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A new diastereoselective multicomponent, one-pot strategy for the synthesis of 3-substituted isoindolinones via efficient C–C bond formation

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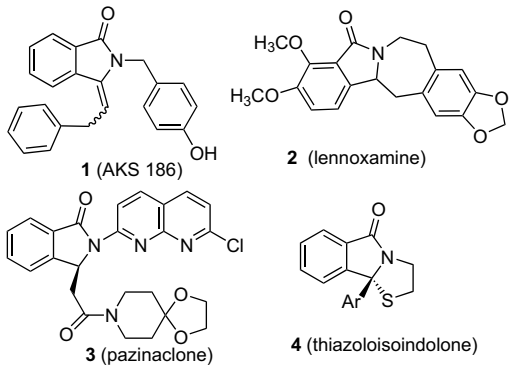
ABSTRACT

A new three-component reaction among *o*-phthalaldehyde, *N*-alkyl/aryl substituted urea, and an aromatic aldehyde has been developed at ambient condition, and a class of isoindolinones with novel C-3 substitution were conveniently synthesized. The general diastereomeric excess as high as over 99% of the products indicated the excellent stereoselectivity posed in this multicomponent reaction.

1. Introduction

Isoindolinone represents a central skeleton in a large number of natural products and pharmacophores.[1] One of the main research interests on isoindolinone motif focuses on the functionalization in its C-3 position as reflected in literature.[2] Many derivatives of this type, both naturally occurring and synthesized ones, have been disclosed as highly valuable candidates in biological study as well as medicinal development. For example (Scheme 1), AKS 186 **1** was found to inhibit vasoconstriction induced by thromboxane A2 analog,[3] and the lennoxamine **2** is a typical alkaloid isolated from barberries species.[4] Pazinaclone **3** is a drug candidate of anxiolytic[5] while the scaffold thiazoloisoindolone **4** is a non-nucleosidic HIV-reverse transcriptase inhibitor.[6] Given the great potential imbedded in these compounds, exploring efficient synthetic methodologies of isoindolinones with diversified C-3 substitution accordingly consists of an issue of high interests. Several practical strategies have been developed to synthesize different 3-substituted isoindolinones. One of the frequently applied approaches is the nucleophilic attack–reduction sequence of phthalimide,[7] which usually involves in the use of active organometallic nucleophiles. The deprotonation reaction of unsubstituted isoindolinone by strong base represents another conventional strategy in providing different 3-substituted isoindolinones.[1d,3a,8] There are also other applicable methods in preparing desired products in particular cases.[9] Despite those well-established routes in the synthesis of C-3 functionalized isoindolinones, more alternative protocols with mild condition, economical expense, and simple operation are still strongly desired.



Scheme 1. Typical scaffolds of 3-substituted isoindolinones.

In recent decades, multicomponent reactions (MCRs) are emerged as powerful synthetic strategy based on their common advantages of high speed, rich diversity, and great efficiency.[10] In our previous studies,[11] we have developed a two-component synthetic system for the preparation of some isoindolinones (no C-3 substitution), in which a nucleophilic intermediate is postulated as

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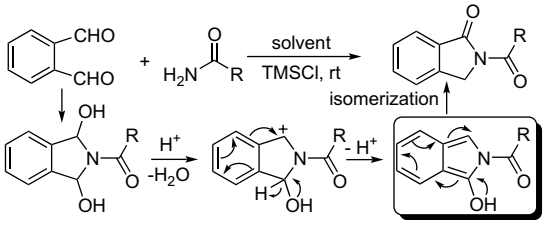
the key point in the whole reaction process (Scheme 2). As no application of MCRs in the synthesis of 3-substituted isoindolinone is previously reported, given our continuous endeavor in the study of MCRs,[12] we hope to develop a practical MCR to synthesize 3-substituted isoindolinones based on our former findings and further prove the existence of the nucleophilic intermediate shown in Scheme 2. Here we present our results of a novel MCR based on this intermediate.



Scheme 2.

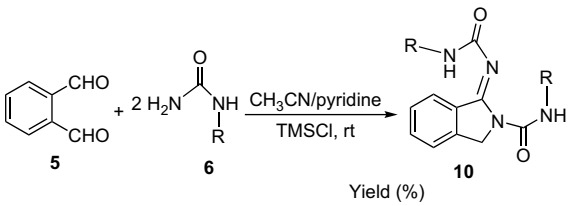
2. Results and discussion

2.1. Screening of reaction parameters

Initially, we selected benzaldehyde as the reaction partner, when mixed with *o*-phthalaldehyde (OPA), ethylurea, and 50 mol % catalyst of trimethylsilyl chloride (TMSCl) at room temperature, the reaction quickly completed to furnish a novel 3-substituted isoindolinone **8aa** in moderate yield (Table 1, entry 6) as well as **9a** after isolation.[13]

In order to achieve better yield, this reaction was then optimized through the screening of different parameters under the stoichiometry displayed in **8aa**. Typical results were highlighted in Table 1. Generally, the yield was improved with present investigation, but not in remarkable manner. According to the obtained results, lower temperature slowed down the speed of the reaction as monitored by TLC, but didn't actually give better yield; higher temperature, on the other hand, provided poorer yields of the target product. The examination on the effect of catalyst amount showed that 70 mol % TMSCl (entry 2) gave the superior result.

Considering that the proton generated in the reaction is the main reason of the side reaction, we also attempted to apply alkaline additives (entries 10 and 11) to check if the desired reaction would be improved. However, the currently referred bases turned out to be ineffective in reducing the side reaction, instead, an unexpected conversion was observed at the presence of pyridine (Scheme 3).[14]

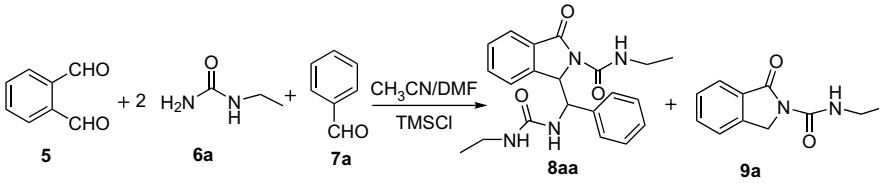


Scheme 3. Unexpected reaction promoted by pyridine.

2.2. Application scope of the multicomponent reaction

Based on the established protocol (entry 2, Table 1), various ureas and aldehydes have been devoted to this reaction, respectively, and typical results are summarized in Table 2. The observed data implied the wide application scope of this reaction, however, when aliphatic aldehydes were subjected to the reaction, no target products were detected (entries 15 and 16) regardless the use of both substrates with or without α-hydrogen. In addition, when used under the standard condition, urea (without N-substitution) didn't follow the reaction, either (entry 37). This phenomenon was probably attributed to the formation of the key intermediate **11** (Scheme 4 on the discussion of the mechanism) in which the primary amino group(s) may induce different conversion on OPA. A wide range of electronically diversified aromatic

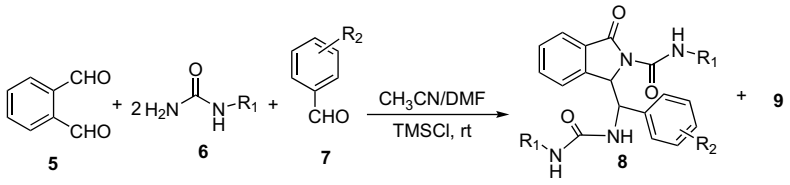
Table 1
Effects of different catalytic conditions on the one-pot synthesis of **8aa**[a]



Entry	Temp (°C)	Catalyst[b] (mol %)	Additive	Yield[c] (%)
1	0	70	No	51
2	rt	70	No	53
3	45	70	No	46
4	60	70	No	47
5	75	70	No	41
6	rt	50	No	51
7	rt	100	No	48
8	rt	150	No	39
9	rt	200	No	38
10[d]	rt	70	Pyridine	—
11[e]	rt	70	Na_2CO_3	—

[a] All reactions were carried out at the scope of 1.5 mmol **5**, 3 mmol **6a**, and 1.5 mmol **7a** in CH_3CN/DMF (2 mL/1 mL).
[b] TMSCl was used as catalyst in all reactions.
[c] Isolated yield.
[d] The product was obtained as **10a** when 1 mL pyridine added (see Scheme 3).
[e] 1 equiv mol Na_2CO_3, no desired product was observed by ESI-MS from the reaction mixture.

Table 2
Expansion of the reaction scope with various aldehydes and ureas[a]



R_1=C_2H_5	**6a**	R_2 = H	**7a**	4-Cl	**7e**	2-F	**7j**
CH_3	**6b**	4-CH_3	**7b**	4-Br	**7f**	2-Cl	**7k**
C_6H_5	**6c**	4-OCH_3	**7c**	4-OH	**7g**	3-OCH_3	**7l**
H	**6d**	4-F	**7d**	4-$N(CH_3)_2$	**7h**	3-NO_2	**7m**
				4-CF_3	**7i**	4-NO_2	**7n**

Entry	Urea	Aldehyde	Product	Yield[b] (%)	de[c] (%)
1	**6a**	**7a**	**8aa**	53	>99
2	**6a**	**7b**	**8ab**	57	70
3	**6a**	**7c**	**8ac**	46	>99
4	**6a**	**7d**	**8ad**	50	42
5	**6a**	**7e**	**8ae**	55	>99
6	**6a**	**7f**	**8af**	49	>99
7	**6a**	**7g**	**8ag**	51	>99
8	**6a**	**7h**	**8ah**	42	>99
9	**6a**	**7i**	**8ai**	40	Racemate
10	**6a**	**7j**	**8aj**	45	>99
11	**6a**	**7k**	**8ak**	45	>99
12	**6a**	**7l**	**8al**	60	>99
13	**6a**	**7m**	**8am**	38	>99
14	**6a**	1-Naphthylaldehyde (**7o**)	**8ao**	32	30
15[d]	**6a**	Isobutyraldehyde	—	—	—
16[d]	**6a**	Pivaldehyde	—	—	—
17	**6b**	**7a**	**8ba**	42	>99
18	**6b**	**7b**	**8bb**	45	>99
19	**6b**	**7c**	**8bc**	53	>99
20	**6b**	**7d**	**8bd**	36	>99
21	**6b**	**7e**	**8be**	39	>99
22	**6b**	**7f**	**8bf**	41	58
23	**6b**	**7i**	**8bi**	43	80
24	**6b**	**7k**	**8bk**	37	>99
25	**6b**	**7m**	**8bm**	34	>99
26	**6b**	**7o**	**8bo**	33	Racemate
27	**6c**	**7a**	**8ca**	63	>99
28	**6c**	**7b**	**8cb**	57	>99
29	**6c**	**7c**	**8cc**	67	Racemate
30	**6c**	**7d**	**8cd**	60	>99
31	**6c**	**7e**	**8ce**	56	52
32	**6c**	**7h**	**8ch**	41	16
33	**6c**	**7i**	**8ci**	63	Racemate
34	**6c**	**7k**	**8ck**	52	>99
35	**6c**	**7l**	**8cl**	65	62
36	**6c**	**7n**	**8cn**	61	>99
37[d]	**6d**	**7a**	—	—	—

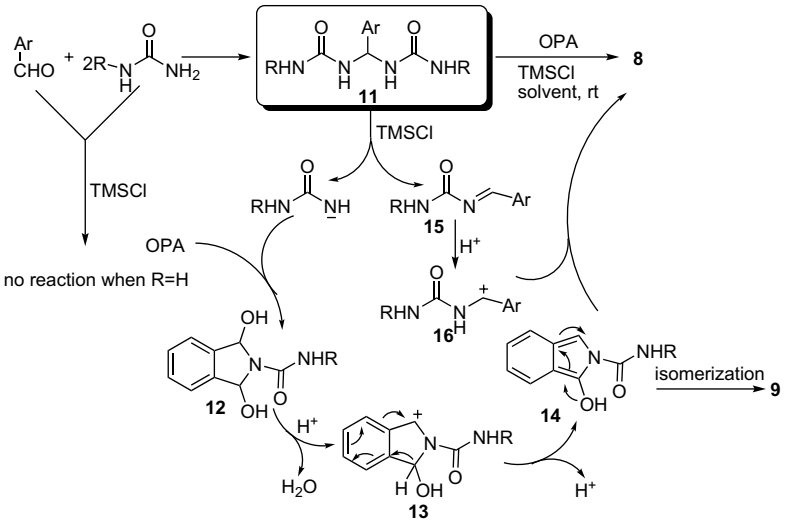
[a] The reactions were all run in 1.5 mmol scale (**5**:**6**:**7**=1:2:1).
[b] Isolated yield calculated from *o*-phthalaldehyde **5**.
[c] The values of diastereomeric excess were calculated from the ^{1}H NMR.
[d] No desired reaction was observed.

aldehydes and alkyl/aryl ureas were applied to give corresponding products in moderate to good yields. Since the formation of two chiral centers was involved in the reaction, it is noteworthy that this reaction showed excellent diastereoselectivity, actually, most of the reactions furnished target products with up to more than 99% de (diastereomeric excess, Table 2). What is interesting is that those several reactions with relatively lower de values came from substrates with both electron withdrawing and donating substituents, suggesting the stereoselectivity of this reaction was influenced by both the electronic and steric effects of all components involved.

The structure of **8al** was unambiguously identified by the X-ray single crystal diffraction (Fig. 1),[15] and the structures of all other products were assigned with accurate spectral analysis. The stereoselective outcome in **8al** (>99% de) illuminated the *syn*-configuration of the major diastereomers.

2.3. Discussion on mechanism of the multicomponent reaction

The mechanism of this reaction is plausibly based on the key intermediate **11**[16] (Scheme 4) as analyzed from the experimental results. Initially, the failure of using urea as substrate in the reaction indicated that the nucleophile and electrophile were not generated in a parallel fashion (path 1 in Scheme 4). Further examination in the reaction led to the isolation of an intermediate of type **11**, to shed light on the possible role of **11** in the reaction, we tried to



Scheme 4. Postulated mechanism for the cascade reaction.

subject the purified compound **11a** (R=Et) directly to the reaction system with OPA, and the corresponding product **8aa** was furnished in equally good yield as in the one-pot fashion. The formation of **11** also accounts for the inaccessibility to corresponding product by utilizing urea in the reaction. Therefore, on the basis of presently observed results, a domino mechanism via **11** in this multicomponent reaction is postulated (path 1 in Scheme 4). After the formation, the decomposition of **11** under catalysis led to the formation of both electrophilic and nucleophilic species. As described in Scheme 2, the nucleophile **14** then attack the in situ generated imine to give the target product, and the isomerization of **14** caused the formation of side product **9**.

3. Conclusion

In conclusion, a new multicomponent reaction of OPA, aromatic aldehyde, and substituted urea was developed under mild condition. Starting from easily available reagents, a series of novel 3-substituted isoindolinones were prepared for the first time. Success of this reaction also further proved the applicability of the in situ generated nucleophilic species in the synthesis of 3-substituted isoindolinone.

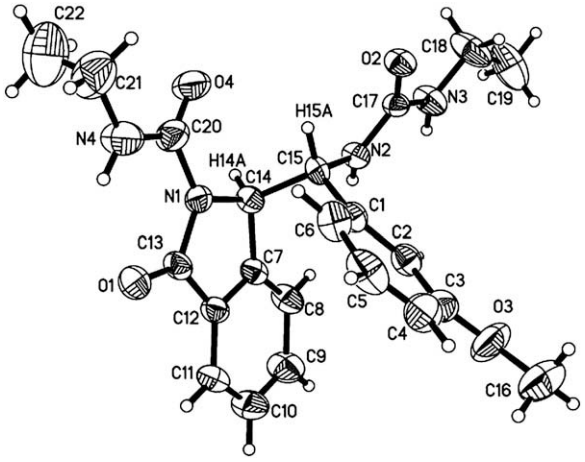


Figure 1. X-ray crystal structure of **8al**.

4. Experimental

4.1. General

All chemicals were obtained from commercial suppliers and used without further purification. Anhydrous conditions are not required for the reaction. Melting points were determined using XT-4 apparatus and were not corrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE DMX-500 spectrometry at 500 MHz and 125 MHz in DMSO-d_6, respectively. Chemical shifts are reported in parts per million (δ), relative to the internal standard of tetramethylsilane (TMS). ^{1}H and ^{13}C NMR spectra were acquired under standard conditions (5 mm QNP probe). Mass spectra were performed on a Bruker Esquire 3000plus mass spectrometer (Bruker-Franzen Analytik GmbH Breman, Germany) equipped with ESI interface and ion trap analyzer. HRMS were obtained on a Bruker 7-tesla FT-ICR MS equipped with an electrospray source (Billelica, MA, USA).

4.2. Synthetic process of 3-substituted isoindolinones: 8aa–8am, 8ao, 8ba–bf, 8bi, 8bk, 8bm, and 8bo

Aromatic aldehyde **7** (1.5 mmol) and substituted urea **6** (3 mmol) were mixed in a flask with the solvents of CH_3CN/DMF (2 mL/1 mL), the *o*-phthalaldehyde **5** (1.5 mmol) and 1 mmol catalyst TMSCl were then added sequentially. The reaction was stirred at room temperature for 4–6 h. The reaction mixture was then extracted with ethyl acetate (10 mL×3). The combined organic solvent was removed by vacuum. Sequentially, the residues were subjected to silica gel chromatography with the tandem elution of 3/1 and 1/5 of petroleum ether/ethyl acetate. The first fraction was found as the product **9** and the following one was target product **8**. The recrystallization in ethanol was applied for further purification when necessary.

*4.2.1. N-Ethyl-1-((3-ethylureido) (phenyl) methyl)-3-oxoisoindoline-2-carboxamide (**8aa**)*

White solid, mp 229–232 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.38 (t, 1H, J=5.5 Hz), 7.83–7.77 (m, 2H), 7.58–7.53 (m, 2H), 7.11–7.02 (m, 3H), 6.54–6.49 (m, 3H), 6.22 (t, 1H, J=5.5 Hz), 5.87 (dd, 1H, J_1=5.5 Hz, J_2=2.5 Hz), 5.54 (d, 1H, J=5.5 Hz), 3.39–3.26 (m, 2H), 3.12–3.06 (m, 2H), 1.16 (t, 3H, J=7.0 Hz), 1.04 (t, 3H, J=7.0 Hz); ^{13}C

NMR (DMSO-d_6, 125 MHz): δ 169.3, 158.2, 153.1, 143.3, 137.9, 134.4, 132.3, 130.2, 128.8, 128.7, 128.1, 125.7, 125.0, 62.7, 55.1, 35.4, 35.3, 16.8, 16.3; IR (KBr, cm^{-1}) 3383, 3301, 3051, 2967, 2925, 2871, 1717, 1668, 1552, 1471, 1447, 1362, 1299, 1253, 1140, 1104, 746, 698; HRMS: Calcd for $C_{21}H_{24}N_4O_3Na$ $[M+Na]^+$, 403.1741. Found, 403.1734.

4.2.2. *N-Ethyl-1-((3-ethylureido) (p-tolyl) methyl)-3-oxoisoindoline-2-carboxamide (**8ab**)*

White solid, mp 200–202 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.38 (t, 1H, *J*=5.5 Hz), 7.82–7.77 (m, 2H), 7.59–7.54 (m, 2H), 6.85–6.83 (m, 2H), 6.45–6.41 (m, 3H), 6.21 (t, 1H, *J*=5.5 Hz), 5.85 (t, 1H, *J*=5.5 Hz), 5.53 (d, 1H, *J*=5.5 Hz), 3.38–3.27 (m, 2H), 3.12–3.07 (m, 2H), 2.13 (s, 3H), 1.16 (t, 3H, *J*=7.0 Hz), 1.04 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.3, 158.2, 153.1, 143.4, 137.9, 134.8, 134.5, 132.4, 130.3, 130.1, 129.3, 128.0, 127.3, 125.7, 125.3, 125.0, 124.9, 124.7, 62.7, 54.8, 35.4, 21.8, 16.8, 16.2; IR (KBr, cm^{-1}) 3309, 2968, 2925, 2873, 1716, 1685, 1626, 1542, 1468, 1371, 1252, 1167, 1041, 1020, 760, 727, 706; HRMS: Calcd for $C_{22}H_{26}N_4O_3Na$ $[M+Na]^+$, 417.1897. Found, 417.1901.

4.2.3. *N-Ethyl-1-((3-ethylureido) (4-methoxyphenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8ac**)*

White solid, mp 219–222 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.43 (t, 1H, *J*=5.5 Hz), 7.78 (d, 1H, *J*=7.5 Hz), 7.63–7.55 (m, 2H), 7.08 (d, 2H, *J*=8 Hz), 6.94 (d, 2H, *J*=8.0 Hz), 6.73 (d, 1H, *J*=7.0 Hz), 6.05 (t, 1H, *J*=5.0 Hz), 5.89 (d, 1H, *J*=10.0 Hz), 5.69 (d, 1H, *J*=9.5 Hz), 5.52 (s, 1H), 3.76 (s, 3H), 3.36–3.31 (m, 2H), 2.94–2.89 (m, 2H), 1.47 (t, 3H, *J*=7.0 Hz), 0.92 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.6, 159.5, 158.4, 153.3, 143.1, 134.5, 132.6, 132.4, 130.3, 128.4, 125.3, 124.8, 114.9, 65.2, 56.2, 53.9, 35.4, 35.2, 16.6, 16.2; IR (KBr, cm^{-1}) 3387, 3302, 2968, 2933, 2864, 2837, 1716, 1666, 1591, 1551, 1470, 1362, 1249, 1137, 1101, 760, 701; HRMS: Calcd for $C_{22}H_{26}N_4O_4Na$ $[M+Na]^+$, 433.1846. Found, 433.1846.

4.2.4. *N-Ethyl-1-((3-ethylureido)(4-fluorophenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8ad**, mixed diastereoisomers)*

Pale yellow solid, mp 206–207 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.37 (t, 1H, *J*=5.5 Hz), 7.81–7.78 (m, 2H), 7.60–7.54 (m, 2H), 7.21–7.16 (m, 1H), 6.90 (t, 2H, *J*=8.5 Hz), 6.58–6.51 (m, 3H), 6.18 (t, 1H, *J*=5.0 Hz), 5.86 (dd, 1H, J_1=5.0 Hz, J_2=3.0 Hz), 5.53 (d, 1H, *J*=5.0 Hz), 3.38–3.27 (m, 4H, mixed isomers and water signal), 3.10–3.07 (m, 2H), 1.17–1.13 (m, 4H, mixed isomers), 1.04 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.3, 163.4, 161.5, 158, 153.0, 143.1, 134.7, 134.5, 134.3, 132.3, 130.4, 129.9, 129.3, 125.7, 125.0, 124.7, 116.4, 115.7, 115.5, 62.7, 54.5, 35.4, 35.2, 16.8, 16.2; IR (KBr, cm^{-1}) 3358, 3307, 3057, 2974, 2933, 2875, 1717, 1686, 1663, 1627, 1546, 1510, 1379, 1251, 1164, 1104, 761, 734, 704; HRMS: Calcd for $C_{21}H_{23}FN_4O_3$ $[M+Na]^+$, 421.1646. Found, 421.1651.

4.2.5. *N-Ethyl-1-((3-ethylureido)(4-chlorophenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8ae**)*

White solid, mp 209–210 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.38 (t, 1H, 5.5 Hz), 7.84–7.78 (m, 2H), 7.61–7.54 (m, 2H), 7.13 (d, 2H, *J*=8.0 Hz), 6.57–6.53 (m, 3H), 6.19 (t, 1H, *J*=5.5 Hz), 5.85 (dd, 1H, J_1=5.5 Hz, J_2=2 Hz), 5.54 (d, 1H, *J*=5.5 Hz), 3.37–3.28 (m, 2H), 3.09–3.06 (m, 2H), 1.16 (t, 3H, *J*=7.0 Hz), 1.03 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.3, 158.1, 153.0, 143.1, 137.2, 134.5, 133.2, 132.1, 130.3, 129.8, 128.8, 125.7, 125.0, 62.6, 54.6, 35.4, 35.3, 16.7, 16.2; IR (KBr, cm^{-1}) 3306, 3049, 2972, 2931, 2875, 1716, 1685, 1625, 1564, 1540, 1492, 1376, 1318, 1252, 1164, 1092, 762, 734, 704; HRMS: Calcd for $C_{21}H_{23}ClN_4O_3$ $[M+Na]^+$, 437.1351. Found, 437.1343.

4.2.6. *N-Ethyl-1-((3-ethylureido)(4-bromophenyl) methyl)-3-oxoisoindoline-2-carboxamide (**8af**)*

White solid, mp 229–232 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.43 (t, 1H, *J*=5.5 Hz), 7.79 (d, 1H, *J*=7.0 Hz), 7.65–7.56 (m, 4H), 7.10 (d, 2H, *J*=8.0 Hz), 6.77 (d, 1H, *J*=8.0 Hz), 6.10 (t, 1H, *J*=5.0 Hz), 5.88–5.80 (m, 2H), 5.57 (d, 1H, *J*=8.0 Hz), 3.34–3.30 (m, 2H), 2.93–2.90 (m, 2H), 1.14 (t, 3H, *J*=7.0 Hz), 0.91 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.4, 158.1, 153.1, 142.7, 140.2, 134.6, 132.2, 130.2, 129.4, 125.2, 124.5, 121.2, 64.6, 54.1, 35.2, 35.0, 16.3, 15.9; IR (KBr, cm^{-1}) 3383, 3310, 2979, 2931, 2877, 1717, 1668, 1552, 1487, 1361, 1252, 1142, 1104, 762, 737, 698; HRMS: Calcd for $C_{21}H_{23}BrN_4O_3$ $[M+Na]^+$, 481.0846. Found, 481.0842.

4.2.7. *N-Ethyl-1-((3-ethylureido)(4-hydroxyphenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8ag**)*

White solid, mp 247–249 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 9.39 (s, 1H), 8.44 (t, 1H, *J*=5.5 Hz), 7.76 (d, 1H, *J*=7.0 Hz), 7.61–7.50 (m, 2H), 6.95 (d, 2H, *J*=8.0 Hz), 6.74 (d, 3H, *J*=8.0 Hz), 6.04 (t, 1H, *J*=5.0 Hz), 5.85 (d, 1H, *J*=10.0 Hz), 5.63 (d, 1H, *J*=8.0 Hz), 5.48 (s, 1H), 3.32–3.29 (m, 2H), 2.93–2.88 (m, 2H), 1.14 (t, 3H, *J*=7.0 Hz), 0.91 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.5, 158.2, 157.3, 153.1, 143.0, 134.2, 132.2, 130.6, 130.0, 128.2, 125.0, 124.6, 116.0, 65.1, 53.7, 35.2, 35.0, 16.3, 16.0; IR (KBr, cm^{-1}) 3395, 3361, 3309, 2972, 2935, 1716, 1656, 1615, 1560, 1465, 1364, 1253, 1101, 761, 731, 702; HRMS: Calcd for $C_{21}H_{24}N_4O_4Na$ $[M+Na]^+$, 419.1690. Found, 419.1692.

4.2.8. *N-Ethyl-1-(((3-ethylureido)-4-(dimethylamino)phenyl)-methyl)-3-oxoisoindoline-2-carboxamide (**8ah**)*

Deep brown solid, mp 229–232 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.43 (t, 1H, *J*=5.5 Hz), 7.77 (d, 1H, *J*=7.5 Hz), 7.62–7.53 (m, 2H), 6.98 (d, 2H, *J*=8.5 Hz), 6.73 (t, 3H, *J*=8.5 Hz), 6.02 (t, 1H, *J*=5.0 Hz), 5.85 (d, 1H, *J*=10.0 Hz), 5.57 (d, 1H, *J*=10.0 Hz), 5.47 (d, 1H, 2.5 Hz), 3.32–3.29 (m, 2H), 2.92–2.89 (m, 8.0H), 1.15 (t, 3H, *J*=7.0 Hz), 0.91 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.5, 158.3, 153.1, 150.4, 143.0, 134.2, 132.2, 130.0, 127.8, 125.0, 124.6, 113.1, 65.1, 53.5, 35.2, 34.9, 16.4, 16.0; IR (KBr, cm^{-1}) 3395, 3311, 3076, 2971, 2932, 2873, 2808, 1716, 1671, 1616, 1545, 1525, 1467, 1367, 1250, 1143, 1102, 762, 730, 701; HRMS: Calcd for $C_{23}H_{29}N_5O_3Na$ $[M+Na]^+$, 446.2163. Found, 446.2155.

4.2.9. *N-Ethyl-1-((3-ethylureido)(4-(trifluoromethyl)-phenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8ai**, racemate)*

White solid, mp 189–192 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.44 (t, 1H, *J*=5.5 Hz), 8.38 (t, 1H, *J*=5.5 Hz), 7.89–7.75 (m, 5H), 7.66–7.53 (m, 4H), 7.44 (d, 2H, *J*=8.0 Hz), 7.39 (d, 2H, *J*=7.5 Hz), 6.81 (d, 2H, *J*=7.5 Hz), 6.75 (d, 1H, *J*=7.0 Hz), 6.66 (d, 1H, *J*=8.0 Hz), 6.22 (t, 1H, *J*=5.5 Hz), 6.15 (t, 1H, *J*=5.5 Hz), 6.01 (d, 1H, *J*=9.5 Hz), 5.93 (s, 2H), 5.64 (s, 1H), 5.56 (d, 1H, *J*=5.5 Hz), 3.36–3.28 (m, 4H), 3.09–3.03 (m, 2H), 2.95–2.90 (m, 2H), 1.17–1.13 (m, 6H), 1.03 (t, 3H, *J*=7.0 Hz), 0.92 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.6, 169.3, 158.3, 158.1, 153.3, 153.0, 145.9, 143.2, 143.0, 142.7, 134.8, 134.6, 132.3, 132.0, 130.5, 130.4, 129.2, 128.9, 128.8, 128.3, 126.5, 125.7, 125.6, 125.5, 125.0, 124.6, 64.7, 62.7, 55.0, 54.6, 35.4, 35.2, 16.7, 16.4, 16.2, 16.1; IR (KBr, cm^{-1}) 3385, 3351, 3316, 2991, 2931, 2871, 1721, 1667, 1618, 1552, 1469, 1360, 1327, 1252, 1166, 1124, 1070, 761, 742, 705; HRMS: Calcd for $C_{22}H_{23}F_3N_4O_3Na$ $[M+Na]^+$, 471.1614. Found, 471.1620.

4.2.10. *N-Ethyl-1-((3-ethylureido)(2-fluorophenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8aj**)*

White solid, mp 214–216 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.28 (t, 1H, *J*=5.5 Hz), 7.84 (d, 1H, *J*=7.5 Hz), 7.79–7.76 (m, 1H), 7.58–7.52 (m, 2H), 7.14–7.10 (m, 1H), 6.99 (t, 1H, *J*=9.0 Hz), 6.77 (t, 1H, 7.5 Hz), 6.55 (d, 1H, *J*=8.5 Hz), 6.41 (t, 1H, *J*=7.5 Hz), 6.26 (t, 1H, *J*=5.5 Hz), 6.13 (dd, 1H, J_1=4.5 Hz, J_2=3.5 Hz), 5.55 (d, 1H, *J*=4.0 Hz), 3.35–3.24 (m, 2H), 3.09–3.01 (m, 2H), 1.14 (t, 3H, *J*=7.0 Hz), 1.02 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.2, 162.0, 160.1, 158.0, 152.8, 143.5, 134.4, 132.0, 130.5, 130.4, 130.3, 129.6, 125.6,

125.4, 125.0, 124.6, 116.2, 116.0, 62.7, 49.2, 35.4, 35.3, 16.7, 16.1; IR (KBr, cm^{-1}) 3324, 2976, 2933, 2871, 1713, 1678, 1627, 1562, 1489, 1378, 1254, 1147, 1104, 756, 706; HRMS: Calcd for $C_{21}H_{23}FN_4O_3$ $[M+Na]^+$, 421.1646. Found, 421.1651.

4.2.11. *N*-Ethyl-1-((3-ethylureido)(2-chlorophenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8ak**)

White solid, mp 186–819 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.21 (s, 1H), 7.77 (s 2H), 7.63–7.55 (m, 2H), 7.31–6.94 (m, 3H), 6.58–6.56 (m, 2H), 6.08 (s, 2H), 5.66 (s, 1H), 3.20–3.33 (m, 2H), 2.99 (s, 2H), 1.09 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.3, 157.8, 152.7, 144.0, 137.2, 134.4, 134.1, 131.8, 130.2, 129.8, 129.5, 127.2, 125.3, 123.0, 62.5, 52.5, 35.3, 35.1, 16.6, 16.0; IR (KBr, cm^{-1}) 3399, 3307, 2970, 2931, 2882, 1716, 1686, 1634, 1541, 1471, 1379, 1319, 1254, 1155, 1101, 762, 731, 710; HRMS: Calcd for $C_{21}H_{23}ClN_4O_3$ $[M+Na]^+$, 437.1351. Found, 437.1343.

4.2.12. *N*-Ethyl-1-((3-ethylureido)(3-methoxyphenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8al**)

White solid, mp 224–225 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.38 (s, 1H), 7.81–7.79 (m, 2H), 7.59–7.56 (m, 2H), 6.98–6.93 (m, 1H), 6.67–6.62 (m, 1H), 6.47–6.45 (m, 1H), 6.19–6.16 (m, 2H), 6.00 (s, 1H), 5.84 (s, 1H), 5.54 (s, 1H), 3.49 (s, 3H), 3.36–3.28 (m, 2H), 3.10–3.09 (s, 2H), 1.16–1.01 (m, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.3, 159.5, 158.2, 153.0, 143.3, 139.3, 134.3, 132.3, 130.1, 129.8, 125.7, 125.0, 120.5, 114.5, 113.4, 62.6, 55.8, 55.0, 35.3, 35.2, 16.8, 16.2; IR (KBr, cm^{-1}) 3329, 3051, 2974, 2935, 2873, 2839, 1712, 1678, 1622, 1564, 1533, 1480, 1376, 1253, 1140, 1101, 764, 749, 710; HRMS: Calcd for $C_{22}H_{26}N_4O_4Na$ $[M+Na]^+$, 433.1846. Found, 433.1855.

4.2.13. *N*-Ethyl-1-((3-ethylureido)(3-nitrophenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8am**)

White solid, mp 220–223 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.37 (t, 1H, J=5.5 Hz), 7.98 (d, 1H, J=8.0 Hz), 7.93 (d, 1H, J=7.5 Hz), 7.83 (t, 1H, J=7.0 Hz), 7.58–7.53 (m, 2H), 7.43–7.39 (m, 2H), 7.11 (d, 1H, J=7.5 Hz), 6.77 (d, 1H, J=8.0 Hz), 6.20 (t, 1H, J=5.5 Hz), 5.97 (dd, 1H, J_1=5 Hz, J_2=2.5 Hz), 5.59 (d, 1H, J=5.0 Hz), 3.39–3.25 (m, 2H), 3.09–3.01 (m, 2H), 1.15 (t, 3H, J=7.0 Hz), 1.02 (t, 3H, J=7.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.0, 157.9, 152.7, 147.9, 142.7, 140.8, 134.5, 131.7, 130.3, 130.2, 125.5, 124.9, 122.2, 62.5, 54.6, 35.2, 35.1, 16.5, 15.9; IR (KBr, cm^{-1}) 3357, 3303, 2973, 2925, 2871, 1716, 1681, 1630, 1561, 1530, 1465, 1377, 1353, 1257, 1164, 1134, 1098, 764, 713; HRMS: Calcd for $C_{21}H_{23}N_5O_5Na$ $[M+Na]^+$, 448.1591. Found, 448.1591.

4.2.14. *N*-Ethyl-1-((3-ethylureido)(naphthalen-1-yl)methyl)-3-oxoisoindoline-2-carboxamide (**8ao**, *mixed diastereoisomers*)

Black solid, mp 152–155 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.20 (d, 1H, J=8.0 Hz), 8.00–7.97 (m, 2H), 7.86–7.84 (m, 4H), 7.70 (d, 1H, J=8.0 Hz), 7.62–7.57 (m, 3H), 7.52–7.49 (m, 3H), 7.06 (t, 1H, J=8.0 Hz), 6.72 (m, 1H), 6.59 (d, 1H, J=8.0 Hz), 6.38 (d, 1H, J=7.5 Hz), 6.17 (t, 1H, J=5.5 Hz), 5.78 (d, 1H, J=5.5 Hz), 5.58 (s, 1H), 3.33–3.30 (m, 1H), 3.23–3.14 (m, 2H), 3.08–3.04 (m, 2H), 2.92–2.89 (m, 1H), 1.21–1.18 (m, 2H), 1.02–1.00 (m, 6H), 0.99–0.89 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.1, 158.0, 153.2, 152.9, 144.0, 135.1, 134.3, 133.9, 133.7, 132.8, 132.5, 132.1, 130.1, 129.5, 128.9, 127.0, 126.5, 125.9, 125.5, 125.3, 125.2, 124.9, 124.0, 63.0, 62.7, 50.7, 35.3, 35.1, 35.0, 16.6, 16.3, 16.1, 15.8; IR (KBr, cm^{-1}) 3369, 3327, 3049, 2972, 2928, 2864, 1717, 1684, 1655, 1544, 1466, 1375, 1325, 1253, 1143, 1100, 779, 764, 704; HRMS: Calcd for $C_{25}H_{26}N_4O_3Na$ $[M+Na]^+$, 453.1897. Found, 453.1898.

4.2.15. *N*-Methyl-1-((3-methylureido)(phenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8ba**)

White solid, mp 221–223 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.34 (q, 1H, J=4.5 Hz), 7.79 (d, 1H, J=7.5 Hz), 7.62–7.55 (m, 2H), 7.40–7.29 (m, 3H), 7.21–7.19 (m, 2H), 6.66 (d, 1H, J=7.0 Hz), 6.01–5.95 (m, 2H), 5.77 (d, 1H, J=8.0 Hz), 5.57 (d, 1H, J=2.5 Hz), 2.86 (d, 3H, J=4.5 Hz), 2.47 (d, 3H, J=4.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 168.9, 158.5, 153.3, 142.3, 140.3, 133.8, 131.7, 129.6, 128.8, 127.6, 126.7, 124.7, 124.0, 64.3, 53.7, 26.8, 26.6; IR (KBr, cm^{-1}) 3332, 3134, 3030, 2937, 2855, 2806, 1716, 1681, 1632, 1575, 1542, 1492, 1414, 1363, 1245, 1148, 1101, 762, 746, 704; HRMS: Calcd for $C_{19}H_{20}N_4O_3Na$ $[M+Na]^+$, 375.1428. Found, 375.1445.

4.2.16. *N*-Methyl-1-((3-methylureido)(p-tolyl)methyl)-3-oxoisoindoline-2-carboxamide (**8bb**)

Colorless crystal, mp 213–214 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.33 (q, 1H, J=4.5 Hz), 7.79 (d, 1H, J=7.5 Hz), 7.62–7.54 (m, 2H), 7.19 (d, 2H, J=7.5 Hz), 7.08 (d, 2H, J=7.5 Hz), 6.69 (d, 1H, J=7.0 Hz), 5.97–5.90 (m, 2H), 5.72 (d, 1H, J=7.5 Hz), 5.54 (s, 1H), 2.84 (d, 3H, J=4.5 Hz), 2.46 (d, 3H, J=4.5 Hz), 2.31 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.4, 158.9, 153.8, 142.8, 140.8, 134.3, 140.8, 134.3, 132.2, 130.1, 129.3, 128.2, 127.2, 125.2, 124.4, 64.8, 54.2, 27.4, 27.1; IR (KBr, cm^{-1}) 3397, 3311, 3039, 2924, 1717, 1669, 1555, 1473, 1368, 1254, 1143, 1101, 764, 725, 702; HRMS: Calcd for $C_{20}H_{22}N_4O_3Na$ $[M+Na]^+$, 389.1584. Found, 389.1577.

4.2.17. *N*-Methyl-1-((3-methylureido)(4-methoxyphenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8bc**)

Gray solid, mp 222–224 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.26 (q, 1H, J=4.5 Hz), 7.82–7.76 (m, 2H), 7.61–7.56 (m, 2H), 6.60 (d, 2H, J=8.5 Hz), 6.47–6.43 (m, 3H), 6.09 (q, 1H, J=4.5 Hz), 5.80 (q, 1H, J_1=5.5 Hz, J_2=2.5 Hz), 5.53 (d, 1H, J=5.5 Hz), 3.61 (s, 3H), 2.85 (d, 3H, J=4.5 Hz), 2.64 (d, 3H, J=4.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.1, 159.3, 158.7, 153.6, 143.2, 134.1, 132.1, 129.9, 129.5, 129.0, 125.5, 124.8, 114.7, 113.9, 62.6, 55.8, 54.5, 27.3, 27.0; IR (KBr, cm^{-1}) 3379, 3307, 3123, 3063, 3003, 2943, 2841, 1717, 1690, 1631, 1579, 1550, 1516, 1472, 1364, 1254, 1146, 1098, 764, 746, 702; HRMS: Calcd for $C_{20}H_{22}N_4O_4Na$ $[M+Na]^+$, 405.1533. Found, 405.1530.

4.2.18. *N*-Methyl-1-((3-methylureido)(4-fluorophenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8bd**)

White solid, mp 227–229 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.26 (d, 1H, J=4.5 Hz), 7.84–7.77 (m, 2H), 7.61–7.55 (m, 2H), 6.91–6.87 (m, 2H), 6.59–6.56 (m, 3H), 6.09 (d, 1H, J=4.5 Hz), 5.85 (t, 1H, J=5.0 Hz), 5.53 (d, 1H, J=10.0 Hz), 2.86 (d, 3H, J=4.5 Hz), 2.63 (d, 3H, J=4.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.0, 158.6, 153.5, 143.0, 134.3, 134.1, 132.0, 130.1, 129.7, 125.5, 124.8, 115.4, 115.3, 62.5, 54.4, 27.4, 27.2; IR (KBr, cm^{-1}) 3339, 3041, 2945, 2812, 1716, 1686, 1628, 1576, 1549, 1510, 1419, 1376, 1259, 1169, 1107, 758, 746, 701; HRMS: Calcd for $C_{19}H_{19}FN_4O_3Na$ $[M+Na]^+$, 393.1333. Found, 393.1325.

4.2.19. *N*-Methyl-1-((3-methylureido)(4-chlorophenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8be**)

White solid, mp 225–228 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.27 (s, 1H), 7.84–7.76 (m, 2H), 7.61–7.54 (m, 2H), 7.13–7.12 (m, 2H), 6.62–6.57 (m, 3H), 6.10 (s, 1H), 5.84 (s, 1H), 5.53 (s, 1H), 2.86 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.0, 158.7, 153.5, 142.9, 137.0, 134.3, 133.0, 131.9, 130.1, 128.6, 125.5, 124.9, 62.5, 54.6, 27.4, 27.3; IR (KBr, cm^{-1}) 3352, 3319, 3049, 2943, 2814, 1716, 1684, 1628, 1569, 1544, 1493, 1417, 1362, 1258, 1140, 1093, 764, 737, 701; HRMS: Calcd for $C_{19}H_{19}ClN_4O_3Na$ $[M+Na]^+$, 409.1038. Found, 409.1031.

4.2.20. *N*-Methyl-1-((3-methylureido)(4-bromophenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8bf**, *mixed diastereoisomers*)

White solid, mp 226–227 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.34 (q, 1H, J=5.0 Hz), 7.80 (d, 1H, J=7.0 Hz), 7.66–7.55 (m, 4H), 7.13 (d, 2H, J=8.5 Hz), 6.78 (d, 1H, J=7.0 Hz), 6.51 (d, 1H, J=8.5 Hz), 6.03–6.00 (m, 1H), 5.89 (s, 1H), 5.57 (s, 1H), 2.85 (d, 3H, J=4.5 Hz), 2.46 (d, 3H, J=4.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.3, 158.8,

153.7, 142.6, 140.3, 134.6, 132.3, 131.5, 123.2, 129.9, 129.4, 125.2, 124.4, 121.3, 64.5, 54.1, 27.3, 27.0; IR (KBr, cm^{-1}) 3393, 3357, 3315, 2931, 1717, 1666, 1630, 1549, 1492, 1414, 1365, 1254, 1140, 1104, 1104, 761, 740, 701; HRMS: Calcd for $C_{19}H_{19}BrN_4O_3Na$ $[M+Na]^+$, 453.0533. Found, 453.0529.

*4.2.21. N-Methyl-1-((3-methylureido)(4-(trifluoromethyl)-phenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8bi**)*

White solid, mp 230–233 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.35 (d, 1H) 7.82–7.76 (m, 3H), 7.66–7.56 (m, 2H), 7.41 (d, 2H, J=7.5 Hz), 6.74 (d, 1H, J=6.0 Hz), 6.07–5.97 (m, 3H), 5.63 (s, 1H), 2.86 (d, 3H, J=4.5 Hz), 2.47 (d, 3H, J=4.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.3, 158.8, 153.8, 145.7, 142.5, 134.6, 132.0, 130.3, 128.1, 126.3, 125.3, 124.4, 64.4, 54.4, 27.4, 27.0; IR (KBr, cm^{-1}) 3396, 3362, 3327, 3129, 3039, 2955, 2879, 2817, 1721, 1672, 1618, 1554, 1471, 1414, 1358, 1328, 1257, 1165, 1126, 1069, 758, 737, 704; HRMS: Calcd for $C_{20}H_{19}F_3N_4O_3Na$ $[M+Na]^+$, 443.1301. Found, 443.1303.

*4.2.22. N-Methyl-1-((3-methylureido)(2-chlorophenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8bk**)*

Yellow solid, mp 219–221 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.01 (d, 1H, J=4.5H), 7.77–7.76 (m, 2H), 7.64–7.55 (m, 2H), 7.31 (d, 1H, J=8.5 Hz), 7.13–6.93 (m, 2H), 6.63–6.52 (m, 2H), 6.08 (s, 1H), 6.00 (s, 1H), 5.66 (d, 1H, J=4.0 Hz), 2.77 (d, 3H, J=4.5 Hz), 2.54 (d, 3H, J=4.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.1, 158.4, 153.3, 143.8, 137.1, 134.4, 134.0, 131.8, 130.0, 129.8, 129.4, 127.0, 125.2, 125.0, 62.4, 52.6, 27.4, 27.2; IR (KBr, cm^{-1}) 3378, 3308, 3066, 2947, 2805, 1723, 1680, 1633, 1560, 1468, 1417, 1372, 1259, 1139, 1098, 761, 731, 698; HRMS: Calcd for $C_{19}H_{19}ClN_4O_3Na$ $[M+Na]^+$, 409.1038. Found, 409.1030.

*4.2.23. N-Methyl-1-((3-methylureido)(3-nitrophenyl)methyl)-3-oxoisoindoline-2-carboxamide (**8bm**)*

White solid, mp 224–226 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.26 (d, 1H, J=4.5 Hz), 7.98–7.92 (m, 2H), 7.81 (t, 1H, J=7.0 Hz), 7.57–7.51 (m, 2H), 7.42–7.39 (m, 2H), 7.15 (d, 1H, 7.5 Hz), 6.86 (d, 1H, J=7.5 Hz), 6.12 (d, 1H, J=4.5 Hz), 5.96 (t, 1H, J=4.0 Hz), 5.58 (d, 1H, J=4.5 Hz), 2.86 (d, 3H, J=4.5 Hz), 2.61 (d, 3H, J=4.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 168.9, 158.6, 153.5, 147.9, 142.7, 140.8, 134.7, 131.7, 130.3, 130.2, 125.6, 124.9, 123.3, 122.1, 62.6, 54.8, 27.4, 27.3; IR (KBr, cm^{-1}) 3368, 3316, 3278, 3075, 3049, 2940, 2887, 2812, 1717, 1689, 1632, 1562, 1530, 1473, 1417, 1378, 1353, 1261, 1151, 1097, 764, 735, 716; HRMS: Calcd for $C_{19}H_{19}N_5O_5Na$ $[M+Na]^+$, 420.1278. Found, 420.1280.

*4.2.24. N-Methyl-1-((3-methylureido)(naphthalen-1-yl)methyl)-3-oxoisoindoline-2-carboxamide (**8bo**, racemate)*

Yellow solid, mp 224–226 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 10.91 (s, 1H), 9.85 (s, 1H), 8.19 (d, 1H, J=8.5 Hz), 7.88–7.83 (m, 7H), 7.77–7.36 (m, 12H), 7.27 (d, 1H, J=7.0 Hz), 70.6–7.03 (m, 1H), 6.73 (s, 1H), 6.63 (d, 1H, J=7.5 Hz), 6.36 (d, 1H, J=7.5 Hz), 6.08 (d, 1H, J=5.0 Hz), 5.79 (d, 1H, J=5.0 Hz), 3.06 (s, 3H), 2.70 (d, 3H, J=4.5 Hz), 2.61 (d, 3H, J=4.5 Hz), ~2.50 (s, 3H, mixed in signal of solvent DMSO); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 168.9, 158.8, 154.5, 153.6, 143.9, 135.0, 134.3, 134.2, 133.9, 133.2, 132.6, 132.5, 132.1, 130.1, 129.9, 129.8, 129.7, 129.1, 128.9, 127.3, 127.0, 126.8, 126.6, 126.3, 125.5, 125.3, 125.2, 124.9, 124.0, 120.2, 118.8, 62.6, 50.0, 29.0, 27.3; IR (KBr, cm^{-1}) 3406, 3369, 3315, 3051, 2931, 2847, 1718, 1687, 1659, 1595, 1545, 1474, 1418, 1379, 1245, 1158, 1101, 776, 742, 708; HRMS: Calcd for $C_{23}H_{22}N_4O_3Na$ $[M+Na]^+$, 425.1584. Found, 425.1576.

4.3. Preparation of 8ca–8ce, 58ci, 8ck, 8cl, and 8cn

The synthetic steps of these compounds follow the same procedure used in the synthesis of **8aa**, etc. While the purification in the silica gel chromatography step involved in the elution of tandem 3:1 and 1:3 (petroleum ether/ethyl acetate) mixture.

*4.3.1. 1-Oxo-N-phenyl-3-(phenyl(3-phenylureido)methyl)-isoindoline-2-carboxamide (**8ca**)*

White solid, mp 216–217 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 10.57 (s, 1H), 8.77 (s, 1H), 7.94–7.87 (m, 2H), 7.69–7.62 (m, 4H), 7.47–7.39 (m, 4H), 7.28–7.25 (m, 2H), 7.17–7.08 (m, 4H), 6.99–6.93 (m, 2H), 6.65 (d, 2H, J=7.5 Hz), 6.03 (dd, 1H, J_1=5.5 Hz, J_2=2.5 Hz), 5.78 (d, 1H, J=5.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.8, 155.3, 150.6, 143.2, 141.0, 138.4, 137.0, 134.9, 131.7, 130.4, 130.1, 129.8, 128.9, 127.9, 125.6, 125.2, 125.0, 122.5, 120.9, 118.7, 62.6, 54.9; IR (KBr, cm^{-1}) 3358, 3279, 3140, 3069, 3036, 2931, 2847, 1721, 1691, 1635, 1599, 1549, 1499, 1442, 1379, 1313, 1235, 1150, 1095, 755, 734, 708; HRMS: Calcd for $C_{29}H_{24}N_4O_3Na$ $[M+Na]^+$, 499.1741. Found, 499.1754.

*4.3.2. 1-Oxo-N-phenyl-3-((3-phenylureido)(p-tolyl)methyl)-isoindoline-2-carboxamide (**8cb**)*

White solid, mp 237–240 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 10.61 (s, 1H), 8.55 (s, 1H), 7.93 (d, 1H, J=7.5 Hz), 7.92–7.79 (m, 4H), 7.40–7.15 (m, 11H), 6.85 (t, 1H, J=7.5 Hz), 6.66 (d, 1H, J=7.5 Hz), 6.15 (d, 1H, J=10.0 Hz), 6.04 (d, 1H, J=10.0 Hz), 5.77 (d, 1H, J=2.5 Hz), 2.35 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 170.0, 155.6, 150.7, 142.6, 140.9, 138.5, 137.7, 136.8, 134.8, 131.9, 130.5, 130.2, 130.0, 129.6, 127.1, 125.6, 125.0, 124.6, 122.3, 120.9, 118.5, 64.9, 53.1, 21.6; IR (KBr, cm^{-1}) 3381, 3143, 3093, 3063, 2923, 2854, 1721, 1671, 1601, 1552, 1499, 1443, 1361, 1311, 1234, 1146, 1125, 754, 716, 692; HRMS: Calcd for $C_{30}H_{26}N_4O_3Na$ $[M+Na]^+$, 513.1897. Found, 513.1898.

*4.3.3. 1-Oxo-N-phenyl-3-((3-phenylureido)(4-methoxyphenyl) methyl)isoindoline-2-carboxamide (**8cc**, racemate)*

White solid, mp 215–217 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 10.62 (s, 1H), 10.58 (s, 1H), 8.76 (s, 1H), 8.55 (s, 1H), 7.92–7.87 (m, 3H), 7.72–7.63 (m, 7H), 7.45–7.41 (m, 6H), 7.26–7.15 (m, 11H), 7.15–7.14 (m, 2H), 6.94–6.85 (m, 3H), 6.67–6.65 (m, 3H), 6.54–6.51 (m, 2H), 6.13–5.96 (m, 3H), 5.75–5.74 (m, 2H), 3.79 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 170.0, 169.8, 159.6, 155.6, 155.3, 150.7, 150.6, 143.3, 142.6, 141.0, 140.9, 138.5, 138.4, 134.8, 131.9, 131.7, 131.6, 130.1, 130.0, 129.8, 129.6, 129.0, 128.9, 128.3, 125.6, 124.9, 124.6, 122.4, 122.3, 120.8, 118.6, 118.5, 115.0, 114.3; IR (KBr, cm^{-1}) 3354, 3143, 3061, 2931, 2835, 1720, 1681, 1651, 1597, 1554, 1511, 1499, 1446, 1365, 1313, 1238, 1147, 1095, 755, 731, 697; HRMS: Calcd for $C_{30}H_{26}N_4O_4Na$ $[M+Na]^+$, 529.1846. Found, 529.1851.

*4.3.4. 1-Oxo-N-phenyl-3-((4-fluorophenyl)(3-phenylureido)-methyl)isoindoline-2-carboxamide (**8cd**)*

White solid, mp 221–222 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 10.56 (s, 1H), 8.75 (s, 1H), 7.96–7.87 (m, 2H), 7.72–7.62 (m, 4H), 7.46–7.38 (m, 4H), 7.28–7.15 (m, 3H), 7.01–6.93 (m, 4H), 6.69 (t, 2H, J=5.0 Hz), 6.02 (t, 1H, J=7.0 Hz), 5.76 (d, 1H, J=5.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.7, 163.4, 161.5, 155.3, 150.5, 143.1, 141.0, 138.4, 135.0, 133.5, 131.6, 130.5, 130.1, 130.0, 130.1, 129.8, 125.6, 125.2, 125.0, 122.5, 120.8, 118.7, 115.9, 115.7, 62.6, 54.2; IR (KBr, cm^{-1}): 3358, 3321, 3145, 3095, 3051, 2923, 2854, 1725, 1693, 1642, 1601, 1557, 1500, 1446, 1365, 1319, 1240, 1224, 1147, 1095, 752, 731, 692; HRMS: Calcd for $C_{29}H_{23}FN_4O_3Na$ $[M+Na]^+$, 517.1646. Found, 517.1627.

*4.3.5. 1-Oxo-N-phenyl-3-((3-phenylureido)(4-chlorophenyl) methyl)isoindoline-2-carboxamide (**8ce**, mixed diastereoisomers)*

Gray solid, mp 207–211 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 10.55 (s, 1H), 8.74 (s, 1H), 7.96–7.86 (m, 2H), 7.72–7.62 (m, 5H),

7.47–7.38 (m, 5H), 7.31–7.18 (m, 7H), 7.03 (d, 1H, J=8.0 Hz), 6.93–6.92 (m, 1H), 6.68 (d, 2H, J=8.0 Hz), 6.00 (q, 1H, J=5.0 Hz), 5.75 (d, 1H, J=5.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.7, 155.2, 150.5, 143.0, 140.9, 138.4, 136.4, 135.0, 133.4, 131.5, 130.5, 130.1, 129.8, 129.6, 129.0, 125.5, 125.3, 125.0, 122.5, 120.9, 118.7, 118.6, 62.6, 54.3; IR (KBr, cm^{-1}) 3369, 3323, 3145, 3087, 3051, 2919, 2852, 1723, 1692, 1645, 1600, 1557, 1499, 1446, 1365, 1319, 1240, 1143, 1095, 755, 729, 692; HRMS: Calcd for $C_{29}H_{23}ClN_4O_3Na$ [M+Na]$^+$, 533.1351. Found, 533.1340.

4.3.6. 1-Oxo-N-phenyl-3-((3-phenylureido)(4-(dimethylamino) phenyl)methyl) isoindoline-2-carboxamide (**8ch**, mixture of diastereoisomers)

White solid, mp 217–220 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.63 (d, 2H), 8.76 (s, 1H), 7.89–7.87 (m, 3H), 7.73–7.63 (m, 7H), 7.48–7.38 (m, 7H), 7.29–6.96 (m, 8H), 6.80–6.70 (m, 5H), 6.40 (s, 4H), 6.06–5.70 (m, 4H), 2.92 (s, 5H), 2.75 (s, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 170.1, 155.5, 150.7, 143.7, 142.8, 141.2, 140.2, 138.6, 134.7, 131.8, 130.1, 129.8, 128.6, 127.8, 125.6, 124.9, 124.7, 122.4, 122.1, 120.8, 118.6, 113.3, 112.4, 65.1, 62.7, 54.4; IR (KBr, cm^{-1}) 3365, 3314, 3140, 3089, 3055, 2924, 2854, 2804, 1720, 1688, 1645, 1600, 1546, 1519, 1499, 1446, 1364, 1234, 1148, 1093, 754, 692; HRMS: Calcd for $C_{31}H_{29}N_5O_3Na$ [M+Na]$^+$, 542.2163. Found, 542.2181.

4.3.7. 1-Oxo-N-phenyl-3-((3-phenylureido)(4-(trifluoromethyl) phenyl)methyl)isoindoline-2-carboxamide (**8ci**, racemate)

White solid, mp 211–214 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.61 (s, 1H), 10.54 (s, 1H), 8.77 (s, 1H), 8.61 (s, 1H), 8.02 (s, 1H), 7.95–7.85 (m, 4H), 7.72–7.57 (m, 12H), 7.53–7.51 (m, 6H), 7.40–7.15 (m, 9H), 7.6.95–6.69 (m, 5H), 6.25 (s, 2H), 6.08 (s, 1H), 5.88 (s, 1H), 5.80 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.9, 169.7, 155.5, 155.3, 150.7, 150.5, 144.8, 143.0, 142.2, 140.9, 140.8, 138.4, 135.2, 135.1, 131.8, 131.4, 130.7, 130.5, 129.8, 129.7, 128.6, 128.1, 126.7, 125.8, 125.5, 125.3, 125.0, 124.5, 122.6, 122.4, 121.0, 120.9, 118.7, 118.6, 64.5, 62.7, 54.7, 53.6; IR (KBr, cm^{-1}) 3357, 3329, 3145, 3091, 2926, 2854, 1721, 1695, 1651, 1600, 1556, 1499, 1448, 1364, 1325, 1237, 1149, 1129, 1069, 755, 692; HRMS: Calcd for $C_{30}H_{23}F_3N_4O_3Na$ [M+Na]$^+$, 567.1614. Found, 567.1636.

4.3.8. 1-Oxo-N-phenyl-3-((3-phenylureido)(2-chlorophenyl)-methyl)isoindoline-2-carboxamide (**8ck**)

White solid, mp 210–212 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.42 (s, 1H), 8.66 (s, 1H), 7.92–7.84 (m, 2H), 7.74–7.51 (m, 4H), 7.38–7.34 (m, 5H), 7.24–6.70 (m, 7H), 6.65 (d, 1H, J=8.0 Hz), 6.26–6.25 (m, 1H), 5.87 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.9, 155.1, 150.3, 143.9, 141.0, 138.5, 136.6, 134.9, 134.0, 131.5, 130.2, 130.0, 129.9, 127.3, 125.4, 124.8, 122.5, 120.7, 118.7, 62.4, 52.3; IR (KBr, cm^{-1}) 3384, 3294, 3142, 3059, 2924, 2847, 1719, 1690, 1650, 1600, 1549, 1499, 1441, 1380, 1319, 1238, 1153, 1092, 753, 734, 713; HRMS: Calcd for $C_{29}H_{23}ClN_4O_3Na$ [M+Na]$^+$, 533.1351. Found, 533.1376.

4.3.9. 1-Oxo-N-phenyl-3-((3-phenylureido)(3-methoxyphenyl)-methyl)isoindoline-2-carboxamide (**8cl**, mixed diastereoisomers)

White solid, mp 173–175 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.58 (s, 1H), 8.76 (s, 1H), 7.95–7.87 (m, 2H), 7.72–7.62 (m, 5H), 7.48–7.38 (m, 4H), 7.29–7.26 (m, 2H), 7.16–7.14 (m, 2H), 7.04–6.95 (m, 4H), 6.72–6.70 (m, 1H), 6.27 (d, 1H, J=5.0 Hz), 6.11 (s, 1H), 6.03 (s, 1H), 5.77 (d, 1H), 3.32 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.7, 159.5, 155.3, 150.6, 143.2, 141.0, 138.5, 138.4, 134.8, 131.7, 130.3, 130.1, 130.0, 125.6, 125.2, 125.0, 122.5, 120.8, 120.3, 118.7, 114.6, 113.2, 62.5, 55.6, 54.7; IR (KBr, cm^{-1}) 3336, 3142, 3086, 3057, 2939, 2837, 1720, 1689, 1642, 1601, 1553, 1499, 1447, 1376, 1313, 1236, 1157, 1095, 755, 709, 692; HRMS: Calcd for $C_{30}H_{26}N_4O_4Na$ [M+Na]$^+$, 529.1846. Found, 529.1826.

4.3.10. 1-Oxo-N-phenyl-3-((3-phenylureido)(4-nitrophenyl) methyl)isoindoline-2-carboxamide (**8cn**)

White solid, mp 201–203 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.54 (s, 1H), 8.76 (s, 1H), 8.04–8.01 (m, 3H), 7.72 (t, 1H, J=7.5 Hz), 7.72–7.60 (m, 4H), 7.42–7.34 (m, 4H), 7.27–7.07 (m, 6H), 6.93 (s, 1H, J_1=4.5 Hz, J_2=3.0 Hz), 6.08 (dd, 1H), 5.83 (d, 1H, J=5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.8, 155.2, 150.4, 147.8, 146.0, 143.0, 140.8, 138.3, 135.1, 131.2, 130.6, 130.0, 129.8, 129.1, 125.3, 125.0, 123.9, 122.6, 120.9, 118.7, 62.8, 54.8; IR (KBr, cm^{-1}) 3368, 3147, 3082, 2926, 2853, 1726, 1694, 1638, 1601, 1557, 1524, 1499, 1446, 1348, 1315, 1240, 1146, 1109, 753, 708, 693; HRMS: Calcd for $C_{29}H_{23}N_5O_5Na$ [M+Na]$^+$, 544.1574. Found, 544.1591.

4.4. General process for synthesis of 10a–c

1.5 mmol *o*-phthalaldehyde and 3 mmol substituted urea were put in a flask. 2 mL CH_3CN and 1 mL pyridine were added as solvents, 1 mmol TMSCl added and the reaction was stirred at room temperature for 5 h. The solvents were removed by vacuum and the residue was executed to silica gel chromatography by the stepwise elution of 3:1 of PE:EA and full EA. The high polar product washed out by EA was recrystallized in ethanol.

4.4.1. N-Ethyl-1-(ethylcarbamoylimino)isoindoline-2-carboxamide (**10a**)

Pale brown solid, mp 159–161 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.06 (s, 1H), 7.81–7.80 (m, 1H), 7.79 (s, 1H), 7.73 (s, 2H), 7.65 (s, 1H), 4.84 (s, 2H), 3.32–3.28 (m, 2H, mixed in water signal), 3.22–3.20 (m, 2H), 1.16–1.10 (m, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 161.1, 156.1, 153.8, 141.5, 133.4, 128.8, 126.6, 126.3, 124.8, 51.1, 35.6, 35.2, 16.1, 15.6; IR (KBr, cm^{-1}) 3292, 3215, 3055, 2968, 2930, 2885, 1689, 1663, 1610, 1562, 1534, 1467, 1378, 1321, 1289, 1221, 1170, 989, 789, 761, 734, 689, 668, 650; HRMS: Calcd for $C_{14}H_{18}N_4O_2Na$ [M+Na]$^+$, 297.1322. Found, 297.1329.

4.4.2. N-Methyl-1-(methylcarbamoylimino)isoindoline-2-carboxamide (**10b**)

White solid, mp 190–192 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.96 (s, 1H), 7.76 (d, 1H, J=8.0 Hz), 7.65 (d, 2H, J=3.5 Hz), 7.48 (m, 1H), 4.85 (s, 2H), 2.88 (s, 3H), 2.79 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 161.8, 156.1, 154.7, 141.5, 135.4, 133.4, 129.7, 129.1, 126.6, 124.8, 51.0, 27.5, 27.3; IR (KBr, cm^{-1}) 3287, 3064, 2945, 2925, 2877, 1694, 1668, 1610, 1567, 1538, 1474, 1379, 1317, 1295, 1224, 1166, 989, 777, 758, 725, 695, 667; HRMS: Calcd for $C_{12}H_{14}N_4O_2Na$ [M+Na]$^+$, 269.1009. Found, 269.1012.

4.4.3. N-Phenyl-1-(phenylcarbamoylimino)isoindoline-2-carboxamide (**10c**)

White solid, mp 187–189 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.50 (s, 1H), 10.20 (s, 1H), 7.87 (d, 1H, J=7.5 Hz), 7.73–7.63 (m, 6H), 7.53–7.51 (m, 1H), 7.38–7.36 (m, 4H), 7.13–7.07 (m, 2H), 5.04 (s, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 160.7, 158.5, 140.3, 138.8, 134.1, 130.0, 129.8, 129.7, 129.5, 129.2, 126.7, 125.0, 124.7, 124.0, 120.7, 119.7, 51.5; IR (KBr, cm^{-1}) 3314, 3186, 3025, 2982, 1694, 1648, 1601, 1560, 1525, 1500, 1440, 1381, 1316, 1282, 1232, 1159, 1017, 755, 743, 691; HRMS: Calcd for $C_{22}H_{18}N_4O_2Na$ [M+Na]$^+$, 393.1322. Found, 393.1329.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.092.

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13. For the formation of **9a**, see Ref. 11.
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15. Crystallographic data (excluding structure factors) for the structure of **8al** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 686121. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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