Novel Angiotensin II Receptor Antagonists. Design, Synthesis, and *in Vitro* Evaluation of Dibenzo[*a*,*d*]cycloheptene and Dibenzo[*b*,*f*]oxepin Derivatives. Searching for Bioisosteres of Biphenylyltetrazole Using a Three-Dimensional Search Technique

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Three-dimensional substructure searching (3D search), using the program MACCS-3D, was utilized for designing novel angiotensin II receptor antagonists which contain a bioisostere of the biphenylyltetrazole moiety of DuP 753. A 3D query was prepared from an overlay model of substructures of several potent AII antagonists. The search system retrieved 139 compounds from the database MDDR-3D, which consisted of 29 400 medicinal patent compounds. A tricyclic compound was selected from the retrieved compounds and then evolved by considering steric fitness to the overlay model and synthetic feasibility. Finally, various novel AII antagonists having dibenzo[*a*,*d*]cycloheptene or dibenzo[*b*,*f*]oxepin were designed and synthesized. The receptor binding activity (K_i) for several members of this series was in the 10^{-10} M range, demonstrating the ability of 3D search technique to explore new lead structures.

Introduction

The renin–angiotensin system (RAS) plays an important role in the regulation of blood pressure and electrolyte homeostasis.[1] Recently, many nonpeptidic angiotensin II receptor antagonists (AII antagonists) have been reported,[2] and several compounds are now entering the late clinical development stage. The prototype nonpeptidic AII antagonists such as CV-2947 and CV-2961 were reported from Takeda in 1982,[3] but these benzylimidazole-based compounds possessed weak activity. Structural evolution for developing more potent compounds revealed a necessity of introducing an acidic substituent into the phenyl ring (Figure 1). Further studies on the general structure–activity relationship of the acidic substituent led to the discovery of a biphenylyltetrazole (BPT) by DuPont group, resulting in the first orally active nonpeptidic AII antagonists known as DuP 753 (losartan).[4]

The BPT was thought to be indispensable in producing not only strong binding affinity to the AII receptor but also oral antihypertensive activity; hence, it has been used almost exclusively in nonpeptidic AII antagonists. With a few exceptions such as GR 117289,[2b] most reported compounds which do not contain the BPT could not show high AII antagonistic activity. We have tried to develop other components which would act as a substitute for the BPT. In this study, three-dimensional structure searching (3D search) technique was employed in order to explore lead chemical structures from which novel bioisosteres of the BPT could be designed.

In recent years, there has been increasing interest in the 3D database searching, and several different 3D search systems have been developed.[5] Some systems screen compounds in a 3D database based on the steric complementarity to a binding pocket of a target protein whose atomic coordinates have been determined by X-ray crystallography or NMR or deduced by protein modeling. However, detailed 3D structures of most membrane-bound proteins including AII receptor have not been determined. In such cases, if several different ligands which are supposed to bind at the same site of the target receptor are known, a particular spatial arrangment of atoms or functional groups common to the ligands can be extracted as pharmacophore, from which a 3D query can be derived. Other search systems utilize the 3D query as a criterion and search a 3D database for compounds which satisfy the substructural and geometric constraints specified in the 3D query.

A number of applications of 3D search to lead discovery have been reported.[6] The program DOCK,[5b–j] which represents the former 3D search systems, has been used successfully in the design of a novel nonpeptidic inhibitor of HIV-1 protease.[6a,b] The utility of the latter search systems also has been demonstrated in the rational design of cyclic ureas as HIV-1 protease inhibitor.[6c] The success of the design should be attributed to the 3D search and the following critical modeling study in which the cyclic ureas have been elaborated.

Searches are often performed over a 3D database of the compounds, the samples of which are commercially available or stored in a corporate compound library, since the compounds retrieved from the database can be immediately submitted to biological assay without chemical synthesis. It is unlikely, however, that the retrieved compounds have structural features resonable for tight receptor binding, that is, steric, electrostatic, and hydrogen bond complementarity to the binding pocket. More often, the compounds searched using 3D queries possess extra parts of molecular structure which are unfavorable for receptor binding. Therefore, the chemical structures of the retrieved compounds usually need to be evolved to reasonable ones by taking account of steric and electrostatic complementarity to the experimentally determined or hypothesized binding pocket. In this process, synthetic feasibility should be imposed for more practical drug design.

In this paper, we describe (1) the preparation of a 3D query for bioisosteres of the BPT, (2) 3D search and selection of a candidate from retrieved compounds, and

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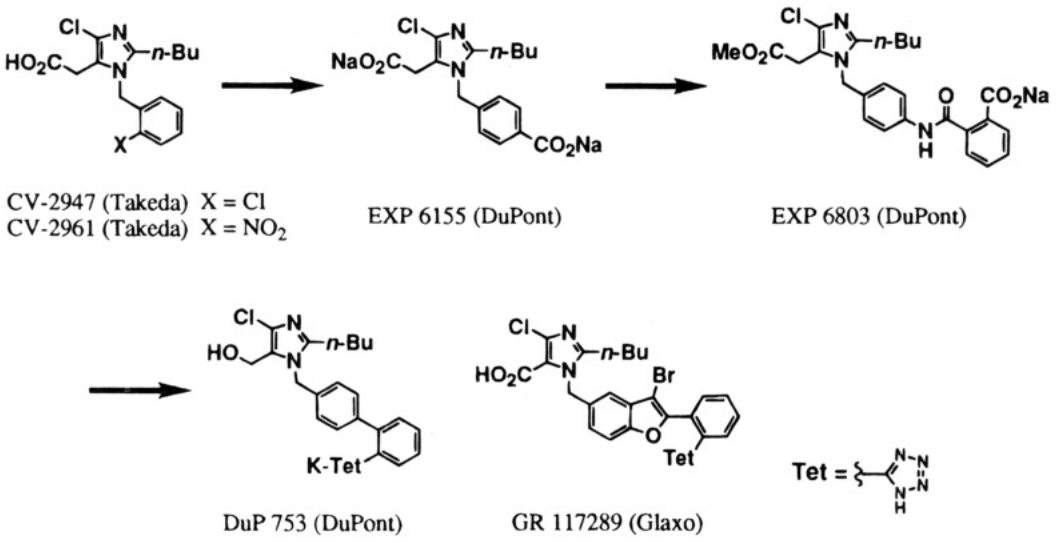


Figure 1. Structural evolution of the acidic substructure of nonpeptidic AII antagonists.

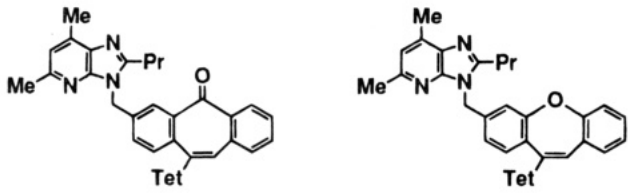


Figure 2. Illustrations of dibenzo[*a*,*d*]cycloheptene- and dibenzo[*b*,*f*]oxepin-based AII antagonist.

(3) design and synthesis of dibenzo[*a*,*d*]cycloheptene- and dibenzo[*b*,*f*]oxepin-based compounds as novel AII receptor antagonists (Figure 2).

Preparation of 3D Query

In several investigations of the structure–activity relationship of the peptidic AII analogues, the C-terminal carboxyl group of AII seemed to be important to the receptor binding.[7] Previously on nonpeptidic AII antagonists, we postulated that the receptor binding affinity would be enhanced by incorporating a substructure which would mimic the C-terminal structure of AII. Figure 3 illustrates a superposition of DuP 753 on a hypothetical active conformational model of AII,[8] showing that the tetrazole and phenyl ring of DuP 753 correspond to the C-terminal carboxyl group and phenylalanine residue of AII, respectively.

Various nonpeptidic substructures (**B**–**F** in Figure 4) were designed by mimicking the C-terminal Pro–Phe (**A**) and then introduced into the 3-position of 5,7-dimethyl-2-propylimidazo[4,5-*b*]pyridine ring. Each of the compounds thus prepared showed high activity in the receptor binding (K_i = 1.4–6.3 nM).[9]

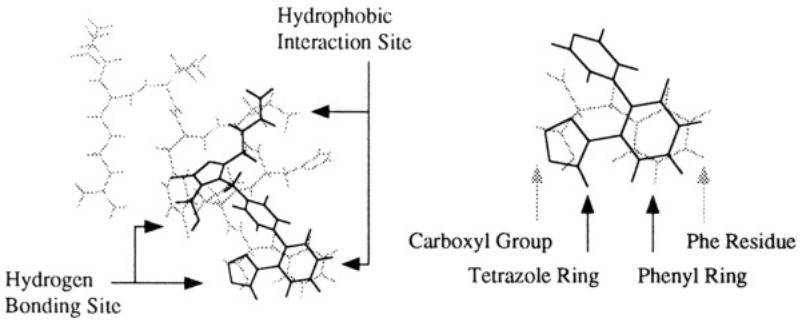


Figure 3. An overlay model of DuP 753 (solid) on a postulated active conformation of AII (shaded).

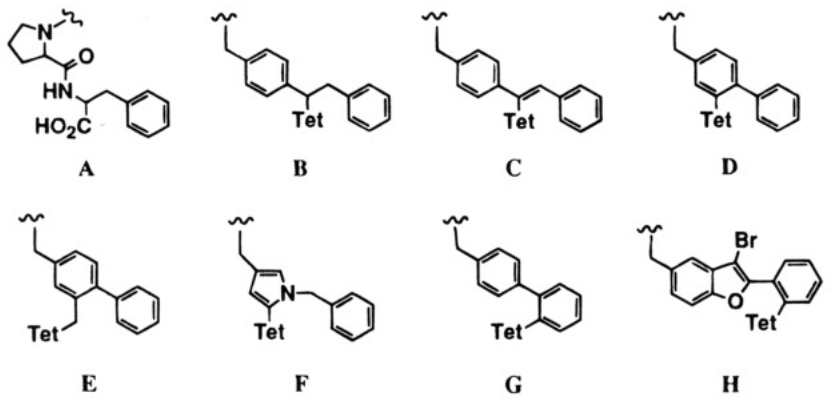


Figure 4. Illustrations of C-terminal Pro-Phe (**A**) of AII and mimic substructures (**B**–**F**) of AII antagonist.

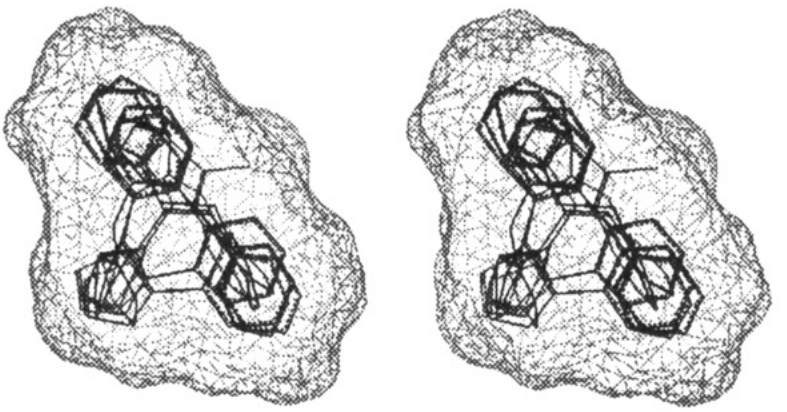


Figure 5. Stereoplot of an overlay model of the BPT, benzofuran moiety of GR 117289 and **B**−**F** in Figure 4. Mesh surface was prepared by calculation of a solvent accessible surface of the overlay model.

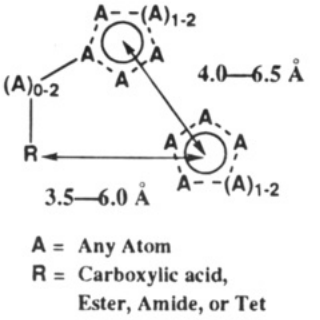


Figure 6. A 3D query derived from the overlay model in Figure 5. The 3D query consists of three features, i.e., two centroids of the 5- or 6-membered aromatic rings and one functional group **R** (carboxylic acid, ester, amide, or tetrazole) linked to one of the aromatic rings, and two ranges of distance between the three features.

A 3D query for substructural and geometric search was prepared from the overlay model (Figure 5) which was constructed from the five substructures **B**−**F**, the BPT (**G**) of DuP 753, and the benzofuran moiety (**H**) of GR 117289. The 3D query consisted of three features, i.e., two centroids of the 5- or 6-membered aromatic rings and one functional group (carboxylic acid, ester, amide, or tetrazole) linked to one of the aromatic rings, and two ranges of distance between the three features. The ranges were determined by measuring the corresponding distances in the seven substructures (Figure 6).

3D Search and Design for Target Compounds

The 3D search was performed using the program MACCS-3D.[10] The database MDDR-3D,[10,11] which consisted of 29 400 medicinal patented compounds, was searched for the compounds that satisfied the 3D query described above, giving 139 hit compounds with a wide variety of chemical structures.[12] Several compounds within the search results had the substructure **G** or **H** or their analogues. A set of 39 highly flexible compounds, which had more than three rotatable bonds within substructures corresponding to the query, were removed from the hit list because of the difficulty in molecular modeling. The remaining 100 compounds were grouped into 19 families based on structural similarity, that is, size of the two aromatic rings and connection pattern of the three features. Out of the 19 families, six families were selected for the following substructure design by taking conformational rigidity and skeletal novelty into account. Figure 7a shows the basic skeletons representing each family.

Next, each of the six families was evaluated for geometric and steric fitness to the overlay model described above by viewing the fitness of solvent accessible surface[13] of each parent compound to that of the overlay model. We selected a tricyclic compound **I**[14] as a lead structure (Figure 7b). The substructure **J** was designed by replacing the carbamoyl group of **I** with a tetrazole ring. To avoid the chiral center in **J**, which might cause synthetic difficulty, the central ring of **J** was enlarged to the 8-membered lactam, affording **K**. However, molecular modeling of **K** revealed that the central ring of **H** had a "tub shape" bent conformation as is observed with cyclooctatetraene[15] and that consequently the molecular surface of **J** could not fit within that of the overlay model. Therefore, the nitrogen atom was eliminated from the lactam ring, finally giving the 10-(1*H*-tetrazol-5-yl)dibenzo[*a*,*d*]cyclohepten-5-one **L** as a target substructure to be synthesized (Figure 8).

Biological Results and Structural Development

The compounds prepared in this study were evaluated as AII antagonists by testing their potency to displace [^{125}I]AII binding to COS cells transfected with a cDNA encoding a human AT_1 angiotensin II receptor.

First, two positional isomers **1** and **2**, which were prepared by linking 5,7-dimethyl-2-propylimidazo[4,5-*b*]pyridine ring to the 3- or 2-position of the substructure **I** by methylene group, were evaluated (Figure 9). The 3-isomer **1** showed high activity (K_i = 0.29 nM) comparable to that of the BPT derivative containing the same imidazopyridine ring (K_i = 0.35 nM). On the other hand, the 2-isomer **2** showed activity (K_i = 88 nM) 2 orders of magnitude weaker than **1**. Next, the effect of the carbonyl group in the 3-isomer **1** was examined by conversion to a methylene (**3**) or an ether (**4**). No significant change was observed between these derivatives. As shown in Table 1, a similar tendency was observed in the benzimidazole derivatives **33** and **45** and the acylvaline derivatives **37** and **46**, suggesting that the carbonyl group did not play an essential role in the receptor binding. Furthermore, various substituents were introduced into the 3-position of **I**, and all compounds prepared showed strong binding affinities (Table 1). Thus it was revealed that the tricyclic substructures designed in this study could be bioisosteres of the BPT in AII antagonist.

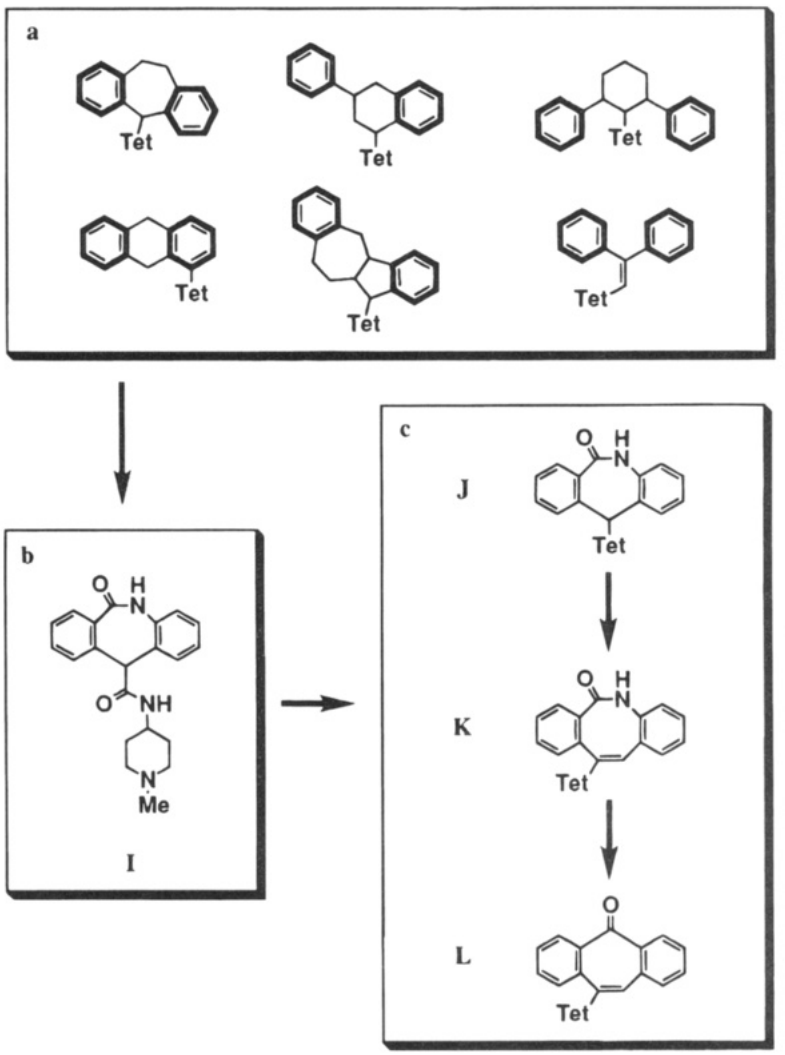


Figure 7. Selection of a candidate and design for a target substructure: (a) basic skeletons representing six families which selected from the retrieved compounds; (b) selected candidate for the lead structure of bioisosteres of the BPT; (c) structural evolution of the candidate to a target substructure.

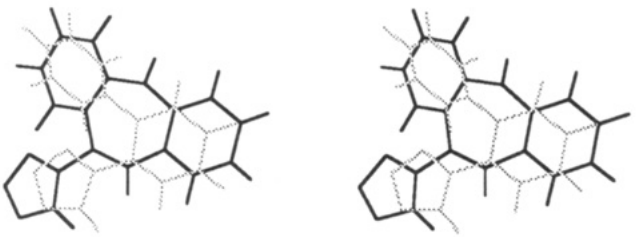


Figure 8. Stereoplot of an overlay of the dibenzo[*a*,*d*]-cycloheptene-based substructure **L** (solid) on the BPT (shaded).

Although antihypertensive activities of these compounds were evaluated using spontaneously hypertensive rats,[16] no marked decrease in blood pressure was observed in intravenous administration. Even with the most potent compound **1** (1.0 mg/kg, $n = 3$), the mean blood pressure was reduced only 15 ± 1 mmHg from the normal value at the maximum point.

Chemistry

The dibenzo[*a*,*d*]cycloheptene derivative **1** was prepared as shown in Scheme 1. Condensation of 4-methylbenzyl cyanide and phthalaldehydic acid gave only *Z*-olefin **5**.[17] Since direct cyclization of **5** to **9** could not be achieved, conversion of **5** to **9** was carried out using the sequence of reduction.[18] Friedel–Crafts cyclization, and oxidation. The methyl group of **9** was brominated with *N*-bromosuccinimide in the presence of dibenzoyl peroxide in 1,2-dichloroethane, which was used for the reason of the low solubility of **9** in carbon tetrachloride.[2a] Reaction of **10** with 5,7-dimethyl-2-propylimidazo[4,5-*b*]pyridine in the presence of NaH gave **11**, which was then converted to the tetrazole **1** by treating with trimethylstannyl azide. The 2-isomer **2** was also prepared using 3-methylbenzyl cyanide as a starting material, according to the same procedure described for **1**. Preparations of **41**, **42**, and **43** were carried out by the similar sequence of reactions.

The methylene analogue **3** was prepared from **11** through the reduction of a carbonyl group by successive treatment with $NaBH_4$ and then Me_2SiCl_2/NaI[19] and the tetrazole formation (Scheme 2).

Scheme 3 describes the preparation of the dibenzo[*b*,*f*]oxepin derivative **4**. Coupling reaction of *m*-cresol and 2-chloro-5-nitrobenzaldehyde in aqueous NaOH gave an ether **13**.[20] The oxazolone derivative **14**, which was prepared from **13** and acetylglycine, was cyclized and then methylated to give the dibenzo[*b*,*f*]oxepin derivative **16**. The nitro group was reduced with $FeSO_4$, and the resulting amino group was removed *via* diazonium salt,[21] giving **18**. After hydrolysis of the methyl

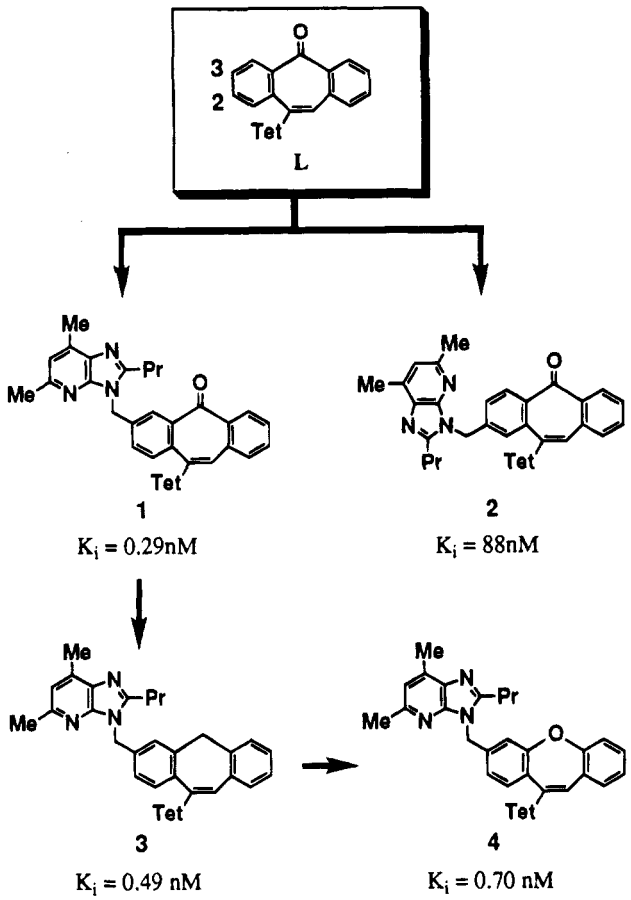


Figure 9. Structural evolution of dibenzo[*a*,*d*]cycloheptene-based substructure.

ester **18**, the carboxylic acid **19** was converted to the corresponding nitrile **21** using conventional procedures. The target compound **4** was prepared from **21** according to procedures similar to those described for **1**.

An alternative strategy was employed to synthesize the trityltetrazole derivative **26** (Scheme 4). The nitrile **9** was converted to the tetrazole **24** with trimethylstannyl azide. After being protected with trityl chloride, **25** was brominated to give the intermediate **26**. Preparation of **27** was accomplished by the reaction of **26** with ethyl 2-ethyl-4-oxo-1,4-dihydroquinoline-6-carboxylate in the presence of K_2CO_3 and the following deprotection of the trityl intermediate using concentrated HCl. The ester **27** was hydrolyzed with NaOH to give the target compound **28**. The preparation of **28**, **44**, and **47**–**51** was carried out by using the bromide **26** as a common intermediate.

Methyl 2-[(*tert*-butoxycarbonyl)amino]-3-nitrobenzoate was alkylated with **10** in the presence of K_2CO_3. Deprotection of the amino group of **29** under an acidic condition afforded **30**; the nitro group of which was then reduced to the amino group with $SnCl_2$, giving **31**. Cyclization of **31** to 2-ethoxybenzimidazole **32** was carried out by using tetraethoxymethane and acetic acid. Finally, **32** was converted to the tetrazole **33** by tetrazole formation followed by ester hydrolysis (Scheme 5).

Alkylation of L-valine methyl ester with **10** was carried out using (*N*,*N*-dimethylamino)pyridine. The secondary amine **34** was acylated with valeryl chloride, and the resulting amide **35** was converted to the tetrazole **37** according to the procedures described for **33** (Scheme 6).

The bromide **10** was converted to a primary amine **38** *via* an azide intermediate. After reaction of **38** with 7-chloro-5-ethylpyrazolo[1,5-*a*]pyrimidine, the resulting nitrile **39** was converted to the tetrazole **40** (Scheme 7).

Conclusion

We have applied the 3D search technique to the design of new bioisosteres of the BPT, which is known as an important substructure for potent AII antagonists. The 3D query has been derived from the superposition of the substructures of the known potent antagonists. Using the query, the database MDDR-3D has been searched to give the 139 hit compounds, from which the tricyclic lead structure has been selected. The lead structure has been evolved to the dibenzo[*a*,*d*]cycloheptene and dibenzo[*b*,*f*]oxepin substructures as novel bioisosteres of the BPT by evaluating the fitness to the overlay model and taking the synthetic feasibility into account. The AII antagonists having these substructures showed the high receptor-binding affinities, demonstrating the utility of 3D search in designing new lead structures.

In this study, the 3D searching technique has been employed to explore the bioisosteric fragment for the BPT rather than the whole structure as novel AII antagonists. This sort of approach to drug design requires the subsequent modeling study in order for hit fragments to be constructed to full structures and then evolved to synthetically reasonable ones. The molecular modeling of synthetic targets is desired to be carried out interactively between modeling chemists and synthetic chemists, while it might be difficult because of the lack of the common background. For more seamless modeling, chemists with a background of both modeling and synthesis should play a central role in the lead generation process.

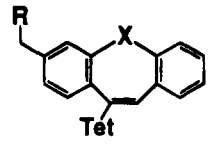
Experimental Section

Molecular Modeling. All molecular models were constructed within the molecular modeling software package SYBYL 5.41, 5.51, 6.01, and 6.10, using molecular fragments and standard bond lengths and angles from the SYBYL structural library. Each structure was optimized by means of the molecular mechanics minimizer MAXIMIN2 (convergence criteria: energy change threshold $\leq$0.05 kcal/mol) and the standard TRIPOS force field by neglecting the electrostatic contribution.

The overlay model in Figure 5 was achieved using a MULTIFIT procedure, which performed a flexible fit between two or several molecules. Seven compounds were built from the substructures **B**–**F** in Figure 4 by replacing the methylene linkage with hydrogen. Three centroids for the aromatic ring were defined in all the compounds and aggregated respectively with all the heavy atoms which composed the corresponding ring. Multifit force was used in order to superimpose the each centroids of all the compounds. Default spring force constant (k) of 20 kcal/mol·Å^2 was applied in multifit energy term ($E = \Sigma kd^2$). The resulting conformers were followed by unconstrained energy minimization and the rigid body least-squares FIT procedure. Repeating the trial using various initial conformers resulted in the satisfactory overlay model consisting of reasonable low-energy conformers shown in Figure 5. All conformers in the final model had steric energies not higher than 3 kcal/mol above that of the corresponding global minimum conformers.

The molecular surface model in Figure 5 was prepared by calculation of a solvent-accessible surface. All atoms in the

Table 1. AII Antagonistic Potencies in Vitro of Dibenzo[*a*,*d*]cycloheptene- and Dibenzo[*b*,*f*]oxepin-based AII Antagonists



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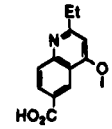
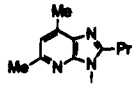
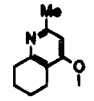
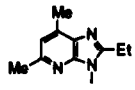
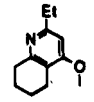
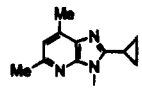
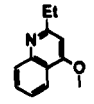
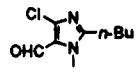
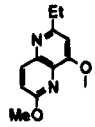
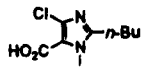
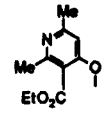
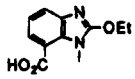
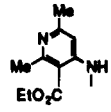
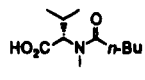
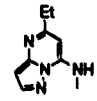
1		-CO-	0.29	28		-CO-	2.7
3		$-CH_2-$	0.49				
4		-O-	0.70	47		-CO-	4.3
41		-CO-	0.66	48		-CO-	1.3
42		-CO-	0.45	49		-CO-	0.65
43		-CO-	12	50		-CO-	0.48
44		-CO-	2.1	51		-CO-	4.3
33		-CO-	2.7	52		-CO-	2.9
45		-O-	3.9				
37		-CO-	8.7	40		-CO-	1.1
46		-O-	9.6				

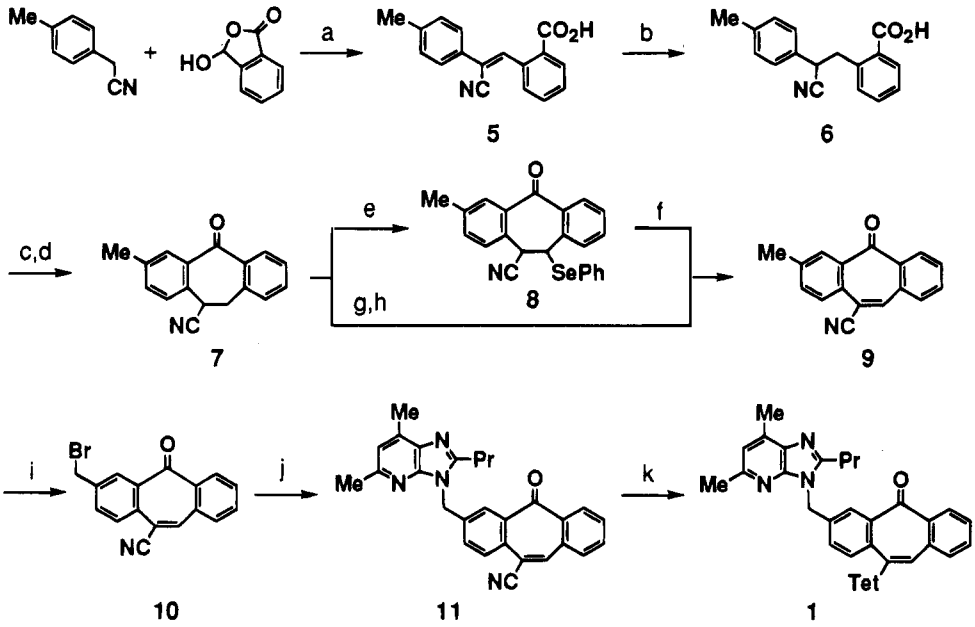
[a] K_i values represent an average of two or more determinations from separate assays.

overlay model described above were merged together in a single coordinate system, ignoring their intermolecular steric repulsion. Connolly surface procedure in SYBYL calculated a solvent accessible surface of the overlay model.

Angiotensin II Receptor Binding Assay. A cDNA encoding human AT_1 angiotensin II receptor, donated by Dr. T. Inagami (Vanderbilt University, Nashville, TN), was inserted into the mammalian expression vector pcDNA1 (Invitrogen). COS-7 cells plated in 175-cm^2 flasks grew to 80% confluency after 3 days. The cells were then transfected with 40 μg DNA by 150 μL of lipofectin reagent (GIBCO). Two or three days after transfection, the binding assay was done as described previously.[22] In brief, cell suspensions (1.2×10^6 cell/mL), dispersed with 0.025% trypsin/1 mM EDTA, were incubated at 25 °C for 60 min in 0.2 mL of Hepes (20 mL)–buffered Hanks' solution containing 1 mg/mL phenylmethanesulfonyl fluoride, 10 μg/mL aprotinin, 10 μg/mL leupeptin, 10 μg/mL pepstatin A, 250 μg/mL bacitracin, 10 μg/mL soybean trypsin inhibitor, and 0.1 mM amastatin with 0.1 nM [^{125}I]AII (81.4 TBq/mmol, New England Nuclear) in the absence or presence of nonradioactive peptides or drugs. Each binding reaction was terminated by addition of 2.5 mL of ice-cold 50 mM Tris-HCl (pH 7.4), followed by rapid filtration through GF/C glass fiber filter under reduced pressure. The filters were then quickly washed four more times with 2.5 mL of the Tris buffer, and the radioactivity retained on the filter was counted. Nonspecific binding, determined in the presence of 10^{-6} M nonradiolabeled AII, was 5–10% of the total binding. K_i values were calculated from the equation $K_i = IC_{50}/(1 + [L]/K_d)$, where IC_{50} = the concentration causing 50% inhibition of specific [^{125}I]AII binding, [L] = [^{125}I]AII concentration, and K_d = the dissociation constant for [^{125}I]AII (0.46 nM).

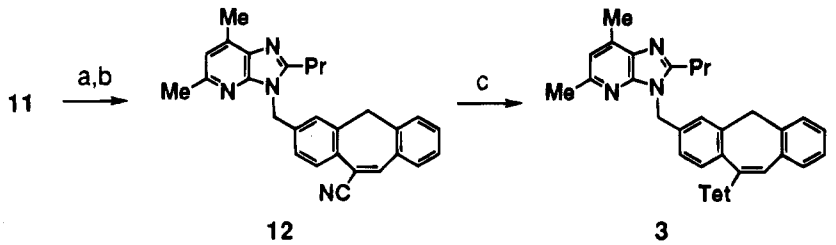
Chemical Synthesis. Melting points were determined on a Yanagimoto hot plate micromelting point apparatus without correction. Infrared (IR) spectra were recorded on a Hitachi 260-10 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian VXR-200 spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are reported as δ values with

Scheme 1[a]



[a] Reagents: (a) NaOMe, MeOH; (b) $NaBH_4$, Et_3N, iPrOH; (c) $SOCl_2$, $ClCH_2CH_2Cl$; (d) $AlCl_3$, $ClCH_2CH_2Cl$; (e) PhSeCl, $(TMS)_2NLi$, THF; (f) mCPBA, CH_2Cl_2; (g) Br_2, CH_2Cl_2; (h) Et_3N, CH_2Cl_2; (i) NBS, dibenzoyl peroxide, $ClCH_2CH_2Cl$; (j) 5,7-dimethyl-2-propylimidazo[4,5-*b*]pyridine, NaH, DMF; (k) Me_3SnN_3, DMF.

Scheme 2[a]



[a] Reagents: (a) $NaBH_4$, EtOH; (b) Me_2SiCl_2, NaI, MeCN; (c) Me_3SnN_3, DMF.

respect to tetramethylsilane (TMS) as an internal standard. Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet), br (broad), and m (multiplet). Abbreviations are as follows: Tet, tetrazole; Tr, trityl; THF, tetrahydrofuran; DMF, *N,N*-dimethylformamide; DMAP, (*N,N*-dimethylamino)pyridine; HMPA, hexamethylphosphoric triamide. Column chromatography was done on Kieselgel 60 (E. Merck, 230–400 mesh). Organic extracts were dried over $MgSO_4$.

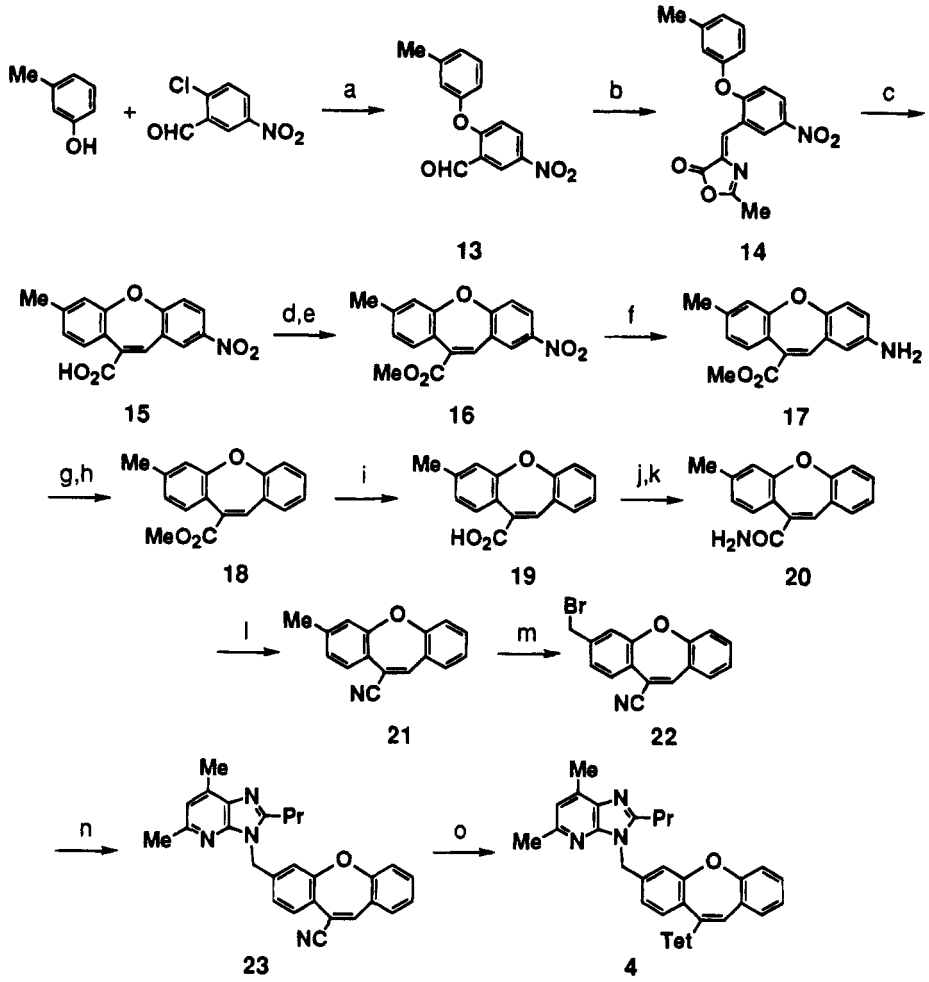
(*Z*)-2-(2-Cyano-2-*p*-tolylvinyl)benzoic Acid (5). To a solution of sodium (17 g, 739 mmol) in MeOH (600 mL) was added 4-methylbenzyl cyanide (103.5 g, 789 mmol) at 0 °C under nitrogen. After the mixture was stirred for 20 min, phthalaldehydic acid (100.7 g, 671 mmol) was added at room temperature. The reaction mixture was heated at reflux for 1 h and concentrated, allowing a half of the solvent to escape. The mixture was allowed to cool to room temperature and poured into 2 L of ice water containing 100 mL of concentrated HCl. After being stirred vigorously for 10 min, the resulting crystals were collected by filtration and washed with water. The wet crystals were dissolved in EtOAc, and the solution was washed with brine and then dried. Removal of solvent afforded 168.0 g (95.1%) of **5**: mp 191–193 °C (*n*-hexane–EtOAc); ^{1}H-NMR ($CDCl_3$) δ 2.40 (s, 3 H), 7.25 and 7.62 (AB q, 2 H × 2, J = 8.6 Hz), 7.50–7.75 (m, 2 H), 7.90 (dd, 1 H, J = 7.0, 0.8 Hz), 8.19 (dd, 1 H, J = 7.8, 1.2 Hz), 8.3 (s, 1 H). Anal. ($C_{17}H_{13}NO_2$) C, H, N.

(*RS*)-2-(2-Cyano-2-*p*-tolylethyl)benzoic Acid (6). A solution of **5** (162.0 g, 627 mmol) and sodium borohydride (36 g, 952 mmol) in 2-propanol (600 mL) was heated at reflux for 8 h under nitrogen. After being allowed to cool to room temperature, the mixture was poured into ice water. The aqueous solution was extracted with EtOAc. The extract was washed successively with water, saturated $NaHCO_3$, and brine and then dried. Removal of the solvent afforded **6** (150.1 g, 90.2%), which was used for the next reaction without further purification: mp 133–134 °C; ^{1}H-NMR ($CDCl_3$) δ 2.35 (s, 3 H), 3.34 (dd, 1 H, J = 12.8, 10.2 Hz), 3.74 (dd, 1 H, J = 12.8, 5.6 Hz), 4.33 (dd, 1 H, J = 10.2, 5.6 Hz), 7.15–7.61 (m, 7 H), 8.21 (dd, 1 H, J = 7.6, 1.4 Hz). Anal. ($C_{17}H_{15}NO_2$) C, H, N.

(*RS*)-7-Methyl-5-oxo-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-10-carbonitrile (7). To a solution of **6** (146.9 g, 554 mmol) in 1,2-dichloroethane (500 mL) was added thionyl chloride (98 g, 823 mmol), and the mixture was heated at reflux for 1 h. After the removal of thionyl chloride completely, the residue was dissolved in 1,2-dichloroethane (500 mL), and then aluminium chloride (170 g, 1.27 mol) was added. The reaction mixture was heated at reflux for 15 min. After being allowed to cool to room temperature, the mixture was poured into ice water. The aqueous solution was extracted with CH_2Cl_2. The organic extract was washed with 1 N NaOH and brine and then dried. The crude product was purified by column chromatography on silica gel with *n*-hexane–EtOAc (v/v, 4/1) to give 130.2 g (95.0 %) of **7**: mp 113–134 °C; ^{1}H-NMR ($CDCl_3$) δ 2.41 (s, 3 H), 3.49 (dd, 1 H, J = 15.8, 8.2 Hz), 3.60 (dd, 1 H, J = 15.8, 2.6 Hz), 4.45 (dd, 1 H, J = 8.2, 2.4 Hz), 7.20–7.61 (m, 5 H), 7.87 (dd, 1 H, J = 1.2, 0.8 Hz), 7.98–8.03 (m, 1 H). Anal. ($C_{17}H_{13}NO$) C, H, N.

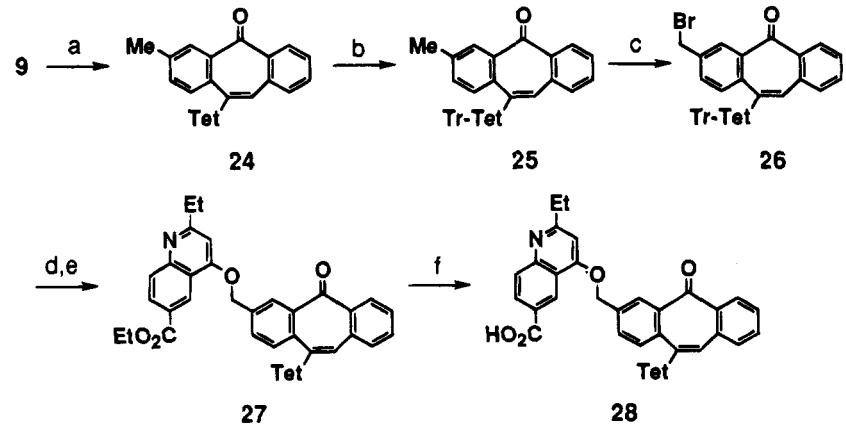
(*RS*)-7-Methyl-5-oxo-10-phenylselenyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-10-carbonitrile (8). To a solution of **7** (2.29 g, 9.26 mmol) in THF (25 mL) was added dropwisely lithium bis(trimethylsilyl) amide (1.0 M, 11.1 mL, 11.1 mmol) at −60 °C under nitrogen. After the mixture was stirred for 10 min, benzeneselenenyl chloride (1.95 g, 1.02 mmol) was added at −70 °C, and then the mixture was stirred for 20 min at the same temperature. The reaction mixture was poured into ice aqueous NH_4Cl and extracted with EtOAc.

Scheme 3[a]



[a] Reagents: (a) aqueous NaOH; (b) AcGly, $KHCO_3$, Ac_2O; (c) concentrated HCl, HOAc, H_2O; (d) $SOCl_2$, DMF, PhH; (e) MeOH, py; (f) $FeSO_4 \cdot 7H_2O$, Et_3N, dioxane, MeOH, H_2O; (g) $NaNO_2$, HCl, H_2O; (h) 50% H_3PO_2; (i) aqueous NaOH; (j) $SOCl_2$, DMF, PhH; (k) NH_4OH; (l) $SOCl_2$; (m) NBS, AIBN, $ClCH_2CH_2Cl$; (n) 5,7-dimethyl-2-propylimidazo[4,5-*b*]pyridine, NaH, DMF; (o) Me_3SnN_3, DMF.

Scheme 4[a]

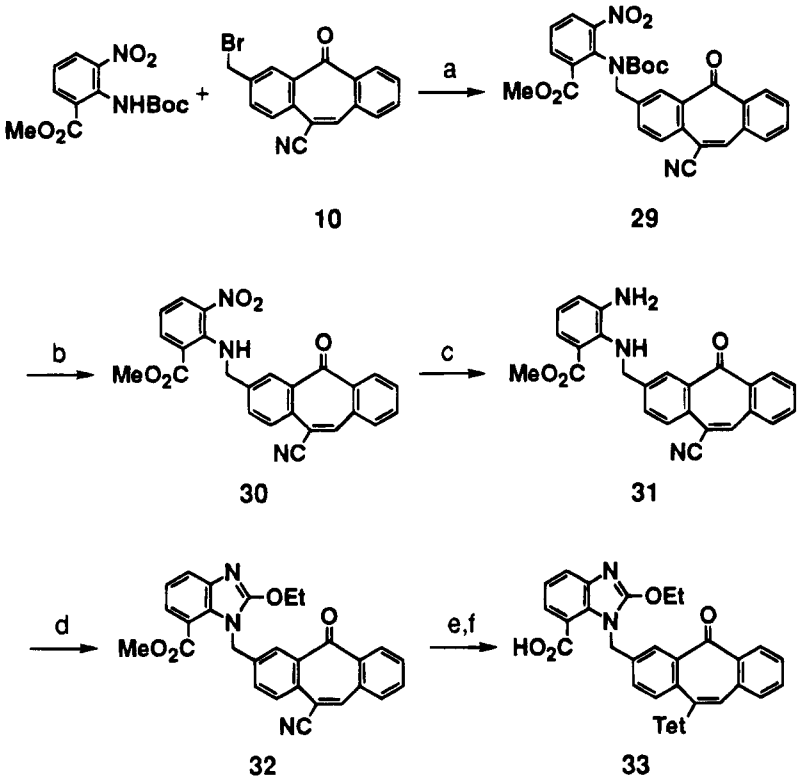


[a] Reagents: (a) Me_3SnN_3, DMF; (b) TrCl, Et_3N, THF; (c) NBS, AIBN, $ClCH_2CH_2Cl$; (d) ethyl 2-ethyl-4-oxo-1,4-dihydroquinoline-6-carboxylate, K_2CO_3, DMF; (e) concentrated HCl, MeOH; (f) aqueous NaOH, MeOH.

The organic extract was washed with brine and then dried. The crude product was purified by column chromatography on silica gel with *n*-hexane–EtOAc (v/v, 8/1) to give 3.34 g (89.6%) of **8** as an oily product: ^{1}H-NMR ($CDCl_3$) δ 2.39 (s, 3 H), 3.66 and 3.96 (AB q, 1 H × 2, J = 16.2 Hz), 7.10–7.56 (m, 10 H), 7.85 (dd, 1 H, J = 1.2, 0.6 Hz), 8.00–8.08 (m, 1 H).

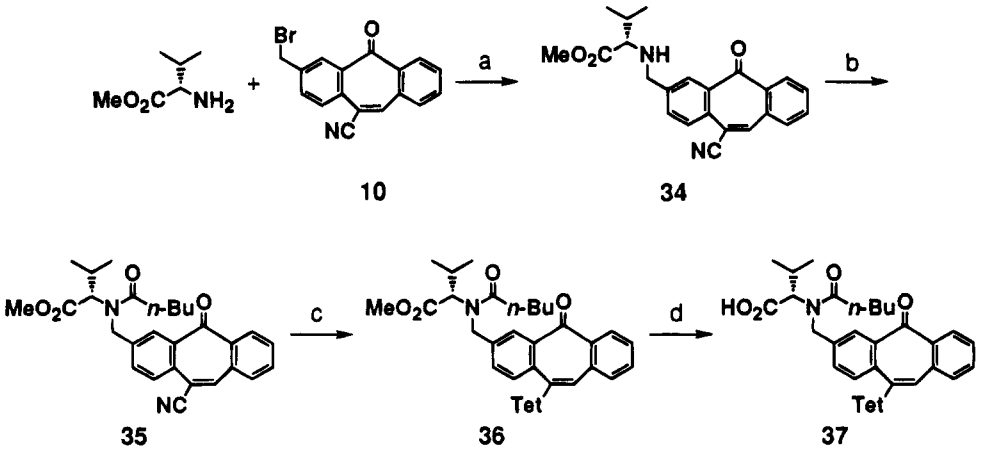
7-Methyl-5-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene-10-carbonitrile (9) (Procedure A). To a solution of **8** (3.34 g, 8.3 mmol) in CH_2Cl_2 (30 mL) was added portionwise *m*-chloroperbenzoic acid (80%, 3.6 g, 16.7 mmol) with ice bath under nitrogen. After being stirred for 30 min at room temperature, the reaction mixture was poured into ice aqueous Na_2SO_3. The solution was extracted with CH_2Cl_2, and the extract was washed with aqueous Na_2SO_3, aqueous $NaHCO_3$, and brine and then dried. Removal of the solvent afforded 1.81 g (92.4%) of **9**. **Procedure B.** To a solution of **7** (120 g, 482 mmol) in CH_2Cl_2 (500 mL) was added bromine (108 g, 675 mmol) at room temperature. The reaction mixture was allowed to stand overnight, and then aqueous Na_2SO_3 was added carefully with an ice bath. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with aqueous $NaHCO_3$ and brine and then dried.

Scheme 5[a]



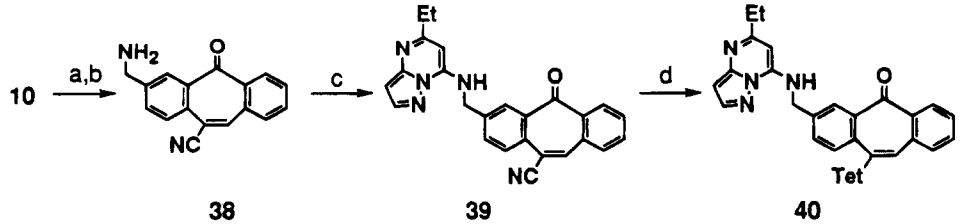
[a] Reagents: (a) K_2CO_3, MeCN; (b) CF_3CO_2H, CH_2Cl_2; (c) $SnCl_2 \cdot 2H_2O$, EtOH, dioxane; (d) $(EtO)_4C$, AcOH; (e) Me_3SnN_3, DMF; (f) aqueous NaOH, MeOH.

Scheme 6[a]



[a] Reagents: (a) DMAP, CH_2Cl_2, MeCN; (b) *n*-BuCOCl, Py; (c) Me_3SnN_3, xylene; (d) aqueous LiOH, MeOH.

Scheme 7[a]



[a] Reagents: (a) NaN_3, HMPA; (b) $SnCl_2 \cdot 2H_2O$, EtOH, THF; (c) 7-chloro-5-ethylpyrazolo[1,5-*a*]pyrimidine, DMAP, DMF; (d) Me_3SnN_3, xylene.

To the crude solution of the bromide was added carefully triethylamine (50 g, 500 mmol) at such a rate that the temperature did not rise above 30 °C. After the mixture was stirred for 30 min at room temperature, removal of the solvent afforded **9** (89.0 g, 75.2%): mp 208–209 °C (*n*-hexane–EtOAc); ^{1}H-NMR ($CDCl_3$) δ 2.51 (s, 3 H), 7.26–7.74 (m, 5 H), 7.94–8.00 (m, 2 H), 8.10–8.16 (m, 1 H). Anal. ($C_{17}H_{11}NO$) C, H, N.

7-(Bromomethyl)-5-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene-10-carbonitrile (10). To a solution of **9** (24.5 g, 100 mmol) in 1,2-dichloroethane (1 L) was added *N*-bromosuccinimide (18

g, 100 mmol) and dibenzoyl peroxide (1 g, 4 mmol). The solution was heated at reflux for 2 h. After being cooled to room temperature, the solution was washed with 1 N NaOH and brine, dried, and then evaporated. Trituration with diisopropyl ether afforded the crude product of **10** (23.6 g, 72.8%). The crude product is routinely used without further purification: ^{1}H-NMR ($CDCl_3$) δ 4.59 (s, 2 H), 7.50–8.18 (m, 8 H).

7-[(5,7-Dimethyl-2-propylimidazo[4,5-*b*]pyridin-3-yl)-methyl]-5-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene-10-carbonitrile (11). Sodium hydride (120 mg, 3 mmol; 60% dispersion in oil) washed with *n*-hexane was suspended in DMF (20 mL). To the above stirred suspension was added 5,7-dimethyl-2-propylimidazo[4,5-*b*]pyridine (380 mg, 2 mmol) at −20 °C under nitrogen. After the mixture was allowed to warm to room temperature and then stirred for 10 min, **10** (700 mg, 2.24 mmol) was added at −40 °C and the resulting mixture was allowed to warm to room temperature and then stirred for 2 h. The reaction mixture was poured into ice water. The mixture was extracted with EtOAc. The organic extract was washed with water and brine and then dried. The crude product was purified by column chromatography on silica gel with EtOAc to give 680 mg (78.6%) of **11**: mp 232–233 °C (*n*-hexane–EtOAc); ^{1}H-NMR ($CDCl_3$) δ 0.97 (t, 3 H, J = 7.4 Hz), 1.72–1.83 (m, 2 H), 2.58 (s, 3 H), 2.64 (s, 3 H), 2.75 (t, 2 H, J = 7.8 Hz), 5.59 (s, 2 H), 6.91 (d, 1 H, J = 0.2 Hz), 7.42 (dd, 1 H, J = 8.4, 2.0 Hz), 7.58–7.78 (m, 4 H), 7.96–8.00 (m, 3 H), 8.01–8.13 (m, 1 H). Anal. ($C_{28}H_{24}N_4O$) C, H, N.

3-[(5,7-Dimethyl-2-propylimidazo[4,5-*b*]pyridin-3-yl)-methyl]-11-(1*H*-tetrazol-5-yl)dibenzo[*a*,*d*]cyclohepten-5-one (1). A suspension of **11** (200 mg, 0.46 mmol) and trimethylstannyl azide (280 mg, 1.36 mmol) in DMF (5 mL) was stirred at 110 °C for 24 h under nitrogen. The reaction mixture was concentrated in vacuo, and the residue was suspended on EtOH (5 mL). To the suspension was added 1 N HCl (1 mL), and the reaction mixture was stirred for 15 min at room temperature. After removal of the solvent, the residue was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layer was dried and concentrated in vacuo. The residue was purified by chromatography on silica gel. Elution with $CHCl_3$–MeOH (v/v, 8/1) afforded 96 mg (44.0%) of **1** as powder: ^{1}H-NMR ($CDCl_3$–CD_3OD) δ 0.96 (t, 3 H, J = 7.3 Hz), 1.69–1.81 (m, 2 H), 2.58 (s, 3 H), 2.63 (s, 3 H), 2.75 (t, 2 H, J = 7.8 Hz), 5.58 (s, 2 H), 6.96 (s, 1 H), 7.18–7.28 (m, 2 H), 7.58–7.98 (m, 6 H). Anal. ($C_{28}H_{25}N_7O$) C, H, N.

2-[(5,7-Dimethyl-2-propylimidazo[4,5-*b*]pyridin-3-yl)-methyl]-11-(1*H*-tetrazol-5-yl)dibenzo[*a*,*d*]cyclohepten-5-one (2). The preparation of **2** was carried out according to the procedure described for **1** (46.2%): ^{1}H-NMR ($CDCl_3$) δ 0.97 (t, 3 H, J = 7.4 Hz), 1.64–1.84 (m, 2 H), 2.56 (s, 3 H), 2.63 (s, 3 H), 2.75 (t, 2 H, J = 7.8 Hz), 5.50 (s, 2 H), 6.94 (s, 1 H), 7.09–7.14 (m, 2 H), 7.58–7.70 (m, 3 H), 7.90–7.98 (m, 2 H), 8.18 (s, 1 H). Anal. ($C_{28}H_{25}N_7O{\cdot}0.2H_2O$) C, H, N.

7-[(5,7-Dimethyl-2-propylimidazo[4,5-*b*]pyridin-3-yl)-methyl]-5*H*-dibenzo[*a*,*d*]cycloheptene-10-carbonitrile (12). To a solution of **11** (430 mg, 1 mmol) in EtOH (10 mL) was added sodium borohydride (76 mg, 2 mmol). After being stirred for 30 min at room temperature, the mixture was diluted with EtOAc and then washed with water and brine. After the solution was dried and evaporated, the residue was dissolved in acetonitrile (10 mL). To the solution was added NaI (600 mg, 4 mmol) and dichlorodimethylsilane (260 mg, 2 mmol), and the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with EtOAc and washed successively with water, aqueous $NaHCO_3$, 10% of $Na_2S_2O_2$, and brine. The mixture was dried and evaporated. The residue was purified by chromatography on silica gel. Elution with $CHCl_3$–EtOAc (v/v, 4/1) gave 190 mg (45.0%) of **3** as an oily product: ^{1}H-NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7.4 Hz), 1.68–1.81 (m, 2 H), 2.58 (s, 3 H), 2.64 (s, 3 H), 2.70 (t, 2 H, J = 7.9 Hz), 3.66 (s, 2 H), 5.48 (s, 2 H), 6.91 (s, 1 H), 7.04–7.08 (m, 2 H), 7.23–7.45 (m, 4 H), 7.61–7.66 (m, 1 H), 7.75 (s, 1 H).

3-[(5,7-Dimethyl-2-propylimidazo[4,5-*b*]pyridin-3-yl)-methyl]-11-(1*H*-tetrazol-5-yl)dibenzo[*a*,*d*]cycloheptene (3). The preparation of **3** was carried out according to the procedure described for **1**: mp 278–281 °C dec (MeOH); ^{1}H-NMR ($CDCl_3$–CD_3OD) δ 0.93 (t, 3 H, J = 7.4 Hz), 1.62–1.81 (m, 2 H), 2.57 (s, 3 H), 2.65 (s, 3 H), 2.70–2.80 (m, 2 H), 3.71 (s, 2 H), 5.47 (s, 2 H), 6.84–7.15 (m, 4 H), 7.25–7.50 (m, 2 H), 8.13 (s, 1 H). Anal. ($C_{28}H_{25}N_7O{\cdot}0.3H_2O$) C, H, N.

5-Nitro-2-(*m*-tolyloxy)benzaldehyde (13). A solution of *m*-cresol (29.3 g, 270 mmol) and 2-chloro-5-nitrobenzaldehyde (50.3 g, 270 mmol) in 0.63 N NaOH (40 mL, 313 mmol) was heated at reflux for 2 h. After being allowed to cool to room temperature, the aqueous solution was extracted with toluene. The organic extract was washed with 1 N NaOH and water and dried. Removal of the solvent afforded 51.8 g (75%) of **13**: mp 74–75 °C (iPr_2O–*n*-hexane); ^{1}H-NMR ($CDCl_3$) δ 2.41 (d, 3 H, J = 0.4 Hz), 6.92 (d, 1 H, J = 9.2 Hz), 6.96 (d, 1 H, J = 7.6 Hz), 6.98 (brs, 1 H), 7.15 (d, 1 H, J = 7.6 Hz), 7.37 (dt, 1 H, J = 7.6, 1.4 Hz), 8.31 (dd, 1 H, J = 9.2, 3.0 Hz), 8.79 (d, 1 H, J = 3.0 Hz). Anal. ($C_{14}H_{11}NO_4$) C, H, N.

2-Methyl-4-[5-nitro-2-(*m*-tolyloxy)benzylidene]-4*H*-oxazol-5-one (14). A mixture of **13** (2.74 g, 10.6 mmol), *N*-acetylglycine (1.25 g, 10.6 mmol), $KHCO_3$ (1.06 g, 10.6 mmol), and AcOH (8 mL) was stirred at 40 °C for 16 h. The reaction mixture was diluted with iPr_2O (10 mL) and *n*-hexane (4 mL). The precipitate was collected, washed with water, and then dried in vacuo to afford 2.16 g (60%) of **14**: mp 165–166 °C (iPr_2O–*n*-hexane); ^{1}H-NMR ($CDCl_3$) δ 2.30 (s, 3 H), 2.48 (d, 3 H, J = 0.4 Hz), 6.83 (d, 1 H, J = 9.2 Hz), 6.89 (d, 1 H, J = 7.6 Hz), 6.91 (brs, 1 H), 7.10 (d, 1 H, J = 7.6 Hz), 7.33 (dt, 1 H, J = 7.6, 1.4 Hz), 7.71 (s, 1 H), 8.14 (dd, 1 H, J = 9.2, 2.8 Hz), 9.65 (d, 1 H, J = 2.8 Hz).

7-Methyl-2-nitrodibenzo[*b*,*f*]oxepin 10-carboxylic Acid (15). A mixture of **14** (8.83 g, 26.1 mmol), AcOH (85 mL), concentrated HCl (30 mL), and water (50 mL) was heated at reflux for 8 h. After the mixture was allowed to cool to room temperature, the resulting precipitate was collected, washed with water, and then dried in vacuo to afford 4.95 g (64%) of **15**: mp 221–222 °C (CH_2Cl_2–MeOH); ^{1}H-NMR (DMSO-d_6) δ 2.33 (s, 3 H), 7.10 (dd, 1 H, J = 8.0, 0.8 Hz), 7.24 (d, 1 H, J = 0.8 Hz), 7.43 (d, 1 H, J = 8.0 Hz), 7.57 (d, 1 H, J = 8.8 Hz), 7.93 (s, 1 H), 8.32 (dd, 1 H, J = 8.8, 2.8 Hz), 8.46 (d, 1 H, J = 2.8 Hz). Anal. ($C_{16}H_{11}NO_5{\cdot}0.5H_2O$) C, H, N.

Methyl 7-Methyl-2-nitrodibenzo[*b*,*f*]oxepin-10-carboxylate (16). To a suspension of **15** (22.5 g, 75.8 mmol) in benzene (150 mL) was added one drop of DMF and thionyl chloride (16.2 mL, 227 mmol). After being heated at reflux for 1 h, the mixture was concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (265 mL). The solution was added dropwise to a mixture of pyridine (12.2 mL) and MeOH (150 mL). After being stirred at room temperature for 1 h, the mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with 1 N HCl, water, and saturated $NaHCO_3$ and then dried. Removal of the solvent afforded 23.2 g (98%) of **16**: mp 148–149 °C (CH_2Cl_2–MeOH); ^{1}H-NMR ($CDCl_3$) δ 2.37 (s, 3 H), 3.94 (s, 3 H), 7.05 (m, 1 H), 7.33 (d, 1 H, J = 8.4 Hz), 7.40 (d, 1 H, J = 8.8 Hz), 7.80 (s, 1 H), 8.20 (d, 1 H, J = 2.6 Hz), 8.23 (dd, 1 H, J = 8.8, 2.6 Hz). Anal. ($C_{17}H_{13}NO_5$) C, H, N.

Methyl 2-Amino-7-methyldibenzo[*b*,*f*]oxepin-10-carboxylate (17). To a solution of $FeSO_4{\cdot}7H_2O$ (25.6 g, 92 mmol) and Et_3N (12.8 mL, 92 mmol) in water (60 mL) was added a solution of **16** (3.12 g, 10 mmol) in MeOH (30 mL) and dioxane (30 mL). After being stirred for 30 min at room temperature, the reaction mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The aqueous layer was further extracted with CH_2Cl_2. The organic extract was washed with water and brine, then dried. Removal of the solvent afforded crude crystals of **17** (2.79 g, 90%): mp 135–136 °C (*n*-hexane–EtOH); ^{1}H-NMR ($CDCl_3$) δ: 2.34 (s, 3 H), 3.89 (s, 3 H), 6.59 (d, 1 H, J = 2.8 Hz), 6.67 (dd, 1 H, J = 8.4, 2.8 Hz), 6.96 (m, 1 H), 7.02 (d, 1 H, J = 8.4 Hz), 7.02 (s, 1 H), 7.35 (d, 1 H, J = 8.0 Hz), 7.76 (s, 1 H). Anal. ($C_{17}H_{15}NO_3$) C, H, N.

Methyl 7-Methyldibenzo[*b*,*f*]oxepin-10-carboxylate (18). A mixture of **17** (2.81 g, 9.53 mmol), 1 N HCl (19 mL), and water (9.5 mL) was stirred at room temperature for 20 min and then cooled to 0 °C. A solution of $NaNO_2$ (0.72 g, 10.5

mmol) in water (4.8 mL) was added dropwise. After being stirred for 100 min, the reaction mixture was added slowly to 50% H_3PO_2 (19 mL) and stirred for 2.5 h. The mixture was extracted with CH_2Cl_2. The organic extract was washed with water and dried. The crude product was purified by column chromatography on silica gel with toluene–*n*-hexane (v/v, 2/1) to give 1.60 g (63%) of **18** as crystals: mp 112 °C (*n*-hexane–iPr_2O); ^{1}H-NMR (CD_3OD) δ 2.34 (s, 3 H), 3.89 (s, 3 H), 7.00 (m, 1 H), 7.07 (s, 1 H), 7.20–7.50 (m, 5 H), 7.82 (s, 1 H). Anal. ($C_{17}H_{14}O_3$) C, H.

7-Methyldibenzo[*b,f*]oxepin-10-carboxylic Acid (19). A solution of **18** (4.0 g, 15.0 mmol) in 1 N NaOH (20 mL) and MeOH (12 mL) was heated at reflux for 1 h. After being allowed to cool to room temperature, the mixture was neutralized with 1 N HCl. The precipitate was collected, washed with water, and dried to afford crude crystals of **19** (3.70 g, 98%): mp 197–199 °C (*n*-hexane–acetone); ^{1}H-NMR ($CDCl_3$) δ 2.36 (s, 3 H), 7.02 (d, 1 H, J = 8.0 Hz), 7.05 (brs, 1 H), 7.15–7.45 (m, 4 H), 7.51 (d, 1 H, J = 8.8 Hz), 8.06 (s, 1 H). Anal. ($C_{16}H_{12}O_3$) C, H.

7-Methyldibenzo[*b,f*]oxepin-10-carboxamide (20). To a suspension of **19** (3.59 g, 14.2 mmol) in benzene (28 mL) was added one drop of DMF and thionyl chloride (3 mL). After being heated at reflux for 1 h, the mixture was concentrated in vacuo. The residue was dissolved in THF (10 mL) and NH_4OH (20 mL). The mixture was stirred at room temperature for 15 min and then concentrated in vacuo. The resulting precipitate was collected, washed with water, and dried to afford crude crystals of **20** (3.59 g, 87%): mp 148–149 °C (EtOH); ^{1}H-NMR ($CDCl_3$) δ 2.35 (s, 3 H), 7.00 (s, 1 H), 7.09 (bs, 1 H), 7.10–7.40 (m, 5 H), 7.31 (s, 1 H). Anal. ($C_{16}H_{13}NO_2$) C, H, N.

7-Methyldibenzo[*b,f*]oxepin-10-carbonitrile (21). A mixture of **20** (160 mg, 0.64 mmol) and thionyl chloride (1 mL) was heated at reflux for 1 h and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel with CH_2Cl_2 to give 140 mg (94%) of **21** as crystals: mp 131–133 °C; ^{1}H-NMR ($CDCl_3$) δ 2.37 (s, 3 H), 7.05 (m, 2 H), 7.10–7.30 (m, 3 H), 7.40–7.50 (m, 3 H). Anal. ($C_{16}H_{11}NO$) C, H, N.

7-(Bromomethyl)dibenzo[*b,f*]oxepin-10-carbonitrile (22). The preparation of **22** was carried out according to the procedure described for **10** (80%): ^{1}H-NMR ($CDCl_3$) δ 4.96 (s, 2 H), 7.20–7.30 (m, 5 H), 7.40–7.60 (m, 3 H).

7-[(5,7-Dimethyl-2-propylimidazo[4,5-*b*]pyridin-3-yl)methyl]dibenzo[*b,f*]oxepin-10-carbonitrile (23). The preparation of **23** was carried out according to the procedure described for **11** (54.4%): mp 198–199 °C (*n*-hexane–EtOAc); ^{1}H-NMR ($CDCl_3$) δ 0.96 (t, 3 H, J = 7.4 Hz), 1.72–1.83 (m, 2 H), 2.58 (s, 3 H), 2.64 (s, 3 H), 2.73 (t, 2 H, J = 7.8 Hz), 5.46 (s, 2 H), 6.92 (s, 1 H), 6.97–6.99 (m, 2 H), 7.10–7.40 (m, 4 H), 7.43 (s, 1 H), 7.50 (s, 1 H). Anal. ($C_{27}H_{24}N_4O\cdot0.2H_2O$) C, H, N.

5,7-Dimethyl-2-propyl-3-[[11-(1*H*-tetrazol-5-yl)dibenzo[*b,f*]oxepin-3-yl]methyl]-3*H*-imidazo[4,5-*b*]pyridine (4). The preparation of **4** was carried out according to the procedure described for **1** (62.9%): mp 233–234 °C (EtOH); ^{1}H-NMR (DMSO-d_6) δ 0.90 (t, 3 H, J = 7.3 Hz), 1.70 (m, 2 H), 2.50 (s, 3 H), 2.51 (s, 3 H), 2.77 (t, 2 H, J = 7.5 Hz), 5.51 (s, 2 H), 6.90–7.00 (m, 2 H), 7.20–7.35 (m, 4 H), 7.40–7.55 (m, 2 H), 7.71 (s, 1 H). Anal. ($C_{27}H_{25}N_7O\cdot0.2H_2O$) C, H, N.

3-Methyl-11-(1*H*-tetrazol-5-yl)dibenzo[*a,d*]cyclohepten-5-one (24). The preparation of **24** was carried out according to the procedure described for **11** (74%): mp 111–112 °C dec (MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.42 (s, 3 H), 7.17 (d, 1 H, J = 8.2 Hz), 7.30–7.38 (m, 1 H), 7.54–7.68 (m, 3 H), 7.72–7.76 (m, 1 H), 7.79 (s, 1 H), 7.92–7.98 (m, 1 H). Anal. ($C_{17}H_{12}N_4O\cdot$MeOH) C, H, N.

3-Methyl-11-(trityl-1*H*-tetrazol-5-yl)dibenzo[*a,d*]cyclohepten-5-one (25). To a solution of **24** (9.36 g, 32.5 mmol) and Et_3N (4.00 g, 39.5 mmol) in THF (100 mL) was added trityl chloride (10.4 g, 37.3 mmol) under nitrogen. After being stirred at room temperature for 1.5 h, the mixture was filtered and washed with THF, water, and EtOH. The crystals were dried to afford **25** (15.1 g, 89%). The filtrate was concentrated in vacuo, and the residue was dissolved in $CHCl_3$. The solution was washed with water and then dried. Removal of the solvent afforded 1.76 g (10%) of **25**: mp 218–220 °C dec (*n*-hexane–EtOAc); ^{1}H-NMR ($CDCl_3$) δ 2.43 (s, 3 H), 7.12–7.40 (m, 17H), 7.45–7.62 (m, 3 H), 7.75–7.80 (m, 1 H), 7.95–8.00 (m, 2 H). Anal. ($C_{36}H_{26}N_4O$) C, H, N.

3-(Bromomethyl)-11-(trityl-1*H*-tetrazol-5-yl)dibenzo[*a,d*]cyclohepten-5-one (26). The preparation of **26** was carried out according to the procedure described for **10** (66.9%): ^{1}H-NMR ($CDCl_3$) δ 1.56 (s, 9 H), 4.54 (s, 2 H), 7.15–8.00 (m, 22H), 8.07 (s, 1 H).

Ethyl 2-Ethyl-4-[[5-oxo-11-(1*H*-tetrazol-5-yl)-5*H*-dibenzo[*a,d*]cyclohepten-3-yl]methoxy]quinoline-6-carboxylate (27). A suspension of **26** (707 mg, 1.72 mmol), ethyl 2-ethyl-4-oxo-1,4-dihydroquinoline-6-carboxylate (400 mg, 1.63 mmol), and K_2CO_3 (340 mg, 2.45 mmol) in MeCN (15 mL) was heated at reflux for 4 h under nitrogen. After being allowed to cool to room temperature, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane–EtOAc (v/v, 2/1). After removal of the solvent, the residue was dissolved in EtOH (20 mL) and concentrated HCl (1 mL), and the mixture was stirred at room temperature for 15 min. The reaction mixture was poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and concentrated in vacuo to afford **27** (520 mg, 60%): mp 171–173 °C (EtOH); ^{1}H-NMR ($CDCl_3$–CD_3OD) δ 1.35–1.45 (m, 6 H), 2.99 (q, 2 H, J = 7.8 Hz), 4.45 (q, 2 H, J = 7.2 Hz), 5.40 (s, 2 H), 6.82 (s, 1 H), 7.42 (d, 1 H, J = 8.2 Hz), 7.60–7.73 (m, 4 H), 7.98–8.11 (m, 4 H), 8.30 (dd, 1 H, J = 9.0, 1.8 Hz), 8.90 (d, 1 H, J = 2.0 Hz). Anal. ($C_{31}H_{25}N_5O_4\cdot0.5$EtOH$\cdot0.5H_2O$) C, H, N.

2-Ethyl-4-[[5-oxo-11-(1*H*-tetrazol-5-yl)-5*H*-dibenzo[*a,d*]cyclohepten-3-yl]methoxy]quinoline-6-carboxylic Acid (28). A mixture of **27** (100 mg, 0.19 mmol), 4 N NaOH (0.5 mL), and EtOH (5 mL) was heated at reflux for 30 min. After removal of the solvent, the residue was dissolved in water. To the aqueous solution was added 1 N HCl (2.5 mL), and the resulting crystal was collected and washed with EtOH to afford **28** (30 mg, 32%): mp >300 °C (MeOH); ^{1}H-NMR (DMSO-d_6) δ 1.33 (t, 3 H, J = 7.7 Hz), 2.92 (q, 2 H, J = 7.7 Hz), 5.49 and 5.60 (each for s, total 2 H), 7.22 (d, 1 H, J = 2.6 Hz), 7.30–7.56 (m, 4 H), 7.64–8.20 (m, 6 H), 8.70–8.74 (m, 1 H). Anal. ($C_{29}H_{21}N_5O_4\cdot1.5H_2O$) C, H, N.

Methyl 2-[(*tert*-Butoxycarbonyl)[(11-cyano-5-oxo-5*H*-dibenzo[*a,d*]cyclohepten-3-yl)methyl]amino]-3-nitrobenzoate (29). A mixture of methyl 2-[(butoxycarbonyl)amino]-3-nitrobenzoate (3.61 g, 12.2 mmol), **10** (3.81 g, 12.2 mmol), K_2CO_3 (1.9 g, 13.7 mmol), and MeCN (100 mL) was heated at reflux for 4 h under nitrogen. After removal of the solvent, the residue was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layer was dried and concentrated in vacuo. The residue was purified by chromatography on silica gel. Elution with CH_2Cl_2–EtOAc (v/v, 50/1) afforded 5.68 g (86%) of **29** as crystals: mp 178–180 °C; ^{1}H-NMR ($CDCl_3$) δ 1.34 and 1.57 (total 9 H, each for s), 3.72 (s, 1 H), 4.72 and 4.85 (AB q, 2 H, J = 16 Hz), 7.45–8.15 (m, 11 H). Anal. ($C_{30}H_{25}N_3O_7$) C, H, N.

Methyl 2-[[(11-Cyano-5-oxo-5*H*-dibenzo[*a,d*]cyclohepten-3-yl)methyl]amino]-3-nitrobenzoate (30). To a solution of **29** (5.5 g, 10.2 mmol) in CH_2Cl_2 (55 mL) was added dropwise CF_3CO_2H (15 mL). The mixture was stirred at room temperature for 1 h under nitrogen. After removal of the solvent, the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was washed with water, dried, and concentrated in vacuo. The residue was crystallized with *n*-hexane to afford 4.39 g (98%) of **30**: mp 204–206 °C; ^{1}H-NMR ($CDCl_3$) δ 3.90 (s, 1 H), 4.32 (d, 2 H, J = 6.0 Hz), 6.76 (t, 1 H, J = 10 Hz), 7.57–7.66 (m, 4 H), 7.80 (s, 1 H), 7.95–8.15 (m, 5 H), 8.90 (t, 1 H, J = 6.0 Hz). Anal. ($C_{25}H_{17}N_3O_5\cdot0.4H_2O$) C, H, N.

Methyl 3-Amino-2-[[(11-cyano-5-oxo-5H-dibenzo[*a,d*]cyclohepten-3-yl)methyl]amino]benzoate (31). A mixture of **30** (4.36 g, 9.91 mmol), $SnCl_2\cdot2H_2O$ (9.3 g, 41.2 mmol), EtOH (30 mL), and dioxane (30 mL) was heated at reflux for 1 h.

After removal of the solvent, the residue was partitioned between EtOAc and 2 N NaOH. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with water, dried, and concentrated in vacuo. The residue was purified by chromatography on silica gel. Elution with CH_2Cl_2–EtOAc (v/v, 10/1) afforded 3.02 g (74%) of **31** as crystals: mp 204–207 °C; ^{1}H-NMR ($CDCl_3$) δ 3.76 (s, 3 H), 3.92 (brs, 1 H), 4.35 (brs, 2 H), 6.80–6.95 (m, 2 H), 7.30–7.38 (m, 1 H), 7.55–7.75 (m, 5 H), 7.92–8.15 (m, 3 H). Anal. ($C_{25}H_{19}N_3O_3 \cdot 0.2H_2O$) C, H, N.

Methyl 3-[(11-Cyano-5-oxo-5*H*-dibenzo[*a*,*d*]cyclohepten-3-yl)methyl]-2-ethoxy-3*H*-benzimidazole-4-carboxylate (32). A mixture of **31** (2.95 g, 7.20 mmol), AcOH (960 mg), and tetraethoxymethane (13 mL) was stirred at 100 °C for 2 h under nitrogen. After the mixture was allowed to cool to room temperature, the resulting precipitate was collected, washed with *n*-hexane, and dried to afford crystals of **32** (2.93 g, 88%): mp 203–205 °C; ^{1}H-NMR ($CDCl_3$) δ 1.49 (t, 3 H, J = 7.2 Hz), 3.90 (s, 3 H), 3.92 (brs, 1 H), 4.68 (q, 2 H, J = 7.2 Hz), 5.78 (s, 2 H), 7.18 (t, 1 H, J = 9.0 Hz), 7.30–7.38 (m, 1 H), 7.55–7.78 (m, 6 H), 7.90–7.96 (m, 2 H), 8.06–8.11 (m, 1 H). Anal. ($C_{28}H_{21}N_3O_4$) C, H, N.

2-Ethoxy-3-[[5-oxo-11-(1*H*-tetrazol-5-yl)-5*H*-dibenzo[*a*,*d*]cyclohepten-3-yl]methyl]-3*H*-benzimidazole-4-carboxylic Acid (33). The nitrile **32** (1.0 g, 2.1 mmol) was converted to a corresponding tetrazole (320 mg, 0.63 mmol) as a powder in a similar manner for preparation of **1**. A solution of the tetrazole in 1 N NaOH (2 mL) and EtOH (6 mL) was heated at reflux for 1.5 h. After removal of the solvent, the residue was partitioned between EtOAc and water. To the aqueous layer was added 1 N HCl (3 mL). The resulting precipitate was collected and dried. Recrystallization from MeOH–$CHCl_3$ gave **33** (220 mg, 20%): mp 209–211 °C; ^{1}H-NMR (DMSO-d_6) δ 1.40 (t, 3 H, J = 7.2 Hz), 4.60 (q, 2 H, J = 7.2 Hz), 5.76 (s, 2 H), 7.15–7.29 (m, 3 H), 7.55 (d, 1 H, J = 7.6 Hz), 7.62–7.94 (m, 7 H). Anal. ($C_{27}H_{20}N_6O_4 \cdot 0.2H_2O$) C, H, N.

Methyl (*S*)-2-[[(11-Cyano-5-oxo-5H-dibenzo[*a*,*d*]cyclohepten-3-yl)methyl]amino]-3-methylbutyrate (34). To a solution of L-valine (830 mg, 7.08 mmol) in MeCN (10 mL) was added a solution of **10** (1.0 g, 2.44 mmol) in CH_2Cl_2 (10 mL) and DMAP (100 mg, 0.82 mmol). After being stirred at room temperature for 16 h under nitrogen, the mixture was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried and concentrated in vacuo. The residue was purified by chromatography on silica gel. Elution with CH_2Cl_2–MeCN (v/v, 50/1) afforded 580 mg (64%) of **34**: mp 54–57 °C (iPr_2O); ^{1}H-NMR ($CDCl_3$) δ 0.96 (d, 6 H, J = 6.8 Hz), 1.60 (brs, 1 H), 1.96 (sextet, 1 H, J = 6.8 Hz), 3.01 (d, 1 H, J = 6.0 Hz), 3.71 (d, 1 H, J = 14 Hz), 3.74 (s, 1 H), 4.01 (d, 1 H, J = 14 Hz), 7.56–7.84 (m, 5 H), 8.03 (d, 1 H, J = 8.2 Hz), 8.06–8.16 (m, 2 H). Anal. ($C_{23}H_{22}N_2O_3$) C, H, N.

Methyl (*S*)-2-[[(11-Cyano-5-oxo-5*H*-dibenzo[*a*,*d*]cyclohepten-3-yl)methyl]pentanoylamino]-3-methylbutyrate (35). To a solution of **34** (630 mg, 1.68 mmol) in pyridine (6 mL) was added dropwise valeryl chloride (0.4 mL, 3.36 mmol) with ice bath. After being stirred at room temperature for 1 h under nitrogen, the reaction mixture was poured into ice. The aqueous solution was extracted with EtOAc. The organic layer was washed with water and dried. The crude product was purified by column chromatography on silica gel with *n*-hexane–EtOAc (v/v, 2/1) to give 725 mg (94%) of **35** as oily product: ^{1}H-NMR (CD_3OD) δ 0.76–1.06 (m, 9 H), 1.14–1.48 (m, 2 H), 1.52–1.80 (m, 2 H), 2.00–2.72 (m, 3 H), 4.08–5.04 (m, 3 H), 7.50–7.80 (m, 5 H), 7.89 (dd, 1 H, J = 8.2, 2.0 Hz), 7.94–8.16 (m, 2 H).

Methyl (*S*)-3-Methyl-2-[[[5-oxo-11-(1*H*-tetrazol-5-yl)-5*H*-dibenzo[*a*,*d*]cyclohepten-3-yl]methyl]pentanoylamino]butyrate (36). The preparation of **36** was carried out according to the procedure described for **1** (42%): powder; ^{1}H-NMR ($CDCl_3$–CD_3OD) δ 0.77–1.00 (m, 9 H), 1.15–1.75 (m, 4 H), 2.10–2.80 (m, 3 H), 3.52 (s, 3 H), 4.10–5.00 (m, 3 H), 7.28 (s, 1 H), 7.36–7.46 (m, 1 H), 7.52–7.86 (m, 5 H), 7.88–7.98 (m, 1 H). Anal. ($C_{28}H_{31}N_5O_4 \cdot 1.4H_2O$) C, H, N.

(*S*)-3-Methyl-2-[[[5-oxo-11-(1*H*-tetrazol-5-yl)-5*H*-dibenzo[*a*,*d*]cyclohepten-3-yl]methyl]pentanoylamino]butyric Acid (37). A mixture of **36** (280 mg, 0.56 mmol), 1 N LiOH (1.7 mL), and MeOH (2 mL) was stirred at room temperature for 17 h. After removal of the solvent, the residue was partitioned between CH_2Cl_2–MeOH (v/v, 9/1) and 1 N HCl. The aqueous layer was extract with CH_2Cl_2. The combined organic layer was dried and concentrated in vacuo to afford **37** (143 mg, 53%): powder; ^{1}H-NMR ($CDCl_3$–CD_3OD) δ 0.76–1.04 (m, 9 H), 1.10–1.42 (m, 2 H), 1.50–1.80 (m, 2 H), 2.20–2.75 (m, 3 H), 4.00–5.05 (m, 3 H), 6.85–7.72 (m, 6 H), 7.78 (s, 1 H), 7.88 (d, 1 H, J = 6.8 Hz). Anal. ($C_{27}H_{29}N_5O_4 \cdot 0.6H_2O$) C, H, N.

7-(Aminomethyl)-5-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene-10-carbonitrile (38). A mixture of **10** (3.0 g, 7.32 mmol), NaN_3 (600 mg, 9.23 mmol), and HMPA (12 mL) was stirred at 50 °C for 1.5 h under nitrogen. The reaction mixture was poured into water and stirred vigorously for 5 min. The resulting precipitate was collected and washed with water. The crystals were dissolved in CH_2Cl_2, dried, and concentrated in vacuo. The residue was dissolved in EtOH (50 mL) and THF (10 mL) and treated with $SnCl_2 \cdot 2H_2O$ (2.42 g, 10.7 mmol) at 80 °C for 1 h. After being allowed to cool to room temperature, the mixture was poured into 2 N NaOH (40 mL) and extracted with EtOAc. The organic layer was extracted with 1 N HCl, and the acidic aqueous layer was alkalized with 2 N NaOH. The aqueous layer was extracted with CH_2Cl_2 and dried. Removal of the solvent afforded **38** (1.28 g, 67.2%), which was used for the next reaction without further purification: ^{1}H-NMR (CD_3OD) δ 4.00 (s, 2 H), 7.60–7.38 (m, 1 H), 7.54–7.82 (m, 4 H), 7.89 (s, 1 H), 8.00–8.15 (m, 3 H).

7-[[(5-Ethylpyrazolo[1,5-*a*]pyrimidin-7-yl)amino]methyl]-5-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene-10-carbonitrile (39). A mixture of **38** (1.50 g, 5.76 mmol), 5-ethyl-7-chloropyrazolo[1,5-*a*]pyrimidine (1.05 g, 5.78 mmol), DMAP (710 mg, 5.81 mmol), and DMF (50 mL) was stirred at 60 °C for 8 h under nitrogen. The reaction mixture was poured into 2 N NaOH and extracted with EtOAc. The organic layer was washed with water, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with CH_2Cl_2–MeCN (v/v, 5/1) to give 1.20 g (51%) of **39**: mp 232–233 °C (*n*-hexane–EtOAc); ^{1}H-NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7.6 Hz), 2.71 (q, 2 H, J = 7.6 Hz), 4.77 (d, 2 H, J = 5.8 Hz), 5.79 (s, 1 H), 6.30 (d, 1 H, J = 2.4 Hz), 6.78–6.90 (m, 1 H), 7.60–7.80 (m, 5 H), 7.98 (d, 1 H, J = 2.2 Hz), 8.05–8.18 (m, 3 H). Anal. ($C_{25}H_{19}N_5O \cdot 0.3H_2O$) C, H, N.

3-[[(5-Ethylpyrazolo[1,5-*a*]pyrimidin-7-yl)amino]methyl]-11-(1*H*-tetrazol-5-yl)dibenzo[*a*,*d*]cyclohepten-5-one (40). The preparation of **40** was carried out according to the procedure described for **1** (68.3%): powder; ^{1}H-NMR ($CDCl_3$–CD_3OD) δ 1.08 (t, 3 H, J = 7.6 Hz), 2.41 (q, 2 H, J = 7.6 Hz), 4.55 (s, 2 H), 5.88 (s, 1 H), 6.24 (d, 1 H, J = 2.4 Hz), 6.71 (d, 1 H, J = 8.2 Hz), 6.98 (dd, 1 H, J = 8.2, 2.0 Hz), 7.58–7.75 (m, 4 H), 7.93 (d, 1 H, J = 2.4 Hz), 7.99 (d, 1 H, J = 7.0 Hz), 8.32 (d, 1 H, J = 2.0 Hz). Anal. ($C_{25}H_{20}N_8O \cdot H_2O \cdot 0.2EtOAc$) C, H, N.

3-[(5,7-Dimethyl-2-ethylimidazo[4,5-*b*]pyridin-3-yl)methyl]-11-(1*H*-tetrazol-5-yl)dibenzo[*a*,*d*]cyclohepten-5-one (41). The preparation of **41** was carried out according to the procedure described for **1**: mp 272–274 °C dec (MeOH); ^{1}H-NMR ($CDCl_3$–CD_3OD) δ 1.32 (t, 3 H, J = 7.6 Hz), 2.59 (s, 3 H), 2.64 (s, 3 H), 2.82 (q, 2 H, J = 7.6 Hz), 5.59 (s, 2 H), 6.97 (s, 1 H), 7.20–7.30 (m, 2 H), 7.60–7.75 (m, 3 H), 7.81 (d, 1 H, J = 0.8 Hz), 7.87 (s, 1 H), 7.96 (d, 1 H, J = 7.0 Hz). Anal. ($C_{27}H_{23}N_7O$) C, H, N.

3-[(2-Cyclopropyl-5,7-dimethylimidazo[4,5-*b*]pyridin-3-yl)methyl]-11-(1*H*-tetrazol-5-yl)dibenzo[*a*,*d*]cyclohepten-5-one (42). The preparation of **42** was carried out according to the procedure described for **1**: mp 261–264 °C dec (MeOH); ^{1}H-NMR ($CDCl_3$–CD_3OD) δ 1.00–1.20 (m, 4 H), 1.80–1.92 (m, 1 H), 2.56 (s, 3 H), 2.59 (s, 3 H), 5.70 (s, 2 H), 6.93 (s, 1 H), 7.28–7.31 (m, 2 H), 7.60–7.70 (m, 3 H), 7.85–7.90 (m, 2 H), 7.96 (d, 1 H, J = 7.0 Hz). Anal. ($C_{28}H_{23}N_7O \cdot 0.3H_2O$) C, H, N.

2-Butyl-5-chloro-3-[[5-oxo-11-(1*H*-tetrazol-5-yl)-5*H*-dibenzo[*a*,*d*]cyclohepten-3-yl]methyl]-3*H*-imidazole-4-carbaldehyde (43). The preparation of **43** was carried out

according to the procedure described for **1**: powder; ^{1}H-NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 7.2 Hz), 1.25–1.45 (m, 2 H), 1.55–1.75 (m, 2 H), 2.64 (t, 2 H, J = 7.6 Hz), 5.60 (s, 2 H), 7.14 (dd, 1 H, J = 7.8, 1.2 Hz), 7.37 (d, 1 H, J = 8.2 Hz), 7.48–7.68 (m, 3 H), 7.93 (d, 1 H, J = 7.8 Hz), 9.68 (s, 1 H). Anal. ($C_{25}H_{21}N_6O_2Cl\cdot1.3H_2O$) C, H, N, Cl.

2-Butyl-5-chloro-3-[[5-oxo-11-(1*H*-tetrazol-5-yl)-5*H*-dibenzo[*a*,*d*]cyclohepten-3-yl]methyl]-3*H*-imidazole-4-carboxylic Acid (44). The preparation of **44** was carried out according to the procedure described for **28**: mp 137–140 °C (Et_2O); ^{1}H-NMR ($CDCl_3$–CD_3OD) δ 0.84 (t, 3 H, J = 7.4 Hz), 1.20–1.40 (m, 2 H), 1.55–1.75 (m, 2 H), 2.63 (t, 2 H, J = 7.6 Hz), 5.62 (s, 2 H), 7.12 (dd, 1 H, J = 8.2, 1.8 Hz), 7.28 (d, 1 H, J = 8.2 Hz), 7.55–7.69 (m, 4 H), 7.89 (s, 1 H), 7.96 (d, 1 H, J = 7.0 Hz). Anal. ($C_{25}H_{21}N_6O_3Cl\cdot0.4H_2O\cdot0.5Et_2O$) C, H, N, Cl.

2-Ethoxy-3-[[11-(1*H*-tetrazol-5-yl)dibenzo[*b*,*f*]oxepin-3-yl]methyl]-3*H*-benzimidazole-4-carboxylic Acid (45). The preparation of **45** was carried out according to the procedure described for **33**: mp 185–187 °C; ^{1}H-NMR (DMSO-d_6) δ 1.39 (t, 3 H, J = 7.0 Hz), 4.60 (q, 2 H, J = 7.0 Hz), 5.66 (s, 2 H), 6.82 (dd, 1 H, J = 8.0, 1.8 Hz), 7.10 (d, 1 H, J = 1.8 Hz), 7.19 (t, 2 H, J = 7.8 Hz), 7.22 (d, 2 H, J = 8.2 Hz), 7.25–7.35 (m, 2 H), 7.40–7.60 (m, 3 H). Anal. ($C_{26}H_{20}N_6O_4\cdot0.1H_2O$) C, H, N.

(*S*)-3-Methyl-2-[pentanoyl[[11-(1*H*-tetrazol-5-yl)dibenzo[*b*,*f*]oxepin-3-yl]methyl]amino]butyric Acid (46). The preparation of **46** was carried out according to the procedure described for **37**: powder; ^{1}H-NMR ($CDCl_3$) δ 0.75–1.10 (m, 9 H), 1.10–1.80 (m, 4 H), 2.36 (t, 2 H, J = 7.6 Hz), 2.55 (m, 1 H), 4.00–5.00 (m, 2 H), 6.70–7.50 (m, 7 H), 7.72 (s, 1 H). Anal. ($C_{26}H_{29}N_5O_4\cdot0.5H_2O$) C, H, N.

3-[[(2-Methyl-5,6,7,8-tetrahydroquinolin-4-yl)oxy]methyl]-11-(1*H*-tetrazol-5-yl)dibenzo[*a*,*d*]cyclohepten-5-one (47). The preparation of **47** was carried out according to the procedure described for **27**: mp 205–207 °C dec (MeOH). ^{1}H-NMR ($CDCl_3$–CD_3OD) δ 1.80–1.95 (m, 4 H), 2.55 (s, 3 H), 2.65–2.78 (m, 2 H), 2.80–2.90 (m, 2 H), 5.38 (s, 2 H), 6.97 (s, 1 H), 7.50–7.76 (m, 5 H), 7.85 (s, 1 H), 7.95–8.00 (m, 2 H). Anal. ($C_{27}H_{23}N_5O_2\cdot H_2O$) C, H, N.

3-[[(2-Ethyl-5,6,7,8-tetrahydroquinolin-4-yl)oxy]methyl]-11-(1*H*-tetrazol-5-yl)dibenzo[*a*,*d*]cyclohepten-5-one (48). The preparation of **48** was carried out according to the procedure described for **27**: mp 189–192 °C dec (MeOH); ^{1}H-NMR ($CDCl_3$–CD_3OD) δ 1.31 (t, 3 H, J = 7.6 Hz), 1.80–1.95 (m, 4 H), 2.68–2.95 (m, 6 H), 5.42 (s, 2 H), 7.00 (s, 1 H), 7.50–7.76 (m, 3 H), 7.65–7.78 (m, 2 H), 7.85 (s, 1 H), 7.90–8.05 (m, 2 H). Anal. ($C_{28}H_{25}N_5O_2\cdot1.6H_2O$) C, H, N.

3-[[(2-Ethylquinolin-4-yl)oxy]methyl]-11-(1*H*-tetrazol-5-yl)dibenzo[*a*,*d*]cyclohepten-5-one Hydrochloride (49). The preparation of **49** was carried out according to the procedure described for **27**: mp 210–212 °C (MeOH); ^{1}H-NMR ($CDCl_3$–CD_3OD) δ 1.54 (t, 3 H, J = 7.6 Hz), 3.26 (q, 2 H, J = 7.6 Hz), 5.72 (s, 2 H), 7.37 (s, 1 H), 7.46 (s, 1 H), 7.57 (d, 1 H, J = 8.2 Hz), 7.60–7.82 (m, 4 H), 7.91 (s, 1 H), 8.00–8.08 (m, 2 H), 8.18–8.28 (m, 2 H), 8.37–8.42 (m, 1 H). Anal. ($C_{28}H_{21}N_5O_2\cdot HCl\cdot0.75H_2O$) C, H, N, Cl.

3-[[(2-Ethyl-6-methoxy[1,5]naphthyridin-4-yl)oxy]methyl]-11-(1*H*-tetrazol-5-yl)dibenzo[*a*,*d*]cyclohepten-5-one (50). The preparation of **50** was carried out according to the procedure described for **27**: mp 119–121 °C (MeOH); ^{1}H-NMR (DMSO-d_6) δ 1.40 (t, 3 H, J = 7.6 Hz), 3.08 (q, 2 H, J = 7.6 Hz), 4.11 (s, 3 H), 5.79 (s, 2 H), 7.49 (d, 1 H, J = 2.4 Hz), 7.53 (d, 1 H, J = 3.2 Hz), 7.65–7.96 (m, 7 H), 8.29 (d, 1 H, J = 1.6 Hz), 8.36 (d, 1 H, J = 9.0 Hz). Anal. ($C_{28}H_{22}N_6O_3\cdot0.4H_2O$) C, H, N.

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