Studies on a Novel, Potent and Orally Effective Cholecystokinin A Antagonist, FK-480. Synthesis and Structure–Activity Relationships of FK-480 and Related Compounds[1)]

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We prepared various novel tricyclic 1,4-benzodiazepine derivatives as cholecystokinin (CCK) A antagonists, which were evaluated preliminarily for inhibition of ^{125}I-CCK-8 binding to rat pancreatic membranes *in vitro* and inhibiting effect on CCK-8-induced inhibition of charcoal meal gastric emptying in mice. On the basis of structure–activity relationship (SAR) studies, as well as the stability and availability of the starting materials of those compounds, (*S*)-*N*-[1-(2-fluorophenyl)-3,4,6,7-tetrahydro-4-oxo-pyrrolo[3,2,1-*jk*][1,4]benzodiazepin-3-yl]-1*H*-indole-2-carboxamide (9f, FK-480) was selected as a candidate compound for further evaluation. The absolute configuration of the precursor of FK-480, (3*S*)-amino-1,4-benzodiazepine derivative ((*S*)-8a, R^1 = F) was determined by an X-ray crystallographic study of its ureido derivative with (*S*)-α-methylbenzyl isocyanate.

FK-480 is now undergoing clinical studies for the treatment of chronic pancreatitis.

Keywords CCK-A antagonist; FK-480; structure–activity relationship; 3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepine; cholecystokinin; chronic pancreatitis

Cholecystokinin (CCK) acts in several peripheral sites as a hormonal regulator of gut function, digestion and ingestion.[2,3)] CCK is also found in the central nervous system (CNS) as a neurotransmitter or a neuromodulator.[4,5)] CCK receptors have recently been subdivided into CCK-A (alimentary) receptors which predominate in the periphery and CCK-B (brain) receptors in the CNS. Devazepide (MK329)[6)] was the first example of a highly potent, orally effective and non-peptidal antagonist of the peptide hormone CCK. The information about MK-329 led us to search for a more potent and effective CCK-A antagonist which could be used in the clinical treatment of diseases such as chronic pancreatitis, irritable bowel syndrome (IBS), *etc.*

As some derivatives of the 1,2-ring-closed benzodiazepines (4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines) have been reported[7)] to have potent receptor binding inhibitory effects, our strategy for finding new compounds was to construct a 1,9-condensed tricyclic benzodiazepine ring system. French chemists simultaneously and independently reported[8)] compounds of this type, but no further details have been reported since their patent publication.

As a result of our studies, we selected FK-480 as a novel, potent and orally effective CCK-A antagonist, which is now undergoing clinical trials for the treatment of chronic pancreatitis. This paper describes the syntheses and the structure–activity relationships of FK-480 and related compounds.

Chemistry

The synthetic scheme is outlined in Chart 1. Of the starting materials (**1**), compounds **1d—f** were prepared by the methods described in the literature,[9)] as they were not commercially available. Compounds (**3**), 2-aminobenzophenone derivatives used as key materials in the construction of the 5-aryl-1,4-benzodiazepine nuclei (**5**), were prepared in moderate yields by regio-selective Friedel–Crafts reactions using benzonitrile derivatives as acylating agents, and boron trichloride and aluminium chloride as condensing reagents.[10)] Details of the intermediates **3** are summarized in Table V.

The NH group of compound **3**, although forming an intramolecular hydrogen bond with the neighbouring carbonyl group, was easily acylated with bromoacetyl bromide in the presence of pyridine in methylene chloride to afford **4a—f** (see Table VI), followed by treatment with an excess of hydroxylamine to construct the novel tricyclic 1,4-benzodiazepine 4-*N*-oxides, **5a—f** (Table VII). The *N*-oxides (**5**) were rearranged to 3-acetoxy-1,4-benzodiazepine derivatives (**6**) with acetic anhydride and they were quantitatively hydrolized to the 3-hydroxy derivatives (**7**). When trifluoroacetic anhydride was used in the rearrangement reaction, the hydrolysis proceeded smoothly, during the work-up because of the instability of the trifluoroacetate, to give a sole product **7**. The physical data and yields of **6** and **7** are shown in Tables VIII and IX.

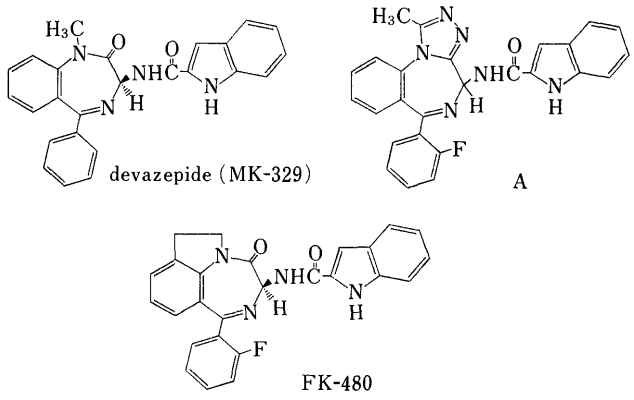


Fig. 1

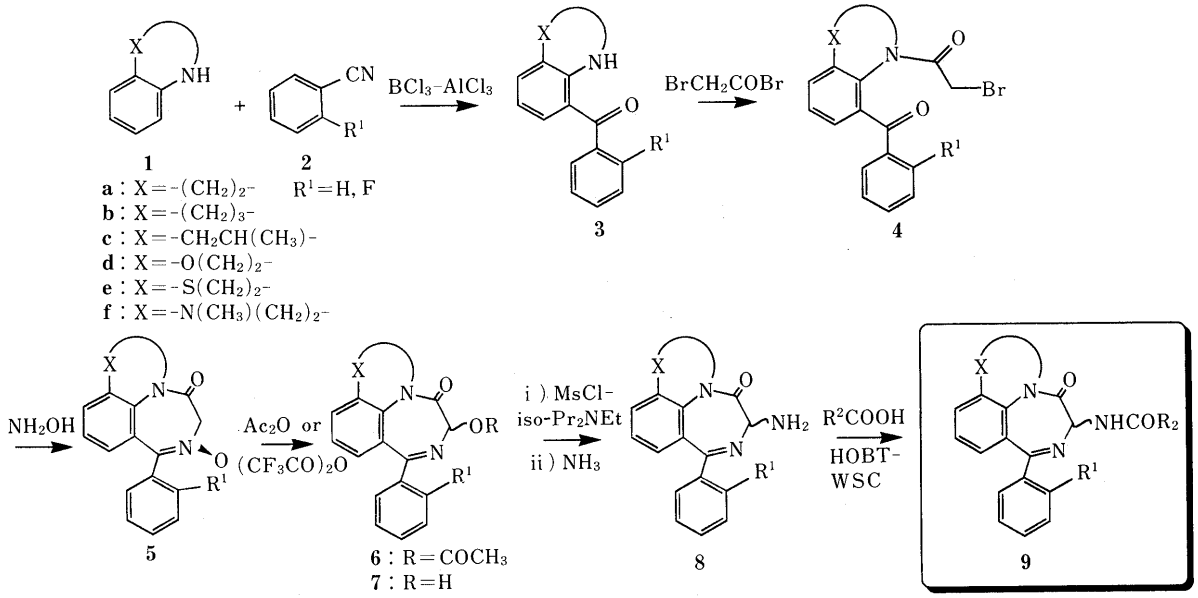


Chart 1

The hydroxy group was activated by mesylation and subsequently substituted with gaseous or aqueous ammonia to afford 3-amino derivatives (**8**). However, when a saturated solution of ammonia in methanol was used, the 3-methoxy derivative was obtained as a by-product in a considerable yield. The reactivities of the mesylates to ammonia differed from one another; for example, with aqueous ammonia **8a** was obtained in high yield, but even under strictly anhydrous conditions, 3-hydroxy derivatives **7** were often recovered in troublesome yields. For mechanistic consideration of the substitution reaction, as shown in Fig. 2, ammonia concurrently attacked two positions of the mesylate, the carbon at the desired 3-position and the sulfur center of the mesylate (shown with arrows (1) and dotted arrows (2), respectively, in Fig. 2). Exchange of mesylate for tosylate in order to decrease the chance of attack of ammonia at the sulfur atom by steric hindrance gave the desired **8a** ($R^1=H$) with a slight increase in the yields. The yields and physical data of intermediates **8** are summarized in Table X.

3-Amino-1,4-benzodiazepine derivatives (**8**) were acylated easily by general methodology, with acid halide, mixed anhydride and carbodiimide, and so on. The final acylated compounds, **9**, are listed in Table I-1—4 with their physical data, yields and synthetic methods.

3-Aminobenzodiazepines, **8a** ($R^1=H$, F) and **8f** ($R^1=F$), whose acylated derivatives possess potent receptor binding inhibiting effects, were optically resolved by the same method reported previously,[11] as shown in Chart 2. This method, however, involves separation of the diastereo-isomers by column chromatography, and it is not suitable for a large-scale preparation. Thus, we investigated the application of optical resolution methods applicable on a large scale. Of a variety of optically active acids, L-tartaric acid was found to be the most suitable for giving a crystalline diastereomeric salt [(−)-**8a** ($R^1=F$) L-tartaric acid] from a solution of racemic **8a** ($R^1=F$). To avoid racemization due to the acidic proton

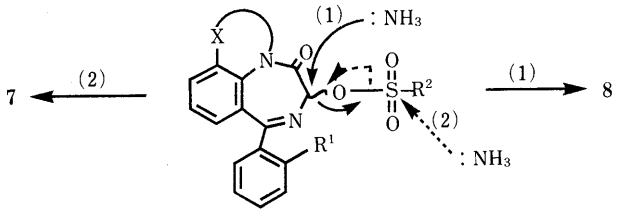


Fig. 2

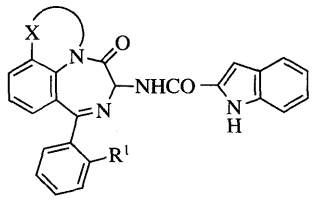
at the 3-position, purification of the salt was performed by a repeated salting-out procedure at ambient temperature in preference to recrystallization by heating. Concurrently, a very efficient method for the optical resolution of the 3-amino precursor of MK-329 using (1*S*)-(+)-10-camphorsulfonic acid (CSA) was disclosed.[12] We applied this method to the resolution of our compound **8a** ($R^1=F$). The desired diastereomeric salt [(−)-**8a** ($R^1=F$) L-tartaric acid] was obtained in 75% yield and treated with an aqueous solution of sodium bicarbonate to afford free (−)-**8a** ($R^1=F$) with a purity of over 99.0% ee as determined by high performance liquid chromatography (HPLC) with a chiral stationary-phase column.

The absolute configuration at the 3-position of (−)-**8a** ($R^1=F$) was determined to be (*S*) by X-ray analysis. A crystal suitable for the X-ray analysis was obtained by recrystallization from EtOH of the urea derivative (**13**) prepared from (−)-**8a** ($R^1=F$) and (*S*)-(−)-α-methylbenzyl isocyanate (**12**) as shown in Chart 3. The ORTEP drawing is shown in Fig. 3. The final product, FK-480, were found to be the (3*S*) enantiomer because acylation of (−)-**8a** ($R^1=F$) with (*S*)-(−)-α-methylbenzyl isocyanate or with indole-2-carboxylic acid (or acid chloride) could be performed without inversion.

Structure–Activity Relationships and Discussion

The biological activities of the compounds prepared in

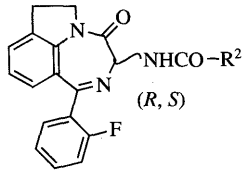
TABLE I-1. Yields, Physical and Spectral Data of Compounds **9a—m**



Compd.	X	R^1	Stereo.	Yield (%) (Method)	mp (°C)	*Anal.* (Calcd/Found)	Spectral data			$[\alpha]_D^{20}$
							IR (Nujol) cm^{-1}	^{1}H-NMR (DMSO-d_6)	MS *m/z*	
9a	$-CH_2CH_2-$	H	*R, S*	62.3 (A)	182—185 (dec.)	$C_{26}H_{20}N_4O_2$ C, 74.26/74.12; H, 4.79/ 4.81; N, 13.33/13.19	NT	2.90—3.50 (2H, m), 3.75—4.20 (1H, m), 4.50—4.85 (1H, m), 5.65 (1H, d, 8 Hz), 6.90—7.70 (13H, m), 8.03 (1H, d, 8 Hz), 9.85 (1H, br s)	420 (M^+)	
9b	$-CH_2CH_2-$	H	*R*	55.9 (A)	172—177 (dec.)	$C_{26}H_{20}N_4O_2$ C, 74.26/74.33; H, 4.79/ 4.71; N, 13.33/13.25	3230, 1674, 1638, 1600, 1530, 1445, 1370, 1300, 1236, 1112, 745, 695	3.0—3.5 (2H, m), 3.8—4.16 (1H, m), 4.5—4.82 (1H, m), 5.67 (1H, d, 7.5 Hz), 7.0—7.75 (13H, m), 8.08 (1H, d, 7.5 Hz), 9.95 (1H, br s)	420 (M^+)	64.88° (c=0.52, $CHCl_3$)
9c	$-CH_2CH_2-$	H	*S*	76.2 (A)	172—178 (dec.)	$C_{26}H_{20}N_4O_2$ C, 74.26/74.27; H, 4.79/ 4.86; N, 13.33/13.30	3230, 1675, 1638, 1600, 1530, 1445, 1372, 1300, 1235, 1110, 745, 694	3.0—3.5 (2H, m), 3.8—4.2 (1H, m), 4.5—4.85 (1H, m), 5.68 (1H, d, 7.5 Hz), 7.0—7.8 (13H, m), 8.07 (1H, d, 7.5 Hz), 9.90 (1H, br s)	420 (M^+)	−64.75° (c=0.52, $CHCl_3$)
9e	$-CH_2CH_2-$	F	*R*	55.5 (A)	262—265 (dec.)	$C_{26}H_{19}FN_4O_2$ C, 66.65/66.51; H, 5.31/ 5.43; N, 13.88/13.75	3391, 3250, 1678, 1640, 1610, 1600, 1580, 1530, 1482	3.10—3.65 (2H, m), 3.71—4.20 (1H, m), 4.31—4.71 (1H, m), 5.57 (1H, d, 8.0 Hz), 6.9—7.75 (12H, m), 9.53 (1H, d, 8.0 Hz)	438 (M^+)	−22.84° (c=0.2, $CHCl_3$)
9f (FK480)	$-CH_2CH_2-$	F	*S*	62.0 (A)	258—262 (dec.)	$C_{26}H_{19}FN_4O_2$ C, 66.65/66.55; H, 5.31/ 5.48; N, 13.83/13.80	3390, 3249, 1679, 1640, 1609, 1600, 1579, 1529, 1481	3.0—3.65 (2H, m), 3.75—4.20 (1H, m), 4.30—4.70 (1H, m), 5.55 (1H, d, 8.0 Hz), 6.9—7.75 (12H, m), 9.53 (1H, d, 8.0 Hz), 11.65 (1H, br s)	438 (M^+)	23.10° (c=0.2, $CHCl_3$)
9g	$-CH_2CH_2CH_2-$	F	*R, S*	48.5 (A)	Amorph.	NT	NT	1.55—2.25 (2H, m), 2.75—3.30 (3H, m), 4.15—4.55 (1H, m), 5.53 (1H, d, 8.0 Hz), 6.85—7.70 (12H, m), 9.40 (1H, d, 8.0 Hz)	452 (M^+)	
9h	$-CH_2CH(CH_3)-$	F	*R, S*	91.6 (A)	>250	$C_{27}H_{21}FN_4O_2$ C, 71.66/71.61; H, 4.68/ 4.76; N, 12.38/12.33	3400, 3270, 1675, 1638, 1610, 1532, 1450, 1373, 1340, 1225, 1118, 770, 755, 738	1.11, 1.54 (3H, each d, each 6 Hz), 2.5—3.8 (2H, m), 4.5—5.1 (1H, m), 5.43, 5.47 (1H, each d, each 8 Hz), 6.9—7.7 (7H, m), 9.43 (1H, d, 8.0 Hz), 11.60 (1H, br s)	452 (M^+)	
9i	$-OCH_2CH_2-$	H	*R, S*	80.0 (A)	182—185 (dec.)	$C_{26}H_{20}FN_4O_3$ C, 71.54/71.46; H, 4.62/ 4.81; N, 12.84/12.80	NT	3.1—3.5 (1H, m), 4.0—4.9 (3H, m), 5.76 (1H, d, 8 Hz), 6.8—7.75 (13H, m), 9.45 (1H, d, 8.0 Hz)	436 (M^+)	
9j	$-SCH_2CH_2-$	F	*R, S*	83.2 (A)	245—250 (dec.)	$C_{26}H_{19}FN_4O_2S$ C, 66.37/66.29; H, 4.07/ 4/21; N, 11.91/11.85	3390, 3270, 1678, 1645, 1530, 1372, 1208, 746	2.98—3.09 (1H, m), 3.2—3.4 (2H, m), 5.0—5.06 (1H, m), 5.70 (1H, d, 8.6 Hz), 6.9—7.7 (12H, m), 9.63 (1H, d, 8.6 Hz), 11.7 (1H, s)	471 (M^++1)	
9k	$-N(CH_3)CH_2CH_2-$	F	*R, S*	55.0 (A)	275—280 (dec.)	$C_{27}H_{22}FN_5O_2$ C, 69.36/69.31; H, 4.74/ 4.80; N, 14.98/14.96	NT	($CDCl_3$) 3.05 (3H, s), 3.0—3.2 (1H, m), 3.4—3.6 (2H, m), 4.96 (1H, br d, 6.4 Hz), 5.92 (1H, d, 4 Hz), 6.5—8.1 (13H, m), 9.78 (1H, s)	467 (M^+)	
9l	$-N(CH_3)CH_2CH_2-$	F	*R*	58.0 (A)	205—210 (dec.)	$C_{27}H_{22}FN_5O_2$ C, 69.36/69.29; H, 4.74/ 4.82; N, 14.98/14.87	3370, 3200, 1676, 1638, 1531, 1489, 1456, 1336, 1220, 1189, 1118, 808, 745	3.04 (3H, s), 3.0—3.1 (1H, m), 3.3—3.5 (2H, m), 4.76 (1H, br d, 6.2 Hz), 5.68 (1H, d, 4.1 Hz), 6.4—7.7 (12H, m), 9.57 (1H, d, 4.1 Hz), 11.64 (1H, s)	467 (M^+)	−79.14° (c=0.80, $CHCl_3$)
9m	$-N(CH_3)CH_2CH_2-$	F	*S*	51.7 (A)	190—194 (dec.)	$C_{27}H_{22}FN_5O_2$ C, 69.36/69.30; H, 4.74/ 4.78; N, 14.98/14.91	3370, 3205, 1678, 1640, 1532, 1490, 1458, 1338, 1216, 1190, 1120, 810, 745	3.04 (3H, s), 3.0—3.1 (1H, m), 3.3—3.5 (2H, m), 4.76 (1H, br d, 6.2 Hz), 5.68 (1H, d, 4.1 Hz), 6.4—7.7 (12H, m), 9.57 (1H, d, 4.1 Hz), 11.64 (1H, s)	467 (M^+)	79.33° (c=0.81, $CHCl_3$)

NT: not tested.

TABLE I-2. Yields, Physical and Spectral Data of Compounds **9n—r**



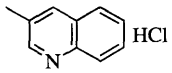
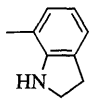
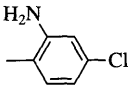
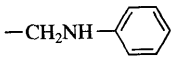
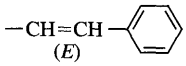
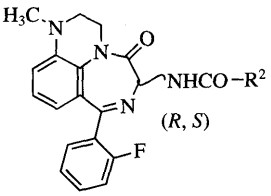
Compound	R^2	Yield (%) (Method)	mp (°C)	*Anal.* (Calcd/Found)	Spectral data		
					IR (Nujol) cm^{-1}	^{1}H-NMR (DMSO-d_6)	MS *m/z*
9n		44.6 (A)	198—200	$C_{27}H_{19}FN_4O_2 \cdot HCl$ C, 66.60/66.45; H, 4.14/ 4.46; N, 11.50/11.34	3550—3100, 2700—2100, 1660, 1605, 1520	3.07—3.55 (2H, m), 3.95—4.20 (1H, m), 4.6—4.8 (1H, m), 5.83 (1H, d, 7.3 Hz), 7.0—7.27 (4H, m), 7.51—7.69 (3H, m), 7.85—7.92 (1H, m), 8.04—8.11 (1H, m), 8.26 (1H, d, 8 Hz), 8.84 (1H, d, 8.5 Hz), 9.47 (1H, d, 7 Hz), 9.60 (1H, s), 9.79 (1H, s)	450 ($M^+ - 36$)
9o		59.1 (A)	165—170 (dec.)	$C_{26}H_{21}FN_4O_2$ C, 70.89/70.82; H, 4.81/ 4.98; N, 12.72/12.70	3310, 1665, 1630, 1590, 1522	3.04 (2H, t, 8.4 Hz), 3.14—3.20 (1H, m), 3.28—3.46 (1H, m), 3.67 (2H, d, 8.4 Hz), 3.96—4.12 (1H, m), 4.61—4.73 (1H, m), 5.62 (1H, d, 7.4 Hz), 6.29 (1H, br s), 6.58—6.66 (1H, m), 6.98—7.71 (9H, m), 7.92 (1H, d, 7.4 Hz)	440 (M^+)
9p		(See Experimental)					
9q		75.1 (A)	135—137 (dec.)	$C_{25}H_{21}FN_4O_2$ C, 70.08/69.11; H, 4.94/ 5.03; N, 13.08/13.02	3450, 3125, 1675, 1650, 1600, 1530	3.06—3.18 (2H, m), 3.89—4.07 (1H, m), 4.57—4.68 (1H, m), 5.48 (1H, d, 8 Hz), 6.7—7.65 (15H, m), 8.21 (1H, d, 8 Hz)	428 (M^+)
9r		53.9 (A)	189—190	$C_{26}H_{20}FN_3O_2$ C, 73.40/73.29; H, 4.74/ 4.63; N, 9.88/ 9.69	3290, 1675, 1650, 1620, 1530	($CDCl_3$) 3.0—3.6 (2H, m), 3.8—4.8 (1H, m), 5.55 (1H, d, 8 Hz), 6.58 (1H, d, 15 Hz), 6.83—7.8 (11H, m)	425 (M^+)

TABLE I-3. Yields, Physical and Spectral Data of Compounds **9s—y**



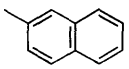
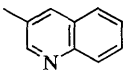
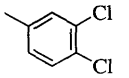
Compound	R^2	Yield (%) (Method)	mp (°C)	*Anal.* (Calcd/Found)	Spectral data		
					IR (Nujol) cm^{-1}	^{1}H-NMR (DMSO-d_6)	MS *m/z*
9s		79.9 (A)	142—145 (dec.)	$C_{29}H_{23}FN_4O_2$ C, 72.79/72.54; H, 4.84/ 4.95; N, 11.71/11.58	3200, 1660, 1656, 1625, 1600, 1495, 1400, 1375, 1337, 1286, 871, 780, 763, 745	3.05 (3H, s), 3.0—3.2 (1H, m), 3.4—3.6 (2H, m), 4.77 (1H, br d, 6.2 Hz), 5.72 (1H, d, 6 Hz), 6.44 (1H, d, 3.5 Hz), 6.95 (1H, d, 3.5 Hz), 7.0—8.1 (11H, m), 8.71 (1H, s), 9.76 (1H, d, 4 Hz)	478 (M^+)
9t		80.3 (A)	246—251 (dec.)	$C_{28}H_{22}FN_5O_2$ C, 70.13/69.96; H, 4.63/ 4.85; N, 14.61/14.52	3390, 1675, 1660, 1610, 1500, 1375, 1340, 1228, 1020, 884, 774, 755, 720	3.05 (3H, s), 3.0—3.2 (1H, m), 3.4—3.6 (2H, m), 4.77 (1H, br d, 6.2 Hz), 5.71 (1H, d, 4 Hz), 6.44 (1H, d, 3.4 Hz), 6.96 (1H, d, 3.4 Hz), 7.0—8.2 (9H, m), 9.06 (1H, d, 1 Hz), 9.73 (1H, d, 1 Hz), 10.08 (1H, d, 4 Hz)	479 (M^+)
9u		95.1 (A)	215—218	$C_{25}H_{19}Cl_2FN_4O_2$ C, 60.37/60.21; H, 3.85/ 3.97; N, 11.27/11.13	3200, 1691, 1647, 1610, 1595, 1530, 1375, 1345, 1280, 1183, 876, 781, 749	3.04 (3H, s), 3.0—3.1 (1H, m), 3.4—3.6 (2H, m), 4.74 (1H, br d, 6.1 Hz), 5.62 (1H, d, 4 Hz), 6.42 (1H, d, 3.5 Hz), 6.94 (1H, d, 3.5 Hz), 7.0—8.3 (9H, m), 9.96 (1H, d, 4 Hz)	497 (M^+)

TABLE I-3. (continued)

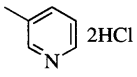
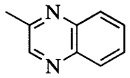
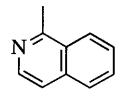
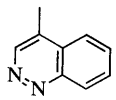
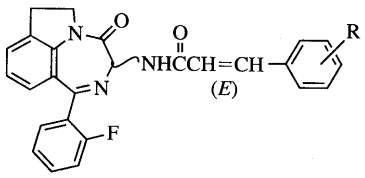
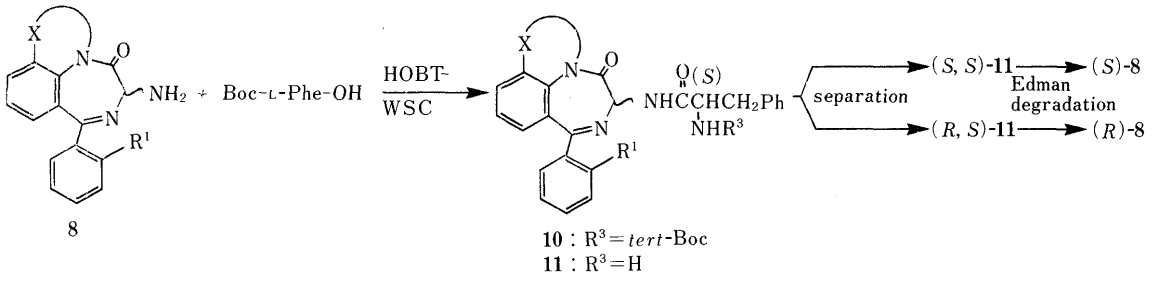
Compound	R^2	Yield (%) (Method)	mp (°C)	*Anal.* (Calcd/Found)	Spectral data		
					IR (Nujol) cm^{-1}	^{1}H-NMR (DMSO-d_6)	MS *m/z*
9v	 2HCl	77.5 (A)	185—190 (dec.)	$C_{24}H_{20}FN_5O_2 \cdot 2HCl$ C, 57.38/57.26; H, 4.42/ 4.65; N, 13.94/13.79	3600—3100, 2700—1900, 1670, 1630, 1610, 1580	3.04—3.50 (6H, m), 4.75 (1H, d, 12.3 Hz), 5.65 (1H, d, 7.6 Hz), 6.48 (1H, d, 7.3 Hz), 6.94—8.09 (7H, m), 8.89 (1H, d, 8.1 Hz), 9.03 (1H, d, 5.3 Hz), 9.36 (1H, s), 10.35 (1H, d, 7.6 Hz)	429 ($M^+ - 73$)
9w		77.3 (A)	278—280	$C_{27}H_{21}FN_6O_2$ C, 67.49/67.34; H, 4.41/ 4.62; N, 17.49/17.41	3350, 1670, 1610, 1575, 1515	3.04—3.5 (6H, m), 4.79 (1H, d, 12.4 Hz), 5.64 (1H, d, 7.9 Hz), 6.47 (1H, d, 7.2 Hz), 6.95—8.36 (10H, m), 9.53—9.6 (2H, m)	480 (M^+)
9x	 HCl	70.8 (A)	160—170 (dec.)	$C_{28}H_{22}FN_5O_2 \cdot HCl$ C, 65.17/64.02; H, 4.49/ 4.57; N, 13.57/13.39	3550—3100, 2700—2000, 1660, 1605, 1580	2.95—3.16 (1H, m), 3.05 (3H, s), 3.39—3.51 (2H, m), 4.80 (1H, d, 12.4 Hz), 5.65 (1H, d, 7.9 Hz), 6.48 (1H, d, 6.9 Hz), 6.95—8.18 (10H, m), 8.67 (1H, d, 55.6 Hz), 9.19 (1H, d, 8.5 Hz), 9.86 (1H, d, 7.9 Hz)	479 ($M^+ - 37$)
9y		72.0 (A)	228—230	$C_{27}H_{21}FN_6O_2$ C, 67.49/67.41; H, 4.41/ 4.58; N, 17.49/17.32	3200, 1690, 1660, 1610, 1595, 1535	2.95—3.63 (6H, m), 4.82 (1H, d, 12.4 Hz), 5.72 (1H, d, 7.6 Hz), 6.47 (1H, d, 7.0 Hz), 6.99—8.60 (10H, m), 9.48 (1H, s), 10.41 (1H, d, 7.6 Hz)	480 (M^+)

TABLE I-4. Yields, Physical and Spectral Data of Compounds **9aa**—**ai**



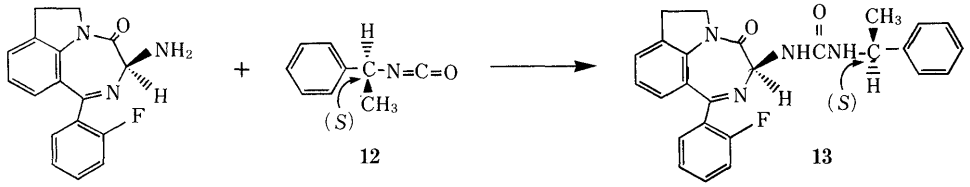
Compound	R	Yield (%) (Method)	mp (°C)	*Anal.* (Calcd/Found)	Spectral data		
					IR (Nujol) cm^{-1}	^{1}H-NMR (DMSO-d_6)	MS *m/z*
9aa	(See Experimental)	(D)					
9ab	2-NH_2 (3-*S* isomer)	51.2 (D)	228—230 (dec.)	$C_{26}H_{21}FN_4O_2$ C, 70.89/70.84; H, 4.78/ 4.81; N, 12.72/12.68	3280, 1670, 1645, 1615, 1545	3.08—3.45 (2H, m), 4.00 (2H, s), 3.94—4.1 (1H, m), 4.6—4.71 (1H, m), 5.06 (1H, d, 7.9 Hz), 6.55 (1H, d, 15.4 Hz), 6.67—7.69 (12H, m), 7.83 (1H, d, 15.5 Hz)	440 (M^+)
9ac	(See Experimental)	(E)					
9ad	2-Cl	67.7 (A)	137—140 (dec.)	$C_{26}H_{19}ClFN_3O_2$ C, 67.90/67.78; H, 4.16/ 4.35; N, 9.14/ 8.97	3250, 1670, 1650, 1635, 1540	3.09—3.47 (2H, m), 3.95—4.11 (1H, m), 4.61—4.73 (1H, m), 5.60 (1H, d, 8 Hz), 6.64 (1H, d, 16 Hz), 6.98—7.71 (12H, m), 8.09 (1H, d, 15.5 Hz)	459 (M^+)
9ae	3-Cl	64.4 (A)	130—135 (dec.)	$C_{26}H_{19}ClFN_3O_2$ C, 67.90/67.85; H, 4.16/ 4.41; N, 9.14/ 9.02	3350—3100, 1690, 1660, 1630	3.09—3.47 (2H, m), 3.95—4.11 (1H, m), 4.61—4.77 (1H, m), 5.58 (1H, d, 8 Hz), 6.64 (1H, d, 16 Hz), 6.99—7.67 (13H, m)	459 (M^+)
9af	4-F	72.1 (A)	186—191	$C_{26}H_{19}F_2N_3O_2$ C, 70.42/70.19; H, 4.32/ 4.54; N, 9.48/ 9.41	3290, 1686, 1655, 1635	3.09—3.47 (2H, m), 3.95—4.11 (1H, m), 4.6—4.73 (1H, m), 5.59 (1H, d, 8 Hz), 6.56 (1H, d, 16 Hz), 6.99—7.7 (13H, m),	443 (M^+)
9ag	2-Cl	57.1 (C)	239—241 (dec.)	$C_{26}H_{20}FN_3O_3$ C, 70.73/70.59; H, 4.57/ 4.64; N, 9.52/ 9.38	3325, 3200—3000, 1670, 1655, 1610, 1600, 1510	2.8—3.5 (2H, m), 3.8—4.3 (1H, m), 4.43—4.93 (1H, m), 5.62 (1H, d, 8 Hz), 6.78—8.1 (14H, m), 8.57 (1H, br s)	441 (M^+)
9ah	2-OH (3-*S* isomer)	80.3 (C)	178—192 (dec.)	$C_{26}H_{20}FN_3O_3$ C, 70.73/70.61; H, 4.57/ 4.72; N, 9.52/ 9.44	3400—3000, 1650, 1600	3.09—3.47 (2H, m), 3.97—4.12 (1H, m), 4.63—4.73 (1H, m), 5.65 (1H, d, 8 Hz), 6.76—7.72 (13H, m), 7.98 (1H, d, 16 Hz), 8.76 (1H, s)	441 (M^+)
9ai	3,4-$(OH)_2$	37.4 (A)	185—195 (dec.)	$C_{26}H_{20}FN_3O_4$ C, 68.26/68.15; H, 4.41/ 4.59; N, 9.19/ 9.08	3550—3000, 1650, 1600, 1510	3.02—3.40 (2H, m), 3.89—4.05 (1H, m), 4.57—4.67 (1H, m), 5.59 (1H, d, 7.6 Hz), 6.29 (1H, d, 15.6 Hz), 6.65—8.09 (14H, m)	457 (M^+)



8

10 : $R^3 = tert$-Boc
11 : R^3=H

Chart 2



8a(−)

12

13

Chart 3

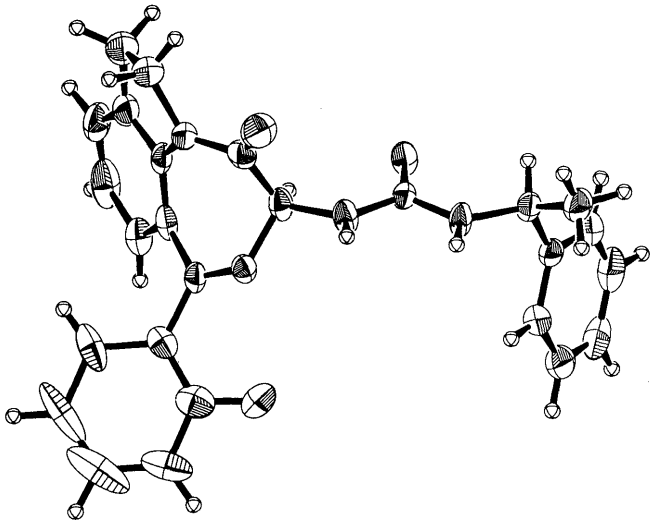


Fig. 3

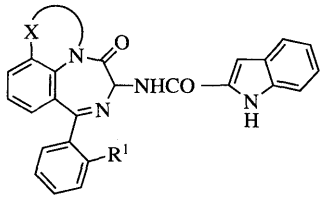
this paper were preliminarily evaluated by means of the following tests; (i) inhibition of ^{125}I-CCK-8 binding in the rat pancreas *in vitro*,[13] and (ii) gastric emptying effect in mice after *p.o.* administration *in vivo*.[14]

Pyrrolo-1,4-benzodiazepine derivatives (**9a**) showed a comparable potency to that of MK-329 and its 1,2-ring closed 4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine (compound A)[7] as shown in Table II. This prompted us to synthesize other novel ring systems bearing trimethylene (**9g**), ethylene substituted by methyl (**9h**), and alkylene replaced by heteroatoms (**9i**—**k**) at the 1,9-positions. All derivatives, which have a variety of novel ring systems, were found to be effective in the same manner as **9a**, except for the morpholinobenzodiazepine system, **9i**. (*S*)-Enantiomers were generally more potent than (*R*)-isomers by about 50—100 folds, which is similar to the cases of MK-329 and related compounds. By comparing **9a** with **9d**, **9b** with **9e** and **9c** with **9f**, the fluorine atom as a substituent of the phenyl ring at the 5-position was found to be slightly more effective. Compounds **9f**, **9h** and **9m** were the most potent in this series. However, **9h** has two asymmetric carbons, and separation of its optical isomers was expected to be difficult on an industrial scale. So we selected **9f** and **9m** as "lead compounds" for optimization studies. The indolyl group of **9f** or **9m** was exchanged for other substituents. New derivatives were prepared in racemic forms and compared with **9d** or **9k**, which are racemic forms of **9f** and **9m**, respectively. The results of the biological evaluations are summarized in Table III-1 and -2. Three compounds, **9n**, **9p** and **9r** were found to be as potent as the reference compound **9d** in the pyrrolo[3,2,1-*jk*][1,4]benzodiazepine series but in the pyrazino[3,2,1-*jk*][1,4]benzodiazepine system, no compound comparable with the reference **9k** could be found.

Structural comparison of **9r** with **9d** was very interesting, because the *E*-cinnamyl moiety could be envisioned as structurally similar to the indolyl group. So we investigated the substituent effects of the *E*-cinnamyl phenyl ring, as summarized in Table IV. First of all, a 2-amino-*E*-cinnamyl group, the 1,2-bond-cleaved form of the 2-indolyl group, was introduced in place of the simple *E*-cinnamyl group (**9aa**). It was found to be more potent in both assays. The optically active (3*S*) derivative, **9ab**, was more potent than the lead compounds **9f** and **9m**. However, acetylation of the 2-amino group halved the potency in comparison to **9aa**, contrary to expectation. Neither chlorine not fluorine was very effective for increasing the potency. But the 2-hydroxy group, which has phenolic acidity, was found to be effective. The potency of the racemate **9ag** was the same as that of **9aa**. The optically resolved **9ah** (3*S*) was as potent as **9ab**, although the *in vivo* gastric emptying effect was slightly weaker than that of **9ab**. 3,4-Dihydroxy-*E*-cinnamyl, however, decreased the potencies dramatically.

These results show that 2-indolyl, 2-amino-*E*-cinnamyl and 2-hydroxy-*E*-cinnamyl moieties are biososters, playing the same biological role. Unfortunately these two potent compounds were found to be unstable to sunlight owing

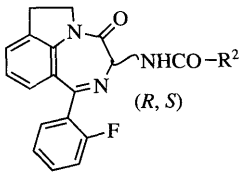
TABLE II. Biological Evaluation Results of Novel Tricyclic 1,4-Benzodiazepine Derivatives (**9a—m**)

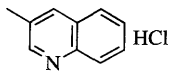
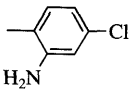
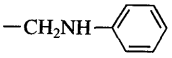
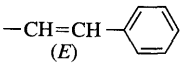
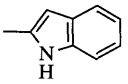


Compound	X	R^1	Stereo.	Inhibition of receptor binding[a]		Gastric emptying effect[b]	
				IC_{50} (M)	(%)	ED_{50} (mg/kg)	*p.o.* (%)
9a	$-CH_2CH_2-$	H	*R,S*	2.5×10^{-9}	(96.5)	0.082	(100)
9b	$-CH_2CH_2-$	H	*R*	7.2×10^{-8}	(11.0)	1.12	(9.5)
9c	$-CH_2CH_2-$	H	*S*	8.0×10^{-10}	(80.0*)	0.032	(86.5*)
9d	$-CH_2CH_2-$	F	*R,S*	1.7×10^{-9}	(96.2)	0.049	(100)
9e	$-CH_2CH_2-$	F	*R*	1.8×10^{-8}	(23.0)	0.672	(19.4)
9f (FK480)	$-CH_2CH_2-$	F	*S*	6.7×10^{-10}	(95.0*)	0.010	(100*)
9g	$-CH_2CH_2CH_2-$	F	*R,S*		(96.0)		
9h	$-CH_2CH(CH_3)-$	F	*R,S*	6.1×10^{-10}	(95.3)	0.03	(100)
9i	$-OCH_2CH_2-$	H	*R,S*	NT	(77.2)	NT	(0)
9j	$-SCH_2CH_2-$	F	*R,S*		(92.5)		
9k	$-N(CH_3)CH_2CH_2-$	F	*R,S*	1.3×10^{-9}	(92.8)	0.007	(100)
9l	$-N(CH_3)CH_2CH_2-$	F	*R*	7.4×10^{-9}	(56.0)	NT	(NT)
9m	$-N(CH_3)CH_2CH_2-$	F	*S*	3.3×10^{-10}	(98.5)	0.01	(90**)
MK-329			*S*	4.4×10^{-10}	(98.7)	0.039	
Compd. A[c]			*R,S*	2.0×10^{-10}		0.05	

a) Inhibition of ^{125}I-CCK-8 binding to rat pancreatic membrane (in parentheses, percentage inhibition at 10^{-8} or 3.2×10^{-9} M (*)). *b*) Inhibitory effect of compounds on CCK-8 induced inhibition of charcoal meal gastric emptying in mice (in parentheses, percentage inhibition at 0.32, 0.1(*) or 0.032(**) mg/kg). *c*) 1-Methyl-4(*R,S*)-4-(2-indolylcarbonyl)amino-6-(2-fluorophenyl)-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine.

TABLE III-1. Biological Evaluation Results of Novel Pyrrolo[3,2,1-*jk*]-[1,4]benzodiazepine Derivatives (**9n—r**)



Compd.	R^2	Inhibition of receptor binding[a]		Gastric emptying effect[b]	
		IC_{50} (M)	(%)	ED_{50} (mg/kg)	*p.o.* (%)
9n		NT	(73.3)	0.026	(100)
9o		NT	(76.3)	NT	(80)
9p		1.5×10^{-9}	(90.3)	0.05	(95)
9q		NT	(16.8)	NT	(NT)
9r	 (*E*)	1.2×10^{-9}	(91.6)	0.10	(85)
Ref. **9d**		1.7×10^{-9}	(96.2)	0.049	(100)

a, b) See footnotes *a*) and *b*) in Table II. NT: not tested.

to *E*- and *Z*-isomerization.

Of all compounds prepared, we selected **9f** (FK-480) as a candidate compound for development because of the easy availability of the starting material indoline and the easy and efficient optical resolution of the intermediate **8a** ($R^1=F$).

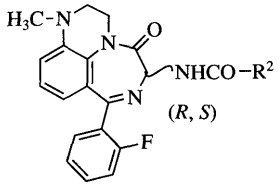
The pharmaceutical evaluation results of FK-480 in comparison to Loxiglumide, a glutamic acid derivative now undergoing clinical trials, will be reported in detail elsewhere.[15]

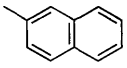
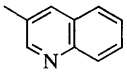
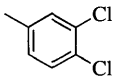
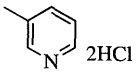
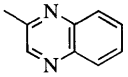
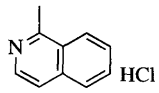
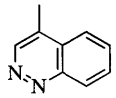
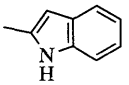
Experimental

All melting points were determined in open glass capillaries on a Thomas–Hoover apparatus and are uncorrected. Infared (IR) spectra were recorded on a Hitach 260-10 IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Hitachi R-90H or Bruker AC-200P NMR spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on JEOL JMS D-300 MS or Hitachi M-1000H (LC-MS system) spectrometer. Column chromatography was performed on a silica gel (Merck Kieselgel 60, 230—400 mesh). Elemental analyses were carried out on a Perkin-Elmer 2400CHN elemental analyzer. Yields were not optimized.

7-(2-Fluorobenzoyl)-indoline (3a, $R^1=F$) A solution of indoline (69.2 g, 0.58 mol) and 2-fluorobenzonitrile (84.5 g, 0.696 mol) in dry toluene (280 ml) was added dropwise to a solution of BCl_3 (75.0 g, 0.64 mol) in dry toluene (415 ml) under cooling in an ice-bath (0 to 5 °C) and stirring over a period of 2.5 h. After the addition was completed, $AlCl_3$ (85.4 g, 0.64 mol) was added portionwise to the above reaction mixture under the same conditions over 30 min. The mixture was allowed to warm to ambient temperature and then refluxed for 16 h with stirring. A 2 N HCl solution (600 ml) was added dropwise to the reaction mixture under stirring at 10 °C. After the addition was completed, the mixture was refluxed for 2.5 h and then cooled to 10 °C. The resultant precipitates were collected by filtration and poured into a mixture of ethyl acetate (2000 ml) and water (1000 ml). The suspension was adjusted to pH 7 to 8 with 25% aqueous NaOH then stirred for about 30 min, and the

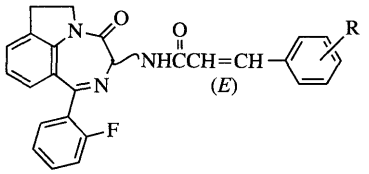
TABLE III-2. Biological Evaluation Results of Novel Pyrazino[3,2,1-*jk*][1,4]benzodiazepine Derivatives (**9s—y**)



Compd.	R^2	Inhibition of receptor binding[a]		Gastric emptying effect[b]	
		IC_{50} (M)	(%)	ED_{50} (mg/kg)	*p.o.* (%)
9s			(77.8)		(80)
9t			(79.9)		(40)
9u			(75.7)		(50)
9v			(−0.7)		(NT)
9w			(26.9)		(NT)
9x			(2.9)		(NT)
9y			(−0.4)		(NT)
Ref. **9k**		1.3×10^{-9}	(92.8)	0.007	(100)

a, b) See footnotes *a*) and *b*) in Table II. NT: not tested.

TABLE IV. Biological Evaluation Results of Novel Pyrrolo[3,2,1-*jk*][1,4]benzodiazepines Containing Substituted Cinnamoylamino Groups at the 3-Position (**9aa—ai**)



Compd.	R^2	Inhibition of receptor binding[a]		Gastric emptying effect[b]	
		IC_{50} (M)	(%)	ED_{50} (mg/kg)	*p.o.* (%)
9aa	2-NH_2		(94.7)	0.010	(100)
9ab	2-NH_2 (3-*S* isomer)	5.7×10^{-10}	(90.4*)	0.0045	(100**)
9ac	2-$NHCOCH_3$		(53.5)		(100)
9ad	2-Cl		(77.2)		(NT)
9ae	3-Cl		(80.2)		(NT)
9af	4-F		(49.5)		(NT)
9ag	2-OH		(94.1)	0.05	(100)
9ah	2-OH (3-*S* isomer)	5.2×10^{-10}	(92.1*)	0.017	(NT)
9ai	3,4-$(OH)_2$		(17.1)		(NT)
Ref. **9r**	H	1.2×10^{-9}	(91.6)	0.10	(85)

a, b) See footnotes *a*) and *b*) in Table II. NT: not tested.

undissolved mass was removed by filtration. The separated organic layer was washed with water twice and dried over $MgSO_4$. Removal of the solvent gave an orange oil, which crystallized on standing (102.30 g, 73.1% yield). This was used in the following reaction without further purification. An analytical sample was obtained by recrystallization from petroleum ether. mp 44—45.5 °C. *Anal.* Calcd for $C_{15}H_{12}FNO$: C, 74.67, H, 5.02; N, 5.81. Found: C, 74.51; H, 4.98; N, 5.92. IR (Nujol) cm^{-1}: 3370, 1615, 1605, 1575, 1565, 1475. ^{1}H-NMR ($CDCl_3$) δ: 3.15 (2H, t, J=8 Hz), 3.57 (2H, t, J=8 Hz), 6.33—6.70 (1H, m), 7.0—7.73 (7H, m). MS *m/z*: 241 (M^+).

The other intermediates **3** were prepared similarly, and the data are summarized in Table V.

1-(Bromoacetyl)-7-(2-fluorobenzoyl)indoline (4a, R^1=F) A solution of bromoacetyl bromide (58.0 g, 0.288 mol) in CH_2Cl_2 (50 ml) was added dropwise to a solution of **3a** (R^1=F) (58.0 g, 0.24 mol) and pyridine (19.0 g, 0.24 mol) in CH_2Cl_2 (1000 ml) under stirring and cooling in an ice-bath over a period of 45 min. After the addition was completed, the mixture was stirred under the same conditions for anothr 1 h. Water (500 ml) was added to the reaction mixture with stirring and the separated organic layer was washed with water twice and dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded a residue, to which was added (iso-Pr)$_2$O (300 ml). Trituration gave crystals, which were collected by filtration and washed with (iso-Pr)$_2$O to give the title compound. It was used in the following reaction without further purification (83.7 g, 96.0% yield). An analytical sample was obtained by recrystallization from EtOH. mp 139—141 °C. *Anal.* Calcd for $C_{17}H_{13}BrFNO_2$: C, 56.37; H, 3.62; N, 3.87. Found: C, 56.22; H, 3.54; N, 3.75. IR (Nujol) cm^{-1}: 1660, 1655, 1602, 1582. ^{1}H-NMR ($CDCl_3$) δ: 3.23 (2H, t, J=8.0 Hz), 3.79 (2H, s), 4.23 (2H, t, J=8.0 Hz), 7.06—7.87 (7H, m). MS *m/z*: 362 (M^+).

The other intermediates **4** were prepared similarly, and the data are summarized in Table VI.

1-(2-Fluorophenyl)-4-oxo-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]-benzodiazepin-2-oxide (5a, R^1=F) **4a** (R^1=F) (82.0 g, 0.226 mol) and EtOH (250 ml) were each added portionwise to a 50% aqueous ethanolic solution (800 ml) of NaOH (40.8 g, 1.02 mol) and $NH_2OH \cdot HCl$ (81.0 g, 1.13 mol) under stirring and warming at 50 °C over a period of 0.5 h. After the addition was completed, the mixture was stirred for 2.5 h at 50—55 °C, then cooled in an ice-bath for 0.5 h. The resultant crystals were collected by filtration and washed with water and cooled ethanol, followed by air-drying to afford the title compound, which was used in the following reaction without further purification (60.5 g 90.3% yield). An analytical sample was obtained by recrystallization from a mixture of EtOH and AcOEt. mp 228.5—229 °C (dec.). *Anal.* Calcd for $C_{17}H_{13}N_2O_2$: C, 73.63; H, 4.72; N, 10.10. Found: C, 73.45; H, 4.79; N, 10.28. IR (Nujol) cm^{-1}: 1675, 1665, 1608, 1585, 1570, 1512, 1488. ^{1}H-NMR (DMSO-d_6) δ: 3.22 (2H, t, J=7.8 Hz), 4.23 (2H, t, J=7.8 Hz), 4.74 (2H, s), 6.72 (1H, d, J=7.9 Hz), 7.09 (1H, t, J=7.4 Hz), 7.2—7.6 (5H, m). MS *m/z*: 296 (M^+).

The other intermediates **5** were prepared similarly and the data are summarized in Table VII.

(3*RS*)-3-Acetoxy-1-(2-fluorophenyl)-3,4,6,7-tetrahydropyrrolo-[3,2,1-*jk*][1,4]-benzodiazepin-4(3*H*)-one (6a, R^1=F) A solution of **5a** (R^1=F) (59.0 g, 0.2 mol) in acetic anhydride (415 ml) was heated gradually to 105 °C. After the mixture turned into a clear solution, the heating was continued for 10 min. The mixture was then cooled in an ice-bath and stirring was continued for a further 30 min. To a suspension of the product, (iso-Pr)$_2$O (1.2 l) was added with stirring. The resultant crystals were collected by filtration, washed with (iso-Pr)$_2$O and air-dried to afford the title compound, which was used in the following reaction without further purification (61.9 g, 91.8% yield). An analytical sample was obtained by recrystallization from EtOH. mp 189—190.5 °C. *Anal.* Calcd for $C_{19}H_{15}FN_2O_3$: C, 67.45; H, 4.47; N, 8.28. Found: C, 67.51; H, 4.44; N, 8.30. IR (Nujol) cm^{-1}: 1746, 1690, 1600, 1581. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s), 2.90—3.60 (2H, m), 3.73—4.20 (1H, m), 4.25—4.65 (1H, m), 5.80 (1H, s), 6.90—7.75 (7H, m). MS *m/z*: 338 (M^+).

The other intermediates **6** were prepared similarly and the data are summarized in Table VIII.

(3*RS*)-3-Hydroxyl-1-(2-fluorophenyl)-3,4,6,7-tetrahydropyrrolo-[3,2,1-*jk*][1,4]-benzodiazepin-4(3*H*)-one (7a, R^1=F) A 1 N NaOH aqueous solution (144 ml) was added dropwise to a solution of **6a** (R^1=

TABLE V. Yields, Physical and Spectral Data of Compounds **3a—f**

Compound	X	R^1	Yield (%)	mp (°C)	*Anal.* (Calcd/Found)	Spectral data		
						IR (Nujol) cm^{-1}	^{1}H-NMR ($CDCl_3$)	MS *m/z*
3a (R^1=H)[a]	$-CH_2CH_2-$	H	88.2					
3b	$-CH_2CH_2CH_2-$	F	65.4	Oil	NT	3300, 3060, 1615, 1609, 1580, 1510, 1490	1.70—2.10 (2H, m), 2.65—2.95 (2H, m), 3.35—3.65 (2H, m), 6.20—6.48 (1H, m), 6.95—7.75 (6H, m), 9.05 (1H, br s)	255 (M^+)
3c	$-CH_2CH(CH_3)-$	F	53.9	64—66	$C_{16}H_{14}FNO$ C, 75.28/75.11; H, 5.53/ 5.65; N, 5.49/ 5.32	3360, 1630, 1570, 1480, 753	1.37 (3H, d, 6.8 Hz), 2.68 (1H, dd, 16, 7 Hz), 3.31 (1H, dd, 16, 9 Hz), 4.0—4.6 (1H, m), 6.3—7.7 (8H, m)	255 (M^+)
3d	$-OCH_2CH_2-$	H	59.5	Oil	NT	3300, 1615, 1595, 1570, 1500	3.50—3.75 (2H, m), 4.20—4.45 (2H, m), 6.30—7.85 (8H, m), 8.35 (1H, br s)	239 (M^+)
3e	$-SCH_2CH_2-$	F	18.1	Oil	NT	3275, 1610, 1505, 985, 828, 745	2.99—3.04 (2H, m), 3.64—3.90 (2H, m), 6.42 (1H, t, 10 Hz), 7.08—7.43 (7H, m), 9.40 (1H, br s)	273 (M^+)
3f	$-NCH_3(CH_2CH_2)-$	F	33.3	90—92	$C_{16}H_{15}FN_2O$ C, 71.09/70.98; H, 5.59/ 5.65; N, 10.30/10.24	3275, 1608, 1520, 1480, 978, 755, 726	2.89 (3H, s), 3.23 (2H, t, 2.6 Hz), 3.71 (2H, m), 6.36—6.77 (3H, m), 7.1—7.4 (4H, m), 9.28 (1H, br s)	270 (M^+)

a) US patent, US-3 597 503. NT: not tested.

TABLE VI. Yields, Physical and Spectral Data of Compounds **4a—f**

Compound	X	R^1	Yield (%)	mp (°C)	*Anal.* (Calcd/Found)	Spectral data		
						IR (Nujol) cm^{-1}	^{1}H-NMR ($CDCl_3$)	MS *m/z*
4a (R^1=H)[a]	$-CH_2CH_2-$	H	96.4	132—133				
4b	$-CH_2CH_2CH_2-$	F	45.2	Amorph.	NT	NT	1.45—4.45 (8H, m), 6.90—7.95 (7H, m)	376 (M^+)
4c	$-CH_2CH(CH_3)-$	F	93.8	110—112	$C_{18}H_{15}BrFNO_2$ C, 57.46/57.35; H, 4.02/ 4.25; N, 3.72/ 3.68	1667, 1639, 1445, 1391, 1275, 1223, 985, 750	1.38 (3H, d, 6.8 Hz), 2.69 (1H, d, 16 Hz), 3.53 (1H, dd, 16, 8 Hz), 3.71 (2H, s), 4.67 (1H, br quintet, *ca.* 7 Hz), 6.9—8.0 (7H, m)	376 (M^+)
4d	$-OCH_2CH_2-$	H	71.2	Oil	NT	(Film) 1675, 1663, 1580	(DMSO-d_6) 3.70—4.25 (2H, m), 4.10 (2H, s), 4.30—4.65 (2H, m), 6.85—7.90 (8H, m)	360 (M^+)
4e	$-SCH_2CH_2-$	F	68.9	106—108	$C_{17}H_{13}BrFNO_2S$ C, 51.78/51.65; H, 3.32/ 3.51; N, 3.55/ 3.38	1662, 1604, 950, 749	2.69—2.84 (1H, m), 2.99—3.09 (1H, m), 3.33—3.47 (1H, m), 3.73 (2H, ABq, 11.5, 20.6 Hz), 4.65—4.76 (1H, m), 7.04—7.81 (7H, m)	394 (M^+)
4f	$-NCH_3(CH_2CH_2)-$	F	98.9	Oil	NT	(Film) 1675, 1662, 1607, 1586, 1500, 1460, 1402, 1335, 1295, 1212, 769, 751	3.25 (3H, s), 3.73 (2H, s), 2.7—4.6 (4H, m), 6.6—7.8 (7H, m)	391 (M^+)

a) US patent, US-3 579 503. NT: not tested.

F) (48.7 g, 0.144 mol) in EtOH (970 ml) under stirring at ambient temperature over a period of 15 min. After the addition was completed, the mixture was stirred under the same conditions for a further 0.5 h. The mixture was adjusted to pH 3—4 with 6 N HCl under ice-bath cooling. EtOH was removed *in vacuo* from the mixture, then CH_2Cl_2 (700 ml) was added to the residual mixture and the whole was vigorously stirred. The separated organic layer was washed with water and dried over $MgSO_4$. The filtrate and washings were combined and evaporated *in vacuo* to give a residue, which was triturated in $(iso\text{-}Pr)_2O$ (200 ml) to afford crystals. Collection by filtration, washing with $(iso\text{-}Pr)_2O$ and air-drying afforded the title compound, which was used in the following reaction without further purification (40.88 g, 95.8% yield). An analytical sample was obtained by recrystallization from AcOEt, mp 167—168.5 °C. *Anal.* Calcd for $C_{17}H_{13}FN_2O_2$: C, 68.91; H, 4.42; N, 9.46. Found: C, 68.88; H, 4.35; N, 9.54. IR (Nujol) cm^{-1}: 3425, 1665, 1609, 1595, 1582. ^{1}H-NMR ($CDCl_3$) δ: 3.03—3.50 (2H, m), 3.60—4.25 (1H, m), 4.25—4.70 (1H, m), 4.78 (1H, d, J=8.0 Hz), 6.40 (1H, d, J=8.0 Hz), 7.0—7.9 (7H, m). MS *m/z*: 296 (M^+).

The other intermediates **7** were prepared similarly and the data are summarized in Table IX.

Compounds **7** could also be prepared from the respective compounds **5** by treatment with trifluoroacetic anhydride in CH_2Cl_2 as follows. A solution of $(CF_3CO)_2O$ (4.15 g, 19.5 mmol) in CH_2Cl_2 (3 ml) was added dropwise to a solution of **5a** (R^1=F) (1.95 g, 6.5 mmol) in CH_2Cl_2 (25 ml) under stirring and cooling in an ice-bath. The mixture was stirred for 2 h under the same conditions and for 4 h at ambient temperature. The reaction mixture was evaporated *in vacuo* below 20 °C. EtOH (50 ml) was added to the residue and the mixture was neutralized with a saturated

TABLE VII. Yields, Physical and Spectral Data of Compounds **5a—f**

Compound	X	R^1	Yield (%)	mp (°C)	*Anal.* (Calcd/Found)	Spectral data		
						IR (Nujol) cm^{-1}	^{1}H-NMR (DMSO-d_6)	MS *m/z*
5a (R^1=H)[a]	$-CH_2CH_2-$	H	75.6	245—250 (dec.)				
5b	$-CH_2CH_2CH_2-$	F	71.2	Amorph.	NT	NT	1.65—2.35 (2H, m), 2.7—3.5 (3H, m), 4.25—4.8 (1H, m), 4.68 (2H, ABq, 12, 80 Hz), 6.75—7.70 (7H, m)	310 (M^+)
5c	$-CH_2CH(CH_3)-$	F	98.8	184—186	$C_{18}H_{15}FN_2O_2$ C, 69.66/69.58; H, 4.82/ 4.86; N, 9.03/ 9.05	1670, 1608, 1448, 1370, 1282, 1260, 1220, 1178, 1040, 760	($CDCl_3$) 1.40 (3H, d, 6.4 Hz), 2.76 (1H, d, 16 Hz), 3.58 (1H, dd, 16, 7.8 Hz), 4.6—5.4 (3H, m), 6.8—7.6 (7H, m)	310 (M^+)
5d	$-OCH_2CH_2-$	H	78.2	145—150 (dec.)	$C_{17}H_{14}FN_2O_3$ C, 69.37/69.11; H, 4.79/ 4.85; N, 9.52/ 9.43	1665, 1580, 1530	2.90—3.50 (1H, m), 4.0—5.15 (5H, m), 6.45—7.75 (8H, m)	294 (M^+)
5e	$-SCH_2CH_2-$	F	26.5	206—206.5	$C_{17}H_{13}FN_2O_2S$ C, 62.18/62.09; H, 3.96/ 4.02; N, 8.53/ 8.44	1670, 1372, 753	($CDCl_3$) 3.05 (1H, dt, 2.8, 12 Hz), 3.24 (1H, dt, 2.8, 12 Hz), 3.44 (1H, dt, 4, 12 Hz), 4.76 (2H, ABq, 12.6, 17.4 Hz), 5.18 (1H, dt, 4, 12 Hz), 6.79—7.51 (8H, m)	329 (M^++1)
3f	$-NCH_3(CH_2CH_2)-$	F	52.2	205—206	$C_{18}H_{16}FN_3O_2$ C, 66.45/66.32; H, 4.96/ 5.05; N, 12.92/12.86	1662, 1609, 1583, 1532, 1493, 1451, 1403, 1335, 1197, 1062, 887, 788, 750	3.01 (3H, s), 3.0—3.0 (1H, m), 3.4—3.5 (2H, m), 4.39 (1H, d, 6.3 Hz), 4.75 (1H, dt, 4.6, 1.3 Hz), 4.89 (1H, d, 6.3 Hz), 6.16 (1H, d, 3.3 Hz), 6.80 (1H, d, 3.3 Hz), 7.04 (1H, t, 4 Hz), 7.2—7.6 (4H, m)	325 (M^+)

a) US patent, US-3 579 503. NT: not tested.

TABLE VIII. Yields, Physical and Spectral Data of Compounds **6a—f**

Compound	X	R^1	Yield (%) (Method)	mp (°C)	*Anal.* (Calcd/Found)	Spectral data		
						IR (Nujol) cm^{-1}	^{1}H-NMR (DMSO-d_6)	MS *m/z*
6a (R^1=H)	$-CH_2CH_2-$	H	91.0 (Ac_2O)	191—193	$C_{19}H_{16}N_2O_3$ C, 71.23/71.15; H, 5.04/ 5.21; N, 8.75/ 8.66	1735, 1700, 1610, 1570	2.22 (3H, s), 3.0—3.4 (2H, m), 3.7—4.1 (1H, m), 4.2—4.6 (1H, m), 5.70 (1H, s), 6.9—7.7 (8H, m)	320 (M^+)
6b	$-CH_2CH_2CH_2-$	F	95.8 (Ac_2O)	Amorph.	NT	NT	1.65—2.40 (2H, m), 2.23 (3H, s), 2.75—3.85 (3H, m), 4.15—4.7 (1H, m), 5.80 (1H, s), 6.95—7.85 (7H, m)	352 (M^+)
6c	$-CH_2CH(CH_3)-$	F	75.0 (Ac_2O)	214—216	$C_{20}H_{17}FN_2O_3$ C, 68.17/68.20; H, 4.86/ 4.88; N, 7.95/ 7.90	1738, 1685. 1609, 1450, 1370, 1235, 1108, 1080, 795, 752	($CDCl_3$) 1.28 (3H, d, 6 Hz), 2.32 (3H, s), 2.69 (1H, d, 16.5 Hz), 3.50 (1H, dd, 16.5, 9 Hz), 4.99 (1H, br quintet, 7.5 Hz), 5.90 (1H, s), 7.0—7.8 (7H, m)	352 (M^+)
6d	$-OCH_2CH_2-$	H	92.3 (Ac_2O)	Oil	NT	(Film) 1727, 1680, 1603, 1580, 1565	2.25 (3H, s), 3.10—3.50 (1H, m), 3.90—4.90 (3H, m), 6.03 (1H, s), 6.80—7.75 (8H, m)	336 (M^+)
6f	$-NCH_3(CH_2CH_2)-$	F	90.2 (Ac_2O)	201—202	$C_{20}H_{18}FN_3O_3$ C, 65.39/65.28; H, 4.94/ 5.01; N, 11.44/11.36	1741, 1690, 1600, 1584, 1455, 1400, 1373, 1229, 1114, 1060, 765, 748	2.20 (3H, s), 3.02 (3H, s), 2.9—3.1 (1H, m), 3.3—3.5 (2H, m), 4.69 (1H, d, 3.5 Hz), 6.92 (1H, d, 3.5 Hz), 7.0—7.6 (5H, m)	367 (M^+)

NT: not tested.

aqueous solution of $NaHCO_3$. The resultant mixture was stirred at ambient temperature overnight. Removal of EtOH afforded an aqueous residue, which was extracted with AcOEt three times. The combined extract was washed with water twice and dried over $MgSO_4$, then the solvent was removed *in vacuo* to give a crystalline mass. Trituration with (iso-Pr)$_2$O and collection by filtration gave the desired 3-hydroxy derivative **7a** (R^1=F) (1.77 g, 92% yield).

(3*RS*)-3-Amino-1-(2-fluorophenyl)-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*]-[1,4]benzodiazepin-4(3*H*)-one (8a, R^1=F) CH_3SO_2Cl (43.0 g, 0.375 mol) was added dropwise to a solution of **7a** (R^1=F) (74 g, 0.25 mol) and (iso-Pr)$_2$NEt (48.4 g, 0.375 mol) in CH_2Cl_2 (740 ml) under cooling in an ice-bath over a period of 20 min with stirring. After the addition

TABLE IX. Yields, Physical and Spectral Data of Compounds **7a—f**

Compound	X	R^1	Yield (%)	mp (°C)	*Anal.* (Calcd/Found)	Spectral data		
						IR (Nujol) cm^{-1}	^{1}H-NMR (DMSO-d_6)	MS *m/z*
7a (R^1=H)	$-CH_2CH_2-$	H	98.0	162—164	$C_{17}H_{14}N_2O_2$ C, 73.36/73.25; H, 5.07/ 5.31; N, 10.07/ 9.95	3160, 1690, 1600, 1580, 1563	3.0—3.5 (2H, m), 3.6—4.1 (1H, m), 4.2—4.6 (1H, m), 4.70 (1H, d, 8 Hz), 6.26 (1H, d, 8 Hz), 6.95—7.6 (8H, m)	278 (M^+)
7b	$-CH_2CH_2CH_2-$	F	91.7	Amorph.	NT	NT	1.63—2.40 (2H, m), 2.73—3.50 (3H, m), 4.0—4.75 (1H, m), 4.83 (1H, d, 9 Hz), 6.35 (1H, d, 9 Hz), 6.90—7.90 (7H, m)	310 (M^+)
7c	$-CH_2CH(CH_3)-$	F	92.9	186—187	$C_{18}H_{15}FN_2O_2$ C, 69.66/69.51; H, 4.87/ 5.01; N, 9.03/ 8.96	3400, 1660, 1610, 1450, 1385, 1345, 1296, 1250, 1142, 762, 750	($CDCl_3$) 1.31 (3H, d, 6 Hz), 2.72 (1H, d, 16.5 Hz), 3.51 (1H, dd, 16.5, 9 Hz), 4.7—5.2 (3H, m), 6.8—7.7 (7H, m)	310 (M^+)
7d	$-OCH_2CH_2-$	H	85.0	205—210 (dec.)	$C_{17}H_{14}FN_2O_3$ C, 69.37/69.21; H, 4.79/ 4.82; N, 9.52/ 9.46	1680, 1600, 1580, 1565	2.90—3.50 (1H, m), 4.0—5.0 (3H, m), 5.0 (1H, d, 9 Hz), 6.40 (1H, d, 9 Hz), 6.75—7.7 (8H, m)	294 (M^+)
7e (From **5e** by treatment with $(CF_3CO)_2O$)	$-SCH_2CH_2-$	F	90.3	195 (dec.)	$C_{17}H_{13}FN_2O_2S$ C, 62.18/62.05; H, 3.96/ 4.03; N, 8.53/ 8.39	3240, 1690, 1610, 1600, 1370, 1308, 1210, 1158, 1136, 1020, 770, 745	2.87—3.01 (1H, m), 3.26—3.36 (2H, m), 4.89 (1H, s), 5.00 (1H, dt, 3.4, 13.2 Hz), 6.57 (1H, br s), 6.89—7.64 (8H, m)	329 (M^++1)
7f	$-NCH_3(CH_2CH_2)-$	F	97.7	225—227 (dec.)	$C_{18}H_{16}FN_3O_2$ C, 66.45/66.41; H, 4.96/ 5.10; N, 12.92/12.79	3375, 1664, 1610, 1578, 1551, 1491, 1428, 1388, 1373, 1332, 1152, 1027, 880, 778, 742	2.99 (3H, s), 2.9—3.1 (1H, m), 3.4—3.5 (2H, m), 4.73 (1H, dt, 5.0, 1.4 Hz), 4.84 (1H, s), 6.3—7.6 (8H, m)	325 (M^+)

NT: not tested.

TABLE X. Yields, Physical and Spectral Data of Compounds **8a—f**

Compound	X	R^1	Yield (%)	mp (°C)	*Anal.* (Calcd/Found)	Spectral data		
						IR (Nujol) cm^{-1}	^{1}H-NMR ($CDCl_3$)	MS *m/z*
8a (R^1=H)	$-CH_2CH_2-$	H	38.2	Amorph.	NT	NT	2.40 (2H, m), 2.9—3.6 (2H, m), 3.73—4.15 (1H, m), 4.35 (1H, s), 4.5—4.85 (1H, m), 6.93—7.65 (8H, m)	277 (M^+)
8b	$-CH_2CH_2CH_2-$	F	27.0	Amorph.	NT	NT	1.6—2.5 (2H, m), 2.6—3.55 (3H, m), 3.08 (2H, s), 4.25—4.85 (1H, m), 4.55 (1H, s), 6.8—7.85 (7H, m)	309 (M^+)
8c	$-CH_2CH(CH_3)-$	F	68.2	Oil	NT	(Film) 3350, 1688, 1610, 1445, 1220, 1042, 750	1.27, 1.73 (3H, each d, each 6 Hz), 2.59 (2H, s), 2.5—3.6 (2H, m), 4.30, 4.47 (1H, each s), 4.5—5.2 (1H, m), 6.8—7.7 (7H, m)	309 (M^+)
8d	$-OCH_2CH_2-$	H	28.0	Amorph.	NT	NT	2.85—3.50 (1H, m), 3.90—5.20 (6H, m), 6.80—8.0 (8H, m)	293 (M^+)
8e	$-SCH_2CH_2-$	F	68.7	162—164 (dec.)	$C_{17}H_{14}FN_3OS$ C, 62.37/62.25; H, 4.31/ 4.46; N, 12.84/12.69	3370, 3300, 1685, 1606, 1595. 1482, 1356, 1310, 1210, 1015, 815, 750	2.22 (2H, br s), 3.01 (1H, dt, 3, 12 Hz), 3.19 (1H, dt, 3, 12 Hz), 3.41 (1H, dt, 4, 12 Hz), 4.57 (1H, s), 5.20 (1H, dt, 4, 12 Hz), 6.9—7.7 (8H, m)	328 (M^++1)
8f	$-NCH_3(CH_2CH_2)-$	F	54.3	Amorph.	NT	NT	2.41 (2H, br s), 3.01 (3H, s), 2.6—3.2 (1H, m), 3.3—3.7 (2H, m), 4.58 (1H, s), 4.9—5.0 (1H, m), 6.4—7.7 (7H, m)	324 (M^+)

NT: not tested.

was completed, the ice-bath was removed and stirring was continued at ambient temperature for 1 h. The reaction mixture was cooled again to 5 °C. A solution of gaseous NH_3 in MeOH (250 g/1.5 l) was added in one portion to the cooled solution under vigorous stirring, and the mixture was stirred at ambient temperature for 2 h. After the reaction was completed, N_2 gas was introduced into the reaction mixture to remove excess NH_3. The solvent was removed *in vacuo* to afford a residue, which was taken up in CH_2Cl_2 (1.5 l) and H_2O (1.5 l) and adjusted to pH 7—8 with aqueous $NaHCO_3$ under stirring. The separated organic layer and the extract with CH_2Cl_2 (500 ml) from the aqueous layer were

combined and dried over $MgSO_4$. The filtrate and the washings were combined and evaporated *in vacuo* to give a residue, which was subjected to column chromatography on silica gel with $CHCl_3$, $CHCl_3$–AcOEt (1 : 1) and $CHCl_3$–MeOH (30 : 1) successively. The fractions containing the desired compound were combined and evaporated *in vacuo* to give an oil, which was pulverized in $(iso\text{-}Pr)_2O$ and air-drying gave the title compound, which was used in the following reaction without further purification (45.0 g, 60.9% yield). An analytical sample was obtained by recrystallization from MeOH, mp 186.5—187.5 °C. *Anal.* Calcd for $C_{17}H_{14}FN_3O$: C, 69.14; H, 4.78; N, 14.23. Found: C, 69.22; H, 4.69; N, 14.28. IR (Nujol) cm^{-1}: 3450, 3230, 1680, 1625 (sh), 1610 (sh), 1575, 1540, 1325, 1115, 1070, 750. ^{1}H-NMR ($CDCl_3$) δ: 2.63 (2H, br s), 3.30—3.50 (2H, m), 3.63—4.35 (1H, m), 4.35—4.95 (1H, m), 4.45 (1H, s), 6.85—7.80 (7H, m). MS *m/z*: 295 (M^+).

The other intermediates **8** were prepared similarly and the physical data are summarized in Table X.

(3*RS*)-1-(2-Fluorophenyl)-3-(2-indolylcarbonylamino)-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepin-4(3*H*)-one (9d). Method A 1-Hydroxybenzotriazole (HOBT, 52.0 g, 0.386 mol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD HCl, 73.8 g, 0.386 mol) and Et_3N (39.0 g, 0.386 mol) were added successively to a solution of **8a** (R^1 = F) (114.0 g, 0.386 mol) and indole-2-carboxylic acid (62.0 g, 0.386 mol) in dimethylformamide (DMF, 2 l) under stirring and cooling in an ice-bath. After the addition was completed, the ice-bath was removed and the mixture was stirred for 30 min at ambient temperature then poured into a mixture of AcOEt (6 l) and H_2O (12.5 l) under stirring. The separated organic layer was washed with water three times and dried over $MgSO_4$. The filtrate and the washings were combined and evaporated *in vacuo* to give a residue, which was subjected to column chromatography on silica gel with $CHCl_3$ then $CHCl_3$ and AcOEt (20 : 1). The fractions containing the desired compound were combined and evaporated *in vacuo* to give an oil, which was dissolved in AcOEt (1.8 l) and allowed to stand overnight to afford pure crystals of the title compound (119.1 g, 70.4% yield). mp 283—285 °C. *Anal.* Calcd for $C_{20}H_{19}FN_4O_2$: C, 66.65; H, 5.31; N, 13.88. Found: C, 66.59; H, 5.18; N, 13.76. IR (Nujol) cm^{-1}: 3390, 3250, 1678, 1640, 1610, 1600, 1580, 1531, 1500, 1482. ^{1}H-NMR (DMSO-d_6) δ: 3.10—3.65 (2H, m), 3.70—4.20 (1H, m), 4.30—4.70 (1H, m), 5.57 (1H, d, J = 8.0 Hz), 6.90—7.75 (12H, m), 9.53 (1H, d, J = 8.0 Hz). MS *m/z*: 438 (M^+).

Method B A solution of indole-2-carbonyl chloride, previously prepared from indole-2-carboxylic acid (1.93 g, 0.012 mol) and $SOCl_2$ (1.43 g, 0.012 mol) in CH_2Cl_2 (20 ml) containing one drop of DMF by refluxing for 1 h, was added dropwise to a solution of **8a** (R^1 = F) (2.95 g, 0.01 mol) and Et_3N (1.21 g, 0.012 mol) in CH_2Cl_2 (30 ml) under stirring at 0 °C. After the addition was completed, the mixture was stirred for 0.5 h under the same conditions. The mixture was poured into water and adjusted to pH 7—8 with saturated aqueous $NaHCO_3$. The separated organic layer was washed with water twice and dried oveer $MgSO_4$. The filtrate and the washings were combined and evaporated *in vacuo* to give an oil. The following purification was performed by the same procedure as described in method A. The yield was 3.35 g (93.0%).

Method C. (3*RS*)-3-(2-Amino-4-chlorobenzoyl)amino-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepin-4(3*H*)-one (9p) Isobutyl chloroformate (333.3 mg) was added dropwise to a solution of 2-amino-4-chlorobenzoic acid (418.7 ng, 2.44 mmol) and *N*-methylmorpholine (246.8 mg) in a mixture of CH_2Cl_2 and DMF (10 : 1/35 ml) under cooling at −10 °C in an ice-salt bath with stirring. The mixture was stirred at the same temperature for 15 min and warmed to 0 °C. A solution of **8a** (R^1 = F) (590.7 mg, 2 mmol) in a mixture of CH_2Cl_2 and DMF (10 : 1/5 ml) was added dropwise to the resultant mixture under the same conditions. The reaction mixture was stirred for 1 h under the same temperature and for 12 h at ambient temperature, then CH_2Cl_2 was removed *in vacuo*, and AcOEt and an aqueous solution of $NaHCO_3$ were added to the residual mixture under vigorous stirring. The separated organic layer was washed with water twice and dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded a brown oil, which was chromatographed on silica gel with $CHCl_3$. The fractions containing the desired compound were combined and evaporated *in vacuo* to give an amorphous mass, which was powdered by stirring in $(iso\text{-}Pr)_2O$, collected by filtration, washed with $(iso\text{-}Pr)_2O$ and air-dried to give pure **9p** (169.7 mg, 18.9% yield). mp 200—205 °C. *Anal.* Calcd for $C_{24}H_{18}ClFN_4O_3$: C, 64.21; H, 4.04; N, 12.48. Found, C, 63.99; H, 4.23; N, 12.42. MS *m/z*: 447 ($M^+ - 1$), IR (Nujol) cm^{-1}: 3420, 3300, 1675, 1640, 1570, 1500, 1255, 915, 755. ^{1}H-NMR (DMSO-d_6) δ: 2.83—3.6 (2H, m), 3.6—4.7 (1H, m), 4.2—4.67 (1H, m), 5.35 (1H, d, J = 8.0 Hz), 6.22 (1H, d, J = 8.0 Hz), 6.33—7.63 (12H, m), 7.72 (1H, d, J = 9 Hz).

Method D. (3*RS*)-3-(2-Aminocinnamoyl)amino-1-(2-fluorophenyl)-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepin-4(3*H*)-one (9aa) (3*RS*)-1-(2-Fluorophenyl)-3-(2-nitrocinnamoyl)amino-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepin-4(3*H*)-one (3.68 g, obtained from **8a** (R^1 = F) and 2-nitrocinnamic acid by method A described above) was added portionwise to a suspension of iron powder (3.68 g) and NH_4Cl (0.44 g) in a mixture of water (9.2 ml) and EtOH (27.6 ml) under stirring and refluxing. After the addition was completed, the mixture was refluxed for 2.5 h with stirring. The reaction mixture was hot-filtered through Celite and the filtered mass was washed with hot EtOH several times. From the filtrate and washings, EtOH was removed *in vacuo* to give a residue, to which was added saturated aqueous $NaHCO_3$ (100 ml). The mixture was extracted with $CHCl_3$. After washing with water and drying over $MgSO_4$, the extract was evaporated *in vacuo* to give a crystalline residue, which was pulverized in $(iso\text{-}Pr)_2O$ (100 ml) and collected by filtration to afford the titled compound (1.56 g, 45.3% yield), as a yellow powder. An analytical sample was obtained by recrystallization from EtOH. mp 237—240 °C (dec.) *Anal.* Calcd for $C_{26}H_{21}FN_4O_2$; C, 70.89; H, 4.78; N, 12.72. Found: C, 70.81; H, 4.90; N, 12.70. MS *m/z*: 440 (M^+). IR (Nujol) cm^{-1}: 3400, 3350, 3125, 1690, 1640, 1600, 1540. ^{1}H-NMR ($CDCl_3$) δ: 3.08—3.45 (2H, m), 3.95—4.14 (3H, m), 4.60—4.71 (1H, m), 5.60 (1H, d, J = 8.0 Hz), 6.51—7.87 (14H, m).

Method E. (3*RS*)-3-(2-Acetylaminocinnamoyl)amino-1-(2-fluorophenyl)-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepin-4(3*H*)-one (9ac) AcCl (0.12 ml) was added dropwise to a suspension of **9aa** (0.5 g) and dry pyridine (0.28 ml) in CH_2Cl_2 (15 ml) under stirring and cooling below 10 °C in an ice-bath. The resultant clear solution was stirred for 0.5 h under the same conditions and for 2 h at ambient temperature. The reaction mixture was washed successively with water, 1 N HCl and brine. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give an oil, which was column chromatographed on silica gel with a mixture fo $CHCl_3$ and MeOH (50 : 1). The fractions containing the desired compound were combined and evaporated *in vacuo* to afford an amorphous mass, which was pulverized in $(iso\text{-}Pr)_2O$. Collection by filtration, washing with $(iso\text{-}Pr)_2O$ and drying under reduced pressure with warming at 50 °C for 6 h gave the title compound (372 mg, 68.1% yield), as a white powder. An analytical sample was obtained by recrystallization from EtOH. mp 180—189 °C (dec.) *Anal.* Calcd for $C_{28}H_{22}FN_4O_3$: C, 69.84; H, 4.61; N, 11.64. Found: C, 69.69; H, 4.85; N, 11.48. MS *m/z*: 482 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s), 3.07—3.36 (2H, m), 3.92—4.08 (1H, m), 4.58—4.69 (1H, m), 5.52 (1H, d, J = 8.0 Hz), 6.56 (1H, d, J = 15 Hz), 6.99—7.89 (13H, m).

The other target compounds **9** were prepared similarly (method A, B, C or D) and the physical data are summarized in Table I-1—4.

Optical Resolution of Compound 8. Method A *Via* diastereo isomers with L-phenylalanine.

(3*RS*)-1-Phenyl-3-[*N*-Boc-(*S*)-phenylalanyl]amino-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepin-4(3*H*)-one (10a, R^1 = H) Boc-L-Phenylalanine (27.33 g, 0.103 mol), HOBT (13.92 g, 0.103 mol), WSCD HCl (21.25 g, 0.103 mol) and Et_3N (10.42 g, 0.103 mol) were added successively to a solution of **8a** (R^1 = H) (28.54 g, 0.103 mol) in DMF (285 ml) under stirring at ambient temperature. The mixture was stirred for 5 h under the same conditions and the resulting precipitate was filtered off. The filtrate and the washings were combined and poured into a mixture of AcOEt (500 ml) and water (500 ml) with stirring. The separated organic layer was washed with water and aqueous $NaHCO_3$. After drying over $MgSO_4$, the organic solvent was removed *in vacuo* to give a residue, which was subjected to column chromatography on silica gel with a mixture of $CHCl_3$ and AcOEt (10 : 1) to afford the title compound as an amorphous mass (48.82 g, 93.3% yield). This was used in the following reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.41, 1.43 (9H, each s), 2.9—3.5 (4H, m), 3.8—4.0 (1H, m), 4.6—4.7 (2H, m), 5.0—5.1 (1H, br s), 5.40 (1H, d, J = 8.0 Hz), 7.0—7.8 (14H, m).

(3*S*)-1-Phenyl-3-[(*S*)-phenylalanyl]amino-3,4,6,7-tetrahydropyrrolo-[3,2,1-*jk*][1,4]benzodiazepin-4(3*H*)-one ((*S,S*)-11a, R^1 = H) and Its Enantiomer ((*R,S*)-11a, R^1 = H) HCl gas was bubbled into a solution of **10a** (R^1 = H) (48.5 g, 0.095 mol) in AcOEt (1 l) under cooling in an ice-bath with slow stirring. After the solution was saturated with HCl, the mixture was stirred at ambient temperature for 1 h. The HCl was removed as thoroughly as possible by bubbling with N_2 gas. Water was

added to the resultant mixture with vigorous stirring. The separated organic layer was washed with water and the combined aqueous layer was neutralized with 20% aqueous NaOH to afford precipitates. The mixture was extracted with AcOEt twice. After drying over $MgSO_4$, the solvent was removed *in vacuo* to give a solid, which was collected by filtration and washed with small amounts of AcOEt and Et_2O in turn to give the crude (3*R*) isomer (13.42 g). Recrystallization from EtOH afforded light pink fine needles (11.33 g).

On the other hand, the filtrate was evaporated *in vacuo* to give a solid, which was triturated with a small amount of AcOEt and collected by filtration to give a mixture (14.84 g) of (3*S*) and (3*R*) isomers (about 10 : 1 mixture from the ^{1}H-NMR spectrum). Recrystallization from EtOH twice afforded the pure (3*S*) isomer as colorless needles (9.70 g).

Second crops of the respective isomers were obtained from the residue of the filtrate by silica gel column chromatography with a mixture of $CHCl_3$ and MeOH (10 : 1), (3*R*) isomer, 3.39 g; (3*S*) isomer, 3.48 g respectively.

(*R,S*)-**11a** (R^1 = H): mp 94—95 °C. IR (Nujol) cm^{-1}: 3350, 3150, 1672, 1644, 1597, 1550, 1445, 1372, 1237, 734, 699. ^{1}H-NMR ($CDCl_3$) δ: 1.62 (2H, br s), 2.74 (1H, dd, J=14.0, 10.5 Hz), 3.1—3.5 (3H, m), 3.75 (1H, dd, J=3.5, 10.5 Hz), 3.92 (1H, q, J=10.5 Hz), 4.66 (1H, t, J=10.5 Hz), 5.45 (1H, d, J=8.4 Hz), 7.06—7.6 (13H, m). MS *m/z*: 424 (M^+).

(*S,S*)-**11a** (R^1 = H): mp 203—204 °C. IR (Nujol) cm^{-1}: 3340, 3250, 1680 (sh), 1674, 1660, 1596, 1485, 1445, 1397, 1328, 890, 756, 732, 702. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (2H, br s), 2.85 (1H, dd, J=14.0, 10.5 Hz), 3.1—3.5 (3H, m), 3.75 (1H, dd, J=3.5, 10.5 Hz), 3.97 (1H, q, J=10.5 Hz), 4.64 (1H, t, J=10.5 Hz), 5.47 (1H, d, J=8.4 Hz), 7.1—7.6 (13H, m), 8.95 (1H, d, J=8.4 Hz). MS *m/z*: 424 (M^+).

(3*S*)-3-Amino-5-phenyl-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepin-4(3*H*)-one ((*S*)-8a, R^1 = H) Phenyl isothiocyanate (1.08 g, 8 mmol) was added to a solution of (*S,S*)-**11a** (R^1 = H) (2.91 g, 6.86 mmol) in CH_2Cl_2 (60 ml) and the mixture was heated to evaporate of the solvent with stirring. This evaporating procedure was repeated four times and the resultant residue was completely evaporated *in vacuo* to give a viscous oil, which was subjected to column chromatography on silica gel with $CHCl_3$ and a mixture of $CHCl_3$ and MeOH (50 : 1) to afford the phenyl thiourea intermediate (2.95 g) as an amorphous mass.

A solution of the intermediate obtained above (2.90 g) in CF_3COOH (10 ml) was stirred at 50 °C for 30 min. The reaction mixture was evaporated *in vacuo* to dryness and the residue was chromatographed on silica gel with a mixture of $CHCl_3$ and MeOH (15 : 1). The fractions containing the desired compound were combined and washed with dilute aqueous $NaHCO_3$. The separated organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give (*S*)-**8a** (R^1 = H) (0.97 g, 52.1% yield) as an amorphous mass. $[\alpha]_D^{20} = -175.1°$ (c=0.518, $CHCl_3$), ^{1}H-NMR ($CDCl_3$) δ: 2.38 (2H, br s), 3.0—3.5 (2H, m), 3.8—4.15 (1H, m), 4.38 (1H, s), 4.5—4.8 (1H, m), 6.95—7.65 (8H, m). This was used in the following reaction without further purification.

(*R*)-**8a** (R^1 = H) was obtained similarly. $[\alpha]_D^{20} = 174.3°$ (c=0.574, $CHCl_3$), ^{1}H-NMR ($CDCl_3$) δ: 2.40 (2H, br s), 3.0—3.5 (2H, m), 3.8—4.3 (1H, m), 4.40 (1H, br s), 4.5—4.8 (1H, m), 7.0—7.8 (8H, m).

Method B *Via* diastereomeric salt formation with L-(+)-tartaric acid with a catalytic amount of 3,5-dichlorosalicylaldehyde.

(3*S*)-3-Amino-5-(2-fluorophenyl)-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*]-[1,4]benzodiazepin-4(3*H*)-one ((*S*)-8a, R^1 = F) (*R,S*)-**8a** (R^1 = H)(248 g, 0.84 mol) was added to a solution of L-(+)-tartaric acid (120 g, 0.8 mol, 0.95 eq mol) in MeOH (2.5 l) under stirring at ambient temperature to give a clear solution, which was seeded with a catalytic amount of the salt of (*S*)-**8a** (R^1 = F) and L-(+)-tartaric acid followed by addition of a catalytic amount of 3,5-dichlorosalicylaldehyde. The mixture was impossible to stir further because of heavy precipitation, and it was allowed to stand for 24 h at the same temperature. The precipitates were collected by filtration and washed with cold MeOH (400 ml × 2) and $(iso\text{-}Pr)_2O$, and air-dried (281.23 g, 78.9%).

The salt obtained above was dissolved in a mixture of H_2O (20 l) and AcOEt (6 l) under stirring. The undissolved mass was filtered off through Celite and the separated aqueous layer was washed with AcOEt (3 l × 2). To the aqueous layer was added $CHCl_3$ (5 l), followed by addition of $NaHCO_3$ (106 g) with vigorous stirring, which was continued for 10 min. The separated $CHCl_3$ layer and the extract from the water layer with $CHCl_3$ (2 l) were combined and washed with water (2 l × 2). After drying over $MgSO_4$, the solvent was removed *in vacuo* to give a crystalline mass (195.5 g, 78.8%). $[\alpha]_D^{20} = -84.0°$ (c=0.5, $CHCl_3$).

The purification of the (3*S*)-amino derivative obtained above was performed by repeating the salt formation without 3,5-dichlorosalicylaldehyde and generating the free base to afford pure (*S*)-**8a** (R^1 = F). 165 g, 66.5% yield, 99.5% ee $[\alpha]_D^{20} = -93.0°$ (c=0.5, $CHCl_3$).

The purity was checked by HPLC under the following conditions; column, YMC-GEL ODS 120A S-5 AM Type, 4 mm × 150 mm, mesh, 4u; column temperature, 35 °C; eluent, AcOH–H_2O–CH_3CN (1 : 100 : 100, v/v); flow rate, 0.8 ml/min; detection, UV 254 nm (Waters instrument).

***N*-[(3*S*)-1-(2-Fluorophenyl)-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]-benzodiazepin-4(3*H*)-one-3-yl]-*N'*-[(1*S*)-(1-methyl)benzyl] Urea (13) for X-Ray Crystal Structure Analysis** (*S*)-(−)-1-Methylbenzyl-1-isocyanate (0.150 g, 1.02 mmol) was added to a solution of (−)-**8a** (R^1 = F), $[\alpha]_D = -96.96°$ (c=1.25, $CHCl_3$), (0.295 g, 1 mmol) in tetrahydrofuran (THF, 2.5 ml) under stirring and cooling in an ice-bath. The mixture was stirred for 0.5 h under the same conditions and for 3 h at ambient temperature. Then $(iso\text{-}Pr)_2O$ (6 ml) was added and the suspension was stirred for a further 1 h. The resultant powder was collected by filtration, washed with $(iso\text{-}Pr)_2O$ and dried to afford the title compound as white powder (405.9 mg, 91.7%). Recrystallization from EtOH afforded colorless pillars which were suitable for X-ray analysis. mp 253—255 °C, $[\alpha]_D^{21.5} = -92.3°$ (c=1.0, $CHCl_3$. *Anal.* Calcd for $C_{26}H_{23}FN_4O_2$: C, 70.57; H, 5.24; N, 12.66. Found: C, 70.54; H, 5.36; N, 12.62. IR (Nujol) cm^{-1}: 3410, 3330, 1692, 1670, 1644, 1609, 1550, 1492, 1375, 1240, 770, 754, 713. NMR (DMSO-d_6) δ: 1.34 (3H, d, J=6.93 Hz), 3.06—3.44 (2H, m), 3.93 (1H, q, J=6.93 Hz), 4.48 (1H, t, J=9.64 Hz), 4.78 (1H, dt, J=14.8, 6.78 Hz), 5.09 (1H, d, J=8.57 Hz), 6.97—7.57 (14H, m). MS *m/z*: 443 ($M^+ + 1$).

X-Ray Crystallography Crystal Data of the Compound **13**: Formula, $C_{26}H_{23}O_2N_4F$; crystal system, monoclinic; space group, $P2_1$(#4); lattice parameters, a=9.784(2) Å, b=9.702(2) Å, c=11.708(2) A, β=102.89(1)°, V=1083.3(3) A^3; $D_{calc.}$, 1.356 g/cm^3; number of formula units Z (Z value), 2; total number of unique reflections (F_{000}), 464.00; final R value, R=0.067, R_W=0.073.

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