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Facile synthesis of 4-arylidene-5-imidazolinones as synthetic analogs of fluorescent protein chromophore☆

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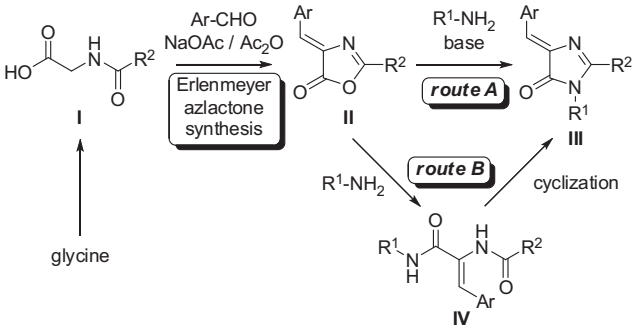
ABSTRACT

A facile and effective synthesis for a wide variety of 4-arylidene-5-imidazolinone derivatives was developed. 4-Arylidene-5-oxazolinones were prepared by Erlenmeyer azlactone synthesis from *N*-acylglycines and arylaldehydes. The ring-opening reactions of the 4-arylidene-5-oxazolinones with primary amines afforded 2-acylamino-3-arylacrylamides in excellent yields. A new dehydrative cyclization of the 2-acylamino-3-arylacrylamides in pyridine under reflux furnished the corresponding 4-arylidene-5-imidazolinones in good yields.

1. Introduction

4-Arylidene-5-imidazolinones exhibit a variety of interesting properties in biology, pharmacology,[1–5] photochemistry and optoelectronics.[6–10] The most representative structure is 4-(*p*-hydroxybenzylidene)-5-imidazolinone, which constitutes the core chromophore of the green fluorescence protein (GFP).[11] The ubiquitous structural motif and their intrinsic photochemical phenomena have made the 4-arylidene-5-imidazolinones intriguing synthetic targets and useful chemical models for investigating the mechanism of the fluorescence proteins.[6,12–32]

Although numerous structural analogs have been synthesized, a literature perusal revealed that only few synthetic routes have been utilized for the synthesis of 4-arylidene-5-imidazolinones (**III**).[12,15,19,22,28,33–36] The previous synthesis mostly started with the Erlenmeyer azlactone synthesis, in which the reaction of *N*-acylglycines (**I**) with arylaldehydes and sodium acetate in acetic anhydride results in the formation of 4-arylidene-5-oxazolinones (**II**). A direct condensation of the oxazolinones **II** with primary amines in the presence of a base has become the most common approach toward 4-arylidene-5-imidazolinones (**III**).[23,30,32,37–42] (*route A* in Scheme 1).



Scheme 1.

2. Results and discussion

In our initial attempts adopting this approach, a series of 2-methyl-4-arylidene-5-oxazolinones (**4**) were reacted with primary amines in the presence of potassium carbonate in ethanol under reflux and the results were summarized in Table 1. Our preliminary studies indicated that this approach requires the use

☆ This paper is dedicated to Professor Jim-Min Fang on the occasion of his 60th birthday.

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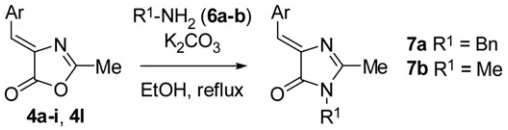
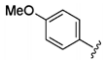
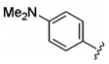
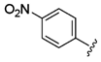
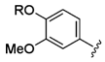
Table 1
Direct condensation of 2-methyl-4-arylidene-5-oxazolinones (**4**) with primary amines (**6a**–**b**) in the presence of K_2CO_3 in ethanol[a]



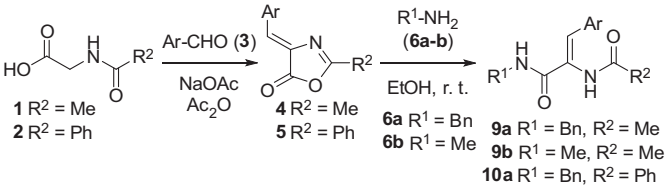
Entry	Ar	R^1	Time (h)	Product (yield)[b]
1		Bn	4	**7aa** (40%)
2		Me[d]	48	**7ba** (9%)
3		Bn	13	**7ab** (44%)
4		Bn	13	**7ac** (41%)
5[c,e]		Bn	6	**7ad** (31%)
6		Bn	4	**7ae** (13%)
7		Me[d]	14	**7be** (5%)
8		Bn	5	**7af** (14%)
9[c]		Me[d]	17	**7bf** (2%)
10		Bn	>12	N.D.[f]
11		Bn	>12	N.D.[f]
12[c,g]		Bn	10	**7ai** (20%)
13		Bn	22	**7al** (38%)

[a] General condition: R^1–NH_2 (5 equiv), K_2CO_3 (1.5 equiv), EtOH, reflux.
[b] Isolated yield.
[c] $BnNH_2$ (5 equiv), K_2CO_3 (2 equiv), EtOH, reflux.
[d] 40% $MeNH_2$ aqueous solution (6.5 equiv), K_2CO_3 (1.5 equiv), EtOH, reflux.
[e] **4d**: R=Ac; **7ad**: R=H.
[f] N.D.=no desired product.
[g] **4i**: R=Ac; **7ai**: R=H.

of excess amines and is only adequate for simple structures. In addition, the 2-methyl-4-arylidene-5-imidazolinones (**7a**–**b**) were obtained in unsatisfactory yields, especially when the aryl groups possessed electron-withdrawing substituents. (entries 6–11 in Table 1).

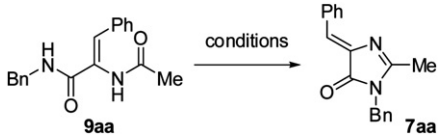
An alternative approach has received our attention. (*route B* in Scheme 1) Nucleophilic ring opening of 4-arylidene-5-oxazolinones (**II**) with primary amines gave the *N*-alkyl-2-acylamino-3-arylacrylamides (**IV**). Subsequent dehydrative cyclization afforded the corresponding 4-arylidene-5-imidazolinones (**III**). Despite various reaction conditions have been employed in the dehydrative cyclization, including acidic (AcOH,[2,43–46] Ac_2O,[47] TFA,[48] TMSCl,[49,50] acidic alumina,[51] $POCl_3$[52]),[49,53–55] basic (DBU,[56] K_2CO_3[28,57,58]),[27] and other special conditions (oxidative,[59,60] thermal,[56,61,62] microwave,[61] and aza-Wittig[28]), these methods are fraught with limitations, such as, harsh conditions or definite scopes. Therefore, we embarked on a study to investigate a feasible synthetic route suitable for a diversity-oriented synthesis of 4-arylidene-5-imidazolinone derivatives.

Our synthetic strategy toward 4-arylidene-5-imidazolinones was based on the *route B* in Scheme 1. *N*-Benzyl-2-acetylamino-3-phenylacrylamide (**9aa**), prepared from the reaction of 2-methyl-4-benzylidene-5-oxazolinone (**4a**) with benzylamine (Scheme 2), was used as a model compound to explore the reaction conditions for the formation of 4-arylidene-5-imidazolinones. In the initial trials, the dehydrative cyclization of *N*-benzyl-2-acetylamino-3-phenylacrylamide (**9aa**) was carried out under several literature conditions but the desired 1-benzyl-2-methyl-4-benzylidene-5-imidazolinone (**7aa**) could only be obtained in low yields (entries 1–5, 13 in Table 2).



Scheme 2.

Table 2
Dehydrative cyclizations of *N*-benzyl-2-acetylamino-3-phenylacrylamide (**9aa**)

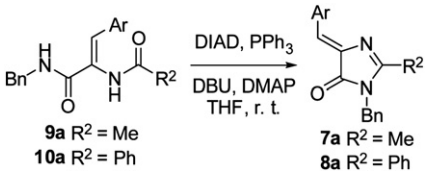


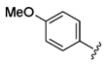
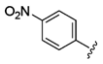
Entry	Reagent(s) (equiv)	Solvent	Temperature	Time (h)	Yield[a]
1	TFA (3)	Toluene	Reflux	9	19%
2	TFA (2)	*o*-Xylene	Reflux	7	15%
3	TsOH[b] (2)	Toluene	Reflux	12	17%
4	$POCl_3$ (1.5)	CH_2Cl_2	rt	24	Trace
5	$POCl_3$ (1.5)	Benzene	Reflux	4	Trace
6	DIAD (2), PPh_3 (2)	CH_2Cl_2	rt	24	N.R.[c]
7	DIAD (2), PPh_3 (2)	THF	rt	24	20%
8	DIAD (2), PPh_3 (2)	THF	−78 °C	24	N.R.[c]
9	DIAD (2), PPh_3 (2), DMAP (0.1)	THF	−78 °C	11	25%
10	DIAD (2), PPh_3 (2), DMAP (0.1), DIPEA (2)	THF	−78 °C	24	Trace
11	DIAD (2), PPh_3 (2), DMAP (0.1), DBU (2)	THF	−78 °C	21	36%
12	DIAD (2), PPh_3 (2), DMAP (0.1), DBU (2)	THF	rt	22	80%
13	K_2CO_3 (1.5)	EtOH	Reflux	7	36%
14	—	Pyridine	Reflux	21	64%

[a] Isolated yield.
[b] Equipped with Dean–Stark apparatus.
[c] N.R.=no reaction.

It is notable that Mitsunobu reaction,[63] commonly used for dehydration-condensation, has also been examined for the dehydrative cyclization. Under a conventional Mitsunobu condition, the reaction of 3-phenylacrylamide **9aa** with triphenylphosphine, diisopropyl azodicarboxylate (DIAD) in CH_2Cl_2 or THF only gave the desired product in low yields. (entries 6–8 in Table 2) It was found that the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base with a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) could overcome the pKa limit[64,65] of the Mitsunobu reaction and resulted in a substantial yield improvement. (entry 12 in Table 2) However, our attempts to apply the optimized Mitsunobu condition to other 3-phenylacrylamides (**9a** and **10a**) showed only partial success. The dehydrative cyclization by the Mitsunobu reaction has a limited reaction scope that was strongly influenced by the substituents on the aryl groups (Table 3).

Table 3
Dehydrative cyclizations of *N*-benzyl-2-acylamino-3-arylacrylamides (**9a** and **10a**) by the Mitsunobu condition



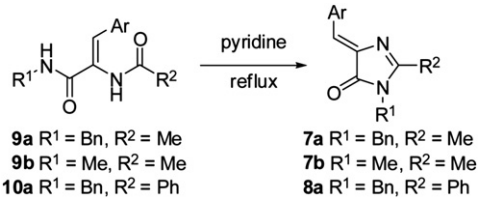
Entry	R^2	Ar	Time (h)	Product (yield)[a]
1	Me		24	**7aa** (80%)
2	Ph		24	**8aa** (25%)
3	Me		24	**7ab** (29%)
4	Ph		24	**8ab** (74%)
5[b]	Me		24	N.R.[d]
6[c]	Ph		24	N.R.[d]
7	Me		24	**7ae** (26%)
8	Ph		24	**8ae** (54%)
9	Me		24	N.D.[e]
10	Ph		15	**8ag** (14%)

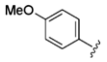
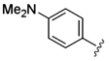
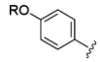
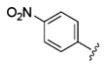
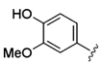
[a] Isolated yield.
[b] **9ad**: R=H.
[c] **10ad**: R=Ac.
[d] N.R.=no reaction.
[e] N.D.=no desired product.

Another optimized condition for the dehydrative cyclization was found to be the reaction of 3-phenylacrylamide **9aa** in pyridine under reflux. (Entry 14 in Table 2) Thus, a variety of *N*-alkyl-2-acylamino-3-arylacrylamides (**9a**, **9b** and **10a** as shown in Table 4) was prepared via the Erlenmeyer azlactone synthesis followed by the ring-opening with primary amines to explore the scope and generality of the reaction. In general, the desired 4-arylidene-5-imidazolinone derivatives were obtained from the corresponding 3-arylacrylamides in good yields under the tested condition. (Table 4) Although the yields for the 2-phenyl-4-arylidene-5-imidazolinone series (R^2=Ph) appear to be lower (entries 6, 9, 12, 15 and 18 in Table 4), they are still comparable to other reported methods. This reaction condition is well applicable to the 4-arylidene-5-imidazolinones bearing with electron-withdrawing groups on the aryl groups (entries 13–23 in Table 4) while the existing methods could only afford minimal yields. *ortho*-Substituted benzylidene imidazolinones (**7aj** and **7ak**) and heteroarylidene imidazolinone (**7bl**) could also be prepared in good yields by this methodology. (entries 26–28 in Table 4) Furthermore, the crude *N*-alkyl-2-acylamino-3-arylacrylamides (**9a**, **9b** and **10a**) obtained from the nucleophilic ring-opening of 4-arylidene-5-oxazolinones (**4** and **5**) after a work-up without purification could be subjected to the dehydrative cyclization in pyridine to afford comparable yields. The spectroscopic properties of the 4-arylidene-5-imidazolinone derivatives (**7a**–**b** and **8a**) were examined and the results were summarized in Table 5.

On the basis of the success in the dehydrative cyclization, the application was extended to more complicated imidazolinone derivatives to demonstrate the versatility of this method. 2-Methyl-4-benzylidene-5-oxazolinone (**4a**) was reacted with glycine methyl ester (Gly–OMe·HCl, **11**) to give the ring-opened adduct **13**. Similarly, the reaction of 2-methyl-4-(*p*-acetyloxybenzylidene)-5-oxazolinone (**4d**) with the methyl esters of glycine or alanine (Gly–OMe·HCl, **11**; Ala–OMe·HCl, **12**) afforded the 2-acetylamino-3-(*p*-acetyloxyphenyl)acrylamides **14** and **15**. These 3-phenylacrylamides (**13**–**15**) represented a series of dipeptides containing α,β-unsaturated phenylalanine or tyrosine (dehydrophenylalanine, ΔPhe; dehydrotyrosine, ΔTyr) derivatives at the *N*-terminal. These dipeptides (**13**–**15**) were subjected to the dehydrative cyclization condition to yield the corresponding 4-arylidene-5-imidazolinones (**16**, **17a**–**b** and **18a**–**b**) in good yields, except the phenolic acetyl groups

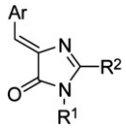
Table 4
Dehydrative cyclizations of *N*-alkyl-2-acylamino-3-arylacrylamides (**9a**–**b** and **10a**)



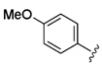
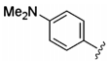
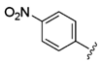
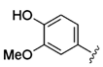
Entry	R^2	R^1	Ar	Time	Product (yield)[a]
1	Me	Bn		21 h	**7aa** (64%)
2	Me	Me		22 h	**7ba** (81%)
3	Ph	Bn		5 d	**8aa** (54%)
4	Me	Bn		47 h	**7ab** (30%)
5	Me	Me		38 h	**7bb** (86%)
6	Ph	Bn		2 d	**8ab** (15%)
7	Me	Bn		20 h	**7ac** (63%)
8	Me	Me		24 h	**7bc** (72%)
9	Ph	Bn		3 d	**8ac** (42%)
10[b]	Me	Bn		37 h	**7ad** (30%)
11[b]	Me	Me		43 h	**7bd** (91%)
12[b]	Ph	Bn		24 h	**8ad** (40%)
13	Me	Bn		19 h	**7ae** (47%)
14	Me	Me		13 h	**7be** (92%)
15	Ph	Bn		18 h	**8ae** (20%)
16	Me	Bn		24 h	**7af** (83%)
17	Me	Me		46 h	**7bf** (98%)
18	Ph	Bn		2 d	**8af** (44%)
19	Me	Bn		19 h	**7ag** (75%)
20	Me	Me		15 h	**7bg** (53%)
21	Ph	Bn		36 h	**8ag** (63%)
22	Me	Bn		12 h	**7ah** (38%)
23[c]	Me	Me		23 h	**7bh** (43%)
24	Me	Bn		42 h	**7ai** (41%)
25	Me	Me		47 h	**7bi** (70%)
26	Me	Bn		24 h	**7aj** (67%)
27	Me	Bn		24 h	**7ak** (51%)
28	Me	Me		23 h	**7bl** (77%)

[a] Isolated yield.
[b] **10ad**: R=Ac; **7ad**, **7bd**, **8ad**, **9ad** and **9bd**: R=H.
[c] *N*-Methyl-2-acetamido-3-(4-cyanophenyl)-2-(methylamino)propanamide (**9bh′**) was used as the linear precursor instead of *N*-methyl-2-acetamido-3-(4-cyanophenyl)acrylamide (**9bh**) (Supplementary data).

Table 5
Spectroscopic properties of 4-arylidene-5-imidazolinones (**7a**–**b** and **8a**) in THF[a]



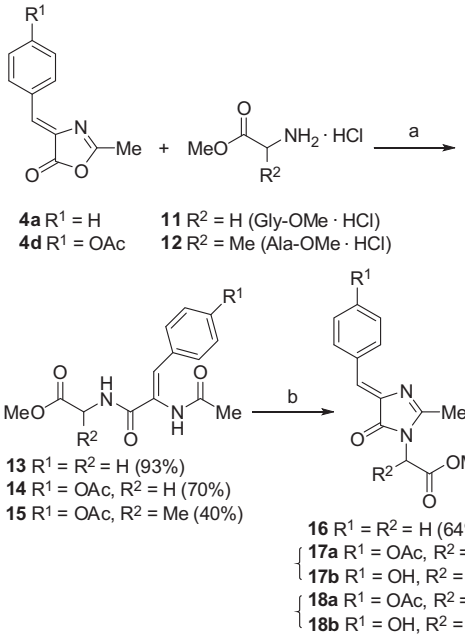
7a R^1 = Bn, R^2 = Me
7b R^1 = Me, R^2 = Me
8a R^1 = Bn, R^2 = Ph

Compound	R^2	R^1	Ar	λ_{max} (nm)	λ_{em} (nm)[b]	ε (M^{-1} cm^{-1})
7aa	Me	Bn		355	430	2.21×10^4
7ba	Me	Me		357	428	2.11×10^4
8aa	Ph	Bn		375	457	3.01×10^4
7ab	Me	Bn		370	423	3.60×10^4
7bb	Me	Me		370	426	3.60×10^4
8ab	Ph	Bn		391	471	3.51×10^4
7ac	Me	Bn		417	477	5.81×10^4
7bc	Me	Me		413	472	4.34×10^4
8ac	Ph	Bn		448	531	4.66×10^4
7ad	Me	Bn		372	429	3.04×10^4
7bd	Me	Me		371	423	3.28×10^4
8ad	Ph	Bn		393	466	3.43×10^4
7ae	Me	Bn		359	425	2.35×10^4
7be	Me	Me		358	427	2.78×10^4
8ae	Ph	Bn		382	463	3.31×10^4
7af	Me	Bn		359	428	2.58×10^4
7bf	Me	Me		360	429	2.67×10^4
8af	Ph	Bn		382	457	3.33×10^4
7ag	Me	Bn		384	485	2.58×10^4
7bg	Me	Me		386	490	2.74×10^4
8ag	Ph	Bn		400	510	3.63×10^4
7ah	Me	Bn		370	445	2.41×10^4
7bh	Me	Me		370	450	2.22×10^4
7ai	Me	Bn		379	437	3.32×10^4
7bi	Me	Me		377	435	3.82×10^4
7aj	Me	Bn		375	434	2.59×10^4
7ak	Me	Bn		361	430	2.48×10^4
7al	Me	Bn		394	452	3.04×10^4
7bl	Me	Me		391	449	3.57×10^4

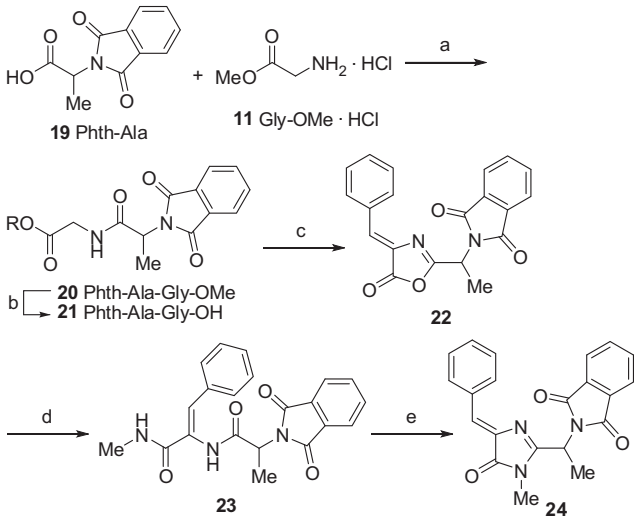
[a] λ_{max}=Absorption maximum; ε=Extinction coefficient; λ_{em}=Emission maximum.
[b] The emission spectra were taken with the excitation at the maximum absorption wavelength (λ_{max}).

of **17** and **18** were partially removed during the reaction (Scheme 3).

The reaction protocol has also been applied to the dipeptide containing ΔPhe at the C-terminal (**23**). The synthesis of the didpeptide **23** started with *N*-phthaloylalanine (*N*-Phth–Ala, **19**) as the *N*-terminal amino acid. Coupling of *N*-Phth–Ala (**19**) and Gly–OMe·HCl (**11**) with EDC and HOBt gave the *N*-phthaloyl-protected didpeptide methyl ester (*N*-Phth–Ala–Gly–OMe, **20**). Saponification of the dipeptide methyl ester **20** followed the Erlenmeyer azlactone synthesis afforded 2-(1-phthalimidoethyl)-4-benzylidene-5-oxazolinone (**22**). Subsequent nucleophilic ring opening of the 4-arylidene-5-oxazolinone **22** with methylamine gave the dipeptide **23** containing ΔPhe at the C-terminal (*N*-Phth–Ala–ΔPhe–NHMe). Didpeptide **23** was placed under the dehydrative cyclization condition to form the 4-arylidene-5-imidazolinone **24** in a good yield (Scheme 4).



Scheme 3. Reagents and conditions: (a) Et_3N (1.5∼2 equiv), EtOH, rt; (b) pyridine, reflux.



Scheme 4. Reagents and conditions: (a) EDC, HOBt, Et_3N, CH_2Cl_2, rt, 15 h, 85%; (b) (i) 1 N aqueous NaOH/EtOH, rt, 5 h; (ii) HCl, quantitatively; (c) PhCHO, NaOAc, Ac_2O, 60 °C, 12 h, 26%; (d) $MeNH_2$·HCl, Et_3N, EtOH, rt, 3 h, 44%; (e) pyridine, reflux, 34 h, 61%.

3. Conclusion

In summary, our synthetic approach invokes the Erlenmeyer azlactone synthesis followed by the nucleophilic ring-opening of amines, which allows numerous commercially available arylaldehydes and alkylamines to be utilized. The subsequent dehydrative cyclization in pyridine under reflux is facile and has a good functional group tolerance. This method has a broad scope and is applicable to a wide variety of 4-arylidene-5-imidazolinones. Moreover, the dehydrative cyclization by the Mitsunobu reaction, despite of its narrower scope, has offered a mild condition as a supplementary route. Our investigation successfully provided a viable synthesis, which is amenable to the preparation of various GFP chromophore derivatives.

4. Experimental section

4.1. General chemical procedures

Nuclear magnetic resonance (NMR) spectra were obtained with Bruker Avance-400 or Avance-500 instruments. The chemical shift values are reported in δ values (parts per million, ppm) relative to the standard chemical shift for the deuterated solvent, $CDCl_3$, or DMSO-d_6.[66] The coupling constant (J) values are expressed in hertz (Hz). Mass spectrometry was acquired on Finnigan Mat 95S (ESI) by the Advanced Instrument Center, Department of Chemistry, National Taiwan University, Taipei, Taiwan. Thin-layer chromatography (TLC) was performed on silica gel GHLF-254 plates (Merck Reagents). Compounds on thin-layer chromatography were visualized by illumination under UV light (254 nm), or dipped into 10% ethanolic sulfuric acid followed by charring on a hot plate. Solvent systems are expressed as a percentage of the more polar component with respect to total volume (*v*/*v*%). Merck Silica gel (230–400 mesh) was used for flash column chromatography and this technique has been described by W. C. Still et al.[67] Evaporations were carried out under reduced pressure (water aspirator) with the bath temperature below 50 °C unless specified otherwise. Materials obtained from commercial suppliers were used without further purification.

4.2. [General procedure A] General procedure for the Erlenmeyer azlactone synthesis (Scheme 2)

To a solution of *N*-acylglycine in acetic anhydride (reaction concentration=1 M) was added sodium acetate (0.63 equiv) and aryl–aldehyde (1.25 equiv) at room temperature. The reaction mixture was heated at 95–135 °C for the specific time (monitored by TLC). Ice was added to the reaction mixture and the resulting solution was cooled to 0 °C overnight. The precipitate was collected by filtration and the solid was recrylstallized to give the product. Alternatively, the aqueous solution was extracted by $CHCl_3$ and the product was purified by flash column chromatography.

4.3. [General procedure B] General procedure for the direct condensation of 2-methyl-4-arylidene-5-oxazolinones (4) with primary amines (Table 1)

*4-(Indol-3-ylmethylidene)-1-benzyl-2-methylimidazol-5-one (**7al**).* To a solution of 4-(3-indol-3-ylmethylidene)-2-methyloxazol-5-one (**4l**, 7.21 g, 26.89 mmol) in ethanol (150 mL) was added K_2CO_3 (6.61 g, 47.83 mmol, 1.5 equiv) and benzylamine (17.4 mL, 17.08 g, 159.45 mmol, 5 equiv). The reaction mixture was stirred at room temperature for 10 min, and then was heated at reflux temperature for 11 h. After cooling to room temperature, the solution was filtered and the filtrate was collected. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (Hex/EtOAc=6:4, R_f=0.20) to give a yellow solid (**7al**, 3.25 g, 10.31 mmol, 38%). An analytical sample of **7al** was obtained by recrystallization from Hex/MeOH. Mp 212–214 °C (Hex/MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 7.24–7.33 (m, 7H), 7.41 (t, 1H, J=4.5 Hz), 7.64 (s, 1H), 7.98 (t, 1H, J=4.3 Hz), 8.55 (d, 1H, J=2.2 Hz), 8.91 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7 (CH_3), 43.9 (CH_2), 111.7 (CH), 112.2, 119.1 (CH), 121.6 (CH), 121.7 (CH), 123.4 (CH), 127.1 (CH), 127.5, 127.9 (CH), 129.0 (CH), 131.8 (CH), 136.0, 136.2, 159.0, 169.2; MS (EI) m/z 91 (100), 155 (72), 315 (88) (M^+); HRMS Calcd for $C_{20}H_{17}N_3O$: 315.1372. Found 315.1377. Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 75.94; H, 5.56; N, 13.48.

4.4. [General procedure C] General procedure for the nucleophilic ring-opening of 4-arylideneoxazol-5-ones by primary amines (Schemes 2 and 3)

To the solution of 2-substituted 4-arylidene-5-oxazolinone (**4** or **5**) in EtOH (reaction concentration=0.2–0.5 M) was added the primary amines (methylamine: 40% aqueous solution, 20 equiv; other primary amines: 1.2–2.4 equiv) and the solution was stirred at room temperature. Upon completion, the solvent was removed under reduced pressure. The residue was purified (recrystallization or flash column chromatography) to give the corresponding *N*-substituted 2-acylamino-3-aryl-acrylamide. (1.5–2 equiv of triethylamine were used to neutralize the HCl when the hydrochloride salts of the amino acid methyl esters (**11** and **12**) were used as the primary amines (Scheme 3)).

4.5. [General procedure D] General procedure for the dehydrative cyclization by the Mitsunobu reaction (Table 3)

To a solution of triphenylphosphine (2 equiv), DBU (2 equiv), DMAP (0.1 equiv) and *N*-substituted 2-acylamino-3-aryl-acrylamide (**9a**, **9b** or **10a**) in THF at 0 °C was added DIAD (2 equiv) dropwise. The reaction mixture was allowed to warm to room temperature with continuous stirring for 24 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography.

4.6. [General procedure E] General procedure for the dehydrative cyclization in pyridine (Table 4, Schemes 3 and 4)

The solution of *N*-substituted 2-acylamino-3-aryl-acrylamide (**9a**, **9b** or **10a**) in pyridine (reaction concentration=0.2–0.5 M) was stirred at reflux temperature. Upon completion, the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography to give the corresponding 1,2-disubstituted 4-arylideneimidazol-5-one.

4.7. General spectroscopic method (Table 5)

4.7.1. UV/Vis spectra. UV/Visible spectra were recorded on Agilent 8453 spectrophotometer. The sample solution was prepared by dissolving approximately 10 mg of the tested compound in THF to result in a 10-mL solution, which was then adequately diluted with THF to form solutions in various concentrations for collecting the absorption maximum (λ_{max}) and extinction coefficient (ε).

4.7.2. Fluorescence spectra. Emission data were collected on Cary Eclipse spectrophotometer at room temperature with 10 mm of emission slit and corrected to the emission of a Xenon flash lamp. The sample solution was prepared by dissolving approximately 10 mg of the tested compound in THF to result in a 10-mL solution, which was then adequately diluted with THF to form solutions in various concentrations as indicated. The solutions were excited at the absorption maximum (λ_{max}), which were obtained in UV/Vis spectra.

*4-Benzylidene-1-benzyl-2-methylimidazol-5-one (**7aa**).* Compound **7aa** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=8:2, R_f=0.25) to give the product as a yellow solid (**7aa**, 64%). An analytical sample of **7aa** was obtained by recrystallization from Hex/MeOH. Mp 137–139 °C (Hex/MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 3H, CH_3), 4.82 (s, 2H, CH_2), 7.19 (s, 1H, C=CH), 7.23–7.31 (m, 5H), 7.33–7.42 (m, 3H), 8.15 (d, 2H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1, 43.9, 127.1, 127.8, 128.0, 128.8, 129.0, 130.2, 132.3,

134.2, 136.1, 138.5, 162.6, 170.7; MS (EI) *m/z* 91 (59), 135 (45), 205 (46), 276 (100) (M^+); HRMS Calcd for $C_{18}H_{16}N_2O$: 276.1263. Found 276.1259. Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.05; H, 5.74; N, 9.93.

*4-(4-Methoxybenzylidene)-1-benzyl-2-methylimidazol-5-one (**7ab**).* Compound **7ab** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=8:2, R_f=0.22) to give the product as a yellow solid (**7ab**, 30%). An analytical sample of **7ab** was obtained by recrystallization from Hex/EtOAc. Mp 127–129 °C (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.82 (s, 2H, CH_2), 6.94 (d, 2H, *J*=8.7 Hz), 7.15 (s, 1H, C=CH), 7.23 (d, 2H, *J*=7.3 Hz), 7.27–7.34 (m, 3H), 8.13 (d, 2H, *J*=8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.0 (CH_3), 43.8 (CH_2), 55.3 (CH_3), 114.3 (CH), 127.0 (CH), 127.1, 127.8 (CH), 128.9 (CH), 134.1 (CH), 136.2, 136.6, 161.1, 161.3, 170.6; MS (EI) *m/z* 91 (100), 146 (42), 306 (68) (M^+); HRMS Calcd for $C_{19}H_{18}N_2O_2$: 306.1368. Found 306.1373. Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.51; H, 5.79; N, 9.09.

*4-(4-Dimethylaminobenzylidene)-1-benzyl-2-methylimidazol-5-one (**7ac**).* Compound **7ac** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=7:3, R_f=0.28) to give the product as a yellow solid (**7ac**, 63%). Mp 153–155 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.22 (s, 3H, CH_3), 3.01 (s, 6H, CH_3), 4.81 (s, 2H, CH_2), 6.75 (d, 2H, *J*=8.8 Hz), 6.96 (s, 1H, C=CH), 7.22–7.37 (m, 5H), 8.08 (d, 2H, *J*=8.7 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 15.4 (CH_3), 39.6 (CH_3), 42.8 (CH_2), 111.6 (CH), 121.5, 126.8 (CH), 127.3 (CH), 127.4 (CH), 128.7 (CH), 133.9 (CH), 134.1, 137.1, 151.4, 159.5, 169.6; MS (EI) *m/z* 159 (35), 227 (35), 319 (100) (M^+); HRMS Calcd for $C_{20}H_{21}N_3O$: 319.1685. Found 319.1681.

*4-(4-Hydroxybenzylidene)-1-benzyl-2-methylimidazol-5-one (**7ad**).* Compound **7ad** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=6:4, R_f=0.25) to give the product as a yellow solid (**7ad**, 30%). An analytical sample of **7ad** was obtained by recrystallization from MeOH/H_2O. Mp 210–212 °C (MeOH/H_2O); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.26 (s, 3H, CH_3), 4.81 (s, 2H, CH_2), 6.84 (d, 2H, *J*=8.5 Hz), 6.98 (s, 1H, C=CH), 7.22 (d, 2H, *J*=7.5 Hz), 7.28–7.37 (m, 3H), 8.09 (d, 2H, *J*=8.5 Hz), 10.2 (br, 1H, OH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 16.0 (CH_3), 43.5 (CH_2), 116.4 (CH), 125.8, 127.0 (CH), 127.4 (CH), 128.0 (CH), 129.3 (CH), 134.8 (CH), 136.3, 137.4, 160.3, 162.0, 170.4; MS (EI) *m/z* 91 (100), 292 (78) (M^+); HRMS Calcd for $C_{18}H_{16}N_2O_2$: 292.1212. Found 292.1214. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.96; H, 5.57; N, 9.56.

*4-(4-Chlorobenzylidene)-1-benzyl-2-methylimidazol-5-one (**7ae**).* Compound **7ae** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=9:1, R_f=0.15) to give the product as a yellow solid (**7ae**, 47%). An analytical sample of **7ae** was obtained by recrystallization from Hex/MeOH. Mp 96–98 °C (Hex/MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 3H, CH_3), 4.82 (s, 2H, CH_2), 7.11 (s, 1H, C=CH), 7.23 (d, 2H, *J*=7.0 Hz), 7.29–7.39 (m, 5H), 8.09 (d, 2H, *J*=8.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1 (CH_3), 44.0 (CH_2), 126.2 (CH), 127.1 (CH), 128.0 (CH), 129.0 (CH), 132.7, 133.3 (CH), 136.0, 136.2, 138.7, 163.0, 170.5; MS (EI) *m/z* 91 (100), 310 (17) (M^+), 312 (5) (M+2); HRMS Calcd for $C_{18}H_{15}N_2OCl$: 310.0873. Found 310.0869. Anal. Calcd for $C_{18}H_{15}N_2OCl$: C, 69.57; H, 4.86; N, 9.01. Found: C, 69.45; H, 4.76; N, 8.91.

*4-(4-Bromobenzylidene)-1-benzyl-2-methylimidazol-5-one (**7af**).* Compound **7af** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=9:1, R_f=0.12) to give the product as a yellow solid (**7af**, 83%). An analytical sample of **7af** was obtained by recrystallization from Hex/MeOH. Mp 122–124 °C (Hex/MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.27 (s, 3H, CH_3), 4.84 (s, 2H, CH_2), 7.05 (s, 1H, C=CH), 7.24–7.38 (m, 5H), 7.66 (d, 2H, *J*=8.3 Hz), 8.17 (d, 2H, *J*=8.3 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 15.7 (CH_3), 43.0 (CH_2), 123.7, 124.1 (CH), 126.8 (CH), 127.5 (CH), 128.8 (CH), 131.7 (CH), 133.2, 133.7 (CH), 136.6, 138.9, 164.3, 169.7; MS (ES) *m/z* 355 (99) (M+1), 357 (100) (M+3), 377 (48) (M+Na), 379 (48) (M+2+Na); HRMS Calcd for $C_{18}H_{16}N_2OBr$ (M+1): 355.0446. Found 355.0435. Anal. Calcd for $C_{18}H_{15}N_2OBr \cdot 1/4H_2O$: C, 60.10; H, 4.34; N, 7.79. Found: C, 60.32; H, 4.45; N, 7.62.

*4-(4-Nitrobenzylidene)-1-benzyl-2-methylimidazol-5-one (**7ag**).* Compound **7ag** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=7:3, R_f=0.30) to give the product as a yellow solid (**7ag**, 75%). An analytical sample of **7ag** was obtained by recrystallization from Hex/EtOAc. Mp 182–184 °C (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H, CH_3), 4.84 (s, 2H, CH_2), 7.13 (s, 1H, C=CH), 7.23 (d, 2H, *J*=7.3 Hz), 7.30–7.38 (m, 3H), 8.24 (d, 2H, *J*=8.1 Hz), 8.30 (d, 2H, *J*=8.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (CH_3), 44.0 (CH_2), 123.7 (CH), 123.8 (CH), 127.0 (CH), 128.1 (CH), 129.1 (CH), 132.5 (CH), 135.6, 140.3, 141.1, 147.8, 165.3, 170.3; MS (EI) *m/z* 91 (100), 321 (88) (M^+); HRMS Calcd for $C_{18}H_{15}N_3O_3$: 321.1113. Found 321.1104. Anal. Calcd for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.31; H, 4.60; N, 13.10.

*4-(4-Cyanobenzylidene)-1-benzyl-2-methylimidazol-5-one (**7ah**).* Compound **7ah** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=7:3, R_f=0.25) to give the product as a yellow solid (**7ah**, 38%). An analytical sample of **7ah** was obtained by recrystallization from Hex/EtOAc. Mp 140–143 °C (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3H, CH_3), 4.82 (s, 2H, CH_2), 7.08 (s, 1H, C=CH), 7.22 (d, 2H, *J*=6.9 Hz), 7.30–7.37 (m, 3H), 7.67 (d, 2H, *J*=8.4 Hz), 8.23 (d, 2H, *J*=8.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (CH_3), 44.0 (CH_2), 112.6, 118.6, 124.3 (CH), 127.0 (CH), 128.1 (CH), 129.0 (CH), 132.2 (CH), 135.7, 138.4, 140.7, 164.8, 170.2; MS (EI) *m/z* 91 (100), 301 (18) (M^+); HRMS Calcd for $C_{19}H_{15}N_3O$: 301.1215. Found 301.1208. Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.67; H, 4.71; N, 14.24.

*4-(4-Hydroxy-3-methoxybenzylidene)-1-benzyl-2-methylimidazol-5-one (**7ai**).* Compound **7ai** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=6:4, R_f=0.25) to give the product as a yellow solid (**7ai**, 41%). An analytical sample of **7ai** was obtained by recrystallization from MeOH/H_2O. Mp 162–164 °C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 4.82 (s, 2H, CH_2), 6.13 (s, 1H C=CH), 6.94 (d, 1H, *J*=8.3 Hz), 7.12 (s, 1H), 7.22 (d, 2H, *J*=7.0 Hz), 7.27–7.35 (m, 3H), 7.52 (dd, 1H, *J*=8.2, 1.4 Hz), 8.02 (d, 1H, *J*=1.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1 (CH_3), 43.8 (CH_2), 56.0 (CH_3), 113.8 (CH), 114.6 (CH), 126.9, 127.0 (CH), 127.7 (CH), 127.9 (CH), 128.4 (CH), 128.9 (CH), 136.2, 136.3, 146.7, 148.2, 161.0, 170.6; MS (EI) *m/z* 91 (100), 162 (26), 322 (73) (M^+); HRMS Calcd for $C_{19}H_{18}N_2O_3$: 322.1317. Found 322.1318. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.95; H, 5.68; N, 8.74.

*4-(2-Methoxybenzylidene)-1-benzyl-2-methylimidazol-5-one (**7aj**).* Compound **7aj** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=8:2, R_f=0.23) to give the product (**7aj**, 67%). Mp 107–108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 4.83 (s, 2H, CH_2), 7.02–7.10 (m, 2H), 7.24–7.42 (m, 7H), 8.73 (d, 1H, *J*=6.8 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 15.6 (CH_3), 43.0 (CH_2), 55.7 (CH_3), 111.3 (CH), 118.7 (CH), 120.6 (CH), 122.2, 126.8 (CH), 127.5 (CH), 128.8 (CH), 132.0 (CH), 132.2 (CH), 136.7, 137.9, 158.5, 163.3,

169.9; MS (EI) *m/z* 91 (100), 275 (12), 306 (24) (M^+); HRMS Calcd for $C_{19}H_{18}N_2O_2$: 306.1368. Found 306.1367.

*4-(2-Chlorobenzylidene)-1-benzyl-2-methylimidazol-5-one (**7ak**).* Compound **7ak** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=9:1, R_f=0.15) to give the product (**7ak**, 51%). Mp 92–94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 7.26–7.32 (m, 4H), 7.35–7.39 (m, 2H), 7.42–7.46 (m, 2H), 7.56–7.58 (m, 1H), 8.82–8.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7 (CH_3), 43.1 (CH_2), 119.0 (CH), 126.9 (CH), 127.5 (CH), 127.6 (CH), 128.8 (CH), 129.8 (CH), 131.2, 131.4 (CH), 132.9 (CH), 134.8, 136.5, 139.9, 165.7, 169.8; MS (EI) *m/z* 91 (100), 92 (8), 275 (99), 276 (39), 310 (8) (M^+), 312 (3) (M+2); HRMS Calcd for $C_{18}H_{15}N_2OCl$: 310.0873. Found 310.0873.

*4-Benzylidene-1,2-dimethylimidazol-5-one (**7ba**).* Compound **7ba** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=5:5, R_f=0.33) to give the product (**7ba**, 81%). An analytical sample of **7ba** was obtained by recrystallization from Hex/EtOAc. Mp 115–117 °C (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (s, 3H, CH_3), 3.19 (s, 3H, NCH_3), 7.11 (s, 1H, C=CH), 7.34–7.44 (m, 3H), 8.13 (d, 2H, *J*=1.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.8, 26.7, 127.4, 128.8, 130.2, 132.3, 134.3, 138.9, 162.8, 170.9; MS (EI) *m/z* 200 (100) (M^+).

*4-(4-Methoxybenzylidene)-1,2-dimethylimidazol-5-one (**7bb**).* Compound **7bb** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=7:3, R_f=0.08) to give the product (**7bb**, 86%). An analytical sample of **7bb** was obtained by recrystallization from Hex/EtOAc. Mp 136–137 °C (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 3.80 (s, 1H, OCH_3), 6.89 (d, 2H, *J*=8.6 Hz), 7.03 (s, 1H, C=CH), 8.07 (d, 2H, *J*=8.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7 (CH_3), 26.6 (CH_3), 55.4 (OCH_3), 114.4 (CH), 127.26, 127.28 (CH), 134.1 (CH), 137.1, 161.3, 161.4, 170.8; MS (EI) *m/z* 56 (100), 230 (20) (M^+); HRMS Calcd for $C_{13}H_{14}N_2O_2$: 230.1055. Found: 230.1048. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.78; H, 6.10; N, 12.38.

*4-(4-Dimethylaminobenzylidene)-1,2-dimethylimidazol-5-one (**7bc**).* Compound **7bc** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=5:5, R_f=0.20) to give the product (**7bc**, 72%). An analytical sample of **7bc** was obtained by recrystallization from Hex/EtOAc. Mp 207–208 °C (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H, CH_3), 3.03 (s, 6H, CH_3), 3.16 (s, 3H, CH_3), 6.69 (d, 2H, *J*=9.0 Hz), 7.07 (s, 1H, C=CH), 8.04 (d, 2H, *J*=8.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7 (CH_3), 26.7 (CH_3), 40.2 (CH_3), 111.9 (CH), 122.4, 129.0 (CH), 134.3 (CH), 134.8, 151.7, 159.2, 170.8; MS (EI) *m/z* 56 (16), 243 (100) (M^+); HRMS Calcd for $C_{14}H_{17}N_3O$: 243.1372. Found 243.1374.

*4-(4-Hydroxybenzylidene)-1,2-dimethylimidazol-5-one (**7bd**).* Compound **7bd** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=4:6, R_f=0.20) to give the product (**7bd**, 91%). An analytical sample of **7bd** was obtained by recrystallization from MeOH/H_2O. Mp 236–238 °C (MeOH/H_2O); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.32 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 6.82 (d, 2H, *J*=9.6 Hz), 6.88 (s, 1H, C=CH), 8.07 (d, 2H, *J*=8.4 Hz), 10.09 (bs, 1H, OH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 15.7 (CH_3), 26.6 (CH_3), 116.2 (CH), 125.8, 125.9 (CH), 134.5 (CH), 136.8, 160.0, 162.7, 170.3; MS (EI) *m/z* 56 (100), 216 (100) (M^+); HRMS Calcd for $C_{12}H_{12}N_2O_2$: 216.0899. Found 216.0902. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.35; H, 5.53; N, 12.97.

*4-(4-Chlorobenzylidene)-1,2-dimethylimidazol-5-one (**7be**).* Compound **7be** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=7:3, R_f=0.25) to give the product (**7be**, 92%). An analytical sample of **7be** was obtained by recrystallization from Hex/EtOAc. Mp 158–160 °C (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H, CH_3), 3.15 (s, 3H, NCH_3), 7.00 (s, 1H, C=CH), 7.35 (d, 2H, *J*=8.5 Hz), 8.04 (d, 2H, *J*=8.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7 (CH_3), 26.6 (CH_3), 125.6 (CH), 128.9 (CH), 132.7, 133.3 (CH), 136.0, 139.0, 163.1, 170.5; MS (EI) *m/z* 234 (100) (M^+), 236 (68) (M+2). HRMS Calcd for $C_{12}H_{11}N_2OCl$: 234.0560. Found: 234.0563. Anal. Calcd for $C_{12}H_{11}N_2OCl$: C, 61.41; H, 4.72; N, 11.94. Found: C, 61.72; H, 4.68; N, 11.83.

*4-(4-Bromobenzylidene)-1,2-dimethylimidazol-5-one (**7bf**).* Compound **7bf** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=7:3, R_f=0.15) to give the product (**7bf**, 98%). An analytical sample of **7bf** was obtained by recrystallization from Hex/MeOH. Mp 154–157 °C (Hex/MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 3H, CH_3), 3.17 (s, 3H, NCH_3), 6.99 (s, 1H, C=CH), 7.52 (d, 2H, *J*=8.5 Hz), 7.98 (d, 2H, *J*=8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9 (CH_3), 26.8 (CH_3), 124.7, 125.8 (CH), 132.1 (CH), 133.3, 133.6 (CH), 139.3, 163.3, 170.7; MS (EI) *m/z* 56 (100), 278 (89) (M^+), 280 (68) (M+2). HRMS Calcd for $C_{12}H_{11}N_2OBr$: 278.0055. Found: 278.0052. Anal. Calcd for $C_{12}H_{11}N_2OBr$: C, 51.63; H, 3.97; N, 10.04. Found: C, 51.40; H, 3.95; N, 9.83.

*4-(4-Nitrobenzylidene)-1,2-dimethylimidazol-5-one (**7bg**).* Compound **7bg** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=6:4, R_f=0.20) to give the product (**7bg**, 53%). An analytical sample of **7bg** was obtained by recrystallization from Hex/EtOAc. Mp 200–202 °C (dec) (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H, CH_3), 3.19 (s, 3H, CH_3), 7.01 (s, 1H, C=CH), 8.20 (d, 2H, *J*=9.1 Hz), 8.24 (d, 2H, *J*=9.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.0 (CH_3), 26.9 (CH_3), 123.3 (CH), 123.8 (CH), 132.6 (CH), 140.6, 141.6, 147.9, 165.6, 170.5; MS (EI) *m/z* 224 (37), 225 (100) (M^+); HRMS Calcd for $C_{12}H_{11}N_3O_3$: 245.0800. Found 245.0802.

*4-(4-Cyanobenzylidene)-1,2-dimethylimidazol-5-one (**7bh**).* Compound **7bh** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=6:4, R_f=0.18) to give the product (**7bh**, 43%). An analytical sample of **7bh** was obtained by recrystallization from Hex/EtOAc. Mp 219–220 °C (dec) (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.39 (s, 3H, CH_3), 3.19 (s, 3H, CH_3), 7.00 (s, 1H, C=CH), 7.66 (d, 2H, *J*=7.8 Hz), 8.20 (d, 2H, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.0 (CH_3), 26.9 (CH_3), 112.8, 118.9, 124.1 (CH), 132.37 (CH), 132.39 (CH), 138.7, 141.2, 165.1, 170.5; MS (EI) *m/z* 56 (100), 224 (20), 225 (94) (M^+); HRMS Calcd for $C_{13}H_{11}N_3O$: 225.0902. Found 225.0904.

*4-(4-Hydroxy-3-methoxybenzylidene)-1,2-dimethylimidazol-5-one (**7bi**).* Compound **7bi** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=4:6, R_f=0.20) to give the product (**7bi**, 70%). An analytical sample of **7bi** was obtained by recrystallization from Hex/MeOH. Mp 196–198 °C (dec) (Hex/MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.32 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.84 (d, 1H, *J*=8.2 Hz), 6.89 (s, 1H), 7.65 (d, 1H, *J*=7.8 Hz), 7.95 (s, 1H), 9.72 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 15.4 (CH_3), 26.2 (CH_3), 55.6 (OCH_3), 115.6, 115.7 (CH), 125.7 (CH), 125.8 (CH), 126.7 (CH), 136.4, 147.5, 149.2, 162.2, 169.8; MS (EI) *m/z* 56 (18), 246 (100) (M^+); HRMS Calcd for $C_{13}H_{14}N_2O_3$:246.1004. Found 246.1002.

*4-(Indol-3-ylmethylidene)-1,2-dimethylimidazol-5-one (**7bl**).* Compound **7bl** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=4:6, R_f=0.13) to give the product (**7bl**, 77%). An analytical sample of

7bl was obtained by recrystallization from Hex/MeOH. Mp 239–241 °C (dec) (Hex/MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.34 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 7.14–7.22 (m, 2H), 7.31 (s, 1H, C=CH), 7.47 (d, 1H, J=7.6 Hz), 8.19 (d, 1H, J=7.6 Hz), 8.39 (d, 1H, J=2.0 Hz), 11.92 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 15.3 (CH_3), 26.2 (CH_3), 111.1, 112.1 (CH), 119.4 (CH), 119.6 (CH), 120.7 (CH), 122.5 (CH), 126.7, 132.7 (CH), 134.0, 136.4, 159.3, 169.2; MS (EI) m/z 56 (18), 239 (100) (M^+); HRMS Calcd for $C_{14}H_{13}N_3O$: 239.1059. Found 239.1060.

4-Benzylidene-1-benzyl-2-phenylimidazol-5-one (***8aa***). Compound **8aa** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=9:1, R_f=0.20) to give the product (**8aa**, 54%). An analytical sample of **8aa** was obtained by recrystallization from Hex/EtOAc. Mp 138–139 °C (Hex/EtOAc); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.98 (s, 2H, CH_2), 7.07–7.09 (m, 2H), 7.27–7.28 (m, 4H), 7.46–7.51 (m, 6H), 7.73–7.75 (m, 2H), 8.31–8.33 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 44.5 (CH_2), 126.3 (CH), 127.4 (CH), 127.8 (CH), 128.3 (CH), 128.7 (CH), 128.8 (CH), 129.0, 130.5 (CH), 131.6 (CH), 132.4 (CH), 134.0, 136.6, 138.5, 162.7, 170.7; MS (EI) m/z 338 (100) (M^+); HRMS Calcd for $C_{23}H_{18}N_2O$: 338.1419. Found 338.1416.

4-(4-Methoxybenzylidene)-1-benzyl-2-phenylimidazol-5-one (***8ab***). Compound **8ab** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=9:1, R_f=0.13) to give the product (**8ab**, 15%). Mp 160–162 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.83 (s, 3H, OCH_3), 4.98 (s, 2H, CH_2), 7.05–7.08 (m, 4H), 7.22–7.30 (m, 4H), 7.48–7.51 (m, 2H), 7.55–7.57 (m, 1H), 7.73 (d, 2H, J=7.4 Hz), 8.31 (d, 2H, J=8.7 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 44.4 (CH_2), 55.4 (CH_3), 114.5 (CH), 126.3 (CH), 126.8, 127.3 (CH), 128.0 (CH), 128.3 (CH), 128.7 (CH), 128.8 (CH), 129.1 (CH), 131.4 (CH), 134.4 (CH), 136.5, 136.8, 161.2, 161.3, 170.6; MS (EI) m/z 91 (57) 368 (100) (M^+); HRMS (EI) Calcd for $C_{24}H_{20}N_2O_2$:368.1525. Found 368.1519.

4-(4-Dimethylaminobenzylidene)-1-benzyl-2-phenylimidazol-5-one (***8ac***). Compound **8ac** was prepared by the general procedure E. The reaction was purified by flash column chromatography (CH_2Cl_2, R_f=0.38) to give the product (**8ac**, 42%). An analytical sample of **8ac** was obtained by recrystallization from EtOAc. Mp 195–197 °C (EtOAc); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.03 (s, 6H, CH_3), 4.98 (s, 2H, CH_2), 6.79 (d, 2H, J=8.4 Hz), 7.06 (d, 2H, J=7.3 Hz), 7.16 (s, 1H), 7.22 (d, 1H, J=7.2 Hz), 7.26–7.30 (m, 2H), 7.46–7.48 (m, 2H), 7.53 (d, 1H, J=6.5 Hz), 7.70 (d, 2H, J=7.5 Hz), 8.18 (d, 2H, J=8.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 40.1 (CH_3), 44.8 (CH_2), 112.3 (CH), 122.0, 126.8 (CH), 127.7 (CH), 128.6 (CH), 129.1 (CH), 129.2 (CH), 130.0 (CH), 131.4 (CH), 134.5, 135.0 (CH), 137.6, 152.2, 159.1, 170.8; MS (EI) m/z 91 (40), 290 (55), 381 (100) (M^+); HRMS Calcd for $C_{25}H_{23}N_3O$: 381.1841. Found 381.1842.

4-(4-Hydroxybenzylidene)-1-benzyl-2-phenylimidazol-5-one (***8ad***). Compound **8ad** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=7:3, R_f=0.18) to give the product (**8ad**, 40%). An analytical sample of **8ad** was obtained by recrystallization from Hex/EtOAc. Mp 248–250 °C (Hex/EtOAc); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.97 (s, 2H, CH_2), 6.88 (d, 2H, J=8.8 Hz), 7.06 (d, 2H, J=6.8 Hz), 7.19–7.30 (m, 4H), 7.47–7.58 (m, 3H), 7.71 (d, 2H, J=7.2 Hz), 8.20 (d, 2H, J=8.8 Hz), 10.33 (bs, 1H, OH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 44.8 (CH_2), 116.5 (CH), 125.8, 126.7 (CH), 127.8 (CH), 128.7 (CH), 129.16 (CH), 129.24 (CH), 129.7, 131.8 (CH), 135.3 (CH), 136.2, 137.3, 160.7, 161.1, 171.1; MS (EI) m/z 354 (100) (M^+); HRMS Calcd for $C_{23}H_{18}N_2O_2$: 354.1368. Found 154.1377.

4-(4-Chlorobenzylidene)-1-benzyl-2-phenylimidazol-5-one (***8ae***). Compound **8ae** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=9:1, R_f=0.25) to give the product (**8ae**, 29%). Mp 164–165 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.98 (s, 2H, CH_2), 7.07–7.09 (m, 2H), 7.22–7.28 (m, 4H), 7.48–7.60 (m, 5H), 7.73 (d, 2H, J=7.4 Hz), 8.33 (d, 2H, J=8.4 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 44.5 (CH_2), 126.1 (CH), 126.3 (CH), 127.4 (CH), 128.3 (CH), 128.7 (CH), 128.8 (CH), 128.9 (CH), 131.7 (CH), 132.9, 133.8 (CH), 135.1, 136.6, 138.8, 163.1, 170.6; MS (EI) m/z 91 (100), 372 (88) (M^+), 374 (29) (M+2); HRMS (EI) Calcd for $C_{23}H_{17}N_2OCl$:372.1029. Found 372.1031.

4-(4-Bromobenzylidene)-1-benzyl-2-phenylimidazol-5-one (***8af***). Compound **8af** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=9:1, R_f=0.25) to give the product (**8af**, 44%). Mp 166–168 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.98 (s, 2H, CH_2), 7.08 (d, 2H, J=8.0 Hz), 7.23–7.31 (m, 4H), 7.49–7.53 (m, 2H), 7.58–7.60 (m, 1H), 7.69–7.75 (m, 4H), 8.26 (d, 2H, J=8.0 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 44.5 (CH_2), 124.1, 126.2 (CH), 126.3 (CH), 127.3 (CH), 128.3 (CH), 128.7 (CH), 128.8 (CH), 131.7 (CH), 131.8 (CH), 133.2, 134.0 (CH), 136.5, 138.9, 163.2, 170.6; MS (EI) m/z 91 (100), 416 (32) (M^+), 418 (34) (M+2); HRMS (EI) Calcd for $C_{23}H_{17}N_2OBr$:416.0524. Found 416.0528.

4-(4-Nitrobenzylidene)-1-benzyl-2-phenylimidazol-5-one (***8ag***). Compound **8ag** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=8:2, R_f=0.27) to give the product (**8ag**, 63%). An analytical sample of **8ag** was obtained by recrystallization from Hex/MeOH. Mp 188–190 °C (Hex/MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.99 (s, 2H, CH_2), 7.10 (d, 2H, J=7.7 Hz), 7.24–7.31 (m, 3H), 7.36 (s, 1H, C=CH), 7.51–7.62 (m, 3H), 7.77 (d, 2H, J=7.3 Hz), 8.29 (d, 2H, J=8.8 Hz), 8.54 (d, 2H, J=8.8 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 44.7 (CH_2), 123.7 (CH), 124.2 (CH), 126.3 (CH), 127.4 (CH), 128.46 (CH), 128.52, 128.7, 128.8 (CH), 132.1 (CH), 132.9 (CH), 136.4, 140.4, 141.0, 147.4, 165.0, 170.6; MS (EI) m/z 91 (18), 383 (100) (M^+); HRMS Calcd for $C_{23}H_{17}N_3O_3$: 383.1270. Found 383.1274.

Methyl 2-(2-acetamido-3-phenylacrylamido)acetate (N-Ac–ΔPhe–Gly–OMe)[56,68] (***13***). Compound **13** was prepared by the general procedure C. The reaction was purified by flash column chromatography (EtOAc, R_f=0.20) to give the product as a solid (**13**, 93%). Mp 128–132 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.00 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.89 (d, 2H, J=5.8 Hz, CH_2), 7.13 (s, 1H, C=CH), 7.33–7.35 (m, 1H), 7.38–7.42 (m, 2H), 7.55 (d, 2H, J=7.6 Hz), 8.39 (t, 1H, J=5.7 Hz, NH), 9.44 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 22.8 (CH_3), 41.2 (CH_2), 51.6 (CH_3), 128.5 (CH), 128.7 (CH), 128.9 (CH), 129.3, 134.0, 165.3, 169.4, 170.2; MS (EI) m/z 234 (100), 276 (22) (M^+).

Methyl 2-(2-acetamido-3-(4-acetoxyphenyl)acrylamido)acetate (N-Ac–ΔTyr(OAc)–Gly–OMe)[56] (***14***). Compound **14** was prepared by the general procedure C. The reaction was purified by flash column chromatography (Hex/EtOAc=2:8, R_f=0.08) to give the product as a solid (**14**, 70%). Mp 110–114 °C (dec); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.00 (s, 3H, CH_3), 2.26 (s, 3H, OAc), 3.63 (s, 3H, OCH_3), 3.88 (d, 2H, J=5.8 Hz, CH_2), 7.13 (s, 1H, C=CH), 7.15 (d, 2H, J=8.6 Hz), 7.58 (d, 2H, J=8.6 Hz), 8.43 (t, 1H, J=5.8 Hz, NH), 9.48 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.0 (CH_3), 23.0 (CH_3), 41.4 (CH_2), 51.9 (CH_3), 122.2 (CH), 128.3 (CH), 129.3, 130.8 (CH), 131.7, 150.7, 165.6, 169.4, 169.9, 170.5; MS (EI) m/z 203 (23), 250 (39), 274 (100), 316 (50), 317 (22), 334 (18) (M^+).

Methyl 2-(2-acetamido-3-(4-acetoxyphenyl)acrylamido)propionate (N-Ac–ΔTyr(OAc)–Ala–OMe)[69–71] (***15***). Compound **15** was prepared by the general procedure C. The reaction was purified by flash column chromatography (Hex/EtOAc=1:9, R_f=0.15) to give the product as a solid (**15**, 40%). Mp 141–144 °C (dec); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.32 (d, 3H, J=7.2 Hz, CH_3), 1.99 (s, 3H, CH_3), 2.26 (s,

3H, OAc), 3.63 (s, 3H, OCH_3), 4.32–4.39 (m, 1H), 7.02 (s, 1H, C=CH), 7.15 (d, 2H, *J*=8.5 Hz), 7.57 (d, 2H, *J*=8.5 Hz), 8.36 (d, 1H, *J*=7.0 Hz, NH), 9.42 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 17.0 (CH_3), 21.0 (CH_3), 23.0 (CH_3), 48.4 (CH), 52.1 (CH_3), 122.2 (CH), 127.4 (CH), 129.6, 130.7 (CH), 131.9, 150.6, 165.2, 169.4, 169.8, 173.2; MS (EI) *m*/*z* 203 (67), 264 (100), 288 (32), 306 (89), 348 (38) (M^+).

Methyl 2-(4-benzylidene-2-methyl-5-imidazolon-1-yl)acetate[19,56,72,73] (***16***). Compound **16** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=7:3, R_f=0.18) to give the product as a solid (**16**, 64%). Mp 110–114 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.40 (s, 2H, CH_2), 7.15 (s, 1H, C=CH), 7.36–7.44 (m, 3H), 8.14 (d, 2H, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7 (CH_3), 41.5 (CH_2), 53.0 (CH_3), 128.6 (CH), 129.0 (CH), 130.6 (CH), 132.5 (CH), 134.2, 138.1, 161.5, 168.2, 170.2; MS (EI) *m*/*z* 258 (100) (M^+). HRMS Calcd for $C_{14}H_{14}N_2O_3$: 258.1004. Found: 258.1007.

Methyl 2-(4-(4-acetoxybenzylidene)-2-methyl-5-imidazolon-1-yl) acetate[56] (***17a***) *and methyl 2-(4-(4-hydroxybenzylidene)-2-methyl-5-imidazolon-1-yl)acetate* (***17b***). Compound **17a** and **17b** were prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=7:3 then 5:5) to give the products as solids (**17a**, 51%, R_f=0.10 (Hex/EtOAc=7:3); **17b**, 22%, R_f=0.13 (Hex/EtOAc=5:5)). **17a**:[56] An analytical sample of **17a** was obtained by recrystallization from Hex/MeOH. Mp 138–140 °C (Hex/MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 3H, CH_3), 2.34 (s, 3H, OAc), 3.78 (s, 3H, OCH_3), 4.39 (s, 2H, CH_2), 7.11 (s, 1H, C=CH), 7.16 (d, 2H, *J*=8.6 Hz), 8.17 (d, 2H, *J*=8.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7 (CH_3), 21.4 (CH_3), 41.5 (CH_2), 53.0 (CH_3), 122.1 (CH), 127.3 (CH), 131.9, 133.7 (CH), 138.0, 152.3, 161.7, 168.2, 169.2, 170.1; MS (EI) *m*/*z* 274 (100), 316 (32) (M^+). **17b**: An analytical sample of **17b** was obtained by recrystallization from Hex/$CHCl_3$. Mp 180–182 °C (Hex/$CHCl_3$); ^{1}H NMR (MeOH-d_4, 400 MHz) δ 2.33 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.51 (s, 2H, CH_2), 6.85 (d, 2H, *J*=8.7 Hz), 7.05 (s, 1H, C=CH), 8.02 (d, 2H, *J*=8.7 Hz); ^{13}C NMR (MeOH-d_4, 100 MHz) δ 15.3 (CH_3), 42.4 (CH_2), 53.4 (CH_3), 117.0 (CH), 127.0, 130.1 (CH), 135.9 (CH), 136.7, 161.9, 162.5, 170.3, 172.0; MS (EI) *m*/*z* 274 (100) (M^+). HRMS Calcd for $C_{14}H_{14}N_2O_4$: 274.0954. Found: 274.0954.

Methyl 2-(4-(4-acetoxybenzylidene)-2-methyl-5-imidazolon-1-yl) propionate (***18a***) *and methyl 2-(4-(4-hydroxybenzylidene)-2-methyl-5-imidazolon-1-yl)propionate* (***18b***). Compound **18a** and **18b** were prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=7:3 then 6:4) to give the products as oils (**18a**, 40%, R_f=0.15 (Hex/EtOAc=7:3); **18b**, 10%, R_f=0.15 (Hex/EtOAc=6:4)). **18a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.66 (d, 3H, *J*=7.4 Hz, CH_3), 2.31 (s, 3H, CH_3), 2.37 (s, 3H, OAc), 3.77 (s, 3H, OCH_3), 4.88 (q, 1H, *J*=7.4 Hz, CH), 7.08 (s, 1H, C=CH), 7.16 (d, 2H, *J*=8.7 Hz), 8.16 (d, 2H, *J*=8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4 (CH_3), 16.9 (CH_3), 21.4 (CH_3), 49.6 (CH), 53.1 (CH_3), 122.1 (CH), 127.1 (CH), 131.9, 133.7 (CH), 137.7, 152.2, 161.8, 169.2, 170.1, 170.6; MS (EI) *m*/*z* 229 (5), 288 (100), 330 (88) (M^+). HRMS Calcd for $C_{17}H_{18}N_2O_5$: 330.1216. Found: 330.1219. **18b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62 (d, 3H, *J*=7.4 Hz, CH_3), 2.32 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.85 (q, 1H, *J*=7.3 Hz, CH), 6.81 (d, 2H, *J*=8.4 Hz), 7.07 (s, 1H, C=CH), 7.93 (d, 2H, *J*=8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (CH_3), 16.4 (CH_3), 49.7 (CH), 53.1 (CH_3), 116.3 (CH), 126.0, 129.8 (CH), 134.7 (CH), 134.9, 159.5, 160.0, 170.3, 170.6; MS (EI) *m*/*z* 229 (17), 288 (100) (M^+). HRMS Calcd for $C_{15}H_{16}N_2O_4$: 288.1110. Found: 288.1112.

4-Benzylidene-2-(1-phthalimidoethyl)-5-oxazolone (***22***). To a mixture of *N*-Phth–Ala–Gly (**21**, prepared from alkaline hydrolysis of *N*-Phth–Ala–Gly-OMe[74,75] (**20**), 9.79 g, 35.5 mmol) and sodium acetate (1.82 g, 22.2 mmol, 0.625 equiv) in acetic anhydride (35 mL) was added benzaldehyde (4.0 mL, 4.14 g, 39 mmol, 1.1 equiv) and the solution was stirred at 60 °C for 12 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc. The organic solution was washed with saturated aqueous Na_2CO_3 solution and saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (Hex/EtOAc=95:5, then 8:2) to give the product as a solid (**22**, 2.72 g, 7.86 mmol), 22%, R_f=0.23 (Hex/EtOAc=8:2). An analytical sample of **22** was obtained by recrystallization from Hex/$CHCl_3$. Mp 146–150 °C (Hex/$CHCl_3$); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.76 (d, 3H, *J*=7.0 Hz, CH_3), 5.54 (q, 1H, *J*=7.0 Hz, CH), 7.38 (s, 1H, C=CH), 7.47–7.50 (m, 3H), 7.90–7.96 (m, 4H), 8.16–8.19 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.5 (CH_3), 43.5 (CH), 123.6 (CH), 129.0 (CH), 131.2, 131.65 (CH), 131.78, 132.27 (CH), 132.32 (CH), 132.8, 135.0 (CH), 166.1, 166.7, 166.9; MS (EI) *m*/*z* 174 (39), 346 (100) (M^+). HRMS Calcd for $C_{20}H_{14}N_2O_4$: 346.0954. Found: 346.0953.

N-Methyl-(2-(2-phthalimidopropionamido))-3-phenylacrylamide (N-Phth–Ala–ΔPhe–NMe) (***23***). Compound **23** was prepared by the general procedure C. The reaction was purified by flash column chromatography (Hex/EtOAc=5:5, R_f=0.08) to give the product as a white solid (**23**, 44%). An analytical sample of **23** was obtained by recrystallization from Hex/EtOAc. Mp 104–110 °C (Hex/EtOAc); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.56 (d, 3H, *J*=7.2 Hz, CH_3), 2.70 (d, 3H, *J*=4.6 Hz, NCH_3), 5.05 (q, 1H, *J*=7.1 Hz, CH), 7.08 (s, 1H, C=CH), 7.29–7.34 (m, 3H), 7.51–7.53 (m, 2H), 7.69 (d, 1H, *J*=4.6 Hz, NH), 7.85–7.87 (m, 2H), 7.92–7.94 (m, 2H), 9.66 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.8 (CH_3), 26.3 (CH_3), 48.1 (CH), 123.2 (CH), 128.4 (CH), 128.7 (CH), 129.5, 129.6 (CH), 131.9, 133.9, 134.5 (CH), 165.0, 167.7, 168.8; MS (EI) *m*/*z* 174 (66), 346 (74), 359 (100), 377 (39) (M^+). HRMS Calcd for $C_{21}H_{19}N_3O_4$: 377.1376. Found: 377.1362.

4-Benzylidene-1-methyl-2-(1-phthalimidoethyl)-5-imidazolone (***24***). Compound **24** was prepared by the general procedure E. The reaction was purified by flash column chromatography (Hex/EtOAc=7:3, R_f=0.20) to give the product as a yellow solid (**24**, 61%). An analytical sample of **24** was obtained by recrystallization from Hex/CH_3CN. Mp 210–212 °C (Hex/CH_3CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.94 (d, 3H, *J*=7.0 Hz, CH_3), 3.06 (s, 3H, NCH_3), 5.40 (q, 1H, *J*=7.0 Hz, CH), 7.17 (s, 1H, C=CH), 7.34–7.36 (m, 3H), 7.76–7.79 (m, 2H), 7.87–7.89 (m, 2H), 8.13–8.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (CH_3), 26.9 (CH_3), 44.2 (CH), 123.7 (CH), 128.6 (CH), 129.4 (CH), 130.4 (CH), 131.6, 132.7 (CH), 134.1, 134.5 (CH), 138.1, 161.4, 167.3, 171.0; MS (EI) *m*/*z* 359 (100) (M^+). HRMS Calcd for $C_{21}H_{17}N_3O_3$: 359.1270. Found: 359.1272.

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Supplementary data

^{1}H, ^{13}C NMR, UV–Vis and fluorescence spectra for representative compounds. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.04.102.

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