Synthesis of Tricyclic Compounds as Steroid 5α-Reductase Inhibitors

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Received August 10, 1999; accepted December 4, 1999

A series of 4-phenoxybutyric acid derivatives attached to a tricyclic skeleton were prepared and evaluated as 5α-reductase inhibitors. Structure activity relationships for these compounds in terms of rat epididymis (type 2) 5α-reductase inhibitory activities reveal that 1) the substitution pattern at the 11-position of dibenz[*b*,*e*]oxepin influenced potency, 2) higher lipophilicity of the tricyclic skeleton improved potency, whereas the existence of a basic nitrogen atom in this skeleton was detrimental to potency, and 3) isobutyl substitution at the 8 positon of the azepine skeleton was tolerated. Among the tricyclic compounds studied, 4-[3-[5-benzyl-8-(2-methyl)propyl-10,11-dihydrodibenz[*b*,*f*]azepine-2-carboxamido]phenoxy]butyric acid (26) was the most potent inhibitor of rat type 2 5α-reductase at 0.1 μM.

Key words 5α-reductase; benign prostatic hyperplasia; structure–activity relationship; tricyclic compounds; substituent effect

5α-Reductase is an enzyme responsible for the conversion of testosterone (T) into the more potent androgenic metabolite, dihydrotestosterone (DHT). 5α-Reductase inhibitors may be a new type of drug for benign prostatic hyperplasia (BPH)[2] and related disorders associated with elevated levels of DHT such as acne,[3] male pattern baldness,[4] and hirsutism.[5] With the discovery of two 5α-reductase isozymes, the physiological and pharmacological roles of these enzymes in BPH are the subject of current research.[6]

We previously reported indole derivatives, such as **1**, exhibiting a potent inhibitory activity for rat prostatic (type 1) 5α-reductase with an IC_{50} value of 9.6±1.0 nM.[7] During the course of structure–activity relationship (SAR) studies of indole derivatives, we discovered that the bulky substituent at the *N*-1 position of indole was required for potent inhibition of type 1 5α-reductase.[7c] These observations led us to design tricyclic compounds such as carbazoles and azepines, which are bulkier than indoles.

When we started our research program, **2**, (±)-ONO-3805[8] was the only compound reported as a nonsteroidal 5α-reductase inhibitor. Consequently, we designed novel compounds analogous to **2** and considered that the lipophilic part of **2** corresponds to a steroidal skeleton.[7a] The benzyloxyphenyl moiety of **2** can be transformed into dibenz[*b*,*e*]oxepin as follows: 1) the three bonds between two benzene rings in conformation **a** are appropriately rotated to conformation **b**, 2) then two benzene rings in **b** are bridged by a C1 unit to afford the dibenz[*b*,*e*]oxepin tricyclic system. Thus, we prepared dibenz[*b*,*e*]oxepins and evaluated them as 5α-reductase inhibitors.

The starting materials, 6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic acids (**3**—**6**) and 5,11-dihydrobenzoxepino[3,4-*b*]pyridine-7-carboxylic acid (**7**) were available by a known method.[9] Carbazole and azepine carboxylic acids (**8**—**13**) were derived from the corresponding aldehydes.[10] Tricyclic carboxylic acids (**3**—**13**) were converted to butyric acids (**15**—**27**) by condensation with a 2-subsituted aniline (**14a**, **b**)[8] using Mukaiyama's reagent,[11] followed by hydrolysis of ethyl ester (see Chart 1).

The final tricyclic compounds (**15**—**27**) were evaluated for inhibitory activity against rat prostatic (type 1) and epididymis (type 2) 5α-reductases in the manner described previously.[7] Rat prostatic 5α-reductase showed a broad, neutral-to-basic, pH optimum, whereas the type 2 isozyme obtained from epididymis exhibited an optimal pH of 5.5.[12] Inhibitory activities, expressed as percent inhibition, are summarized in Table 1.

Initially, compounds **16** and **19** were tested for inhibitory effects both on rat prostatic (type 1) and epididymis (type 2) 5α-reductases. Though both compounds showed weak potency for type 1 isozyme, even at 1 μM drug concentration, they exhibited potent activity against type 2 isozyme at 0.1 μM. The 11-hydroxy derivative (**19**) exhibited 73% inhibition at 0.1 μM, which is better than the ketone (**16**). Thus, tricyclic compounds were more responsive to type 2 isozyme and discriminated between subtle structural differences in the same manner as our previous observation: non-steroidal inhibitors, such as indole derivatives and (±)-ONO-3805, more potently inhibited type 2 *versus* type 1 isozyme.[7b] Consequently, we evaluated the tricyclic compounds for inhibitory activity against type 2 isozyme to investigate structure–activity relationships.

Oxepins with a methylene group at the 11-position showed more potent inhibitory activity than the ketone (**17**, **18** *vs*. **15**, **16**). Substitution of one of the benzene rings in dibenz[*b*,*e*]-oxepin with a pyridine ring apparently led to a loss of inhibitory activity (**21** *vs.* **20**). C log P values[13] of tricyclic skeletons corresponding to **15**, **17**, **20** and **21**, in which the left part of the molecule was replaced by the acetyl substitutent, were calculated as 2.87, 3.98, 2.94 and 1.45, respectively. These results suggest that the higher lipophilicity in dibenz[*b*,*e*]oxepin is desirable for potent activity.

It is obvious that the substitution pattern at the 11-position of dibenz[*b*,*e*]oxepins influenced potency. Hydroxy and methoxy groups were more potent than ketone (**19**, **20** *vs*. **15**, **16**). From the result that compound **19** showed more potent activity than **16**, it was concluded that substitution pattern rather than the lipophilicity of this moiety influenced the potency. The configuration of the 11-carbon atom affects the conformation of the dibenz[*b*,*e*]oxepin ring system, as we previously reported.[14] Ring inversion occurs easily in the case of the trigonal sp^2 carbon, whereas such a conformational change hardly ever occurs in physiological conditions in tetrahedral sp^3 carbon at the 11 position. ^{1}H-NMR spectra

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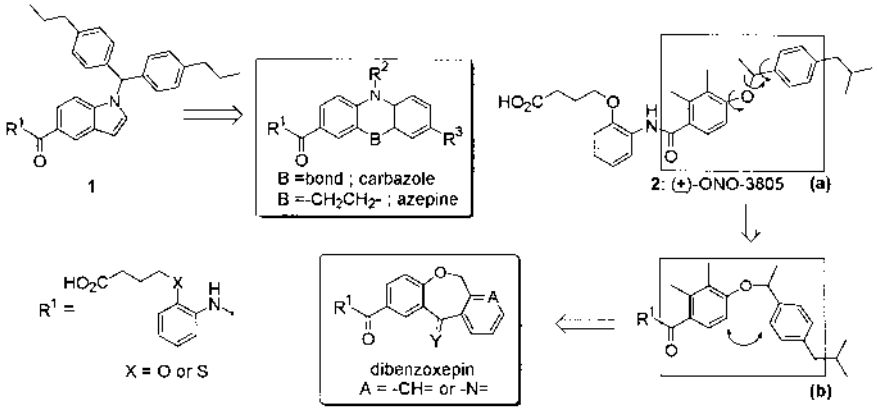
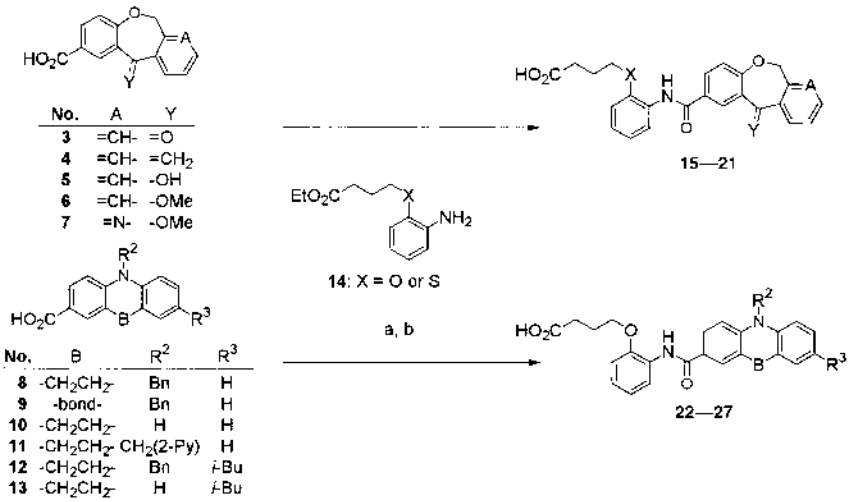


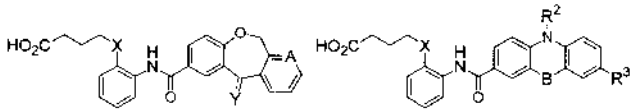
Fig. 1. Design of Tricyclic Compounds



a, **14**, 2-chloro-*N*-methylpyridinium iodide, NBu_3/CH_2Cl_2; b, NaOH/aqueous EtOH

Chart 1

Table 1. 5α-Reductase Inhibitory Activity of Tricyclic Compounds



No.	A	X	Y	B	R^2	R^3	% inhibition (drug concentration)	
							Type 1 (1 μM)	Type 2 (0.1 μM)
15	–CH=	O	=O	—	—	—	—	28
16	–CH=	S	=O	—	—	—	33	39
17	–CH=	O	$=CH_2$	—	—	—	—	73
18	–CH=	S	$=CH_2$	—	—	—	—	63
19	–CH=	S	–H, –OH	—	—	—	45	73
20	–CH=	O	–H, –OMe	—	—	—	—	69
21	–N=	O	–H, –OMe	—	—	—	—	22
22	—	O	—	$–CH_2CH_2–$	CH_2Ph	H	—	88
23	—	O	—	Bond	CH_2Ph	H	—	72
24	—	O	—	$–CH_2CH_2–$	H	H	—	75
25	—	O	—	$–CH_2CH_2–$	CH_2(2-Py)	H	—	42
26	—	O	—	$–CH_2CH_2–$	CH_2Ph	iso-Bu	—	93
27	—	O	—	$–CH_2CH_2–$	H	iso-Bu	—	76
1							87[a)]	—
2							96[a)]	100

a) % inhibition at 0.1 μM.

also indicated these phenomena. The C-6 methylene hydrogen atoms at the linkage of dibenz[*b*,*e*]oxepin were observed as a singlet peak for the two protons in the case of ketone at the 11-position (**15**—**18**). On the other hand, a doublet in the AB-pattern was observed in compounds possessing hydroxy or methoxy at the 11-position (**19**, **20**). These observations suggest that one of the enantiomers in compound **19**, **20** has a higher affinity against type 2 isozyme, and the ring inversion of dibenz[*b*,*e*]oxepin might cause decreased potency. Replacement of the ether bond of the phenoxy part by thioether did not show any significant change in potency.

When compared with **22** and **23**, dibenzazepine is relatively more potent than carbazole. The substituent (R^2) on the nitrogen of azepine notably influenced inhibitory activity. The *N*-benzyl azepines (**22** and **26**) showed potent inhibitory activity. Non-substitution (*N*-H) retained potency, whereas substitution of the picolyl group caused a drop in potency, even though C log P values of the tricyclic moiety of **24** and **25** were over 4.5. From this result, the existence of a basic nitrogen atom of this moiety appears to be undesirable for potent inhibitory activity. As for the substituent (R^3) at the 8 position of dibenzazepine, the introduction of isobutyl retained potency (**26**, **27** *vs*. **22**, **24**). This result indicates that bulkier substitutents in the tricyclic ring systems are allowed as a lipophilic part of the molecule.

In conclusion, we designed tricyclic compounds, such as dibenzoxepins, carbazole and azepines, and evaluated them as 5α-reductase inhibitors. Several compounds showed potent inhibitory activity for rat type 2 5α-reductase, which were comparable with parent indole derivative **1** and (±)-ONO-3805. These results reveal interesting features of the nonsteroidal 5α-reductase inhibitors and provide a new prototype for novel synthetic candidates.

Experimental

Melting points were determined with a Büchi-510 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Jasco IR-810 spectrometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a JEOL JNM GX-270 or EX-270 (270 MHz) spectrometer with Me_4Si as an internal standard. Elemental analyses were performed by the analytical department of our laboratories.

5-Benzyl-2-isobutyl-10,11-dihydrodibenz[*b*,*f*]azepine To a solution of 1-(5-benzyl-10,11-dihydrodibenz[*b*,*f*]azepine-2-carbaldehyde (4.17 g, 13.3 mmol) in tetrahydrofuran (THF) (125 ml), isopropyl magnesium chloride (2 M in THF solution; 13.3 ml, 26.6 mmol) was added at −50 °C. After being stirred at the same temperature for 1 h, 50 ml of water was added and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine, dried and evaporated *in vacuo*. The oil was dissolved in 200 ml of toluene, then activated MnO_2 (11.7 g, 133 mmol) was added. After being stirred under refluxing for 3 h, the reaction mixture was cooled to 25 °C. The mixture was filtered through Celite and the filtrate was evaporated *in vacuo*. The resulting oil was chromatographed on silica gel and eluted with hexane–AcOEt (5 : 1) to afford ketone (2.5 g, 53%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (6H, d, J=6.7 Hz), 3.24 (4H, s), 3.42—3.47 (1H, m), 5.02 (2H, s), 6.97—7.27 (8H, m), 7.35 (2H, d, J=6.9 Hz), 7.62 (1H, dd, J=2.2 Hz, 8.6 Hz), 7.69 (1H, d, J=2.2 Hz). To a solution of ketone (2.5 g, 7.03 mmol) in 38 ml of trifluoroacetic acid (TFA), Et_3SiH (11.4 ml, 70.3 mmol) was added dropwise. After being stirred at the same temperature for 1 h, 50 ml of iced water was added. The reaction mixture was extracted with toluene. The organic layer was washed with saturated aqueous $NaHCO_3$, water and brine successively, dried and evaporated *in vacuo*. The residue was chromatographed on silica gel and eluted with hexane–AcOEt (10 : 1) to afford an isobutyl substituted compound (2.4 g, 100%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (6H, d, J=6.7 Hz), 1.63—1.82 (1H, m), 2.34 (2H, s), 3.18 (4H, s), 4.88 (2H, s), 6.74—6.82 (3H, m), 6.90—7.20 (8H, m), 2.30 (2H, d, J=7.2 Hz).

5-Benzyl-8-isobutyl-10,11-dihydrodibenz[*b*,*f*]azepine-2-carboxylic Acid (12) To a solution of phosphorous oxychloride ($POCl_3$) (0.18 ml, 2.20 mmol) and 0.5 ml of dichloroethane, *N*,*N*-dimethylformamide (DMF) (0.17 ml, 2.20 mmol) was added at 0 °C. After the mixture was stirred at 25 °C for 1 h, a solution of 5-benzyl-2-isobutyl-10,11-dihydrodibenz[*b*,*f*]-azepine (0.5 g, 1.46 mmol) in 1.0 ml of dichloroethane was added dropwise over a period of 10 min. After being stirred at 60 °C for 2 h, the reaction mixture was poured into 20 ml of aqueous sodium acetate (2.4 g, 29 mmol). The mixture was stirred at 25 °C for 30 min and extracted with CH_2Cl_2. The organic layer was washed with brine, dried and evaporated *in vacuo*. The residue was chromatographed on silica gel and eluted with hexane–AcOEt (3 : 1) to afford 2-aldehyde (0.4 g, 74%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, d, J=6.7 Hz), 1.80—1.85 (1H, m), 2.39 (2H, d, J=6.7 Hz), 3.19—3.27 (4H, m), 5.05 (2H, s), 6.91 (1H, dd, J=1.9 Hz, 8.6 Hz), 6.92 (1H, d, J=1.9 Hz), 7.09 (2H, d, J=8.6 Hz), 7.17—7.39 (5H, m), 7.51 (1H, dd, J=1.9 Hz, 8.6 Hz), 7.57 (1H, d, J=1.9 Hz), 9.80 (1H, s). To a solution of 2-aldehyde (0.4 g, 1.08 mmol) in methanol (20 ml), a 2.62 ml of 2 M KOH in methanol and iodine (0.14 g, 0.54 mmol) were added and the resulting mixture was stirred at 0—5 °C for 24 h. Methanol was evaporated *in vacuo*. The residue was dissolved in 1.0 l of water and acidified with 4 M HCl to pH 5. The reaction mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous $Na_2S_2O_3$ and brine, successively, dried, and evaporated *in vacuo*. The yellow oil was chromatographed on silica gel and eluted with hexane–AcOEt (3:1) to afford methyl ester (0.43g, 74%), which was obtained as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=6.8 Hz), 1.80—1.85 (1H, m), 2.41 (2H, d, J=6.8 Hz), 3.09—3.17 (4H, m), 3.86 (3H, s), 5.03 (2H, s), 6.91 (1H, dd, J=2.0 Hz, 8.6 Hz), 6.92 (1H, d, J=2.0 Hz), 7.10 (2H, d, J=8.6 Hz), 7.17—7.39 (5H, m), 7.51 (1H, dd, J=1.9 Hz, 8.6 Hz), 7.57 (1H, d, J=1.9 Hz). The methyl ester was hydrolyzed to afford carboxilic acid (0.33 g, 59%) as amorphous. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (6H, d, J=6.8 Hz), 1.78—1.84 (1H, m), 2.38 (2H, d, J=6.8 Hz), 3.22 (4H, br s), 5.02 (2H, s), 6.87—6.91 (1H, m), 7.01—7.08 (2H, m), 7.16—7.28 (4H, m), 7.35 (2H, d, J=6.9 Hz), 7.72 (1H, dd, J=2.0, 8.6 Hz), 7.72 (1H, d, J=2.0 Hz).

8-Isobutyl-10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepine-2-carboxylic Acid (13) To a solution of **12** (0.52 g, 1.30 mmol), 10 ml of AcOEt and 10 ml of AcOH, Pd–C (5 wt.%, 0.13 g) were added. The reaction mixture was stirred under atmospheric hydrogen at 25 °C for 48 h. After the reaction was completed, the mixture was filtered with Celite, and the filtrate was evaporated *in vacuo* to afford **13** (0.25 g, 62%) as a yellow amorphous substance. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=6.8 Hz), 1.80—1.84 (1H, m), 2.84 (2H, d, J=6.8 Hz), 3.07 (4H, s), 6.28 (1H, br s), 6.89 (1H, d, J=7.6 Hz), 7.73 (1H, d, J=7.6 Hz), 7.74 (1H, s).

4-[2-[(6,11-Dihydro-11-oxo-dibenz[*b*,*e*]oxepin-2-yl)carboxamido]phenoxy]butyric Acid (15) To a mixture of ethyl 4-(2-aminophenoxy)butyrate (**14**) (1.23 g, 5.51 mmol), 2-chloro-1-methylpyridinium iodide (1.20 g, 4.72 mmol), and tributylamine (2.3 ml, 9.43 mmol) in 40 ml of CH_2Cl_2, was added under reflux a suspension of **3** (1.0 g, 3.93 mmol) in 10 ml of CH_2Cl_2, and the mixture was stirred at reflux for 1 h. After the addition of water, the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with 1 M HCl, water, and brine, dried and evaporated *in vacuo* to afford ethyl 4-[2-(6,11-dihydro-11-oxo-dibenz[*b*,*e*]oxepine-2-carboxamido)phenoxy]-butyrate (1.41 g, 78%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7.1 Hz), 2.23—2.33 (2H, m), 2.63 (2H, t, J=6.9 Hz), 4.08 (2H, q, J=7.1 Hz), 4.18 (2H, t, J=6.3 Hz), 5.27 (2H, s), 6.93 (1H, dd, J=2.0, 7.6 Hz), 6.99—7.11 (2H, m), 7.19 (1H, d, J=8.9 Hz), 7.40—7.63 (3H, m), 7.91 (1H, dd, J=1.3, 7.6 Hz), 8.15 (1H, dd, J=2.3, 8.6 Hz), 8.50 (1H, dd, J=2.0, 7.6 Hz), 8.71 (1H, br s), 8.77 (1H, d, J=2.3 Hz). A mixture of the obtained ethyl ester (1.41 g, 2.57 mmol), 0.77 ml of 10 M NaOH, and 42 ml of EtOH was stirred at 50 °C for 1 h. The mixture was evaporated *in vacuo* and the residue was dissolved in 50 ml of water. The mixture was acidified with 4 M HCl to pH 3 and extracted with AcOEt. The organic layer was washed with brine, dried, and evaporated *in vacuo*. The pale yellow amorphous substance was recrystallized from isopropylether to give pure **15** (0.86 g, 78%) as colorless crystals, mp 159—160 °C. ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 2.21—2.31 (2H, m), 2.62 (2H, t, J=6.8 Hz), 4.19 (2H, t, J=6.1 Hz), 5.28 (2H, s), 6.94 (1H, dd, J=1.7, 7.8 Hz), 6.97—7.10 (2H, m), 7.19 (1H, d, J=8.6 Hz), 7.42 (1H, d, J=7.8 Hz), 7.48—7.54 (1H, m), 7.58—7.64 (1H, m), 7.91 (1H, d, J=6.3 Hz), 8.12 (1H, dd, J=2.3, 8.6 Hz), 8.47 (1H, dd, J=1.7, 7.8 Hz), 8.74 (1H, s), 8.76 (1H, d, J=2.3 Hz). IR (KBr) cm^{-1}: 3200, 1732, 1605, 1495, 1450, 1301, 1245, 1175, 747. *Anal.* Calcd for $C_{25}H_{21}NO_6$: C, 69.60; H, 4.91; N, 3.25. Found: C, 69.56; H, 4.90; N, 3.15.

4-[2-[(6,11-Dihydro-11-oxo-dibenz[*b*,*e*]oxepin-2-yl)carboxamido]-phenylthio]butyric Acid (16) **16**: As a pale yellow crystals, mp 111—112 °C (iso-Pr_2O). ^{1}H-NMR (DMSO-d_6) δ: 1.69—1.93 (2H, m), 2.36 (2H, t,

J=7.1 Hz), 2.94 (2H, t, J=7.1 Hz), 5.40 (2H, br s), 7.15—7.32 (3H, m), 7.40—7.70 (5H, m), 7.74 (1H, d, J=8.8 Hz), 8.17 (1H, dd, J=2.2, 8.6 Hz), 8.78 (1H, d, J=2.2 Hz). IR (KBr) cm^{-1}: 3430, 3335, 1732, 1668, 1643, 1519, 1487, 1300, 1254, 1174, 763. *Anal.* Calcd for $C_{25}H_{21}NO_5S$: C, 67.10; H, 4.73; N, 3.13. Found: C, 67.31; H, 4.60; N, 2.94.

4-[2-[(11-Methylidene-6,11-dihydrodibenz[*b*,*e*]oxepin-2-yl)carboxamido]phenoxy]butyric Acid (17) **17**: As amorphous. ^{1}H-NMR (DMSO-d_6) δ: 1.90—2.10 (2H, m), 2.45—2.55 (2H, m), 4.00—4.15 (2H, m), 5.23 (2H, s), 5.37 (1H, s), 5.96 (1H, s), 6.85—6.95 (2H, m), 7.00—7.15 (2H, m), 7.35—7.46 (4H, m), 7.85 (2H, d, J=7.3 Hz), 8.12 (1H, s), 9.52 (1H, s). IR (KBr) cm^{-1}: 3440, 1578, 1542, 1494, 1451, 1249, 751. *Anal.* Calcd for $C_{26}H_{23}NO_5 \cdot 0.5H_2O$: C, 71.22; H, 5.52; N, 3.19. Found: C, 71.10; H, 5.17; N, 3.20.

4-[2-[(11-Methylidene-6,11-dihydrodibenz[*b*,*e*]oxepin-2-yl)carboxamido]phenylthio]butyric Acid (18) **18**: As pale yellow crystals, mp 116—125 °C (iso-Pr_2O). ^{1}H-NMR ($CDCl_3$) δ: 1.68—1.80 (2H, m), 2.28 (2H, t, J=7.1 Hz), 2.70 (2H, t, J=7.1 Hz), 5.16 (2H, s), 5.31 (1H, s), 5.78 (1H, s), 6.84 (1H, d, J=8.6 Hz), 6.97 (1H, t, J=7.6 Hz), 7.26—7.33 (5H, m), 7.55 (1H, dd, J=1.5, 7.6 Hz), 7.71 (1H, dd, J=2.3, 8.6 Hz), 8.11 (1H, d, J=2.3 Hz), 8.57 (1H, dd, J=1.3, 8.2 Hz), 9.33 (1H, s). IR (KBr) cm^{-1}: 3450, 1580, 1525, 1490, 1437, 1303, 1239, 759. *Anal.* Calcd for $C_{26}H_{23}NO_4S \cdot 0.5H_2O$: C, 68.70; H, 5.32; N, 3.08. Found: C, 68.40; H, 5.54; N, 3.04.

4-[2-[(11-Hydroxy-6,11-dihydrodibenz[*b*,*e*]oxepin-2-yl)carboxamido]-phenylthio]butyric Acid (19) **19**: As pale yellow crystals, mp 152—154 °C (iso-Pr_2O). ^{1}H-NMR (DMSO-d_6) δ: 1.67—1.90 (2H, m), 2.34 (2H, t, J=7.1 Hz), 2.91 (2H, t, J=7.1 Hz), 5.31 and 5.79 (2H, AB pattern, J=12.3 Hz), 5.95 (1H, s), 6.86 (1H, d, J=8.6 Hz), 7.15—7.70 (9H, m), 7.80 (1H, dd, J=1.3, 9.2 Hz), 8.12 (1H, d, J=1.3 Hz), 9.66 (1H, s). IR (KBr) cm^{-1}: 3350, 1646, 1579, 1521, 1496, 1436, 1316, 1238, 763. *Anal.* Calcd for $C_{25}H_{23}NO_5S$: C, 66.80; H, 5.16; N, 3.12. Found: C, 66.75; H, 5.00; N, 2.98.

4-[2-[(6,11-Dihydro-11-methoxydibenz[*b*,*e*]oxepin-2-yl)carboxamido]-phenoxy]butyric Acid (20) **20**: As amorphous. ^{1}H-NMR ($CDCl_3$) δ: 2.12—2.34 (2H, m), 2.58 (2H, t, J=6.4 Hz), 3.31 (3H, s), 4.02—4.09 (1H, m), 4.16—4.24 (1H, m), 4.91 and 6.08 (2H, AB pattern, J=12.4 Hz), 5.22 (1H, s), 6.89 (1H, dd, J=2.0, 7.6 Hz), 6.94 (1H, d, J=8.6 Hz), 6.97—7.08 (2H, m), 7.30—7.38 (4H, m), 7.79 (1H, dd, J=2.3, 8.6 Hz), 7.96 (1H, d, J=2.3 Hz), 8.44 (1H, br s), 8.49 (1H, dd, J=2.3, 7.3 Hz). IR (KBr) cm^{-1}: 3418, 2934, 1728, 1667, 1611, 1537, 1503, 1452, 1240, 1208, 755. *Anal.* Calcd for $C_{26}H_{25}NO_6 \cdot 0.25H_2O$: C, 69.09; H, 5.69; N, 3.11. Found: C, 69.09; H, 5.59; N, 2.81.

4-[2-[(5,11-Dihydro-5-methoxybenzoxepino[3,4-*b*]pyridin-2-yl)carboxamido]phenoxy]butyric Acid (21) **21**: As white crystals, mp 78—82 °C (iso-Pr_2O trituration). ^{1}H-NMR ($CDCl_3$) δ: 2.21—2.30 (2H, m), 2.61 (2H, t, J=6.9 Hz), 3.39 (3H, s), 4.08—4.23 (2H, m), 5.20 and 5.90 (2H, AB pattern, J=13.2 Hz), 5.32 (1H, s), 6.91 (1H, dd, J=2.0, 7.6 Hz), 6.97—7.09 (3H, m), 7.20 (1H, dd, J=5.1, 7.8 Hz), 7.72 (1H, dd, J=1.7, 7.6 Hz), 7.84 (1H, dd, J=2.3, 8.6 Hz). 7.98 (1H, d, J=2.3 Hz), 8.43 (1H, dd, J=1.7, 5.0 Hz), 8.52 (1H, dd, J=2.1, 7.8 Hz), 8.56 (1H, s). IR (KBr) cm^{-1}: 3428, 2934, 1607, 1535, 1500, 1452, 1256, 1228, 745. *Anal.* Calcd for $C_{25}H_{24}N_2O_6$: C, 66.95; H, 5.39; N, 6.25. Found: C, 66.69; H, 5.54; 6.02.

4-[2-[(5-Benzyl-10,11-dihydrodibenz[*b*,*f*]azepin-2-yl)carboxamido]-phenoxy]butyric Acid (22) **22**: As amorphous. ^{1}H-NMR ($CDCl_3$) δ: 2.14—2.23 (2H, m), 2.56 (2H, t, J=7.1 Hz), 3.27 (4H, s), 4.11 (2H, t, J=6.1 Hz), 5.02 (2H, s), 6.87 (1H, dd, J=2.5,7.1 Hz), 6.93—7.05 (2H, m), 7.10—7.27 (8H, m), 7.35—7.38 (2H, m), 7.53 (1H, dd, J=2.2, 8.4 Hz), 7.64 (1H, d, J=2.2 Hz), 8.04 (1H, s), 8.45 (1H, dd, J=2.3, 7.3 Hz). IR (KBr) cm^{-1}: 3434, 1716, 1608, 1534, 1496, 1452, 1339, 749. *Anal.* Calcd for $C_{32}H_{30}N_2O_4 \cdot 0.25H_2O$: C, 75.20; H, 6.01; N, 5.48. Found: C, 75.40; H, 6.25; N, 5.35.

4-[2-[(9-Benzylcarbazol-3-yl)carboxamido]phenoxy]butyric Acid (23) **23**: As white crystals, mp 110—111 °C (iso-Pr_2O trituration). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 2.15—2.25 (2H, m), 2.54 (2H, t, J=7.1 Hz), 4.15 (2H, t, J=6.1 Hz), 5.53 (2H, s), 6.90 (1H, dd, J=2.6, 6.9 Hz), 6.96—7.03 (2H, m), 7.10—7.13 (2H, m), 7.22—7.31 (4H, m), 7.38—7.47 (3H, m), 7.98 (1H, dd, J=2.0, 8.6 Hz), 8.19 (1H, d, J=7.9 Hz), 8.55 (1H, dd, J=2.5, 7.1 Hz), 8.75 (2H, br s). IR (KBr) cm^{-1}: 3430, 1727, 1599, 1542, 1453, 1330, 756. *Anal.* Calcd for $C_{30}H_{26}N_2O_4$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.38; H, 5.59; N, 5.76.

4-[2-[(10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepin-2-yl)carboxamido]phenoxy]butyric Acid (24) **24**: As white crystals, mp 162—165 °C (iso-Pr_2O trituration). ^{1}H-NMR ($CDCl_3$) δ: 2.17—2.26 (2H, m), 2.55 (2H, t, J=7.1 Hz), 3.09 and 3.13 (4H, AB pattern, J=8.4 Hz), 4.17 (2H, t, J=5.9 Hz), 6.79 (1H, t, J=7.3 Hz), 6.91—7.12 (6H, m), 7.48 (2H, s), 7.59 (1H, t, J=2.3 Hz), 7.62 (1H, s), 7.77 (1H, s), 8.46 (1H, dd, J=1.7, 7.6 Hz), 8.57 (1H, s). IR (KBr) cm^{-1}: 3366, 1714, 1647, 1522, 1503, 1486, 1449, 1342, 1215, 749. *Anal.* Calcd for $C_{25}H_{24}N_2O_4 \cdot 0.25H_2O$: C, 71.33; H, 5.87; N, 6.65. Found: C, 71.16; H, 6.12; N, 6.35.

4-[2-[[5-(2-Pyridyl)methyl-10,11-dihydrodibenz[*b*,*f*]azepin-2-yl]carboxamido]phenoxy]butyric Acid (25) **25**: As amorphous. ^{1}H-NMR ($CDCl_3$) δ: 2.17—2.27 (2H, m), 2.59 (2H, t, J=7.1 Hz), 3.25 (4H, br s), 4.14 (2H, t, J=5.8 Hz), 5.14 (2H, s), 6.89 (1H, d, J=8.9 Hz), 6.98—7.07 (3H, m), 7.12—7.18 (4H, m), 7.34 (1H, d, J=8.3 Hz), 7.52—7.60 (2H, m), 7.69 (1H, d, J=1.7 Hz), 8.45—8.48 (2H, m), 8.52 (1H, s). IR (KBr) cm^{-1}: 3416, 2930, 1602, 1598, 1525, 1508, 1494, 1451, 1250. *Anal.* Calcd for $C_{31}H_{29}N_3O_4 \cdot 0.5H_2O$: C, 72.08; H, 5.85; N, 8.13. Found: C, 72.24; H, 6.05; N, 8.03.

4-[2-[[5-Benzyl-8-(2-methyl)propyl-10,11-dihydrodibenz[*b*,*f*]azepin-2-yl]carboxamido]phenoxy]butyric Acid (26) **26**: As amorphous. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (6H, d, J=6.4 Hz), 1.77—1.82 (1H, m), 2.13—2.22 (2H, m), 2.36 (2H, d, J=6.4 Hz), 2.55 (2H, t, J=7.1 Hz), 3.20—3.30 (4H, m), 4.11 (2H, t, J=6.1 Hz), 5.00 (2H, s), 6.85—7.30 (11H, m), 7.36 (2H, d, J=8.3 Hz), 7.51 (1H, d, J=8.6 Hz), 7.64 (1H, s), 8.38 (1H, s), 8.44 (1H, dd, J=2.3, 7.3 Hz). IR (KBr) cm^{-1}: 3435, 2950, 1706, 1601, 1530, 1493, 1452, 1334, 1250, 747. *Anal.* Calcd for $C_{36}H_{38}N_2O_4 \cdot 0.25H_2O$: C, 76.23; H, 6.84; N, 4.94. Found: C, 76.12; H, 7.10; N, 4.86.

4-[2-[[8-(2-Methyl)propyl-5*H*-10,11-dihydrodibenz[*b*,*f*]azepin-2-yl]-carboxamido]phenoxy]-butyric Acid (27) **27**: As white crystals, mp 144—145 °C (iso-Pr_2O trituration). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=6.8 Hz), 1.78—1.84 (1H, m), 2.17—2.24 (2H, m), 2.38 (2H, d, J=6.8 Hz), 2.59 (2H, t, J=7.1 Hz), 3.03—3.13 (4H, m), 4.14 (2H, t, J=5.9 Hz), 6.28 (1H, br s), 6.69 (1H, d, J=7.9 Hz), 6.73 (1H, d, J=8.5 Hz), 6.84 (1H, s), 6.86—6.90 (2H, m), 6.97—7.06 (2H, m), 7.57 (1H, dd, J=2.1, 8.5 Hz), 7.63 (1H, d, J=2.1 Hz), 8.44 (1H, s), 8.47—8.50 (1H, m). IR (KBr) cm^{-1}: 3340, 2948, 1601, 1504, 1452, 1348, 1249, 752. *Anal.* Calcd for $C_{29}H_{32}N_2O_4$: C, 73.71; H, 6.83; N, 5.93. Found: C, 73.39; H, 7.04; N, 5.86.

Acknowledgment We thank Y. Arai and T. Suzuki for their excellent technical assistance. We are also grateful to Dr. T. Hirata, director of Pharmaceutical Research Laboratories, for his continuous support.

References and Notes

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