mixture was refluxed for 4 h under Ar atmosphere. After cooling to room temperature, MeOH was removed under reduced pressure. The residue was poured into saturated NaHCO₃ aqueous solution (30 mL) and extracted with CHCl₃ (80 mL, 60 mL, 40 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/ethyl acetate = 2/1) to give the isomeric mixture of **11b** (2.98g, 8.03 mmol, 87% in 3 steps) as a brown amorphous.

To a solution of isomeric mixture of **11b** (2.48 g, 6.67 mmol) in CHCl₃ (10 mL) were added glycolaldehyde dimer (273.8 mg, 2.26 mmol) and 10-camphorsulfonic acid (1.05 g, 4.53 mmol) at room temperature and the mixture was stirred at the same temperature for 14 h under Ar atmosphere. The reaction mixture was poured into sat. NaHCO₃ aq. solution (15 mL) and extracted with CHCl₃ (10 mL, 25 mL, 20 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1) and recycle GPC (CHCl₃) to obtain compound **12b** (0.57g, 18%), **13b** (0.50 g, 16%), **14b** (0.38 g, 12%) and **15b** (0.48 g, 15%) as white solid, respectively.

12b: IR (KBr, cm^{-1}) 2929, 1526, 1450, 1350, 1102. ^1H NMR (400 MHz, CDCl_3) δ 1.72 (s, 6H), 3.85 (dd, $J = 2.8, 10.0$ Hz, 1H), 4.35 (d, $J = 10.0$ Hz, 1H), 5.04 (d, $J = 2.8$ Hz, 1H), 5.08 (s, 1H), 5.14 (s, 1H), 7.56 (dd, $J = 8.0, 16.0$ Hz, 1H), 7.62 (dd, $J = 8.0, 16.0$ Hz, 1H), 7.69–7.72 (m, 1H), 7.80–7.83 (m, 1H), 8.13–8.16 (m, 1H), 8.19–8.21 (m, 1H), 8.28–8.29 (m, 1H), 8.34–8.35 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.21, 24.22, 71.5, 86.8, 87.2, 95.6, 99.8, 101.2, 120.2 ($\times 2$), 122.9, 123.0, 129.9, 130.1, 131.2, 131.4, 144.7, 144.8, 148.7, 148.8. HR-MS (ESI): Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{NaO}_7[\text{M}+\text{Na}]^+$, 436.1121. Found, 436.1111.

13b: IR (KBr, cm^{-1}) 2901, 1526, 1352, 1116. ^1H NMR (400 MHz, CDCl_3) δ 1.47 (s, 3H), 1.65 (s, 3H), 3.94 (dd, $J = 2.8, 10.0$ Hz, 1H), 4.42 (d, $J = 10.0$ Hz, 1H), 4.86 (s, 1H), 5.16 (s, 1H), 5.33 (d, $J = 2.8$ Hz, 1H), 7.54–7.60 (m, 2H), 7.64–7.66 (m, 1H), 8.14–8.17 (m, 2H), 8.19–8.22 (m, 1H), 8.40 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.6, 23.9, 71.5, 86.7, 87.1, 95.3, 100.1, 101.3, 120.1, 121.6, 122.7, 122.9, 128.9, 129.9, 131.1, 132.5, 142.7, 144.6, 148.2, 148.6. HR-MS (ESI): Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{NaO}_7[\text{M}+\text{Na}]^+$, 436.1121. Found, 436.1119.

14b: IR (KBr, cm^{-1}) 2903, 1529, 1351, 1106. ^1H NMR (400 MHz, CDCl_3) δ 1.72 (s, 3H), 1.77 (s, 3H), 3.70 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.13 (d, $J = 10.5$ Hz, 1H), 4.93 (s, 1H), 5.08 (d, $J = 2.8$ Hz, 1H), 5.46 (s, 1H), 7.56–7.64 (m, 2H), 7.81–7.83 (m, 2H), 8.18–8.22 (m, 2H), 8.35–8.37 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.3, 24.6, 71.7, 86.8, 87.3, 95.3, 99.8, 101.7, 120.4, 121.0, 122.7, 122.9, 129.2, 130.0, 131.4, 132.0, 143.2, 144.9, 148.3, 148.8. HR-MS (ESI): Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{NaO}_7[\text{M}+\text{Na}]^+$, 436.1121. Found, 436.1115.

15b: IR (KBr, cm^{-1}) 2914, 1524, 1353, 1110. ^1H NMR (400 MHz, CDCl_3) δ 1.59 (s, 3H), 1.77 (s, 3H), 3.78 (dd, $J = 2.8, 10.5$ Hz, 1H), 4.20 (d, $J = 10.7$ Hz, 1H), 4.94 (s, 1H), 5.21 (s, 1H), 5.38 (d, $J = 2.8$ Hz, 1H), 7.37–7.44 (m, 2H), 7.66 (dd, $J = 8.2, 16.0$ Hz, 1H), 7.88 (m, 1H), 7.93–7.96 (m,

1H), 8.06–8.09 (m, 1H), 8.24–8.27 (m, 1H), 8.35 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 22.4, 22.9, 71.7, 86.8, 86.9, 95.1, 100.2, 101.7, 121.05, 121.04, 122.5, 122.8, 129.0, 129.2, 131.6, 132.5, 142.9, 148.0, 148.2. HR-MS (ESI): Calcd for C₂₀H₁₉N₃NaO₇ [M+Na]⁺, 436.1121. Found, 436.1129.

4,6-Dimethyl-4,6-bis(4-nitrophenyl)hexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene (12c–15c)

According to the synthetic protocol of **12b–15b**, 4'-nitroacetophenone (**8c**, 1.00 g, 6.06 mmol) was converted to compound **12c** (0.34 g, 27%), **13c** (0.28 g, 22%), **14c** (0.10 g, 12%) and **15c** (0.13 g, 18%) as white solid, respectively.

12c: IR (KBr, cm⁻¹) 2917, 1517, 1348, 1116. ¹H NMR (400 MHz, CDCl₃) δ 1.699 (s, 3H), 1.704 (s, 3H), 3.84 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.33 (d, *J* = 10.1 Hz, 1H), 5.02 (d, *J* = 2.8 Hz, 1H), 5.08 (s, 1H), 5.11 (s, 1H), 7.56–7.58 (m, 2H), 7.63–7.65 (m, 2H), 8.20–8.23 (m, 2H), 8.26–8.28 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 24.11, 24.14, 71.4, 87.1, 87.5, 95.5, 99.6, 101.2, 124.0, 124.2, 126.1, 126.2, 147.5, 147.6, 149.6, 149.7. HR-MS (ESI): Calcd for C₂₀H₁₉N₃NaO₇ [M+Na]⁺, 436.1121. Found, 436.1111.

13c: IR (KBr, cm⁻¹) 2926, 1519, 1116. ¹H NMR (400 MHz, CDCl₃) δ 1.43 (s, 3H), 1.62 (s, 3H), 3.93 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.39 (d, *J* = 10.1 Hz, 1H), 4.88 (s, 1H), 5.14 (s, 1H), 5.33 (d, *J* = 2.8 Hz, 1H), 7.47–7.49 (m, 2H), 7.66–7.69 (m, 2H), 8.22–8.27 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 22.9, 23.8, 71.4, 87.1, 87.3, 95.4, 100.2, 101.1, 123.3, 124.0, 126.0, 127.0, 147.4, 147.6, 148.0, 149.5. HR-MS (ESI): Calcd for C₂₀H₁₉N₃NaO₇ [M+Na]⁺, 436.1121. Found, 436.1127.

14c: IR (KBr, cm^{-1}) 2925, 1520, 1349, 1122. ^1H NMR (400 MHz, CDCl_3) δ 1.69 (s, 3H), 1.74 (s, 3H), 3.70 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.11 (d, $J = 10.1$ Hz, 1H), 4.94 (s, 1H), 5.07 (d, $J = 2.8$ Hz, 1H), 5.45 (s, 1H), 7.65 (d, $J = 8.2$ Hz, 4H), 8.26 (d, $J = 9.2$ Hz, 2H), 8.28 (d, $J = 9.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.3, 24.4, 71.7, 87.1, 87.6, 95.3, 99.7, 101.8, 123.5, 124.1, 126.2, 126.7, 147.3, 147.6, 148.3, 149.8. HR-MS (ESI): Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, 436.1121. Found, 436.1117.

15c: IR (KBr, cm^{-1}) 2930, 1520, 1350, 1118. ^1H NMR (400 MHz, CDCl_3) δ 1.57 (s, 3H), 1.72 (s, 3H), 3.79 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.17 (d, $J = 10.1$ Hz, 1H), 4.97 (s, 1H), 5.26 (s, 1H), 5.37 (d, $J = 2.8$ Hz, 1H), 7.15–7.17 (m, 2H), 7.66–7.68 (m, 2H), 8.09–8.11 (m, 2H), 8.26–8.28 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.0, 23.2, 71.7, 87.21, 87.24, 95.2, 100.3, 101.7, 123.3, 123.4, 126.4, 126.9, 147.2, 147.4, 148.0, 148.3. HR-MS (ESI): Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, 436.1121. Found, 436.1099.

2,2'-((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)dianiline (16a)

To a solution of **12a** (107 mg, 0.258 mmol) in ethyl acetate (20 mL) was added 5% Pd/C (Degussa type, 109.1 mg, 19.9 mol%) at room temperature. The mixture was stirred for 17 h at the same temperature under hydrogen atmosphere (balloon pressure). The reaction mixture was filtrated with Celite and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (chloroform/methanol = 40/1) to give **11a** (91.1 mg, 100%) as a colorless amorphous.

IR (KBr, cm^{-1}) 3477, 3375, 2933, 1127. ^1H NMR (400 MHz, CDCl_3) δ 1.73 (s, 3H), 1.75 (s, 3H), 3.79 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.23 (d, $J = 10.1$ Hz, 1H), 4.58 (brs, 4H), 4.92 (d, $J = 2.8$ Hz, 1H), 5.26 (s, 1H), 5.41 (s, 1H), 6.59–6.64 (m, 2H), 6.67–6.74 (m, 2H), 6.98–7.05 (m, 2H), 7.08–7.13 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 20.2, 20.9, 70.6, 87.3, 87.7, 95.1, 97.0, 99.6, 117.6, 117.7, 117.9, 118.0, 123.7, 123.8, 126.2, 126.4, 128.8, 145.1, 145.2. HR-MS (ESI): Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{NaO}_3$ $[\text{M}+\text{Na}]^+$, 376.1637. Found, 376.1651.

2,2'-((2*aS/R*,4*R/S*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)dianiline (17a)

According to the synthetic protocol of **16a**, **13a** (172 mg, 0.417 mmol) was converted to **17a** (138 mg, 94%) as a pale brown amorphous.

IR (KBr, cm^{-1}) 3469, 3378, 2931, 1114. ^1H NMR (400 MHz, CDCl_3) δ 1.56 (s, 3H), 1.61 (s, 3H), 3.90 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.29 (d, $J = 10.1$ Hz, 1H), 4.44 (brs, 2H), 4.52 (brs, 2H), 4.88 (s, 1H), 5.35 (d, $J = 2.8$ Hz, 1H), 5.45 (s, 1H), 6.64–6.73 (m, 4H), 7.04–7.14 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 20.4, 22.2, 70.8, 87.4, 89.1, 95.1, 99.0, 99.7, 117.5, 117.6, 117.85, 117.89, 123.5, 124.7, 126.0, 127.4, 128.2, 128.9, 145.2, 145.3. HR-MS (ESI): Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{NaO}_3$ $[\text{M}+\text{Na}]^+$, 376.1637. Found, 376.1651.

2,2'-((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)dianiline (18a)

According to the synthetic protocol of **16a**, **14a** (136 mg, 0.329 mmol) was converted to **18a** (112 mg, 96%) as a pale brown amorphous.

IR (KBr, cm⁻¹) 3467, 3378, 2929, 1118. ¹H NMR (400 MHz, CDCl₃) δ 1.69 (s, 3H), 1.75 (s, 3H), 3.75 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.17 (d, *J* = 10.1 Hz, 1H), 4.52 (brs, 4H), 4.95 (d, *J* = 2.8 Hz, 1H), 5.11 (s, 1H), 5.69 (s, 1H), 6.64–6.69 (m, 2H), 6.72–6.78 (m, 2H), 7.05–7.12 (m, 2H), 7.19–7.21 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 20.9, 22.1, 71.2, 88.0, 88.8, 94.8, 97.2, 102.1, 117.7, 118.0, 123.8, 126.3, 127.7, 128.4, 128.9, 145.2. HR-MS (ESI): Calcd for C₂₀H₂₃N₃NaO₃ [M+Na]⁺, 376.1637. Found, 376.1637.

2,2'-((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)dianiline (19a)

According to the synthetic protocol of **16a**, **15a** (28.0 mg, 0.0677 mmol) was converted to **19a** (22.1 mg, 92%) as a colorless amorphous.

IR (KBr, cm⁻¹) 3460, 3374, 2927, 1118. ¹H NMR (400 MHz, CDCl₃) δ 1.63 (s, 3H), 1.69 (s, 3H), 3.83 (dd, *J* = 2.8, 10.4 Hz, 1H), 4.18 (brs, 4H), 4.23 (d, *J* = 10.4 Hz, 1H), 5.12 (s, 1H), 5.33 (s, 1H), 5.35 (d, *J* = 2.8 Hz, 1H), 6.49–6.51 (m, 1H), 6.61–6.71 (m, 3H), 6.94–6.99 (m, 2H), 7.04 (ddd, *J* = 1.2, 7.6, 7.6 Hz, 1H), 7.17–7.24 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 22.0, 22.7, 71.3, 89.3, 89.6, 94.8, 100.3, 102.4, 117.3, 117.5, 117.77, 117.82, 117.96, 117.99, 127.6, 127.7, 128.2,

128.4, 145.3, 145.4. HR-MS (ESI): Calcd for $C_{20}H_{23}N_3NaO_3$ $[M+Na]^+$, 376.1637. Found, 376.1632.

3,3'-((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)dianiline (16b)

According to the synthetic protocol of **16a**, **15a** (106.7 mg, 0.258 mmol) was converted to **19a** (91.1 mg, 100%) as a colorless amorphous.

IR (KBr, cm^{-1}) 3444, 3365, 2932, 1110. 1H NMR (400 MHz, $CDCl_3$) δ 1.641 (s, 3H), 1.644 (s, 3H), 3.66 (brs, 2H), 3.71 (brs, 2H), 3.77 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.25 (d, $J = 10.1$ Hz, 1H), 5.03 (d, $J = 2.8$ Hz, 1H), 5.09 (s, 1H), 5.11 (s, 1H), 6.54–6.57 (m, 1H), 6.59–6.62 (m, 1H), 6.70–6.71 (m, 1H), 6.73–6.75 (m, 1H), 6.78–6.82 (m, 2H), 7.10 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.16 (dd, $J = 8.0, 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 24.3, 71.2, 86.7, 87.3, 95.1, 99.4, 101.4, 111.7, 111.8, 114.3, 114.4, 115.4, 115.5, 129.6, 129.7, 143.8, 146.6, 146.7. HR-MS (ESI): Calcd for $C_{20}H_{23}N_3NaO_3$ $[M+Na]^+$, 376.1637. Found, 376.1646.

3,3'-((2*aS/R*,4*R/S*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)dianiline (17b)

According to the synthetic protocol of **16a**, **13b** (172 mg, 0.417 mmol) was converted to **17b** (138 mg, 94%) as a colorless amorphous.

IR (KBr, cm^{-1}) 3438, 3361, 2929, 1112. ^1H NMR (400 MHz, CDCl_3) δ 1.44 (s, 3H), 1.53 (s, 3H), 3.66 (brs, 4H), 3.87 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.31 (d, $J = 10.1$ Hz, 1H), 4.87 (s, 1H), 5.12 (s, 1H), 5.27 (d, $J = 2.8$ Hz, 1H), 6.56–6.59 (m, 1H), 6.60–6.63 (m, 1H), 6.70–6.71 (m, 1H), 6.83–6.86 (m, 1H), 6.88–6.89 (m, 1H), 7.12 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.16 (dd, $J = 7.8, 7.8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.5, 24.1, 71.3, 87.0, 87.1, 94.8, 99.7, 101.2, 111.7, 113.2, 114.1, 114.3, 115.3, 116.4, 128.8, 129.6, 142.3, 143.7, 146.0, 146.7. HR-MS (ESI): Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{NaO}_3$ $[\text{M}+\text{Na}]^+$, 376.1637. Found, 376.1633.

3,3'-((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)dianiline (18b)

According to the synthetic protocol of **16a**, **14b** (136 mg, 0.329 mmol) was converted to **18c** (112 mg, 96%) as a colorless amorphous.

IR (KBr, cm^{-1}) 3437, 3361, 2931, 1115. ^1H NMR (400 MHz, CDCl_3) δ 1.62 (s, 3H), 1.70 (s, 3H), 3.65 (dd, $J = 2.8, 10.1$ Hz, 1H), 3.70 (brs, 4H), 4.12 (d, $J = 10.1$ Hz, 1H), 4.85 (s, 1H), 5.09 (d, $J = 2.8$ Hz, 1H), 5.39 (s, 1H), 6.60–6.63 (m, 2H), 6.79–6.88 (m, 4H), 7.168 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.173 (dd, $J = 8.0, 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.5, 24.5, 71.6, 86.9, 87.4, 94.9, 99.5, 102.0, 111.8, 112.6, 114.3, 115.3, 115.8, 129.1, 129.7, 142.5, 144.0, 146.2, 146.7. HR-MS (ESI): Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{NaO}_3$ $[\text{M}+\text{Na}]^+$, 376.1637. Found, 376.1644.

3,3'-((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)dianiline (19b)

According to the synthetic protocol of **16a**, **15b** (636 mg, 0.154 mmol) was converted to **19b** (153 mg, 99%) as a colorless amorphous.

IR (KBr, cm^{-1}) 3387, 3336, 2933, 1115. ^1H NMR (400 MHz, CDCl_3) δ 1.51 (s, 3H), 1.68 (s, 3H), 3.74 (dd, $J = 2.8, 10.1$ Hz, 1H), 3.75 (brs, 4H), 4.20 (d, $J = 10.1$ Hz, 1H), 4.87 (s, 1H), 5.05 (s, 1H), 5.30 (d, $J = 2.8$ Hz, 1H), 6.50–6.53 (m, 2H), 6.61–6.62 (m, 1H), 6.68 (ddd, $J = 0.9, 2.3, 7.8$ Hz, 1H), 6.82–6.85 (m, 1H), 7.06 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.08–7.10 (m, 1H), 7.18 (dd, $J = 8.0, 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 21.9, 23.3, 71.8, 87.0, 94.6, 100.3, 102.2, 113.3, 113.7, 114.7, 115.1, 116.2, 128.75, 128.80, 141.8, 142.3, 145.6, 146.3. HR-MS (ESI): Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{NaO}_3$ $[\text{M}+\text{Na}]^+$, 376.1637. Found, 376.1636.

4,4'-((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)dianiline (16c)

According to the synthetic protocol of **16a**, **12c** (102 mg, 0.246 mmol) was converted to **16c** (86.6 mg, 100%) as a colorless amorphous.

IR (KBr, cm^{-1}) 3425, 3369, 2931, 1115. ^1H NMR (400 MHz, CDCl_3) δ 1.62 (s, 3H), 1.63 (s, 3H), 3.67 (brs, 4H), 3.76 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.24 (d, $J = 10.1$ Hz, 1H), 4.97 (d, $J = 2.8$ Hz, 1H), 5.04 (s, 1H), 5.06 (s, 1H), 6.61–6.63 (m, 2H), 6.67–6.69 (m, 2H), 7.13–7.16 (m, 2H), 7.21–7.24 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.2, 24.3, 71.2, 86.5, 87.0, 94.9, 99.3, 101.4, 115.1, 115.2, 126.1, 126.2, 132.2, 132.4, 145.7, 145.8. HR-MS (ESI): Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{NaO}_3$ $[\text{M}+\text{Na}]^+$, 376.1637. Found, 376.1639.

4,4'-((2*aS/R*,4*R/S*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)dianiline (17c)

According to the synthetic protocol of **16a**, **13c** (50.3 mg, 0.122 mmol) was converted to **17c** (23.7 mg, 55%) as a colorless amorphous.

IR (KBr, cm⁻¹) 3455, 3364, 1118. ¹H NMR (400 MHz, CDCl₃) δ 1.45 (s, 3H), 1.54 (s, 3H), 3.65 (brs, 4H), 3.86 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.30 (d, *J* = 10.1 Hz, 1H), 4.75 (s, 1H), 5.09 (s, 1H), 5.25 (d, *J* = 2.8 Hz, 1H), 6.63–6.65 (m, 2H), 6.67–6.70 (m, 2H), 7.09–7.11 (m, 2H), 7.30–7.32 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 22.8, 24.1, 71.4, 86.7, 94.6, 99.8, 101.4, 114.6, 115.2, 126.1, 127.4, 130.8, 132.2, 145.6, 145.7. HR-MS (ESI): Calcd for C₂₀H₂₃N₃NaO₃ [M+Na]⁺, 376.1637. Found, 376.1635.

4,4'-((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)dianiline (18c)

According to the synthetic protocol of **16a**, **14c** (25.4 mg, 0.0612 mmol) was converted to **18c** (20.2 mg, 93%) as a colorless amorphous.

IR (KBr, cm⁻¹) 3466, 3373, 2903, 1111. ¹H NMR (400 MHz, CDCl₃) δ 1.62 (s, 3H), 1.68 (s, 3H), 3.64 (dd, *J* = 2.8, 10.1 Hz, 1H), 3.67 (brs, 4H), 4.11 (d, *J* = 10.1 Hz, 1H), 4.76 (s, 1H), 5.04 (d, *J* = 2.8 Hz, 1H), 5.35 (s, 1H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 22.9, 24.5, 71.5, 86.5, 87.2, 94.8,

99.3, 102.0, 114.9, 115.2, 126.2, 126.8, 131.0, 132.5, 145.7, 145.8. HR-MS (ESI): Calcd for $C_{20}H_{23}N_3NaO_3$ $[M+Na]^+$, 376.1637. Found, 376.1648.

4,4'-((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)dianiline (19c)

According to the synthetic protocol of **16a**, **15c** (60.7 mg, 0.147 mmol) was converted to **19c** (51.6 mg, 99%) as a colorless amorphous.

IR (KBr, cm^{-1}) 3431, 3357, 2926, 1119. 1H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 3H), 1.66 (s, 3H), 3.62 (brs, 4H), 3.73 (dd, $J = 2.0$ 10.1 Hz, 1H), 4.18 (d, $J = 10.1$ Hz, 1H), 4.83 (s, 1H), 5.02 (s, 1H), 5.29 (d, $J = 2.0$ Hz, 1H), 6.59 (d, $J = 8.0$ Hz, 2H), 6.70 (d, $J = 8.0$ Hz, 2H), 7.01 (d, $J = 8.0$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 23.1, 71.7, 86.78, 86.83, 94.4, 99.8, 102.0, 114.6, 114.8, 126.6, 127.4, 130.6, 131.3, 145.4, 145.7. HR-MS (ESI): Calcd for $C_{20}H_{23}N_3NaO_3$ $[M+Na]^+$, 376.1637. Found, 376.1652.

2,2'-((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(*N,N*-dimethylaniline) (20a)

To a solution of **16a** (10.0 mg, 0.0283 mmol) in ethyl acetate (0.5 mL) were added formaldehyde (37% Solution, 104.4 μ L, 1.415 mmol) and acetic acid (50 μ L) at room temperature. After stirring for 10 min, the mixture was added 5% Pd/C (Degussa type, 10.0 mg, 17.7 mol%) and continued to stir for 2h under hydrogen atmosphere (balloon pressure). The reaction mixture was filtrated

with Celite and the filtrate was washed with CHCl₃ (5 mL, 4 mL, 3 mL) and CHCl₃/MeOH mixtures (3/1, 5 mL × 3). After removal of organic solvent under reduced pressure, the residue was extracted with CHCl₃ (8 mL, 5 mL, 3 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by preparative TLC (hexane/ethyl acetate = 3/1) to give the mixture of **20a** (10.1 mg, 87%) as a white solid.

IR (KBr, cm⁻¹) 2935, 1483, 1140. ¹H NMR (400 MHz, CDCl₃) δ 1.82 (s, 3H), 1.85 (s, 3H), 2.60 (s, 6H), 2.65 (s, 6H), 3.78 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.28 (d, *J* = 10.1 Hz, 1H), 5.11 (d, *J* = 2.8 Hz, 1H), 5.39 (s, 1H), 5.47 (s, 1H), 7.16 (ddd, *J* = 1.2, 8.0, 8.0 Hz, 1H), 7.18 (ddd, *J* = 1.2, 8.0, 8.0 Hz, 1H), 7.26 (ddd, *J* = 1.2, 8.0, 8.0 Hz, 1H), 7.27 (ddd, *J* = 1.2, 8.0, 8.0 Hz, 1H), 7.37 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.38 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.56 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.73 (dd, *J* = 1.2, 8.0 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 23.0, 23.3, 47.3, 47.5, 71.4, 87.2, 88.2, 95.1, 99.2, 101.5, 125.0, 125.1, 126.06, 126.14, 126.6, 128.86, 128.90, 138.8, 139.5, 152.9, 153.1. HR-MS (ESI): Calcd for C₂₄H₃₂N₃O₃ [M+H]⁺, 410.2444. Found, 410.2431.

3,3'-((2*aS*/R,4*S*/R,4*aS*/R,6*S*/R,6*aS*/R)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(*N,N*-dimethylaniline) (20b)

According to the synthetic protocol of **20a**, **16b** (10.0 mg, 0.0283 mmol) was converted to **20b** (7.9 mg, 68%) as a white solid.

IR (KBr, cm⁻¹) 2923, 1496, 1112. ¹H NMR (400 MHz, CDCl₃) δ 1.69 (s, 6H), 2.93 (s, 6H), 2.97 (s, 6H), 3.79 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.28 (d, *J* = 10.1 Hz, 1H), 5.08 (d, *J* = 2.8 Hz, 1H), 5.12 (s, 1H), 5.23 (s, 1H), 6.59–6.63 (m, 1H), 6.64–6.67 (m, 2H), 6.76–6.83 (m, 3H), 7.18 (dd, *J* = 8.0,

8.0 Hz, 1H), 7.23 (dd, $J = 8.0, 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.38, 24.44, 40.9, 71.4, 87.1, 87.6, 95.2, 99.8, 101.9, 109.1, 109.2, 111.75, 111.84, 113.4, 113.6, 129.2, 129.4, 143.3, 143.5, 150.9. HR-MS (ESI): Calcd for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{NaO}_3$ $[\text{M}+\text{Na}]^+$, 432.2263. Found, 432.2248.

4,4'-((2*aS*/R,4*S*/R,4*aS*/R,6*S*/R,6*aS*/R)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(*N,N*-dimethylaniline) (20c)

According to the synthetic protocol of **20a**, **16c** (10.1 mg, 0.0286 mmol) was converted to **20c** (9.3 mg, 80%) as a white solid.

IR (KBr, cm^{-1}) 2932, 1523, 1124. ^1H NMR (400 MHz, CDCl_3) δ 1.647 (s, 3H), 1.652 (s, 3H), 2.90 (s, 6H), 2.94 (s, 6H), 3.77 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.24 (d, $J = 10.1$ Hz, 1H), 4.99 (d, $J = 2.8$ Hz, 1H), 5.08 (s, 1H), 5.09 (s, 1H), 6.66–6.67 (m, 2H), 6.72–6.75 (m, 2H), 7.22–7.24 (m, 2H), 7.30–7.33 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.10, 24.14, 40.7, 71.2, 86.4, 86.9, 95.0, 99.3, 101.4, 112.57, 112.65, 125.9, 126.0, 130.0, 130.2, 150.0, 150.02. HR-MS (ESI): Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$, 410.2444. Found, 410.2459.

2,2'-((2*aS*/R,4*R*/S,4*aS*/R,6*S*/R,6*aS*/R)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(*N,N*-dimethylaniline) (21a)

According to the synthetic protocol of **20a**, **17a** (10.0 mg, 0.0283 mmol) was converted to **21a** (7.9 mg, 68%) as a white solid.

IR (KBr, cm^{-1}) 2936, 1490, 1101. ^1H NMR (400 MHz, CDCl_3) δ 1.50 (s, 3H), 1.63 (s, 3H), 2.59 (s, 6H), 2.79 (brs, 6H), 3.88 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.33 (d, $J = 10.1$ Hz, 1H), 5.23 (d, $J = 2.8$ Hz, 1H), 5.33 (s, 1H), 5.43 (s, 1H), 7.15–7.24 (m, 2H), 7.27–7.34 (m, 2H), 7.39 (dd, $J = 1.2, 7.6$ Hz, 1H), 7.42 (dd, $J = 1.2, 7.6$ Hz, 1H), 7.67 (dd, $J = 1.2, 7.6$ Hz, 1H), 7.77 (dd, $J = 1.2, 7.6$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.2, 47.3, 47.8, 71.3, 87.9, 88.2, 93.6, 99.7, 101.6, 123.5, 125.1, 125.79, 125.84, 126.5, 127.4, 128.2, 128.8, 139.7, 139.9, 151.6, 152.9.

HR-MS (ESI): Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$, 410.2444. Found, 410.2428.

3,3'-((2*aS/R*,4*R/S*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(*N,N*-dimethylaniline) (21b)

According to the synthetic protocol of **20a**, **13b** (10.0 mg, 0.0283 mmol) was converted to **21b** (6.9 mg, 60%) as a white solid.

IR (KBr, cm^{-1}) 2925, 1498, 1119. ^1H NMR (400 MHz, CDCl_3) δ 1.48 (s, 3H), 1.56 (s, 3H), 2.94 (s, 6H), 2.99 (s, 6H), 3.89 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.33 (d, $J = 10.1$ Hz, 1H), 4.94 (s, 1H), 5.19 (s, 1H), 5.28 (d, $J = 2.8$ Hz, 1H), 6.63–6.66 (m, 1H), 6.68–6.73 (m, 3H), 6.81–6.83 (m, 1H), 6.94 (dd, $J = 1.2, 2.4$ Hz, 1H), 7.21 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.25 (dd, $J = 8.0, 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.9, 24.3, 40.8, 40.9, 71.4, 87.3, 87.5, 94.9, 99.7, 101.5, 109.2, 110.9, 111.7, 111.8, 113.4, 114.5, 128.5, 129.3, 142.0, 143.3, 150.3, 150.9. HR-MS (ESI): Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$, 410.2444. Found, 410.2430.

4,4'-((2*aS/R*,4*R/S*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(*N,N*-dimethylaniline) (21c)

According to the synthetic protocol of **20a**, **17c** (7.6 mg, 0.0215 mmol) was converted to **21c** (9.4 mg, 81%) as a white solid.

IR (KBr, cm⁻¹) 2925, 1523, 1110. ¹H NMR (400 MHz, CDCl₃) δ 1.49 (s, 3H), 1.55 (s, 3H), 2.92 (s, 6H), 2.96 (s, 6H), 3.87 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.31 (d, *J* = 10.1 Hz, 1H), 4.77 (s, 1H), 5.12 (s, 1H), 5.25 (d, *J* = 2.8 Hz, 1H), 6.69–6.75 (m, 4H), 7.19–7.21 (m, 2H), 7.39–7.41 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 22.9, 24.1, 40.71, 40.74, 71.4, 86.66, 94.6, 99.8, 101.4, 111.8, 112.6, 125.9, 127.2, 128.6, 130.0, 149.8, 150.0. HR-MS (ESI): Calcd for C₂₄H₃₂N₃O₃ [M+H]⁺, 410.2444. Found, 410.2447.

2,2'-((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(*N,N*-dimethylaniline) (22a)

According to the synthetic protocol of **20a**, **18a** (10.0 mg, 0.0283 mmol) was converted to **22a** (7.3 mg, 63%) as a white solid.

IR (KBr, cm⁻¹) 2935, 1486, 1135. ¹H NMR (400 MHz, CDCl₃) δ 1.66 (s, 3H), 1.84 (s, 3H), 2.64 (s, 6H), 2.68 (s, 6H), 3.62 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.08 (d, *J* = 10.1 Hz, 1H), 5.12 (d, *J* = 2.8 Hz, 1H), 5.21 (s, 1H), 5.65 (s, 1H), 7.19–7.25 (m, 2H), 7.29–7.34 (m, 2H), 7.38 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.44 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.59 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.83 (dd, *J* = 1.2, 7.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 22.2, 23.3, 46.8, 47.3, 71.5, 86.7, 88.2, 94.8, 98.1, 101.7,

123.8, 125.2, 126.1, 126.2, 126.5, 127.1, 128.4, 128.9, 139.7, 140.5, 151.2, 153.2. HR-MS (ESI): Calcd for C₂₄H₃₂N₃O₃ [M+H]⁺, 410.2444. Found, 410.2427.

3,3'-((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(*N,N*-dimethylaniline) (22b)

According to the synthetic protocol of **20a**, **18b** (10.0 mg, 0.0283 mmol) was converted to **22b** (7.3 mg, 63%) as a white solid.

IR (KBr, cm⁻¹) 2906, 1496, 1119. ¹H NMR (400 MHz, CDCl₃) δ 1.65 (s, 3H), 1.74 (s, 3H), 2.97 (s, 6H), 2.98 (s, 6H), 3.66 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.13 (d, *J* = 10.1 Hz, 1H), 4.88 (s, 1H), 5.15 (d, *J* = 2.8 Hz, 1H), 5.44 (s, 1H), 6.66–6.68 (m, 2H), 6.75–6.79 (m, 2H), 6.83–6.84 (m, 1H), 6.98–6.99 (m, 1H), 7.25 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.23–7.28 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 23.8, 24.7, 40.7, 40.9, 71.8, 87.2, 87.9, 95.0, 99.9, 102.1, 109.2, 110.0, 111.6, 111.8, 113.6, 113.7, 128.8, 129.4, 142.2, 143.7, 150.4, 151.0. HR-MS (ESI): Calcd for C₂₄H₃₁N₃NaO₃ [M+H]⁺, 432.2263. Found, 432.2279.

4,4'-((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(*N,N*-dimethylaniline) (22c)

According to the synthetic protocol of **20a**, **14c** (10.0 mg, 0.0283 mmol) was converted to **22c** (7.3 mg, 63%) as a white solid.

IR (KBr, cm^{-1}) 2926, 1524, 1117. ^1H NMR (400 MHz, CDCl_3) δ 1.64 (s, 3H), 1.70 (s, 3H), 2.945 (s, 6H), 2.950 (s, 6H), 3.64 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.12 (d, $J = 10.1$ Hz, 1H), 4.77 (s, 1H), 5.05 (d, $J = 2.8$ Hz, 1H), 5.38 (s, 1H), 6.74–6.76 (m, 4H), 7.31–7.34 (m, 2H), 7.38–7.40 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.9, 24.5, 40.7, 40.8, 71.6, 86.5, 87.2, 94.9, 99.3, 102.0, 112.2, 112.7, 126.0, 126.5, 128.9, 130.4, 149.9, 150.1. HR-MS (ESI): Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$, 410.2444. Found, 410.2439.

2,2'-((2*aS*/R,4*R*/S,4*aS*/R,6*R*/S,6*aS*/R)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(*N,N*-dimethylaniline) (23a)

According to the synthetic protocol of **20a**, **19a** (10.0 mg, 0.0283 mmol) was converted to **23a** (5.9 mg, 51%) as a white solid.

IR (film, cm^{-1}) 2933, 1490, 1115. ^1H NMR (400 MHz, CDCl_3) δ 1.59 (s, 3H), 1.72 (s, 3H), 2.59 (brs, 6H), 2.69 (brs, 6H), 3.72 (dd, $J = 2.8, 10.0$ Hz, 1H), 4.15 (d, $J = 10.0$ Hz, 1H), 5.25 (s, 1H), 5.30 (d, $J = 2.8$ Hz, 1H), 5.56 (s, 1H), 6.73 (ddd, $J = 1.6, 8.0$ Hz, 1H), 6.85–6.90 (m, 1H), 7.14–7.19 (m, 2H), 7.24–7.28 (m, 1H), 7.33 (ddd, $J = 1.6, 8.0, 8.0$ Hz, 1H), 7.41 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.63 (dd, $J = 1.6, 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.1, 22.6, 46.7 ($\times 2$), 46.9 ($\times 2$), 71.3, 86.7, 87.7, 93.8, 98.0, 101.7, 123.5, 123.6, 125.8, 126.0, 126.6, 126.8, 128.0, 128.2, 140.2, 140.6, 151.1, 151.4. HR-MS (ESI): Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$, 410.2444. Found, 410.2424.

3,3'-((2*aS*/R,4*R*/S,4*aS*/R,6*R*/S,6*aS*/R)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(*N,N*-dimethylaniline) (23b)

According to the synthetic protocol of **20a**, **19b** (5.1 mg, 0.144 mmol) was converted to **23b** (3.9 mg, 66%) as a white solid.

IR (KBr, cm^{-1}) 2916, 1604, 1121. ^1H NMR (400 MHz, CDCl_3) δ 1.54 (s, 3H), 1.69 (s, 3H), 2.78 (s, 6H), 2.94 (s, 6H), 3.75 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.20 (d, $J = 10.1$ Hz, 1H), 4.91 (s, 1H), 5.17 (s, 1H), 5.32 (d, $J = 2.8$ Hz, 1H), 6.49–6.56 (m, 3H), 6.63–6.66 (m, 1H), 6.85–6.87 (m, 1H), 6.93 (dd, $J = 2.0, 2.0$ Hz, 1H), 7.10–7.14 (m, 1H), 7.23 (dd, $J = 8.0, 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.2, 23.4, 40.6, 40.8, 71.8, 87.2, 87.6, 94.6, 100.1, 102.1, 110.2, 110.4, 111.2, 111.3, 113.5, 114.6, 128.4, 128.5, 142.0, 150.19, 150.24. HR-MS (ESI): Calcd for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{NaO}_3$ $[\text{M}+\text{Na}]^+$, 432.2263. Found, 432.2276.

4,4'-((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(*N,N*-dimethylaniline) (23c**)**

According to the synthetic protocol of **20a**, (10.0 mg, 0.0283 mmol) was converted to **23c** (7.6 mg, 66%) as a white solid.

IR (KBr, cm^{-1}) 2893, 1523, 1119. ^1H NMR (400 MHz, CDCl_3) δ 1.53 (s, 3H), 1.68 (s, 3H), 2.91 (s, 6H), 2.97 (s, 6H), 3.74 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.20 (d, $J = 10.1$ Hz, 1H), 4.84 (s, 1H), 5.03 (s, 1H), 5.30 (d, $J = 2.8$ Hz, 1H), 6.63–6.66 (m, 2H), 6.76–6.69 (m, 2H), 7.09–7.12 (m, 2H), 7.43–7.45 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.3, 23.0, 40.7, 40.9, 71.8, 86.78, 86.82, 94.4, 99.8, 102.0, 112.09, 112.10, 126.3, 127.2, 128.4, 129.1, 149.7, 150.1. HR-MS (ESI): Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$, 410.2444. Found, 410.2434.

Di-*tert*-butyl (((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(2,1-phenylene))dicarbamate (24a)

To a solution of **16a** (4.9 mg, 0.0139 mmol) in 1,2-dichloromethane (1 mL) were added Boc₂O (20 µL, 0.0871 mmol) and triethylamine (20 µL, 0.144 mmol) at room temperature and the mixture was refluxed for 17 h under Ar atmosphere. After cooling to room temperature, the reaction mixture was poured into saturated NaHCO₃ aqueous solution (2 mL) and extracted with CHCl₃ (6 mL, 5 mL, 4 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by preparative TLC (chloroform/methanol = 40/1) to give **24a** (4.9 mg, 64%) as a white solid.

IR (KBr, cm⁻¹) 3373, 2978, 2929, 1728, 1162, 1119. ¹H NMR (400 MHz, CDCl₃) δ 1.42 (s, 9H), 1.53 (s, 9H), 1.60 (s, 3H), 1.63 (s, 3H), 3.94 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.38 (d, *J* = 10.1 Hz, 1H), 4.68 (s, 1H), 5.40 (d, *J* = 2.8 Hz, 1H), 5.47 (s, 1H), 6.98–7.04 (m, 2H), 7.14–7.16 (m, 1H), 7.18–7.20 (m, 1H), 7.23–7.32 (m, 2H), 8.11–8.18 (m, 2H), 8.24 (brs, 1H), 8.69 (brs, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 21.3, 22.8, 28.4, 28.5, 70.7, 79.6, 80.2, 87.7, 95.7, 98.9, 100.4, 121.6, 122.5, 122.7, 125.2, 126.9, 127.1, 128.5, 129.0, 137.5, 137.6, 153.1, 153.3. HR-MS (ESI): Calcd for C₃₀H₃₉N₃NaO₇ [M+Na]⁺, 576.2686. Found, 576.2663.

Di-*tert*-butyl (((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl) bis(3,1-phenylene))dicarbamate (24b)

According to the synthetic protocol of **24a**, **16b** (10.0 mg, 0.0283 mmol) was converted to **24b** (7.5 mg, 48%) as a white solid.

IR (KBr, cm^{-1}) 3330, 2978, 2933, 1705, 1159, 1111. ^1H NMR (400 MHz, CDCl_3) δ 1.50 (s, 9H), 1.53 (s, 9H), 1.66 (s, 6H), 3.78 (dd, $J = 2.8, 10.0$ Hz, 1H), 4.27 (d, $J = 10.0$ Hz, 1H), 5.03 (d, $J = 2.8$ Hz, 1H), 5.12 (s, 1H), 5.15 (s, 1H), 6.49 (brs, 1H), 6.57 (brs, 1H), 7.03–7.05 (m, 1H), 7.09–7.11 (m, 1H), 7.22–7.35 (m, 6H), 7.46–7.48 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.20, 24.24, 28.5, 71.3, 80.7, 86.8, 87.3, 95.2, 99.5, 101.5, 115.4, 117.8, 119.7, 119.9, 129.3, 129.4, 138.7, 138.8, 143.4, 143.6, 152.77, 152.82. HR-MS (ESI): Calcd for $\text{C}_{30}\text{H}_{39}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, 576.2686. Found, 576.2709.

Di-*tert*-butyl (((2*aS*/*R*,4*S*/*R*,4*aS*/*R*,6*S*/*R*,6*aS*/*R*)-4,6-dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(4,1-phenylene))dicarbamate (24c)

According to the synthetic protocol of **24a**, **16a** (5.00 mg, 0.0141 mmol) was converted to **24c** (7.7 mg, 99%) as a white solid.

IR (KBr, cm^{-1}) 3339, 2978, 2929, 1729, 1160, 1102. ^1H NMR (400 MHz, CDCl_3) δ 1.50 (s, 9H), 1.52 (s, 9H), 1.63 (s, 3H), 1.64 (s, 3H), 3.78 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.26 (d, $J = 10.1$ Hz, 1H), 4.98 (d, $J = 2.8$ Hz, 1H), 5.05 (s, 1H), 5.08 (s, 1H), 6.45 (brs, 1H), 6.49 (brs, 1H), 7.27–7.36 (m, 8H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.3 ($\times 2$), 28.5, 71.3, 80.8, 86.6, 87.0, 93.0, 95.1, 99.4, 101.4, 118.7, 118.8, 125.76, 125.82, 137.0, 137.1, 137.7, 137.8, 152.8, 152.9. HR-MS (ESI): Calcd for $\text{C}_{30}\text{H}_{39}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, 576.2686. Found, 576.2679.

Di-*tert*-butyl (((2*aS*/*R*,4*R*/*S*,4*aS*/*R*,6*S*/*R*,6*aS*/*R*)-4,6-dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(2,1-phenylene))dicarbamate (25a)

According to the synthetic protocol of **24a**, **17a** (4.9 mg, 0.0139 mmol) was converted to **25a** (7.7 mg, 100%) as a white solid.

IR (KBr, cm^{-1}) 3372, 2979, 1731, 1161, 1120. ^1H NMR (400 MHz, CDCl_3) δ 1.48 (s, 9H), 1.52 (s, 9H), 1.74 (s, 3H), 1.78 (s, 3H), 3.82 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.31 (d, $J = 10.1$ Hz, 1H), 4.82 (d, $J = 2.8$ Hz, 1H), 5.28 (s, 1H), 5.40 (s, 1H), 6.90–6.94 (m, 1H), 7.01–7.05 (m, 2H), 7.18 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.24–7.28 (m, 1H), 7.32 (ddd, $J = 1.2, 8.0, 8.0$ Hz, 1H), 8.04–8.08 (m, 1H), 8.23–8.25 (m, 1H), 8.55 (brs, 1H), 8.99 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 21.1, 23.0, 28.49 ($\times 3$), 28.54 ($\times 3$), 70.4, 80.4 ($\times 2$), 87.8, 88.0, 95.3, 96.8, 100.4, 121.2, 122.2, 122.8, 122.9, 125.5, 126.4, 126.9, 127.5, 128.9, 129.1, 137.46, 137.50, 153.2, 153.3. HR-MS (ESI): Calcd for $\text{C}_{30}\text{H}_{39}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, 576.2686. Found, 576.2711.

Di-*tert*-butyl (((2*aS/R*,4*R/S*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl) bis(3,1-phenylene))dicarbamate (25b)

According to the synthetic protocol of **24a**, **17b** (10.0 mg, 0.0283 mmol) was converted to **25b** (11.6 mg, 74%) as a white solid.

IR (KBr, cm^{-1}) 3340, 2977, 2931, 1710, 1160, 1115. ^1H NMR (400 MHz, CDCl_3) δ 1.43 (s, 3H), 1.52 (s, 9H), 1.53 (s, 9H), 1.55 (s, 3H), 3.88 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.31 (d, $J = 10.1$ Hz, 1H), 4.89 (s, 1H), 5.15 (s, 1H), 5.27 (d, $J = 2.8$ Hz, 1H), 6.56 (brs, 2H), 6.96–7.00 (m, 1H), 7.16–7.19 (m, 1H), 7.24–7.44 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.20, 24.20, 28.5, 71.3, 80.7, 86.8, 87.3, 95.2, 99.5, 101.5, 115.4, 117.8, 119.7, 119.9, 129.3, 129.4, 138.7, 138.8, 143.4, 143.6, 152.77, 152.82. HR-MS (ESI): Calcd for $\text{C}_{30}\text{H}_{39}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, 576.2686. Found, 576.2673.

Di-*tert*-butyl (((2*aS/R*,4*R/S*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(4,1-phenylene))dicarbamate (25c)

According to the synthetic protocol of **24a**, **17c** (5.0 mg, 0.0141 mmol) was converted to **25c** (8.2 mg, 100%) as a white solid.

IR (KBr, cm⁻¹) 3342, 2977, 2929, 1728, 1161, 1119. ¹H NMR (400 MHz, CDCl₃) δ 1.43 (s, 3H), 1.51 (s, 9H), 1.52 (s, 9H), 1.55 (s, 3H), 3.88 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.32 (d, *J* = 10.1 Hz, 1H), 4.77 (s, 1H), 5.11 (s, 1H), 5.26 (d, *J* = 2.8 Hz, 1H), 6.47 (brs, 1H), 6.50 (brs, 1H), 7.21–7.23 (m, 2H), 7.31–7.70 (m, 4H), 7.41–7.43 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 22.9, 24.1, 28.5, 71.4, 86.8, 94.8, 99.8, 101.3, 118.0, 118.8, 125.7, 126.9, 137.0, 137.5, 137.7, 152.9. HR-MS (ESI): Calcd for C₃₀H₃₉N₃NaO₇ [M+Na]⁺, 576.2686. Found, 576.2693.

Di-*tert*-butyl (((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(2,1-phenylene))dicarbamate (26a)

According to the synthetic protocol of **24a**, **18a** (5.3 mg, 0.0150 mmol) was converted to **26a** (4.3 mg, 52%) as a white solid.

IR (KBr, cm⁻¹) 3371, 2927, 1728, 1161, 1111. ¹H NMR (400 MHz, CDCl₃) δ 1.490 (s, 9H), 1.494 (s, 9H), 1.69 (brs, 3H), 1.80 (s, 3H), 3.77 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.19 (d, *J* = 10.1 Hz, 1H), 4.86 (d, *J* = 2.8 Hz, 1H), 5.14 (brs, 1H), 5.78 (s, 1H), 7.06 (ddd, *J* = 1.2, 7.6, 7.6 Hz, 1H), 7.25–7.34 (m, 5H), 8.11–8.13 (m, 2H), 8.58 (brs, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 21.9, 23.7, 28.5,

28.6, 70.9, 80.4, 87.8, 95.0, 97.4, 99.2, 122.3, 122.9, 125.5, 127.4, 127.8, 128.4, 129.1, 137.6, 153.3. HR-MS (ESI): Calcd for C₃₀H₃₉N₃NaO₇ [M+Na]⁺, 576.2686. Found, 576.2697.

Di-*tert*-butyl (((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dicarbamate (26b)

According to the synthetic protocol of **24a**, **18b** (5.0 mg, 0.0141 mmol) was converted to **26b** (5.6 mg, 72%) as a white solid.

IR (KBr, cm⁻¹) 3351, 2932, 1708, 1160, 1119. ¹H NMR (400 MHz, CDCl₃) δ 1.515 (s, 9H), 1.522 (s, 9H), 1.64 (s, 3H), 1.71 (s, 3H), 3.65 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.10 (d, *J* = 10.1 Hz, 1H), 4.87 (s, 1H), 5.09 (d, *J* = 2.8 Hz, 1H), 5.40 (s, 1H), 6.52–6.53 (m, 2H), 7.10–7.16 (m, 2H), 7.28–7.33 (m, 3H), 7.35–7.46 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 23.5, 24.6, 28.5, 71.6, 80.6, 80.7, 86.9, 87.5, 95.0, 99.6, 101.9, 115.3, 115.7, 117.6, 117.8, 119.8, 120.2, 128.9, 129.4, 138.2, 138.8, 142.3, 143.8, 152.8. HR-MS (ESI): Calcd for C₃₀H₃₉N₃NaO₇ [M+Na]⁺, 576.2686. Found, 576.2680.

Di-*tert*-butyl (((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(4,1-phenylene))dicarbamate (26c)

According to the synthetic protocol of **24a**, **18c** (5.0 mg, 0.0141 mmol) was converted to **26c** (5.8 mg, 74%) as a white solid.

IR (KBr, cm⁻¹) 3340, 2978, 2930, 1729, 1161, 1119. ¹H NMR (400 MHz, CDCl₃) δ 1.51 (s, 9H), 1.52 (s, 9H), 1.63 (s, 3H), 1.68 (s, 3H), 3.65 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.10 (d, *J* = 10.1 Hz, 1H),

4.81 (s, 1H), 5.04 (d, $J = 2.8$ Hz, 1H), 5.38 (s, 1H), 6.48 (brs, 1H), 6.50 (brs, 1H), 7.34–7.43 (m, 8H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.2, 24.6, 28.5, 71.6, 86.7, 87.3, 94.9, 99.5, 101.9, 118.3, 118.8, 125.8, 126.4, 135.8, 137.3, 137.6, 137.7, 152.9. HR-MS (ESI): Calcd for $\text{C}_{30}\text{H}_{40}\text{N}_3\text{O}_7$ $[\text{M}+\text{H}]^+$, 554.2866. Found, 554.2894.

Di-*tert*-butyl (((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(2,1-phenylene))dicarbamate (27a)

According to the synthetic protocol of **24a**, **19a** (5.0 mg, 0.0142 mmol) was converted to **27a** (5.6 mg, 71%) as a white solid.

IR (KBr, cm^{-1}) 3385, 2978, 2928, 1726, 1165, 1116. ^1H NMR (400 MHz, CDCl_3) δ 1.32 (brs, 9H), 1.48 (s, 9H), 1.54 (brs, 3H), 1.70 (s, 3H), 3.92 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.26 (d, $J = 10.1$ Hz, 1H), 5.21 (s, 1H), 5.30 (brs, 1H), 5.04 (d, $J = 2.8$ Hz, 1H), 6.99–7.07 (m, 2H), 7.14–7.20 (m, 2H), 7.25–7.29 (m, 3H), 7.41–8.59 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.0, 23.2, 28.3, 28.6, 71.3, 79.4, 80.1, 89.5, 100.7, 113.6, 123.0, 123.2, 126.0, 126.1, 127.2, 128.1, 128.6, 138.0, 138.2, 151.0, 151.3. HR-MS (ESI): Calcd for $\text{C}_{30}\text{H}_{39}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, 576.2686. Found, 576.2670.

Di-*tert*-butyl (((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dicarbamate (27b)

According to the synthetic protocol of **24a**, **19b** (10.0 mg, 0.0283 mmol) was converted to **27b** (12.7 mg, 81%) as a white solid.

IR (KBr, cm^{-1}) 3336, 2977, 1728, 1161, 1121. ^1H NMR (400 MHz, CDCl_3) δ 1.50 (s, 9H), 1.518 (s, 9H), 1.524 (s, 3H), 1.68 (s, 3H), 3.75 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.18 (d, $J = 10.1$ Hz, 1H), 4.92 (s, 1H), 5.13 (s, 1H), 5.31 (d, $J = 2.8$ Hz, 1H), 6.37 (brs, 1H), 6.55 (brs, 1H), 6.77–6.80 (m, 1H), 6.99 (brs, 1H), 7.16 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.19–7.21 (m, 1H), 7.26–7.30 (m, 1H), 7.33 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.40–7.41 (m, 1H), 7.45–7.48 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.8, 23.6, 28.50, 28.52, 71.8, 80.4, 80.5, 87.1, 87.2, 94.7, 100.2, 101.9, 115.8, 116.8, 117.5, 117.9, 120.2, 121.0, 128.5, 128.7, 138.0, 141.9, 142.1, 152.8, 153.0. HR-MS (ESI): Calcd for $\text{C}_{30}\text{H}_{39}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, 576.2686. Found, 576.2664.

Di-*tert*-butyl (((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(4,1-phenylene))dicarbamate (27c)

According to the synthetic protocol of **24a**, **19c** (5.0 mg, 0.0141 mmol) was converted to **27c** (6.1 mg, 78%) as a white solid.

IR (KBr, cm^{-1}) 3339, 2977, 2930, 1728, 1161, 1120. ^1H NMR (400 MHz, CDCl_3) δ 1.50 (s, 9H), 1.51 (s, 3H), 1.54 (s, 9H), 1.67 (s, 3H), 3.74 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.17 (d, $J = 10.1$ Hz, 1H), 4.86 (s, 1H), 5.07 (s, 1H), 5.31 (d, $J = 2.8$ Hz, 1H), 6.41 (brs, 1H), 6.52 (brs, 1H), 7.06–7.08 (m, 2H), 7.22–7.27 (m, 2H), 7.35–7.38 (m, 2H), 7.43–7.46 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.5, 23.1, 28.4, 28.5, 71.7, 86.86, 86.92, 94.6, 100.0, 102.0, 117.8, 118.0, 126.2, 126.9, 135.2, 135.8, 137.3, 137.7, 152.8. HR-MS (ESI): Calcd for $\text{C}_{30}\text{H}_{39}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, 576.2686. Found, 576.2671.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(2,1-phenylene))dibenzamide (28a)**

To a solution of **16a** (10.0 mg, 0.0283 mmol) in 1,2-dichloromethane (1 mL) was added triethylamine (40 μ L, 0.287 mmol) and benzoyl chloride (20 μ L, 0.0283 mmol) and the mixture was stirred at room temperature for 1 h. After that, the reaction mixture was poured into saturated NaHCO₃ aqueous solution (1 mL) and extracted with CHCl₃ (7 mL, 5 mL, 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by preparative TLC (ethyl acetate/hexane = 2/1) to give the mixture of **28a** (10.8 mg, 68%) as a white solid.

IR (KBr, cm⁻¹) 3357, 2932, 1677, 1534, 1102. ¹H NMR (400 MHz, CDCl₃) δ 1.71 (s, 3H), 1.87 (s, 3H), 3.86 (dd, *J* = 2.8, 10.8 Hz, 1H), 4.30 (d, *J* = 10.8 Hz, 1H), 4.97 (d, *J* = 2.8 Hz, 1H), 5.33 (s, 1H), 5.56 (s, 1H), 6.98–7.03 (m, 2H), 7.17 (ddd, *J* = 1.2, 8.0, 8.0 Hz, 1H), 7.31–7.35 (m, 2H), 7.42–7.60 (m, 7H), 7.92–7.97 (m, 4H), 8.51–8.53 (m, 1H), 8.66 (dd, *J* = 1.2, 8.0 Hz, 1H), 10.29 (brs, 1H), 10.45 (brs, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 21.9, 22.2, 70.4, 87.9, 88.2, 95.5, 97.1, 99.2, 123.2, 123.3, 124.2, 124.3, 125.7, 125.8, 127.1, 127.7, 128.0, 128.9, 129.0, 129.3, 129.4, 132.07, 132.14, 134.9, 135.0, 137.1, 137.3, 165.0, 165.2. HR-MS (ESI): Calcd for C₃₄H₃₁N₃NaO₅ [M+Na]⁺, 584.2161. Found, 584.2144.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dibenzamide (28b)**

According to the synthetic protocol of **28a**, **16b** (10.0 mg, 0.0283 mmol) was converted to **28b** (14.5 mg, 91%) as a white solid.

IR (KBr, cm^{-1}) 3301, 2931, 1651, 1543, 1108. ^1H NMR (400 MHz, CDCl_3) δ 1.696 (s, 3H), 1.701 (s, 3H), 3.76 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.26 (d, $J = 10.1$ Hz, 1H), 5.05 (d, $J = 2.8$ Hz, 1H), 5.10 (s, 1H), 5.28 (s, 1H), 7.19–7.21 (m, 2H), 7.33 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.35–7.43 (m, 5H), 7.47–7.52 (m, 2H), 7.54–7.57 (m, 1H), 7.65–7.67 (m, 2H), 7.79–7.87 (m, 5H), 8.05 (brs, 1H), 8.07 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.0, 24.2, 71.3, 86.8, 87.2, 95.3, 99.6, 101.5, 117.2, 117.6, 119.4, 119.8, 121.2, 121.5, 127.15, 127.18, 128.8, 128.9, 129.4, 129.6, 131.9, 132.0, 134.97, 134.99, 138.2, 138.4, 143.4, 143.7, 166.0, 166.2. HR-MS (ESI): Calcd for $\text{C}_{34}\text{H}_{31}\text{N}_3\text{NaO}_5$ $[\text{M}+\text{Na}]^+$, 584.2161. Found, 584.2161.

N,N'-(((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(4,1-phenylene))dibenzamide (28c)

According to the synthetic protocol of **28a**, **16c** (10.0 mg, 0.0283 mmol) was converted to **28c** (12.8 mg, 81%) as a colorless amorphous.

IR (KBr, cm^{-1}) 3423, 2930, 1654, 1524, 1100. ^1H NMR (400 MHz, CDCl_3) δ 1.67 (s, 6H), 3.80 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.28 (d, $J = 10.1$ Hz, 1H), 5.02 (d, $J = 2.8$ Hz, 1H), 5.12 (s, 1H), 5.13 (s, 1H), 7.37 (d, $J = 8.8$ Hz, 2H), 7.43–7.56 (m, 8H), 7.61 (d, $J = 8.8$ Hz, 2H), 7.67 (d, $J = 8.8$ Hz, 2H), 7.83–7.87 (m, 4H), 7.95 (brs, 1H), 8.00 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.3, 71.3, 86.7, 87.2, 95.2, 99.4, 101.3, 120.4, 120.6, 125.88, 125.95, 127.2, 128.9, 129.0, 132.0, 132.1, 134.9,

137.3, 137.4, 138.60, 138.69, 165.9, 166.0. HR-MS (ESI): Calcd for C₃₄H₃₁N₃NaO₅ [M+Na]⁺, 584.2161. Found, 584.2190.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(2,1-phenylene))dibenzamide (29a)**

According to the synthetic protocol of **28a**, **17a** (10.0 mg, 0.0283 mmol) was converted to **29a** (15.2 mg, 96%) as a white solid.

IR (KBr, cm⁻¹) 3355, 2939, 1673, 1531, 1114. ¹H NMR (400 MHz, CDCl₃) δ 1.59 (s, 3H), 1.71 (s, 3H), 3.86 (dd, *J* = 2.8, 10.8 Hz, 1H), 4.12 (d, *J* = 10.8 Hz, 1H), 4.76 (s, 1H), 5.41 (d, *J* = 2.8 Hz, 1H), 5.54 (s, 1H), 6.54–6.58 (m, 1H), 6.99–7.00 (m, 1H), 7.13–7.20 (m, 2H), 7.29–7.38 (m, 3H), 7.43 (ddd, *J* = 1.2, 8.0, 8.0 Hz, 1H), 7.47–7.58 (m, 6H), 7.91–7.92 (m, 2H), 8.53 (dd, *J* = 1.2, 8.0 Hz, 2H), 9.68 (brs, 1H), 10.25 (brs, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 20.6, 23.7, 70.2, 87.2, 90.2, 95.8, 98.3, 100.5, 124.3, 124.4, 125.1, 126.7, 127.1, 127.3, 128.6, 128.8, 129.2, 129.3, 131.8, 134.0, 137.2, 165.0, 166.0. HR-MS (ESI): Calcd for C₃₄H₃₁N₃NaO₅ [M+Na]⁺, 584.2161. Found, 584.2162.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dibenzamide (29b)**

According to the synthetic protocol of **28a**, **17b** (10.0 mg, 0.0283 mmol) was converted to **29b** (11.9 mg, 75%) as a white solid.

IR (KBr, cm^{-1}) 3298, 2925, 1652, 1544, 1121. ^1H NMR (400 MHz, CDCl_3) δ 1.67 (s, 3H), 1.76 (s, 3H), 3.66 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.11 (d, $J = 10.1$ Hz, 1H), 4.90 (s, 1H), 5.13 (d, $J = 2.8$ Hz, 1H), 5.47 (s, 1H), 7.24–7.29 (m, 2H), 7.40 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.41 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.47–7.51 (m, 4H), 7.53–7.59 (m, 2H), 7.60–7.62 (m, 1H), 7.66–7.68 (m, 1H), 7.74–7.90 (m, 4H), 7.90 (brs, 1H), 7.97 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.5, 24.6, 71.7, 86.9, 87.5, 95.0, 99.6, 101.9, 117.0, 117.3, 119.3, 119.4, 121.4, 121.8, 127.2, 128.94, 128.98, 129.04, 129.6, 132.0, 132.1, 135.0, 135.2, 137.8, 138.4, 142.5, 143.9, 165.9. HR-MS (ESI): Calcd for $\text{C}_{34}\text{H}_{31}\text{N}_3\text{NaO}_5$ $[\text{M}+\text{Na}]^+$, 584.2161. Found, 584.2188.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(4,1-phenylene))dibenzamide (29c)**

According to the synthetic protocol of **28a**, **17c** (20.0 mg, 0.0566 mmol) was converted to **29c** (26.5 mg, 90%) as a colorless amorphous.

IR (KBr, cm^{-1}) 3423, 2928, 1649, 1528, 1117. ^1H NMR (400 MHz, CDCl_3) δ 1.47 (s, 3H), 1.60 (s, 3H), 3.91 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.36 (d, $J = 10.1$ Hz, 1H), 4.85 (s, 1H), 5.16 (s, 1H), 5.30 (d, $J = 2.8$ Hz, 1H), 7.33–7.35 (m, 2H), 7.49–7.59 (m, 8H), 7.62–7.64 (m, 2H), 7.67–7.69 (m, 2H), 7.80 (brs, 1H), 7.83 (brs, 1H), 7.86–7.89 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.9, 24.1, 71.4, 86.9, 95.0, 99.9, 101.4, 119.6, 120.4, 125.9, 127.0, 127.2, 129.0, 132.0, 132.1, 134.9, 137.1, 137.2, 137.3, 138.6, 165.8, 166.0. HR-MS (ESI): Calcd for $\text{C}_{34}\text{H}_{31}\text{N}_3\text{NaO}_5$ $[\text{M}+\text{Na}]^+$, 584.2161. Found, 584.2136.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(2,1-phenylene))dibenzamide (30a)**

According to the synthetic protocol of **28a**, **18a** (10.0 mg, 0.0283 mmol) was converted to **30a** (16.6 mg, 100%) as a white solid.

IR (KBr, cm⁻¹) 3362, 2928, 1672, 1535, 1114. ¹H NMR (400 MHz, CDCl₃) δ 1.69 (s, 3H), 1.78 (s, 3H), 3.85 (dd, *J* = 2.0, 10.8 Hz, 1H), 4.27 (d, *J* = 10.8 Hz, 1H), 4.97 (d, *J* = 2.0 Hz, 1H), 5.27 (s, 1H), 5.85 (s, 1H), 7.12–7.24 (m, 2H), 7.30–7.62 (m, 11H), 7.87–7.91 (m, 4H), 8.64 (dd, *J* = 1.2, 8.0 Hz, 1H), 10.01 (brs, 1H), 10.37 (brs, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 22.4, 24.0, 71.1, 88.0, 89.5, 94.9, 97.9, 101.9, 123.4, 124.2, 125.6, 127.1, 127.2, 127.6, 128.0, 128.6, 128.7, 128.9, 129.0, 129.4, 130.3, 132.0, 132.1, 133.7, 134.8, 137.4, 164.9, 165.8. HR-MS (ESI): Calcd for C₃₄H₃₁N₃NaO₅ [M+Na]⁺, 584.2161. Found, 584.2170.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dibenzamide (30b)**

According to the synthetic protocol of **28a**, **18b** (10.0 mg, 0.0283 mmol) was converted to **30b** (15.9 mg, 100%) as a white solid.

IR (KBr, cm⁻¹) 3304, 2929, 1652, 1542, 1112. ¹H NMR (400 MHz, CDCl₃) δ 1.47 (s, 3H), 1.57 (s, 3H), 3.93 (dd, *J* = 3.2, 10.1 Hz, 1H), 4.29 (d, *J* = 10.1 Hz, 1H), 5.05 (s, 1H), 5.24 (s, 1H), 5.35 (d, *J* = 2.8 Hz, 1H), 7.04–7.06 (m, 1H), 7.20–7.28 (m, 4H), 7.32–7.42 (m, 5H), 7.52–7.55 (m, 1H), 7.71–7.73 (m, 2H), 7.80–7.83 (m, 3H), 7.97–7.98 (m, 1H), 8.00–8.01 (m, 1H), 8.18 (brs, 1H), 8.55 (brs, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 24.2, 24.5, 71.2, 86.8, 87.8, 95.6, 98.9, 101.1, 116.6,

117.7, 118.6, 118.8, 120.8, 121.6, 127.1, 127.3, 128.6, 128.7, 128.9, 129.6, 131.7, 131.8, 135.1, 135.4, 137.8, 139.2, 142.9, 143.3, 166.5, 166.7. HR-MS (ESI): Calcd for C₃₄H₃₁N₃NaO₅ [M+Na]⁺, 584.2161. Found: 584.2180.

***N,N'*-(((2*aS*/*R*,4*S*/*R*,4*aS*/*R*,6*R*/*S*,6*aS*/*R*)-4,6-dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(4,1-phenylene))dibenzamide (30c)**

According to the synthetic protocol of **28a**, **18c** (20.0 mg, 0.0566 mmol) was converted to **30c** (1.5 mg, 68%) as a colorless amorphous.

IR (KBr, cm⁻¹) 3306, 2929, 1655, 1518, 1119. ¹H NMR (400 MHz, CDCl₃) δ 1.68 (s, 3H), 1.74 (s, 3H), 3.68 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.13 (d, *J* = 10.1 Hz, 1H), 4.87 (s, 1H), 5.10 (d, *J* = 2.8 Hz, 1H), 5.44 (s, 1H), 7.46–7.52 (m, 10H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.85–7.92 (m, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 23.2, 24.6, 71.6, 86.8, 87.4, 95.0, 99.5, 102.0, 119.9, 120.5, 126.0, 126.5, 127.2, 128.95, 128.97, 132.0, 132.1, 134.9, 135.1, 137.2, 137.35, 137.41, 138.8, 165.8, 165.9. HR-MS (ESI): Calcd for C₃₄H₃₁N₃NaO₅ [M+Na]⁺, 584.2161. Found, 584.2175.

***N,N'*-(((2*aS*/*R*,4*R*/*S*,4*aS*/*R*,6*R*/*S*,6*aS*/*R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(2,1-phenylene))dibenzamide (31a)**

According to the synthetic protocol of **28a**, **19a** (10.0 mg, 0.0283 mmol) was converted to **31a** (16.1 mg, 99%) as a white solid.

IR (KBr, cm^{-1}) 3355, 2925, 1665, 1526, 1116. ^1H NMR (400 MHz, CDCl_3) δ 1.54 (brs, 3H), 1.78 (brs, 3H), 3.47–3.65 (m, 2H), 5.12 (s, 1H), 5.14 (s, 1H), 5.30 (d, $J = 2.4$ Hz, 1H), 7.00–7.53 (m, 16H), 7.96–8.25 (m, 2H), 9.17 (brs, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 21.9, 22.8, 70.4, 88.8, 89.8, 94.9, 101.4, 101.6, 123.9, 124.6, 125.0, 126.4, 127.0, 127.1, 127.6, 127.9, 128.1, 128.6, 128.8, 131.1, 131.4, 134.8, 135.7, 135.9, 136.3, 138.1, 165.4, 167.0. HR-MS (ESI): Calcd for $\text{C}_{34}\text{H}_{31}\text{N}_3\text{NaO}_5$ $[\text{M}+\text{Na}]^+$, 584.2161. Found, 584.2138.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dibenzamide (31b)**

According to the synthetic protocol of **28a**, **19b** (10.0 mg, 0.0283 mmol) was converted to **31b** (15.8 mg, 100%) as a white solid.

IR (KBr, cm^{-1}) 3298, 2925, 1652, 1544, 1121. ^1H NMR (400 MHz, CDCl_3) δ 1.56 (s, 3H), 1.72 (s, 3H), 3.78 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.21 (d, $J = 10.1$ Hz, 1H), 4.96 (s, 1H), 5.18 (s, 1H), 5.35 (d, $J = 2.8$ Hz, 1H), 6.90–6.92 (m, 1H), 7.25 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.29–7.49 (m, 9H), 7.71–7.76 (m, 7H), 8.12 (brs, 1H), 8.15 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.9, 23.6, 71.7, 87.1, 87.2, 94.8, 100.1, 101.9, 117.6, 119.2, 119.8, 120.8, 121.4, 122.7, 127.1, 127.2, 128.67, 128.73, 131.7, 131.8, 134.8, 135.2, 137.5, 137.9, 142.1, 142.2, 166.1, 166.3. HR-MS (ESI): Calcd for $\text{C}_{34}\text{H}_{31}\text{N}_3\text{NaO}_5$ $[\text{M}+\text{Na}]^+$, 584.2161. Found, 584.2162.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(4,1-phenylene))dibenzamide (31c)**

According to the synthetic protocol of **28a**, **19c** (10.0 mg, 0.0283 mmol) was converted to **31c** (14.6 mg, 92%) as a colorless amorphous.

IR (KBr, cm^{-1}) 3423, 2927, 1655, 1522, 1120. ^1H NMR (400 MHz, CDCl_3) δ 1.53 (s, 3H), 1.70 (s, 3H), 3.75 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.18 (d, $J = 10.1$ Hz, 1H), 4.89 (s, 1H), 5.11 (s, 1H), 5.32 (d, $J = 2.8$ Hz, 1H), 7.12–7.14 (m, 2H), 7.43–7.54 (m, 10H), 7.69 (d, $J = 8.4$ Hz, 2H), 7.82–7.84 (m, 2H), 7.89–7.91 (m, 2H), 7.98 (brs, 1H), 8.18 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.4, 23.2, 71.7, 86.9, 87.0, 94.6, 100.1, 102.0, 119.6 ($\times 4$), 126.3 ($\times 2$), 127.0 ($\times 2$), 127.2 ($\times 2$), 127.3 ($\times 2$), 128.9 ($\times 4$), 131.9 ($\times 2$), 135.1 ($\times 2$), 136.8, 137.0, 137.3, 137.4, 165.8, 166.0. HR-MS (ESI): Calcd for $\text{C}_{34}\text{H}_{31}\text{N}_3\text{NaO}_5$ $[\text{M}+\text{Na}]^+$, 584.2161. Found, 584.2156.

***N,N'*-(((2*aS/R*,4*aS/R*,4*aS/R*,6*aS/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(2,1-phenylene))dibenzenesulfonamide (32a)**

To a solution of **16a** (10.0 mg, 0.0283 mmol) in 1,2-dichloromethane (1 mL) were added anhydrous pyridine (0.25 mL) and benzenesulfonyl chloride (3.6 μL , 0.0283 mmol) and the mixture was stirred at room temperature for 10 h. After that, the reaction mixture was poured into saturated NaHCO_3 aqueous solution (3 mL) and extracted with CHCl_3 (9 mL, 5 mL, 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC (hexane/ethyl acetate = 1/1) to give the mixture of **32a** (17.8 mg, 100%) as a white solid.

IR (KBr, cm^{-1}) 3247, 1335, 1163, 1092. ^1H NMR (400 MHz, CDCl_3) δ 1.32 (s, 3H), 1.40 (s, 3H), 3.75 (dd, $J = 2.8, 10.4$ Hz, 1H), 4.28 (d, $J = 10.4$ Hz, 1H), 4.30 (d, $J = 2.8$ Hz, 1H), 5.16 (s, 1H),

5.27 (s, 1H), 6.98–7.10 (m, 4H), 7.23–7.26 (m, 2H), 7.45–7.61 (m, 7H), 7.78–7.83 (m, 3H), 7.88–7.92 (m, 2H), 9.16 (brs, 1H), 9.40 (brs, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 22.4, 23.1, 70.6, 88.2, 88.6, 95.4, 97.5, 100.1, 120.0, 121.1, 124.0, 124.4, 126.6, 126.8, 127.1, 127.2, 127.5, 128.0, 129.2, 129.3, 129.4, 133.3, 136.0, 136.3, 139.9, 140.2. HR-MS (ESI): Calcd for C₃₂H₃₁N₃NaO₇S₂ [M+Na]⁺, 656.1501. Found, 656.1510.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dibenzenesulfonamide (32b)**

According to the synthetic protocol of **32a**, **16b** (10.0 mg, 0.0283 mmol) was converted to **32b** (6.4 mg, 36%) as a white solid.

IR (KBr, cm⁻¹) 3256, 2931, 1327, 1160, 1108, 1092. ¹H NMR (400 MHz, CDCl₃) δ 1.53 (s, 3H), 1.56 (s, 3H), 3.73 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.22 (d, *J* = 10.1 Hz, 1H), 4.83 (d, *J* = 2.8 Hz, 1H), 4.94 (s, 1H), 4.95 (s, 1H), 6.75 (brs, 1H), 6.85 (brs, 1H), 6.93–6.97 (m, 1H), 7.01–7.04 (m, 1H), 7.11–7.15 (m, 2H), 7.20–7.26 (m, 3H), 7.33–7.46 (m, 5H), 7.49–7.53 (m, 1H), 7.68–7.70 (m, 2H), 7.73–7.75 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 24.0, 24.1, 71.3, 86.7 87.1, 95.2, 99.6, 101.5, 118.9, 119.0, 120.9, 121.2, 122.2, 122.4, 127.3, 127.4, 129.1, 129.3, 129.7, 129.8, 133.1, 133.3, 136.81, 136.84, 138.9, 139.1, 144.0, 144.1. HR-MS (ESI): Calcd for C₃₂H₃₁N₃NaO₇S₂ [M+Na]⁺, 656.1501. Found, 656.1525.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(4,1-phenylene))dibenzenesulfonamide (32c)**

According to the synthetic protocol of **32a**, **19c** (7.0 mg, 0.0198 mmol) was converted to **32c** (12.4 mg, 99%) as a white solid.

IR (KBr, cm^{-1}) 3258, 2932, 1331, 1162, 1094. ^1H NMR (400 MHz, CDCl_3) δ 1.56 (s, 3H), 1.57 (s, 3H), 3.79 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.24 (d, $J = 10.1$ Hz, 1H), 4.94 (s, 1H), 4.96 (d, $J = 2.8$ Hz, 1H), 5.03 (s, 1H), 6.99 (d, $J = 8.8$ Hz, 2H), 7.00 (d, $J = 8.8$ Hz, 2H), 7.16–7.21 (m, 3H), 7.25–7.28 (m, 3H), 7.38–7.42 (m, 4H), 7.49–7.54 (m, 2H), 7.73–7.75 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.2, 71.3, 86.7, 87.1, 95.2, 99.4, 101.2, 121.5, 121.7, 126.0, 126.1, 127.2, 129.2, 133.2, 135.8, 135.9, 139.2, 139.3. HR-MS (ESI): Calcd for $\text{C}_{32}\text{H}_{31}\text{N}_3\text{NaO}_7\text{S}_2$ $[\text{M}+\text{Na}]^+$, 656.1501. Found, 656.1492.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(2,1-phenylene))dibenzenesulfonamide (33a)**

According to the synthetic protocol of **32a**, **17a** (10.2 mg, 0.0289 mmol) was converted to **33a** (17.9 mg, 98%) as a white solid.

IR (KBr, cm^{-1}) 3261, 2933, 1335, 1164, 1092. ^1H NMR (400 MHz, CDCl_3) δ 0.99 (s, 3H), 1.24 (s, 3H), 3.90 (dd, $J = 2.8, 10.4$ Hz, 1H), 4.38 (d, $J = 10.4$ Hz, 1H), 4.80 (s, 1H), 5.28 (d, $J = 2.8$ Hz, 1H), 5.28 (s, 1H), 7.02–7.05 (m, 2H), 7.11–7.17 (m, 1H), 7.23–7.54 (m, 9H), 7.57–7.61 (m, 2H), 7.62–7.70 (m, 1H), 7.75–7.83 (m, 3H), 8.92 (brs, 1H), 9.03 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.8, 23.5, 70.8, 88.4, 90.4, 95.9, 100.1, 100.3, 121.2, 124.2, 126.3, 127.0, 127.5, 127.6, 128.0, 128.6, 129.0, 129.2, 132.9, 133.1, 135.8, 136.0, 139.86, 139.90. HR-MS (ESI): Calcd for $\text{C}_{32}\text{H}_{31}\text{N}_3\text{NaO}_7\text{S}_2$ $[\text{M}+\text{Na}]^+$, 656.1501. Found, 656.1502.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dibenzenesulfonamide (33b)**

According to the synthetic protocol of **32a**, **17b** (10.0 mg, 0.0283 mmol) was converted to **33b** (5.8 mg, 32%) as a white solid.

IR (KBr, cm⁻¹) 3258, 2927, 1327, 1161, 1114, 1092. ¹H NMR (400 MHz, CDCl₃) δ 1.31 (s, 3H), 1.46 (s, 3H), 3.89 (dd, *J* = 3.2, 10.1 Hz, 1H), 4.25 (d, *J* = 10.0 Hz, 1H), 4.63 (s, 1H), 5.11 (s, 1H), 5.28 (d, *J* = 3.2 Hz, 1H), 6.54 (brs, 1H), 6.63–6.66 (m, 1H), 6.98–7.01 (m, 2H), 7.17 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.20–7.21 (m, 1H), 7.24–7.34 (m, 8H), 7.36–7.40 (m, 1H), 7.44–7.49 (m, 1H), 7.65–7.68 (m, 2H), 7.71–7.74 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 24.3, 24.4, 71.2, 86.4, 87.4, 95.5, 99.0, 100.7, 118.5, 120.3, 121.06, 121.10, 121.7, 123.0, 127.3, 127.5, 128.9, 129.0, 129.3, 129.9, 132.9, 133.1, 135.8, 137.7, 138.6, 139.0, 143.4, 143.5. HR-MS (ESI): Calcd for C₃₂H₃₁N₃NaO₇S₂ [M+Na]⁺, 656.1501. Found, 656.1497.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(4,1-phenylene))dibenzenesulfonamide (33c)**

According to the synthetic protocol of **32a**, **17c** (7.0 mg, 0.0198 mmol) was converted to **33c** (11.0 mg, 88%) as a white solid.

IR (KBr, cm⁻¹) 3260, 2929, 1330, 1115, 1092. ¹H NMR (400 MHz, CDCl₃) δ 1.34 (s, 3H), 1.51 (s, 3H), 3.85 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.28 (d, *J* = 10.1 Hz, 1H), 4.71 (s, 1H), 5.03 (s, 1H), 5.23 (d,

$J = 2.8$ Hz, 1H), 6.85 (brs, 1H), 7.01–7.06 (m, 5H), 7.13–7.15 (m, 2H), 7.34–7.36 (m, 2H), 7.38–7.47 (m, 4H), 7.50–7.57 (m, 2H), 7.76–7.80 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.7, 24.0, 71.4, 86.7, 86.8, 94.9, 99.8, 101.3, 121.2, 121.6, 126.0, 127.3, 127.3, 127.4, 129.1, 129.3, 133.1, 133.2, 135.4, 135.8, 138.0, 139.2, 139.3. HR-MS (ESI): Calcd for $\text{C}_{32}\text{H}_{31}\text{N}_3\text{NaO}_7\text{S}_2$ $[\text{M}+\text{Na}]^+$, 656.1501. Found, 656.1532.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(2,1-phenylene))dibenzenesulfonamide (34a)**

According to the synthetic protocol of **32a**, **18a** (10.0 mg, 0.0283 mmol) was converted to **34a** (9.4 mg, 52%) as a white solid.

IR (KBr, cm^{-1}) 3264, 2925, 1333, 1163, 1109, 1092. ^1H NMR (400 MHz, CDCl_3) δ 1.35 (s, 3H), 1.37 (brs, 3H), 3.68–3.70 (m, 1H), 4.09 (d, $J = 10.8$ Hz, 1H), 4.79 (d, $J = 2.8$ Hz, 1H), 5.03 (brs, 1H), 5.57 (s, 1H), 7.04–7.33 (m, 6H), 7.43–7.59 (m, 7H), 7.78–7.88 (m, 5H), 8.63 (brs, 1H), 9.17 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.1, 23.8, 71.0, 88.5, 95.1, 100.0, 101.7, 102.1, 121.3, 124.3, 126.5, 127.1 ($\times 2$), 127.4 ($\times 2$), 128.0, 128.3, 128.6, 129.2 ($\times 3$), 129.3 ($\times 5$), 133.1, 133.4, 135.7, 136.2, 139.1, 139.9. HR-MS (ESI): Calcd for $\text{C}_{32}\text{H}_{31}\text{N}_3\text{NaO}_7\text{S}_2$ $[\text{M}+\text{Na}]^+$, 656.1501. Found, 656.1499.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dibenzenesulfonamide (34b)**

According to the synthetic protocol of **32a**, **18b** (10.0 mg, 0.0283 mmol) was converted to **34b** (6.1 mg, 34%) as a white solid.

IR (KBr, cm^{-1}) 3257, 2929, 1328, 1161, 1118, 1092. ^1H NMR (400 MHz, CDCl_3) δ 1.55 (s, 3H), 1.57 (s, 3H), 3.59 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.00 (d, $J = 10.1$ Hz, 1H), 4.78 (s, 1H), 4.85 (d, $J = 2.8$ Hz, 1H), 5.24 (s, 1H), 6.51 (brs, 1H), 6.52 (brs, 1H), 6.94–6.97 (m, 1H), 7.01–7.03 (m, 1H), 7.09–7.10 (m, 1H), 7.18–7.31 (m, 5H), 7.42–7.47 (m, 4H), 7.52–7.57 (m, 2H), 7.74–7.80 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.3, 24.5, 71.5, 86.7, 87.3, 94.9, 99.5, 101.8, 118.9, 119.4, 120.8, 121.4, 122.5, 122.7, 127.5, 129.1, 129.17, 129.22, 129.9, 133.1, 133.2, 136.2, 136.8, 139.0, 139.2, 142.7, 144.3. HR-MS (ESI): Calcd for $\text{C}_{32}\text{H}_{31}\text{N}_3\text{NaO}_7\text{S}_2$ $[\text{M}+\text{Na}]^+$, 656.1501. Found, 656.1513.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(4,1-phenylene))dibenzenesulfonamide (34c)**

According to the synthetic protocol of **32a**, **18c** (7.0 mg, 0.0198 mmol) was converted to **34c** (12.3 mg, 98%) as a white solid.

IR (KBr, cm^{-1}) 3259, 2930, 1330, 1162, 1119, 1092. ^1H NMR (400 MHz, CDCl_3) δ 1.58 (s, 3H), 1.61 (s, 3H), 3.62 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.04 (d, $J = 10.1$ Hz, 1H), 4.78 (s, 1H), 4.97 (d, $J = 2.8$ Hz, 1H), 5.30 (s, 1H), 6.95 (brs, 1H), 7.03–7.10 (m, 5H), 7.29–7.36 (m, 4H), 7.43–7.49 (m, 4H), 7.52–7.57 (m, 2H), 7.79–7.83 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.0, 24.5, 71.5, 86.6, 87.2, 94.9, 99.4, 101.8, 121.1, 121.6, 126.2, 126.8, 127.3, 129.2, 129.3, 133.2, 133.3, 135.6, 135.9, 138.1, 139.3, 139.4, 139.5. HR-MS (ESI): Calcd for $\text{C}_{32}\text{H}_{31}\text{N}_3\text{NaO}_7\text{S}_2$ $[\text{M}+\text{Na}]^+$, 656.1501. Found, 656.1526.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(2,1-phenylene))dibenzenesulfonamide (35a)**

According to the synthetic protocol of **32a**, **19a** (10.0 mg, 0.0283 mmol) was converted to **35a** (12.4 mg, 69%) as a white solid.

IR (KBr, cm⁻¹) 3281, 2929, 1339, 1162, 1113, 1092. ¹H NMR (400 MHz, CDCl₃) δ 1.44 (s, 3H), 1.47 (s, 3H), 3.86–3.92 (m, 1H), 4.30 (d, *J* = 11.2 Hz, 1H), 5.16 (s, 1H), 5.36–5.40 (m, 2H), 6.91–7.36 (m, 14H), 7.39–7.48 (m, 1H), 7.52–7.60 (m, 1H), 7.67–7.73 (m, 2H), 8.18 (brs, 1H), 8.97 (brs, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 23.1, 24.5, 71.2, 89.5, 90.1, 100.5, 101.7, 120.0, 121.1, 125.3, 125.4, 126.9, 127.2, 127.4, 127.9, 128.4, 128.6, 128.9, 129.0, 132.6, 132.7, 135.4, 135.7, 139.7, 140.6. HR-MS (ESI): Calcd for C₃₂H₃₁N₃NaO₇S₂ [M+Na]⁺, 656.1501. Found, 656.1499.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dibenzenesulfonamide (35b)**

According to the synthetic protocol of **32a**, **19b** (10.0 mg, 0.0283 mmol) was converted to **35b** (8.0 mg, 45%) as a white solid.

IR (KBr, cm⁻¹) 3257, 2925, 1328, 1162, 1120, 1091. ¹H NMR (400 MHz, CDCl₃) δ 1.47 (s, 3H), 1.61 (s, 3H), 3.72 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.07 (d, *J* = 10.1 Hz, 1H), 4.80 (s, 1H), 5.08 (s, 1H), 5.29 (d, *J* = 2.8 Hz, 1H), 6.81–6.85 (m, 2H), 6.94–6.97 (m, 2H), 7.11 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.17–7.20 (m, 1H), 7.23–7.25 (m, 1H), 7.32–7.40 (m, 5H), 7.45–7.49 (m, 2H), 7.73–7.75 (m, 2H),

7.79–7.81 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 22.6, 22.8, 71.5, 86.7, 87.0, 94.8, 99.9, 101.8, 119.7, 120.3, 120.5, 121.2, 122.1, 123.0, 127.38, 127.43, 128.8, 128.86, 128.93, 129.1, 132.8, 133.0, 136.1, 136.2, 139.3, 139.5, 142.2, 142.5. HR-MS (ESI): Calcd for C₃₂H₃₁N₃NaO₇S₂ [M+Na]⁺, 656.1501. Found, 656.1493.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(4,1-phenylene))dibenzenesulfonamide (35c)**

According to the synthetic protocol of **32a**, **19c** (7.0 mg, 0.0198 mmol) was converted to **35c** (11.3 mg, 90%) as a white solid.

IR (KBr, cm⁻¹) 3258, 2927, 1331, 1162, 1119, 1092. ¹H NMR (400 MHz, CDCl₃) δ 1.47 (s, 3H), 1.62 (s, 3H), 3.70 (dd, *J* = 2.8, 10.4 Hz, 1H), 4.10 (d, *J* = 10.4 Hz, 1H), 4.81 (s, 1H), 5.04 (s, 1H), 5.28 (d, *J* = 2.8 Hz, 1H), 6.92–6.96 (m, 6H), 7.07–7.09 (m, 2H), 7.35–7.42 (m, 6H), 7.47–7.52 (m, 2H), 7.75–7.78 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 22.6, 23.0, 71.6, 86.7, 86.8, 94.7, 100.0, 101.8, 121.1, 121.4, 126.5, 127.1, 127.26, 127.30, 129.2, 133.1, 133.3, 135.4, 135.6, 138.1, 139.1, 139.4. HR-MS (ESI): Calcd for C₃₂H₃₁N₃NaO₇S₂ [M+Na]⁺, 656.1501. Found, 656.1509.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2a¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))bis(2-methoxybenzamide) (36b)**

To a solution of **16b** (10.0 mg, 0.0283 mmol) in 1,2-dichloromethane (1 mL) was added triethylamine (40 μL, 0.287 mmol) and 2-methoxybenzoyl chloride (20 μL, 0.149 mmol) and the

mixture was stirred at room temperature for 2 h. After that, the reaction mixture was poured into saturated NaHCO₃ aqueous solution (1 mL) and extracted with CHCl₃ (5 mL, 4 mL, 3 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by preparative TLC (ethyl acetate/hexane = 2/1) to give the mixture of **36b** (16.4 mg, 93%) as a white solid.

IR (KBr, cm⁻¹) 3357, 2932, 1665, 1546, 1234, 1111, 1022. ¹H NMR (400 MHz, CDCl₃) δ 1.72 (s, 3H), 1.73 (s, 3H), 3.81 (dd, *J* = 2.8, 10.0 Hz, 1H), 3.99 (s, 3H), 4.07 (s, 3H), 4.30 (d, *J* = 10.0 Hz, 1H), 5.10 (d, *J* = 2.8 Hz, 1H), 5.18 (s, 1H), 5.23 (s, 1H), 6.98–7.05 (m, 2H), 7.09–7.16 (m, 3H), 7.24–7.26 (m, 1H), 7.32 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.39 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.46–7.52 (m, 2H), 7.56–7.61 (m, 2H), 7.69 (dd, *J* = 2.0, 2.0 Hz, 1H), 7.83 (dd, *J* = 2.0, 2.0 Hz, 1H), 8.24 (dd, *J* = 2.0, 8.0 Hz, 1H), 8.27 (dd, *J* = 2.0, 8.0 Hz, 1H), 9.76 (brs, 1H), 9.83 (brs, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 24.27, 24.34, 56.4, 56.5, 71.4, 86.9, 87.4, 95.3, 99.7, 101.5, 111.6, 111.7, 117.3, 117.4, 119.8, 119.9, 120.8, 121.1, 121.77, 121.83 (×2), 121.9, 129.3, 129.4, 132.60, 132.63, 133.39, 133.43, 138.7, 138.8, 143.5, 143.7, 157.3 (×2), 163.4 (×2). HR-MS (ESI): Calcd for C₃₆H₃₅N₃NaO₇ [M+Na]⁺, 644.2373. Found, 644.2356.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))bis(3-methoxybenzamide) (37b)**

According to the synthetic protocol of **36b**, **16b** (10.0 mg, 0.0283 mmol) was converted to **37b** (15.5 mg, 88%) as a white solid.

IR (KBr, cm^{-1}) 3312, 2933, 1654, 1541, 1234, 1108, 1039. ^1H NMR (400 MHz, CDCl_3) δ 1.69 (s, 3H), 1.70 (s, 3H), 3.76 (dd, $J = 2.8, 10.1$ Hz, 1H), 3.805 (s, 3H), 3.814 (s, 3H), 4.26 (d, $J = 10.1$ Hz, 1H), 5.05 (d, $J = 2.8$ Hz, 1H), 5.11 (s, 1H), 5.25 (s, 1H), 7.01–7.06 (m, 3H), 7.18–7.42 (m, 9H), 7.55 (dd, $J = 0.8, 8.0$ Hz, 1H), 7.64–7.66 (m, 2H), 7.81 (dd, $J = 2.0, 2.0$ Hz, 1H), 8.04 (brs, 1H), 8.06 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.1, 24.2, 55.6, 71.3, 86.8, 87.2, 95.3, 99.6, 101.5, 112.4, 112.6, 117.1, 117.5, 118.22, 118.25, 118.8, 118.9, 119.4, 119.7, 121.2, 121.5, 129.4, 129.6, 129.8, 129.9, 136.4, 138.2, 138.3, 143.4, 143.7, 160.0, 160.1, 165.8, 166.0. HR-MS (ESI): Calcd for $\text{C}_{36}\text{H}_{35}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, 644.2373. Found, 644.2392.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))bis(4-methoxybenzamide) (38b)**

According to the synthetic protocol of **36b**, **16b** (10.0 mg, 0.0283 mmol) was converted to **38b** (15.3 mg, 87%) as a white solid.

IR (KBr, cm^{-1}) 3327, 2933, 1649, 1543, 1252, 1107, 1029. ^1H NMR (400 MHz, CDCl_3) δ 1.687 (s, 3H), 1.692 (s, 3H), 3.73 (dd, $J = 2.8, 10.1$ Hz, 1H), 3.82 (s, 3H), 3.83 (s, 3H), 4.24 (d, $J = 10.1$ Hz, 1H), 5.03 (d, $J = 2.8$ Hz, 1H), 5.08 (s, 1H), 5.29 (s, 1H), 6.81–6.84 (m, 2H), 6.87–6.89 (m, 2H), 7.16–7.19 (m, 2H), 7.30 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.35 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.53 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.64–7.67 (m, 2H), 7.74–7.76 (m, 2H), 7.81–7.83 (m, 3H), 8.06 (brs, 1H), 8.07 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.0, 24.2, 55.5, 55.6, 71.3, 86.8, 87.2, 95.3, 99.7, 101.5, 113.9, 114.0, 117.2, 117.7, 119.4, 119.8, 120.9, 121.3, 127.12, 127.14, 129.07, 129.10, 129.4, 129.5, 138.4, 138.6, 143.3, 143.6, 162.5, 162.6, 165.6, 165.7. HR-MS (ESI): Calcd for

$\text{C}_{36}\text{H}_{35}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, 644.2373. Found, 644.2366. (+)-**38b**: $[\alpha]_{\text{D}}^{25} = +68.5$ (c 0.040, CHCl_3), (–)-**38**: $[\alpha]_{\text{D}}^{25} = -75.0$ (c 0.040, CHCl_3).

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))bis(2-methoxybenzamide) (39b)**

According to the synthetic protocol of **36b**, **19b** (10.0 mg, 0.0283 mmol) was converted to **39b** (16.2 mg, 92%) as a white solid.

IR (KBr, cm^{-1}) 3360, 2927, 1666, 1552, 1234, 1120, 1019. ^1H NMR (400 MHz, CDCl_3) δ 1.57 (s, 3H), 1.76 (s, 3H), 3.75 (s, 3H), 3.81 (dd, $J = 2.8, 10.1$ Hz, 1H), 3.93 (s, 3H), 4.22 (d, $J = 10.1$ Hz, 1H), 5.04 (s, 1H), 5.15 (s, 1H), 5.36 (d, $J = 2.8$ Hz, 1H), 6.86–6.97 (m, 5H), 7.13 (dd, $J = 1.6, 1.6$ Hz, 1H), 7.24–7.30 (m, 2H), 7.34–7.40 (m, 2H), 7.43 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.52 (dd, $J = 1.6, 1.6$ Hz, 1H), 7.94–8.01 (m, 3H), 8.25 (dd, $J = 1.6, 8.0$ Hz, 1H), 9.75 (brs, 1H), 10.09 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.1, 24.1, 56.0, 56.5, 71.9, 86.6, 87.4, 94.7, 100.1, 101.9, 111.4, 111.5, 116.6, 119.1, 119.3, 119.4, 121.0, 121.15, 121.22, 121.38, 121.42, 121.5, 128.6, 128.9, 132.1, 132.3, 133.1, 138.2, 138.5, 141.1, 142.5, 157.2, 157.3, 163.2, 163.3. HR-MS (ESI): Calcd for $\text{C}_{36}\text{H}_{35}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, 644.2373. Found, 644.2348.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))bis(3-methoxybenzamide) (40b)**

According to the synthetic protocol of **36b**, **19b** (10.0 mg, 0.0283 mmol) was converted to **40b** (14.3 mg, 81%) as a white solid.

IR (KBr, cm^{-1}) 3314, 2929, 1654, 1543, 1238, 1121, 1041. ^1H NMR (400 MHz, CDCl_3) δ 1.57 (s, 3H), 1.72 (s, 3H), 3.76–3.79 (m, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.22 (d, $J = 10.1$ Hz, 1H), 4.95 (s, 1H), 5.19 (s, 1H), 5.35 (d, $J = 2.8$ Hz, 1H), 6.90–6.95 (m, 2H), 6.98–7.01 (m, 1H), 7.23–7.31 (m, 9H), 7.43 (dd, $J = 7.6, 7.6$ Hz, 1H), 7.69 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.74–7.77 (m, 2H), 8.12 (brs, 1H), 8.13 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.9, 23.5, 55.5, 71.8, 87.1, 87.2, 94.8, 100.1, 101.9, 112.4, 112.5, 117.6, 117.8, 118.3, 118.8, 118.9, 119.2, 119.7, 120.5, 121.3, 122.6, 128.69, 128.74, 129.7, 129.8, 136.2, 136.6, 137.5, 137.9, 142.1, 142.2, 159.8, 159.9, 165.8, 166.1. HR-MS (ESI): Calcd for $\text{C}_{36}\text{H}_{35}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, 644.2373. Found, 644.2353.

N,N'-(((2*aS*/R,4*R*/S,4*aS*/R,6*R*/S,6*aS*/R)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))bis(4-methoxybenzamide) (41b)

According to the synthetic protocol of **36b**, **19b** (10.0 mg, 0.0283 mmol) was converted to **41b** (15.0 mg, 85%) as a white solid.

IR (KBr, cm^{-1}) 3313, 2929, 1648, 1543, 1253, 1120, 1031. ^1H NMR (400 MHz, CDCl_3) δ 1.56 (s, 3H), 1.72 (s, 3H), 3.77 (dd, $J = 2.8, 10.1$ Hz, 1H), 3.79 (s, 3H), 3.82 (s, 3H), 4.21 (d, $J = 10.1$ Hz, 1H), 4.94 (s, 1H), 5.17 (s, 1H), 5.34 (d, $J = 2.8$ Hz, 1H), 6.79–6.84 (m, 3H), 6.88–6.91 (m, 1H), 7.22–7.28 (m, 3H), 7.41 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.68–7.76 (m, 7H), 8.08 (brs, 1H), 8.11 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.8, 23.5, 55.47, 55.52, 71.7, 87.1, 87.2, 94.8, 100.1, 101.9, 113.9, 117.5, 119.2, 119.7, 120.6, 121.1, 122.4, 127.0, 127.4, 128.6, 128.7, 129.0, 129.1, 137.7,

138.2, 142.0, 142.1, 162.3, 162.4, 165.6, 165.8. HR-MS (ESI): Calcd for $C_{36}H_{35}N_3NaO_7$ $[M+Na]^+$, 644.2373. Found, 644.2366. (+)-**41b**: $[\alpha]_D^{25} = +55.0$ (c 0.040, $CHCl_3$), (–)-**41b**: $[\alpha]_D^{25} = -55.0$ (c 0.040, $CHCl_3$).

***N,N'*-(((2*aS*/*R*,4*S*/*R*,4*aS*/*R*,6*S*/*R*,6*aS*/*R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))bis(2-(dimethylamino)benzamide) (42b)**

To a solution of **16b** (10.0 mg, 0.0283 mmol) in 1,2-dichloromethane (1 mL) was added 2-(dimethylamino) benzoic acid (48 mg, 0.283 mmol), HATU (107.6 mg, 0.283 mmol) and DIPEA (49.3 μ L, 0.283 mmol), then the mixture was stirred at room temperature for 15 h. After that, 1,2-dichloromethane was removed in reduced pressure and the residue was diluted with ethyl acetate (5 mL), washed with water (10 mL) and brine (1 mL $\times$ 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC (ethyl acetate/hexane = 1/1) to give the mixture of **42b** (17.0 mg, 93%) as a pale yellow amorphous.

IR (KBr, cm^{-1}) 2934, 1670, 1552, 1109. 1H NMR (400 MHz, $CDCl_3$) δ 1.73 (s, 3H), 1.74 (s, 3H), 2.79 (s, 6H), 2.84 (s, 6H), 3.82 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.31 (d, $J = 10.1$ Hz, 1H), 5.13 (d, $J = 2.8$ Hz, 1H), 5.18 (s, 1H), 5.23 (s, 1H), 7.11–7.13 (m, 1H), 7.22–7.33 (m, 6H), 7.39 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.45–7.51 (m, 4H), 7.81 (dd, $J = 1.6, 1.6$ Hz, 1H), 7.92 (dd, $J = 1.6, 1.6$ Hz, 1H), 8.21 (dd, $J = 1.6, 8.0$ Hz, 1H), 8.25 (dd, $J = 1.6, 8.0$ Hz, 1H), 12.10 (brs, 1H), 12.21 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 45.57, 45.63, 71.4, 86.9, 87.4, 95.3, 99.8, 101.6, 116.9, 119.2, 120.3, 120.37, 120.43, 120.7, 125.05, 125.13, 127.68, 127.73, 129.2, 129.3, 131.7, 131.8, 132.50, 132.54,

139.2, 139.3, 143.6, 143.8, 152.21, 152.24, 164.3. HR-MS (ESI): Calcd for $C_{38}H_{41}N_5NaO_5$ $[M+Na]^+$, 670.3005. Found, 670.2981.

***N,N'*-(((2*aS*/*R*,4*S*/*R*,4*aS*/*R*,6*S*/*R*,6*aS*/*R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))bis(3-(dimethylamino)benzamide)**
(43b)

According to the synthetic protocol of **42b**, **16b** (10.0 mg, 0.0283 mmol) was converted to **43b** (8.5 mg, 46%) as a colorless amorphous.

IR (KBr, cm^{-1}) 2925, 1650, 1537, 1109. 1H NMR (400 MHz, $CDCl_3$) δ 1.698 (s, 3H), 1.703 (s, 3H), 2.97 (s, 6H), 2.98 (s, 6H), 3.77 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.27 (d, $J = 10.1$ Hz, 1H), 5.06 (d, $J = 2.8$ Hz, 1H), 5.13 (s, 1H), 5.24 (s, 1H), 6.81–6.86 (m, 2H), 7.02–7.04 (m, 1H), 7.08–7.10 (m, 1H), 7.16–7.29 (m, 6H), 7.33 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.38 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.55 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.63–7.68 (m, 2H), 7.81–7.82 (m, 1H), 7.96 (brs, 1H), 7.97 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 24.2, 40.6, 71.3, 86.8, 87.3, 95.3, 99.6, 101.5, 111.4, 113.8, 113.9, 115.58, 115.60, 117.0, 117.3, 119.3, 119.5, 121.1, 121.2, 129.38, 129.42, 129.46, 129.51, 135.8, 135.9, 138.49, 138.53, 143.5, 143.6, 150.86, 150.91, 166.8, 166.9. HR-MS (ESI): Calcd for $C_{38}H_{41}N_5NaO_5$ $[M+Na]^+$, 670.3005. Found, 670.2986.

***N,N'*-(((2*aS*/*R*,4*S*/*R*,4*aS*/*R*,6*S*/*R*,6*aS*/*R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))bis(4-(dimethylamino)benzamide)**
(44b)

According to the synthetic protocol of **42b**, **16b** (10.0 mg, 0.0283 mmol) was converted to **44b** (10.8 mg, 59%) as a colorless amorphous.

IR (KBr, cm^{-1}) 2929, 1607, 1522, 1108. ^1H NMR (400 MHz, CDCl_3) δ 1.69 (s, 3H), 1.70 (s, 3H), 3.00 (s, 6H), 3.02 (s, 6H), 3.76 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.26 (d, $J = 10.1$ Hz, 1H), 5.05 (d, $J = 2.8$ Hz, 1H), 5.12 (s, 1H), 5.28 (s, 1H), 6.59–6.61 (m, 2H), 6.64–6.67 (m, 2H), 7.13–7.17 (m, 2H), 7.31 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.36 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.54–7.57 (m, 1H), 7.62 (dd, $J = 1.6, 1.6$ Hz, 1H), 7.68–7.69 (m, 1H), 7.72–7.75 (m, 2H), 7.78–7.81 (m, 3H), 7.919 (brs, 1H), 7.923 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.0, 24.2, 40.2, 71.3, 86.8, 87.2, 95.2, 99.5, 101.5, 111.16, 111.21, 116.9, 117.3, 119.2, 119.5, 120.5, 120.7, 121.3, 128.7, 128.8, 129.3, 129.4, 138.8, 138.9, 143.2, 143.5, 152.66, 152.72, 165.8, 165.9. HR-MS (ESI): Calcd for $\text{C}_{38}\text{H}_{41}\text{N}_5\text{NaO}_5$ $[\text{M}+\text{Na}]^+$, 670.3005. Found, 670.3021.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))bis(2-(dimethylamino)benzamide)**
(45b)

According to the synthetic protocol of **42b**, **19b** (10.0 mg, 0.0283 mmol) was converted to **45b** (8.7 mg, 47%) as a pale red amorphous.

IR (KBr, cm^{-1}) 3449, 1665, 1559, 1120. ^1H NMR (400 MHz, CDCl_3) δ 1.60 (s, 3H), 1.74 (s, 3H), 2.71 (s, 6H), 2.74 (s, 6H), 3.80 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.20 (d, $J = 10.1$ Hz, 1H), 5.01 (s, 1H), 5.22 (s, 1H), 5.36 (d, $J = 2.8$ Hz, 1H), 6.90–6.92 (m, 1H), 7.17–7.31 (m, 6H), 7.38–7.48 (m, 4H), 7.55–7.57 (m, 1H), 7.70 (dd, $J = 1.6, 1.6$ Hz, 1H), 7.83–7.85 (m, 1H), 8.14–8.17 (m, 2H), 12.04

(brs, 1H), 12.25 (brs, 1H) ^{13}C NMR (100 MHz, CDCl_3) δ 23.1, 23.8, 45.6, 71.8, 87.1, 87.3, 94.8, 100.0, 101.8, 116.9, 118.1, 119.1, 119.3, 120.35, 120.38, 121.2, 121.7, 125.0, 125.1, 127.67, 127.70, 128.5, 128.6, 131.6, 131.7, 132.4, 138.6, 141.8, 142.3, 152.2, 152.3, 164.2, 164.3. HR-MS (ESI): Calcd for $\text{C}_{38}\text{H}_{41}\text{N}_5\text{NaO}_5$ $[\text{M}+\text{Na}]^+$, 670.3005. Found, 670.2981.

***N,N'*-(((2*aS*/*R*,4*R*/*S*,4*aS*/*R*,6*R*/*S*,6*aS*/*R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))bis(3-(dimethylamino)benzamide) (46b)**

According to the synthetic protocol of **42b**, **19b** (10.0 mg, 0.0283 mmol) was converted to **46b** (8.5 mg, 46%) as a colorless amorphous.

IR (KBr, cm^{-1}) 2925, 1655, 1542, 1120. ^1H NMR (400 MHz, CDCl_3) δ 1.57 (s, 3H), 1.72 (s, 3H), 2.960 (s, 6H), 2.962 (s, 6H), 3.77 (dd, $J = 2.8, 10.1$ Hz, 1H), 4.22 (d, $J = 10.1$ Hz, 1H), 4.96 (s, 1H), 5.19 (s, 1H), 5.34 (d, $J = 2.8$ Hz, 1H), 6.79 (dd, $J = 2.0, 8.0$ Hz, 1H), 6.82 (dd, $J = 2.0, 8.0$ Hz, 1H), 6.89–6.91 (m, 1H), 6.98–7.33 (m, 9H), 7.42 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.69–7.74 (m, 3H), 8.00 (brs, 1H), 8.02 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.9, 23.6, 40.6, 71.8, 87.1, 87.2, 94.8, 100.1, 101.9, 111.5, 113.9, 114.0, 115.49, 115.52, 117.3, 119.0, 119.1, 120.2, 121.2, 122.4, 128.6, 128.8, 129.30, 129.33, 135.7, 136.0, 137.8, 138.0, 142.07, 142.14, 150.8, 166.7, 166.9. HR-MS (ESI): Calcd for $\text{C}_{38}\text{H}_{41}\text{N}_5\text{NaO}_5$ $[\text{M}+\text{Na}]^+$, 670.3005. Found, 670.3000.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))bis(4-(dimethylamino)benzamide) (47b)**

According to the synthetic protocol of **42b**, **19b** (10.0 mg, 0.0283 mmol) was converted to **47b** (28.9 mg, 52%) as a white solid.

IR (KBr, cm⁻¹) 2905, 1607, 1523, 1121. ¹H NMR (400 MHz, CDCl₃) δ 1.56 (s, 3H), 1.72 (s, 3H), 3.00 (s, 6H), 3.02 (s, 6H), 3.78 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.23 (d, *J* = 10.1 Hz, 1H), 4.96 (s, 1H), 5.19 (s, 1H), 5.34 (d, *J* = 2.8 Hz, 1H), 6.61–6.64 (m, 4H), 6.86–6.88 (m, 1H), 7.17 (dd, *J* = 1.6, 1.6 Hz, 1H), 7.22–7.28 (m, 2H), 7.42 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.65 (dd, *J* = 1.6, 1.6 Hz, 1H), 7.68–7.71 (m, 4H), 7.74–7.84 (m, 5H), 7.89 (brs, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 22.9, 23.6, 40.2, 71.8, 87.1, 87.3, 94.8, 100.2, 102.0, 111.2, 111.3, 117.1, 118.8, 119.0, 120.0, 120.7, 121.4, 121.6, 121.9, 128.6, 128.67, 128.73, 128.8, 138.2, 138.4, 142.01, 142.04, 152.66, 152.69, 165.7, 165.9. HR-MS (ESI): Calcd for C₃₈H₄₁N₅NaO₅ [M+Na]⁺, 670.3005. Found, 670.2997.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dipicolinamide (48b)**

According to the synthetic protocol of **36b**, **16b** 10.0 mg, 0.0283 mmol) was converted to **48b** (17.3 mg, 100%) as a colorless amorphous.

IR (KBr, cm⁻¹) 2929, 1685, 1536, 1111. ¹H NMR (400 MHz, CDCl₃) δ 1.72 (s, 3H), 1.73 (s, 3H), 3.82 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.32 (d, *J* = 10.1 Hz, 1H), 5.11 (d, *J* = 2.8 Hz, 1H) 5.20 (s, 1H), 5.22 (s, 1H), 7.16–7.18 (m, 1H), 7.27–7.30 (m, 1H), 7.36 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.43 (dd, *J* =

8.0, 8.0 Hz, 1H), 7.45–7.51 (m, 2H), 7.74–7.76 (m, 2H), 7.81–7.83 (m, 1H), 7.87–7.93 (m, 3H), 8.26–8.32 (m, 2H), 8.57–8.58 (m, 1H), 8.63–8.65 (m, 1H), 10.0 (brs, 1H), 10.1 (brs, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 24.3, 71.3, 86.8, 87.3, 95.3, 99.6, 101.4, 116.4, 116.6, 118.9, 119.0, 121.0, 121.3, 122.5, 122.6, 126.64, 129.5, 129.6, 137.8, 137.9, 138.1, 138.2, 143.65, 143.74, 148.08, 148.12, 149.88, 162.1, 162.2. HR-MS (ESI): Calcd for C₃₂H₂₉N₅NaO₅ [M+Na]⁺, 586.2066. Found, 586.2039.

***N,N'*-(((2*aS*/*R*,4*S*/*R*,4*aS*/*R*,6*S*/*R*,6*aS*/*R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dinicotinamide (49b)**

According to the synthetic protocol of **36h**, **16b** (10.0 mg, 0.0283 mmol) was converted to **49b** (16.0 mg, 100%) as a colorless amorphous.

IR (KBr, cm⁻¹) 3309, 2931, 1656, 1549, 1111. ¹H NMR (400 MHz, CDCl₃) δ 1.656 (s, 3H), 1.664 (s, 3H), 3.69 (dd, *J* = 2.8, 10.0 Hz, 1H), 4.22 (d, *J* = 10.0 Hz, 1H), 5.00 (d, *J* = 2.8 Hz, 1H), 5.06 (s, 1H), 5.20 (s, 1H), 7.20 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.27–7.36 (m, 4H), 7.55–7.80 (m, 4H), 8.09–8.16 (m, 2H), 8.63–8.66 (m, 2H), 8.72 (brs, 1H), 8.76 (brs, 1H), 9.00–9.08 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 24.00, 24.04, 71.3, 86.8, 87.2, 95.3, 99.6, 101.4, 117.6, 117.8, 119.8, 120.2, 121.6, 121.9, 123.76, 123.79, 129.5, 129.6, 130.80, 130.82, 135.57, 135.63, 137.9, 138.0, 143.4, 143.7, 148.0, 148.1, 152.37, 152.42, 164.3, 164.5. HR-MS (ESI): Calcd for C₃₂H₂₉N₅NaO₅ [M+Na]⁺, 586.2066. Found, 586.2063.

***N,N'*-(((2*aS/R*,4*S/R*,4*aS/R*,6*S/R*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))diisonicotinamide (50b)**

According to the synthetic protocol of **36b**, **16b** (10.0 mg, 0.0283 mmol) was converted to **50b** (14.2 mg, 89%) as a colorless amorphous.

IR (KBr, cm⁻¹) 3489, 2924, 1656, 1550, 1120. ¹H NMR (400 MHz, CDCl₃) δ 1.668 (s, 3H), 1.674 (s, 3H), 3.70 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.23 (d, *J* = 10.1 Hz, 1H), 5.00 (d, *J* = 2.8 Hz, 1H), 5.07 (s, 1H), 5.19 (s, 1H), 7.22–7.24 (m, 2H), 7.33 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.36 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.54–7.67 (m, 7), 7.78–7.80 (m, 1H), 8.54 (brs, 1H), 8.60 (brs, 1H), 8.63 (d, *J* = 6.0 Hz, 2H), 8.67 (d, *J* = 6.0 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 24.0, 24.1, 71.3, 86.8, 87.2, 95.3, 99.6, 101.4, 117.5, 117.8, 119.7, 120.1, 121.0, 121.1, 121.9, 122.2, 129.6, 129.7, 137.6, 137.7, 142.08, 142.10, 143.5, 143.9, 150.68, 150.74, 164.1, 164.3. HR-MS (ESI): Calcd for C₃₂H₂₉N₅NaO₅ [M+Na]⁺, 586.2066. Found, 586.2076.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dipicolinamide (51b)**

According to the synthetic protocol of **36b**, **19b** (10.0 mg, 0.0283 mmol) was converted to **51b** (30.6 mg, 96%) as a colorless amorphous.

IR (KBr, cm⁻¹) 2926, 1685, 1541, 1121. ¹H NMR (400 MHz, CDCl₃) δ 1.57 (s, 3H), 1.77 (s, 3H), 3.79 (dd, *J* = 2.8, 10.1 Hz, 1H), 4.26 (d, *J* = 10.1 Hz, 1H), 4.99 (s, 1H), 5.17 (s, 1H), 5.36 (d, *J* = 2.8 Hz, 1H), 6.91–6.94 (m, 1H), 7.27–7.31 (m, 2H), 7.40–7.43 (m, 3H), 7.55 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.77–7.82 (m, 5H), 7.95 (dd, *J* = 2.0, 8.0 Hz, 1H), 8.12–8.15 (m, 3H), 8.52–8.53 (m, 1H),

8.62–8.63 (m, 1H), 9.91 (brs, 1H), 10.1 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.3, 23.7, 71.9, 87.11, 87.14, 94.8, 100.3, 102.0, 116.7, 118.0, 118.4, 119.0, 121.2, 122.2, 126.4, 128.8, 129.0, 137.6, 141.8, 142.3, 148.0, 148.1, 149.8, 161.9, 162.1. HR-MS (ESI): Calcd for $\text{C}_{32}\text{H}_{29}\text{N}_5\text{NaO}_5$ $[\text{M}+\text{Na}]^+$, 586.2066. Found, 586.2043.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))dinicotinamide (52b)**

According to the synthetic protocol of **36b**, **19b** (10.0 mg, 0.0283 mmol) was converted to **52b** (14.5 mg, 91%) as a colorless amorphous.

IR (KBr, cm^{-1}) 3489, 2924, 1656, 1550, 1120. ^1H NMR (400 MHz, CDCl_3) δ 1.56 (s, 3H), 1.71 (s, 3H), 3.74 (dd, $J = 2.8, 10.0$ Hz, 1H), 4.08 (d, $J = 10.0$ Hz, 1H), 4.95 (s, 1H), 5.18 (s, 1H), 5.33 (d, $J = 2.8$ Hz, 1H), 6.95–6.97 (m, 1H), 7.19–7.28 (m, 5H), 7.41 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.67–7.69 (m, 1H), 7.80–7.82 (m, 2H), 7.91–7.93 (m, 1H), 8.03–8.05 (m, 1H), 8.50 (dd, $J = 1.2, 4.4$ Hz, 1H), 8.59 (dd, $J = 1.2, 4.4$ Hz, 1H), 8.72 (brs, 1H), 8.81–8.88 (m, 2H), 8.96 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.8, 23.4, 71.6, 87.06, 87.10, 94.7, 100.0, 101.9, 117.9, 119.7, 120.7, 121.3, 121.7, 123.0, 123.6, 123.7, 128.76, 128.84, 130.5, 131.3, 135.4, 135.8, 137.1, 137.7, 142.1, 147.9, 148.2, 152.0, 152.3, 164.3, 164.8. HR-MS (ESI): Calcd for $\text{C}_{32}\text{H}_{29}\text{N}_5\text{NaO}_5$ $[\text{M}+\text{Na}]^+$, 586.2066. Found, 586.2081.

***N,N'*-(((2*aS/R*,4*R/S*,4*aS/R*,6*R/S*,6*aS/R*)-4,6-Dimethylhexahydro-1,3,5-trioxa-2*a*¹-azacyclopenta[*cd*]pentalene-4,6-diyl)bis(3,1-phenylene))diisonicotinamide (53b)**

According to the synthetic protocol of **36b**, **19b** (10.0 mg, 0.0283 mmol) was converted to **53b** (6.3 mg, 39%) as a colorless amorphous.

IR (KBr, cm^{-1}) 2934, 1656, 1550, 1120. ^1H NMR (400 MHz, CDCl_3) δ 1.57 (s, 3H), 1.70 (s, 3H), 3.76 (dd, $J = 2.8, 10.0$ Hz, 1H), 4.03 (d, $J = 10.0$ Hz, 1H), 4.99 (s, 1H), 5.21 (s, 1H), 5.33 (d, $J = 2.8$ Hz, 1H), 6.94 (ddd, $J = 1.2, 1.2, 8.0$ Hz, 1H), 7.24–7.30 (m, 3H), 7.40 (d, $J = 5.2$ Hz, 2H), 7.45 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.56 (d, $J = 5.2$ Hz, 2H), 7.62–7.63 (m, 1H), 7.73–7.80 (m, 2H), 8.42 (brs, 1H), 8.57 (d, $J = 5.2$ Hz, 2H), 8.65 (d, $J = 5.2$ Hz, 2H), 8.84 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.1, 23.8, 71.6, 87.09, 87.11, 94.7, 100.1, 101.9, 117.5, 119.6, 120.2, 121.1 ($\times 4$), 121.3, 122.0, 123.2, 128.9, 129.0, 136.8, 137.4, 141.9, 142.2, 142.3, 142.5, 150.5, 150.7, 164.2, 164.6. HR-MS (ESI): Calcd for $\text{C}_{32}\text{H}_{29}\text{N}_5\text{NaO}_5$ $[\text{M}+\text{Na}]^+$, 586.2066. Found, 586.2057.

Biology

In vitro Ca^{2+} mobilization assay (Agonist activity)¹⁰

Chinese hamster ovary (CHO)-K1 cells stably expressing human OX_1R (CHOOX_1R) or OX_2R (CHOOX_2R) were seeded in a 96-well-plate (10,000 cells/well) and incubated with 5% FBS/DMEM at 37 °C for 48 h. Then, cells were loaded with 5 μM fluorescent calcium indicator Fura 2-AM (Cayman Chemical) in Hanks balanced salt solution (HBSS: GIBCO) including 20 mM HEPES (Sigma-Aldrich), 2.5 mM Probenecid (WAKO), 5% CremophorEL (Fluka), and 0.1% BSA (SigmaAldrich) at 37 °C for 1 h. The cells were washed once and added with 75 μL of HBSS buffer. Then, cells were treated with 25 μL of various concentrations of test compounds or orexin A (OXA: diluted in PBS/0.1% BSA, Peptide Institute. Inc.). The increase of the intracellular Ca^{2+}

concentration after the application of test compounds or OXA was monitored by FDSS 7000 system (Hamamatsu Photonics). The EC₅₀ value of each compounds was calculated by Graph Pad Prism 5J (MDF).

Luciferase assay (Agonist activity) ¹⁰

CHOOX₁R or CHOOX₂R cells were seeded (10,000 cells/well) in a 96-well-plate and grown to confluence for 24 h. Cells were treated with indicated test compounds or OXA. OXA (diluted in PBS/0.1%BSA) was used positive control. Six hours later, the medium was removed by suction. The cell monolayer was lysed in 50 µL of Steady-Glo luciferase reagent (Promega) and luciferase activity was determined by ARVO x5 (PerkinElmer). The Steady-Glo reagent was diluted 10-fold in 25 mM Tris (pH 7.5)/10% Glycerol/1% triton X-100 as Working solution.

***In vitro* Ca²⁺ mobilization assay (Antagonist activity) ¹¹**

CHO-K1 cells stably expressing human OX₁R (CHOOX₁R) or OX₂R (CHOOX₂R) were seeded in a 96-well-plate (10 000 cells per well) and then were incubated with 5% fetal bovine serum (FBS)/Dulbecco's modified Eagle medium (DMEM) at 37 °C for 48 h. After the incubation, cells were loaded with 4 µM fluorescent calcium indicator Fura 2-AM (Cayman Chemical) in Hanks' balanced salt solution (HBSS, GIBCO) including 20 mM HEPES (Sigma-Aldrich), 2.5 mM Probenecid (WAKO), 5% CremophorEL (Fluka), and 0.1% bovine serum albumin (BSA) (Sigma-Aldrich) at 37 °C for 1 h. The cells were washed once and added with 50 µL of HBSS buffer. Cells were pretreated with 25 µL of various concentrations of test compounds for 15 min. After that,

submaximal concentration of human orexin-A (OXA, 0.3 nM, Peptide Institute, Inc.) at 25 μ L was added to the cells. The increase of the intracellular Ca^{2+} concentration was measured from the ratio of emission fluorescence of 510 nm by excitation at 340 or 380 nm using the Functional Drug Screening System 7000 system (Hamamatsu Photonics). The IC_{50} values of compound to orexin A were calculated using GraphPad Prism 5J (MDF). K_i values were calculated by using the Cheng–Prusoff formula $K_i = \text{IC}_{50}/[1 + (\text{L}/\text{EC}_{50})]$, where IC_{50} is IC_{50} value of each test compound, L is orexin A concentration at IC_{50} experiments, EC_{50} is the half-maximal effective concentration of orexin A.

Opioid Receptor Binding

HEK cells stably expressing human μ , δ , or κ opioid receptor were provided from Drs. Uezono (The Jikei University School of Medicine, Japan) and Miyano (National Cancer Center Research Institute, Jaoan); these cell membranes were used for opioid receptor binding assay. Binding affinity for μ , δ , or κ opioid receptor in test compounds was measured by displacement of [^3H]-DAMGO, [^3H]-DPDPE, or [^3H]-U69,593 (each 2 nM), respectively. Nonspecific binding was measured in the presence of 10 μM unlabeled DAMGO, DPDPE, or U-69,593. Radioactivity in the test samples was determined by a MicroBeta scintillation counter with 96-well microplate (PerkinElmer). The value of each test sample was calculated as $[(T_1 - T_0)/(T_2 - T_0)] \times 100$, where T_0 is the nonspecific binding, T_1 is the [^3H]-labeled ligand binding in the presence of various concentrations of test compounds (10^{-5} – 10^{-11} M), and T_2 is the [^3H]-labeled ligand binding in the absence of respective test compounds. Sigmoidal concentration–response curve and K_i value were calculated by Prism software (version 6.05).

Caco-2 Permeability Assay

Assays and data analysis were performed by Eurofins Panlabs (MO, USA) according to the literature.²⁵

Human Liver Microsome Stability

Assays and data analysis were performed by Eurofins Panlabs (MO, USA) according to the literature.²⁶

***In vivo* experiments**

Animal experiments were carried out in a humane manner after receiving approval from the Institutional Animal Care and Use Committee of the University of Tsukuba and Tohoku University, and in accordance with the Regulation for Animal Experiments in our university and Fundamental Guideline for Proper Conduct of Animal Experiments and Related Activities in Academic Research Institutions under the jurisdiction of the Ministry of Education, Culture, Sports, Science and Technology.

Determination of brain concentrations of **38b and **41b****

C57BL/6J mice received i.p. administration of **38b** or **41b**. At the indicated time after administration, the mice were sacrificed, and the cerebral hemisphere of each mouse was collected, and homogenized in the 3:7 mixture of MeOH:MeCN including 100 pM risperidone as internal standard (5 mL: 1 g brain) with beads shaker (Precellys Evolution, Zirconia beads 1.0 mm (20

beads/tube), 2 ml tube, 8500 rpm, and 30 seconds). Then, the samples were centrifuged at 4°C and 17,360 g for 5 min, and 750 µL of supernatant was evaporated by centrifugation under vacuum, and the residue was reconstituted in 100 µL of 0.1% formic acid/90% water/10% acetonitrile. This solution was centrifuged at 4°C and 17,360 g for 5 min and the supernatant was subjected to LC-MS/MS analysis with an electrospray ionization–triple quadrupole mass spectrometer (QTRAP5500; SCIEX, Framingham, MA) coupled to a UPLC system (Waters) equipped with a C18 column (ACQUITY UPLC BEH C18, 1.7 µm, 2.1 × 50 mm, Waters). Mobile phases A and B consisted of 0.1% formic acid in water and 0.1% formic acid in acetonitrile, respectively. The flow rate was 0.3 mL/min. The compounds were separated and eluted from the column with a linear gradient as follows: 1% B (0–1 min), rapidly increased to 100% B (1–3 min), maintained at 100% B (3–4 min), rapidly reduced to 0% B for 0.1 min (4–4.1 min), and then maintained at 1% B (4.1–6 min). The target compounds eluted from the UPLC column were detected by means of electrospray ionization in SRM mode. The SRM transitions were m/z 622.7→135.1 for **38b**, m/z 622.7→135.1 for **41b** and m/z 411.2→191.1 for risperidone.

Sleep recordings

These protocols of sleep recording were described previously.^{39, 40} EEG/EMG recordings were performed for 12 consecutive hours in the dark phase. EEG/EMG data were analyzed as previously described¹, and EEG/EMG signals were scored in wakefulness, NREM sleep, and REM sleep state. All analyses were calculated by Sleep Sign (KISSEI COMTEC).

For (±)-**38b** intraperitoneal administration (i.p.) experiment, 8- to 12-wk-old male C57BL/6J mice (ID# 000664 from Charles River) were administered (±)-**38b** or vehicle (0.3 mL/30 g body weight)

by intraperitoneal injection at ZT 12. DORA ($\pm$)-**38b** was dissolved in saline (50%), polyethylene glycol 400 (PEG400) (45%) and DMSO (5%) to a concentration of 1 mg/mL. Data are presented as the mean $\pm$ SEM of 8 mice.

Locomotor assay

4- to 6-wk-old male ICR mole mice (Japan SLC., Inc., Shizuoka, Japan) were individually placed in cages equipped with a running wheel and light-tight chamber under 12 h light/dark cycle (lights on 9:00 A.M. to 9:00 P.M.). The locomotor activity of mice was measured by infrared light beam-braking system locomotor recording system (wireless locomotor sensor: W03, wireless device USB Hub: DIG-807, software: SOF-860, BrainScience Idea. Co., Ltd., Osaka Japan). Briefly, a mouse was placed in a recording acrylic cage with infrared beam sensor. Horizontal locomotor activity was tracked by invisible infrared light beams that do not interfere with the normal mouse behavior. Counts of horizontal locomotor activity were collected in 10 min intervals for 120 min after orexin A (3 nmol/mouse). Test compound ($\pm$)-**41b** (3 or 10 mg/kg, i.p.) was administered intraperitoneally 30 min before intracerebroventricular treatment with orexin A. Statistical significance of total horizontal locomotor activity was determined by one-way ANOVA followed by Bonferroini test in GraphPad Prism software (version 6.05; GraphPad Software Inc., La Jolla, CA, USA). Data are presented as the mean $\pm$ SEM of 5–13 mice.

Intracerebroventricular administration of orexin A

Intracerebroventricular administration was performed according to the method described previously (Haley and McCormick, 1957). To make a hole in the skull for injection, 1–2 days before locomotor assay, mice were briefly anesthetized with isoflurane, and a 2 mm double needle (KN-386-4-4, Natsume Seisakusho, Tokyo, Japan) attached to a 25 μ L Hamilton micro syringe was inserted into the unilateral injection site using a V-shaped holder to hold the head of the mouse. On the day of the locomotor assay, orexin A (3 nmol/mouse) was injected into the hole using 2 mm double needle attached to a 25 μ L Hamilton micro syringe. The injection volume was 4 μ L for each mouse.

SUPPORTING INFORMATION

Molecular formula strings (CSV)

Determination of the relative configurations of the synthesized compounds, Chiral column analysis

Calculation of the CD spectra of simplified models **38b** and **41b**, CD spectrum analysis of **38b** and **41b**, Docking experiments, HPLC trace, Assay results of **38b** and **41b** for opioid receptor, In vitro membrane permeability and metabolic stability of **38b** and **41b** (PDF)

OX₁R in complex with docking poses of compound (–)-**38b** (PDB)

OX₂R in complex with docking poses of compound (–)-**38b** (PDB)

OX₁R in complex with docking poses of compound (–)-**41b** (PDB)

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

1-SORA, selective orexin 1 receptor antagonist; Boc, *tert*-butoxycarbonyl; Bz, benzoyl; CHO, Chinese hamster ovary, CNS, central nervous system; DORA, dual orexin receptor antagonist; EEG, electroencephalogram; EMG, electromyography; KOR, kappa opioid receptor; NREM, non-rapid eye movement; OXR, orexin receptor; OX1R, orexin 1 receptor; OX2R, orexin 2 receptor; PMI, principal moment of inertia; REM, rapid eye movement; SEM, standard error of the mean; TosMIC, *p*-toluenesulfonylmethyl isocyanide; TriMER, 1,3,5-trioxazatriquinane bearing multiple effective residues; ZT, zeitgeber time.

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