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Synthesis and structure–activity relationship of tricyclic carboxylic acids as novel anti-histamines

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ABSTRACT

A series of tricyclic carboxylic acids having 6-amino-pyrimidine-2,4(1*H*,3*H*)-dione with piperazino or homopiperazino moiety linked by propylene, were synthesized and evaluated for their affinity toward human histamine H_1 receptor and Caco-2 cell permeability. Selected compounds were further evaluated for their oral anti-histaminic activity in mice, bioavailability in rats, and their anti-inflammatory activity in mice OVA-induced biphasic cutaneous reaction model. Among the compounds tested, dibenzoxazepine carboxylic acid **13b** showed both histamine H_1 receptor antagonistic activity and anti-inflammatory activity in vivo. In addition, **13b** exhibited low affinity toward α_1 receptor and low occupancy of H_1 receptor in the brain. It is therefore, believed that **13b** is a potential candidate for development as 3rd generation anti-histamine.

1. Introduction

Allergic rhinitis (AR) is a high-prevalence disease, affecting 30–39% of the general population in Japan.[1] Patients with AR suffer from three typical symptoms, that is, sneezing, nasal hypersecretion, and nasal congestion, that are associated with Th2 immune response.[2] The former two symptoms are IgE mediated events and the latter one is a result of allergic inflammation. Treatment with anti-histamines is overall effective in controlling IgE mediated symptoms, but does not alleviate the allergic inflammatory symptom. Based on this fact, the consensus group on new-generation anti-histamines (CONGA) has recommended the development of new anti-histamines that can be effective not only against IgE mediated symptoms but also aginst the allergic inflammatory symptom.[3] Takeda group had reported **TAK-427** as novel anti-histamine with anti-inflammatory effect in several experimental animal models.[4] This compound proceeded to clinical evaluation, but its development has recently been suspended (Fig. 1).

We have previously reported that the phenothiazine carboxylic acid **1** containing piperazino pyrimidine moiety shows potent histamine H_1 receptor antagonistic activity in mouse skin vascular permeability model and strong anti-inflammatory activity in mice OVA-induced biphasic cutaneous reaction model.[5] Detailed SAR studies suggested that the piperazino-pyrimidine-dione structure is effective for anti-inflammatory activity and that a propylene linker is appropriate to keep both high H_1 binding affinity and good Caco-2 cell permeability. However, no information was revealed from these studies regarding the effects of the tricyclic anti-histaminic parts except for the phenothiazine.

Sedation and drowsiness are the main side effects of 1st generation anti-histamines, which can penetrate the brain and bind to H_1 receptor in the central nerve system. Such side effects could be suppressed by 2nd generation anti-histamines having a carboxyl gourp, such as Olopatadine[6] and Fexofenadine,[7] which are known to induce low H_1 receptor occupancy in the central nerve system. Although in our preparation of **1** we incorporated a carboxyl group in the structure to minimize sedation and drowsiness side effects, we have so far not evaluated occupancy of **1** of H_1 receptor in the brain.

We herein report the synthesis and structure activity relationship of a series of tricyclic carboxylic acids, having pyrimidine-2,4(1*H*,3*H*)-dione with piperazino or homopiperazino moiety linked by a propylene, as novel anti-histamines. We also describe our evaluation of selected compounds occupancy of H_1 receptor in the brain.

As several tricyclic-ring systems, such as dibenzoxazepine,[8] dibenzoazepine (for Imipramine[9]), dibenzocycloheptane (for Amitriptyline), and dibenzooxepine (for Olopatadine) (Fig. 2),[10] have been reported as important for anti-histaminic activity, we replaced the phenothiazine part in **1** with these tricyclic-rings.

The synthetic route of the N-linked compounds (type I compounds) **13a–j** is shown in Scheme 1.

Compound **2** was converted to **3** by benzylation with 2-bromobenzyl bromide. Reduction of the nitro group in **3** with iron, followed by acylation gave **4** in excellent yield. Copper catalyzed

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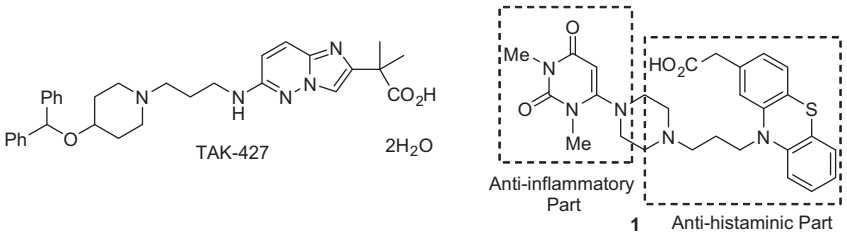


Figure 1. Chemical structures of **TAK-427** and **1**.

intramolecular cyclization[11] of **4** led to **5** in moderate yield, and allylation of **5** afforded the key intermediate **6a**. Reduction of the ester in **6a** with DIBAL followed by conversion of the hydroxygroup to a cyano group via mesylate and hydrolysis of the cyano group, and finally esterification gave **6b**. Methylation of **6b** with iodomethane gave the mono-methylated compound **6c** and the dimethylated compound **6d**. Hydroboration of the allyl group in **6a**–**d** gave the corresponding 3-hydroxypropyls **11a**–**d**.

Compound **11e**, the regioisomer of **11a**, was prepared from the 3-bromo-4-methyl-benzoic acid **7** by similar way to **11a**.[12]

The dibenzoazepine **11f**–**h** were prepared as follows. The tricyclic intermediate **9** was prepared as described in the literature,[13] and benzyloxypropylation of **9** gave **10**. Cyanation of **10** with copper cyanide followed by hydrolysis of the nitrile and benzylether, and finally esterification gave **11f**. The phenylacetate **11g** was prepared by coupling reaction of **10** with dimethyl malonate followed by hydrolysis of the methylester, decarboxylation, esterification, and finally removal of the benzyl group by Pd-catalyzed hydrogenation. The phenylisobutylate **11h** was synthesized by coupling reaction of **10** with methyl isobutylate,[14] followed by removal of the benzyl group under hydrogenation.

Finally, conversion of the hydroxy group in **11** to a methanesulfonate followed by coupling reaction with **12a** or **12b**,[5] and hydrolysis of the ester afforded the desired compounds **13a**–**j** (Scheme 1).

The synthetic route of the olefin linked compounds (type II compounds) **19a**–**h** is shown in Scheme 2. Wittig reaction of **14a** with phosphorane ($Ph_3P{=}CH(CH_2)_2OTHP$)[15] and THP deprotection gave **15a** as a 7:3 mixture of (*Z*)- and (*E*)-isomers. Coupling reaction of **15a** with *N*-methyl piperazine or *N*-methyl homopiperazine afforded **16a** or **16b**, respectively.

The bromine atom in **16a** or **16b** was replaced with a methyl malonate by palladium coupling,[16] followed by hydrolysis, decarboxylation, and esterification to give **17a** or **17b** in good yields (69% or 71%, respectively). The bromine atom in **16a** or **16b** was also converted to a methoxy carbonyl group by palladium catalyzed insertion reaction of carbon monoxide in methanol to afford **17c** or **17d**, respectively. The dibenzocycloheptane **17e**–**17g** were prepared in a similar way, except that addition of cyclopropyl magnesium bromide to the dibenzocycloheptanone **14b**,[17] followed by ring opening reaction with hydrogen bromide was carried out for the bromide **15b**. The ratio of (*Z*)- and (*E*)-isomers was 1:1. Cyanation of **16c** followed by hydrolysis gave **17g**. Desmethylation of **17**, carried out via conversion to 2,2,2-trichloroethyl formate,[18] followed by deprotection afforded the unsubstituted piperazines or homopiperazines **18a**–**g**. Condensation of **18** with the commercially available 6-chloro-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione followed by hydrolysis of the ester gave the desired **19a**–**g** as a mixture of (*Z*)- and (*E*)-isomers. Each isomer of **19** was next separated by preparative TLC.

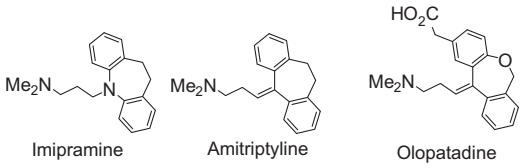


Figure 2. Chemical structures of tricyclic compounds having anti-histaminic activity.

The geometry of **19** was determined by NOESY spectra (Fig 3). The (*Z*)-isomer of the dibenzooxepine **19a** showed a cross peak between the vinylic proton H^{1a} and the aromatic proton H^{2b}, and a cross peak between the allylic proton H^{1b} and H^{2a}. On the other hand, the (*E*)-isomer of **19a** showed a cross peak between the vinylic proton $H^{1a'}$ and the aromatic proton $H^{2a'}$. These results strongly suggest that the geometry of **19a** is as assigned.

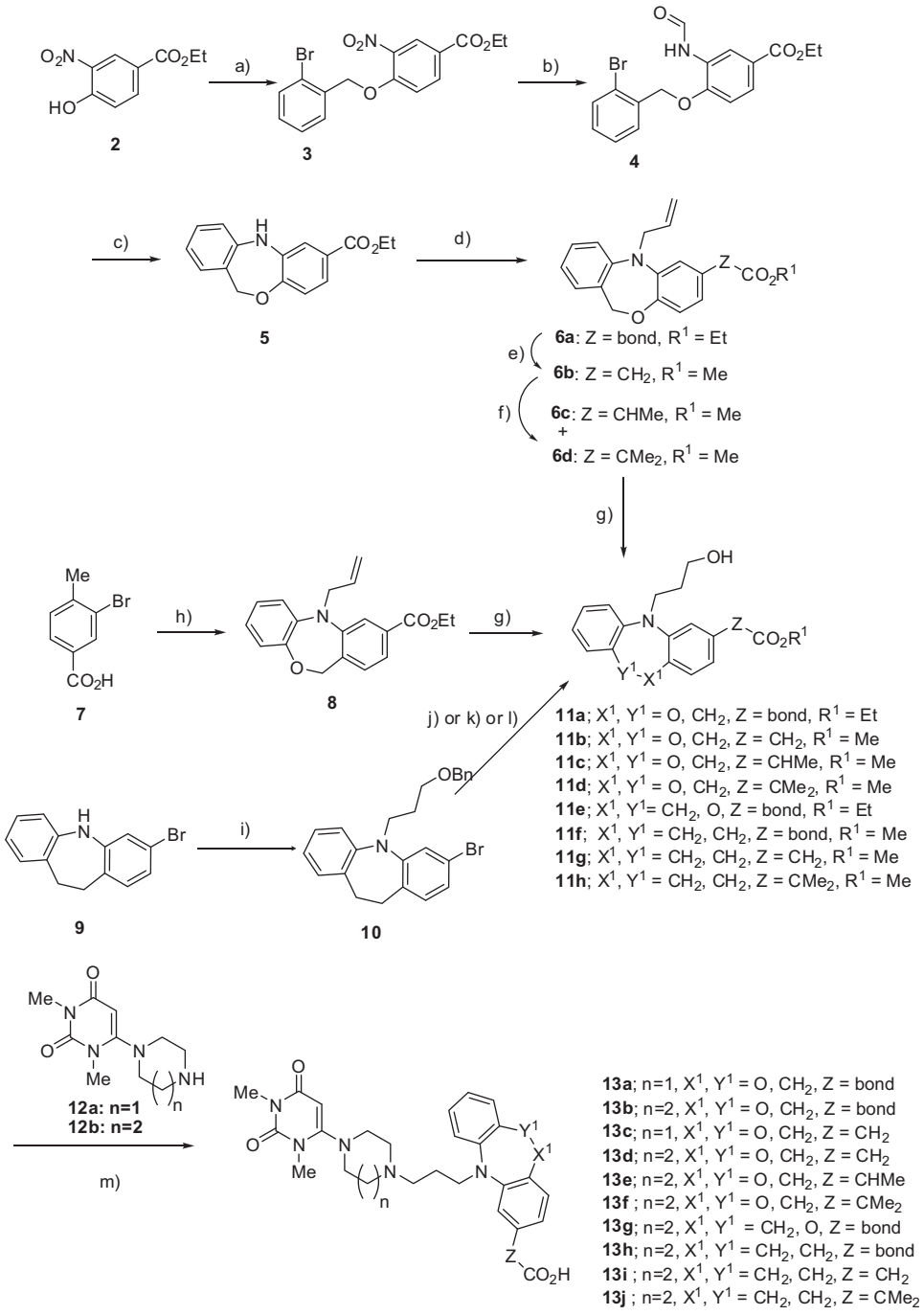
As for the dibenzocycloheptane **19g**, a cross peak between the vinylic proton H^{3a} and the aromatic proton H^{3b} was observed in (*Z*)-**19g**, and a cross peak between vinylic proton $H^{3a'}$ and aromatic proton $H^{3b'}$ in (*E*)-**19g** were observed.

2. Results and discussion

All compounds were evaluated for their affinity toward human histamine H_1 receptor using radioligand binding assay and for their Caco-2 cell permeability. Compounds that exhibited high affinity toward the H_1 receptor (IC_{50}; <100 nM) as well as high Caco-2 cell permeability (>40 nm/s) were further evaluated for their oral anti-histaminic activity in mice using histamine-induced skin vascular permeability. Compounds that exhibited good in vivo anti-histaminic activity (>50% inhibition at 3 mg/kg, po) were evaluated for their oral bioavailability in rats. Furthermore, compounds that exhibited good bioavailability in rats (>20%) were examined for their anti-inflammatory potential in mice OVA-induced biphasic cutaneous reaction model.[19] Finally, promising compounds were evaluated for their H_1 receptor occupancy in the mouse brain.

First of all, we evaluated compounds anti-histaminic activity to clarify the SAR of type I compounds (Table 1).

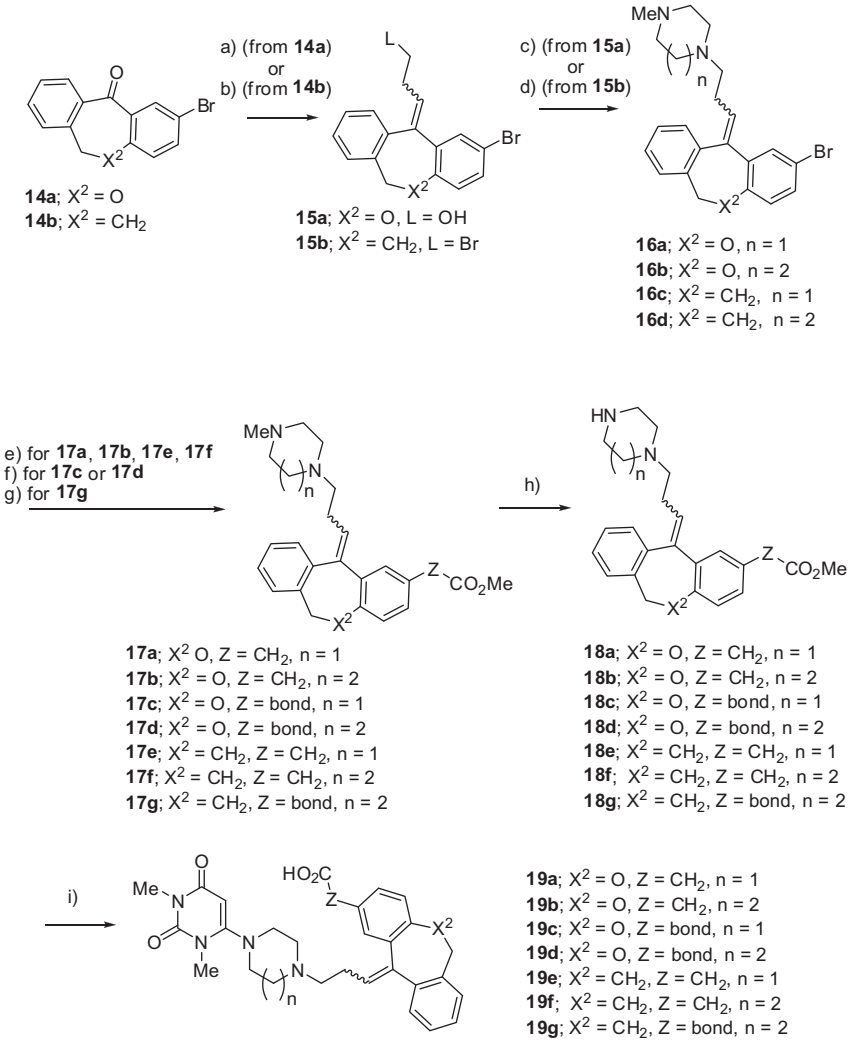
The dibenzoxazepin-3-carboxylic acid **13a** showed moderate H_1 receptor binding affinity (IC_{50}; 140 nM). Our previous work[5] had indicated that replacement of the piperazine in **13a** by a homopiperazine is effective in increasing H_1 receptor binding affinity. Based on this information, we prepared the homopiperazine **13b**, which was subsequently found to be equipotent to the phenothiazine **1** with an IC_{50} value of 41 nM. Our previous work had also indicated that conversion of the benzoic acid on phenothiazine to a phenylacetic acid was effective in increasing H_1 receptor binding affinity. We therefore synthesized the phenylacetic acid **13c** and **13d**, but both compounds showed weaker H_1 receptor binding affinity than the corresponding benzoic acids **13a** and **13b**. These findings indicate that SAR of tricyclic compounds is not completely the same between the phenothiazines and dibenzoxazepines. As phenothiazine compounds, the α-methyl phenylacetic acid **13e** and α,α′-dimethyl phenylacetic acid **13f** did not show improved H_1 binding affinity.[5] In addition, the dibenzoxazepin-7-carbxylic acid **13g** showed very weak H_1 binding affinity (IC_{50} = 530 nM), being almost 10-fold weaker than that of the regioisomer **13b**. Similar



Scheme 1. Reagents and conditions: (a) 2-bromobenzyl bromide, K_2CO_3, 2-butanone, reflux; (b) (i) Fe, AcOH, NH_4Cl, THF/EtOH, 75 °C; (ii) HCO_2Na, HCO_2H, 100 °C; (c) K_2CO_3, Cu, DMF, 155 °C; (d) allyl bromide, NaH, DMF, 0 °C; (e) (i) DIBAL, THF, −78–0 °C; (ii) NaH, MsCl, DMF, 0 °C to rt; (iii) KCN, DMF, rt; (iv) NaOH, MeOH/THF/H_2O, reflux; (v) K_2CO_3, MeI, DMF, rt; (f) ^{t}BuOK, MeI, THF, 0 °C to rt; (g) (i) BH_3/THF or 9-BBN, THF, 0 °C to rt; (ii) H_2O_2, NaOH, THF/H_2O, rt; (h) (i) EtI, K_2CO_3, DMF, rt; (ii) NBS, BPO, CCl_4, reflux; (iii) sodium *o*-nitrophenolate, TBAB, EtOH/DMF, 90 °C; (iv) Fe, AcOH, NH_4Cl, THF/EtOH, 75 °C; (v) HCO_2Na, HCO_2H, 100 °C; (vi) K_2CO_3, Cu, DMF, 155 °C; (vii) allyl bromide, NaH, DMF, 0 °C to rt; (i) $BnO(CH_2)_3Br$, K_2CO_3, DMF, rt; (j)(i) CuCN, DMF, reflux; (ii) concd HCl, reflux; (iii) MeOH, concd H_2SO_4; (k) (i) dimethylmalonate, NaH, $Pd_2(dba)_3$ $P(^tBu)_3$, THF reflux; (ii) 1 N aq NaOH, 50 °C; (iii) 3 N aqHCl, reflux; (iv) concd H_2SO_4, MeOH, reflux; (v) H_2, 10% Pd/C, MeOH, THF, 40 °C; (l) (i) methylisobutyrate, LiHMDS, $Pd_2(dba)_3$ $P(^tBu)_3$, toluene, rt; (ii) H_2, 10% Pd/C, MeOH, THF, 45 °C; (m) (i) MsCl, pyridine, CH_2Cl_2; (ii) **12a** or **12b**, KI, ^{i}Pr$_2$NEt, THF/^{i}PrOH/DMF, 90–100 °C; (iii) NaOH, MeOH/H_2O, 60 °C.

results were reported with Olopatadine-related compounds, that is, dibenzoxepin-7-carboxylic acid compounds showed weaker H_1 binding affinity than dibenzooxepin-3-carboxylic acid compounds.[20] Thangapandian et al. have reported that the lipophilic cavity in H_1 receptor take part in antagonist binding,[21] and Ram et al. have reported that phenyl or indole rings interact with electron rich group in H_1 receptor.[22] Therefore, it is believed that the position of the oxygen atom in dibenzooxazepins can affect lipophilic interaction.

We next designed and synthesized dibenzoazepine derivatives to confirm the importance of the oxygen atom in **13b** and to clarify the lipophilicity-activity relationship. Compound **13h** showed slightly weak activity compared to **13b** (70 nM vs 41 nM), however, both **13i** and **13j** showed twofold more potent activity than



Scheme 2. Reagents and conditions: (a) (i) $Ph_3P{=}CH(CH_2)_2OTHP$, THF, reflux; (ii) $TsOH/H_2O$, MeOH, reflux; (b) (i) *c*-PrMgBr, THF, rt; (ii) HBr/AcOH; (c) (i) MsCl, Et_3N, THF, rt; (ii) *N*-methylpiperazine or *N*-methylhomopiperazine, CH_3CN, reflux; (d) *N*-methylpiperazine or *N*-methylhomopiperazine, K_2CO_3, DMF; (e) (i) $CH_2(CO_2Me)_2$, NaH, $[(allyl)PdCl]_2$, (*o*-biphenyl)P(^{t}Bu)$_2$, THF, reflux; (ii) aq NaOH, MeOH/THF, 50 °C; (iii) pH 6–7, 100 °C; (iv) concd H_2SO_4, MeOH, reflux; (f) CO (gas), cat. $Pd(dppf)Cl_2$, MeOH, 110 °C; (g) (i) CuCN, DMF, reflux; (ii) 6 N HCl, reflux; (iii) MeOH, concd H_2SO_4, reflux; (h) (i) Troc-Cl, Et_3N, toluene, 80 °C; (ii) Zn, AcOH, 70 °C; (i) (i) 6-chloro-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, ^{i}Pr$_2$NEt, ^{i}PrOH, 80 °C; (ii) aq NaOH, MeOH/THF, rt.

13e and **13f**, respectively. Therefore, no clear lipophilicity-activity relationship could be seen with these compounds. Generally lipophilicity correlates with cell permeability. *C* log *P* values of **13b** and **13h** were calculated as 2.45 and 3.35, respectively, but clear improvement in cell permeability was not seen in these dibenzoazepin compounds.

In all type I compounds, the homopiperazine contributed to enhancement of H_1 binding affinity. This was also seen with our previous phenothiazine compounds. Benzoic acid was better than phenyacetic acid in term of Caco-2 permeability.

Next, we proceeded with further evaluation of compounds **13b**, **13h**, and **13j**, that showed good H_1 binding affinity (IC_{50} = <100 nM) with good Caco-2 permeability (>40 nm/s). All three compounds exhibited oral in vivo anti-histaminic activity with over 50% inhibition at 3 mg/kg. However, the bioavailability of **13j** in rat pharmacokinetics study was not high enough (14%). As a result, compound **13b** and **13h** satisfied our criteria and were selected among all type I compounds for further evaluation.

Next, we examined the SAR of type II compounds. A summary of our results is shown in Table 2.

As we reported in the previous paper, phenothiazine acetic acid with piperazine **1** showed better results than others,[5] we first synthesized the dibenzooxepineacetic acid with piperazine **19a** and evaluated its binding affinity for the H_1 receptor. Considering the geometry of the olefin part, the (*Z*)-isomer of **19a** showed better H_1 receptor binding affinity (IC_{50}; 84 nM) than the corresponding (*E*)-isomer (IC_{50}; 540 nM). Oshima et al reported that the affinity of (*Z*)-dibenzooxepineacetic acid is higher than that of (*E*)-dibenzooxepineacetic acid, so our finding is in agreement with their results.[10] In addition (*Z*)-**19a** showed better Caco-2 permeability than (*E*)-**19a.** We therefore focused our attention on this isomer. Compound (*Z*)-**19b**, obtained by replacing the piperazine of (*Z*)-**19a** with a homopiperazine, had an H_1 receptor binding affinity equivalent to that of (*Z*)-**19a** (IC_{50}; 92 nM), but showed low Caco-2 permeability (40 nm/s). Next, we evaluated the benzoic acids (*Z*)-**19c** and (*Z*)-**19d**, obtained by replacement of phenylacetic acid by benzoic acid. (*Z*)-**19c** showed weak H_1 receptor binding affinity (IC_{50}; 325 nM), and (*Z*)-**19d** did not satisfy Caco-2 permeability criteria (38 nm/s). As for the dibenzocycloheptanes ((*Z*)-**19e**, (*Z*)-**19f**, (*Z*)-**19g**), they showed decreased H_1 receptor binding affinity

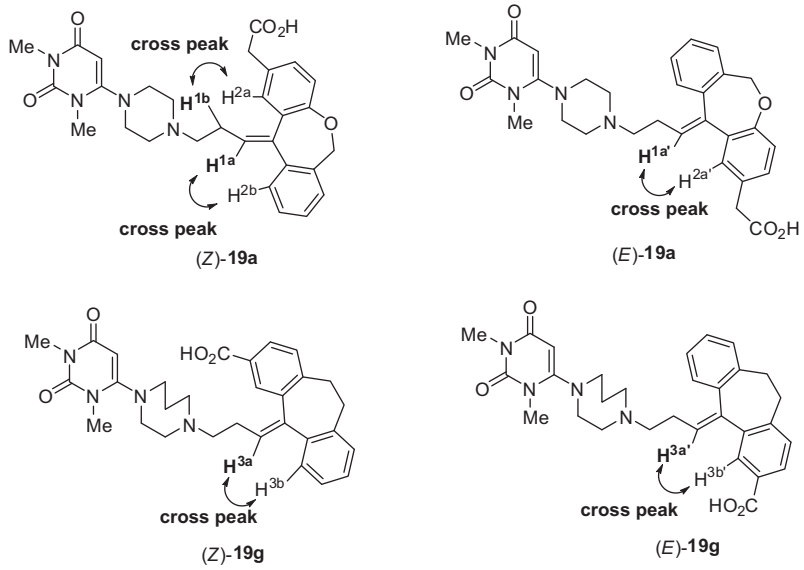
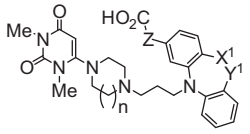


Figure 3. Results of NOESY analysis.

Table 1
Pharmacological profiles of dibenzoxazepine and dibenzoazepine[a]



Compound	*n*	X^1–Y^1	Z	H_1 binding IC_{50} (nM)	Caco-2 (nM/s)	H_1[b] (vivo)	BA[c] (%)
1				40	123	82 ± 6	27
13a	1	O–CH_2	Bond	140	76	—	—
13b	2	O–CH_2	Bond	41	63	87 ± 6	23
13c	1	O–CH_2	CH_2	255	30	—	—
13d	2	O–CH_2	CH_2	128	16	—	—
13e	2	O–CH_2	CHMe	128	19	—	—
13f	2	CH_2–CH_2	CMe_2	150	46	—	—
13g	2	CH_2–CH_2	Bond	530	16	—	—
13h	2	CH_2–CH_2	Bond	70	44	50 ± 5	33
13i	2	CH_2–CH_2	CH_2	54	26	—	—
13j	2	CH_2–CH_2	CMe_2	75	70	67 ± 10	14

[a] All the experiments were carried out in single.
[b] Histamine-induced skin vascular permeability. % inhibition at 3 mg/kg, po. The mean ± SE of six mice.
[c] Bioavailability in rat.

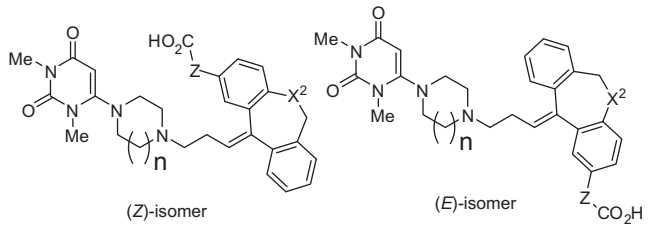
compared to the dibenzooxepines ((*Z*)-**19a**, (*Z*)-**19b**, (*Z*)-**19d**), though the dibenzocycloheptane was more lipophilic than the dibenzooxepine. Based on these finding, it is believed that H_1 receptor binding does not correlate with lipophilicity in tricyclic systems.

Next, compounds (*Z*)-**19a** and (*Z*)-**19b** were selected for in vivo evaluation. (*Z*)-**19a**, but not (*Z*)-**19b,** showed good in vivo anti-histaminic activity (53% inhibition at 3 mg/kg, po). This finding suggests that the criteria set for Caco-2 permeability (>40 nm/s) are appropriate. Compound (*Z*)-**19a** also showed good oral bioavailability in rat (76%), and was therefore selected among all type II compounds for further evaluation.

We next evaluated the anti-inflammatory activity of all selected compounds (**13b**, **13h**, and (*Z*)-**19a**) in OVA-induced biphasic cutaneous reaction model (Table 3). In this model, late type reaction (LTR) is characterized by local accumulation of activated inflammatory cells, including eosinophils, monocytes, and T lymphocytes.[23] On the other hand, immediate type reaction (ITR) is primarily caused by IgE mediated activation of mast cells/basophils to release chemical mediators such as histamine,[24] and in this case the use of anti-histamines has proven to be effective as shown in Table 3.

All three compounds (**13b**, **13h**, and (*Z*)-**19a**) showed potent LTR inhibitory activity, suggesting their ability to exert anti-inflammatory effect. As for ITR, both **13b** and (*Z*)-**19a** showed potent inhibitory activity, while **13h** was inactive. The reason for this discrepancy is unclear, although it might be attributed to **13h** low skin permeation or time-dependent tissue concentration. To clearly explain this discrepancy, mouse PK analysis of **13h** and clarification of the anti-inflammatory mechanism of compounds related to **13h**, is required. Therefore, only **13b** and (*Z*)-**19a** satisfied all criteria, and had a profile similar to that of compound **1**.

Table 2
Pharmacological profiles of dibenzocycloheptane and dibenzoxepin derivatives[a]



Compound	*n*	X^2	Z	H_1 binding IC_{50} (nM)	Caco-2 (nM/s)	H_1[b] (vivo)	BA[c] (%)
1				40	123	82 ± 6	27
(*Z*)-**19a**	1	O	CH_2	84	73	53 ± 6	76
(*E*)-**19a**	1	O	CH_2	540	47	—	—
(*Z*)-**19b**	2	O	CH_2	92	40	32 ± 8	
(*Z*)-**19c**	1	O	Bond	325	85	—	—
(*Z*)-**19d**	2	O	Bond	63	38	—	—
(*Z*)-**19e**	1	CH_2	CH_2	195	147	—	—
(*Z*)-**19f**	2	CH_2	CH_2	135	48	—	—
(*Z*)-**19g**	2	CH_2	Bond	153	69	—	—

[a] All the experiments were carried out in single.
[b] Histamine-induced skin vascular permeability. % inhibition at 3 mg/kg, po. The mean ± SE of six mice.
[c] Bioavailability in rat.

Table 3
Anti-inflammatory effect of selected compounds in OVA model[a]

Compound	H_1 binding IC_{50} (nM)	OVA[b]	
		ITR (%)	LTR (%)
1	40	73 ± 5	64 ± 4
13a	41	104 ± 17	59 ± 9
13h	70	30 ± 8	46 ± 4
(*Z*)-**19a**	84	105 ± 16	78 ± 9
Fexofenadine	78	61 ± 10	6 ± 24
Ketotifen	1	119 ± 12	3 ± 9

[a] All the experiments were carried out in single.
[b] OVA-induced biphasic cutaneous reaction model. ITR; immediate type reaction. LTR; late type reaction. % inhibition at 10 mg/kg, po. The mean ± SE of six mice.

Anti-histamines often exhibit affinity against various amine receptors, such as serotonin, dopamine, and adrenaline. Compound **1** showed affinity toward adrenaline α_1 receptor with an IC_{50} value of about 430 nM. This means that the difference in compound **1** affinity between H_1 and α_1 receptor is approximately 11 times. On the other hand, the IC_{50} of compounds **13b** and (*Z*)-**19a** toward α_1 receptor were estimated as >10,000 and 4800 nM, respectively. In particular, the margin of **13b** was over 240-fold larger than that of **1**. These results suggest that **13b** with superior selectivity might have a better safety profile.[25]

Finally, we evaluated compound **1**, compound **13b**, Ketotifen, and Fexofenadine H_1 receptor occupancy in the brain. For that we first evaluated the in vivo anti-histaminic activity of these test compounds in mice using histamine-induced skin vascular permeability and calculated the ED_{70} values.[26] Each test compound at its ED_{70} value was then administered to mice, and its H_1 receptor occupancy in the brain was determined. The results for all test compounds are summarized in Table 4. Ketotifen occupied 62% of H_1 receptor in the brain, whereas the occupancy of Fexofenadine was 12%. These occupancy values are in agreement with those reported for human after single oral clinical dose administration.[27,28] Therefore, it is suggested that this animal model is useful for estimation of brain H_1 receptor occupancy in human. Compounds **1** and **13b** occupancy of brain H_1 receptor was 38% and 20%, respectively, suggesting that **13b** side effects in the brain are of the same magnitude as those of Fexofenadine, a 2nd generation anti-histamine.

In summary, we carried out an optimization study of tricyclic carboxylic acid with pyrimidine-dione to identify 3rd generation anti-histaminic agents. The phenothiazine part in **1** could be replaced with various tricyclic components, and we found the dibenzoxazepine **13b** as the most promising compound with both anti-histaminic and anti-inflammatory activities. Compound **13b** occupancy of H_1 receptor in the brain was comparable to that of Fexofenadine, indicating low occurence of side effects. It is therefore believed that **13b** would be an ideal 3rd generation anti-histamine.

3. Experimental section

3.1. Biological assays

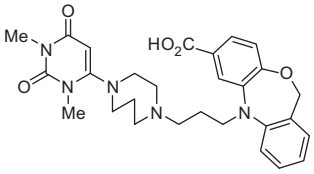
3.1.1. Human H_1 receptor binding assay

Membrane of stable recombinant CHO-K1 cells expressing the human histamine H_1 receptor (Euroscreen) was incubated with various concentrations of test compounds and 1.25 nM [^{3}H]-Pyrilamine in a total of 200 μL of binding buffer (50 mM Tris–HCl, pH 7.5). Nonspecific binding was determined in the presence of 1.25 μM Triprolidine (Sigma). The assay mixture was incubated for 3 h at room temperature and then filtered through GF/B filters. These were washed and counted by a scintillation counter. Specific binding was calculated as the difference between total and non-specific bindings.

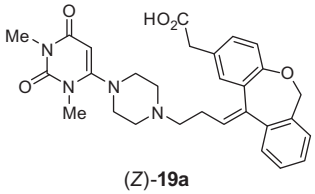
3.1.2. Caco-2 cell permeability

The apical side of Caco-2 cell line monolayer was incubated with test compounds at 37 °C for 120 min. Test compound concentration in the apical side and basal side of the cells was measured, and the permeability coefficient (P_{app}) was calculated by the following equation.

Table 4
Evaluation of selected compounds with side effect factors[a]



13b



(*Z*)-**19a**

Compound	H_1 binding IC_{50} (nM)	α_1 binding IC_{50} (nM)	Ratio[b]	H_1 in vivo[c] ED_{70} (mg/kg)	CNS[d] (%)
1	40	430	11	161 ± 0.31	38 ± 8
13a	41	>10,000	>240	187 ± 0.38	20 ± 4
(*Z*)-**19a**	84	4800	57	—	12 ± 3
Fexofenadine	78	—	—	4.84 ± 0.30	62 ± 7
Ketotifen	1	—	—	0.067 ± 0.003	

[a] All the experiments were carried out in single.
[b] α_1 binding IC_{50}/H_1 binding IC_{50}.
[c] ED_{70} (dose, po for histamine-induced skin vascular permeability 70% inhibition). The mean ± SE of six mice.
[d] Mouse brain H_1 receptor occupancy at ED_{70}. The mean ± SE of six mice.

P_{app} = dC/dt × VR/($A \times C_0$); C_0: initial donor concentration (μM), VR: volume of reserver well (mL), A: membrane surface area (cm^2), dC/dt: slope of the cumulative reserver concentration (μM/s).

3.1.3. Histamine-induced dye leakage into skin in mice

Eight-week old female mice (ddY, SLC) were administered orally with various doses of test compounds suspended in 0.5% methylcellulose 1 h before intradermal injection of histamine (4 mg/site) into the back skin following intravenous injections of Evans' blue solution. Thirty minutes after histamine injection of histamine, the mice were sacrificed and the area of dye was measured.

3.1.4. Pharmacokinetic (PK) studies

Test compounds (1 mg/kg, dissolved in 5% glucose/0.1 N HCl = 9:1) were dosed intravenously to the fasted male rats (n = 3). Test compounds (10 mg/kg, suspended in 0.5% methyl cellulose solution) were dosed orally to the fasted male rats (n = 3). After dosing, blood samples (250 μL) were collected from the jugular vein using a heparinized syringe at the selected time points (iv: pre-dosing, 5, 15, 30 min, 1, 2, 4, 6, 24 h; po: 15, 30 min, 1, 2, 4, 6, and 24 h, respectively). The blood samples were ice-chilled and then centrifuged at 12,000 rpm for 2 min at room temperature to obtain plasma, which was preserved at −70 °C in a freezer. The AUC was obtained by measuring the time course of the plasma concentration of the test compounds. Bioavailability (BA) was calculated according to the following equation.

$$BA(\%) = (AUC_{po}/D_{po})/(AUC_{iv}/D_{iv}) \times 100$$

3.1.5. OVA-induced biphasic allergic reaction in mice skin

Eight-week old female mice (Balb/c, SLC) were sensitized by intraperitoneal injection of OVA with alum. Two week later, test compounds suspended in 0.5% methylcellulose were administered orally to the mice 1 h before intradermal injection of OVA into the ear. Ear swelling was determined 1 h and 24 h after elicitation.

3.1.6. Human α_1 receptor binding assay

Membrane of stable recombinant CHO-K1 cells expressing the human adrenaline α_1 receptor was incubated with various concentrations of test compounds and 0.3 nM [^{3}H]-Prazosin (Amersham Bioscience) in a total of 200 μL of binding buffer (50 mM Tris–HCl, pH 7.6). Nonspecific binding was determined in the presence of 1 μM Prazosin (Wako Pure Chemical Industries, Ltd). The assay mixture was incubated for 30 min at room temperature and then filtered through GF/B filters. These were washed and counted by a scintillation counter. Specific binding was calculated as the difference between total and nonspecific bindings.

3.1.7. Ex vivo H_1 receptor occupancy in mouse brain

After measurement of anti-histamine activity, the brain without the cerebellum was homogenized in 10 mL of 320 mM sucrose and centrifuged for 1 h at 3000 g. The precipitate was then dissolved in 1 mL of 50 mM Tris–HCl buffer (pH 7.4). A sample of this solution at a concentration 2 mg/mL was then incubated for 30 min with 2 nM [^{3}H]-Pyrilamine in a total of 200 μL of binding buffer (50 mM Tris–HCl, pH 7.5). Specific binding was determined as described in Human H_1 receptor binding assay. Percentage of H_1 receptor occupancy was calculated as the ratio to specific binding of the vehicle-treated sample.

3.2. Synthesis

Proton nuclear magentic resonance spectra (^{1}H NMR) were recorded on a Bruker AVANCE 400 spectrometer. All spectra were determined in $CDCl_3$, MeOH-d_4, or DMSO-d_6. Chemical shifts are reported in δ units. Splitting pattern designed as follows: s, singlet; d, doublet, t, triplet; q, quartet; m, multiplet; br s, broad singlet; dd, double doublet; dt, double triplet; and ddt, double double triplet. Elemental analyses and high resolution mass spectrometry were performed by the analytical department of our laboratories as follows. The carbon, hydrogen, and nitrogen elements of organic materials were analyzed by an EA1110 CHN elemental analyzer (CE Instruments) with separation column. High resolution mass spectrometry were carried out using Thermo Fisher SIENTIFIC LTQ Orbitrap Discovery.

3.2.1. Ethyl 4-(2-bromobenzyloxy)-3-nitrobenzoate (3)

A mixture of ethyl 4-hydroxy-3-nitrobenzoate (**2**) (15.2 g, 72 mmol), K_2CO_3 (9.95 g, 72 mmol), and 2-bromobenzylbromide (18 g, 72 mmol) in 2-butanone (200 mL) was refluxed for 21 h. The reaction mixture was poured into water, and the solid was filtered through a filtrate paper. A residual solid was washed with water 2 times, and dried in vacuo to afford the title compound (**3**) as a solid (26.6 g, 97% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 8.56 (1H, d, J = 2.2 Hz), 8.23 (1H, dd, J = 0.6, 7.6 Hz), 7.65 (1H, dd, J = 0.6, 7.6 Hz), 7.60 (1H, dd, J = 1.1, 8.0 Hz), 7.37 (1H, dt, J = 1.1, 7.6 Hz), 7.18–7.23 (2H, m), 5.35 (2H, s), 4.43 (2H, q, J = 7.1 Hz), 1.41 (3H, t, J = 7.1 Hz).

3.2.2. Ethyl 4-(2-bromobenzyloxy)-3-formamidobenzoate (4)

A mixture of (**3**) (26.6 g, 70 mmol), ammonium chloride (3.74 g, 70 mmol), Fe powder (27.3 g), and acetic acid (8.0 mL, 140 mmol) in ethanol (200 mL)/THF (200 mL)/water (10 mL) was refluxed for 4 h. After cooling to room temperature, the reaction mixture was basified with saturated sodium bicarbonate solution, then the mixture was extracted with ethyl acetate 3 times, and the combined extracts were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford ethyl 3-amino-4-(2-bromobenzyloxy)benzoate as a white solid.

The obtained ethyl 3-amino-4-(2-bromobenzyloxy)benzoate and sodium formate (9.7 g, 143 mmol) in formic acid (108 mL) were heated at 100 °C for 2 h. The reaction mixture was poured into water, and the solid was filtered through a filtrate paper. A residual solid was washed with water 2 times, and dried in vacuo to afford the title compound (**4**) as a pale yellow solid (25.8 g, 98% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 9.02 (0.5H, d, J = 2.0 Hz), 8.49 (0.5H, d, J = 1.5 Hz), 7.82–7.94 (2H, m), 7.63–7.66 (1H, m), 7.35–7.46 (2H, m), 6.98–7.03 (1H, m), 5.22–5.27 (2H, m), 4.32–4.40 (2H, m), 1.36–1.41 (3H, m).

3.2.3. Ethyl 5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepine-7-carboxylate (5)

A mixture of (**4**) (25.8 g, 68 mmol), K_2CO_3 (10.4 g, 75 mmol), and Cu powder (2.6 g) in DMF (100 mL) was heated at 155 °C for 5 h. After cooling to room temperature, water was added. The mixture was extracted with ethyl acetate 2 times, and the combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford the title compound (**5**) as a light yellow solid (12.2 g, 66% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.49 (1H, d, J = 2.0 Hz), 7.40 (1H, dd, J = 2.0, 8.3 Hz), 7.22 (1H, dt, J = 1.3, 7.4 Hz), 7.13 (1H, d, J = 7.4 Hz), 6.96 (1H, d, J = 8.3 Hz), 6.85 (1H, dt, J = 0.8, 7.4 Hz), 6.80 (1H, d, J = 8.0 Hz), 6.02 (1H, s), 5.07 (2H, s), 4.37 (2H, q, J = 7.1 Hz), 1.39 (3H, t, J = 7.1 Hz).

3.2.4. Ethyl 5-allyl-5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepine-7-carboxylate (6a)

To a suspension of NaH (55 wt % in oil, 217 mg, 5.0 mmol) in DMF (20 mL) was added (**5**) (1.03 g, 3.8 mmol) at 0 °C. After 20 min, allyl bromide (0.66 mL, 7.6 mmol) was added, and the mixture was stirred for 3 h. H_2O and ethy acetate were added to the reaction mixture, and the mixtrure was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with ethyl acetate 3 times, and the combined extracts were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford the title compound (**6a**) as an oil (1.03 g, 87%yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.79 (1H, d, J = 1.4 Hz), 7.67 (1H, dd, J = 1.5, 7.7 Hz), 7.28 (1H, d, J = 7.8 Hz), 7.04 (1H, dd, J = 1.2, 7.9 Hz), 6.82–6.87 (3H, m), 5.82–5.93 (1H, m), 5.34 (1H, dd, J = 1.4, 17.3 Hz), 5.28 (2H, s), 5.23 (1H, dd, J = 1.4, 10.4 Hz), 4.45–4.47 (2H, m), 4.37 (2H, q, J = 7.1 Hz), 1.39 (3H, t, J = 7.1 Hz).

3.2.5. Methyl 2-(5-allyl-5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepin-7-yl)acetate (6b)

To a solution of (**6a**) (1.03 g, 3.3 mmol) in THF (20 mL) was added 0.95 M DIBAL in hexane (10.5 mL, 10 mmol) at −70 °C. The mixture was stirred at −70 °C for 30 min, and then the mixture was stirred at room temperature for 1 h. H_2O was added to the reaction mixture, and the mixtrure was extracted with ethyl acetate/hexane 3 times, and the combined extracts were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford (5-allyl-5,11-dihydrodibenzo[*b*,*e*]-[1,4]oxazepin-7-yl)methanol as a white solid (0.97 g, 109% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.24–7.31 (2H, m), 7.12 (1H, d, J = 7.7 Hz), 7.00–7.04 (2H, m), 6.73–6.81 (2H, m), 5.87 (1H, dt, J = 5.3, 10.4, 17.3 Hz), 5.32 (1H, dd, J = 1.4, 17.3 Hz), 5.27 (2H, s), 5.21 (1H, dd, J = 1.4, 10.4 Hz), 4.56 (2H, d, J = 5.8 Hz), 4.43 (2H, dt, J = 1.4, 5.3 Hz), 3.49 (1H, d, J = 5.8 Hz).

To a suspension of NaH (55 wt % in oil, 126 mg, 2.9 mmol) in DMF (10 mL) was added (5-allyl-5,11-dihydrodibenzo[*b*,*e*][1,4]-oxazepin-7-yl)methanol (702 mg, 2.6 mmol) in DMF (2.0 mL) with cooling ice/water bath. After stirring for 10 min at room temperature, the mixture was cooled to 0 °C, and methanesulfonyl chloride (305 μL, 3.9 mmol) was added. The mixture was gradually warmed to room temperature, and then KCN (430 mg, 6.6 mmol) was added. The mixture was stirred for 3 days, then heated at 50 °C for 5 h. After cooling to room temperature, H_2O was added to the reaction mixture, and the mixtrure was extracted with ethyl acetate/hexane 3 times, and the combined extracts were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford 2-(5-allyl-5,11-dihydrodibenzo[*b*,*e*]-[1,4]oxazepin-7-yl)acetonitrile as a brown paste (503 mg, 69% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.25–7.31 (2H, m), 7.13 (1H, d, J = 7.8 Hz), 7.04 (1H, dt, J = 0.9, 7.4 Hz), 6.93 (1H, d, J = 2.0 Hz), 6.79 (1H, d, J = 8.2 Hz), 6.69 (1H, dd, J = 2.1, 8.2 Hz), 5.87 (1H, ddt, J = 5.2, 10.4, 17.3 Hz), 5.35 (1H, dd, J = 1.4, 17.3 Hz), 5.26 (2H, s), 5.25 (1H, dd, J = 1.4, 10.4 Hz), 4.42 (2H, dt, J = 1.4, 5.2 Hz), 3.63 (2H, s).

To a solution of 2-(5-allyl-5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepin-7-yl)acetonitrile in THF (4 mL)/MeOH (4 mL) was added 2 N aq NaOH (2 mL), and the mixture was refluxed for 44 h. After cooling to room temperature, the reaction mixture was acidified with 1 N aq HCl. The mixture was concentrated under reduced pressure and the residual mixture was suspended in DMF (20 mL), then K_2CO_3 (470 mg, 3.4 mmol) and iodomethane (2 mL) were added, and the mixture was stirred at room temperature over night. H_2O and ethyl acetate were added to the reaction mixture, and the mixtrure was extracted with ethyl acetate/hexane 3 times, and the combined extracts were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford the title compound (**6b**) as a colorless oil (345 mg, 65% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.23–7.30 (2H, m), 7.11 (1H, d, J = 7.5 Hz), 7.01 (1H, dt, J = 1.0, 7.5 Hz), 6.90 (1H, d, J = 2.0 Hz), 6.76 (1H, d, J = 8.2 Hz), 6.68 (1H, dd, J = 2.0, 8.2 Hz), 5.87 (1H, ddt, J = 5.3, 10,4, 17.3 Hz), 5.31 (1H, dd, J = 1.5, 17.3 Hz), 5.25 (2H, s), 5.21 (1H, dd, J = 1.5, 10.4 Hz), 4.41 (2H, dt, J = 1.5, 5.3 Hz), 3.68 (3H, s), 3.50 (2H, s).

3.2.6. Methyl 2-(5-allyl-5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepin-7-yl)propanoate (6c) and Methyl 2-(5-allyl-5,11-dihydrodibenzo-[*b*,*e*][1,4]oxazepin-7-yl)-2-methylpropanoate (6d)

To a solution of (**6b**) (110 mg, 0.36 mmol) in THF (2 mL) were added potassium *tert*-butoxide (92 mg, 0.82 mmol) and iodomethane (90 μL, 1.44 mmol) at room temperature, and the mixture was stirred for 1 h. H_2O and ethyl acetate were added to the reaction mixture, and the mixtrure was extracted with ethyl acetate/hexane 3 times, and the combined extracts were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel

(AcOEt/hexane) to afford (**6c**) as a pale yellow oil (13 mg, 11% yield) and (**6d**) as a colorless oil (70 mg, 58% yield).

3.2.7. Methyl 2-(5-allyl-5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepin-7-yl)propanoate (6c)

^{1}H NMR ($CDCl_3$, δ ppm): 7.31 (1H, dt, J = 1.6, 8.0 Hz), 7.26 (1H, dd, J = 1.5, 7.4 Hz), 7.14 (1H, d, J = 7.6 Hz), 7.03 (1H, dt, J = 1.0, 7.5 Hz), 6.93 (1H, d, J = 2.0 Hz), 6.77 (1H, d, J = 8.2 Hz), 6.72 (1H, dd, J = 2.0, 8.2 Hz), 5.89 (1H, ddt, J = 5.5, 10.3, 17.3 Hz), 5.34 (1H, ddt, J = 1.4, 1.5, 17.3 Hz), 5.21–5.30 (3H, m), 4.44 (dt, J = 1.4, 5.5 Hz), 3.67 (3H, s), 1.46 (3H, d, J = 7.2 Hz).

3.2.8. Methyl 2-(5-allyl-5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepin-7-yl)-2-methylpropanoate (6d)

^{1}H NMR ($CDCl_3$, δ ppm): 7.23–7.29 (2H, m), 7.12 (1H, d, J = 8.1 Hz), 7.01 (1H, dt, J = 1.0, 7.4 Hz), 6.94 (1H, s), 6.76 (2H, s), 5.85–5.95 (1H, m), 5.33 (1H, dd, J = 1.4, 17.3 Hz), 5.21–5.24 (3H, m), 4.41 (2H, dd, J = 1.4, 5.2 Hz), 3.63 (3H, s), 1.52 (6H, s).

3.2.9. Ethyl 5-allyl-5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepine-3-carboxylate (8)

To a solution of 3-bromo-4-methylbenzoic acid (**7**) (9.66 g, 44.5 mmol) in DMF (60 mL) were added K_2CO_3 (7.7 g, 55.7 mmol) and iodoethane (12.4 g, 80 mmol), and the mixture was stirred for 7 days. H_2O and ethy acetate were added to the reaction mixture, and the mixtrure was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with ethyl acetate, and the combined extracts were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to get ethyl 3-bromo-4-methylbenzoate as a pale brown oil (8.4 g, 78% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 8.20 (1H, d, J = 1.6 Hz), 7.87 (1H, dd, J = 1.6, 7.9 Hz), 7.30 (1H, d, J = 7.9 Hz), 4.36 (2H, q, J = 7.1 Hz), 2.45 (3H, s), 1.39 (3H, t, J = 7.1 Hz).

A mixture of ethyl 3-bromo-4-methylbenzoate (8.4 g, 35 mmol), *N*-bromosuccinimide (6.2 g, 35 mmol), and benzoyl peroxide (0.44 g, 1.8 mmol) in CCl_4 (62 mL) was heated for reflux for 7 h. H_2O and ethy acetate were added to the reaction mixture, and the mixtrure was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with ethyl acetate, and the combined extracts were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford ethyl 3-bromo-4-(bromomethyl)benzoate as a brown oil (11.0 g, 99% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 8.24 (1H, d, J = 1.7 Hz), 7.96 (1H, dd, J = 1.7, 8.0 Hz), 7.53 (1H, d, J = 8.0 Hz), 4.61 (2H, s), 4.39 (2H, q, J = 7.2 Hz), 1.40 (3H, t, J = 7.2 Hz).

To a suspension of ethyl 3-bromo-4-(bromomethyl)benzoate (6.4 g, 20 mmol) in ethanol (60 mL)/DMF (100 mL) were added sodium 2-nitrophenolate (3.2 g, 20 mmol) and tetrabutylammonium bromide (0.50 g, 1.6 mmol), and the mixture was heated at 90 °C for 10 h. The reaction mixture was poured into water, and extracted with ethyl acetate 2 times. The combined extracts were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford ethyl 3-bromo-4-((2-nitrophenoxy)methyl)benzoate as a solid (3.95 g, 52% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 8.26 (1H, d, J = 1.6 Hz), 8.06 (1H, dd, J = 1.6, 8.1 Hz), 7.94 (1H, dd, J = 1.6, 8.1 Hz), 7.82 (1H, d, J = 8.1 Hz), 7.57 (1H, dt, J = 1.6, 8.1 Hz), 7.09–7.16 (2H, m), 5.30 (2H, s), 4.39 (2H, q, J = 7.1 Hz), 1.41 (3H, t, J = 7.1 Hz).

To a suspension of ethyl 3-bromo-4-((2-nitrophenoxy)methyl)benzoate (1.0 g, 2.6 mmol), acetic acid (1.0 mL), and ammonium chloride (200 mg, 3.7 mmol) in THF (10 mL)/ethanol (10 mL)/water (5 mL) was added Fe powder (1.01 g, 16 mmol), and the mixture was heated at 75 °C for 1.5 h. After cooling to room temperature, the reaction mixture was basified with saturated sodium bicarbonate solution, then the mixture was extracted with ethyl acetate 4 times, and the combined extracts were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford ethyl 4-((2-aminophenoxy)methyl)-3-bromobenzoate as a solid (0.92 g, 99% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 8.26 (1H, d, J = 1.6 Hz), 8.00 (1H, dd, J = 1.6, 8.0 Hz), 7.61 (1H, d, J = 8.0 Hz), 6.68–6.84 (4H, m), 5.20 (2H, s), 4.39 (2H, q, J = 7.2 Hz), 3.88 (2H, br s), 1.40 (3H, t, J = 7.2 Hz).

Ethyl 3-bromo-4-((2-formamidophenoxy)methyl)benzoate was synthesized from ethyl 4-((2-aminophenoxy)methyl)-3-bromobenzoate according to the procedure to prepare (**4**) (89% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 8.77 (0.3H, d, J = 11.6 Hz), 8.48 (1H, d, J = 1.7 Hz), 8.40 (0.7H, dd, J = 1.7, 7.7 Hz), 8.28–8.30 (1H, m), 8.00–8.03 (1H, m), 7.72–7.86 (1H, m), 7.50–7.54 (1H, m), 6.98–7.17 (2H, m), 6.88–6.96 (1H, m), 5.23–5.25 (2H, m), 4.40 (2H, q, J = 7.2 Hz), 1.41 (3H, t, J = 7.2 Hz).

Ethyl 5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepine-3-carboxylate was synthesized from ethyl 3-bromo-4-((2-formamidophenoxy)methyl)benzoate according to the procedure to prepare (**5**) (41% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.46 (2H, d, J = 1.2 Hz), 7.14 (1H, d, J = 7.6 Hz), 6.99 (1H, dd, J = 1.3, 7.8 Hz), 6.94 (1H, dt, J = 1.3, 7.6 Hz), 6.74–6.79 (2H, m), 6.12 (1H, s), 5.05 (1H, s), 4.39 (2H, q, J = 7.2 Hz), 1.40 (3H, t, J = 7.2 Hz).

To a suspension of NaH (55 wt % in oil, 44 mg, 1.0 mmol) in DMF (10 mL) was added ethyl 5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepine-3-carboxylate (182 mg, 0.68 mmol) at 0 °C. After stirring for 10 min at room temperature, the mixture was cooled to 0 °C, then allyl bromide (118 μL, 1.4 mmol) was added. The mixture was stirred for 30 min at 0 °C, and stirred for 1 h at room temperature. Water and ethyl acetate were added to the reaction mixture. The mixture was extracted with ethyl acetate 2 times, and the combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford (**8**) as a pale brown oil (195 mg, 93% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.79 (1H, d, J = 1.4 Hz), 7.67 (1H, dd, J = 1.5, 7.7 Hz), 7.28 (1H, d, J = 7.8 Hz), 7.04 (1H, dd, J = 1.2, 7.9 Hz), 6.82–6.87 (3H, m), 5.82–5.93 (1H, m), 5.34 (1H, dd, J = 1.4, 17.3 Hz), 5.23 (1H, dd, J = 1.4, 10.4 Hz), 5.28 (2H, s), 4.45–4.47 (2H, m), 4.37 (2H, q, J = 7.1 Hz), 1.39 (3H, t, J = 7.1 Hz).

3.2.10. 5-(3-(Benzyloxy)propyl)-3-bromo-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (10)

To a suspension of NaH (55 wt % in oil, 253 mg, 5.8 mmol) in DMF (12 mL) was added 3-bromo-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (**9**) (1.4 g, 5.1 mmol) in DMF (12 mL) at 0 °C. After stirring for 10 min at room temperature, the mixture was cooled to 0 °C, and then benzyl 3-bromopropyl ether (1.37 g, 5.8 mmol) was added. The mixture was stirred for 1 h at room temperature, then 10% aq NH_4Cl and ethyl acetate were added to the reaction mixture. The mixture was extracted with ethyl acetate 2 times, and the combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford (**10**) as a colorless oil (1.71 g, 79% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 6.85–7.47 (12H, m), 4.43 (2H, s), 3.80 (2H, t, J = 6.4 Hz), 3.46 (2H, t, J = 6.0 Hz), 2.92–3.10 (4H, m), 1.77–1.92 (2H, m).

3.2.11. Ethyl 5-(3-hydroxypropyl)-5,11-dihydrodibenzo[*b*,*e*][1, 4]oxazepine-7-carboxylate (11a)

To a solution of (**6a**) (0.65 g, 2.0 mmol) in THF (10 mL) was added 1.0 M borane tetrahydrofurane complex in THF (10 mL, 10 mmol) at 0 °C. After stirring for 1.5 h, ice was added to the reaction mixture, then hydrogen peroxide in H_2O (30 wt %, 17 mL) and 2 N aq NaOH (33 mL) were added, and the mixture was stirred for 3 h. Saturated sodium thiosulfate was added, then acidified with 1 N HCl. The mixture was extracted with ethyl acetate 3 times, and the combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford the title compound (**11a**) as a colorless oil (0.49 g, 72% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.72 (1H, d, J = 2.0 Hz), 7.49 (1H, dd, J = 2.0, 8.4 Hz), 7.31–7.37 (2H, m), 7.15 (1H, d, J = 7.6 Hz), 7.09 (1H, t, J = 7.4 Hz), 6.77 (1H, d, J = 8.4 Hz), 5.36 (2H, s), 4.33 (2H, q, J = 7.1 Hz), 3.91 (2H, t, J = 6.7 Hz), 3.72 (2H, dt, J = 5.3, 6.0 Hz), 1.87–1.94 (2H, m), 1.37 (3H, t, J = 7.1 Hz).

3.2.12. Methyl 2-(5-(3-hydroxypropyl)-5,11-dihydrodibenzo[*b*, *e*][1,4]oxazepin-7-yl)acetate (11b)

To a solution of (**6b**) (235 mg, 0.76 mmol) in THF (10 mL) was added 1.0 M borane tetrahydrofurane complex in THF (1.5 mL, 1.5 mmol) at 0 °C. After stirring for 1.5 h, ice was added to the reaction mixture, then hydrogen peroxide in H_2O (30 wt %, 2.5 mL) and 2 N aq NaOH (5 mL) were added, and the mixture was stirred for 3 h. Saturated sodium thiosulfate was added, then acidified with 1 N HCl. The mixture was extracted with ethyl acetate 3 times, and the combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford the title compound (**11b**) as a colorless oil (33 mg, 13% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.27–7.32 (2H, m), 7.12 (1H, d, J = 7.8 Hz), 7.06 (1H, dt, J = 0.9, 7.4 Hz), 6.96 (1H, d, J = 1.8 Hz), 6.70–6.77(2H, m), 5.27 (2H, s), 3.88 (2H, t, J = 6.7 Hz), 3.65–3.71 (2H, m), 3.68 (3H, s), 3.50 (2H, s), 1.87–1.94 (2H, m).

3.2.13. Methyl 2-(5-(3-hydroxypropyl)-5,11-dihydrodibenzo[*b*, *e*][1,4]oxazepin-7-yl)propanoate (11c)

The title compound was synthesized from (**6c**) according to the procedure to prepare (**11b**) (45% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.26–7.33 (2H, m), 7.13 (1H, d, J = 7.5 Hz), 7.04 (1H, dt, J = 1.0, 7.4 Hz), 6.97 (1H, s), 6.67–6.73 (2H, m), 5.29 (1H, d, J = 11.9 Hz), 5.24 (1H, d, J = 11.9 Hz), 3.83–3.95 (2H, m), 3.67–3.74 (2H, m), 3.65 (3H, s), 3.61 (1H, q, J = 7.2 Hz), 1.87–1.91 (2H, m), 1.45 (3H, d, J = 7.2 Hz).

3.2.14. Methyl 2-(5-(3-hydroxypropyl)-5,11-dihydrodibenzo[*b*, *e*][1,4]oxazepin-7-yl)-2-methylpropanoate (11d)

To a solution of (**6d**) (70 mg, 0.21 mmol) in THF (3 mL) was added 0.5 M 9-BBN in THF (0.8 mL, 0.40 mmol) at 0 °C. After 10 min, the reaction mixture was warmed to room temperature. After stirring for 1.5 h, water was added to the reaction mixture, then hydrogen peroxide in H_2O (30 wt %, 1 mL) and 2 N aq NaOH (2 mL) were added, and the mixture was stirred for 3 h. Saturated sodium thiosulfate was added, then acidified with 1 N HCl. The mixture was extracted with ethyl acetate 3 times, and the combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford the title compound (**11d**) as a colorless oil (53 mg, 72% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.32 (1H, dt, J = 1.4, 7.7 Hz), 7.26–7.28 (1H, m), 7.13 (1H, d, J = 8.0 Hz), 7.05 (1H, dt, J = 0.9, 7.4 Hz), 6.98 (1H, d, J = 2.2 Hz), 6.79 (1H, dd, J = 2.2, 7.2 Hz), 6.73 (1H, d, J = 7.2 Hz), 5.27 (2H, s), 3.87 (2H, d, J = 6.7 Hz), 3.71 (2H, dt, J = 5.6, 5.9 Hz), 3.64 (3H, s), 1.86–1.92 (2H, m), 1.54 (6H, s).

3.2.15. Ethyl 5-(3-hydroxypropyl)-5,11-dihydrodibenzo[*b*,*e*][1, 4]oxazepine-3-carboxylate (11e)

To a solution of (**8**) (195 mg, 0.63 mmol) in THF (7.5 mL) was added boran tetrahydrofuran complex in THF (2 M, 1.0 mL, 2.0 mmol) with cooling ice/water bath. After 10 min, the reaction mixture was warmed to room temperature. After stirring for 1.5 h, water was added to the reaction mixture, then hydrogen peroxide in H_2O_2 (30 wt %, 5 mL) and 2 N aq NaOH (5 mL) were added, and the mixture was stirred for 1 h. Saturated sodium thiosulfate was added, then acidified with 1 N HCl. The mixture was extracted with ethyl acetate 3 times, and the combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford the title compound (**11e**) as a colorless oil (152 mg, 74% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.78 (1H, d, J = 1.4 Hz), 7.70 (1H, dd, J = 1.5, 7.7 Hz), 7.31 (1H, d, J = 7.8 Hz), 7.06 (1H, d, J = 7.7 Hz), 6.83–6.88 (3H, m), 5.32 (2H, s), 4.38 (2H, q, J = 7.1 Hz), 3.94 (2H, t, J = 6.6 Hz), 3.71 (2H, dt, J = 5.4, 6.0 Hz), 1.91 (2H, tt, J = 6.0, 6.6 Hz), 1.39 (3H, t, J = 7.1 Hz).

3.2.16. Methyl 5-(3-hydroxypropyl)-10,11-dihydro-5*H*-dibenzo-[*b*,*f*]azepine-3-carboxylate (11f)

A mixture of (**10**) (400 mg, 0.95 mmol) and CuCN (851 mg, 9.5 mmol) in DMF (6 mL) was refluxed for 6 h. After cooling to the room temperature, the reaction mixture was poured into 33% aq NH_3 solution and extracted with toluene for 2 times, and the combined extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to get 5-(3-(benzyloxy)propyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-3-carbonitrile as a colorless oil (309 mg, 88% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 6.93–7.33 (12H, m), 4.44 (2H, s), 3.77 (2H, t, J = 6.4 Hz), 3.40 (2H, t, J = 6.0 Hz), 2.96–3.10 (4H, m), 1.77–1.93 (2H, m).

A suspension of 5-(3-(benzyloxy)propyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-3-carbonitrile (300 mg, 0.81 mmol) in concd HCl was refluxed for 15 h, and the solvent were removed under reduced pressure. The residual paste was dissolved in MeOH (10 mL), and concd H_2SO_4 (0.5 mL) was added. The mixture was refluxed for 3 h. After cooling to the room temperature, the reaction mixture was poured into satd $NaHCO_3$, and the mixture was extracted with ethyl acetate 3 times. The combined extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford (**11f**) as a colorless oil (220 mg, included unknown impurity).

^{1}H NMR ($CDCl_3$, δ ppm): 7.74 (1H, d, J = 1.6 Hz), 7.54 (1H, dd, J = 1.6, 7.6 Hz), 7.08–7.18 (4H, m), 6.94 (1H, dt, J = 1.6, 7.6 Hz), 3.82–3.94 (5H, m), 3.67 (2H, t, J = 6.4 Hz), 3.12–3.22 (4H, m), 1.79–1.85 (2H, m).

3.2.17. Methyl 2-(5-(3-hydroxypropyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-3-yl)acetate (11g)

To a suspension of NaH (55 wt % in oil, 74 mg, 1.7 mmol) in THF (5 mL) was added dimethylmalonate (343 mg, 2.6 mmol) in THF (2 mL) at 0 °C. After stirring for 10 min, (**10**) (363 mg, 0.86 mmol), tris (dibenzylideneacetone) dipalladium (0) (37 mg, 0.04 mmol) and tri-*tert*-butylphosphine (32 mg, 0.16 mmol) were added, and the mixture was reflux for 7 h. Aqueous 10% NH_4Cl and ethyl acetate were added to the reaction mixture. The mixture was extracted with ethyl acetate 2 times, and the combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was

removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford dimethyl 2-(5-(3-(benzyloxy)propyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-3-yl)malonate as a colorless oil (dimethylmalonate was included as impurity).

^{1}H NMR ($CDCl_3$, δ ppm): 7.18–7.32 (5H, m), 7.02–7.12 (5H, m), 6.87–6.93 (2H, m), 4.55 (1H, s), 4.42 (2H, s), 3.84 (2H, t, J = 6.4 Hz), 3.69 (6H, s), 3.47 (2H, t, J = 6.4 Hz), 2.98–3.08 (4H, m), 1.82–1.88 (2H, m).

To a solution of dimethyl 2-(5-(3-(benzyloxy)propyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-3-yl)malonate (ca. 0.86 mmol) in MeOH (10 mL) was added 1 N aq NaOH (10 mL), then the mixture was refluxed for 3 h. Half volume of the solvent was removed under reduced pressure, and the residual solution was acidified with 3 N aq HCl around pH 2. 1,4-Dioxane (10 mL) was added, and the mixture was refluxed for 4 h. The reaction mixture was concentrated under reduced pressure. The residual paste was dissolved in MeOH, and concd H_2SO_4 was added and the mixture was refluxed for 10 min. The reaction mixture was poured into satd $NaHCO_3$ and extracted with ethyl acetate 3 times. The combined extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford methyl 2-(5-(3-(benzyloxy)propyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-3-yl)acetate as a colorless oil (dimethylmalonate was included as impurity).

^{1}H NMR ($CDCl_3$, δ ppm): 7.18–7.32 (5H, m), 7.04–7.15 (3H, m), 6.99 (1H, d, J = 7.6 Hz), 6.96 (1H, t, J = 1.6 Hz), 6.91 (1H, dt, J = 1.6, 7.2 Hz), 6.79 (1H, dd, J = 1.6, 7.6 Hz), 4.42 (2H, s), 3.84 (2H, t, J = 6.4 Hz), 3.64 (3H, s), 3.52 (2H, s), 3.47 (2H, t, J = 6.4 Hz), 2.99–3.08 (4H, m), 1.82–1.88 (2H, m).

A mixture of methyl 2-(5-(3-(benzyloxy)propyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-3-yl)acetate (0.86 mmol) and 10% Pd/C (60 mg) in MeOH (3 mL)/THF (6 mL) was stirred under hydrogen atomosphere for 8 h. The reaction mixture was filtered and the filtrate was concentrated. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford (**11g**) as a colorless oil (200 mg, 71% yield from (**10**) in 3 steps).

^{1}H NMR ($CDCl_3$, δ ppm): 7.07–7.15 (3H, m), 6.98–7.03 (2H, m), 6.91 (1H, dt, J = 1.6, 7.2 Hz), 6.80 (1H, dd, J = 1.6, 7.6 Hz), 3.85 (2H, t, J = 6.8 Hz), 3.58–3.73 (5H, m), 3.54 (2H, s), 3.01–3.21(4H, m), 1.77–1.88 (2H, m), 1.45 (1H, t, J = 6.8 Hz).

3.2.18. Methyl 2-(5-(3-hydroxypropyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-3-yl)-2-methylpropanoate (11h)

To a solution of methylisobutlate (229 μL, 2.0 mmol) in toluene (10 mL) was added 1.0 M LiHMDS in hexane (4 mL, 4.0 mmol), then (**10**) (420 mg, 0.99 mmol), tri-*tert*-butylphosphine (59 mg, 0.29 mmol), and tris (dibenzylideneacetone) dipalladium (0) (128 mg, 0.14 mmol) were added, and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into 1 N aq HCl, and the mixture was extracted with ethyl acetate 3 times, and the combined extracts were washed with satd $NaHCO_3$ and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford the methyl 2-(5-(3-(benzyloxy)propyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-3-yl)-2-methylpropanoate as a colorless oil (267 mg, 61% yield). (methylisobutylate was included as impurity).

^{1}H NMR ($CDCl_3$, δ ppm): 7.18–7.29 (5H, m), 7.04–7.15 (3H, m), 6.97–7.02 (2H, m), 6.90 (1H, dt, J = 1.2, 7.2 Hz), 6.84 (1H, dd, J = 2.0, 8.0 Hz), 4.42 (2H, s), 3.84 (2H, t, J = 6.4 Hz), 3.60 (3H, s), 3.47 (2H, t, J = 6.4 Hz), 3.00–3.08 (4H, m), 1.80–1.85 (2H, m), 1.52 (6H, s).

Compound (**11h**) was synthesized from methyl 2-(5-(3-(benzyloxy)propyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-3-yl)-2-methylpropanoate according to the procedure to prepare (**11g**) (>99% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.00–7.16 (5H, m), 6.92 (1H, dt, J = 1.2, 7.2 Hz), 6.86 (1H, dd, J = 2.0, 8.0 Hz), 3.85 (2H, t, J = 6.4 Hz), 3.66 (2H, t, J = 6.4 Hz), 3.62 (3H, s), 3.08–3.16 (4H, m), 1.78–1.83 (2H, m), 1.41 (6H, s).

3.2.19. 5-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl)propyl)-5,11-dihydrodibenzo[*b*, *e*][1,4]oxazepine-7-carboxylic acid (13b)

To a solution of (**11a**) (2.47 g, 7.5 mmol) in CH_2Cl_2 (52 mL) were added methanesulfonyl chloride (2.9 mL, 37.5 mmol), pyridine (3.1 mL, 38 mmol), and 4-dimethylaminopyridine (10 mg), then the mixture was stirred for 45 min at 0 °C and for 1 h at room temperature. Water and ethyl acetate were added. The mixture was extracted with ethyl acetate 3 times, and the combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was dissolved in THF (30 mL)/isopropanol (6 mL)/DMF (10 mL), and KI (1.25 g, 7.5 mmol), diisopropylethylamine (3.9 mL, 22 mmol), (**12b**) (3.60 g, 16 mmol) were added. The mixture was stirred at 90 °C for 3 h and at 100 °C for 1 h. After cooling to room temperature, H_2O, ethyl acetate, and chloroform were added to the reaction mixture. The mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extraxted with $CHCl_3$ 3 times, and the combined extractes were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford ethyl 5-(3-(4-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl)propyl)-5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepine-7-carboxylate (3.77 g, 91% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.71 (1H, d, J = 1.7 Hz), 7.48 (1H, dd, J = 1.5, 8.4 Hz), 7.31–7.39 (2H, m), 7.05–7.15 (2H, m), 6.77 (1H, d, J = 8.4 Hz), 5.35 (2H, s), 5.18 (1H, s), 4.33 (2H, q, J = 7.0 Hz), 3.84 (2H, t, J = 6.6 Hz), 3.33 (3H, s), 3.31 (3H, s), 3.06–3.21 (4H, m), 2.61–2.67 (4H, m), 2.55 (2H, t, J = 7.1 Hz), 1.77–1.90 (4H, m), 1.37 (3H, t, J = 7.0 Hz).

To a solution of ethyl 5-(3-(4-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl)propyl)-5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepine-7-carboxylate (3.77 g, 6.9 mmol) in MeOH (10 mL)/THF (30 mL) was added 2 N aq NaOH. The mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the reaction mixture was neutralized with 1 N aq HCl, then the mixture was concentrated in reduced pressure. The residual solid was chromatographed on silica gel (MeOH/$CHCl_3$) to afford the title compound (**13b**) as a white solid (2.67 g, 75% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 7.64 (1H, d, J = 1.5 Hz), 7.35–7.44 (3H, m), 7.27 (1H, d, J = 7.9 Hz), 7.09 (1H, t, J = 7.3 Hz), 6.76 (1H, d, J = 8.4 Hz), 5.35 (2H, s), 5.04 (1H, s), 3.80 (2H, t, J = 6.4 Hz), 3.21 (3H, s), 3.10–3.21 (4H, m), 3.10 (3H, s), 2.45–2.65 (6H, m), 1.69–1.75 (4H, m). ^{13}C NMR (DMSO-d_6, δ ppm): 167.7, 162.3, 160.2, 153.0, 152.6, 150.7, 135.5, 131.6, 130.0, 129.2, 124.6, 124.1, 123.6, 121.3, 121.1, 119.1, 85.5, 69.2, 55.5, 54.9, 53.6, 52.6, 51.4, 47.8, 34.6, 27.5, 26.9, 25.2. Anal. Calcd for $C_{28}H_{33}N_5O_5 \cdot 1.5H_2O$: C, 61.52; H, 6.64; N, 12.81. Found: C, 61.53; H, 6.40; N, 12.67. HRMS (ESI+) calcd for $C_{28}H_{34}N_5O_5$ ($M+H^+$): 520.2554, found: 520.2544.

3.2.20. 5-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)propyl)-5,11-dihydrodibenzo[*b*,*e*][1, 4]oxazepine-7-carboxylic acid (13a)

The title compound was synthesized from (**11a**) and (**12a**) according to the procedure to prepare (**13b**) (41% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 7.63 (1H, d, J = 1.7 Hz), 7.35–7.45 (3H, m), 7.28 (1H, d, J = 7.7 Hz), 7.10 (1H, t, J = 7.1 Hz), 6.77 (1H, d, J = 8.4 Hz), 5.37 (2H, s), 5.14 (1H, s), 3.80 (2H, t, J = 6.6 Hz), 3.24 (3H, s), 3.11 (3H, s), 2.83–2.97 (4H, m), 2.33–2.51 (6H, m), 1.67–1.78 (2H, m). Anal. Calcd for $C_{27}H_{31}N_5O_5 \cdot 1.0H_2O$: C, 61.94;

H, 6.35; N, 13.38. Found: C, 61.76; H, 6.18; N, 13.23. HRMS (ESI+) calcd for $C_{27}H_{32}N_5O_5$ (M+H$^+$): 506.2398, found: 506.2388.

3.2.21. 2-(5-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)propyl)-5,11-dihydrodibenzo[*b*, *e*][1,4]oxazepin-7-yl)acetic acid (13c)

The title compound was synthesized from (**11b**) and (**12a**) according to the procedure to prepare (**13b**) (47% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 7.34–7.39 (2H, m), 7.15–7.27 (1H, m), 7.06 (1H, t, J = 7.4 Hz), 6.95 (1H, s), 6.61–6.69 (2H, m), 5.25 (2H, s), 5.12 (1H, s), 3.75 (2H, t, J = 6.6 Hz), 3.42 (2H, s), 3.23 (3H, s), 3.11 (3H, s), 2.80–2.92 (4H, m), 2.32–2.47 (6H, m), 1.67–1.77 (2H, m). Anal. Calcd for $C_{28}H_{33}N_5O_5\cdot2.0H_2O$: C, 60.52; H, 6.71; N, 12.60. Found: C, 60.63; H, 6.34; N, 12.27. HRMS (ESI+) calcd for $C_{28}H_{34}N_5O_5$ (M+H$^+$): 520.2554, found: 520.2543.

3.2.22. 2-(5-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl)propyl)-5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepin-7-yl)acetic acid (13d)

The title compound was synthesized from (**11b**) and (**12b**) according to the procedure to prepare (**13b**) (29% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 7.33–7.38 (2H, m), 7.20 (1H, d, J = 7.5 Hz), 7.05 (1H, t, J = 7.4 Hz), 6.96 (1H, s), 6.60–6.70 (2H, m), 5.23 (2H, s), 5.04 (1H, s), 3.75 (2H, br s), 3.21 (3H, s), 3.10 (3H, s), 3.05–3.30 (6H, m), 2.44–2.60 (6H, m), 1.65–1.78 (4H, m). Anal. Calcd for $C_{29}H_{35}N_5O_5\cdot1.25H_2O$: C, 62.63; H, 6.80; N, 12.59. Found: C, 62.31; H, 6.65; N, 12.56. HRMS (ESI+) calcd for $C_{29}H_{36}N_5O_5$ (M+H$^+$): 534.2711, found: 534.2699.

3.2.23. 2-(5-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl)propyl)-5,11-dihydrodibenzo[*b*,*e*][1,4]oxazepin-7-yl)propanoic acid (13e)

The title compound was synthesized from (**11c**) and (**12b**) according to the procedure to prepare (**13b**) (73% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 7.34–7.38 (2H, m), 7.13–7.28 (1H, m), 7.05 (1H, t, J = 7.3 Hz), 6.96 (1H, s), 6.63–6.69 (2H, m), 5.20–5.26 (2H, m), 3.76 (2H, br s), 3.45–3.60 (1H, m), 3.20 (3H, s), 3.10–3.20 (4H, m), 3.10 (3H, s), 2.40–2.60 (6H, m), 1.64–1.78 (4H, m), 1.30 (3H, d, J = 7.0 Hz). HRMS (ESI+) calcd for $C_{30}H_{38}N_5O_5$ (M+H$^+$): 548.2867, found: 548.2851.

3.2.24. 2-(5-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl)propyl)-5,11-dihydrodibenzo-[*b*,*e*][1,4]oxazepin-7-yl)-2-methylpropanoic acid (13f)

The title compound was synthesized from (**11d**) and (**12b**) according to the procedure to prepare (**13b**) (54% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 12.21 (1H, br s), 10.43 (1H, br s), 7.37–7.43 (1H, m), 7.23–7.28 (1H, m), 7.18 (1H, d, J = 7.4 Hz), 7.12 (1H, d, J = 7.3 Hz), 6.97 (1H, d, J = 1.7 Hz), 6.79 (1H, dd, J = 1.9, 8,4 Hz), 6.68 (1H, s, d, J = 8.4 Hz), 5.29 (2H, s), 5.14 (1H, s), 3.82 (2H, t, J = 6.1 Hz), 3.25 (3H, s), 3.13–3.28 (4H, m), 3.12 (3H, s), 2.43–2.57 (6H, m), 1.94–2.11 (4H, m), 1.45 (6H, s). HRMS (ESI+) calcd for $C_{31}H_{40}O_5N_5$ (M+H$^+$): 562.3024, found: 562.3000.

3.2.25. 5-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl)propyl)-5,11-dihydrodibenzo[*b*, *e*][1,4]oxazepine-3-carboxylic acid (13g)

The title compound was synthesized from (**11e**) and (**12b**) according to the procedure to prepare (**13b**) (44% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 7.71 (1H, d, J = 1.2 Hz), 7.62 (1H, dd, J = 1.4, 7.7 Hz), 7.49 (1H, d, J = 7.8 Hz), 7.13 (1H, dd, J = 1.3, 8.1 Hz), 6.78–6.89 (2H, m), 6.75 (1H, dd, J = 1.8, 7.9 Hz), 5.32 (2H, s), 5.12 (1H, s), 3.82 (2H, t, J = 6.6 Hz), 3.23 (3H, s), 3.11 (3H, s), 2.84–2.92 (4H, m), 2.34–2.48 (6H, m), 1.67–1.78 (2H, m). Anal. Calcd for $C_{28}H_{33}N_5O_5$: C, 64.72; H, 6.40; N, 13.48. Found: C, 64.36; H, 6.42; N, 13.42. HRMS (ESI+) calcd for $C_{28}H_{34}N_5O_5$ (M+H$^+$): 520.2554, found: 520.2547.

3.2.26. 5-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl)propyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-3-carboxylic acid (13h)

To a mixture of (**11f**) (220 mg, included unknown impurity, ca. 0.51 mmol) and triethylamine (279 μL, 2.0 mmol) in dichloromethane was added methanesulfonyl chloride (154 μL, 2.0 mmol) at 0 °C, and the mixture was stirred for 1 h. Lithium bromide (430 mg, 2.0 mmol) was added to the reaction mixture, and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into satd $NaHCO_3$ and extracted with ethyl acetate 3 times, and the combined extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (AcOEt/hexane) to afford methyl 5-(3-bromopropyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-3-carboxylate as a colorless oil (72 mg, 23% yield form (**10**) in 3 steps).

^{1}H NMR ($CDCl_3$, δ ppm): 7.73 (1H, d, J = 1.2 Hz), 7.56 (1H, dd, J = 1.6, 7.6 Hz), 7.07–7.18 (4H, m), 6.95 (1H, dt, J = 1.2, 7.2 Hz), 3.93 (2H, t, J = 6.4 Hz), 3.88 (3H, s), 3.34 (2H, t, J = 6.4 Hz), 3.12–3.22 (4H, m), 2.05–2.14 (2H, m).

The title compound (**13h**) was synthesized from methyl 5-(3-bromopropyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-3-carboxylate and (**12b**) according to the procedure to prepare (**13b**) (38% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 7.65 (1H, d, J = 1.2 Hz), 7.45 (1H, dd, J = 1.6, 7.6 Hz), 7.10–7.22 (4H, m), 6.92–6.97 (1H, m), 5.03 (1H, s), 3.77 (2H, t, J = 6.4 Hz), 3.05–3.20 (14H, m), 2.45–2.78 (6H, m), 1.72–1.83 (2H, br s), 1.57–1.68 (2H, br s). Anal. Calcd for $C_{29}H_{35}N_5O_4\cdot1.0H_2O$: C, 65.03; H, 6.96; N, 13.07. Found: C, 65.16; H, 6.90; N, 13.10. HRMS (ESI+) calcd for $C_{29}H_{36}N_5O_4$ (M+H$^+$): 518.2762, found: 518.2754.

3.2.27. 2-(5-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl)propyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-3-yl)acetic acid (13i)

The title compound was synthesized from (**11g**) and (**12b**) according to the procedure to prepare (**13b**) (55% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 6.97–7.15 (4H, m), 6.88–6.95 (2H, m), 6.79 (1H, br. d, J = 7.6 Hz), 5.06 (1H, s), 3.72 (2H, t, J = 6.0 Hz), 3.51 (2H, s), 2.53–3.25 (20H, m), 1.60–2.00 (4H, br s). Anal. Calcd for $C_{30}H_{37}N_5O_4\cdot1.5H_2O$: C, 64.50; H, 7.22; N, 12.54. Found: C, 64.58; H, 7.02; N, 12.64. HRMS (ESI+) calcd for $C_{30}H_{38}N_5O_4$ (M+H$^+$): 532.2918, found: 532.2904.

3.2.28. 2-(5-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl)propyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-3-yl)-2-methylpropanoic acid (13j)

The title compound was synthesized from (**11h**) and (**12b**) according to the procedure to prepare (**13b**) (49% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 6.98–7.18 (5H, m), 6.86–6.95 (2H, m), 5.07 (1H, br s), 3.74 (2H, br s), 3.00–3.23 (14H, m), 2.40–2.74 (6H, m), 1.53–1.90 (4H, m), 1.43 (6H, s). Anal. Calcd for $C_{32}H_{41}N_5O_4\cdot2.0H_2O$: C, 64.51; H, 7.61; N, 11.75. Found: C, 64.43; H, 7.24; N, 11.68. HRMS (ESI+) calcd for $C_{32}H_{42}N_5O_4$ (M+H$^+$): 560.3231, found: 560.3220.

3.2.29. 3-(2-Bromodibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)propan-1-ol (15a)

To a suspension of 3-(tetrahydro-2*H*-pyrane-2-yl)oxypropyltriphenylphosphonium bromide (503 mg, 1.03 mmol) in THF (3.5 mL) was added *n*-BuLi (0.61 mL, 1.58 M in hexane, 0.97 mmol) at 0 °C, then the mixture was stirred for 1 h. (**14a**) (100 mg, 0.346 mmol) was added to the prepared solution, and the mixture was refluxed for 15 min. After cooling to room temperature, water

was added, and the mixture was extracted with ethyl acetate. The organic extract was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residual paste was purified by silica gel column chromatography (AcOEt/hexane) to afford 2-bromo-11-(3-(tetrahydro-2*H*-pyran-2-yloxy)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepine (142 mg, 99% yield) as a colorless oil. The ration of (*Z*)- and (*E*)-isomer was 2:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.21–7.43 (6H, m), 6.71 (0.67H, d, J = 8.8 Hz), 6.63 (0.33H, d, J = 8.6 Hz), 6.08 (0.33H, t, J = 7.5 Hz), 5.77 (0.67H, t, J = 7.5 Hz), 4.73–5.70 (2H, br s), 4.53–4.64 (1H, m), 3.81–3.92 (2H, m), 3.49–3.57 (2H, m), 2.70–2.73 (1.33H, m), 2.41–2.48 (0.67H, m), 1.51–1.84 (6H, m).

A mixture of 2-bromo-11-(3-(tetrahydro-2*H*-pyran-2-yloxy)-propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepine (259 mg, 0.624 mmol) and *p*-toluenesulfonic acid monohydrate (2.3 mg, 0.012 mmol) in methanol (6 mL) was refluxed for 4 h. Saturated $NaHCO_3$ and ethyl acetate were added at room temperature, and the mixture was separated into an aqueous layer and an organic layer. The organic layer was washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane) to give the title compound (**15a**) (189 mg, 92% yield) as colorless oil. The ration of (*Z*)- and (*E*)-isomer was 2:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.21–7.36 (6H, m), 6.73 (0.67H, d, J = 8.7 Hz), 6.63 (0.33H, d, J = 8.7 Hz), 6.08 (0.33H, t, J = 7.5 Hz), 5.77 (0.67H, t, J = 7.4 Hz), 4.63–5.51 (2H, br s), 3.72–3.83 (2H, m), 2.67–2.72 (1.33H, m), 2.42–2.47 (0.67H, m).

3.2.30. 1-(3-(2-Bromodibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)propyl)-4-methylpiperazine (16a)

To a mixture of (**15a**) (1.04 g, 3.14 mmol) and triethylamine (1.31 mL, 9.42 mmol) in THF (30 mL) was added methanesulfonic anhydride (1.64 g, 9.42 mmol). After stirring for 30 min, the reaction mixture was diluted with ethyl acetate, then the mixture was washed with satd $NaHCO_3$ 5 times and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure.

The residue was dissolved to acetonitrile (45 mL), and 1-methylpiperazine (0.695 mL, 6.28 mmol), K_2CO_3 (866 mg, 6.28 mmol) and KI (1.04 g, 6.28 mmol) were added, and the mixture was refluxed for 4.5 h. After cooling to room temperature, satd $NaHCO_3$ was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1:20) to give title compound (1.00 g, 77% yield) as a colorless oil.

The ration of (*Z*)- and (*E*)-isomer was 7:3, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.19–7.38 (6H, m), 6.81 (0.67H, d, J = 8.7 Hz), 6.62 (0.33H, d, J = 8.7 Hz), 6.01 (0.33H, t, J = 7.4 Hz), 5.70 (0.67H, t, J = 7.3 Hz), 4.50–5.58 (2H, br s), 2.31–2.63 (12H, m), 2.28 (2H, s), 2.26 (1H, s).

3.2.31. 1-(3-(2-Bromodibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)propyl)-4-methyl-1,4-diazepane (16b)

The title compound was prepared from (**15a**) and *N*-methyl homopiperazine by same procedure to prepare (**16a**) (179 mg, 74% yield). The ration of (*Z*)- and (*E*)-isomer was 7:3, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.13–7.38 (6H, m), 6.97 (0.7H, d, J = 8.8 Hz), 6.67 (0.3H, d, J = 8.8 Hz), 6.00 (0.3H, t, J = 7.2 Hz), 5.69 (0.7H, t, J = 7.2 Hz), 4.54–5.59 (2H, br s), 2.46–2.80 (12H, m), 2.26–2.34 (3H, m), 1.71–1.82 (2H, m).

3.2.32. Methyl 2-(11-(3-(4-methylpiperazin-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetate (17a)

The title compound was synthesized from (**16a**) according to the procedure to prepare (**11g**) (69% yield). The ration of (*Z*)- and (*E*)-isomer was 6:4, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.03–7.39 (6H, m), 6.79 (0.6H, d, J = 8.2 Hz), 6.71 (0.4H, d, J = 8.3 Hz), 6.00 (0.4H, t, J = 7.3 Hz), 5.68 (0.6H, t, J = 7.1 Hz), 4.40–5.50 (2H, br s), 3.52–3.87 (5H, m), 2.27 (1.8H, s), 2.25 (1.2H, s), 2.21–2.62 (12H, m).

3.2.33. Methyl 2-(11-(3-(4-methyl-1,4-diazepan-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetate (17b)

The title compound was synthesized from (**16b**) according to the procedure to prepare (**11g**) (>71% yield). The ration of (*Z*)- and (*E*)-isomer was 7:3, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 6.98–7.36 (6H, m), 6.78 (0.7H, d, J = 8.4 Hz), 6.69 (0.3H, d, J = 8.4 Hz), 5.99 (0.3H, t, J = 7.2 Hz), 5.67 (0.7H, t, J = 7.2 Hz), 4.60–5.40 (2H, br s), 3.67 (0.9H, s), 3.65 (2.1H, s), 3.51 (0.6H, s), 3.50 (1.4H, s), 2.50–2.75 (11.3H, m), 2.30–2.32(3.7H, m), 1.72–1.83 (2H, m).

3.2.34. Methyl 2-(11-(3-(piperazin-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetate (18a)

A mixture of (**17a**), triethylamine (0.318 mL, 2.29 mmol), 2,2,2-trichloroethyl chloroformate (0.612 mL, 4.59 mmol) in toluene (10 mL) was heated at 80 °C for 1 h. The reaction mixture was diluted with ethyl acetate, and washed with satd $NaHCO_3$ and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane) to give 2,2,2-trichloroethyl 4-(3-(2-(2-methoxy-2-oxoethyl)dibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)propyl)-piperazine-1-carboxylate (430 mg, 67% yield) as an yellow oil.

^{1}H NMR ($CDCl_3$, δ ppm): 7.04–7.36 (6H, m), 6.80 (0.6H, d, J = 8.7 Hz), 6.72 (0.4H, d, J = 8.3 Hz), 6.01 (0.4 H, t, J = 7.3 Hz), 5.69 (0.6H, t, J = 7.1 Hz), 4.87–5.61 (2H, br s), 4.74 (1.2H, s), 4.73 (0.8H, s), 3.48–3.88 (9H, m), 2.32–2.77 (8H, m).

A mixture of 2,2,2-trichloroethyl 4-(3-(2-(2-methoxy-2-oxoethyl)dibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)propyl)piperazine-1-carboxylate (430 mg, 0.758 mmol) and Zn powder (396 mg, 6.06 mmol) in AcOH (3 mL) was heated at 70 °C for 20 min. The reaction mixture was poured into aq $NaHCO_3$, and the mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$/aq NH_3 = 1:50:0 to 1:10:0.1) to give the title compound (**18a**) (274 mg, 92% yield) as a pale yellow oil. The ration of (*Z*)- and (*E*)-isomer was 6:4, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.03–7.33 (6H, m), 6.80 (0.6H, d, J = 8.4 Hz), 6.71 (0.4H, d, J = 8.4 Hz), 6.00 (0.4H, t, J = 7.3 Hz), 5.68 (0.6H, t, J = 7.2 Hz), 4.55–5.58 (2H, br s), 3.52–3.74 (5H, m), 2.93–3.00 (4H, m), 2.34–2.61 (8H, m).

3.2.35. Methyl 2-(11-(3-(1,4-diazepan-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetate (18b)

2,2,2-Trichloroethyl 4-(3-(2-(2-methoxy-2-oxoethyl)dibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)propyl)-1,4-diazepane-1-carboxylate was synthesized from (**17b**) according to the procedure to prepare 2,2,2-trichloroethyl 4-(3-(2-(2-methoxy-2-oxoethyl)dibenzo[*b*,*e*]-oxepin-11(6*H*)-ylidene)propyl)piperazine-1-carboxylate (82% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 6.99–7.38 (6H, m), 6.78 (0.7H, d, J = 8.0 Hz), 6.69 (0.3H, d, J = 8.4 Hz), 5.99 (0.3H, t, J = 7.2 Hz), 5.67 (0.7H, t, J = 7.2 Hz), 4.80–5.55 (2H, br s), 4.74–4.77 (2H, m), 3.68–3.71 (3H, m), 3.45–3.57 (6H, m), 2.50–2.74 (7.3H, m), 2.28–2.33 (0.7H, m), 2.30–2.32(3H, m), 1.75–1.87 (2H, m).

The title compound (**18b**) was synthesized from 2,2,2-trichloroethyl 4-(3-(2-(2-methoxy-2-oxoethyl)dibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)propyl)-1,4-diazepane-1-carboxylate according to the procedure to prepare (**18a**) (96% yield). The ration of (*Z*)- and (*E*)-isomer was 7:3, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 6.98–7.34 (6H, m), 6.78 (0.7H, d, J = 8.4 Hz), 6.69 (0.3H, d, J = 8.4 Hz), 6.00 (0.3H, t, J = 7.2 Hz), 5.68 (0.7H, t, J = 7.2 Hz), 4.60–5.40 (2H, br s), 3.68 (0.9H, s), 3.66 (2.1H, s), 3.48 (0.6H, s), 3.46 (1.4H, s), 2.78–2.91 (4H, m), 2.51–2.69 (7.3H, m), 2.28–2.34(0.7H, m), 1.66–1.77 (2H, m).

3.2.36. Methyl 11-(3-(4-methylpiperazin-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepine-2-carboxylate (17c)

Compound (**16a**) (990 mg, 2.4 mmol), $PdCl_2$(dppf) (200 mg, 0.27 mmol), and triethylamine (1.02 mL, 7.3 mmol) were mixed in methanol (15 mL) in a pressure vessel. The reaction vessel was charged with CO (500 psi), and the mixture was heated at 120 °C for 16 h. The reaction mixture was cooled to room temperature, and the mixture was filtered through a filtrate paper. The filtrate was concentrated in vacuo. The residual oil was purified by silica gel column chromatography (AcOEt/hexane) to give the title compound (**17c**) (430 mg, 67% yield) as yellow oil. The ration of (*Z*)- and (*E*)-isomer was 7:3, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.91 (0.3H, d, J = 2.2 Hz), 7.81 (0.7H, d, J = 2.2 Hz), 7.74–7.68 (1H, m), 7.32–7.13 (4H, m), 6.77 (0.7H, d, J = 8.5 Hz), 6.70 (0.3H, d, J = 8.5 Hz), 5.99 (0.3H, t, J = 7.4 Hz), 5.63 (0.7H, t, J = 7.4 Hz), 5.47 (2H, br s), 3.80 (0.9H, s), 3.77 (2.1H, s), 2.68–2.39 (12H, m), 2.32 (2.1H, s), 2.30 (0.9H, s).

3.2.37. Methyl 11-(3-(4-methyl-1,4-diazepan-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepine-2-carboxylate (17d)

The title compound was synthesized from (**16b**) according to the procedure to prepare (**17c**) (55% yield). The ration of (*Z*)- and (*E*)-isomer was 7:3, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.90 (0.3H, d, J = 2.2 Hz), 7.78 (0.7H, d, J = 2.2 Hz), 7.73–7.68 (1H, m), 7.30–7.16 (4H, m), 6.77 (0.7H, d, J = 8.6 Hz), 6.70 (0.3H, d, J = 8.6 Hz), 6.02 (0.3H, t, J = 7.5 Hz), 5.65 (0.7H, t, J = 7.3 Hz), 5.27 (2H, br s), 3.81 (3H, s), 2.76–2.51 (12H, m), 2.36 (2.1H, s), 2.34 (0.9H, s), 1.87–1.75 (2H, m).

3.2.38. Methyl 11-(3-(piperazin-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepine-2-carboxylate (18c)

The title compound was synthesized from (**17c**) according to the procedure to prepare (**18a**) (67% yield). The ration of (*Z*)- and (*E*)-isomer was 7:3, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.91 (0.3H, d, J = 2.2 Hz), 7.80 (0.7H, d, J = 2.2 Hz), 7.73–7.68 (1H, m), 7.31–7.14 (4H, m), 6.76 (0.7H, d, J = 8.6 Hz), 6.70 (0.3H, d, J = 8.6 Hz), 6.01 (0.3H, t, J = 7.1 Hz), 5.66 (0.7H, t, J = 7.3 Hz), 5.27 (2H, br s), 3.81 (0.9H, s), 3.80 (2.1H, s), 2.81–2.74 (4H, m), 2.59–2.55 (1.4H, m), 2.47–2.20 (6.6H, m).

3.2.39. Methyl 11-(3-(1,4-diazepan-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepine-2-carboxylate (18d)

The title compound was synthesized from (**17d**) according to the procedure to prepare (**18a**) (74% yield). The ration of (*Z*)- and (*E*)-isomer was 7:3, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.91 (0.3H, d, J = 2.2 Hz), 7.82 (0.7H, d, J = 2.2 Hz), 7.73–7.68 (1H, m), 7.30–7.16 (4H, m), 6.77 (0.7H, d, J = 8.6 Hz), 6.70 (0.3H, d, J = 8.6 Hz), 6.03 (0.3H, t, J = 7.5 Hz), 5.67 (0.7H, t, J = 7.3 Hz), 5.22 (2H, br s), 3.81 (0.9H, s), 3.80 (2.1H, s), 2.86–2.50 (12H, m), 1.70–1.60 (2H, m).

3.2.40. 3-Bromo-5-(3-bromopropylidene)-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulene (15b)

To a solution of 3-bromo-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]-annulen-5-one (**14b**) (580 mg, 2.0 mmol) in THF (20 mL) was added 0.5 M cyclopropylmagnesium bromide in THF (7.5 mL), and the mixture was stirred for 0.5 h. The reaction mixture was poured into 10% aq ammonium chloride and the mixture was extracted with ethyl acetate 2 times. The combined extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (EtOAc/hexane) to afford 3-bromo-5-cyclopropyl-10,11-dihydro-5*H*-dibenzo-[*a*,*d*][7]annulen-5-ol as a colorless oil (553 mg, 85% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 8.02 (1H, d, J = 1.6 Hz), 7.81–7.85 (1H, m), 7.25–7.29 (1H, dd, J = 2.0, 8.0 Hz), 7.14–7.21 (2H, m), 7.07–7.12 (1H, m), 6.97 (1H, d, J = 8.0 Hz), 3.53–3.62 (2H, m), 2.88–3.00 (2H, m), 2.22 (1H, s), 1.48–1.69 (1H, m), 0.58–0.66 (2H, m), 0.36–0.47 (2H, m).

To a solution of 3-bromo-5-cyclopropyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ol (553 mg, 1.7 mmol) in acetic acid (10 mL) was added 25% hydrobromic acid in acetic acid (1.5 mL) at 0 °C, and the mixture was stirred for 10 min. The reaction mixture was poured into crashed ice and the mixture was extracted with ethyl acetate, and the combined extracts were washed with satd $NaHCO_3$ and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (EtOAc/hexane) to afford the title compound (**15b**) as a colorless oil (666 mg, 99% yield). The ration of (*Z*)- and (*E*)-isomer was 1:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.42 (0.5H, d, J = 1.6 Hz), 7.31 (0.5H, dd, J = 1.6, 8.0 Hz), 7.15–7.27 (4H, m), 7.06–7.09 (1H, m), 7.01–7.04 (0.5H, m), 6.90 (1H, d, J = 8.0 Hz), 5.83–5.87 (1H, m), 3.22–3.46 (4H, m), 2.87–2.96 (1H, m), 2.61–2.80 (2H, m).

3.2.41. 1-[3-(3-Bromo-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl]-4-methylpiperazine (16c)

A mixture of (**15b**) (1.20 g, 3.1 mmol), methylpiperazine (3.0 g, 30 mmol), potassium carbonate (1.38 g, 10 mmol), and potassium iodide (106 mg, 1.0 mmol) in DMF (5 mL) was stirred for 17 h at room temperature. The reaction mixture was poured into satd $NaHCO_3$ and the mixture was extracted with ethyl acetate 3 times. The combined extracts were washed with satd $NaHCO_3$ and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residual paste was chromatographed on silica gel (methanol/chloroform/NH_3 aq) to afford the title compound (**16c**) as a colorless oil (1.2 g, 93% yield). The ration of (*Z*)- and (*E*)-isomer was 1:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 6.87–7.40 (7H, m), 5.84 (1H, t, J = 7.4 Hz), 3.16–3.47 (2H, m), 2.65–3.00 (2H, m), 2.20–2.63 (15H, m).

3.2.42. 1-[3-(3-Bromo-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]-annulen-5-ylidene)propyl]-4-methyl-1,4-diazepane (16d)

The title compound was synthesized from (**15b**) and 1-methylhomopiperadine according to the procedure to prepare (**16c**) (69% yield). The ration of (*Z*)- and (*E*)-isomer was 1:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 6.86–7.40 (7H, m), 5.82–5.87 (1H, m), 3.10–3.40 (2H, m), 2.49–2.99 (12H, m), 2.32 (1.5H, s), 2.31 (1.5H, s), 2.18–2.28 (2H, m), 1.71–1.78 (2H, m), 1.58–1.75 (2H, br).

3.2.43. Methyl {5-[3-(4-methylpiperazin-1-yl)propylidene]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-3-yl}acetate (17e)

The title compound was synthesized from (**16c**) according to the procedure to prepare (**11g**) (52% yield). The ration of (*Z*)- and (*E*)-isomer was 1:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 6.96–7.26 (7H, m), 5.80–5.84 (1H, m), 3.66 (1.5H, s), 3.64 (1.5H, s), 3.56 (1H, s), 3.54 (1H, s), 3.18–3.43 (2H, m), 2.82–3.03 (2H, m), 2.10–2.81 (15H, m).

3.2.44. Methyl {5-[3-(4-methyl-1,4-diazepan-1-yl)propylidene]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-3-yl}acetate (17f)

The title compound was synthesized from (**16d**) according to the procedure to prepare (**11g**) (79% yield). The ration of (*Z*)- and (*E*)-isomer was 1:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 6.96–7.25 (7H, m), 5.81–5.85 (1H, m), 3.66 (1.5H, s), 3.64 (1.5H, s), 3.56 (1H, s), 3.55 (1H, s), 3.18–3.43 (2H, m), 2.79–3.02 (1H, m), 2.48–2.76 (11H, m), 2.31 (3H, s), 2.19–2.30 (2H, m), 1.65–1.74 (2H, m).

3.2.45. Methyl-5-[3-(4-methyl-1,4-diazepan-1-yl)propylidene]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulene-3-carboxylate (17g)

The title compound was synthesized from (**16d**) according to the procedure to prepare (**11f**) (48% yield). The ration of (*Z*)- and (*E*)-isomer was 1:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.93 (0.5H, d, J = 2.0 Hz), 7.85 (0.5H, dd, J = 1.6, 8.0 Hz), 7.78 (0.5H, d, J = 1.6 Hz), 7.76 (0.5H, dd, J = 2.0, 8.0 Hz), 7.00–7.26 (5H, m), 5.86–5.91 (1H, m), 3.88 (1.5H, s), 3.87 (1.5H, s), 3.10–3.48 (2H, m), 2.50–3.07 (12H, m), 2.18–2.36 (5H, m), 1.69–1.79 (2H, m), 1.50–1.68 (2H, br s).

3.2.46. Methyl {5-[3-(piperazin-1-yl)propylidene]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-3-yl}acetate (18e)

2,2,2-Trichloroethyl 4-{3-[3-(2-methoxy-2-oxoethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene]propyl}piperazine-1-carboxylate was synthesized from (**17e**) according to the procedure to prepare 2,2,2-trichloroethyl 4-(3-(2-(2-methoxy-2-oxoethyl)-dibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)propyl)piperazine-1-carboxylate (69% yield). The ration of (*Z*)- and (*E*)-isomer was 1:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 6.96–7.26 (7H, m), 5.81–5.86 (1H, m), 4.71 (2H, s), 3.65 (1.5H, s), 3.61 (1.5H, s), 3.56 (1H, s), 3.55 (1H, s), 3.18–3.53 (6H, m), 2.63–3.01 (2H, m), 2.25–2.51 (8H, m).

The title compound was synthesized from 2,2,2-trichloroethyl 4-{3-[3-(2-methoxy-2-oxoethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-[7]annulen-5-ylidene]propyl}piperazine-1-carboxylate according to the procedure to prepare (**18a**) (44% yield). The ration of (*Z*)- and (*E*)-isomer was 1:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 6.95–7.28 (7H, m), 5.80–5.84 (1H, m), 3.66 (1.5H, s), 3.64 (1.5H, s), 3.56 (1H, s), 3.55 (1H, s), 3.17–3.44 (2H, m), 2.62–2.99 (6H, m), 2.20–2.44 (8H, m).

3.2.47. Methyl {5-[3-(1,4-diazepan-1-yl)propylidene]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-3-yl}acetate (18f)

2,2,2-Trichloroethyl 4-{3-[3-(2-methoxy-2-oxoethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene]propyl}-1,4-diazepane-1-carboxylate was synthesized from (**17f**) according to the procedure to prepare 2,2,2-trichloroethyl 4-(3-(2-(2-methoxy-2-oxoethyl)dibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)propyl)piperazine-1-carboxylate (77% yield). The ration of (*Z*)- and (*E*)-isomer was 1:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 6.94–7.20 (7H, m), 5.81–5.84 (1H, m), 4.72 (1H, s), 4.71 (1H, s), 3.64–3.71 (3H, m), 3.25–3.59 (6H, m), 3.18–3.41 (2H, m), 2.87–2.95 (1H, m), 2.66–2.82 (1H, m), 2.48–2.63 (6H, m), 2.22–2.29 (2H, m), 1.71–1.83 (2H, m).

The title compound was synthesized from 2,2,2-trichloroethyl 4-{3-[3-(2-methoxy-2-oxoethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-[7]annulen-5-ylidene]propyl}-1,4-diazepane-1-carboxylate according to the procedure to prepare (**18a**) (68% yield). The ration of (*Z*)- and (*E*)-isomer was 1:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): ^{1}H NMR ($CDCl_3$, δ ppm): 6.94–7.19 (7H, m), 5.81–5.86 (1H, m), 3.68 (1.5H, s), 3.67 (1.5H, s), 3.56 (1H, s), 3.55 (1H, s), 3.20–3.42 (2H, m), 2.49–2.97 (12H, m), 2.23–2.31 (2H, m), 1.65–1.71 (2H, m).

3.2.48. Methyl-5-[3-(1,4-diazepan-1-yl)propylidene]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulene-3-carboxylate (18g)

2,2,2-Trichloroethyl 4-{3-[3-(methoxycarbonyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene]propyl}-1,4-diazepane-1-carboxylate compound was synthesized from 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulene-3-carboxylate was synthesized from (**17g**) according to the procedure to prepare 2,2,2-trichloroethyl 4-(3-(2-(2-methoxy-2-oxoethyl)dibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)propyl)piperazine-1-carboxylate (89% yield). The ration of (*Z*)- and (*E*)-isomer was 1:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.93 (0.5H, d, J = 2.0 Hz), 7.85 (0.5H, dd, J = 1.6, 8.0 Hz), 7.78 (0.5H, d, J = 2.0 Hz), 7.77 (0.5H, dd, J = 1.6, 8.0 Hz), 7.01–7.26 (5H, m), 5.83–5.91 (1H, m), 3.88 (1.5H, s), 3.87 (1.5H, s), 3.10–3.58 (6H, m), 2.65–3.08 (2H, m), 2.40–2.63 (6H, m), 2.18–2.33 (2H, m), 1.75–1.86 (2H, br).

The title compound was synthesized from 2,2,2-trichloroethyl 4-{3-[3-(methoxycarbonyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]-annulen-5-ylidene]propyl}-1,4-diazepane-1-carboxylate according to the procedure to prepare (**18a**) (87% yield). The ration of (*Z*)- and (*E*)-isomer was 1:1, determined by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, δ ppm): 7.93 (0.5H, d, J = 1.6 Hz), 7.85 (0.5H, dd, J = 1.6, 8.0 Hz), 7.79 (0.5H, d, J = 1.6 Hz), 7.75 (0.5H, dd, J = 1.6, 8.0 Hz), 7.00–7.26 (5H, m), 5.83–5.92 (1H, m), 3.88 (1.5H, s), 3.87 (1.5H, s), 3.20–3.51 (2H, m), 2.58–3.08 (12H, m), 2.19–2.34 (2H, m), 1.601.73 (2H, m).

3.2.49. (*Z*)-2-(11-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetic acid ((*Z*)-19a) and (*E*)-2-(11-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]-oxepin-2-yl)acetic acid ((*E*)-19a)

A mixture of (**18a**) (69 mg, 0.176 mmol), 6-chloro-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (61 mg, 0.35 mmol) and diisopropylethylamine (0.152 mL, 0.880 mmol) in isopropyl alcohol (0.5 mL) was heated at 80 °C for 7 h. The reaction mixture was diluted with ethyl acetate, washed with satd $NaHCO_3$ and brine, dried over $NaSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane, and then MeOH/$CHCl_3$) to give methyl 2-(11-(3-(4-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetate (87 mg, 93% yield) as amorphous.

To a solution of the methyl 2-(11-(3-(4-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetate (87 mg, 0.16 mmol) in MeOH (0.75 mL)/THF (0.75 mL) was added 1 M aq NaOH at room temperature. After stirring for 3 h, the solution was neutralized with 2 M aq HCl, and the mixture was extracted with $CHCl_3$ 3 times. The organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residual solid was purified by preparative TLC (H_2O/CH_3CN = 1/2, extracted from silica gel with MeOH/$CHCl_3$) to give ((*Z*)-**19a**) (40 mg, 47% yield) and ((*E*)-**19a**) (25 mg, 30% yield), both as white solid.

3.2.50. (*Z*)-2-(11-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetic acid ((*Z*)-19a)

^{1}H NMR (DMSO-d_6, δ ppm): 11.0–13.2 (1H, br s), 7.22–7.39 (4H, m), 7.01–7.07 (2H, m), 6.74 (1H, d, J = 8.4 Hz), 5.68 (1H, t, J = 7.2 Hz), 4.70–5.60 (3H, br s), 3.47 (2H, s), 3.09–3.25 (12H, m), 2.59–2.72 (6H, m), 1.73–1.84 (2H, m). ^{13}C NMR (DMSO-d_6, δ ppm): 173.3, 162.5, 159.8, 154.1, 152.7, 145.7, 139.3, 133.9,

132.4, 131.3, 130.6, 129.5, 128.1, 127.9, 127.2, 126.2, 123.4, 119.4, 86.8, 79.5, 69.7, 57.4, 52.1 (2C), 50.1 (2C), 32.9, 27.6, 26.9. Anal. Calcd for $C_{29}H_{32}N_4O_5 \cdot 1.5H_2O$: C, 65.15; H, 6.15; N, 10.42. Found: C, 65.15; H, 6.41; N, 10.48. HRMS (ESI+) calcd for $C_{29}H_{33}N_4O_5$ ($M+H^+$): 517.2445, found: 517.2431.

3.2.51. (*E*)-2-(11-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetic acid ((*E*)-19a)

^{1}H NMR (DMSO-d_6, δ ppm): 11.8–12.8 (1H, br s), 7.47 (1H, dd, J = 1.2, 7.2 Hz), 7.28–7.41 (2H, m), 7.25 (1H, dd, J = 1.2, 7.2 Hz), 7.13 (1H, d, J = 2.0 Hz), 7.00 (1H, dd, J = 2.0, 7.6 Hz), 6.64 (1H, d, J = 8.4 Hz), 6.02 (1H, t, J = 7.6 Hz), 4.40–5.70 (3H, br s), 3.45 (2H, s), 3.07–3.23 (12H, m), 2.20–2.68 (6H, m), 1.69–1.78 (2H, m). Anal. Calcd for $C_{29}H_{32}N_4O_5 \cdot 0.5H_2O$: C, 66.27; H, 6.33; N, 10.66. Found: C, 66.10; H, 6.30; N, 10.65. HRMS (ESI+) calcd for $C_{29}H_{33}N_4O_5$ ($M+H^+$): 517.2445, found: 517.2433.

3.2.52. (*Z*)-2-(11-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetic acid (19b)

The title compound was synthesized from (**18b**) according to the procedure to prepare (**19a**) (78% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 11.0–13.2 (1H, br s), 7.22–7.39 (4H, m), 7.01–7.07 (2H, m), 6.74 (1H, d, J = 8.4 Hz), 5.68 (1H, t, J = 7.2 Hz), 4.70–5.60 (3H, br s), 3.47 (2H, s), 3.09–3.25 (12H, m), 2.59–2.72 (6H, m), 1.73–1.84 (2H, m). Anal. Calcd for $C_{30}H_{34}N_4O_5 \cdot 2.4H_2O$: C, 62.79; H, 6.81; N, 9.76. Found: C, 62.72; H, 6.42; N, 9.72. HRMS (ESI+) calcd for $C_{30}H_{35}N_4O_5$ ($M+H^+$): 531.2602, found: 531.2586.

3.2.53. (*Z*)-11-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)propylidene)-6,11-dihydrodibenzo[*b*,*e*]oxepine-2-carboxylic acid (19c)

The title compound was synthesized from (**18c**) according to the procedure to prepare (**19a**) (48% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.85 (1H, d, J = 2.1 Hz), 7.72 (1H, dd, J = 2.1, 8.6 Hz), 7.28–7.36 (4H, m), 6.83 (1H, d, J = 8.6 Hz), 5.69 (1H, t, J = 7.2 Hz), 5.27 (1H, s), 4.70–5.55 (2H, br s), 3.35 (3H, s), 3.30 (3H, s), 2.92–3.04 (4H, m), 2.62–2.80 (8H, m). Anal. Calcd for $C_{28}H_{30}N_4O_5 \cdot 1.5H_2O$: C, 63.50; H, 6.28; N, 10.58. Found: C, 63.26; H, 5.98; N, 10.33. HRMS (ESI+) calcd for $C_{28}H_{31}N_4O_5$ ($M+H^+$): 503.2289, found: 503.2277.

3.2.54. (*Z*)-11-(3-(4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl)propylidene)-6,11-Dihydrodibenzo[*b*,*e*]oxepine-2-carboxylic acid (19d)

The title compound was synthesized from (**18d**) according to the procedure to prepare (**19a**) (41% yield).

^{1}H NMR ($CDCl_3$, δ ppm): 7.73–7.86 (2H, m), 7.25–7.36 (4H, m), 6.84 (1H, d, J = 8.6 Hz), 5.67 (1H, t, J = 7.3 Hz), 5.27 (1H, s), 4.70–5.79 (2H, br s), 3.40 (3H, s), 3.30 (3H, s), 3.24–3.35 (4H, m), 2.69–2.92 (8H, m), 1.97–2.04 (2H, m). Anal. Calcd for $C_{29}H_{32}N_4O_5 \cdot 1.5H_2O$: C, 64.07; H, 6.49; N, 10.31. Found: C, 63.77; H, 6.20; N, 10.14. HRMS (ESI+) calcd for $C_{29}H_{33}N_4O_5$ ($M+H^+$): 517.2445, found: 517.2432.

3.2.55. [(5*Z*)-5-{3-[4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl]propylidene}-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-3-yl]acetic acid (19e)

The title compound was synthesized from (**18e**) according to the procedure to prepare (**19a**) (35% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 11.4–13.0 (1H, br s), 6.97–7.26 (7H, m), 5.81 (1H, t, J = 7.2 Hz), 5.12 (1H, s), 3.52 (2H, s), 3.18–3.43 (5H, m), 3.10 (3H, s), 2.67–2.95 (6H, m), 2.18–2.47 (8H, m). Anal. Calcd for $C_{30}H_{34}N_4O_4 \cdot 1.5H_2O$: C, 66.52; H, 6.89; N, 10.34. Found: C, 66.26; H, 6.62; N, 10.18. HRMS (ESI+) calcd for $C_{30}H_{35}N_4O_4$ ($M+H^+$): 515.2653, found: 515.2639.

3.2.56. [(5*Z*)-5-{3-[4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl]propylidene}-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-3-yl]acetic acid (19f)

The title compound was synthesized from (**18f**) according to the procedure to prepare (**18a**) (35% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 11.8–12.7 (1H, br s), 7.14–7.27 (3H, m), 7.07–7.13 (2H, m), 6.94–7.05 (2H, m), 5.80–5.84 (1H, m), 5.03 (1H, s), 3.50 (2H, s), 3.13–3.35 (9H, m), 3.50 (3H, s), 2.41–2.90 (8H, m), 2.17–2.28 (2H, m), 1.68–1.79 (2H, m). Anal. Calcd for $C_{31}H_{36}N_4O_4 \cdot 0.75H_2O$: C, 68.68; H, 6.97; N, 10.33. Found: C, 68.77; H, 6.95; N, 10.25. HRMS (ESI+) calcd for $C_{31}H_{37}N_4O_4$ ($M+H^+$): 529.2809, found: 529.2793.

3.2.57. (5*Z*)-5-{3-[4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1,4-diazepan-1-yl]propylidene}-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulene-3-carboxylic acid (19g)

The title compound was synthesized from (**18g**) according to the procedure to prepare (**19a**) (40% yield).

^{1}H NMR (DMSO-d_6, δ ppm): 7.75 (1H, d, J = 7.6 Hz), 7.65 (1H, br s), 7.31 (1H, d, J = 8.0 Hz), 7.02–7.29 (4H, m), 5.86 (1H, t, J = 7.2 Hz), 5.03 (1H, s), 3.12–3.30 (9H, m), 3.01 (3H, s), 2.72–2.90 (2H, m), 2.41–2.63 (6H, m), 2.10–2.30 (2H, m), 1.70–1.79 (2H, m). Anal. Calcd for $C_{30}H_{34}N_4O_4 \cdot 1.0H_2O$: C, 67.65; H, 6.81; N, 10.52. Found: C, 67.43; H, 6.69; N, 10.35. HRMS (ESI+) calcd for $C_{30}H_{35}N_4O_4$ ($M+H^+$): 515.2653, found: 515.2640.

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Supplementary data

Supplementary data (synthetic scheme and characterization data of novel compounds not listed in Section 2) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.03.003.

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