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Access to Indole- And Pyrrole-Fused Diketopiperazines via Tandem Ugi-4CR/Intramolecular Cyclization and Its Regioselective Ring-Opening by Intermolecular Transamidation

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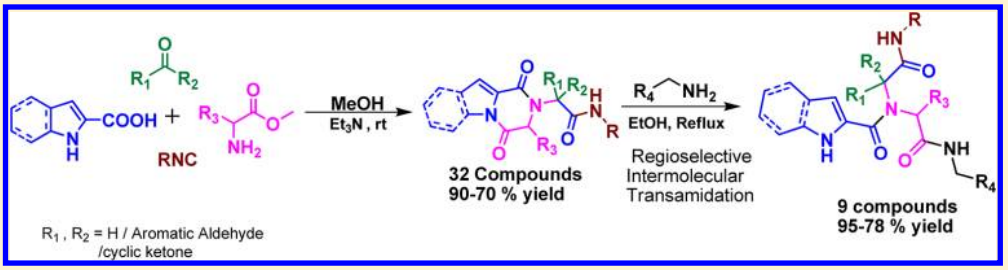
Supporting Information



ABSTRACT: An efficient approach for the synthesis of indole- and pyrrole-fused diketopiperazines has been developed. This protocol involves the Ugi four-component reaction (U-4CR) followed by an intramolecular cyclization of the Ugi products at room temperature to afford the desired products in good to excellent yields. In addition, it is interesting to report the subsequent regioselective ring-opening of diketopiperazine unit occurring via an intermolecular transamidation reaction under mild condition, resulting in the formation of highly functionalized indole-2-carboxamides and pyrrole-2-carboxamides.

INTRODUCTION

Multicomponent reactions[1] (MCRs, especially isocyanide based multicomponent reactions I-MCRs[2]) have attracted considerable attention from the synthetic organic chemistry community owing to their utility in rapid construction of structurally diverse, complex, and biologically relevant molecules from simple precursors. Moreover, these MCRs are highly flexible, often (chemo and/or regio) selective, convergent, operationally simple, and atom-efficient, not only providing molecular diversity and complexity in resulting molecules but also capable of providing scaffolds with appropriate functionalities suitable for further transformations.[3]

Recently, IMCR coupled with postchemical transformations such as condensation,[4] ring-closure metathesis,[5] cycloaddition,[6] macrolactonization,[7] and so forth in preorganized structures has emerged as a promising strategy for the creation of highly diverse heterocyclic scaffolds.[8]

Among the various bioactive heterocyclic molecules, Diketopiperazines (DKPs) constitute a unique class of compounds as a "privileged" scaffold present in many natural products and are responsible for a wide range of biological activities[9,23b] as antitumor,[10] antiviral,[11] antifungal,[12] antibacterial,[13] and antihyperglycemic agents,[14] GABA-ergic,[15] serotonergic 5-HT1A[16] and oxytocin receptors,[17] and so forth. Several natural products such as Gliotoxin,[18] Glionitrin B,[19] Spirotryprostatin A,[20] Demethoxyfumitremorgine C,[21] WIN 64821, and WIN 64745[22] contain heterofused DKP fragments (Figure 1).

Due to the immense significance of these DKPs, cost-effective and diversity-oriented synthesis is warranted. Although several synthetic protocols for the preparation of these DKPs are available in the literature,[23] either they are not cost-effective or they lack the feature of diversity within the same molecular framework. The structural diversity can be generated by the use of MCRs . In this context, the Ugi reaction had been extensively utilized for the construction of 2,5 DKPs[24] as well as heterofused DKPs.[25−28]

In the recent past, Kaim et al. reported the synthesis of fused tricyclic 2,5 DKP by Ugi reaction followed by Pictet-Spengler,[25] Hulme et al. reported the tetrazole-fused ketopiperazine through Ugi reaction followed by intramolecular cyclization,[26] and Krasavin and co-worker reported 2,3-dihydropyrazino[1,2-a]indole-1,4-diones via a one-pot, two-step procedure involving Ugi reaction followed by microwave-assisted cyclization.[27] Very recently, Orru et al. reported the elegant synthesis of fused-DKPs by a tandem biocatalysis/Ugi/Pictet−Spengler-type cyclization sequence.[28] Although the above procedures for preparation of monocyclic as well as polycyclic DKPs present an efficient approach to expand the structural diversity, they still suffer from the limitation of multistep synthesis, prolonged time

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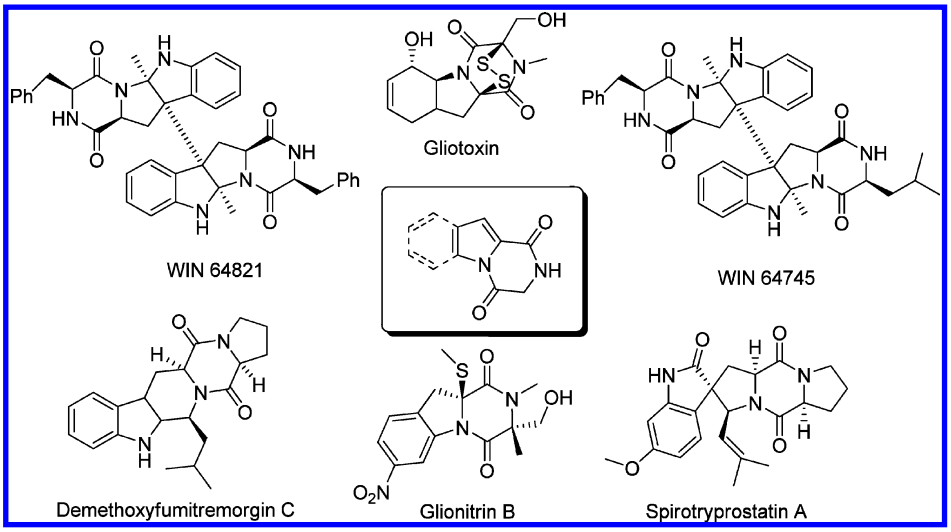
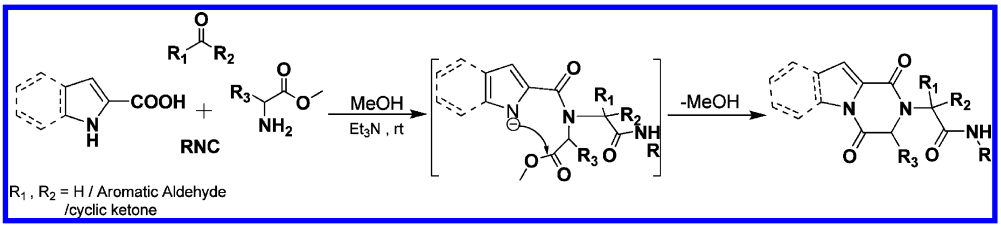
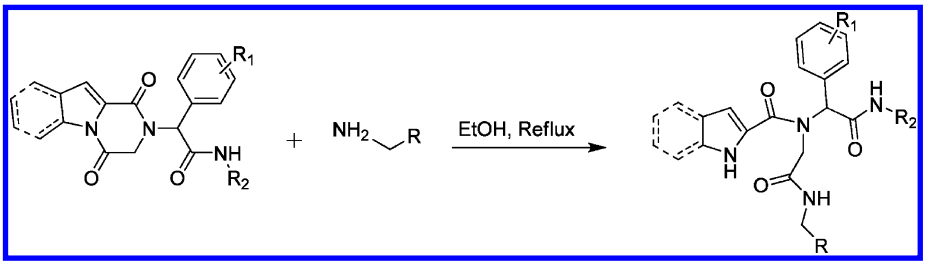


Figure 1. Example of some biologically active natural products containing "fused- DKP" scaffolds.

Scheme 1. Synthesis of Indole- and Pyrrole-Fused DKPs



Scheme 2. Synthesis of Highly Diverse *1H*-Indole-2-carboxamides and *1H*-Pyrrole-2-carboxamides



period, stringent reaction conditions including refluxing or microwave conditions, and low yield. Clearly, there is an urgent need to develop an alternative procedure for the simple and rapid synthesis of heteroaryl-fused DKPs.

As a part of our continuing interest in the development of a novel strategy for synthesis of biologically important *N*-heterocyclic scaffolds[29] and encouraged by skeletal diversity provided by IMCRs,[30] herein we report a mild and efficient protocol for the synthesis of heteroaryl-fused DKPs via Ugi-4CR followed by intramolecular cyclization in one-pot operation (Scheme 1).

Moreover, we also report the further transformation of these fused-DKPs to densely functionalized *1H*-indole-2-carboxamides and *1H*-pyrrole-2-carboxamides resulting from regioselective ring-opening of DKPs unit via intermolecular transamidation with various primary amines under mild reaction conditions (Scheme 2). To the best of our knowledge, this is the first example of a regioselectivity transamidation reaction of heterofused diketopiperazines under mild conditions.

RESULTS AND DISCUSSION

Initially, glycine ester (**1**), 4-chlorobenzaldehyde (**2**), *tert*-butyl isocyanide (**3**), and *1H*-indole-2-carboxylic acid (**4**) in equimolar amounts were chosen as a model substrate to establish the feasibility of the strategy and to optimize the reaction conditions including bases and solvents (Table 1). It was found that when the reaction was carried out without any base only normal Ugi product (**5**) was obtained in low yield of 45% even after 24 h (Table 1, entry 1). Then, we carried out this model reaction by employing a variety of bases (Table 1, entries 2−6). In the presence of base, the desired cyclized product (**6a**) was obtained. We reasoned that addition of base not only neutralized the glycine methyl ester hydrochloride, but also accelerated the cyclization step. While examining the effect of bases, 1.1 mmol of Et_3N was found to be effective as base (Table 1, entry 3); however, DIPEA, KOH, and K_2CO_3 gave inferior results (Table 1, entries 2, 5, and 6). Next, we carried out reaction with 2 mmol of Et_3N; the reaction was very sluggish and furnished a mixture of products with the formation of (**6a**) in 60% isolated yield (Table 1, entry 10). To see the effect of solvents, we examined our reaction in different solvent

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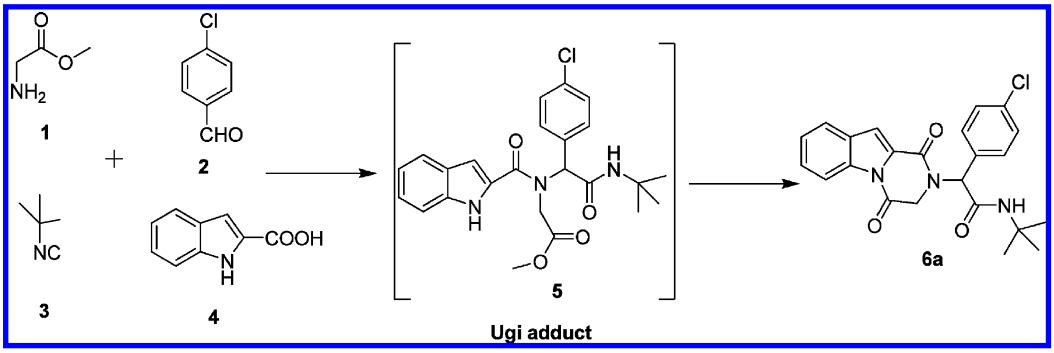
Table 1. Optimization of reaction conditions for the synthesis of indole-fused DKPs[a]



entry	base (mmol)	solvent	time	yield[b] of **6a**
1	-	MeOH	24 h	Nr[c]
2	DIPEA (1.1)	MeOH	60 min	82%
3	Et_3N (1.1)	MeOH	50 min	90%
4	DBU(1.1)	MeOH	24 h	20%
5	KOH (1.1)	MeOH	7 h	80%
6	K_2CO_3(1.1)	MeOH	3 h	84%
7	Et_3N (1.1)	EtOH	2 h	80%
8	Et_3N (1.1)	THF	24 h	30%
9	Et_3N (1.1)	CH_2Cl_2	2 h	70%
10	Et_3N (2)	MeOH	50 min	60%

[a]Reaction conditions: Glycine methyl ester as HCl salt (1 mmol), 4-chlorobenzaldehyde (1 mmol), *tert*-butyl isocyanide (1 mmol), and *1H*-indole-2-carboxylic acid (1 mmol) in 3 mL solvent at room temperature . [b]Isolated yield. [c]Nr uncyclized Ugi product (**5**) was obtained .

systems as depicted in (Table 1). When the reaction solvent was changed from MeOH to EtOH and CH_2Cl_2, a significant reduction in isolated product yields of 80% and 70%, respectively, were observed (Table 1, entries 7 and 9). This suggests that, among the solvent systems examined, MeOH is the favored solvent system for this reaction.

With the optimized conditions established above for the synthesis of (**6a**), we decided to probe the generality of the reaction to construct indole-fused DKP derivatives. The reaction appears to be versatile, and 27 compounds **6(a−z)** and **6aa** were synthesized in 70−90% yield (Table 2, entries 1−27) by treating aldehydes, amino acid esters as amine input, two different isocyanides, and *1H*-indole-2-carboxylic acid.

The protocol was effective with aromatic aldehydes having either electron-withdrawing or electron donating groups. It is noteworthy that the reactions of halo-substituted benzaldehydes proceeded in shorter time. In the case of ortho-substituted aldehydes, the reaction time was significantly longer, which is likely due to its steric properties (Table 2, entries 19 and 20). The furan-2-carbaldehyde, as a hetero-aromatic aldehyde, was used in this reaction and gave moderate yield (Table 2, entry 14). We have also examined the alicyclic ketones to survey the scope and generality of our methodology; the reaction of alicyclic ketones with *1H*-indole-2-carboxylic acid, glycine methyl ester, and *tert*-butyl isocyanide went smoothly, and products were obtained in good yields (Table 2, entries 21 and 22).

The structure of the products **6(a−z)** and **6aa** were deduced from their IR, HRMS, ^{1}H NMR, and ^{13}C NMR spectra. Furthermore, the disappearance of two characteristic peaks, that is, the singlet of three protons of -$OCOCH_3$ of amino ester (around δ 3.8 ppm) and singlet of -NH proton of indole (around δ 9.7 ppm) in ^{1}H NMR, confirmed the formation of cyclized product (see the Experimental Section).

With the success of our strategy, we wish to expand the scope of the reaction by employing the *1H*-pyrrole-2-carboxylic acid instead of *1H*-indole-2-carboxylic acid under optimized reaction conditions as described earlier, which afforded the required pyrrole-fused DKPs in 75−82% yields, and results were summarized in Table 3.

Additionally, to examine the effect of a substituent on the heterocyclic scaffold on the reaction sequence we synthesized 3-iodo-*1H*-indole-2-carboxylic acid and 3,4,5-tribromo-*1H*-pyrrole-2-carboxylic acid by following the method reported in the literature[31] and applied our protocol; in the case of 3-iodo-*1H*-indole-2-carboxylic acid, the reaction went smoothly, resulting in product **6aa** (Table 2, entry-27). Moreover, we believe that this iodo substitution can be further utilized for various palladium and copper catalyzed coupling reactions as Suzuki-miyuara, Heck, Sonogashira reactions. However, with 3,4,5-tribromo-*1H*-pyrrole-2-carboxylic acid reaction failed to yield desired product.

Next, to further explore the synthetic potential of these highly diverse DKPs we treated fused DKPs with different amines leading to the formation of densely functionalized *1H*-indole-2-carboxamides and *1H*-pyrrole-2-carboxamides via intermolecular transamidation. It is noteworthy that carboxamide is omnipresent in numerous biological and synthetic polymers, as well as being extensively utilized for the preparation of pharmaceuticals and agrochemicals, and in synthetic organic chemistry.[32] Furthermore, *1H*-indole-2-carboxamide and *1H*-pyrrole-2-carboxamide templates are present in natural products,[33] as well as in numerous biologically active compounds associated with a wide range of biological activity as fibrinogen receptor antagonists,[34] glycogen phosphorylase inhibitors,[35] inhibitors of human LDL copper-induced peroxidation,[36] potent Bcl-2/Bcl-xL inhibitors,[38] and allosteric modulators of the Cannabinoid CB1 receptor,[40] as well as anti-HIV-1 activity[37] and antiviral activity against

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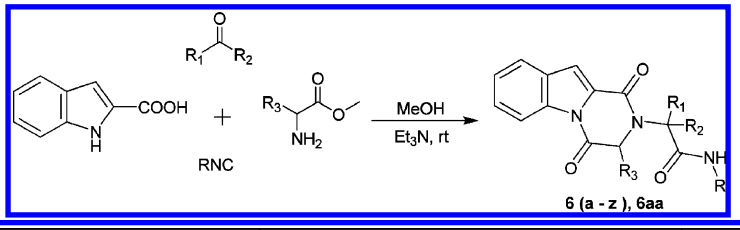
Table 2. Synthesis of Indole-Fused DKPs by Utilizing Ugi-4CR



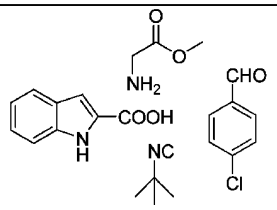
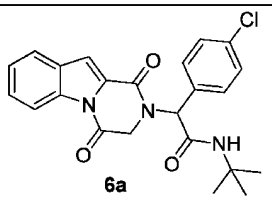
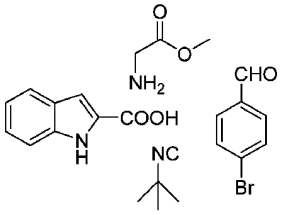
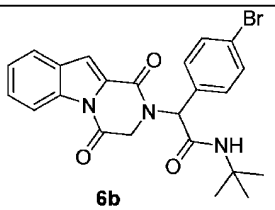
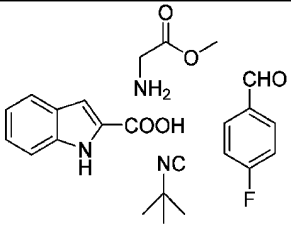
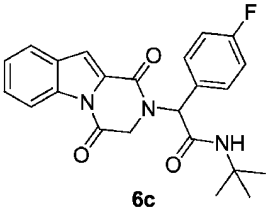
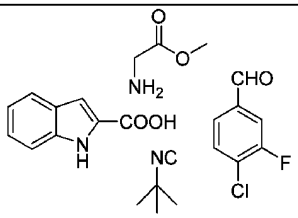
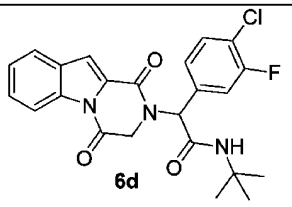
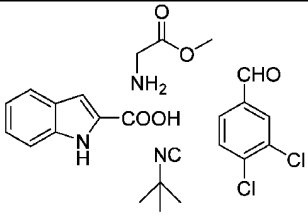
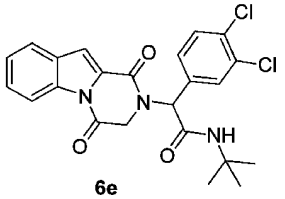
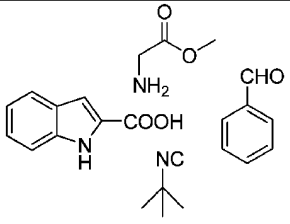
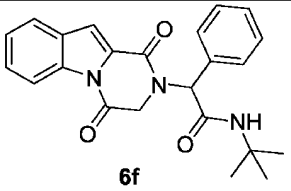
Entry	Substrate	Product **6**	Time (min)	Product (%yield)[b]
1		 **6a**	50	90
2		 **6b**	75	86
3		 **6c**	90	82
4		 **6d**	80	82
5		 **6e**	75	84
6		 **6f**	95	86

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Table 2. continued

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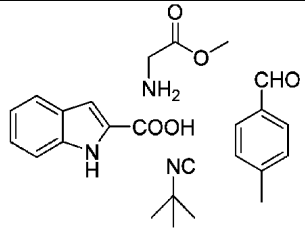
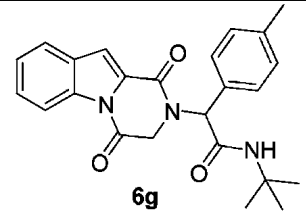
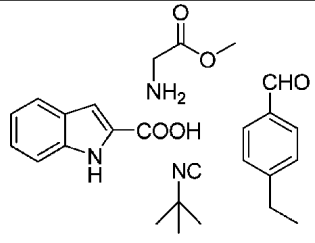
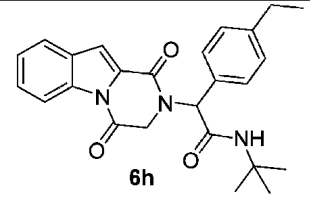
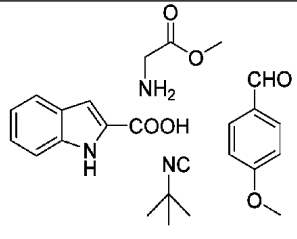
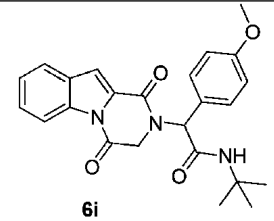
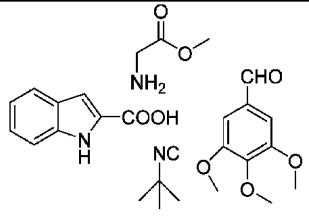
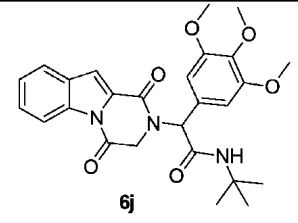
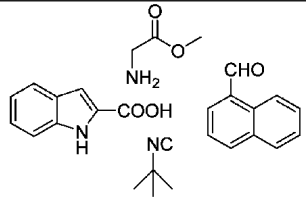
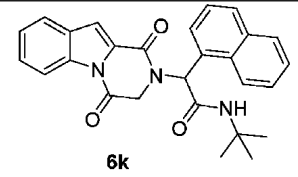
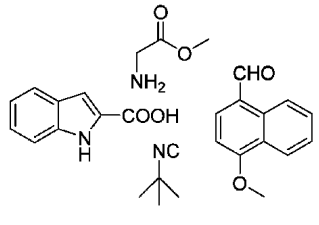
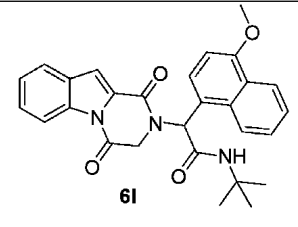
7		 **6g**	120	80
8		 **6h**	120	76
9		 **6i**	100	79
10		 **6j**	120	82
11		 **6k**	90	84
12		 **6l**	110	78

dx.doi.org/10.1021/jo3018704 | *J. Org. Chem.* 2012, 77, 10211−10227

Table 2. continued

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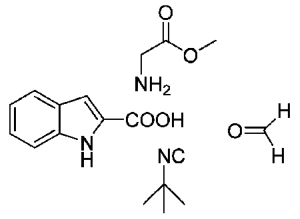
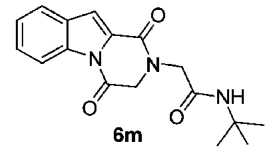
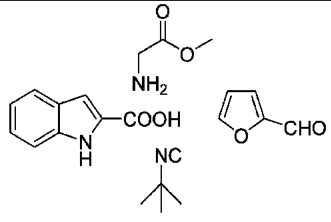
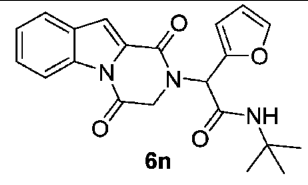
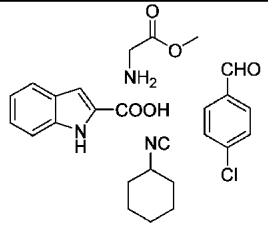
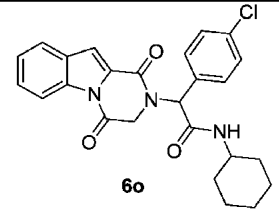
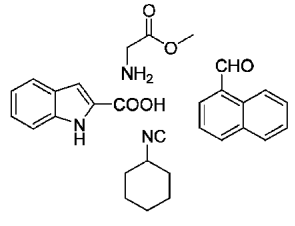
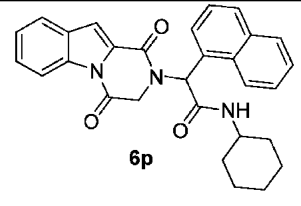
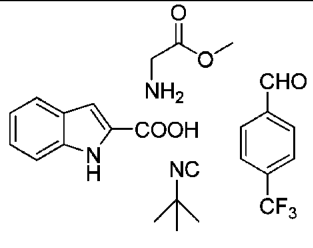
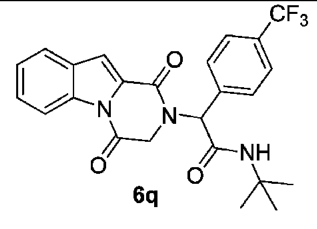
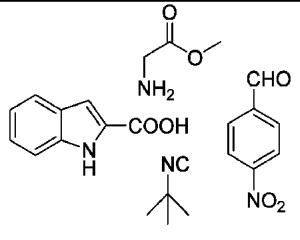
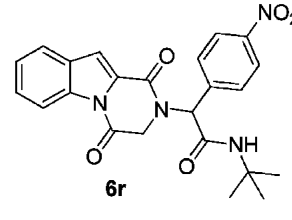
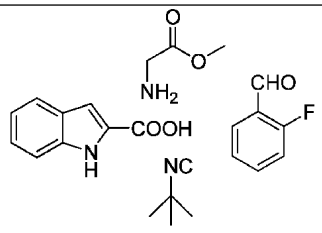
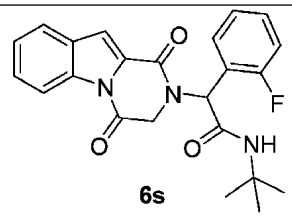
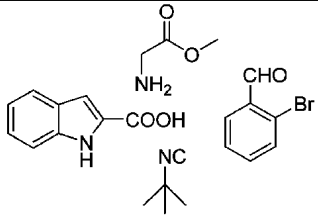
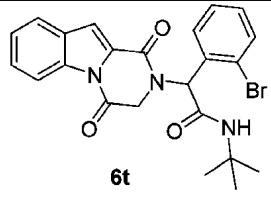
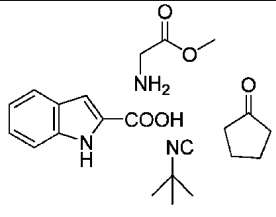
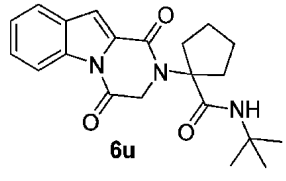
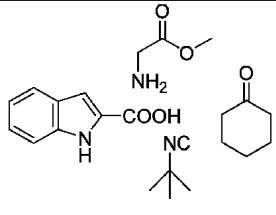
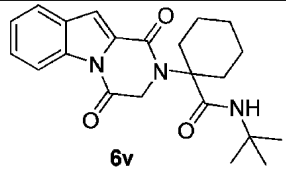
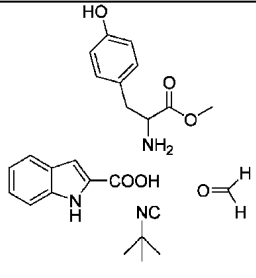
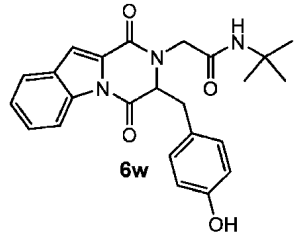
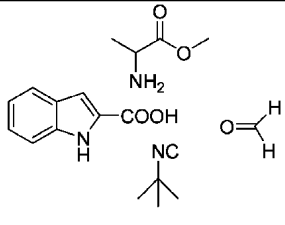
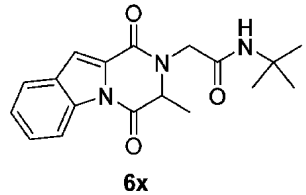
13		 **6m**	190	70
14		 **6n**	140	70
15		 **6o**	65	86
16		 **6p**	110	80
17		 **6q**	90	83
18		 **6r**	120	82

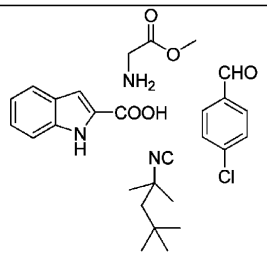
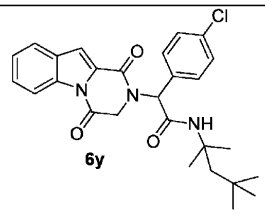
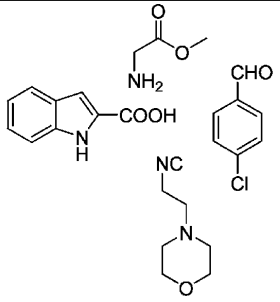
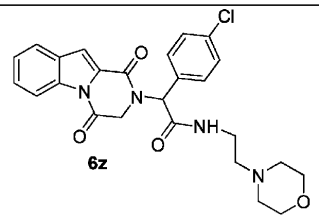
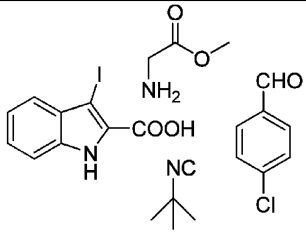
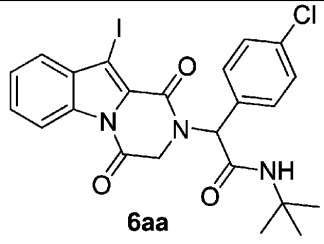
dx.doi.org/10.1021/jo3018704 | *J. Org. Chem.* 2012, 77, 10211−10227

Table 2. continued

Entry	Substrate	Product **6**	Time (min)	Product (%yield)[b]
19		 **6s**	230	78
20		 **6t**	210	81
21		 **6u**	190	78
22		 **6v**	150	80
23		 **6w**	240	70
24		 **6x**	210	75

dx.doi.org/10.1021/jo3018704 | *J. Org. Chem.* 2012, 77, 10211−10227

Table 2. continued

Entry	Substrate	Product **6**	Time (min)	Product (%yield)[b]
25		 **6y**	70	86
26		 **6z**	150	70
27		 **6aa**	60	88

[a]Reaction conditions: Amino acid methyl ester as HCl salt (1 mmol), Et_3N (1.1 mmol), corresponding aldehydes (1 mmol), isocyanide (1 mmol), and *1H*-indole-2-carboxylic acid (1 mmol) in 3 mL methanol at room temperature. [b]Isolated yield.

virulent neurotropic alphaviruses,[39] thus remaining target structures of interest to synthetic chemists.

For the synthesis of these *1H*-indole-2-carboxamides and *1H*-pyrrole-2-carboxamides, initially we treated the indole-fused DKP (**6a**) and benzyl amine in ethanol under reflux. The progress of the reaction was monitored by TLC, and after 4 h, we observed the complete disappearance of (**6a**) followed by the emergence of a new spot on TLC (Scheme 3).

The synthesized product was well-characterized as **9a** by their IR, HRMS, ^1H NMR, and ^{13}C NMR spectra. The molecular formula of product **9a** was suggested to be $C_{30}H_{31}ClN_4O_3$ by the HRMS peak $(M + H)^+$ at 531.2153. Moreover, the appearance of a characteristic sharp singlet of −NH proton of indole at around δ 9.58 ppm further confirms the formation of **9a**.

It is also interesting to note that regioselectivity was observed during the intermolecular transamidation reaction on **6a**. Remarkably, apart from **9a**, two other structures **10** and **11** could also form; however, **9a** was formed exclusively. This regioselectivity may be due to the higher electrophilicity of carbonyl carbon of amide (marked with *) as compared to the other two in **6a** (Scheme 4).

Furthermore, the series of highly substituted indole 2-carboxamides and pyrrole 2-carboxamides **9(a−h)** were easily obtained in good to excellent yield by treating various amines with fused DKPs in ethanol at reflux (Table-4). Thus, the above transformation provides a novel, mild, and efficient approach for the synthesis of biologically relevant, densely functionalized indole 2-carboxamides.

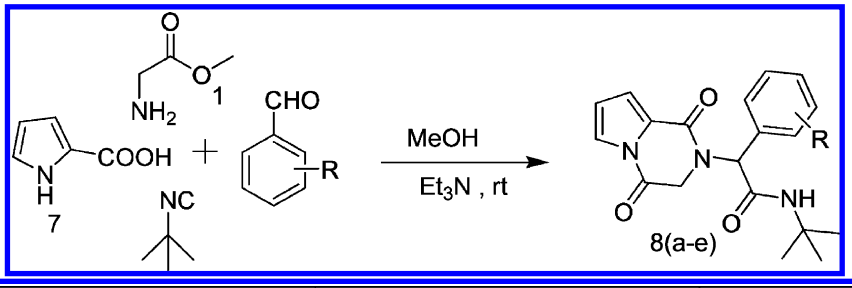
CONCLUSION

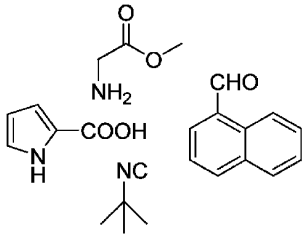
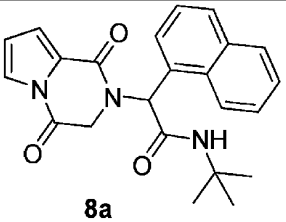
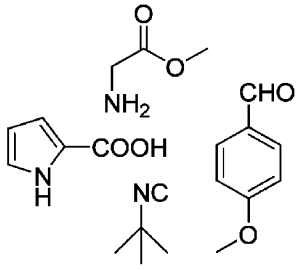
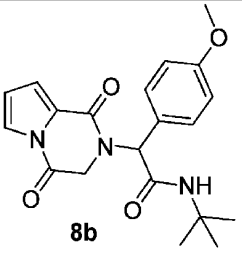
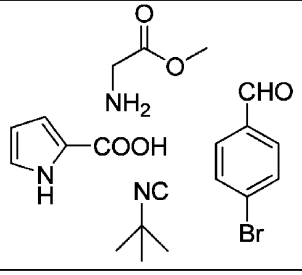
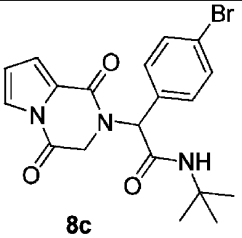
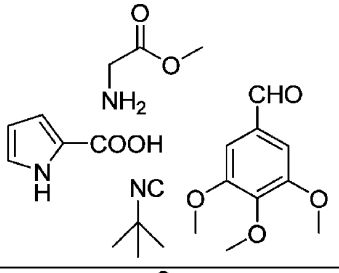
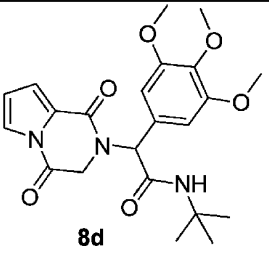
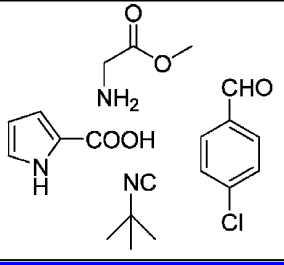
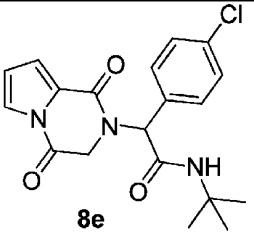
In summary, we have developed the most concise, mild, and efficient strategy to construct the highly functionalized indole- and pyrrole-fused DKPs via tandem Ugi-4CR/intramolecular cyclization in good to excellent yields. The operational simplicity, mild reaction condition, and high efficiency nature make this synthetic strategy highly attractive and promising for the construction of heteroaryl-fused DKPs, which are of considerable interest as potential biologically active compounds or pharmaceuticals. In addition, we have also described the mild protocol for the synthesis of pharmacologically active highly diverse *1H*-indole-2-carboxamides and *1H*-pyrrole-2-carboxamides, which involves the reigioselective intermolecular transamidation under mild reaction condition. Biological screening of synthesized compounds are currently under progress in our laboratory and will be reported in due course.

EXPERIMENTAL SECTION

General Procedure for the Preparation of Compound 5. To a stirred solution of glycine methyl ester hydrochloride (1 mmol) in

Table 3. Synthesis of Pyrrole-Fused DKPs by Utilizing Ugi-4CR



Entry	Substrate	Product	Time (min)	Product (%yield)[b]
1		 **8a**	150	80
2		 **8b**	120	75
3		 **8c**	100	80
4		 **8d**	130	78
5		 **8e**	90	82

[a]Reaction conditions: Glycine methyl ester as HCl salt (1 mmol), Et_3N (1.1 mmol), benzaldehydes (1 mmol), isocyanide (1 mmol), and *1H*-pyrrole-2-carboxylic acid (1 mmol) in 3 mL methanol at room temperature. [b]Isolated yield.

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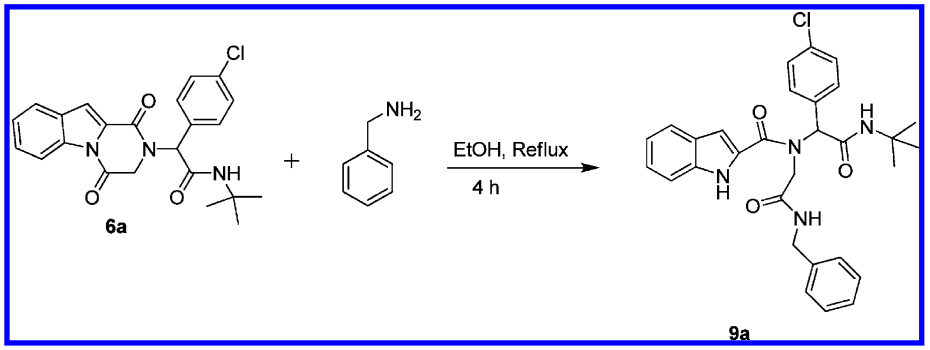
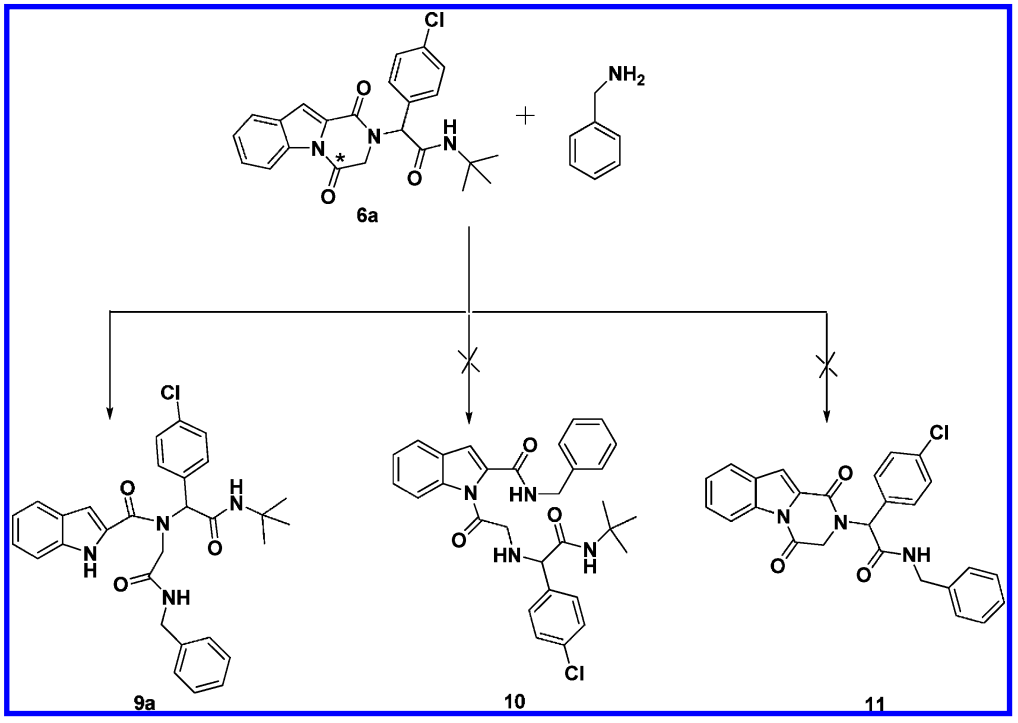
Scheme 3. Synthesis of Indole 2-Carboxamide Derivative by Ring-Opening of DKP Unit via Intermolecular Transamidation



Scheme 4. Three Possibilities for the Formation of Products (9−11) by Regioselective Intermolecular Transamidation



methanol (3 mL) were added successively 4-chlorobenzaldehyde (1 mmol), *1H*-indole-2-carboxylic acid **4** (1 mmol), and *tert*-butyl isocyanide (1 mmol). The mixture was stirred at room temperature for 24 h. After completion of the reaction, solvent was evaporated at reduced pressure and purified through column chromatography (eluent: $CHCl_3$/MeOH) using 100−200 mesh silica gel to afford the desired product.

*[tert-Butylcarbamoyl-(4-chloro-phenyl)-methyl]-(1H-indole-2-carbonyl)-amino]-acetic Acid Methyl Ester (**5**).* White solid; Mp 180−181 °C; Yield 45% (205 mg); IR (KBr) ν_{max}: 3433, 3015, 1729, 1661 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.69 (s, 1H), 8.64 (s, 1H), 7.69 (d, 1H, *J* = 7.3 Hz), 7.59 (d, 1H, *J* = 7.7 Hz), 7.45−7.29 (m, 4H), 7.25−7.20 (m, 1H), 7.15 (t, 1H, *J* = 7.4 Hz), 7.04 (s, 1H), 6.39 (s, 1H), 4.09 (d, 1H, *J* = 16.2 Hz), 3.74 (s, 3H), 3.35 (d, 1H, *J* = 16.2 Hz), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.7, 168.3, 165.3, 136.1, 135.0, 133.7, 130.9, 130.4, 128.0, 127.8, 126.4, 125.2, 122.7, 120.6, 111.7, 106.9, 67.6, 52.6, 52.2, 46.9, 28.5; HRMS (ESI TOF (+)) calcd for $[C_{24}H_{26}ClN_3O_4 + H^+]$ 456.1685; found 456.1689.

General Procedure for the Preparation of Compound 6(a-w). To a solution of amino ester hydrochloride (1 mmol) in methanol (3 mL) was added triethylamine (1.1 mmol), and the resulting solution was stirred at room temperature for 10 min. To the stirred solution were successively added corresponding aldehdye (1 mmol), *1H*-indole-2-carboxylic acid **4** (1 mmol), and isocyanide (1 mmol). The mixture was stirred at room temperature for the specified period of time as indicated in Table 2. The progress of the reaction was monitored by TLC. After completion of the reaction, solvent was evaporated at reduced pressure and purified through column chromatography (eluent: $CHCl_3$/MeOH) using 100−200 mesh silica gel to afford the desired product **6**(**a**-**z**) and **6aa**.

*N-tert-Butyl-2-(4-chlorophenyl)-2-(1,4-dioxo-3,4-dihydro-pyrazino[1,2-a]indol-2(1H)-yl) acetamide (**6a**).* White solid; Yield 90% (381 mg); Mp: 238−239 °C; IR (KBr) ν_{max}: 3423, 3338, 1716, 1640, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.41 (d, 1H, *J* = 8.0 Hz), 7.71 (d, 1H, *J* = 7.7 Hz), 7.52−7.47 (m, 2H), 7.43−7.36 (m, 5H), 6.33 (s, 1H), 5.69 (s, 1H), 5.04 (d, 1H, *J* = 19.4 Hz), 3.91 (d, 1H, *J* = 19.4 Hz), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.6, 161.7, 156.7, 135.4, 134.7, 132.0, 130.9, 129.5, 128.9, 128.1, 128.0, 125.3, 122.4, 116.5, 114.9, 58.5, 52.1, 49.0, 28.6; HRMS (ESI TOF (+)) calcd for $[C_{23}H_{22}ClN_3O_3 + H^+]$ 424.1422; found 424.1423.

*2-(4-Bromophenyl)-N-tert-butyl-2-(1,4-dioxo-3,4-dihydro-pyrazino[1,2-a]indol-2(1H)-yl) acetamide (**6b**).* White solid; Yield 86% (402 mg); Mp: 235−236 °C; IR (KBr) ν_{max}: 3423, 3304, 1722, 1626, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.41 (d, 1H, *J* = 7.9 Hz), 7.71 (d, 1H, *J* = 7.6 Hz), 7.59 (d, 2H, *J* = 7.7 Hz), 7.49 (s, 2H), 7.41−7.30 (m, 3H), 6.31 (s, 1H), 5.67 (s, 1H), 5.04 (d, 1H, *J* = 19.3 Hz), 3.91 (d, 1H, *J* = 19.5 Hz), 1.38 (s, 9H); ^{13}C NMR (50 MHz, DMSO-d_6) δ = 167.7, 162.4, 155.8, 134.3, 133.9, 131.7, 131.3, 129.0, 128.7, 127.5, 125.0, 122.6, 121.6, 115.6, 113.2, 58.0, 50.7, 49.5, 28.3;

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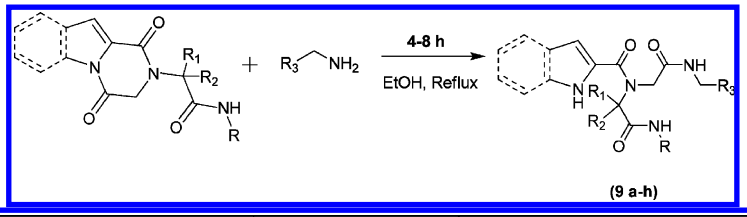
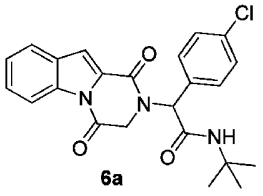
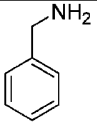
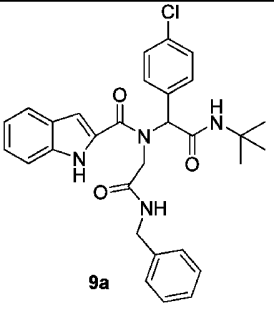
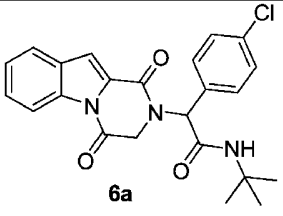
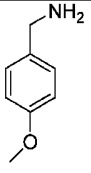
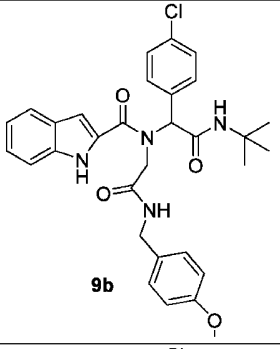
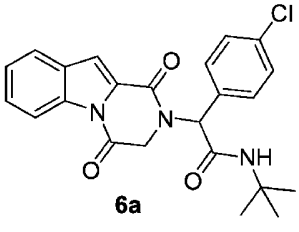
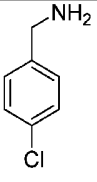
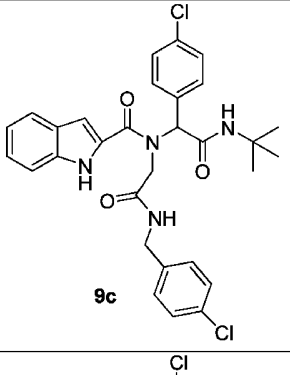
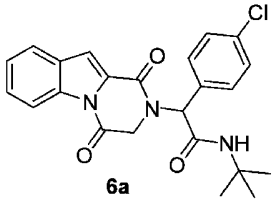
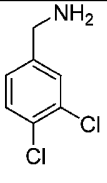
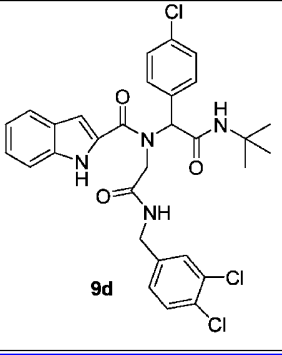
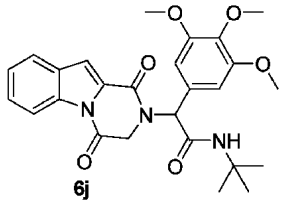
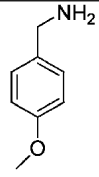
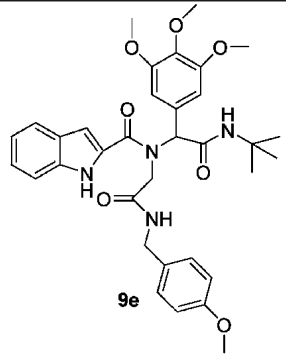
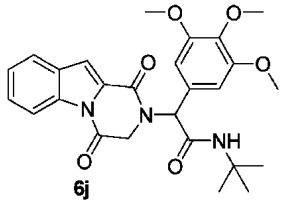
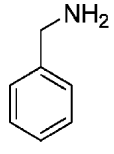
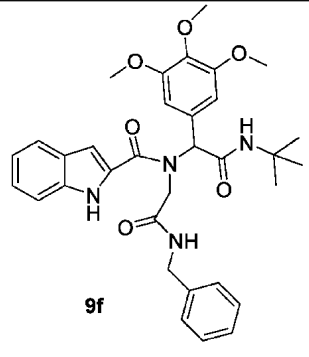
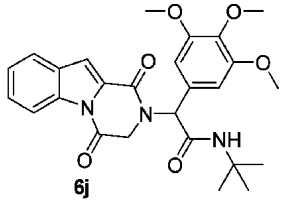
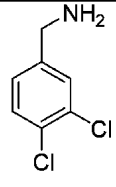
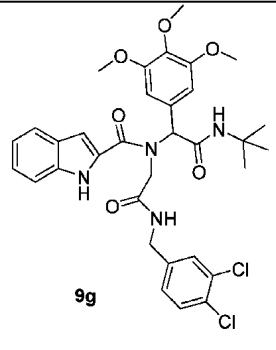
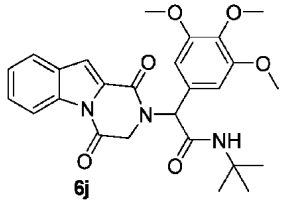
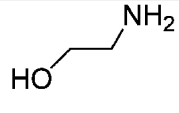
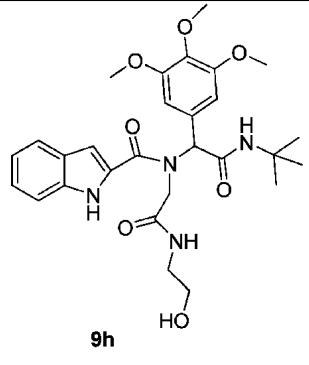
Table 4. . Synthesis of *1H*-Indole-2-Carboxamide and *1H*-Pyrrole-2-Carboxamide Derivatives via Regioselective Intermolecular Transamidation



Entry	Substrate	Amine	Product	Product (%yield)[b]
1	 **6a**		 **9a**	90
2	 **6a**		 **9b**	84
3	 **6a**		 **9c**	95
4	 **6a**		 **9d**	86

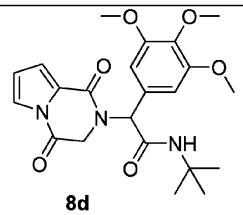
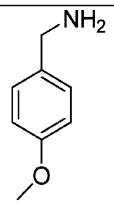
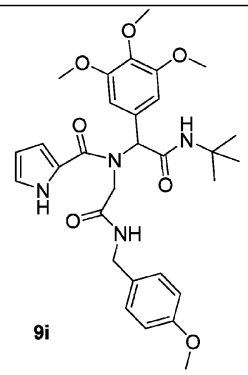
dx.doi.org/10.1021/jo3018704 | *J. Org. Chem.* 2012, 77, 10211−10227

Table 4. continued

Entry	Substrate	Amine	Product	Product (%yield)[b]
5	 6j		 9e	82
6	 6j		 9f	90
7	 6j		 9g	78
8	 6j		 9h	78

dx.doi.org/10.1021/jo3018704 | J. Org. Chem. 2012, 77, 10211−10227

Table 4. continued

Entry	Substrate	Amine	Product	Product (%yield)[b]
9	 8d		 9i	80

[a]Reaction conditions: Fused diketopiperazine (1 mmol), amine (1.2 mmol) in 5 mL ethanol at reflux. [b]Isolated yield.

HRMS (ESI TOF (+)) calcd for $[C_{23}H_{22}BrN_3O_3 + H^+]$ 468.0917; found 468.0918.

*N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(4-fluorophenyl) acetamide (**6c**).* White solid; Yield 82% (334 mg); Mp: 216−218 °C; IR (KBr) ν_{max}: 3496, 3301, 1722, 1627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.34 (d, 1H, J = 8.1 Hz), 7.64 (d, 1H, J = 7.6 Hz), 7.44−7.39 (m, 2H), 7.38−7.29 (m, 3H), 7.09 (t, 2H, J = 8.4 Hz), 6.27 (s, 1H), 5.62 (s, 1H), 4.97 (d, 1H, J = 19.5 Hz), 3.84 (d, 1H, J = 19.5 Hz), 1.31 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.9, 161.8, 156.6, 134.6, 131.5, 131.3, 129.4, 128.9, 128.2, 127.9, 125.3, 122.3, 116.5, 116.4, 116.1, 114.8, 58.4, 52.0, 49.0, 28.6; HRMS (ESI TOF (+)) calcd for $[C_{23}H_{22}FN_3O_3 + H^+]$ 408.1718; found 408.1718.

*N-tert-Butyl-2-(4-chloro-3-fluorophenyl)-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2 (1H)-yl)acetamide (**6d**).* White solid; Yield 82% (362 mg); Mp: 228−229 °C; IR (KBr) ν_{max}: 3428, 3021, 1639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.42 (d, 1H, J = 8.2 Hz), 7.72 (d, 1H, J = 7.7 Hz), 7.53−7.44 (m, 3H), 7.42−7.29 (m, 2H), 7.19 (d, 1H, J = 8.2 Hz), 6.31 (s, 1H), 5.74 (s, 1H), 5.05 (d, 1H, J = 19.4 Hz), 3.94 (d, 1H, J = 19.4 Hz), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.1, 161.5, 156.8, 134.7, 134.2, 134.1, 131.5, 128.9, 128.1, 127.9, 125.8, 125.7, 125.4, 122.4, 117.9, 117.6, 116.5, 115.2, 58.1, 52.2, 49.02, 28.6; HRMS (ESI TOF (+)) calcd for $[C_{23}H_{21}ClFN_3O_3 + Na^+]$ 464.1148; found 464.1139.

*N-tert-Butyl-2-(3,4-dichlorophenyl)-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl) acetamide (**6e**).* White solid; Yield 84% (385 mg); Mp: 218−220 °C; IR (KBr) ν_{max}: 3417, 3311, 1725, 1677, 1628 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.42 (d, 1H, J = 8.1 Hz), 7.72 (d, 1H, J = 7.8 Hz), 7.55−7.50 (m, 4H), 7.42−7.37 (m, 1H), 7.31−7.29 (m, 1H), 6.30 (s, 1H), 5.77 (s, 1H), 5.06 (d, 1H, J = 19.4 Hz), 3.94 (d, 1H, J = 19.4 Hz), 1.39 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.9, 161.5, 156.8, 134.7, 133.6, 131.4, 131.1, 128.8, 128.6, 128.1, 127.9, 125.4, 122.4, 116.4, 115.2, 57.9, 52.2, 49.0, 28.6; HRMS (ESI TOF (+)) calcd for $[C_{23}H_{21}Cl_2N_3O_3 + H^+]$ 458.1033; found 458.1033.

*N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-phenylacetamide (**6f**).* White solid; Yield 86% (335 mg); Mp: 228−229 °C; IR (KBr) ν_{max}: 3335, 3015, 1716, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.41 (d, 1H, J = 8.0 Hz), 7.71 (d, 1H, J = 7.7 Hz), 7.49−7.36 (m, 8H), 6.37 (s, 1H), 5.61 (s, 1H), 5.04 (d, 1H, J = 19.6 Hz), 3.91 (d, 1H, J = 19.6 Hz), 1.39 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 168.0, 161.9, 156.6, 134.6, 133.5, 129.5, 129.3, 129.2, 128.9, 128.3, 127.8, 125.2, 122.3, 116.4, 114.7, 59.3, 52.0, 49.1, 28.6; HRMS (ESI TOF (+)) calcd for $[C_{23}H_{23}N_3O_3 + H^+]$ 390.1812; found 390.1813.

*N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-p-tolylacetamide (**6g**).* White solid; Yield 80% (323 mg); Mp: 216 °C; IR (KBr) ν_{max}: 3488, 3368, 1713, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.40 (d, 1H, J = 7.9 Hz), 7.70 (d, 1H, J = 7.5 Hz), 7.50−7.47 (m, 2H), 7.39−7.35 (m, 1H), 7.31−7.22 (m, 4H), 6.33 (s, 1H), 5.64 (s, 1H), 5.00 (d, 1H, J = 19.6 Hz), 3.91 (d, 1H, J = 19.6 Hz), 2.37 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 168.2, 162.0, 156.6, 139.2, 134.6, 130.3, 129.9, 129.5, 128.9, 128.4, 127.7, 125.2, 122.3, 116.4, 114.6, 59.1, 51.9, 49.1, 28.6, 21.1; HRMS (ESI TOF (+)) calcd for $[C_{24}H_{25}N_3O_3 + H^+]$ 404.1969; found 404.1969.

*N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(4-ethylphenyl) acetamide (**6h**).* White solid; Yield 76% (317 mg); Mp: 186−187 °C; IR (KBr) ν_{max}: 3336, 1716, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.41 (d, 1H, J = 8.1 Hz), 7.71 (d, 1H, J = 7.7 Hz), 7.50−7.45 (m, 2H), 7.40−7.38 (m, 1H), 7.34−7.24 (m, 4H), 6.34 (s, 1H), 5.60 (s, 1H), 5.01 (d, 1H, J = 19.6 Hz), 3.92 (d, 1H, J = 19.6 Hz), 2.71 (q, 2H, J = 7.5 Hz), 1.38 (s, 9H), 1.28 (t, 3H, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.1, 162.1, 156.6, 145.6, 134.7, 130.6, 129.6, 129.0, 128.9, 128.5, 127.8, 125.3, 122.4, 116.5, 114.7, 59.2, 52.1, 49.1, 28.6, 28.5, 15.34; HRMS (ESI TOF (+)) calcd for $[C_{25}H_{27}N_3O_3 + H^+]$ 418.2125; found 418.2122.

*N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(4-methoxyphenyl) acetamide (**6i**).* White solid; Yield 79% (331 mg); Mp: 194−195 °C; IR (KBr) ν_{max}: 3359, 3188, 1715, 1639, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.41 (d, 1H, J = 8.1 Hz), 7.71 (d, 1H, J = 7.7 Hz), 7.51−7.46 (m, 2H), 7.40−7.32 (m, 3H), 6.96 (d, 2H, J = 8.5 Hz), 6.31 (s, 1H), 5.58 (s, 1H), 4.99 (d, 1H, J = 19.6 Hz), 3.92 (d, 1H, J = 19.7 Hz), 3.83 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 168.3, 162.1, 160.1, 156.5, 134.6, 130.9, 128.9, 128.4, 127.7, 125.2, 122.3, 116.4, 114.6, 58.9, 55.3, 51.9, 49.0, 28.6; HRMS (ESI TOF (+)) calcd for $[C_{24}H_{25}N_3O_4 + H^+]$ 420.1918; found 418.1917.

*N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(3,4,5-trimethoxy phenyl) acetamide (**6j**).* White solid; Yield 82% (393 mg); Mp: 235−236 °C; IR (KBr) ν_{max}: 3384, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.43 (d, 1H, J = 8.1 Hz), 7.72 (d, 1H, J = 7.5 Hz), 7.50−7.47 (m, 2H), 7.41 (t, 1H, J = 7.4 Hz), 6.63 (s, 2H), 6.26 (s, 1H), 5.60 (s, 1H), 5.08 (d, 1H, J = 19.6 Hz), 3.98 (d, 1H, J = 19.7 Hz), 3.87 (s, 3H), 3.85 (s, 6H), 1.39 (s, 9H); ^{13}C NMR (50 MHz, DMSO-d_6) δ = 168.3, 162.7, 155.7, 153.0, 137.4, 133.9, 130.1, 129.2, 128.7, 127.5, 125.0, 122.6, 115.7, 113.0, 106.4, 60.0, 58.8, 55.8, 50.7, 49.5, 28.3; HRMS (ESI TOF (+)) calcd for $[C_{26}H_{29}N_3O_6 + H^+]$ 480.2129; found 480.2126.

*N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(naphthalen-1-yl) acetamide (**6k**).* White solid; Yield 84% (369 mg); Mp >240 °C; IR (KBr) ν_{max}: 3305, 3084, 1725, 1653 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 8.24−8.21 (m, 2H), 8.04−7.91 (m, 3H), 7.84 (d, 1H, J = 8.07 Hz), 7.65−7.48 (m, 6H), 7.43−7.38 (m, 1H), 7.01 (s, 1H), 4.88 (d, 1H, J = 19.0 Hz), 3.49 (d, 1H, J = 19.9 Hz),

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1.31 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 168.5, 161.2, 154.3, 133.0, 130.9, 130.6, 128.8, 128.3, 126.6, 126.4, 125.7, 124.9, 124.8, 122.7, 118.4, 117.6, 115.0, 54.5, 50.2, 48.6, 27.8; HRMS (ESI TOF (+)) calcd for [$C_{27}H_{25}N_3O_3$ + H^+] 440.1969; found 440.1969.

N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(4-methoxnaphthalene-1-yl)acetamide (**6l**). White solid; Yield 78% (366 mg); Mp >240 °C; IR (KBr) ν_{max}: 3449, 3307, 1716, 1697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.35 (d, 2H, J = 7.7 Hz), 7.89 (d, 1H, J = 7.5 Hz), 7.70 (d, 1H, J = 7.8 Hz), 7.60−7.52 (m, 4H), 7.48−7.42 (m, 1H), 7.38−7.33 (m, 1H), 6.93 (s, 1H), 6.87 (d, 1H, J = 8.1 Hz), 5.60 (s, 1H), 5.00 (d, 1H, J = 19.7 Hz), 4.06 (s, 3H), 3.65 (d, 1H, J = 19.7 Hz), 1.41 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 169.0, 162.1, 156.7, 156.4, 134.6, 132.7, 129.0, 128.5, 128.1, 127.7, 125.8, 125.2, 123.0, 122.4, 120.8, 116.4, 114.6, 102.9, 56.0, 55.6, 52.1, 49.2, 28.6; HRMS (ESI TOF (+)) calcd for [$C_{28}H_{27}N_3O_4$ + Na^+] 492.1894; found 492.1892.

N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)acetamide (**6m**). White solid; Yield 70% (219 mg); Mp: 203−205 °C; IR (KBr) ν_{max}: 3520, 3379, 1724, 1656 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.46 (d, 1H, J = 8.3 Hz), 7.72 (d, 1H, J = 7.7 Hz), 7.55−7.48 (m, 2H), 7.43−7.40 (m, 1H), 5.89 (s, 1H), 4.62 (s, 2H), 4.08 (s, 2H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.2, 161.2, 156.6, 134.9, 128.9, 128.1, 128.0, 125.4, 122.5, 116.5, 114.9, 53.1, 51.8, 50.4, 28.7; HRMS (ESI TOF (+)) calcd for [$C_{17}H_{19}N_3O_3$ + H^+] 314.1499; found 314.1497.

N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(furan-2-yl) acetamide (**6n**). White solid; Yield 70% (265 mg); Mp: 200 °C; IR (KBr) ν_{max}: 3488, 3410, 3314, 1644 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.46 (d, 1H, J = 8.1 Hz), 7.73 (d, 1H, J = 8.0 Hz), 7.52 (s, 3H), 7.43−7.38 (m, 1H), 6.65 (s, 1H), 6.47 (s, 1H), 6.39 (s, 1H), 5.72 (s, 1H), 4.95 (d, 1H, J = 19.5 Hz), 4.11 (d, 1H, J = 19.4 Hz), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.5, 161.8, 156.4, 146.9, 144.0, 134.7, 128.9, 128.1, 127.9, 125.3, 122.4, 116.4, 114.9, 112.5, 110.8, 54.0, 52.1, 49.3, 28.5; HRMS (ESI TOF (+)) calcd for [$C_{21}H_{21}N_3O_4$ + H^+] 380.1605; found 380.1600.

2-(4-Chlorophenyl)-N-cyclohexyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl) acetamide (**6o**). White solid; Yield 86% (387 mg); Mp >240 °C; IR (KBr) ν_{max}: 3246, 3084, 3021, 1717, 1643 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ +TFA-d_1) δ = 8.40 (d, 1H, J = 8.1 Hz), 7.77 (d, 1H, J = 7.7 Hz), 7.61−7.55 (m, 2H), 7.48−7.36 (m, 5H), 6.42 (s, 1H), 4.94 (d, 1H, J = 19.7 Hz), 4.08 (d, 1H, J = 19.5 Hz), 3.87 (br s, 1H), 1.92−1.88 (m, 2H), 1.73−1.60 (m, 3H), 1.37−1.16 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$+TFA-d_1) δ = 168.5, 168.4, 161.9, 158.2, 136.6, 134.9, 130.9, 130.1, 129.8, 129.3, 128.9, 126.5, 126.2, 123.0, 117.7, 116.6, 59.9, 49.9, 49.4, 32.3, 32.2, 25.09, 24.4; HRMS (ESI TOF (+)) calcd for [$C_{25}H_{24}ClN_3O_3$ + H^+] 450.1579; found 450.1573.

N-Cyclohexyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(naphthalen-1-yl) acetamide (**6p**). White solid; Yield 80% (372 mg); Mp >240 °C; IR (KBr) ν_{max}: 3427, 3288, 3020, 1720, 1642 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+TFA-d_1) δ = 8.32 (d, 1H, J = 8.1 Hz), 8.03−7.94 (m, 2H), 7.84−7.82 (m, 1H), 7.78 (d, 1H, J = 7.7 Hz), 7.69−7.56 (m, 6H), 7.48−7.43 (m, 1H), 7.22 (s, 1H), 4.93 (d, 1H, J = 20.0 Hz), 3.87 (br s, 1H), 3.76 (d, 1H, J = 20.0 Hz), 1.95 (s, 2H), 1.73−1.61 (m, 3H), 1.39−1.16 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$+TFA-d_1) δ = 169.8, 162.6, 158.2, 134.9, 134.1, 131.4, 131.3, 129.5, 129.4, 128.9, 128.3, 128.2, 127.0, 126.9, 126.4, 126.3, 125.4, 123.1, 121.6, 118.0, 116.6, 57.3, 50.1, 49.4, 32.3, 32.2, 25.1, 24.4; HRMS (ESI TOF (+)) calcd for [$C_{29}H_{27}N_3O_3$ + Na^+] 488.1945; found 488.1933.

N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(4-(trifluoromethyl) phenyl)acetamide (**6q**). White solid; Yield 83% (379 mg); Mp: 231−232 °C; IR (KBr) ν_{max}: 3481, 3314, 1721, 1652 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.41 (d, 1H, J = 8.1 Hz), 7.72−7.69 (m, 3H), 7.59 (d, 2H, J = 8.0 Hz), 7.52−7.48 (m, 2H), 7.42−7.37 (m, 1H), 6.43 (s, 1H), 5.82 (s, 1H), 5.09 (d, 1H, J = 19.4 Hz), 3.89 (d, 1H, J = 19.4 Hz), 1.39 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.3, 161.5, 156.8, 137.6, 134.7, 129.8, 128.8, 128.1, 127.9, 126.3, 125.4, 122.4, 116.4, 115.2, 58.5, 52.2, 49.1, 28.6; HRMS (ESI TOF (+)) calcd for [$C_{24}H_{22}F_3N_3O_3$ + H^+] 458.1686; found 458.1685.

N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(4-nitrophenyl) acetamide (**6r**). White solid; Yield 82% (356 mg); Mp >240 °C; IR (KBr) ν_{max}:3306, 3077, 1724, 1676 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.39 (d, 1H, J = 8.1 Hz), 8.29 (d, 2H, J = 8.5 Hz), 7.71−7.63 (m, 3H), 7.53−7.48 (m, 2H), 7.42−7.37 (m, 1H), 6.48 (s, 1H), 6.03 (s, 1H), 5.11 (d, 1H, J = 19.3 Hz), 3.92 (d, 1H, J = 19.3 Hz), 1.40 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 167.0, 162.3, 155.9, 147.3, 142.6, 134.0, 130.3, 129.2, 128.9, 128.6, 128.5, 127.6, 125.0, 123.8, 122.6, 115.6, 113.3, 58.3, 50.9, 49.7, 28.3; HRMS (ESI TOF (+)) calcd for [$C_{23}H_{22}N_4O_5$ + Na^+] 457.1482; found 457.1458.

N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(2-fluorophenyl) acetamide (**6s**). White solid; Yield 78% (318 mg); Mp: 229−231 °C; IR (KBr) ν_{max}: 3433, 1629, 1548 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.41 (d, 1H, J = 8.1 Hz), 7.70 (d, 1H, J = 7.6 Hz), 7.58−7.53 (m, 1H), 7.51−7.35 (m, 4H), 7.25−7.23 (m, 1H), 7.18−7.11 (m, 1H), 6.58 (s, 1H), 5.76 (s, 1H),), 5.02 (d, 1H, J = 19.5 Hz), 3.94 (d, 1H, J = 19.4 Hz), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.4, 161.8, 156.3, 134.7, 131.5, 131.4, 131.1, 131.1, 128.9, 128.2, 127.8, 125.2, 124.8, 124.8, 122.3, 120.9, 120.8, 116.4, 116.3, 116.1, 114.8, 53.8, 52.0, 49.3, 28.6; HRMS (ESI TOF (+)) calcd for [$C_{23}H_{22}FN_3O_3$+ H^+] 408.1718; found 408.1699.

2-(2-Bromophenyl)-N-tert-butyl-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl) acetamide (**6t**). White solid; Yield 81% (379 mg); Mp: 226−228 °C; IR (KBr) ν_{max}: 3429, 3282, 3077, 1714, 1678, 1640; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.41 (d, 1H, J = 8.1 Hz), 7.70−759 (m, 3H), 7.47−7.30 (m, 5H), 6.39 (s, 1H), 5.79 (s, 1H), 4.88 (d, 1H, J = 19.4 Hz), 3.75 (d, 1H, J = 19.4 Hz), 1.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.9, 161.8, 156.3, 134.7, 133.9, 132.8, 131.2, 130.9, 129.1, 128.3, 128.1, 127.8, 125.9, 125.3, 122.4, 116.5, 114.8, 60.1, 52.2, 49.6, 28.6. HRMS (ESI TOF (+)) calcd for [$C_{23}H_{22}BrN_3O_3$ + H^+] 468.0917; found 468.0919.

N-tert-Butyl-1-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)cyclopentanecarboxamide (**6u**). White solid; Yield 78% (286 mg); Mp: 208 °C; IR (KBr) ν_{max}: 3401, 2961, 1708, 1644, 1578 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.43 (d, 1H, J = 8.1 Hz), 7.70 (d, 1H, J = 7.6 Hz), 7.54−7.49 (m, 1H), 7.42−7.37 (m, 2H), 6.47 (s, 1H), 4.58 (s, 2H), 2.67−2.63 (m, 2H), 2.06−2.01 (m, 2H), 1.78−1.77 (m, 4H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.1, 161.7, 157.9, 134.3, 129.0, 127.8, 125.3, 122.3, 116.2, 114.5,73.1, 51.2, 50.9, 35.5, 28.5, 22.5; HRMS (ESI TOF (+)) calcd for [$C_{21}H_{25}N_3O_3$ + Na^+] 390.1788; found 390.1786.

N-tert-Butyl-1-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)cyclohexanecarboxamide (**6v**). White solid; Yield 80% (305 mg); Mp: 224−226 °C; IR (KBr) ν_{max}: 3422, 1748, 1614, 1580 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.42 (d, 1H, J = 8.1 Hz), 7.69 (d, 1H, J = 7.7 Hz), 7.53−7.48 (m, 1H), 7.40−7.36 (m, 2H), 6.19 (s, 1H), 4.60 (s, 2H), 2.37−2.31 (m, 2H), 2.14−2.11 (m, 2H), 1.69 (br s, 2H), 1.57−1.52 (m, 4H), 1.36 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 171.8, 162.0, 158.5, 134.2, 129.3, 129.1, 127.7, 125.3, 122.3, 116.2, 114.5, 66.0, 51.3, 49.8, 32.5, 28.6, 25.3, 22.7; HRMS (ESI TOF (+)) calcd for [$C_{22}H_{27}N_3O_3$ + H^+] 382.2125; found 382.2123.

N-tert-Butyl-2-(3-(4-hydroxybenzyl)-1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl) acetamide (**6w**). White solid; Yield 70% (293 mg); Mp: 230−231 °C; IR (KBr) ν_{max}: 3433, 2962, 1636, 1517 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.10 (s, 1H), 8.34−8.29 (m, 2H), 7.72−7.67 (m, 2H), 7.54−7.49 (m, 1H), 7.39 (t, 1H, J = 7.5 Hz), 7.08 (s, 1H), 6.70 (d, 2H, J = 8.2 Hz), 6.34 (d, 1H, J = 8.2 Hz), 4.75 (s, 1H), 4.58 (d, 1H, J = 16.1 Hz), 3.88 (d, 1H, J = 16.1 Hz), 3.28−3.10 (m, 2H),1.28 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 165.9, 164.5, 155.7, 155.2, 133.1, 129.5, 128.0, 128.0, 126.9, 124.4, 123.5, 121.9, 114.9, 114.3, 111.8, 63.3, 49.9, 46.2, 28.0; HRMS (ESI TOF (+)) calcd for [$C_{24}H_{25}N_3O_4$ + H^+] 420.1918; found 420.1921.

N-tert-Butyl-2-(3-methyl-1,4-dioxo-3,4-dihydropyrazino[1,2-a]-indol-2(1H)-yl)acetamide (**6x**). White solid; Yield 75% (245 mg); Mp: 174−175 °C; IR (KBr) ν_{max}: 3431, 2970, 1711, 1640, 1570; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.45 (d, 1H, J = 8.2 Hz), 7.72 (d, 1H, J = 7.7 Hz), 7.55−7.48 (m, 2H), 7.43−7.38 (m, 1H), 6.42 (s, 1H), 4.57

(q, 1H, J = 7.0 Hz), 4.23 (m, 2H), 1.76 (d, 3H, J = 7.0 Hz), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.3, 165.0, 156.8, 134.9, 129.0, 128.1, 127.7, 125.4, 122.5, 116.5, 114.8, 60.1, 51.5, 50.3, 28.6, 19.9; HRMS (ESI TOF (+)) calcd for $[C_{18}H_{21}N_3O_3 + H^+]$ 328.1656; found 328.1656.

*2-(4-Chlorophenyl)-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]-indol-2(1H)-yl)-N-(2,4,4-trimethylpentan-2-yl)acetamide (**6y**).* White solid; Yield 86% (412 mg); Mp: 236 °C; IR (KBr) ν_{max}: 3436, 2962, 1640, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.39 (d, 1H, J = 8.2 Hz), 7.69 (d, 1H, J = 7.7 Hz), 7.50−7.35 (m, 7H), 6.35 (s, 1H), 5.85 (s, 1H), 5.04 (d, 1H, J = 19.4 Hz), 3.94 (d, 1H, J = 19.5 Hz), 1.89 (d, 1H, J = 14.8 Hz), 1.61 (d, 1H, J = 14.8 Hz), 1.46 (d, 1H, J = 12.1 Hz), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.1, 161.6, 156.6, 135.3, 134.7, 131.8, 130.9, 129.4, 128.9, 128.1, 127.9, 125.3, 122.4, 116.4, 115.0, 58.7, 56.2, 52.2, 48.9, 31.5, 31,4, 28.9, 28.5; HRMS (ESI TOF (+)) calcd for $[C_{27}H_{30}ClN_3O_3 + Na^+]$ 502.1868; found 502.1865.

*2-(4-Chlorophenyl)-2-(1,4-dioxo-3,4-dihydropyrazino[1,2-a]-indol-2(1H)-yl)-N-(2-morpholinoethyl)acetamide (**6z**).* White solid; Yield 70% (336 mg); Mp >240 °C; IR (KBr) ν_{max}: 3430, 2077, 1695, 1652,1580 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.43 (br s, 1H), 8 32 (d, 1H, J = 8.1 Hz), 7.84 (d, 1H, J = 8.1 Hz), 7.56−7.42 (m, 7H), 6.29 (s, 1H), 4.68 (d, 1H, J = 18.8 Hz), 3.96 (d, 1H, J = 18.9 Hz), 3.56 (s, 4H), 3.29−3.27 (m, 2H), 2.38 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 167.1, 161.8, 155.3, 133.5, 132.9, 132.5, 130.9, 128.6, 128.1, 128.0, 127.0, 124.5, 122.1, 115.1, 112.5, 65.6, 57.9, 56.6, 48.9, 35.3; HRMS (ESI TOF (+)) calcd for $[C_{25}H_{25}ClN_4O_4 + H^+]$ 481.1637; found 481.1620.

*N-tert-Butyl-2-(4-chlorophenyl)-2-(10-iodo-1,4-dioxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)acetamide (**6aa**).* White solid; Yield 88% (483 mg); Mp: 230−231 °C; IR (KBr) ν_{max} 3434, 2098, 1639, 1549 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.39 (d, 1H, J = 8.1 Hz), 7.61−7.53 (m, 2H), 7.48−7.37 (m, 5H), 6.46 (s, 1H), 5.93 (s, 1H), 5.09 (d, 1H, J = 19.6 Hz),3.90 (d, 1H, J = 19.6 Hz), 1.38.(s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA) δ = 167.5, 160.7, 155.3, 134.1, 133.4, 132.4, 131.9, 130.3, 128.5, 125.2, 122.8, 115.8, 57.4, 51.1, 49.3, 48.4, 28.0; HRMS (ESI TOF (+)) calcd for $[C_{23}H_{21}ClIN_3O_3 + H^+]$ 550.0389; found 550.0371.

General Procedure for the Preparation of Compound 8(a−e). To a solution of glycine methyl ester hydrochloride (1 mmol) in methanol (3 mL) was added triethylamine (1.1 mmol), and the resulting solution was stirred at room temperature for 10 min. To the stirred solution were added successively corresponding benzaldehdye (1 mmol), *1H*-pyrrole-2-carboxylic acid (1 mmol), and isocyanide (1 mmol). The mixture was stirred at room temperature for the specified period of time as indicated in Table 3. The progress of the reaction was monitored by TLC. After completion of the reaction, solvent was evaporated at reduced pressure and purified through column chromatography (eluent: $CHCl_3$/MeOH) using 100−200 mesh silica gel to afford the desired product **8(a−e)**.

*N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-2-(naphthalene-1-yl) acetamide (**8a**).* White solid; Yield 80% (311 mg); Mp > 240 °C; IR (KBr) ν_{max}: 3782, 3313, 2854, 1679, 1636, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.97−7.89 (m, 3H), 7.67 (d, 1H, J = 6.8 Hz), 7.55−7.50 (m, 3H), 7.41−7.40 (m, 1H), 7.20−7.19 (m, 1H), 6.99 (s, 1H), 6.51−6.49 (m, 1H), 5.67 (s, 1H), 5.02 (d, 1H, J = 20.4 Hz), 3.55 (d, 1H, J = 20.4 Hz), 1.40 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 168.9, 161.6, 155.7, 133.9, 131.7, 130.2, 129.5, 129.0, 127.9, 127.6, 126.5, 125.3, 125.1, 122.7, 119.0, 118.7, 115.5, 55.7, 52.1, 49.0, 28.6; HRMS (ESI TOF (+)) calcd for $[C_{23}H_{23}N_3O_3 + H^+]$ 390.1808; found 390.1804.

*N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-2-(4-methoxyphenyl) acetamide (**8b**).* White solid; Yield 75% (277 mg); Mp: 198−199 °C; IR (KBr) ν_{max}: 3433, 3368, 1723, 1650, 1590 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.45 (s, 1H), 7.32 (d, 2H, J = 8.2 Hz), 7.16 (s, 1H), 6.95 (d, 2H, J = 7.8 Hz), 6.51 (s, 1H), 6.27 (s, 1H), 4.97 (d, 1H, J = 20.1 Hz), 3.86−3.80 (m, 4H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.4, 161.8, 160.1, 156.0, 130.9, 125.6, 125.4, 119.0, 118.7, 115.6, 114.7, 58.4, 55.3, 52.0, 48.8, 28.6; HRMS (ESI TOF (+)) calcd for $[C_{20}H_{23}N_3O_4 + H^+]$ 370.1761; found 370.1767.

*2-(4-Bromophenyl)-N-tert-butyl-2-(1,4-dioxo-3,4-dihydropyrrolo-[1,2-a]pyrazin-2(1H)-yl) acetamide (**8c**).* White solid; Yield 80% (334 mg); Mp: 170−171 °C; IR (KBr) ν_{max}: 3429, 1760, 1634, 1580. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.47−46 (m, 1H), 7.42−7.31 (m, 4H), 7.14−7.13 (m, 1H), 6.53−6.50 (m, 1H), 6.31 (s, 1H), 5.71 (br s, 1H), 5.03 (d, 1H, J = 19.9 Hz), 3.85 (d, 1H, J = 20.1 Hz), 1.36 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.9, 161.5, 156.1, 135.3, 132.2, 130.8, 129.6, 125.3, 119.3, 119.0, 115.7, 58.0, 52.2, 48.8, 28.6. HRMS (ESI TOF (+)) calcd for $[C_{19}H_{20}BrN_3O_3 + H^+]$ 418.0761; found 418.0769.

*N-tert-Butyl-2-(1,4-dioxo-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-2-(3,4,5-trimethoxyphenyl) acetamide (**8d**).* White solid; Yield 78% (335 mg); Mp: 215−216 °C; IR (KBr) ν_{max}: 3356, 2931, 2839, 1735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.48 (s, 1H), 7.16 (s, 1H), 6.60 (s, 2H), 6.54−6.52 (m, 1H), 6.25 (s, 1H), 5.63 (s, 1H), 5.07 (d, 1H, J = 20.3 Hz), 3.93−3.84 (m, 10H), 1.38 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 168.3, 161.7, 155.9, 153.6, 138.4, 128.8, 125.3, 118.9, 118.8, 115.6, 106.4, 60.7, 58.8, 56.1, 51.9, 48.8, 28.5; HRMS (ESI TOF (+)) calcd for $[C_{22}H_{27}N_3O_6 + H^+]$ 430.1973; found 430.1965.

*N-tert-Butyl-2-(4-chlorophenyl)-2-(1,4-dioxo-3,4-dihydropyrrolo-[1,2-a]pyrazin-2(1H)-yl) acetamide (**8e**).* White solid; Yield 82% (306 mg); Mp: 176−178 °C; IR (KBr) ν_{max}: 3457, 2970, 1645, 1567 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.56−7.55 (m, 2H), 7.46−7.45 (m, 1H), 7.29−7.27 (m, 2H), 7.09 (s, 1H), 6.51−6.49 (m, 1H), 6.36 (s, 1H), 5.99−5.96 (m, 1H), 5.05 (d, 1H, J = 20.2 Hz), 3.85 (d, 1H, J = 20.2 Hz), 1.32 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.9, 161.4, 155.9, 132.8, 132.4, 131.0, 125.1, 123.3, 119.2, 118.9, 115.6, 57.9, 51.9, 48.7, 28.5; HRMS (ESI TOF (+)) calcd for $[C_{19}H_{20}ClN_3O_3 + H^+]$ 374.1266; found 374.1259.

General Procedure for the Preparation of Compound 9(a−h). To a stirred solution of requisite fused diketopiperazine (1 mmol) in ethanol (5 mL) was added corresponding amine (1.2 mmol), and the reaction mixture was heated at reflux for 4−8 h. The progress of the reaction was monitored by TLC. After completion of the reaction, solvent was evaporated at reduced pressure and purified through column chromatography (eluent: $CHCl_3$/MeOH) using 100−200 mesh silica gel to afford the desired product **9(a−h)**.

*N-(2-(Benzylamino)-2-oxoethyl)-N-(2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-1H-indole-2-carboxamide (**9a**).* White solid; Yield 90% (447 mg); Mp: 126−128 °C; IR (KBr): 3433, 2925, 1645 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.91 (br s, 1H), 9.58 (s, 1H), 7.64 (d, 1H, J = 7.8 Hz), 7.40 (d, 1H, J = 8.2 Hz), 7.30−7.23 (m, 8H), 7.14 (d, 3H, J = 7.4 Hz), 6.88 (s, 1H), 5.82 (s, 1H), 5.53 (s, 1H), 4.59−4.37 (m, 3H), 3.72−3.68 (m, 1H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.2, 164.2, 138.1, 135.9, 131.3, 129.7, 128.4, 127.8, 127.3, 125.3, 122.7, 120.7, 111.6, 107.2, 66.2, 52.0, 50.8, 43.5, 28.3; HRMS (ESI TOF (+)) calcd for $[C_{30}H_{32}ClN_4O_3 + H^+]$ 531.2157; found 531.2153.

*N-(2-(tert-Butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-N-(2-(4-methoxybenzylamino)-2-oxoethyl)-1H-indole-2-carboxamide (**9b**).* White solid; Yield 84% (471 mg); Mp: 134−136 °C; IR (KBr): 3434, 2921, 1647, 1516 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.86 (br s, 1H), 9.77 (s, 1H), 7.61 (d, 1H, J = 7.6 Hz), 7.39 (d, 1H, J = 8.1 Hz), 7.28−7.21 (m, 5H), 7.12−7.10 (m, 3H), 6.83 (br s, 1H), 6.77 (d, 2H, J = 8.5 Hz), 5.99 (s, 1H), 5.56 (s, 1H), 4.52−4.27 (m, 3H), 3.73−3.62 (m, 4H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.46, 169.1, 164.3, 158.8, 136.0, 135.7, 131.4, 130.4, 129.6, 127.9, 127.7, 125.2, 122.6, 120.6, 113.8, 111.7, 107.2, 65.99, 55.2, 52.0, 50.8, 42.9, 28.2; HRMS (ESI TOF (+)) calcd for $[C_{31}H_{33}ClN_4O_4 + H^+]$ 561.2263; found 561.2257.

*N-(2-(tert-Butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-N-(2-(4-chlorobenzylamino)-2-oxoethyl)-1H-indole-2-carboxamide (**9c**).* White solid; Yield 95% (537 mg); Mp: 136−138 °C; IR (KBr): 3435, 2918, 1647, 1520 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.90 (br s, 1H), 9.72 (s, 1H), 7.61 (d, 1H, J = 7.6 Hz), 7.40 (d, 1H, J = 8.1 Hz), 7.28−7.25 (m, 7H), 7.14−7.08 (m, 2H), 7.02 (br s, 1H), 6.87 (s, 1H), 5.97 (s, 1H), 5.59 (s, 1H), 4.56−4.52 (m, 2H), 4.41 (d, 1H, J = 18.4 Hz), 3.78 (d, 1H, J = 14.8 Hz), 1.19 (s, 9H); ^{13}C NMR (75 MHz,

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$CDCl_3$) δ = 169.5, 169.4, 164.1, 136.0, 135.3, 133.5, 131.3, 130.3, 129.7, 129.3, 128.6, 127.8, 126.7, 125.3, 122.7, 120.7, 111.7, 107.1, 65.99, 51.9, 50.8, 41.3, 28.1; HRMS (ESI TOF (+)) calcd for [$C_{30}H_{30}Cl_2N_4O_3$ + Na^+] 587.1586; found 587.1587.

N-(2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-N-(2-(3,4-dichlorobenzylamino)-2-oxoethyl)-1H-indole-2-carboxamide (**9d**). White solid; Yield 86% (516 mg); Mp: 127−128 °C; IR (KBr) ν_{max}: 3287, 3062, 2964, 1657, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 10.34 (br s, 1H), 9.57 (s, 1H), 7.64 (d, 1H, J = 7.7 Hz), 7.42−7.39 (m, 2H), 7.35−7.30 (m, 3H), 7.22−7.01 (m, 5H), 6.84 (s, 1H), 5.76 (s, 1H), 5.54 (br s, 1H), 4.55−4.30 (m, 3H), 3.75−3.70 (m, 1H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.7, 169.5, 164.0, 138.5, 135.9, 132.3, 131.2, 130.2, 130.0, 129.8, 127.8, 127.6, 125.4, 122.7, 120.8, 111.6, 107.1, 66.3, 52.1, 50.7, 42.3, 28.2; HRMS (ESI TOF (+)) calcd for [$C_{30}H_{30}Cl_3N_4O_3$ + H^+] 599.1378; found 599.1360.

N-(2-(tert-butylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-N-(2-(4-methoxybenzylamino)-2-oxoethyl)-1H-indole-2-carboxamide (**9e**). White solid; Yield 82% (505 mg); Mp: 116−119 °C; IR (KBr): 3450, 2980, 1674, 1520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 10.12 (br s, 1H), 9.66 (s, 1H), 7.65 (d, 1H, J = 7.4 Hz), 7.42 (d, 1H, J = 8.1 Hz), 7.31−7.23 (m, 3H), 7.14−7.09 (m, 1H), 6.89 (s, 1H), 6.72 (d, 2H, J = 7.6 Hz), 6.49 (s, 2H), 5.86 (s, 1H), 5.61(s, 1H), 4.48−4.30 (m, 3H), 3.85−3.65 (m, 13H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.0, 169.6, 164.0, 158.7, 153.8, 138.9, 135.8, 130.4, 129.4, 128.0, 127.9, 125.1, 122.7, 120.6, 113.7, 111.5, 107.1, 107.0, 66.8, 60.8, 56.0, 55.1, 51.9, 50.4, 42.8, 28.3; HRMS (ESI TOF (+)) calcd for [$C_{34}H_{40}N_4O_7$ + H^+] 617.2970; found 617.2955.

N-(2-(Benzylamino)-2-oxoethyl)-N-(2-(tert-butylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl) ethyl)-1H-indole-2-carboxamide (**9f**). White solid; Yield 90% (528 mg); Mp: 210−212 °C; IR (KBr) ν_{max}: 3259, 2919, 1656, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 10.24 (br s, 1H), 9.64 (s, 1H), 7.66 (d, 1H, J = 7.3 Hz), 7.42 (d, 1H, J = 8.0 Hz), 7.32−7.29 (m, 3H), 7.18−7.10 (m, 4H), 6.93 (s, 1H), 6.49 (s, 2H), 5.82 (s, 1H), 5.62 (s, 1H), 4.59−4.37 (m, 3H), 3.85−3.63 (m, 10 H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.1, 169.7, 164.0, 153.9, 138.9, 138.2, 135.9, 128.3, 128.1, 128.0, 127.9, 127.1, 125.2, 122.8, 120.6, 111.5, 107.1, 107.0, 66.8, 60.8, 56.0, 51.9, 43.4, 28.3; HRMS (ESI TOF (+)) calcd for [$C_{33}H_{38}N_4O_6$ + H^+] 587.2864; found 587.2853.

N-(2-(tert-butylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-N-(2-(3,4-dichlorobenzyl amino)-2-oxoethyl)-1H-indole-2-carboxamide (**9g**). White solid; Yield 78% (511 mg); Mp: 205−207 °C; IR (KBr) ν_{max}: 3277, 2920, 1653, 1591 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 10.51 (br s, 1H), 9.61 (s, 1H), 7.66 (d, 1H, J = 7.8 Hz), 7.43−7.41 (m, 2H), 7.33−7.26 (m, 1H), 7.20−7.08 (m, 3H), 6.89 (s, 1H), 6.50 (s, 1H), 5.80 (s, 1H), 5.62 (br s, 1H), 4.53−4.31 (m, 3H), 3.87−3.69 (m, 10 H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.3, 170.0, 163.8, 154.0, 139.1, 138.6, 135.8, 132.4, 131.1, 130.3, 130.0, 128.0, 127.9, 127.6, 125.4, 122.9, 120.8, 111.5, 107.1, 107.0, 67.2, 60.9, 56.1, 52.2, 50.3, 42.3, 28.3; HRMS (ESI TOF (+)) calcd for [$C_{33}H_{36}Cl_2N_4O_6$ + H^+] 655.2085; found 655. 2070.

N-(2-(tert-butylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-N-(2-(2-hydroxyethylamino)-2-oxoethyl)-1H-indole-2-carboxamide (**9h**). White solid; Yield 78% (421 mg); Mp: 117−119 °C; IR (KBr) ν_{max}: 3443, 2920, 1652 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.76 (br s, 1H), 9.49 (s, 1H), 7.69 (d, 1H, J = 7.8 Hz), 7.42 (d, 1H, J = 8.1 Hz), 7.32−7.27 (m, 1H), 7.15−7.10 (m, 1H), 6.92 (s, 1H), 6.62 (s, 1H), 5.87 (s, 1H), 5.51 (s, 1H), 4.42−4.30 (m, 1H), 3.88−3.76 (m, 12 H), 3.52−3.21 (m, 2H), 3.10 (s, 1H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.6, 164.1, 154.0, 139.1, 135.9, 127.9, 125.3, 122.7, 120.8, 111.6, 107.1, 67.2, 61.7, 60.9, 56.3, 52.3, 50.7, 42.9, 28.3. HRMS (ESI TOF (+)) calcd for [$C_{28}H_{36}N_4O_7$ + H^+] 541.2657; found 541.2651.

N-(2-(tert-butylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-N-(2-(4-methoxybenzyl amino)-2-oxoethyl)-1H-pyrrole-2-carboxamide (**9i**). White solid; Yield 80% (453 mg); Mp: 122−123 °C; IR (KBr) ν_{max}: 3277, 2920,1653,1591, 1335 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 10.11 (br s, 1H), 9.88 (s, 1H), 7.26 (d, 1H, J = 10.5 Hz), 6.96 (s, 1H), 6.79 (d, 1H, J = 8.4 Hz), 6.67 (s, 1H), 6.45 (s, 2H), 6.24 (s, 1H), 5.76 (s, 1H), 5.58 (s, 1H), 4.48−4.27 (m, 3H), 3.83−3.63 (m, 13H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.3, 169.8, 163.3, 158.7, 153.8, 138.7, 130.5, 129.4, 128.4, 123.6, 122.3, 114.0, 113.7, 110.8, 106.9, 66.4, 60.8, 55.9, 55.1, 51.8, 50.1, 42.7, 28.3; HRMS (ESI TOF (+)) calcd for [$C_{30}H_{38}N_4O_7$ + H^+] 567.2813; found 567.2813.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra of selected compounds are available online. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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