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Conformationally restrained carbazolone-containing α,γ-diketo acids as inhibitors of HIV integrase

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Abstract—Since α,γ-diketo acid (DKA) compounds were identified as potent and selective inhibitors for HIV integrase, numerous structural modification studies have been carried out to search for a clinical candidate as a supplement for the highly active anti-retroviral therapy regimen. Due to the lack of structural information on inhibitor–integrase interactions, a comprehensive structure–activity relationship study is necessary. Most of the reported modification studies on the key α,γ-diketo acid pharmacophore focused on substituting the carboxylate moiety with its bioisosteres or other electron-pair bearing heterocycles. We were interested in studying the conformation and geometry of the central diketo moiety. A series of carbazolone-containing α,γ-diketo acids were designed and synthesized by applying conformational restraint onto the open-chain form of the diketo acid. These compounds showed anti-integrase activity in the low micromolar range, and integrase assay results indicated that the geometry of the diketo acid moiety is crucial to potency. Carbazol-1-one containing DKA analogs (**7**–**8**) showed a 2- to 3-fold increase in activity compared with those of carbazol-4-one containing DKA analogs (**5** and **6**). Alkylation of carbazol-4-one DKA nitrogen (**6a**–**c**) led to a loss of activity, suggesting this nitrogen atom may directly interact with the active site of integrase. The halogens (**7b**–**d**) and *para*-fluorobenzyl substituents (**8a**–**d**) on carbazol-1-one ring had little effect on potency.

1. Introduction

HIV integrase is one of the three essential viral enzymes encoded by HIV *pol* gene. It catalyzes the integration of viral DNA onto the host genome-a critical step for viral replication-in a two-step process, 3′-processing and strand transfer.[1] Since integrase has no human counterpart, it is considered to be a promising target for developing new anti-HIV drugs that can be used as alternatives to current therapeutic agents suffering drug resistance. HIV integrase was first recognized as a novel anti-AIDS target in the early 1990s (see reviews[1–6]). Several classes of HIV integrase inhibitors have since been developed, including dinucleotides,[7] hydroxylated aromatics,[8–12] and α,γ-diketo acids.[13–19] Among these inhibitors, only the diketo acid compounds (DKAs) were biologically validated as targeting integrase by specifically inhibiting the strand transfer step in the integration process.[14] The inhibition is dependent on the presence of divalent metal ions.[17] It is believed that the α,γ-diketo acid moiety chelates with two Mg^{2+} ions in the integrase active site to form a tertiary DKA–Mg^{2+}-integrase complex, thus blocking substrate DNA binding.[17,20]

The first DKA types of inhibitors were independently reported by Shionogi & Co. and Merck.[15,14] In their patent, authors from Shionogi & Co. revealed that

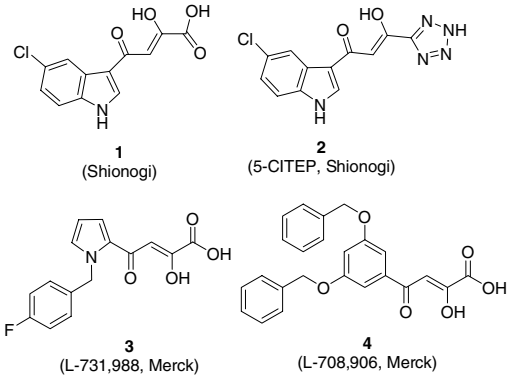

Figure 1. Reported α,γ-diketo acids as HIV integrase inhibitors.

Keywords: HIV integrase inhibitor; α,γ-Diketo acids; Carbazolone; Conformationally restrained.
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indole-containing α,γ-diketo acid (Fig. 1) showed good potency against integrase with an IC_{50} less than 1 μM.[15] They also disclosed the tetrazole-containing 5-CITEP (**2**, Fig. 1) as carboxylic acid bioisostere with an IC_{50} of 2.1 μM.[13] Similar α,γ-diketo acids (**3**–**4**, Fig. 1) with anti-integrase activities were also reported by Merck. L-731,988 (**3**) showed good potency against integrase, particularly in the strand transfer step with an IC_{50} of 0.08 μM compared with 6 μM in the 3′-processing step.[14]

One obstacle to the efficient and successful development of integrase inhibitors is due to the lack of inhibitor–integrase interaction information on molecular basis. One co-crystal structure of DKA compound 5-CITEP and integrase was available,[13] but its reliability might be compromised by crystal packing.[21] Therefore, a comprehensive structure–activity relationship (SAR) needs to be established. The general structure of DKAs contains a central α,γ-diketo moiety flanked by an aromatic ring and a carboxylic acid group (Fig. 2). It is believed that the diketo acid moiety is the key pharmacophore for enzyme inhibition,[17] and that an aromatic group adjacent to the diketo acid moiety improves potency and selectivity.[16,18,22] Many SAR studies on DKAs have been reported and provided very useful information. Most of them either focused on the carboxylate moiety by changing to its bioisosteres and other electron-bearing heterocycles,[18,23] or on the aromatic moiety by changing its substituents or replacing by other heteroaromatics.[23,16,18,19] However, direct modifications on the central α,γ-diketo moiety are very limited. Since the diketo group chelates to Mg^{2+} and mediates inhibitor binding to integrase, it is necessary to explore the structural features of this moiety. We were interested in substituting the β-carbon of the α,γ-diketo group and adding conformational restraint onto the open-chain form of diketo acid. The effect of β-substitution and conformational restraint on potency was investigated. In addition, the geometry between the aromatic substituents was examined since the angle of bisection is believed to be crucial for potency.[16]

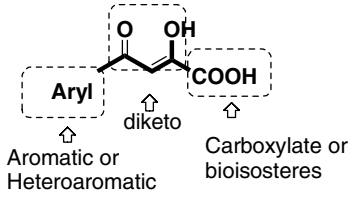


Figure 2. General structure of DKAs.

In our SAR study, two of the reported potent integrase inhibitors, compounds **1** and **3** (Fig. 1), were used as the lead. By combining the important features of these two molecules, we designed the conformationally restrained β-cyclized DKA analogs by connecting the β carbon of α,γ-diketo acid to the indole ring via a methylene chain bridge (Fig. 3). This modification afforded a 'drug-like' tricyclic carbazolone molecule, which is an important pharmacophore present in many pharmaceutical agents such as $5HT_3$ inhibitors and anti-tumor natural alkaloids.[24–27] Three other major modifications on the carbazolone core were made to further examine the effects of substitutions on activity. First, we investigated the substitution position of the DKA group to look for the optimal geometry. The 2-hydroxy-acrylic acid side chain was substituted either at the 3 position of carbazol-4-one (**5**–**6**, Fig. 3) derived from compound **1** or at the 2 position of carbazol-1-one (**7**–**8**, Fig. 3) derived from compound **3**. Second, a *para*-fluorobenzyl group was introduced to carbazolone core (**6** and **8**) because its presence was reported to improve activity.[16,18] Last, the effect of halogen substitution on the carbazolone ring was examined. Based on these modifications, four series of molecules (**5**–**8**, Fig. 3) were synthesized and their biological activities were evaluated.

2. Results and discussion

2.1. Chemistry

The carbazolone-containing diketo acids **5**–**8** were synthesized by coupling the corresponding carbazolones with acylating reagents ethyl chlorooxoacetate **9** or diethyl oxalate **10** in the presence of sodium hydride or sodium ethoxide.[28,29] The 6(7)-halo-carbazol-4-ones **12a**–**d** were prepared via Fischer-indole synthesis from 4(3)-halo-phenylhydrazine hydrochloride **11a**–**d** and 1,3-cyclohexanedione **13**[30,31] (Scheme 1). We also used microwave-assisted synthesis and optimized the reaction

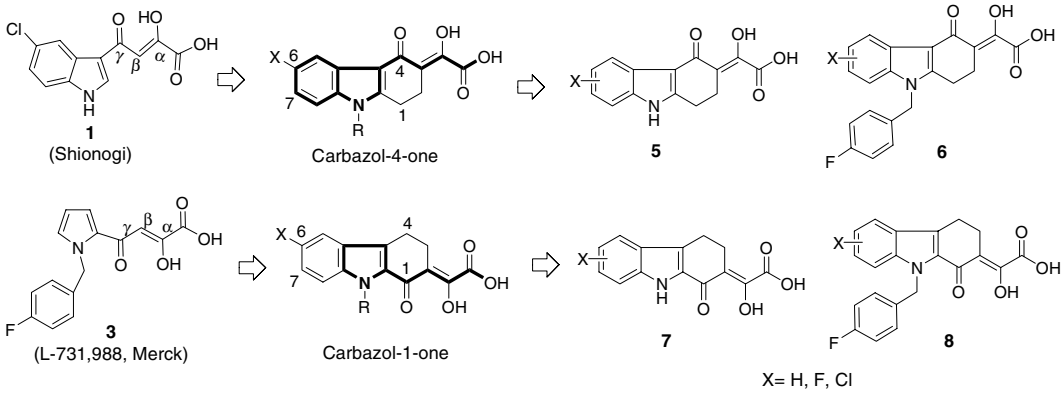
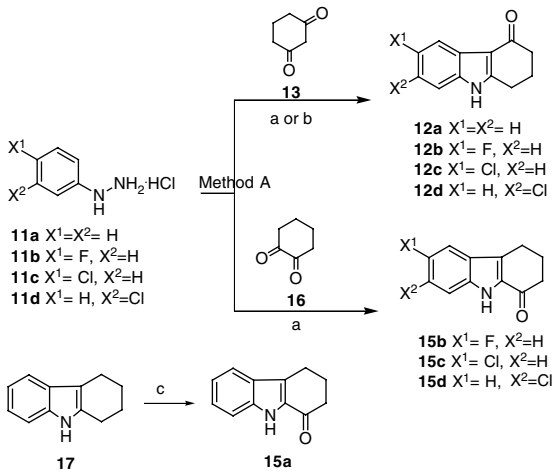


Figure 3. Design of carbazolone-containing DKA analogs as HIV integrase inhibitors.



Scheme 1. Reagents and conditions: (a) i—H_2O, rt, overnight; ii—TFA, 90 °C, overnight; (b) TFA or H_2O, 10 min in microwave; (c) I_2O_5, THF/H_2O, rt, 30 min.

conditions in one-pot and one-step with satisfactory yields. Similarly, carbazol-1-ones **15b–d** were synthesized via Fischer-indole synthesis from phenylhydrazine hydrochloride **11b–d** and 1,2-cyclohexanedione **16**. Carbazol-1-one can also be obtained by oxidizing commercially available carbazole **17** with diiodine pentoxide[32] (Scheme 1). Interestingly, direct coupling of carbazol-4-one **12** with acylating reagents **9** or **10** afforded less than 30% of the C-acylation product because of the multi-products formed in the reaction mixture, and both N-acylated and O-acylated products were found. The yield could not be improved by adding more acylating reagent and base or by applying a higher temperature and a longer reaction time. Reasoning that the free NH group may affect the reaction, we therefore protected the indole nitrogen before carrying out the coupling step.

Since tosyl is a good indole-protecting group, we first protected carbazol-4-one **12b** with tosyl chloride. The resulting *N*-tosyl carbazol-4-one (**18**, Scheme 2) was treated with acylating reagents **9** or **10** and base, but no reaction products were detected. Similarly, when Boc was used as the protecting group (**19**), no coupling reactions occurred. Since in both of the molecules, the protecting groups are electron withdrawing, we surmised that the loss of reactivity was due to the very stable and highly conjugated enolate (Fig. 4). To test this hypothesis, we placed a nonelectron-withdrawing methyl group onto carbazol-4-one (**12b**, Scheme 2). As expected, the resulting methylated compound **20** was readily coupled with compound **9** and gave the desired C-acylated product. Ester **21** was then hydrolyzed under acidic conditions to give the carboxylic acid **22** (Scheme 2). Considering a nonelectron-withdrawing group should be used to protect the carbazol-4-ones, we first chose the easily removable silanyl group. However, the low yield of the protection step due to the labile N–Si bond, coupled with the isolation of the O-acylated product, led to the selection of an alternate protecting group. We therefore selected diethoxymethyl (DEM) as the protecting group, which can be removed under acidic conditions. The coupling reaction worked best with diethyl oxalate **10** and sodium ethoxide. The DEM

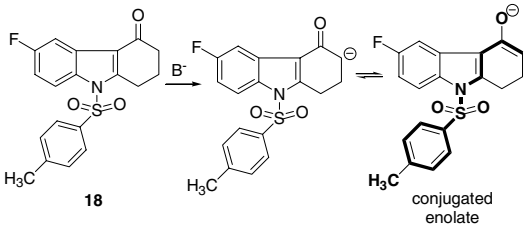
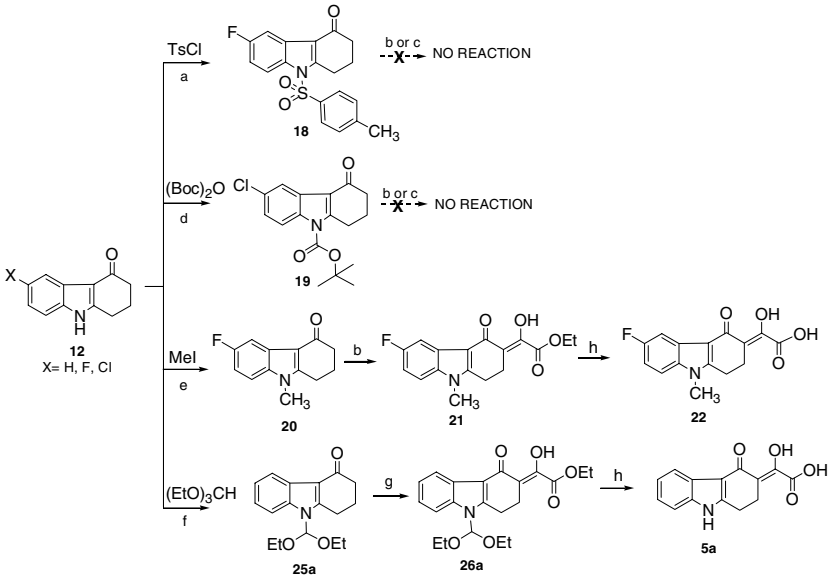


Figure 4. The highly stable enolate is unreactive toward acylating reagents.



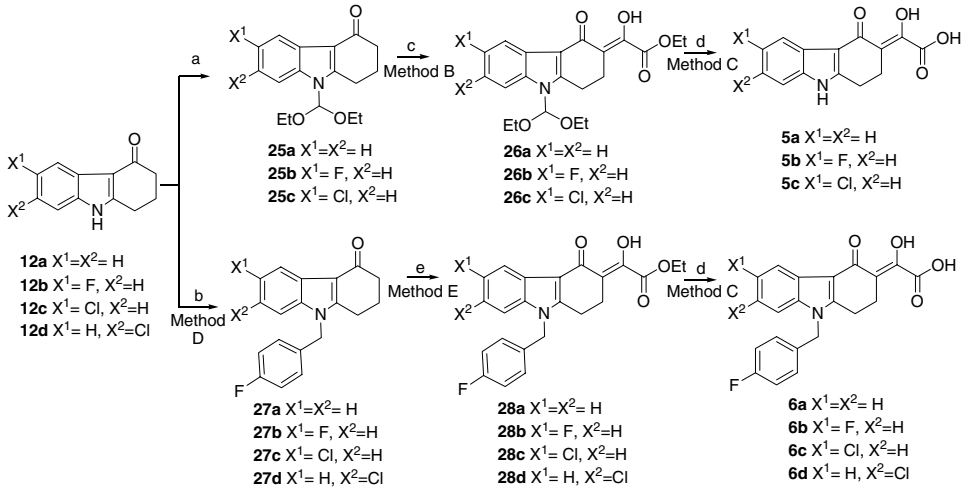
Scheme 2. Selection of protecting groups for carbazol-4-ones. Reagents and conditions: (a) NaH, DMF, TsCl, rt, overnight; (b) NaH, THF, **9**, 60 °C, overnight; (c) Na/EtOH, **10**, rt, overnight; (d) $(Boc)_2O$, Et_3N, DMAP, DMF, rt, overnight; (e) NaH, DMF, CH_3I, rt, overnight; (f) $(EtO)_3CH$, DMF, toluene, CSA (cat), 130–140 °C, 2 d; (g) Na/EtOH, **10**, rt, 1 h; (h) 1 N HCl, 1,4-dioxane, 100–110 °C, 4–10 h.

group was removed in the same step with the hydrolysis of the ester (Scheme 2).

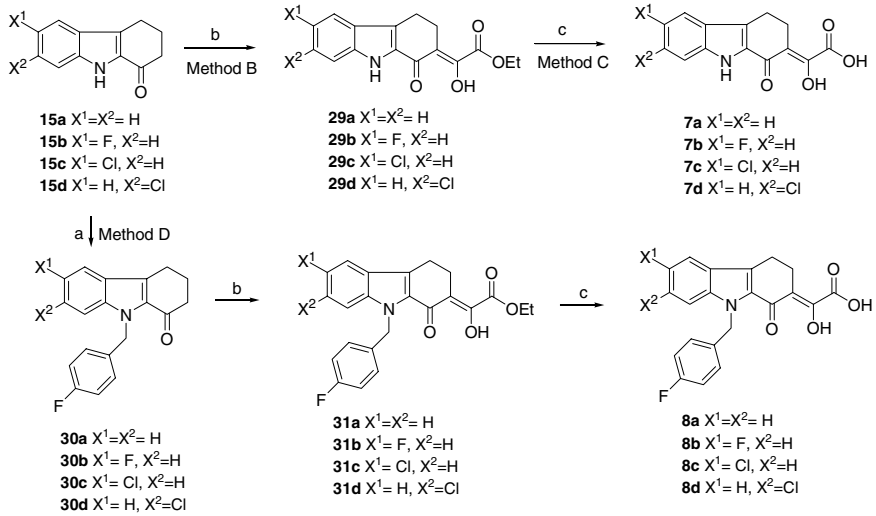
With the selection of DEM as the protecting group, target compounds **5a–c** were synthesized (Scheme 3). Carbazol-4-ones (**12a–c**) were first protected with DEM by refluxing with triethyl orthoformate,[33] the resulting compounds **25a–c** subsequently reacted with diethyl oxalate **10** to give the esters **26a–c**. The DEM groups were removed together with the hydrolysis of the esters to give the carbazol-4-one-containing DKAs (**5a–c**). The benzylated DKAs **6a–d** were synthesized from carbazol-4-ones **12a–d**, which were first benzylated with 4-fluorobenzyl bromide to give **27a–d**. Compounds **27a–d** were then acylated with ethyl chlorooxoacetate **9** in the presence of sodium hydride to give the coupling products **28a–d**. The esters were hydrolyzed by refluxing in dilute HCl to give the free acids **6a–d** (Scheme 3).

Target molecules **7** and **8** were synthesized from carbazole-1-ones **15a–d** (Scheme 4). Carbazole-1-ones can readily react with diethyl oxalate **10** in the presence of sodium ethoxide to give the coupling products **29a–d**, which were hydrolyzed to give the free acids **7a–d**. Similarly, target compounds **8a–d** were made by first alkylating the carbozol-1-ones **15a–d** with 4-fluorobenzyl bromide. Subsequent coupling with diethyl oxalate **10**, followed by ester hydrolysis gave the final free acids (Scheme 4).

In the course of synthesis of target compounds **5** and **7**, we found that the carbazol-1-one **15** and carbazol-4-one **12** showed different reactivity toward C-acylation in thermodynamic-controlled conditions. Compound **15** readily reacted with acylating reagent to give the coupling product **29** with 70–80% yield (Scheme 4). However, the acylation reactions under similar conditions with compound **12** only afforded less than 30% product. This is possibly due to the different conjugation systems in each molecule resulting in differences in enolate stability. For the fully conjugated carbazol-4-one (**12**, Fig. 5), enolate **33** that is in equilibrium with **32** is more stable than enolate **34**. As a result, C-acylation is not the major



Scheme 3. Synthesis of target compounds **5** and **6**. Reagents and conditions: (a) $(EtO)_3CH$, DMF, toluene, CSA (cat), 130–140 °C, 2 d; (b) NaH, DMF, 4-fluorobenzyl bromide, rt, 4 h; (c) Na/EtOH, **10**, rt, 1 h; (d) 1 N HCl, 1,4-dioxane, 100–110 °C, 4 h; (e) NaH, THF, **9**, 50 °C, overnight.



Scheme 4. Synthesis of target compounds **7** and **8**. Reagents and conditions: (a) NaH, DMF, 4-fluorobenzyl bromide, rt, 4 h; (b) Na/EtOH, **10**, rt, 1 h; (c) 1 N HCl, 1,4-dioxane, 100–110 °C, 4 h.

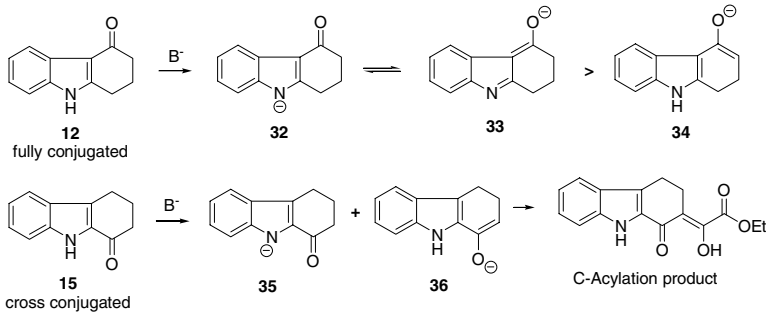


Figure 5. Fully conjugated carbazol-4-one **12** and cross-conjugated carbazol-1-one **15** showed different reactivity toward acylating reagents.

reaction and both N- and O-acylation products were found. Whereas for the cross-conjugated carbazol-1-one **15**, enolate **36** is stable and the C-acylation product is the major product under thermodynamic conditions.

2.2. Structure–activity relationship studies

All target compounds were tested against HIV integrase in microtiter and radioactive gel assays. In general, carbazolone-containing α,γ-diketo acid analogs inhibited recombinant HIV integrase at low micromolar range (Table 1). Modification of lead compound **1** to the conformationally restrained and β-substituted carbazol-4-one DKA (**5c**) reduced potency by 4- to 5-fold, suggesting that the open-chain form of DKA adopts a better conformation for binding to integrase. This reduction in activity might also be attributed to the steric hindrance introduced by the methylene bridge or might result from a twisted coplanarity of Mg^{2+} and α,γ-diketo complex with bulky β-substituents leading to a decrease in chelating strength.[34] Replacing the chlorine atom on carbazol-4-one (**5c**) with either a hydrogen (**5a**) or fluorine (**5b**) had little effect on potency, with the fluorine substitution (**5b**) exhibiting a better activity. Alkylation of the carbazol-4-one nitrogen with a *para*-fluorobenzyl group (**6a–c**) or a methyl group (**22**) led to significant decrease in activity. This alkylation effect was different from that found in indole DKAs (**1**), in which the size of the alkylating group affected potency.[22] Our results suggest that the free NH group of carbazol-4-one possibly hydrogen bonded with Gln 148 in the active site of integrase, which is similar to the indolic nitrogen and Gln 148 hydrogen bond found in the co-crystal structure of CITEP and integrase.[13] Interestingly, the decreased activity due to alkylation was recovered by changing the position of chlorine substituent from 6 (**6c**) to 7 (**6d**), which might be attributed to the increased binding affinity.

Our results also indicated that the geometry of the diketo acid side chain was crucial for potency; changing the position of the α,γ-diketo acid from carbazol-4-one (**5a–c**) to carbazol-1-one (**7a–d**) increased activity by 2- to 3-fold. Substituting the hydrogen (**7a**) with halogen atoms (**7b–d**) on carbazol-1-one only slightly increased activity, with the fluorine substitution (**7b**) being the most active one, which is similar to the observation with carbazol-4-one (**5b**). In contrast to the significant loss of activity on carbazol-4-one (**6a–c**), adding a *para*-fluorobenzyl group to carbazol-1-ones (**8a–d**) had little impact on activity. Interestingly, fluorine substitution (**8b**) was less active among this series, and changing the chlorine position from 6 (**8c**) to 7 (**8d**) slightly decreased potency.

3. Experimental

3.1. Biological assays

All the synthesized compounds were tested in a dual microtiter assay and radioactive gel assay[35,36] (data provided by Southern Research Institute, Birmingham, AL). The results were shown as the combined activity of both 3′-processing and strand transfer steps given as percentage of inhibition at 10 μM.

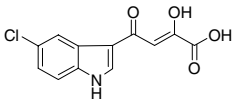
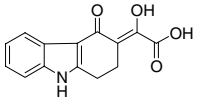
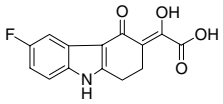
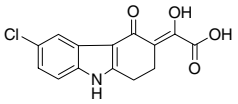
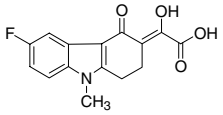
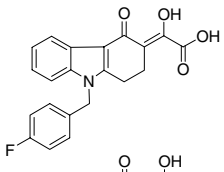
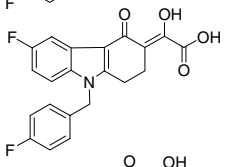
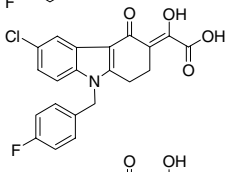
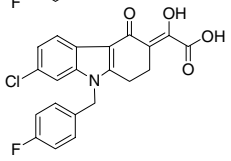
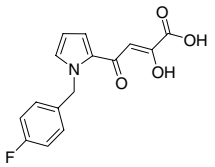
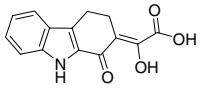
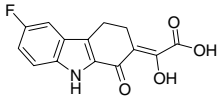
3.2. Chemistry

All reactions were performed in septum-sealed flasks under argon atmosphere. Progress of the reaction was followed by TLC. Organic solutions were dried over $MgSO_4$ and evaporated on a rotary evaporator under reduced pressure. Melting points were determined on a Mel-Temp II apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained using a Varian Unity VAC-300 spectrometer operating at a field strength of 300 MHz. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) in hertz. Standard and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; p, pentet; br s, broad singlet; and m, multiplet. Mass spectra were determined using Bruker BioTOF II spectrometer. Elemental analyses were performed by M-H-W laboratories (Phoenix, AZ) and gave results within ±0.4% of the theoretical values. Flash chromatography was performed using a 200–300 mesh silica gel. All commercial solvents were of reagent grade or better and used directly as supplied. Yields refer to purified products and were not optimized.

3.3. Method A: General procedure for the preparation of 6(7)-halo-1,2,3,9-tetrahydrocarbazol-4-ones (12a–d)

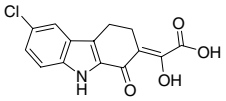
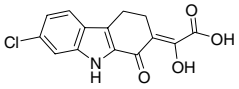
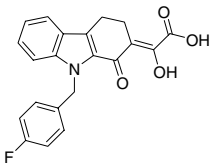
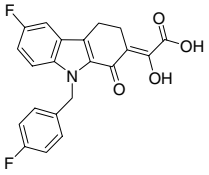
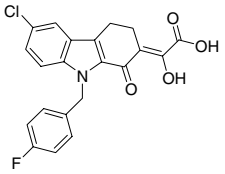
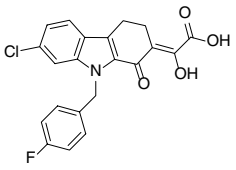
The title compound was prepared as described.[31] To a solution of 1,3-cyclohexanedione (**13**, 10 mmol) in water (15 mL) was added 4(3)-halo-phenylhydrazine hydrochloride salt (**11a–d**, 10 mmol) portionwise. The mixture was allowed to stir for one day at room temperature (rt).

Table 1. Anti-HIV integrase activities of carbazol-4-one- (**5** and **6**) and carbazol-1-one- (**7** and **8**) containing DKAs in microtiter and radioactive gel assays[b]

Compound	Structure	Inhibition at 10 μM (%)	
		Microtiter assay	Gel assay
1		83.3	54.4
5a		12.9	15.4
5b		36.9	31.5
5c		16.4[a]	16.6
22		1.0[a]	2.7[a]
6a		0[a]	1.8[a]
6b		5.6[a]	0.7[a]
6c		8.0[a]	2.3[a]
6d		51.3	52.4
3		79.0	61.4
7a		37.3	26.3
7b		55.0	57.7

(*continued on next page*)

Table 1 (*continued*)

Compound	Structure	Inhibition at 10 μM (%)	
		Microtiter assay	Gel assay
7c		46.4	26.1
7d		46.6	46.7
8a		48.2	37.0
8b		33.3	24.5
8c		54.7	54.9
8d		47.1	44.2

[a] % of inhibition at 25 μM.
[b] Reactions were done in duplicate.

The solid precipitated was collected by filtration and washed with water to give the hydrazone. The dried hydrazone was treated with 9 mL trifluoroacetic acid at 90 °C. After the mixture was refluxed overnight, the excess TFA was removed in vacuo. The mixture was washed with water and saturated sodium bicarbonate. The resulting solid was recrystallized with dichloromethane to give the title compound.

3.3.1. 1,2,3,9-Tetrahydrocarbazol-4-one (12a). Yield 40%; mp 223–224 °C (218–220 °C[30]); ^{1}H NMR (DMSO-d_6): δ 11.75 (1H, br s, NH), 7.90 (1H, m), 7.38 (1H, m), 7.11 (2H, m), 2.93 (2H, t, J = 6 Hz), 2.40 (2H, t, J = 6 Hz), 2.09 (2H, p, J = 6 Hz); ^{13}C NMR (DMSO-d_6): δ 193.4, 152.9, 136.5, 125.2, 123.1, 122.2, 120.8, 112.4 (2), 38.6, 24.3, 23.6.

3.3.2. 6-Fluoro-1,2,3,9-tetrahydrocarbazol-4-one (12b). Yield 75%; mp 253 °C (254 °C[30]); ^{1}H NMR (DMSO-d_6): δ 12.0 (1H, s, NH), 7.56 (1H, dd, J = 2.4, 9.6 Hz), 7.37 (1H, dd, J = 4.5, 9.0 Hz), 6.98 (1H, dt, J = 2.4, 9.0 Hz), 2.93 (2H, t, J = 6.3 Hz), 2.40 (2H, t, J = 6.9 Hz), 2.08 (2H, p, J = 6.3 Hz); ^{13}C NMR (DMSO-d_6): δ 193.4, 154.4, 133.0, 125.8, 113.4, 112.5, 111.0, 110.7, 106.0, 38.4, 24.1, 23.6.

3.3.3. 6-Chloro-1,2,3,9-tetrahydrocarbazol-4-one (12c). Yield 69%; mp 282–284 °C (285 °C[30]); ^{1}H NMR (CD_3OD): δ 7.97 (1H, d, J = 1.5 Hz), 7.32 (1H, d, J = 7.8 Hz), 7.16 (1H, dd, J = 1.8, 9.0 Hz), 3.0 (2H, t, J = 6 Hz), 2.54 (2H, t, J = 6 Hz), 2.22 (2H, m).

3.3.4. 7-Chloro-1,2,3,9-tetrahydrocarbazol-4-one (12d). Yield 22%; mp 225–229 °C (140 °C[30]); ^{1}H NMR (DMSO-d_6): δ 12.00 (1H, s, NH), 7.91 (1H, d, J = 9 Hz), 7.44 (1H, d, J = 2 Hz), 7.15 (1H, dd, J = 1.5, 9 Hz), 2.96 (2H, t, J = 6 Hz), 2.43 (2H, t, J = 6 Hz), 2.12 (2H, p, J = 6 Hz); ^{13}C NMR (CD_3OD): δ 192.0, 154.2, 138.4, 126.1, 124.0, 123.6, 122.3, 121.9, 111.7, 110.6, 24.0, 23.3.

3.4. General procedure for the synthesis of diethoxymethyl (DEM) protected 1,2,3,9-tetrahydrocarbazol-4-ones (25a–c)[33]

A solution of 1,2,3,9-tetrahydrocarbazol-4-one (**12a**–**c**, 1 mmol) in 1 mL dry DMF was treated with triethyl

orthoformate (10 mmol), camphor sulfonic acid (16 mg), and 2.5 mL benzene. The mixture was heated to reflux for two days. After cooling down, the reaction mixture was concentrated and purified by flash column (EtOAc/hexanes, 1/4) to give the target compound.

3.4.1. 9-Diethoxymethyl-1,2,3,9-tetrahydrocarbazol-4-one (25a). Yield 71%; mp 85–87 °C; ^{1}H NMR ($CDCl_3$): δ 8.26 (1H, m), 7.60 (1H, m), 7.25 (2H, m), 6.29 (1H, s), 3.70 (2H, m), 3.50 (2H, m), 3.13 (2H, t, J = 6.0 Hz), 2.58 (2H, t, J = 6.0 Hz), 2.24 (2H, p, J = 6.0 Hz), 1.24 (6H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 194.6, 150.9, 136.0, 125.2, 123.6, 123.0, 121.8, 114.4, 111.3, 102.5, 62.9, 38.4, 23.9, 23.6, 15.2; MS (ESI): m/z 288.2 $[M+H]^+$, 310.1 $[M+Na]^+$.

3.4.2. 6-Fluoro-9-diethoxymethyl-1,2,3,9-tetrahydrocarbazol-4-one (25b). Yield 78%; mp 130–133 °C; ^{1}H NMR ($CDCl_3$): δ 7.91 (1H, dd, J = 2.4, 9.0 Hz), 7.56 (1H, dd, J = 4.5, 9.0 Hz), 7.25 (1H, dt, J = 2.7, 9.0 Hz), 6.21 (1H, s), 3.68 (2H, m), 3.51 (2H, m), 3.08 (2H, t, J = 6.0 Hz), 2.56 (2H, t, J = 6.0 Hz), 2.24 (2H, p, J = 6.0 Hz), 1.24 (6H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 194.3, 161.4, 158.2, 151.8, 132.2, 126.1, 125.9, 112.7, 112.6, 111.8, 111.4, 107.5, 107.2, 102.6, 62.9, 38.2, 23.8, 23.5, 15.1; MS (ESI): m/z 328 $[M+Na]^+$.

3.4.3. 6-Chloro-9-diethoxymethyl-1,2,3,9-tetrahydrocarbazol-4-one (25c). Yield 84%; mp 109–110 °C; ^{1}H NMR ($CDCl_3$): δ 8.24 (1H, d, J = 2.1 Hz), 7.55 (1H, d, J = 6.0 Hz), 7.19 (1H, dd, J = 2.4, 6.0 Hz), 6.22 (1H, s), 3.70 (2H, m), 3.49 (2H, m), 3.09 (2H, t, J = 6.0 Hz), 2.57 (2H, t, J = 6.0 Hz), 2.24 (2H, p, J = 6.0 Hz), 1.24 (6H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 194.2, 151.6, 134.2, 128.9, 126.3, 123.8, 121.3, 113.8, 112.8, 102.6, 62.9, 38.2, 23.8, 23.5, 15.1; MS (ESI): m/z 322 $[M+H]^+$, 344 $[M+Na]^+$.

3.5. Method B[37]: General procedure for the synthesis of (9-diethoxymethyl-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene)-hydroxyacetic acid ethyl esters (26a–c)

9-(Diethoxymethyl)-1,2,3,9-tetrahydrocarbazol-4-one (**25a–c**, 1 mmol) was suspended in 1 mL absolute ethanol, to which sodium (30 mg, 1.3 equiv) was added portionwise. The reaction mixture was stirred at room temperature under argon until all the sodium was consumed. To the mixture was then added diethyl oxalate (**10**, 200 μL, 1.5 equiv) dropwise and stirring was continued at room temperature for 1 h. The reaction was quenched by pouring into 10 mL ice water and the pH was adjusted to 6 with 1 N HCl. The aqueous layer was extracted with ethyl acetate and the organic extracts were combined and dried over $MgSO_4$. After concentrated, the crude residue was purified by flash chromatography (EtOAc/hexanes, 1/10–1/5) to give the title compound.

3.5.1. (9-Diethoxymethyl-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene)-hydroxyacetic acid ethyl ester (26a). Yield 66%; mp 68–70 °C; ^{1}H NMR ($CDCl_3$): δ 8.47 (1H, m), 7.88 (1H, m), 7.54 (2H, m), 6.54 (1H, m), 4.62 (2H, m), 3.96 (2H, m), 3.77 (2H, m), 3.49 (2H, m), 3.42 (2H, m), 1.65 (3H, m), 1.50 (6H, m); ^{13}C NMR ($CDCl_3$): δ 189.5, 163.6, 157.2, 151.2, 136.6, 125.0, 124.2, 123.5, 121.8, 113.9, 111.7, 110.6, 102.5, 63.1, 62.1, 23.6, 22.8, 15.2, 14.6; MS (ESI): m/z 388.2 $[M+H]^+$, 410.2 $[M+Na]^+$, 426.1 $[M+K]^+$.

3.5.2. (9-Diethoxymethyl-6-fluoro-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene)-hydroxyacetic acid ethyl ester (26b). Yield 53%; mp 91–92 °C; ^{1}H NMR ($CDCl_3$): δ 8.26 (1H, dd, J = 2.7, 9.3 Hz), 7.97 (1H, dd, J = 4.2, 9.0 Hz), 7.38 (1H, dt, J = 2.4, 9.0 Hz), 6.61 (1H, s), 4.76 (2H, q, J = 6.9 Hz), 4.08 (2H, m), 3.88 (2H, m), 3.64 (2H, t, J = 6.6 Hz), 3.51 (2H, t, J = 6.6 Hz), 1.79 (3H, t, J = 7.2 Hz), 1.62 (6H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 189.3, 163.6, 161.6, 158.4, 157.3, 151.9, 132.8, 125.9, 113.6, 113.1, 112.3, 112.0, 110.4, 107.7, 107.4, 102.6, 63.0, 62.2, 23.4, 22.7, 15.1, 14.6; MS (ESI): m/z 428.2 $[M+Na]^+$; Anal. ($C_{21}H_{24}FNO_6$) C, H, N.

3.5.3. (9-Diethoxymethyl-6-chloro-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene)-hydroxyacetic acid ethyl ester (26c). Yield 66%; ^{1}H NMR ($CDCl_3$): δ 8.58 (1H, d, J = 1.8 Hz), 7.97 (1H, d, J = 9.0 Hz), 7.61 (1H, dd, J = 2.1, 9.0 Hz), 6.63 (1H, s), 4.76 (2H, q, J = 7.5 Hz), 4.10 (2H, m), 3.91 (2H, m), 3.65 (2H, t, J = 6.6 Hz), 3.53 (2H, t, J = 6.6 Hz), 1.80 (3H, t, J = 6.9 Hz), 1.64 (6H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 189.2, 163.5, 157.4, 151.8, 134.8, 129.3, 126.1, 124.4, 121.4, 113.2, 110.3, 102.6, 63.1, 62.2, 23.4, 22.6, 15.1, 14.6; MS (ESI): m/z 444.1 $[M+Na]^+$.

3.6. Method C: General procedure for the synthesis of (4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene)-hydroxyacetic acids (5a–c)

(9-Diethoxymethyl-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene)-hydroxyacetic acid ethyl ester (**26a–c**, 1 mmol) was suspended in 4 mL of 1 N HCl and 5 mL of 1,4-dioxane. The mixture was heated to reflux for 4 h. After cooling down, the solid precipitated out was filtered and washed with water, diethyl ether, and methanol. The resulting solid was recrystallized with methanol to give the title compound.

3.6.1. (4-Oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene)-hydroxyacetic acid (5a). Yield 91%; mp 217–219 °C; ^{1}H NMR (DMSO-d_6): (enol form:ketone form = 4:1) enol form δ 12.46 (1H, s), 8.15 (1H, d, J = 6 Hz), 7.65–7.60 (1H, m), 7.45–7.35 (2H, m), 3.23 (4H, m); ketone form δ 12.25 (1H, s), 8.07 (1H, d, J = 6 Hz), 4.65 (1H, dd, J = 4.8, 12 Hz), 2.60 (1H, m), 2.48 (1H, m); ^{13}C NMR (DMSO-d_6): δ 189.0, 165.2, 163.3, 159.0, 153.8, 137.2, 125.0, 123.9, 123.5, 123.0, 122.6, 121.1, 112.8, 111.7, 108.9, 55.8, 26.1, 23.7, 22.7, 22.4; HRMS (ESI): m/z 280.0575 $[M+Na]^+$; Anal. ($C_{14}H_{11}NO_4$) C, H, N.

3.6.2. (6-Fluoro-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene)-hydroxyacetic acid (5b). Yield 91%; mp 223–225 °C; ^{1}H NMR (DMSO-d_6): (enol form:ketone form = 2.7:1) enol form δ 12.35 (1H, s), 7.61 (1H, dd, J = 2.1, 9 Hz), 7.47–7.39 (1H, m), 7.10–6.99 (1H, m), 3.01 (4H, m); ketone form δ 12.16 (1H, s), 7.52 (1H, dd, J = 2.4, 9 Hz), 4.45 (1H, dd, J = 4.8, 12 Hz), 2.40 (1H, m), 2.26 (1H, m); ^{13}C NMR (DMSO-d_6): δ 197.3, 190.1, 189.0, 165.1, 163.2, 159.0, 155.1, 133.8, 133.3, 125.6,

114.1, 111.8, 111.5, 108.8, 106.4, 106.1, 55.7, 25.9, 23.6, 22.7; MS (ESI): *m/z* 274.1 $[M-H]^-$; HRMS (ESI): Calcd for $(C_{14}H_{10}FNO_4)H^+$: 276.0667. Found: 276.0650.

3.6.3. (6-Chloro-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene)-hydroxyacetic acid (5c). Yield 91%; mp >240 °C (dec.); ^{1}H NMR (DMSO-d_6): (enol form:ketone form = 2:1) enol form δ 12.83 (1H, s), 8.30 (1H, d, J = 1.5 Hz), 7.85 (1H, t, J = 7.5 Hz), 7.65–7.59 (1H, m), 3.42 (4H, m); ketone form δ 12.64 (1H, s), 8.22 (1H, d, J = 2 Hz), 4.85 (1H, dd, J = 4.8, 12 Hz), 2.80 (1H, m), 2.55 (1H, m); ^{13}C NMR (DMSO-d_6) δ 197.3, 190.2, 189.0, 165.0, 163.3, 159.2, 155.0, 154.8, 135.8, 135.3, 127.5, 127.2, 126.2, 126.0, 123.8, 123.5, 120.1, 119.8, 114.4, 114.1, 111.4, 108.8, 55.7, 25.9, 23.6, 22.7, 22.4; MS (ESI): *m/z* 313.9 $[M+Ma]^+$; Anal. ($C_{14}H_{10}ClNO_4$) C, H, N.

3.7. Method D: General procedure for the synthesis of 9-(4-fluorobenzyl)-1,2,3,9-tetrahydrocarbazol-4-ones (27a–d)

To a solution of 1,2,3,9-tetrahydrocarbazol-4-one (**12a–d**, 1 mmol) in anhydrous DMF (3 mL) was added sodium hydride (1.2 equiv) portionwise under ice bath. After 20 min of stirring at 0 °C, the ice bath was removed and 4-fluorobenzyl bromide (1.05 equiv) was added to the reaction mixture dropwise. The resulting mixture was stirred at room temperature for 4 h. After the reaction was complete, the mixture was poured into 30 mL saturated sodium bicarbonate and extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$. After concentrated, the crude product was purified by flash chromatography (EtOAc/hexanes, 1/4) to give the title compound.

3.7.1. 9-(4-Fluorobenzyl)-1,2,3,9-tetrahydrocarbazol-4-one (27a). Yield 83%; mp 148–150 °C; ^{1}H NMR ($CDCl_3$): δ 8.29 (1H, d, J = 7.2 Hz), 7.25–7.22 (3H, m), 6.99 (4H, d, J = 7.2 Hz), 5.30 (2H, s), 2.87 (2H, t, J = 6.3 Hz), 2.60 (2H, t, J = 6.0 Hz), 2.37 (2H, p, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$): δ 194.0, 151.7, 137, 128.0, 123.6 (2), 122.1, 116.4 (2), 109.7, 46.8, 38.2, 23.8, 22.7; MS (EI): *m/z* 293.1 (M^+), 265, 236, 157, 156, 128, 109; Anal. ($C_{19}H_{16}NOF$) C, H, N, F.

3.7.2. 6-Fluoro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydrocarbazol-4-one (27b). Yield 71%; mp 181–183 °C; ^{1}H NMR ($CDCl_3$): δ 7.92 (1H, m), 7.12 (1H, dd, J = 3.9, 8.7 Hz), 7.0–6.9 (5H, m), 5.26 (2H, s), 2.85 (2H, t, J = 6.0 Hz), 2.56 (2H, t, J = 6.3 Hz), 2.22 (2H, p, J = 6 Hz); ^{13}C NMR ($CDCl_3$): δ 193.8, 164.1, 161.5, 160.8, 158.3, 152.9, 133.6, 131.6, 128.0, 125, 116.5 (2), 111.7, 111.4, 107.7, 101.6, 46.9, 38.0, 23.6, 22.8; HRMS (EI): Calcd for $(C_{19}H_{15}F_2NO)^+$: 311.1122. Found: 311.1114 $[M^+]$.

3.7.3. 6-Chloro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydrocarbazol-4-one (27c). Yield 90%; mp 204–205 °C; ^{1}H NMR ($CDCl_3$): δ 8.26 (1H, d, J = 1.5Hz), 7.14 (2H, m), 6.99 (4H, m), 5.26 (2H, s), 2.85 (2H, t, J = 6.0 Hz), 2.56 (2H, t, J = 6Hz), 2.23 (2H, p, J = 6 Hz); ^{13}C NMR ($CDCl_3$): δ 193.7, 164.1, 152.6, 135.5, 131.6, 128.8, 127.9, 126.1, 123.7, 121.6, 116.5, 116.2, 113.0, 110.8, 46.9, 38.1, 23.6, 22.7; HRMS (EI): Calcd for $(C_{19}H_{15}ClFNO)^+$: 327.0826. Found: 327.0818 $[M^+]$.

3.7.4. 7-Chloro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydrocarbazol-4-one (27d). Yield 82%; mp 122–125 °C; ^{1}H NMR ($CDCl_3$): δ 8.1 (1H, d, J = 8.1 Hz), 7.25–6.93 (6H, m), 5.25 (2H, d, J = 16.2 Hz), 2.83 (2H, t, J = 6 Hz), 2.58 (2H, q, J = 6.6 Hz), 2.19 (2H, m, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 193.9, 191.5, 164.1, 152.7, 138.9, 131.4, 129.4, 127.9, 124 (4), 116 (2), 113, 109, 108, 46, 39, 38, 23; MS (ESI): *m/z* 350.1 $[M+Na]^+$.

3.8. Method E: General procedure for the synthesis of [9-(4-fluorobenzyl)-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene]-hydroxyacetic acid ethyl esters (28a–d)

To a solution of 9-(4-fluorobenzyl)-1,2,3,9-tetrahydrocarbazol-4-one (**27a–d**, 1 mmol) in 5 mL anhydrous THF was added sodium hydride (2 mmol) at 45 °C. The mixture was stirred at the same temperature for 20 min, followed by the addition of ethyl chlorooxoacetate (**9**, 2 mmol). The resulting mixture was heated at 45–50 °C for 4 h, and an additional 1 mmol of **9** was added. The reaction was complete after heating overnight. After cooling down, the crude mixture was poured into 30 mL cold sodium bicarbonate solution. The aqueous part was extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride, and dried over $MgSO_4$. The concentrated crude product was purified by flash chromatography (EtOAc/hexanes, 1/10–1/4) to give the title compound.

3.8.1. [9-(4-Fluorobenzyl)-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene]-hydroxyacetic acid ethyl ester (28a). Yield 74%; mp 184–186 °C; ^{1}H NMR ($CDCl_3$): δ 8.17 (1H, d), 7.25 (3H, m), 6.99 (4H, m), 5.31 (2H, s), 4.35 (2H, q, J = 6.9 Hz), 3.26 (2H, t, J = 6.9 Hz), 2.90 (2H, t, J = 6.9 Hz), 1.4 (3H, t, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 185.6, 166.8, 164.1, 160.8, 145.5, 143.9, 137.9, 131.5, 128.1, 125.3, 123.4, 122.7, 121.2, 121.1, 119.1, 116.5, 116.2, 111.2, 110.6, 62.6, 46.8, 24.7, 21.0, 14.2; MS (EI): *m/z* 393.2 $[M^+]$; Anal. ($C_{23}H_{20}FNO_4$) C, H, N.

3.8.2. [6-Fluoro-9-(4-fluorobenzyl)-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene]-hydroxyacetic acid ethyl ester (28b). Yield 68%; mp 176–177 °C; ^{1}H NMR ($CDCl_3$): δ 7.93 (1H, dd, J = 2.7, 9.0 Hz), 7.17 (2H, dd, J = 3.9, 9.0 Hz), 7.0 (5H, m), 5.29 (2H, s), 4.35 (2H, q, J = 7.2 Hz), 3.25 (2H, t, J = 7.2 Hz), 2.90 (2H, t, J = 7.2 Hz), 1.4 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 188.8, 163.6, 157.3, 152.8, 131.1, 128.0 (2), 116.6 (2), 112.3, 112.0, 111.1, 110.1, 108.0, 107.7, 62.2, 47.1, 23.2, 21.9, 14.5; MS (FAB): *m/z* 412.0 $[M+H]^+$; Anal. ($C_{23}H_{19}ClFNO_4$) C, H, N, F.

3.8.3. [6-Chloro-9-(4-fluorobenzyl)-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene]-hydroxyacetic acid ethyl ester (28c). Yield 90%; mp 123–124 °C; ^{1}H NMR ($CDCl_3$): δ 8.12 (1H, s), 7.16 (2H, s), 6.97 (5H, m), 5.28 (2H, s), 4.4 (2H, q, J = 7.2 Hz), 2.9 (4H, m), 1.41 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$): δ 185.7, 166.5, 164.2, 160.9, 146.2, 142.9, 136.3, 131.2, 128.5, 128.0, 126.2, 123.6, 120.7, 119.6, 116.6, 116.3, 111.6, 110.7, 62.6, 47.1, 24.7, 20.9, 14.3; MS (FAB): *m/z* 428.0 $[M+H]^+$; Anal. ($C_{20}H_{19}ClFNO_4$) C, H, N.

3.8.4. [7-Chloro-9-(4-fluorobenzyl)-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene]-hydroxyacetic acid ethyl ester (28d). Yield 78%; mp 214–217 °C; ^{1}H NMR ($CDCl_3$): δ 8.15 (1H, d, J = 8.4 Hz), 7.26 (2H, m), 7.0 (4H, m), 5.27 (2H, s), 4.35 (2H, q, J = 6.9 Hz), 3.26 (2H, t, J = 6.9 Hz), 2.89 (2H, t, J = 6.6 Hz), 1.40 (3H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 201, 152.4, 130.9, 128.0, 124.1, 123.0, 116.7, 116.4, 110.4, 62, 46.9, 23.3, 21.9, 14.5; Anal. ($C_{20}H_{19}ClFNO_4$) C, H, N, Cl.

3.9. [9-(4-Fluorobenzyl)-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene]-hydroxyacetic acids (6a–d)

The title compounds were prepared from [9-(4-Fluorobenzyl)-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene]-hydroxyacetic acid ethyl ester (**28a–d**) according to Method C. The crude product was recrystallized with EtOAc/hexanes.

3.9.1. [9-(4-Fluorobenzyl)-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene]-hydroxyacetic acid (6a). Yield 54%; mp 177–179 °C; ^{1}H NMR ($CDCl_3$): (enol form:ketone form = 6.3:1) enol form δ 8.29 (1H, d, J = 6 Hz), 7.39–7.28 (2H, m), 7.07–7.00 (2H, m), 5.35 (2H, s), 3.23 (2H, t, J = 6.9 Hz), 3.01 (2H, t, J = 6.9 Hz); ketone form δ 8.22 (1H, d), 5.33 (2H, s), 3.50 (2H, t, J = 7.5 Hz), 2.94 (2H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 164.6, 152.6, 128.2, 125.4, 125.1, 124.5, 122.8, 116.7, 116.4, 114.5, 110, 47.2, 25.0, 21.5; MS (FAB): m/z 366.0 $[M+H]^+$; Anal. ($C_{21}H_{16}FNO_4$) C, H, N, F.

3.9.2. [6-Fluoro-9-(4-fluorobenzyl)-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene]-hydroxyacetic acid (6b). Yield 19% (not optimized); mp 199–200 °C; ^{1}H NMR ($CDCl_3$): (enol form:ketone form = 2:1) enol form δ 7.96 (1H, dd, J = 2.4, 8.7 Hz), 7.23–7.17 (2H, m), 7.07–7.00 (4H, m), 5.34 (2H, s), 3.25 (2H, t, J = 6 Hz), 3.02 (2H, t, J = 6 Hz); ketone form δ 7.88 (1H, dd, J = 2.4, 9 Hz), 5.31 (2H, s), 3.52 (2H, t, J = 6.9 Hz), 2.95 (2H, t, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 184.3, 164.4, 161.0, 158.9, 157.8, 155.6, 152.7, 130.4, 128.2 (2), 116.8 (2), 114.3, 113.2, 112.9, 111.6, 108.9 (2), 47.5, 24.9, 21.5; MS (ESI): m/z 405.97 $[M+Na]^+$; Anal. ($C_{21}H_{15}F_2NO_4$) C, H, N, F.

3.9.3. [6-Chloro-9-(4-fluorobenzyl)-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene]-hydroxyacetic acid (6c). Yield 64%; mp 210–212 °C; ^{1}H NMR (acetone-d_6): (enol form:ketone form = 2:1) enol form δ 8.18–8.03 (1H, m), 7.60–7.49 (1H, m), 7.34–7.25 (3H, m), 7.15–7.08 (2H, m), 5.59 (2H, s), 3.27 (2H, t, J = 6.3 Hz), 3.15 (2H, t, J = 6.3 Hz); ketone form δ 5.65 (2H, s); MS (FAB): m/z 400.0 $[M+H]^+$; Anal. ($C_{21}H_{15}ClFNO_4$) C, H, N, F.

3.9.4. [7-Chloro-9-(4-fluorobenzyl)-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene]-hydroxyacetic acid (6d). Yield 57%; mp 191–193 °C; ^{1}H NMR ($CDCl_3$): (enol form:ketone form = 6.4:1) enol form δ 8.22 (1H, d, J = 9 Hz), 7.35–7.29 (3H, m), 7.05–7.02 (3H, m), 5.31 (2H, s), 3.26 (t, 2H, J = 6.9 Hz), 3.01 (t, 2H, J = 6.9 Hz); ketone form δ 8.12 (1H, m), 3.52 (2H, t), 2.94 (2H, t); MS (FAB): m/z 399.9 $[M+H]^+$; Anal. ($C_{21}H_{15}ClFNO_4$) C, H, N.

3.10. 2,3,4,9-Tetrahydrocarbazol-1-one (15a)[32]

To a stirred solution of 1,2,3,4-tetrahydrocarbazole (**17**, 5.0 g, 29.2 mmol) in 300 mL THF and 75 mL water was added diiodine pentoxide (11.7 g, 35.1 mmol). After stirring for 20 min at room temperature, the solvent was removed in vacuo at room temperature. The residue was extracted with ethyl acetate. The organic portion was washed with water, 5% $Na_2S_2O_3$, saturated sodium bicarbonate and brine, and dried over $MgSO_4$. After removing the solvent, the crude product was purified by flash chromatography (EtOAc/hexanes, 1/20–1/15) to give 3.35 g white solid as a title compound. Yield 55%; mp 164–165 °C (165–168 °C[32]); ^{1}H NMR ($CDCl_3$): δ 8.98 (1H, br s, NH), 7.66 (1H, d, J = 9.0 Hz), 7.44–7.34 (2H, m), 7.15 (1H, t, J = 6.0 Hz), 3.02 (2H, t, J = 6.0 Hz), 2.67 (2H, t, J = 6.0 Hz), 2.27 (2H, p, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$): δ 191.5, 129.7, 127.2, 121.6, 120.6, 112.7, 38.6, 25.4, 21.8; MS (ESI): m/z 208.1 $[M+Na]^+$.

3.11. Synthesis of 6-halo-2,3,4,9-tetrahydrocarbazol-1-ones (15b–d)

The title compounds were prepared from 1,2-cyclohexanedione (**16**) and 4(3)-halo-phenylhydrazine hydrochloride salt (**11b–d**) according to Method A.

3.12. 6-Fluoro-2,3,4,9-tetrahydrocarbazol-1-one (15b)

Yield 75%; mp 202–206 °C; ^{1}H NMR ($CDCl_3$): δ 9.42 (1H, br s, NH), 7.40 (1H, dd, J = 4.2, 9.0 Hz), 7.27 (1H, dd, J = 2.4, 9.0 Hz), 7.12 (1H, dt, J = 2.4, 9.0 Hz), 2.97 (2H, t, J = 6.0 Hz), 2.68 (2H, t, J = 6.0 Hz), 2.27 (2H, p, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$): δ 191.7, 134.7, 132.8, 126.2, 116.4, 116.1, 113.9, 113.8, 106.0, 105.7, 38.6, 25.3, 21.7; MS (ESI): m/z 226.0 $[M+Na]^+$; Anal. ($C_{12}H_{10}FNO$) C, H, N.

3.12.1. 6-Chloro-2,3,4,9-tetrahydrocarbazol-1-one (15c). Yield 69%; mp 223–225 °C; ^{1}H NMR ($CDCl_3$): δ 9.56 (1H, br s, NH), 7.61 (1H, s), 7.40 (1H, d, J = 9.0 Hz), 7.29 (1H, t, J = 9.0 Hz), 2.97 (2H, t, J = 6.0 Hz), 2.68 (2H, t, J = 6.0 Hz), 2.27 (2H, p, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$): δ 191.7, 136.3, 132.4, 128.9, 127.6, 127.0, 126.2, 120.8, 114.0, 38.6, 25.2, 21.6; MS (ESI): m/z 242.0 $[M+Na]^+$; Anal. ($C_{12}H_{10}ClNO + 0.2H_2O$) C, H, N, Cl.

3.12.2. 7-Chloro-2,3,4,9-tetrahydrocarbazol-1-one (15d). Yield 48%; mp 218–221 °C; ^{1}H NMR ($CDCl_3$): δ 9.46 (1H, br s, NH), 7.57 (1H, d, J = 9.0 Hz), 7.46 (1H, d, J = 1.8 Hz), 7.11 (1H, dd, J = 1.8, 9.0 Hz), 2.99 (2H, t, J = 6.0 Hz), 2.68 (2H, t, J = 6.0 Hz), 2.28 (2H, p, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$): δ 191.6, 138.4, 133.0, 131.9, 129.7, 124.6, 122.5, 121.7, 112.7, 38.5, 25.2, 21.7; HRMS (ESI): Calcd for $(C_{12}H_{10}ClNO)Na^+$: 242.0343. Found: 242.0332.

3.12.3. Synthesis of 6(7)-halo-(1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene)-hydroxyacetic acid ethyl esters (29a–d). The title compounds were prepared from 2,3,4,9-tetrahydrocarbazol-1-one (**15a–d**) according to Method B.

3.13. (1-Oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene)-hydroxyacetic acid ethyl ester (29a)

Yield 77%; mp 155–156 °C (156–157 °C[37]); ^{1}H NMR ($CDCl_3$): δ 8.9 (1H, br s, NH), 7.64 (1H, d), 7.40 (2H, m), 7.20 (1H, m), 4.37 (2H, q, J = 6.9 Hz), 3.25 (2H, m), 3.0 (2H, m), 1.42 (3H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 128.1, 121.8, 121.1, 112.7, 62.3, 24.5, 20.7, 14.5; HRMS (ESI): Calcd for $(C_{16}H_{15}NO_4)Na^+$: 308.0893. Found: 308.0896 $[M+Na]^+$.

3.13.1. (6-Fluoro-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene)-hydroxyacetic acid ethyl ester (29b). Yield 66%; mp 165–167 °C; ^{1}H NMR ($CDCl_3$): δ 9.07 (1H, br s, NH), 7.35 (1H, dd, J = 4.5, 9.0 Hz), 7.28 (1H, dd, J = 2.4, 9.0 Hz), 7.15 (1H, dt, J = 2.4, 9.0 Hz), 4.10 (2H, q, J = 6.9 Hz), 3.24 (2H, t, J = 6.6 Hz), 2.99 (2H, t, J = 6.6 Hz), 1.42 (3H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 185.0, 163.0, 159.8, 158.0, 156.6, 135.7, 132.6, 129.7, 126.1, 117.4, 117.1, 113.8, 112.1, 106.2, 105.9, 62.4, 24.4, 20.6, 14.5; MS (ESI): m/z 358.1 $[M+Na+MeOH]^+$, 326.0 $[M+Na]^+$; Anal. ($C_{16}H_{14}FNO_4$) C, H, N.

3.13.2. (6-Chloro-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene)-hydroxyacetic acid ethyl ester (29c). Yield 72%; mp 198–200 °C; ^{1}H NMR ($CDCl_3$): δ 8.95 (1H, br s, NH), 7.63 (1H, s), 7.34 (2H, m), 4.38 (2H, q, J = 6.9 Hz), 3.24 (2H, t, J = 6.9 Hz), 2.99 (2H, t, J = 6.9 Hz), 1.42 (3H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 185.0, 163.0, 158.0, 137.4, 132.2, 129.2, 128.4, 126.8, 121.0, 113.9, 112.0, 62.4, 24.4, 20.5, 14.5; MS (ESI): m/z 374.0 $[M+Na+MeOH]^+$, 342.0 $[M+Na]^+$; Anal. ($C_{16}H_{14}ClNO_4$+ 0.4H_2O) C, H, N.

3.13.3. (7-Chloro-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene)-hydroxyacetic acid ethyl ester (29d). Yield 67%; mp 171–173 °C; ^{1}H NMR ($CDCl_3$): δ 8.86 (1H, br s, NH), 7.57 (1H, d, J = 9 Hz), 7.41 (1H, d, J = 1.2 Hz), 7.14 (1H, dd, J = 1.2, 9 Hz), 4.39 (2H, q, J = 6.9 Hz), 3.24 (2H, t, J = 6.9 Hz), 3.01 (2H, t, J = 6.9 Hz), 1.42 (3H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 132.0, 124.5, 122.7, 122.3, 112.5, 62.4, 24.4, 20.6, 14.5; HRMS (ESI): Calcd for $(C_{16}H_{14}ClNO_4)Na^+$: 342.0504. Found: 342.0515 $[M+Na]^+$.

3.13.4. Synthesis of 6(7)-halo-(1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene)-hydroxyacetic acids (7a–d). The title compounds were prepared from 6(7)-halo-(1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene)-hydroxyacetic acid ethyl ester (**29a**–**d**, 1 mmol) according to method C. The crude product was recrystallized with EtOAc/MeOH to give the title compound.

3.14. (1-Oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene)-hydroxyacetic acid (7a)

Yield 55%; mp 177–179 °C; ^{1}H NMR ($CDCl_3$): (enol form:ketone form = 6.2:1) enol form δ 8.92 (1H, br s), 7.68 (1H, d, J = 8.4 Hz), 7.44 (2H, t, J = 6 Hz), 7.20 (1H, m), 3.28 (2H, t, J = 6 Hz), 3.15 (2H, t, J = 6 Hz); ketone form δ 8.10 (1H, s), 3.49 (2H, t), 3.08 (2H, m); ^{13}C NMR ($CDCl_3$): δ 129.6, 122.4, 121.6, 112.9, 26.5, 20.4; MS (ESI): m/z 279.99 $[M+Na]^+$; HRMS (ESI): Calcd for $(C_{14}H_{11}NO_4)Na^+$: 280.0580. Found: 280.0586.

3.14.1. (6-Fluoro-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene)-hydroxyacetic acid (7b). Yield 69%; mp 190–192 °C; ^{1}H NMR (DMSO-d_6): (enol form:ketone form = 1.5:1) enol form δ 11.89 (1H, br s), 7.50–7.37 (2H, m), 7.23–7.15 (1H, m), 2.93 (4H, m); ketone form δ 11.80 (1H, s), 4.47 (1H, dd, J = 4.5, 11 Hz), 2.35 (1H, m); ^{13}C NMR (DMSO-d_6): δ 196.3, 187.7, 164.0, 162.9, 159.2, 135.8, 132.2, 125.7, 116.6, 115.0, 110.3, 106.3, 56.6, 27.7, 24.5, 20.5; MS (ESI): m/z 297.98 $[M+Na]^+$; Anal. ($C_{14}H_{10}FNO_4$ + 1H_2O) C, H, N, F.

3.14.2. (6-Chloro-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene)-hydroxyacetic acid (7c). Yield 69%; mp 188 °C (dec.); ^{1}H NMR (DMSO-d_6): (enol form:ketone form = 1.5:1) enol form δ 11.98 (1H, br s), 7.77 (1H, m), 7.44–7.39 (1H, m), 7.33–7.29 (1H, m), 2.95 (4H, m); ketone form δ 11.91 (1H, s), 4.49 (1H, dd, J = 4.8, 11 Hz); ^{13}C NMR (CD_3OD): δ 170.5, 128.7, 127.7, 126.0, 120.5, 114.0, 112.2, 24.5, 20.4; MS (ESI): m/z 290.1 $[M-H]^-$; Anal. ($C_{14}H_{10}ClNO_4$ + 0.8H_2O) C, H, N, Cl.

3.14.3. (7-Chloro-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene)-hydroxyacetic acid (7d). Yield 64%; mp 208–210 °C; ^{1}H NMR (DMSO-d_6): (enol form:ketone form = 1.5:1) enol form δ 11.94 (1H, br s), 7.73–7.68 (1H, m), 7.40 (1H, m), 7.10 (1H, m), 2.95 (4H, m); ketone form δ 11.86 (1H, s), 4.48 (1H, dd), 2.34 (2H, m); ^{1}H NMR (CD_3OD): δ 11.48 (1H, br s), 7.62 (1H, d, J = 9 Hz), 7.43 (1H, dd, J = 2.1, 0.6 Hz), 7.08 (1H, dd, J = 9, 1.8 Hz), 3.18 (2H, t, J = 6 Hz), 3.00 (2H, t, J = 6 Hz); ^{13}C NMR (DMSO-d_6): δ 196.3, 187.6, 162.9, 139.8, 139.3, 131.9, 131.6, 129.7, 124.4, 123.8, 121.3, 112.9, 110.2, 73.0, 61.0, 56.5, 27.6, 24.5, 20.5; MS (ESI): m/z 314.0 $[M+Na]^+$; Anal. ($C_{14}H_{10}ClNO_4$+ 0.8 H_2O) C, H, N.

3.14.4. Synthesis of 9-(4-fluorobenzyl) 2,3,4,9-tetrahydrocarbazol-1-ones (30a–d). The title compounds were prepared from 2,3,4,9-tetrahydrocarbazol-1-one (**15a**–**d**) according to Method D. The crude product was purified by flash chromatography (EtOAc/hexanes 1/30–1/20).

3.15. 9-(4-Fluorobenzyl)-2,3,4,9-tetrahydrocarbazol-1-one (30a)

Yield 66% (semi-solid); ^{1}H NMR ($CDCl_3$): δ 7.60 (1H, d), 7.45 (2H, m), 7.00 (3H, m), 6.8 (2H, m), 5.6 (2H, d), 2.9 (2H, m), 2.5 (2H, m), 2.1 (2H, m); ^{13}C NMR ($CDCl_3$): δ 192.1, 164, 160, 139, 135, 130.3, 128.7, 127.2, 125.3, 121.7, 121, 115 (m), 113, 111, 47.5, 40.4, 25.1, 22.3; HRMS (ESI): Calcd for $(C_{19}H_{16}FNO)Na^+$: 316.1108. Found: 316.1123.

3.15.1. 6-Fluoro-9-(4-fluorobenzyl) 2,3,4,9-tetrahydrocarbazol-1-one (30b). Yield 80%; mp 122–123 °C; ^{1}H NMR ($CDCl_3$): δ 7.25 (2H, m), 7.08 (3H, m), 6.93 (2H, t, J = 9.0 Hz), 7.75 (2H, s), 2.99 (2H, t, J = 6.0 Hz), 2.66 (2H, t, J = 6.0 Hz), 2.34 (2H, p, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$): δ 192.2, 164, 156, 136.0, 134.0, 131.1, 128.6, 128.5, 116.4, 116.1, 115.8, 115.5, 112.1, 111.9, 106.1,

105.8, 47.8, 40.3, 24.9, 22.2; MS (ESI): *m/z* 334.1 $[M+Na]^+$; Anal. ($C_{19}H_{15}F_2NO$) C, H, N, F.

3.15.2. 6-Chloro-9-(4-fluorobenzyl)-2,3,4,9-tetrahydrocarbazol-1-one (30c). Yield 84%; mp 134–135 °C; ^1H NMR ($CDCl_3$): δ 7.64 (1H, s), 7.32–7.26 (2H, m), 7.08 (2H, m), 6.92 (2H, m), 5.75 (2H, s), 2.99 (2H, t, $J = 6.0$ Hz), 2.66 (2H, t, $J = 6.0$ Hz), 2.23 (2H, p, $J = 6.0$ Hz); ^{13}C NMR ($CDCl_3$): δ 192.2, 163.8, 160.5, 137.7, 133.9, 130.9, 129.3, 128.6, 127.5, 126.3, 120.9, 115.8, 115.5, 112.2, 47.7, 40.3, 24.9, 22.1; MS (ESI): *m/z* 350.0 $[M+Na]^+$; Anal. ($C_{19}H_{15}ClFNO$) C, H, N.

3.15.3. 7-Chloro-9-(4-fluorobenzyl)-2,3,4,9-tetrahydrocarbazol-1-one (30d). Yield 80%; mp 95–97 °C; ^1H NMR ($CDCl_3$): δ 7.55 (1H, d, $J = 9$ Hz), 7.29 (1H, d, $J = 1.5$ Hz), 7.08 (3H, m), 6.91 (2H, t, $J = 9$ Hz), 5.69 (2H, s), 2.99 (2H, t, $J = 6.0$ Hz), 2.63 (2H, t, $J = 6.0$ Hz), 2.21 (2H, p, $J = 6.0$ Hz); ^{13}C NMR ($CDCl_3$): δ 191.9, 163.8, 160.6, 139.7, 133.8, 133.1, 130.5, 130.2, 128.6, 123.9, 122.7, 121.7, 115.8, 115.6, 110.8, 47.7, 40.2, 24.9, 22.1; HRMS (ESI): Calcd for $(C_{19}H_{15}ClFNO)Na^+$ 350.0718: Found: 350.0715.

3.15.4. Synthesis of 6(7)-halo-[9-(4-fluorobenzyl)-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene]-hydroxyacetic acid ethyl esters (31a–d). The title compounds were prepared from 9-(4-fluorobenzyl)-2,3,4,9-tetrahydrocarbazol-1-one (**30a–d**) according to Method B. The crude product was recrystallized with diethyl ether to afford the title compound.

3.16. [9-(4-Fluorobenzyl)-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene]-hydroxyacetic acid ethyl ester (31a)

Yield 71%; mp 132–134 °C; ^1H NMR ($CDCl_3$): δ 7.66 (1H, d, $J = 9.0$ Hz), 7.36 (2H, m), 7.12 (3H, m), 6.94 (2H, m), 5.78 (2H, s), 4.37 (2H, q, $J = 7.2$ Hz), 3.16 (2H, dt, $J = 1.8$, 6.0 Hz), 3.04 (2H, dt, $J = 1.2$, 6.0 Hz), 1.41 (3H, t, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$): δ 185.9, 158.3, 140.7, 131.0, 130.2, 128.6, 128.0, 125.0, 121.9, 121.1, 115.9, 115.6, 112.5, 111.1, 62.3, 47.8, 24.5, 20.9, 14.5; HRMS (ESI): Calcd for $(C_{23}H_{20}FNO_4)H^+$: 394.1449. Found: 394.1456.

3.16.1. [6-Fluoro-9-(4-fluorobenzyl)-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene]-hydroxyacetic acid ethyl ester (31b). Yield 70%; mp 151–152 °C; ^1H NMR ($CDCl_3$): δ 7.30 (2H, m), 7.10 (3H, m), 6.95 (2H, m), 5.77 (2H, s), 4.38 (2H, q, $J = 7.5$ Hz), 3.15 (2H, t, $J = 6.9$ Hz), 2.98 (2H, t, $J = 6.9$ Hz), 1.41 (3H, t, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$): δ 186.0, 163.1, 158.8, 137.3, 128.5, 117.3, 116.9, 115.9, 115.6 112.3, 112.2, 106.3, 106.0, 62.4, 48.0, 24.4, 20.8, 14.5; MS (ESI): *m/z* 466.1 $[M+Na+MeOH]^+$; 434.1 $[M+Na]^+$; Anal. ($C_{23}H_{19}F_2NO_4$) C, H, N, F.

3.16.2. [6-Chloro-9-(4-fluorobenzyl)-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene]-hydroxyacetic acid ethyl ester (31c). Yield 50%; mp 167–170 °C; ^1H NMR ($CDCl_3$): δ 7.64 (1H, s), 7.29 (2H, m), 7.07 (2H, m), 6.94 (2H, m), 5.76 (2H, s), 4.38 (2H, q, $J = 6.9$ Hz), 3.15 (2H, t, $J = 6.9$ Hz), 2.98 (2H, t, $J = 6.6$ Hz), 1.41 (3H, t, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$): δ185.9, 163.1, 158.9, 138.9, 129.8, 128.6, 128.3, 126.8, 125.8, 121.1, 116.0, 115.7, 112.3, 62.4, 48.0, 24.4, 20.8, 14.5; MS (ESI): *m/z* 482.0 $[M+Na+MeOH]^+$, 450.0 $[M+Na]^+$; Anal. ($C_{23}H_{19}ClFNO_4$) C, H, N, Cl.

3.16.3. [7-Chloro-9-(4-fluorobenzyl)-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene]-hydroxyacetic acid ethyl ester (31d). Yield 71%; mp 146–148 °C; ^1H NMR ($CDCl_3$): δ 7.82 (1H, d, $J = 9$ Hz), 7.30 (1H, d, $J = 1.2$ Hz), 7.15–7.07 (3H, m), 6.96 (2H, t, $J = 9$ Hz), 5.73 (2H, s), 4.37(2H, q, $J = 6$ Hz), 3.15 (2H, t, $J = 7.5$ Hz), 3.00 (2H, t, $J = 7.5$ Hz), 1.40 (3H, t, $J = 6$ Hz); ^{13}C NMR ($CDCl_3$): δ185.7, 163.1, 158.6, 134.1, 130.7, 128.6, 128.5, 123.5, 122.9, 122.2, 116.0, 115.7, 112.1, 110.6, 62.3, 47.9, 24.5, 20.8, 14.5; HRMS (ESI): Calcd for $(C_{23}H_{19}ClFNO_4)Na^+$: 450.0879. Found: 450.0888.

3.16.4. Synthesis of [9-(4-fluorobenzyl)-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene]-hydroxyacetic acids (8a–d). The title compounds were prepared from 6(7)-halo-[9-(4-fluorobenzyl)-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene]-hydroxyacetic acid ethyl ester (**31a–d**) according to Method C. The reaction was complete by refluxing for 10 h and the crude product was crystallized with diethyl ether to give the title compound.

3.17. [9-(4-Fluorobenzyl)-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene]-hydroxyacetic acid (8a)

Yield 67%; mp 146–149 °C; ^1H NMR ($CDCl_3$): (enol form:ketone form = 2.8:1) enol form 7.76 (1H, t, $J = 7.5$ Hz), 7.52 (1H, q, $J = 7.2$ Hz), 7.43 (1H, q, $J = 8$ Hz), 7.27 (1H, m), 7.14 (2H, t, $J = 8.4$ Hz), 7.00 (2H, t, $J = 9$ Hz), 5.84 (2H, s), 3.30 (2H, m), 3.22 (2H, m); ketone form δ 3.52 (2H, t, $J = 6$ Hz), 3.14 (2H, t, $J = 6$ Hz); ^{13}C ($CDCl_3$): δ 181.7, 164.1, 153.1, 142.2, 135.4, 129.8, 128.5, 124.7, 122.5, 122.2, 121.7, 121.4, 117.9, 116.0, 115.7, 111.4, 111.2, 48.2, 47.9, 26.6, 24.0, 20.8; MS (ESI): *m/z* 388.1 $[M+Na]^+$; Anal. ($C_{21}H_{16}FNO_4$) C, H, N.

3.17.1. [6-Fluoro-9-(4-fluorobenzyl)-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene]-hydroxyacetic acid (8b). Yield 62%; mp 164–165 °C; ^1H NMR ($CDCl_3$): (enol form:ketone form = 2.7:1) enol form δ 7.53–7.10 (7H, m), 5.95 (2H, s), 3.42 (2H, t, $J = 6$ Hz), 3.28 (2H, t, $J = 6$ Hz); ketone form δ 3.64 (2H, t, $J = 6.6$ Hz), 3.21 (2H, t, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 182.0, 163.9, 162.7, 160.7, 159.9, 156.8, 153.4, 138.7, 134.4, 133.3, 131.7, 128.5, 124.7, 119.2, 118.8, 118.1, 117.8, 116.0, 115.8, 112.7, 106.6, 48.4, 26.5, 23.9, 20.6; MS (ESI): *m/z* 382.2 $[M-H]^-$; Anal. ($C_{21}H_{15}F_2NO_4$) C, H, N.

3.17.2. [6-Chloro-9-(4-fluorobenzyl)-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene]-hydroxyacetic acid (8c). Yield 76%; mp 147–149 °C; ^1H NMR ($CDCl_3$): (enol form:ketone form = 2.4:1) enol form δ 7.90 (1H, m), 7.64–7.47 (2H, m), 7.33–7.16 (4H, m), 6.0 (2H, s), 3.47 (2H, m), 3.34 (2H, m); ketone form δ 3.67 (2H, t, $J = 6.6$ Hz), 3.26 (2H, t, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 182.1, 163.8, 153.5, 133.9, 130.0, 129.0, 128.5, 128.3, 127.4, 125.4, 121.6, 117.7, 116.1, 115.8, 112.6, 48.4, 26.5, 23.9, 20.6; MS (ESI): *m/z* 398 $[M-H]^-$; HRMS (ESI):

Calcd for $(C_{21}H_{15}ClFNO_4)Na^+$: 422.0566. Found: 422.0540.

3.17.3. [7-Chloro-9-(4-fluorobenzyl)-1-oxo-1,3,4,9-tetrahydrocarbazol-2-ylidene]-hydroxyacetic acid (8d). Yield 52%; mp 208–210 °C; ^{1}H NMR ($CDCl_3$): (enol form:ketone form = 2.8:1) enol form δ 7.63 (1H, t, J = 9 Hz), 7.36 (1H, d, J = 1 Hz), 7.19–7.17 (1H, m), 7.10–7.05 (2H, m), 7.01–6.98 (2H, m), 5.73 (2H, s), 3.24 (2H, m), 3.14 (2H, m); ketone form δ 7.32 (1H, d, J = 1 Hz), 3.46 (2H, t, J = 6.6 Hz), 3.06 (2H, t J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 163.9, 128.5, 128.3, 123.5, 122.9, 116.1, 115.8, 111.2, 48.3, 26.4, 20.6; MS (ESI): m/z 422.0 $[M+Na]^+$; Anal. ($C_{21}H_{15}ClFNO_4$) C, H, N.

3.17.4. 6-Fluoro-9-tosyl -1,2,3,9-tetrahydrocarbazol-4-one (18). To a solution of 6-fluoro-1,2,3,9-tetrahydrocarbazol-4-one (**12b**, 203 mg, 1 mmol) in 2.5 mL of anhydrous DMF were added tosyl chloride (229 mg, 1.2 mmol), triethylamine (250 μL, 1.8 mmol), and DMAP (9 mg, 0.07 mmol). The mixture was stirred at room temperature under argon for 8 h. After the reaction was complete, the mixture was poured into 40 mL saturated ammonium chloride solution and extracted with methylene chloride. The organic portion was dried over $MgSO_4$. After concentrated, the crude product was purified by flash chromatography (EtOAc/hexanes, 1/4) to give the title compound. Yield 59%; mp 159–160 °C; ^{1}H NMR ($CDCl_3$): δ 8.10 (1H, dd, J = 4.5, 9.0 Hz), 7.91 (1H, dd, J = 2.4, 9.0 Hz), 7.74 (2H, dt, J = 1.5, 8.4 Hz), 7.29–7.25 (2H, m), 7.07 (1H, td, J = 2.7, 9.0, 9.0 Hz), 3.31 (2H, t, J = 6.0 Hz), 2.55 (2H, t, J = 6.3 Hz), 2.20 (2H, p, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 194.8, 162, 152.3, 146.2, 135.4, 130.5, 126.8, 115.2 (2), 113.5 (2), 107.8, 38.1, 24.9, 23.5, 22.1; HRMS (EI): Calcd for $(C_{19}H_{16}FO_3S)^+$: 357.0835. Found: 357.0845.

3.18. *N*-Boc protected 6-chloro-1,2,3,9-tetrahydrocarbazol-4-one (19)

To a solution of 6-chloro-1,2,3,9-tetrahydrocarbazol-4-one (**12c**, 219.5 mg, 1 mmol) in 2.5 mL anhydrous DMF were added $(Boc)_2O$ (262 mg, 1.2 mmol), triethyl amine (250 μL, 1.8 mmol), and DMAP (15 mg, 0.125 mmol). The mixture was stirred at room temperature overnight. After the reaction was complete, the mixture was diluted with 20 mL ethyl acetate and poured into 20 mL saturated sodium chloride solution. The organic portion was washed with saturated NH_4Cl and NaCl, and dried over $MgSO_4$. After removing the solvent, the crude product was recrystallized with EtOAc/hexanes to give 300 mg white fine needle crystals as the title compound. Yield 94%; mp 138–140 °C; ^{1}H NMR ($CDCl_3$): δ 8.20 (1H, d, J = 1.5 Hz), 7.93 (1H, d, J = 9.0 Hz), 7.20 (2H, m), 3.23 (2H, t, J = 6 Hz), 2.51 (2H, t, J = 6 Hz), 2.16 (2H, p, J = 6 Hz), 1.60 (9H, s); ^{13}C NMR ($CDCl_3$): δ 130.4, 125.2, 121.4, 116.4, 110.0, 86.1, 38.1, 28.5, 26.3, 23.6; MS (ESI): m/z 342 $[M+Na]^+$.

3.19. 6-Fluoro-9-methyl-1,2,3,9-tetrahydrocarbazol-4-one (20)

The title compound was prepared from 6-fluoro-1,2,3,9-tetrahydrocarbazol-4-one (**12b**) and methyl iodide according to Method D. The crude product was recrystallized with diethyl ether to give the final product as white fine needles. Yield 92%; mp 158–160 °C; ^{1}H NMR ($CDCl_3$): δ 7.91 (1H, dd, J = 2.7, 9 Hz), 7.20 (1H, dd, J = 4.5, 9 Hz), 6.99 (1H, dt, J = 2.7, 9 Hz), 3.7 (3H, s), 2.93 (2H, t, J = 6 Hz), 2.56 (2H, t, J = 6 Hz), 2.25 (2H, p, J = 6 Hz); ^{13}C NMR ($CDCl_3$): δ 167.7, 111.3, 111.0, 110.0, 109.9, 107.6, 107.3, 38.1, 30.5, 23.6, 22.7; MS (ESI): m/z 218 $[M+H]^+$, 240 $[M+Na]^+$.

3.20. (6-Fluoro-9-methyl-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene)-hydroxyacetic acid ethyl ester (21)

The title compound was prepared from 6-fluoro-9-methyl-1,2,3,9-tetrahydrocarbazol-4-one (**20**) according to Method E. Yield 70%; mp 161–162 °C; ^{1}H NMR ($CDCl_3$): δ 7.78 (1H, dd, J = 3, 9 Hz), 7.18 (1H, m), 6.97 (1H, dt, J = 3, 9 Hz), 4.36 (2H, q, J = 6 Hz), 3.66 (3H, s), 3.18 (2H, t, J = 6 Hz), 2.85 (2H, t, J = 6 Hz), 1.40 (3H, t, J = 6 Hz); ^{13}C NMR ($CDCl_3$): δ 189, 162, 160, 158, 157, 153, 135, 126, 113, 112 (2), 111 (m), 105, 60, 31, 22, 20, 15; MS (ESI): m/z 340.1 $[M+Na]^+$; Anal. ($C_{17}H_{16}FNO_4$) C, H, N.

3.21. (6-Fluoro-9-methyl-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene)-hydroxyacetic acid (22)

The title compound was prepared from (6-fluoro-9-methyl-4-oxo-1,2,4,9-tetrahydrocarbazol-3-ylidene)-hydroxyacetic acid ethyl ester (**21**) according to Method C. After cooling down, the mixture was diluted with water and extracted with ethyl acetate. The organic portion was concentrated and purified by flash chromatography to give a 130 mg yellow solid as the title compound. Yield 68%; mp 205–207 °C; ^{1}H NMR (DMSO-d_6): (enol form:ketone form = 3.5:1) enol form δ 8.05–7.96 (2H, m), 7.52 (1H, dt, J = 2.4, 9 Hz), 4.13 (3H, s), 3.42 (4H, m); ketone form δ 4.82 (1H, dd, J = 5, 12 Hz), 2.80–2.68 (2H, m); ^{13}C NMR (DMSO-d_6): δ 188.5, 165.0, 163.2, 158.9, 155.6, 135.3, 113.0, 111.4, 111.1, 108.7, 55.4, 45.9, 31.1, 23.2, 21.5; MS (ESI): m/z 301.2 $[M+Na]^+$; Anal. ($C_{15}H_{12}FNO_4$) C, H, N.

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