Benzofused Tricycles Based on 2-Quinoxalinol

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Received March 24, 2006

This paper describes our recent efforts to synthesize novel compound scaffolds integrating 2-quinoxalinol with privileged structures of 1,3-dihydro-benzoimidazol-2-one, 1,3-dihydro-benzoimidazole-2-thione, 3-hydroxy-1*H*-quinoxalin-2-one, 2*H*-benzo[1,4]oxazin-3-ol, 2*H*-benzo[1,4]thiazin-3-ol, and 1,3,4,5-tetrahydro-benzo[1,4]diazepin-2-one, respectively. Eight novel benzofused tricycles and their substituent diversity points were developed. These include pyrazino[2,3-*g*]quinoxaline-2,8-diol (**I**), 3-hydroxy-6,8,9,10-tetrahydro-1,4,6,-10-tetraaza-cyclohepta[*b*]naphthalen-7-one (**II**), 6-hydroxy-4*H*-1-oxa-4,5,8-triaza-anthracen-3-one (**III**), 6-hydroxy-4*H*-1-thia-4,5,8-triaza-anthracen-3-one (**IV**), 6-hydroxy-1,1-dioxo-1,4-dihydro-2*H*-1λ^6-thia-4,5,8-triaza-anthracen-3-one (**V**), 6-hydroxy-1,3-dihydro-imidazo[4,5-*g*]quinoxalin-2-one (**VI**), 6-hydroxy-1,3-dihydro-imidazo[4,5-*g*]quinoxaline-2-thione (**VII**), and 7-hydroxy-1,4-dihydro-pyrazino[2,3-*g*]quinoxaline-2,3-dione (**VIII**). This strategy of integrating two benzofused privileged structures into one molecule may provide a greater chance for the discovery of novel lead compounds.

Introduction

Heterocyclic compounds offer a high degree of structural diversity and opportunities for the discovery of new drug candidates because of their ability to bind to multiple receptors with high affinity and favorable pharmacokinetic properties. Privileged structures are those scaffolds or fragments that appeared frequently in drugs and biologically active compounds,[1] and they have been extensively investigated in both academic and industrial institutions. The development of efficient synthetic methods for the synthesis of such compounds is of great interest to organic synthesis in general and medicinal chemistry in particular. The insertion of privileged substructures into one heterocyclic molecule may provide a greater chance for the discovery of novel lead compounds using one chemical transformation. Therefore, a facile synthesis leading to interesting benzofused privileged heterocycles is highly attractive. We have successfully developed "scaffold-directed" methods in a parallel solution-phase manner to efficiently generate 2-quinoxalinol analogs,[2,3] 5-aminobenzimidazoles,[4] and novel 1,2,7-trialkyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol scaffolds[5] using 1,5-difluoro-2,4-dinitrobenzene (DFDNB). This paper describes the synthesis of eight novel benzofused tricyclic compound scaffolds based on 2-quinoxalinol.

Results and Discussions

Our previous studies[2−5] demonstrated that ordinal replacement of two fluorine groups of DFDNB can be achieved. Particularly, when a α-amino acid methyl or ethyl ester is used to nucleophilically substitute one fluorine group, it can offer 2-quinoxalinol scaffold compounds. Then the other fluorine group can be quantitatively replaced by various nucleophilic reagents, which lead us to develop many benzofused heterocycles using DFDNB. We are herein interested in developing benzofused tricycles of privileged structures based on 2-quinoxalinol.

Table 1 lists several druggable benzofused scaffold compounds including 1,3-dihydro-benzoimidazol-2-one, 1,3-dihydro-benzoimidazole-2-thione, 3-hydroxy-1*H*-quinoxalin-2-one, 2*H*-benzo[1,4]oxazin-3-ol, 2*H*-benzo[1,4]thiazin-3-ol, and 1,3,4,5-tetrahydro-benzo[1,4]diazepin-2-one. All these scaffolds display multiple biological activities. On the basis of our "scaffold-directed" method, they can be integrated with 2-quinoxalinol using the starting material of DFDNB when a proper chemistry is selected. Thus, eight novel compound scaffolds were developed in this paper including pyrazino[2,3-*g*]quinoxaline-2,8-diol (**I**), 3-hydroxy-6,8,9,10-tetrahydro-1,4,6,10-tetraaza-cyclohepta[*b*]naphthalene-7-one (**II**), 6-hydroxy-4*H*-1-oxa-4,5,8-triaza-anthracen-3-one (**III**), 6-hydroxy-4*H*-1-thia-4,5,8-triaza-anthracen-3-one (**IV**), 6-hydroxy-1,1-dioxo-1,4-dihydro-2*H*-1λ^6-thia-4,5,8-triaza-anthracen-3-one (**V**), 6-hydroxy-1,3-dihydro-imidazo[4,5-*g*]-quinoxalin-2-one (**VI**), 6-hydroxy-1,3-dihydro-imidazo[4,5-*g*]quinoxaline-2-thione (**VII**), and 7-hydroxy-1,4-dihydro-pyrazino[2,3-*g*]quinoxaline-2,3-dione (**VIII**).

As illustrated in Scheme 1, compound **2** can be quantitatively obtained by the reaction of α-amino acid methyl or ethyl ester with DFDNB.[2] Further, the remaining fluorine group was replaced by $NH_2CH(R_2)COOCH_3$ or $NH_2CH(R_2)$-$CH(R_3)COOCH_3$ in the presence of DIPEA to offer intermediates **3** and **6**. The reduction of *m*-dinitrobenzene was completed with treatment of Pd−C and $HCOONH_4$ in appropriate solvents. Intermediates **4** and **5** from **3** were initially anticipated; however, they are generally unstable.

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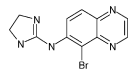
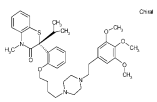
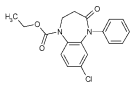
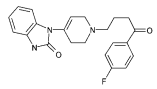
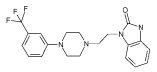
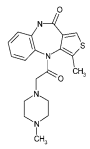
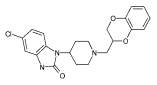
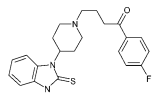
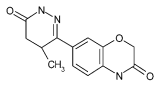
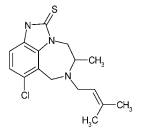
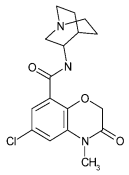
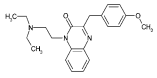
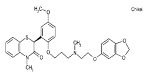
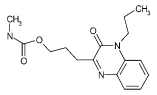
10.1021/cc060034o CCC: $37.00
Published on Web 12/16/2006

Table 1. Drugs with Related Privileged Structures in This Paper[a]

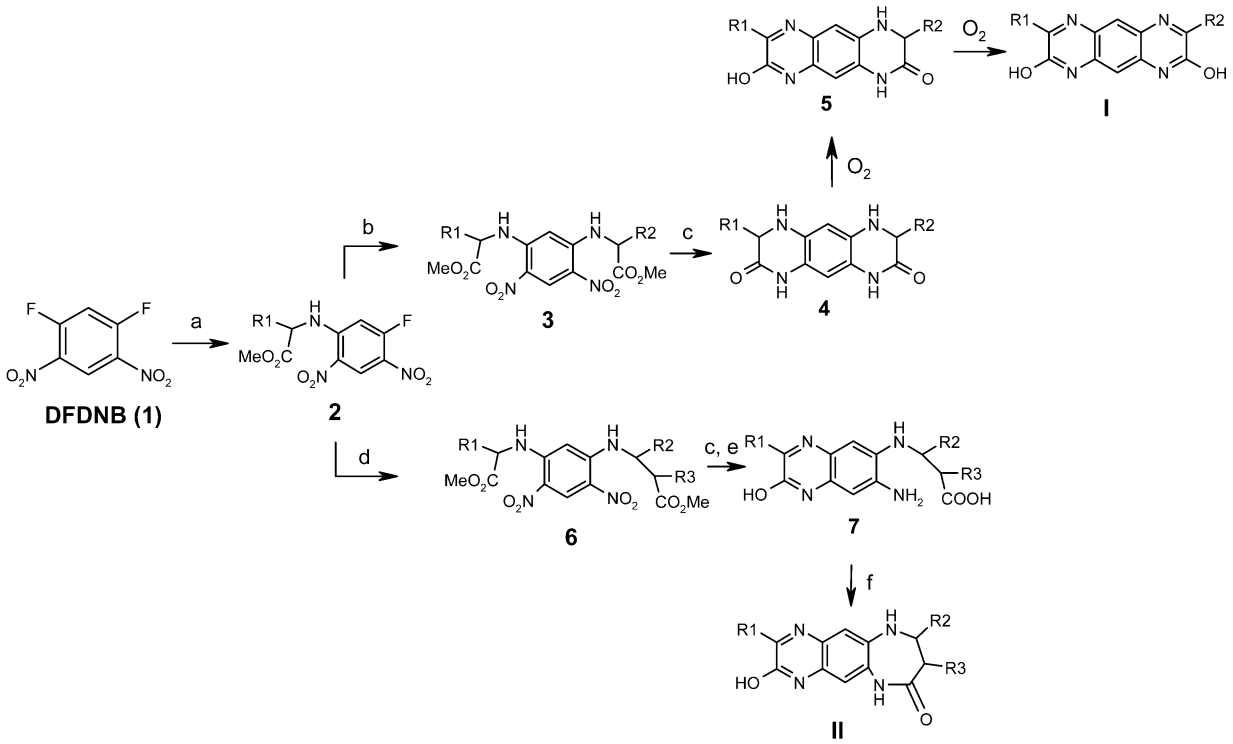
structure	INN name[#]	activity	structure	INN name	activity
	Brimonidine	Adrenergic		Iprotiazem	Vasodilator (coronary)
	Arfendazam	Anxiolytic		Droperidol	Antipsychotic
	Lofendazam	Anxiolytic		Flibanserin	Antidepressant
	Telezepine	Antisecretory (gastric acid)		Axamozide	Neuroleptic
	Paraxazone	Antidepressant		Tolopelon	Anxiolytic
	Bemoradan	Cardiotonic		Tivarapine	Antiviral
	Azasetron	5-HT receptor antagonist		Caroverine	Antispasmodic
	Levosemotiadil	Antiarrhythmic		Bamaquimast	Antiasthmatic

[a] The data is from MDL Comprehensive Medicinal Chemistry 3D, version 2002.2, MDL Information Systems Inc., San Leandro, CA, 2002. [b] International Nonproprietary Names (INN).

Only three compounds (**4b**, **5a**, and **5b**) were isolated as solid products in our studies (Table 2). It was found that **4a** changed into **5a** very quickly and subsequently transformed into the final product **Ia** slowly. These changes were monitored by HPLC-MS as an example in Scheme 2. After **3a** was reduced by Pd−C/$HCOONH_4$ in DMF/water (4/1, v/v) at 50 °C for 4 h, the reaction solution was immediately detected by LC-MS. The purity of **4a** was more than 95% at this time. However, **4a** was very susceptible to dehydrogenation during the process and could not be obtained through silica chromatography preparation. After an additional 3 h at room temperature, 30% of **4a** changed into **5a**, and no more **4a** was detectable by LC-MS after 72 h. At this stage, LC-MS detection indicated that the purity of **5a** was approximately 80% by monitoring at 397 $[M + H]^+$, and it could be obtained by column chromatography. Then, intermediate **5a** slowly and continuously transformed into **Ia** at room temperature when exposed to the air. HPLC analysis showed that **5a** and **Ia** staged only at 42 and 24% after 3 months. To confirm this transformation, IR data of more stable intermediates **4b** and **5b** and the relative final product **Ib** were listed in the Experimental Section. Our results indicated that air bubbling and heat could promote this transformation. However, this phenomenon makes it difficult for the parallel synthesis of the scaffold **I** library in the solution phase.

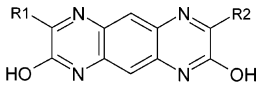
1,5-Benzodiazepin-2-one provided diverse biological activities. Typically, it represents the drugs as anxiolytic and antisecretory of gastric acid (Table 1). After intermediate **6** was reduced by Pd−C/$HCOONH_4$ (Scheme 1), the formation of 1,5-benzodiazepin-2-one was not achieved using various literature methods such as (1) reflux in xylene,[6] (2) reflux in dichloromethane with trifluoroacetic acid,[7] and (3) reflux in acetonitrile with the trace concentrate H_2SO_4.[8] Even with

Scheme 1. Synthetic Route for Scaffolds Pyrazino[2,3-*g*]quinoxaline-2,8-diol (**I**) and 3-Hydroxy-6,8,9,10-tetrahydro-1,4,6,10-tetraaza-cyclohepta[*b*]naphthalen-7-one (**II**)[a]



[a] (a) $NH_2CH(R_1)COOCH_3$, DIPEA, THF/EtOH, room temp, 24 h; (b) $NH_2CH(R_2)COOCH_3$, DIPEA, THF/EtOH, room temp, 120 h; (c) Pd−C, $HCOONH_4$, EtOH, room temp, 3 h; (d) $NH_2CH(R_2)CH(R_3)COOCH_3$, DIPEA, THF, room temp, 24 h; (e) 1.0 N LiOH, THF + H_2O, room temp, 1 h; (f) PS-EDC, THF, room temp, 6 h.

Table 2. Scaffold **I** Compounds and Their Intermediates



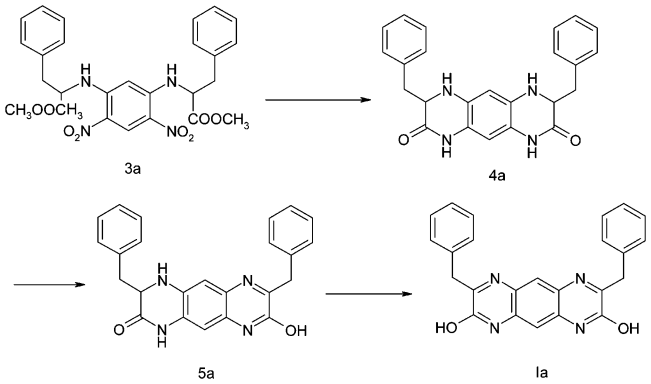
I

	R_1	R_2	yield[a] (%)
4b	(4-$(CH_3)_3CO$)$PhCH_2$−	(4-$(CH_3)_3CO$)$PhCH_2$−	62
5a	$PhCH_2$−	$PhCH_2$−	40
5b	(4-$(CH_3)_3CO$)$PhCH_2$−	(4-$(CH_3)_3CO$)$PhCH_2$−	42
Ia	$PhCH_2$−	$PhCH_2$−	59
Ib	(4-$(CH_3)_3CO$)$PhCH_2$−	(4-$(CH_3)_3CO$)$PhCH_2$−	41
Ic	Ph−	Ph−	53
Id	$PhCH_2$−	CH_3−	21
Ie	(4-$(CH_3)_3CO$)$PhCH_2$−	$PhCH_2$−	44
If	$(CH_2)_5CHCH_2$−	$(CH_2)_5CHCH_2$−	26

[a] Overall yield from DFDNB after purification.

the strong base sodium hydride and microwave assistance, the cyclization to form 1,5-benzodiazepin-2-one failed. An alternative approach was then investigated. The reduction product **7** was hydrolyzed in the presence of 1.0 N LiOH in a solution of 50% THF/H_2O. After neutralization with 1.0 N HCl and removal of solvent in vacuum, the crude **7** was desalted efficiently using a phase separator through extraction by a solution of 75% DCM/THF against water. Subsequently, cyclization was achieved by using DIC as an intramolecular amide bond formation reagent[9] in high yield of scaffold **II**. To avoid the separation of the side product DIU from DIC, we finally employed polymer-supported reagent PS-EDC.[10] This route gave scaffold **II** compounds in good purity without any chromatography purification,

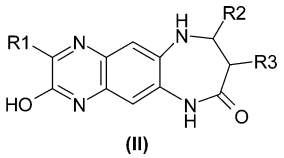
Scheme 2. Pathway to Make Compound **Ia**



which is adaptable to building the corresponding chemical library. After validation of this route, eleven compounds were prepared (Table 3, **IIa**−**IIk**). Three diversity points were introduced into this new type of scaffold compound.

Benzoxazine and benzothiazine both frequently appear as substructures in drugs such as antidepressants, cardiotonics, and vasodilators (Table 1). They can also be introduced to form novel scaffolds **III** and **IV** (Table 4) from DFDNB when the second fluorine atom is replaced by methyl or ethyl α-hydroxyl acetate in the presence of K_2CO_3/acetone or ethyl α-mercaptoacetate in DIPEA/THF to generate intermediates **8**, **9**, and **10** (Schemes 3 and 4). A full-length description regarding the synthesis of benzoxazine and benzothiazine using DFDNB has been reported in other papers.[11,12] General reduction of *m*-dinitro groups was also carried out using Pd−C/$HCOONH_4$ to obtain **III** from **8** (Scheme 3). However, to avoid catalyst poisoning by the sulfur moiety, intermediate **9** was alternatively treated with $SnCl_2 \cdot 2H_2O$ to produce

Table 3. Scaffold **II** Compounds Synthesized Through a Parallel Solution-phase Method

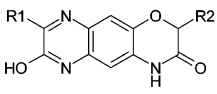


(II)

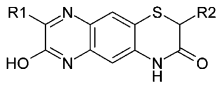
	R_1	R_2	R_3	yield[a] (%)
IIa	CH_3−	CH_3−	H−	49
IIb	CH_3−	Ph−	H−	40
IIc	CH_3−	(4′-F)Ph−	H−	44
IId	CH_3−	Naph−	H−	47
IIe	CH_3−	H−	H−	53
IIf	CH_3−	H−	CH_3−	48
IIg	$(CH_3)_2CH$−	(4′-F)Ph−	H−	65
IIh	$(CH_3)_2CH$−	H−	CH_3−	63
IIi	$PhCH_2$−	Ph−	H−	70
IIj	$PhCH_2$−	Naph−	H−	63
IIk	$PhCH_2$−	CH_3−	H−	64

[a] Overall yield from DFDNB after purification.

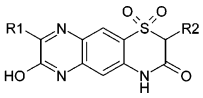
Table 4. Scaffolds **III**, **IV**, and **V** Compounds Synthesized from DFDNB



(III)



(IV)



(V)

	R_1	R_2	yield[a] (%)
IIIa	$(CH_3)_2CH$−	Ph−	55
IIIb	$(CH_3)_2CH$−	CH_3−	47
IVa	CH_3−	H−	59
IVb	CH_3−	CH_3−	65
IVc	$PhCH_2$−	H−	53
IVd	$PhCH_2$−	CH_3−	64
Va	$PhCH_2$−	CH_3−	44
Vb	CH_3−	CH_3−	39

[a] Overall yield from DFDNB after purification.

scaffold **IV** in this paper (Scheme 4). Unfortunately, the posttreatment of stannous chloride reduction is very laborious. When we sought the optimal preparative conditions of scaffold **V** from **10**, we decided to oxidize the sulfur atom of **9** before the reduction step to use the convenient method of Pd−C/$HCOONH_4$. UHP (urea hydroperoxide) in the presence of $(CF_3CO_2)O$[13] has been found to be an inexpensive and effective oxidant to yield intermediate **10**. Because of the weak nucleophilicity of the free aromatic amino group and the steric hindrance problems, the reduced product of **10** was not cyclized to form scaffold **V**. Thus, a microwave-assisted environment or a strong inorganic base such as sodium hydride (NaH) was optimized to facilitate the cyclization as previously reported.[11]

Scaffolds **VI** and **VII** are regarded as the integration of 2-quinoxalinol and benzimidazole substructures. 2-Quinoxalinol could represent quinoxaline's properties as an adrenergic drug (Table 1). It also represents a glutamate blocker,[14] a treatment for sensorineural smell disorders,[15] a DNA topoisomerase (Topo) II β inhibitor,[16] an antimycobacterial compound,[17] and a selective inhibitor of I κ B kinase.[18] Benzimidazalone is a very important moiety incorporated into many drugs including antipsychotic, antidepressant, neuroleptic, anxiolytic, and antiviral activity (Table 1). Quinoxalin-2-one is an interesting structure because it represents antispasmodic and antiasthmatic drugs (Table 1). Therefore, integration of 2-quinoxalinol with benzimidazalone or quinoxalin-2-one into one molecule will ideally extend the scaffold diversity for medicinal chemists. To obtain scaffold **VI**, **VII**, and **VIII** compounds, intermediates **12** were prepared from **11** as previously described[2,3] (Scheme 5). The common methods[19−22] of constructing benzimidazalone and thiobenzimidazalone on the solid phase include the use of carbondiimidazole and thiocarbondiimidazole. However, these methods produce imidazole as a byproduct in the solution phase. A cheap and low toxic reagent triphosgene was then selected to replace carbondiimidazole in the presence of Et_3N to give **VI**. This offered the advantage of removing the need for the separation of the solid byproduct. Carbon disulfide was used when making scaffold **VII**. Although we tried the literature method[23] using diethyl oxalate to form **VIII**, it failed even at high temperature. The more active oxalic chloride was finally selected, and it gave a very good yield at room temperature in the presence of Et_3N (Table 5). Thus, treatment of **12** with triphosgene, carbon disulfide, and oxalic chloride in the presence of Et_3N successfully synthesized **VI**, **VII**, and **VIII**, respectively.

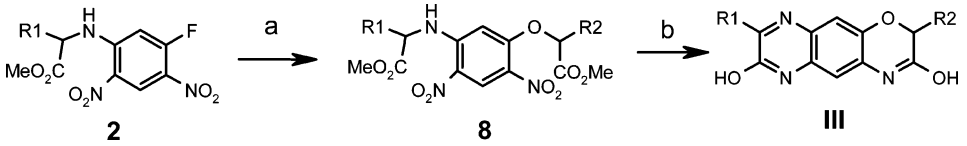
Conclusion

Scaffold-directed small molecular heterocycles synthesis was established using 1,5-difuloro-2,4-dinitrobenzene as the starting material. In this paper, eight novel benzofused tricycles have been developed that integrate the privileged structures of 2-quinoxalinol with 1,3-dihydro-benzoimidazol-2-one, 1,3-dihydro-benzoimidazole-2-thione, 3-hydroxy-1H-quinoxalin-2-one, 2H-benzo[1,4]oxazin-3-ol, 2H-benzo[1,4]-thiazin-3-ol, and 1,3,4,5-tetrahydro-benzo[1,4]diazepin-2-one, respectively, and thus gave eight novel compound scaffolds including pyrazino[2,3-*g*]quinoxaline-2,8-diol (**I**), 3-hydroxy-6,8,9,10-tetrahydro-1,4,6,10-tetraaza-cyclohepta[*b*]naphthalen-7-one (**II**), 6-hydroxy-4*H*-1-oxa-4,5,8-triaza-anthracen-3-one (**III**), 6-hydroxy-4H-1-thia-4,5,8-triaza-anthracen-3-one (**IV**), 6-hydroxy-1,1-dioxo-1,4-dihydro-2*H*-1λ^6-thia-4,5,8-triaza-anthracen-3-one (**V**), 6-hydroxy-1,3-dihydro-imidazo[4,5-*g*]quinoxalin-2-one (**VI**), 6-hydroxy-1,3-dihydro-imidazo[4,5-*g*]quinoxaline-2-thione (**VII**), and 7-hydroxy-1,4-dihydro-pyrazino[2,3-*g*]quinoxaline-2,3-dione (**VIII**). This may provide us with a greater chance to identify new drug lead compounds. As presented at the 2005 Diversity-Oriented Synthesis Conference in Boston on September 22−23, we have successfully developed over 30 privileged and benzo-fused privileged structures with more diversity points. Details for all of them will be published soon as full-length papers.

Experimental Section

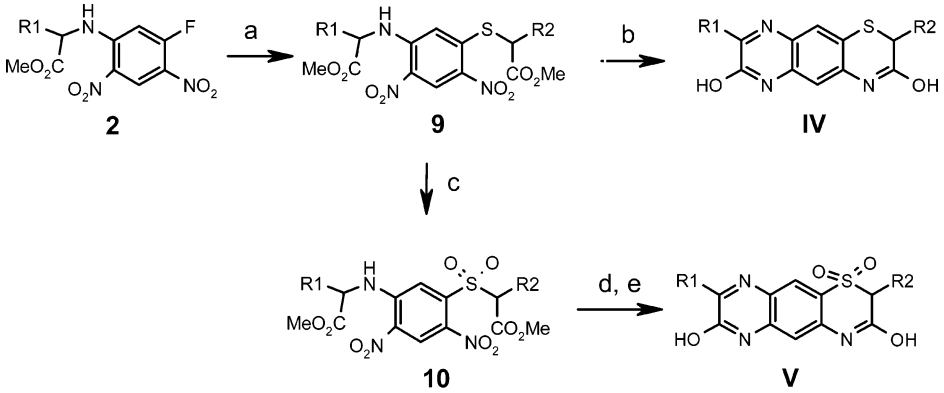
General Remarks. Methyl β-amino acetate ester hydrochloride derivatives were prepared from β-amino acid (20 mmol) in a saturated HCl/MeOH solution (30 mL) at room temperature for 3 days. The products were recrystallized from Et_2O/MeOH (6:1) in about an 85% yield. PS-EDC was prepared from Merrifield resin (5 mmol, loading

Scheme 3. Synthesis of Scaffold 6-Hydroxy-4*H*-1-oxa-4,5,8-triaza-anthracen-3-one (**III**)[a]



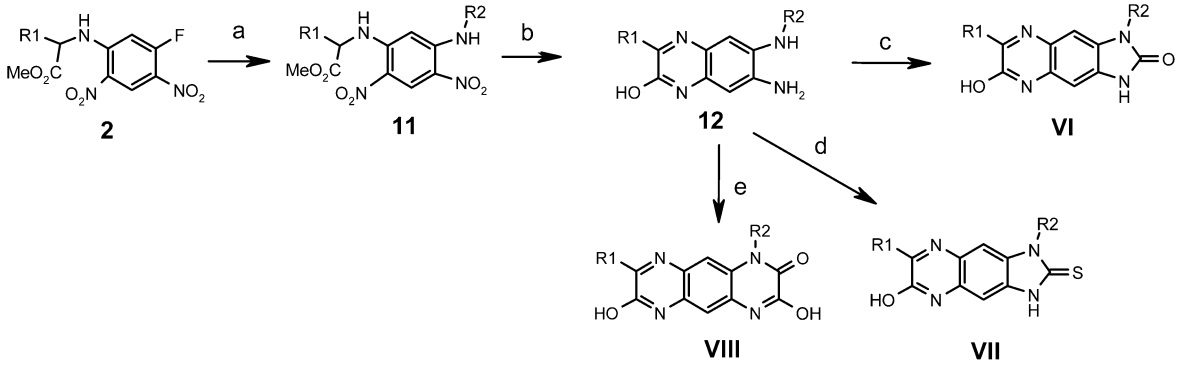
[a] (a) $HOCH(R_2)COOCH_3$, K_2CO_3, acetone; (b) Pd−C, $HCOONH_4$, EtOH, room temp, 3 h.

Scheme 4. Synthesis of Scaffolds 6-Hydroxy-4*H*-1-thia-4,5,8-triaza-anthracen-3-one (**IV**) and 6-Hydroxy-1,1-dioxo-1,4-dihydro-2*H*-1λ^6-thia-4,5,8-triaza-anthracen-3-one (**V**)[a]



[a] (a) $HSCH(R_2)COOCH_3$, DIPEA, THF, room temp, 24 h; (b) $SnCl_2 \cdot 2H_2O$, concentrated HCl, EtOH/THF, reflux, 3 h; (c) urea hydroperoxide (UHP), CH_3CN, $(CF_3CO)_2O$, 0 °C; (d) Pd−C, $HCOONH_4$, EtOH, room temp, 3 h; (e) microwave condition (100 W, 100 PSI, 140 °C, 60 min) or NaH, THF.

Scheme 5. Synthesis of Scaffolds 6-Hydroxy-1,3-dihydro-imidazo[4,5-*g*]quinoxalin-2-one (**VI**), 6-Hydroxy-1,3-dihydro-imidazo[4,5-*g*]quinoxaline-2-thione (**VII**), and 7-Hydroxy-1,4-dihydro-pyrazino[2,3-*g*]quinoxaline-2,3-dione (**VIII**)[a]

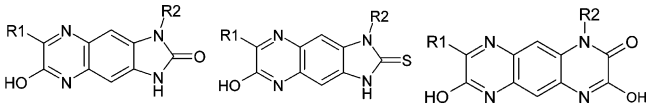


[a] (a) R_2NH_2, DIPEA, THF/EtOH, room temp, 24 h; (b) Pd−C, $HCOONH_4$, EtOH, room temp, 3 h; (c) triphosgene, Et_3N, THF, 30 min; (d) CS_2, Et_3N, DMF/EtOH, reflux, 6 h; (e) ClCOCOCl, Et_3N, THF, 30 min.

of 1.0 mmol/g), which was reacted with EDC (10 mmol) in DMF (30 mL) at 100 °C for 14 h; then the resin was washed with DMF (×3), MeOH (×3), and DCM (×3) and dried under a stream of N_2 gas.

All other chemicals were of reagent grade and were used as purchased. ^1H and ^{13}C NMR spectra were recorded on Varian Unity 300 or 400 MHz NMR spectrometers at ambient temperature using deuterated DMSO as the solvent. Infrared spectra were recorded using KBr pellets on a Nicolet impact 400 spectrometer. Reactions were monitored by HPLC and HPLC-MS analysis. Auto HPLC-MS analysis was performed on a Thermo Finnigan, LCQ-Advantage mass spectrometer equipped with Agilent 1100 HPLC system and a fluent splitter. The column employed was a Kromasil C18 column (4.6 μm, 4.6 × 50 mm) from DIKMA. The eluent was a mixture of acetonitrile and water containing 0.05% HCOOH, with a linear gradient from 5/95 v/v acetonitrile/H_2O to 95/5 v/v acetonitrile/water over 5 min at a 1 mL/

Table 5. Scaffolds **VI**, **VII**, and **VIII** Compounds Synthesized from DFDNB



	R_1	R_2	yield[a] (%)
VIa	CH_3-	$(3,4\text{-}(CH_3O)_2)PhCH_2CH_2-$	69
VIb	CH_3-	$PhCH_2CH_2-$	60
VIc	CH_3-	$CH_3O(CH_2)_3-$	58
VId	$(CH_3)_2CHCH_2-$	$PhCH_2CH_2-$	63
VIIa	$PhCH_2-$	$PhCH_2CH_2-$	59
VIIIa	CH_3-	$(3,4\text{-}(CH_3O)_2)PhCH_2CH_2-$	61
VIIIb	$(CH_3)_2CHCH_2-$	$PhCH_2CH_2-$	55
VIIIc	$(CH_3)_2CHCH_2-$	$(3,4\text{-}(CH_3O)_2)PhCH_2CH_2-$	59
VIIId	CH_3-	$CH_3O(CH_2)_3-$	72

[a] Overall yield from DFDNB after purification.

min flow rate. The UV detection was done at 254 nm. Five percent of the eluent was split into MS system. Mass spectra were recorded in either positive- or negative-ion mode using electrospray ionization. Flash column chromatography was carried out on silica gel (200−300 mesh).

General Procedure for the Synthesis of Scaffold I Compounds. (1) General Procedure for the Synthesis of Intermediates 4. 1,5-Difluoro-2,4-dinitrobenzene (1 mmol) was added to a flask which contained 10 mL of DMF and 1 mmol of methyl α-amino acetate hydrochloride; 2.2 mmol of DIPEA was added under stirring. After the mixture was stirred at 25 °C for 24 h, another 1 mmol of methyl α-amino acetate hydrochloride and 2 mmol of DIPEA were added, and the mixture was stirred at 25 °C for 120 h. The solution was mixed with a solution of 20 mmol of $HCOONH_4$ in 2.5 mL of H_2O and treated with 30 mg of 10% Pd−C at 50 °C for 4 h. Filtration of the resulting mixture and evaporation of the volatile afforded crude **4**, and recrystalization from ethyl acetate and hexane may give pure products.

(a) 3,7-Bis-(4-tert-butoxy-benzyl)-4,6,7,9-tetrahydro-1H,3H-pyrazino[2,3-g]quinoxaline-2,8-dione (4b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.23 (s, 18H), 2.76−2.82 (m, 4H), 3.79 (m, 2H), 6.08 (s, 1H), 6.19 (s, 1H), 6.81 (d, J = 8 Hz, 4H), 7.07 (d, J = 8 Hz, 4H), 9.86 (s, 2H). MS (*m/z*): 543.2 $[M + H]^+$. IR (KBr, cm^{-1}): 3205, 2976, 2931, 1666, 1608, 1506.

(2) General Procedure for the Synthesis of 5. Continuous stirring of the resulting mixture **4** for a further 72 h at 25 °C and evaporation of the filtration afforded crude **5**. Pure **5** was obtained after flash column chromatography with ethyl acetate and petroleum ether.

(a) 3,7-Dibenzyl-8-hydroxy-3,4-dihydro-1H-pyrazino-[2,3-g]quinoxalin-2-one (5a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.64 (dt, J_1=8 Hz, J_2=2 Hz, 1H), 4.03 (d, J = 8 Hz, 2H), 4.09 (s, 2H), 6.10 (s, 1H), 6.69 (s,1H), 6.98 (s,1H), 7.14−7.32 (m, 10H), 7.97 (s,1H), 10.68 (s, 1H). MS (*m/z*): 397.2 $[M + H]^+$.

(b) 3,7-Bis-(4-tert-butoxy-benzyl)-8-hydroxy-3,4-dihydro-1H-pyrazino[2,3-g]quinoxalin-2-one (5b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03 (s, 9H), 1.23 (s, 9H), 2.87 (d, J = 5 Hz, 2H), 3.93−4.09 (m, 3H), 6.16 (s, 1H), 6.50 (s, 1H), 6.67 (d, J = 8 Hz, 2H), 6.85 (d, J = 8 Hz, 2H), 6.86 (s,1H), 7.02 (d, J = 8 Hz, 2H), 7.20 (d, J = 8 Hz, 2H), 10.61 (s, 1H), 11.97 (s, 1H). MS (*m/z*): 541.6 $[M + H]^+$. IR (KBr, cm^{-1}): 3375, 3188, 2976, 2870, 1653, 1606, 1508, 1398.

(3) General procedure for the synthesis of I. Continuous stirring of the resulting mixture **4** for a further 72 h at 80 °C and evaporation of the filtration afforded crude **I**. Pure **I** was obtained after flash column chromatography with ethyl acetate and petroleum ether.

(a) 3,7-Dibenzyl-pyrazino[2,3-g]quinoxaline-2,8-diol (Ia). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.10 (s, 4H), 7.10 (s, 1H), 7.30 (m, 10H), 7.98 (s, 1H), 12.49 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.7, 98.8, 126.3, 127.2, 128.2, 129.0, 133.2, 137.2, 154.4,159.1. MS (*m/z*): 395.2 $[M + H]^+$.

(b) 3,7-Bis-(4-tert-butoxy-benzyl)-pyrazino[2,3-g]quinoxaline-2,8-diol (Ib). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.23 (s, 18H), 4.04 (s, 4H), 6.86 (d, J = 8 Hz, 4H), 7.09 (s, 1H), 7.22 (d, J = 8 Hz, 4H), 7.97 (s, 1H), 12.28 (s, 2H). MS (*m/z*): 539.1 $[M + H]^+$. IR (KBr, cm^{-1}): 3305, 3180, 3060, 2976, 2929, 1658, 1630, 1506.

(c) 3,7-Diphenyl-pyrazino[2,3-g]quinoxaline-2,8-diol (Ic). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.17 (s, 1H), 7.50 (m, 6H), 8.17 (s, 1H), 8.28 (m, 4H), 12.67 (s, 2H). MS (*m/z*): 367.2 $[M + H]^+$.

(d) 3-Benzyl-7-methyl-pyrazino[2,3-g]quinoxaline-2,8-diol (Id). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.38 (s, 3H), 4.10 (s, 2H), 7.10 (s, 1H), 7.20−7.35 (m, 5H), 7.95 (s, 1H), 12.41 (s, 1H), 12.47 (s, 1H). MS (*m/z*): 319.2 $[M + H]^+$.

(e) 3-Benzyl-7-(4-tert-butoxy-benzyl)-pyrazino[2,3-g]-quinoxaline-2,8-diol (Ie). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.23 (s, 9H), 4.04 (s, 2H), 4.09 (s, 2H), 6.88 (d, J = 8 Hz, 2H), 7.11 (s, 1H), 7.20−7.34 (m, 7H), 8.00 (s, 1H), 12.52 (s, 2H). MS (*m/z*): 467.1 $[M + H]^+$.

(f) 3,7-Bis-cyclohexylmethyl-pyrazino[2,3-g]quinoxaline-2,8-diol (If). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.01−1.88 (m, 20H), 2.65 (m, 2H), 3.44 (d, J = 6 Hz, 4H), 7.10 (s, 1H), 7.96 (s, 1H), 12.39 (s, 2H). MS (*m/z*): 407.2 $[M + H]^+$.

General Procedure for the Synthesis of Scaffold II Compounds. 1,5-Difluoro-2,4-dinitrobenzene (1 mmol) was added to a flask which contained 10 mL of DMF and 1 mmol of methyl α-amino acetate hydrochloride; then 2.2 mmol of DIPEA was added under stirring. After the mixture was stirred at 25 °C for 6 h, 1.0 equiv of methyl β-amino acetate hydrochloride was added to the reaction mixture. Then the solution was stirred at room temperature for 18 h. The desired intermediates **6** were detected by HPLC at 254 nm (purity >98%) and ESI-MS (correct molecular weight was recorded with expectation). The solvent was evaporated until half of the volume remained, and 10 mL of ethanol was added, followed by the addition of Pd−C (0.1 equiv) and $HCOONH_4$ (10 equiv). After the reaction mixture was stirred at 60 °C for 0.5 h, the solvent was evaporated to dryness, and the residue was then dissolved in a solution of 5 mL of THF and 2.0 N LiOH in water (5 mL). The mixture was stirred for 1 h at room temperature, and then 1.0 N HCl aqueous solution was added to adjust the pH to 6−7. The solvent was evaporated to dryness, and the residue was extracted with 5 mL of THF and 15 mL of DCM against 20 mL of water. The organic layers were combined, dried over Na_2SO_4, and evaporated under vacuum to give intermediate **7**, which was analyzed by UV-HPLC at 254 nm and ESI-MS. Crude **7** was then dissolved in 15 mL of THF; PS-EDC (1.5 equiv) was added into the reaction system, and the mixture was continuously stirred for 6 h at room temperature. After the resin was filtered off, the desired product **II** in the filtrate was detected by the LC-MS system. All compounds were further purified with a short silica gel column eluting with DCM /MeOH (12:1).

(1) 3-Hydroxy-2,9-dimethyl-6,8,9,10-tetrahydro-1,4,6,-10-tetraaza-cyclohepta[b]-naphthalene-7-one (IIa). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16 (d, J = 6 Hz, 3H), 2.11 (m, 1H), 2.33 (s, 3H), 2.48 (m, 1H), 3.83 (m, 1H), 5.24 (brs, 1H), 6.83 (s, 1H), 7.22 (s, 1H), 9.79 (brs, 1H), 12.12 (brs, 1H). ^{13}C NMR(100 MHz, DMSO-d_6): δ 20.5, 22.8, 40.7,

54.6, 106.5, 118.5, 126.5, 129.2, 133.1, 135.9, 154.7, 157.2,-171.7. MS (*m/z*): 259.0 $[M + H]^+$.

(2) 3-Hydroxy-2-methyl-9-phenyl-6,8,9,10-tetrahydro-1,4,6,10-tetraaza-cyclohepta[b]-naphthalene-7-one (IIb). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H), 2.53−2.63 (m, 2H), 4.90 (t, J = 7 Hz, 1H), 5.72 (brs, 1H), 6.59 (s, 1H), 6.87 (s, 1H), 7.28−7.43 (5H), 9.88(brs, 1H), 12.09 (brs, 1H). MS (*m/z*): 321.0 $[M + H]^+$.

(3) 9-(4-Fluoro-phenyl)-3-Hydroxy-2-methyl-6,8,9,10-tetrahydro-1,4,6,10-tetraaza-cyclohepta[b]-naphthalene-7-one (IIc). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.35 (s, 3H), 2.61−2.66 (m, 2H), 4.93 (t, J = 7 Hz, 1H), 5.77 (brs, 1H), 6.86 (s, 1H), 7.15 (dd, J_1=7 Hz, J_2=2 Hz, 2H), 7.29 (s, 1H), 7.46 (dd, J_1=7 Hz, J_2=2 Hz, 2H), 9.93 (brs, 1H), 12.15 (brs, 1H). MS (*m/z*): 339.0 $[M + H]^+$.

(4) 3-Hydroxy-2-methyl-9-naphthalen-1yl-6,8,9,10-tetrahydro-1,4,6,10-tetraaza-cyclohepta[b]-naphthalene-7-one (IId). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H), 2.55−2.92 (m, 2H), 5.81 (t, J = 7 Hz, 1H), 5.86 (brs, 1H), 6.86 (s, 1H), 7.39 (s, 1H), 7.50−8.12 (7H), 9.96 (brs, 1H), 12.17 (brs, 1H). MS (*m/z*): 371.1 $[M + H]^+$.

(5) 3-Hydroxy-2-methyl-6,8,9,10-tetrahydro-1,4,6,10-tetraazacyclo-hepta[b]-naphthalene-7-one (IIe). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.32 (s, 3H), 2.46 (t, J = 7 Hz, 2H), 3.47 (m, 2H), 5.57 (brs, 1H), 6.83 (s, 1H), 7.13 (s, 1H), 9.80 (brs, 1H), 12.06 (brs, 1H). MS (*m/z*): 245.0 $[M + H]^+$.

(6) 3-Hydroxy-2,8-dimethyl-9-6,8,9,10-tetrahydro-1,4,6,-10-tetraaza-cyclohepta[b]-naphthalene-7-one (IIf). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.97 (d, J = 7 Hz, 3H), 2.33 (s, 3H), 2.67 (m, 1H), 3.16 (m, 1H), 3.42 (m, 1H), 5.50 (brs, 1H), 6.59 (s, 1H), 6.82 (s, 1H), 7.15 (s, 1H), 9.80 (brs, 1H), 12.06 (brs, 1H). MS (*m/z*): 259.0 $[M + H]^+$.

(7) 9-(4-Fluoro-phenyl)-3-Hydroxy-2-isopropyl-6,8,9,-10-tetrahydro-1,4,6,10-tetraaza-cyclohepta[b]-naphthalene-7-one (IIg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (d, J = 6 Hz, 6H), 2.63 (dd, J_1 = 6 Hz, J_2 = 2 Hz, 2H), 3.42 (m, 1H), 4.95 (t, J = 7 Hz, 1H), 5.73 (brs, 1H), 6.88 (s, 1H), 7.19 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 2H), 7.33 (s, 1H), 7.48 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 2H), 9.93 (brs, 1H), 12.13 (brs, 1H). MS (*m/z*): 367.1 $[M + H]^+$.

(8) 3-Hydroxy-2-isopropyl-8-methyl-6, 8, 9, 10-tetrahydro-1, 4, 6, 10-tetraaza-cyclohepta[b]-naphthalene-7-one (IIh). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.97 (d, J = 7 Hz, 3H), 1.18 (d, J = 7 Hz, 3H), 1.34 (d, J = 6 Hz, 3H), 2.49 (m, 1H), 3.19 (m, 1H), 3.42 (m, 1H), 3.44 (m, 1H), 5.45 (brs, 1H), 6.82 (s, 1H), 7.19 (s, 1H), 9.80 (brs, 1H), 12.05 (brs, 1H). MS (*m/z*): 287.0 $[M + H]^+$.

(9) 2-Benzyl-3-Hydroxy-9-phenyl-6,8,9,10-tetrahydro-1,4,6,10-tetraaza-cyclohepta[b]-naphthalene-7-one (IIi). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.56−2.65 (m, 2H), 4.05 (s, 2H), 4.90 (t, J = 6 Hz, 1H), 5.77 (brs, 1H), 6.83 (s, 1H), 7.20−7.42 (11H), 9.94 (brs, 1H), 12.22 (brs, 1H). MS (*m/z*): 397.1 $[M + H]^+$.

(10) 2-Benzyl-3-Hydroxy-9-naphthalen-1yl-6,8,9,10-tetrahydro-1,4,6,10-tetraaza-cyclohepta[b]-naphthalene-7-one (IIj). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.56−2.90 (m, 2H), 4.07 (s, 2H), 5.79 (t, J = 7 Hz, 1H), 5.81 (brs, 1H), 6.90 (s, 1H), 7.20−8.11 (13H), 9.99 (brs, 1H), 12.25 (brs, 1H). MS (*m/z*): 447.2 $[M + H]^+$.

(11) 2-Benzyl-3-Hydroxy-9-methyl-6,8,9,10-tetrahydro-1,4,6,10-tetraaza-cyclohepta[b]-naphthalene-7-one (IIk). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.96 (d, J = 7 Hz, 3H), 2.65 (m, 1H), 3.15 (m, 1H), 3.44 (m, 1H), 4.04 (s, 2H), 5.20 (brs, 1H), 6.81 (s, 1H), 7.15−7.31 (6H), 9.82 (brs, 1H), 12.17 (brs, 1H). MS (*m/z*): 335.0 $[M + H]^+$.

General Procedure for the Synthesis of Scaffold III Compounds. 1,5-Difluoro-2,4-dinitrobenzene (1 mmol) was added to a flask which contained 10 mL of THF and 1 mmol of α-amino acid methyl ester hydrochloride; then 2.2 mmol of DIPEA was added under stirring. After the mixture was stirred at 25 °C for 6 h, the solvents and volatiles were evaporated to dryness, and the residue was washed with water. The solid was then dissolved in dry acetone suspended with freshly dried K_2CO_3. Ethyl α-hydroxyl acetate (1 mmol) was added, and the mixture was shaken at 25 °C until the primary substitute intermediates disappeared, as determined by HPLC. Water was then added, and the precipitate was collected by filtration. The solid was then dissolved in 10 mL of THF/EtOH (v/v 3/1), and 30 mg of 10% Pd−C and 20 mmol of $HCOONH_4$ were added to the solution. After the mixture was stirred at room temperature for 30 min, it was filtered with funnel. After evaporation of the filtrate, the residue was purified by column chromatography using ethyl acetate and petroleum ether as eluents to give **III**.

(1) 6-Hydroxy-7-isopropyl-2-phenyl-4H-1-oxa-4,5,8-triaza-anthracen-3-one (IIIa). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (d, J = 7 Hz, 6H), 5.83 (s, 1H), 6.87 (s, 1H), 7.32 (s, 1H), 7.36−7.41 (m, 5H), 11.32 (s, 1H), 12.23 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.0, 20.1, 29.7, 77.4, 100.0, 114.9, 127.0, 127.6, 127.8, 128.6, 128.7, 129.1,-135.4, 138.6, 154.0, 165.3. MS (*m/z*): 336.2 $[M + H]^+$.

(2) 6-Hydroxy-7-isopropyl-2-methyl-4H-1-oxa-4,5,8-triaza-anthracen-3-one (IIIb). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (d, J = 7 Hz, 6H), 3.39 (m, 1H), 4.68 (m, 1H), 6.84 (s, 1H), 7.23 (s, 1H), 11.00 (s, 1H), 12.21 (s, 1H). MS (*m/z*): 274.2 $[M + H]^+$.

General Procedure for the Synthesis of Scaffold IV Compounds. 1,5-Difluoro-2,4-dinitrobenzene (1 mmol) was added to a flask which contained 10 mL of THF and 1 mmol of methyl α-amino acid ester hydrochloride; then 2.2 mmol of DIPEA was added under stirring. After the mixture was stirred at 25 °C for 6 h, another 1 mmol of ethyl α-mercaptoacetate and 1.1 mmol of DIPEA were added, and the mixture was stirred at 25 °C for 24 h. The solvents and volatiles were evaporated to dryness, and the residue was washed with enough water. The solid thus obtained was then treated with $SnCl_2 \cdot 2H_2O$ and concentrated HCl in 10 mL of THF and 10 mL of EtOH at 70 °C for 3 h. After it was washed with concentrated NaOH aqueous solution and extracted by DCM against water, the organic layer was dried over Na_2SO_4, Evaporation of the solvent and purification by column chromatography using ethyl acetate and petroleum ether as eluents gave scaffold **IV** compounds.

(1) 6-Hydroxy-7-methyl-4H-1-thia-4,5,8-triaza-anthracen-3-one (IVa). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.34 (s, 3H), 3.49 (s, 2H), 6.91 (s, 1H), 7.62 (s, 1H), 10.86 (s, 1H), 12.28 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.1,

28.9, 101.2, 114.4, 125.1, 127.0, 127.8, 131.4, 138.2, 154.9,-165.8. MS (*m/z*): 248.2 $[M + H]^+$.

(2) 6-Hydroxy-2,7-dimethyl-4H-1-thia-4,5,8-triaza-anthracen-3-one (IVb). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (s, 3H), 2.44 (s, 3H), 3.92 (m, 1H), 7.65 (s, 1H), 10.88 (s, 1H), 12.25 (s, 1H). MS (*m/z*): 262.1 $[M + H]^+$.

General Procedure for the Synthesis of Scaffold V Compounds. 1,5-Difluoro-2,4-dinitrobenzene (1 mmol) was added to a flask which contained 10 mL of THF and 1 mmol of amino acid methyl ester hydrochloride; then 2.2 mmol of DIPEA was added under stirring. After the mixture was stirred at 25 °C for 6 h, another 1 mmol of ethyl α-mercaptyl acetate hydrochloride and 2.2 mmol of DIPEA were added, andthe mixture was stirred at 25 °C for 24 h. The solvents and volatiles were evaporated to dryness, and the residue was dissolved in 10 mL of CH_3CN. Oxidant UHP was prepared according to literature method[13]. Freshly prepared UHP was added to the reaction mixture, and 15 mmol $(CF_3CO)_2O$ was then added dropwise to keep the temperature lower than 40 °C. When the reaction finished, as indicated by HPLC analysis, the mixture was extracted with 30 mL of water against 3 × 30 mL of DCM. The organic layer was combined and washed with saturated NaCl solution, and the organic layer was dried over Na_2SO_4. Evaporation of the solvent gave intermediate **10**, which was then dissolved in 10 mL of THF and 5 mL of EtOH. The solution was treated with 30 mg of 10% Pd−C and 20 mmol of $HCOONH_4$ at 50 °C for 4 h. Filtration of the reaction mixture and evaporation of the filtrate yielded the reduction product, which was redissolved in 20 mL of THF and protected under Ar gas. Sodium hydride was added slowly, and the mixture was stirred at 70 °C. When cyclization was complete, as indicated by HPLC-MS analysis, anhydrous EtOH was added to quench the excess NaH. The mixture was evaporated, desalted, and purified by column chromatography using ethyl acetate and petroleum ether as eluents to give pure **V**.

(1) 6-Hydroxy-7-benzyl-2-methyl-1,1-dioxo-1,4-dihydro-2H-1λ^6-thia-4,5,8-triaza-anthracen-3-one (Va). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.45 (d, J = 7 Hz, 3H), 4.09 (s, 2H), 4.78 (q, J = 7 Hz, 1H), 7.07(s, 1H), 7.28 (m, 5H), 8.00 (s, 1H), 11.51 (s, 1H), 12.68 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 5.3, 31.3, 59.0, 103.4, 120.4, 124.1, 126.4, 127.3, 128.3, 129.2, 136.2, 136.9, 137.3, 154.6, 160.4, 170.3. MS (*m/z*): 370.1 $[M + H]^+$.

(2) 6-Hydroxy-2,7-dimethyl-1,1-dioxo-1,4-dihydro-2H-1λ^6-thia-4,5,8-triaza-anthracen-3-one (Vb). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.45 (d, J = 7 Hz, 3H), 2.38 (s, 3H), 4.94 (m, J = 7 Hz, 1H), 7.06 (s, 1H), 7.98 (s, 1H), 11.48 (brs, 1H), 12.58 (brs, 1H). MS (*m/z*): 294.1 $[M + H]^+$.

General Procedure for 6-hydroxy-1,3-dihydro-imidazo-[4,5-g]quinoxalin-2-one (VI). *o*-Phenylenediamine **12** was prepared as our previous reports.[2,3] A solution of triphosgene (6.7 mg) in dry THF (1.5 mL) was added dropwise to a stirred solution of *o*-phenylenediamine (0.048 mmol) and triethylamine (20 μL) in dry THF (2 mL), and the mixture was stirred at room temperature for 30 min. The white precipitate (Et_3N·HCl) was filtered off and washed with dry THF. The combined filtrate was concentrated in vacuum to give product **VI**.

(1) 1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6-hydroxy-7-methyl-1,3-dihydro-imidazo[4,5-g]quinoxalin-2-one (VIa). ^{1}H NMR (300 MHz, DMSO-d_6 + D_2O): δ 2.36 (s, 3H), 2.88 (t, J = 7 Hz, 2H), 3.66 (s, 3H), 3.67 (s, 3H), 4.01 (t, J = 7 Hz, 2H), 6.71 (dd, J_o = 8 Hz, J_m = 2 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 6.83 (s, 2H), 7.44 (s, 1H), 11.07 (s, 1H, exchangeable with D_2O), 12.19 (s, 1H, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2, 33.0, 41.6, 55.3, 55.5, 93.9, 105.9, 111.9, 112.7, 120.8, 127.0, 127.5, 127.6, 130.3, 130.9, 147.4, 148.6, 154.5, 154.8, 155.0. MS (*m/z*): 381.2 $[M + H]^+$.

(2) 6-Hydroxy-7-methyl-1-phenethyl-1,3-dihydro-imidazo[4,5-g]quinoxalin-2-one (VIb). ^{1}H NMR (300 MHz, DMSO-d_6 + D_2O): δ 2.35 (s, 3H), 2.96 (t, J = 7 Hz, 2H), 4.03 (t, J = 7 Hz, 2H), 6.82 (s, 1H), 7.16−7.24 (m, 5H), 7.40 (s, 1H), 11.07 (s, 1H, exchangeable with D_2O), 12.19 (s, 1H, exchangeable with D_2O). MS (*m/z*): 321.2 $[M + H]^+$.

(3) 6-Hydroxy-1-(3-methoxy-propyl)-7-methyl-1,3-dihydro-imidazo[4,5-g]- quinoxalin-2-one (VIc). ^{1}H NMR (300 MHz, DMSO-d_6 + D_2O): δ 1.85 (m, 2H), 2.35 (s, 3H), 3.20 (s, 3H), 3.30 (m, 2H), 3.84 (t, J = 7 Hz, 2H), 6.85 (s, 1H), 7.37 (s, 1H), 11.10 (s, 1H, exchangeable with D_2O), 12.20 (s, 1H, exchangeable with D_2O). MS (*m/z*): 289.1 $[M + H]^+$.

(4) 6-Hydroxy-7-isobutyl-1-phenethyl-1,3-dihydro-imidazo[4,5-g]quinoxalin-2-one (VId). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.94 (d, J = 7 Hz, 6H), 2.22 (m, 1H), 2.63 (d, J = 6 Hz, 2H), 2.97 (t, J = 7 Hz, 2H), 4.06 (t, J = 7 Hz, 2H), 6.85 (s, 1H), 7.16−7.26 (m, 5H), 7.46 (s, 1H), 11.12 (s, 1H), 12.22 (s, 1H). MS (*m/z*): 363.2 $[M + H]^+$.

General Procedure for 6-Hydrox-1,3-dihydro-imidazo-[4,5-g]quinoxaline-2-thione (VII). Carbon disulfide was added to a stirred solution of *o*-phenylenediamine (0.048 mmol) and triethylamine (20 μL) in DMF/EtOH (2/1 v/v). The mixture was refluxed for 12 h, and then it was cooled to room temperature. After evaporation of solvents, water was added to give a greenish precipitate. Filtration and washing with water gave product **VII**.

(1) 7-Benzyl-6-hydroxy-1-phenethyl-1,3-dihydro-imidazo[4,5-g]quinoxaline-2-thione (VIIa). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.02 (t, J = 8 Hz, 2H), 4.11 (s, 2H), 4.46 (t, J = 8 Hz, 2H), 7.02 (s, 1H), 7.18−7.34 (m, 10H), 7.72 (s, 1H), 12.38 (s, 1H), 12.93 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.6, 33.1, 44.7, 94.1, 108.1, 126.5, 126.9, 127.2, 127.4, 127.7, 128.0, 128.4, 129.0, 129.8, 132.6, 138.0, 141.9, 153.7, 158.6, 170.2. MS (*m/z*): 413.1 $[M + H]^+$.

General Procedure for Hydroxy-1,4-dihydro-pyrazino-[2,3-g]quinoxaline-2,3-dione (VIII). A solution of oxalic chloride (20 μL) in dry THF (1.5 mL) was added dropwise to a stirred solution of *o*-phenylenediamine (0.026 mmol) and triethylamine (30 μL) in dry THF (2 mL), and the mixture was stirred at room temperature for 30 min. The reaction was quenched with water (2 mL). Evaporation of THF, filtration, and washing with water gave **VIII** as red precipitate.

(1) 1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3,7-dihydroxy-8-methyl-1H-pyrazino [2,3-g]quinoxalin-2-one (VIIIa). ^{1}H

NMR (300 MHz, DMSO-d_6 + D_2O): δ 2.39 (s, 3H), 2.88 (t, J = 7 Hz, 2H), 3.69 (s, 3H), 3.73 (s, 3H), 4.35 (t, J = 7 Hz, 2H), 6.78 (d, J = 8 Hz, 1H), 6.86 (d, J = 8 Hz, 1H), 6.91 (s, 1H), 7.09 (s,1H), 7.70 (s, 1H), 12.24 (s, 1H, exchangeable with D_2O), 12.32 (s, 1H, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.3, 31.8, 43.7, 55.4, 55.5, 100.5, 111.9, 112.7, 113.4, 120.7, 122.9, 127.4, 127.9, 128.4, 130.6, 147.5, 148.6, 153.6, 154.2, 154.8, 158.0. MS (*m/z*): 409.2 $[M + H]^+$.

(2) 3,7-Dihydroxy-8-isobutyl-1-phenethyl-1H-pyrazino-[2,3-g]quinoxalin-2-one (VIIIb). ^1H NMR (300 MHz, DMSO-d_6): δ 0.93 (d, J = 7 Hz, 6H), 2.22 (m, 1H), 2.65 (d, J = 7 Hz, 2H), 2.94 (t, J = 8 Hz, 2H), 4.39 (t, J = 8 Hz, 2H), 7.10 (s, 1H), 7.20−7.30 (m, 5H), 7.69 (s, 1H), 12.25 (s, 1H), 12.32 (s, 1H). MS (*m/z*): 391.2 $[M + H]^+$.

(3) 1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3,7-dihydroxy-8-isobutyl-1H-pyrazino [2,3-g]quinoxalin-2-one (VIIIc). ^1H NMR (300 MHz, DMSO-d_6): δ 0.93 (d, J = 7 Hz, 6H), 2.21 (m, 1H), 2.64 (d, J = 7 Hz, 2H), 2.88 (t, J = 7 Hz, 2H), 3.67 (s, 3H), 3.71 (s, 3H), 4.37 (t, J = 7 Hz, 2H), 6.77 (d, J = 8 Hz, 1H), 6.84 (s, J = 8 Hz, 1H), 6.90 (s,1H), 7.10 (s,1H), 7.68 (s, 1H), 12.25 (s, 1H), 12.31 (s, 1H). MS (*m/z*): 451.1 $[M + H]^+$.

(4) 3,7-Dihydroxy-1-(3-methoxy-propyl)-8-methyl-1H-pyrazino[2,3-g]quinoxalin-2-one (VIIId). ^1H NMR (300 MHz, DMSO-d_6 + D_2O): δ 1.86 (m, 2H), 2.38 (s, 3H), 3.25 (s, 3H), 3.43 (t, J = 6 Hz, 2H), 4.18 (t, J = 7 Hz, 2H), 7.10 (s, 1H), 7.64 (s, 1H), 12.23 (s, 1H, exchangeable with D_2O), 12.31 (s, 1H, exchangeable with D_2O). MS (*m/z*): 317.0 $[M + H]^+$.

Acknowledgment. The authors wish to thank the National High Technology Research and Development Program of China (2005BA711A02).

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CC060034O