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A CONVENIENT SYNTHESIS OF PAPAVERINE ANALOGS *VIA* PHOTOCYCLIZATION OF *N*-ACYL-α-DEHYDROARYLALANIN-AMIDE DERIVATIVES

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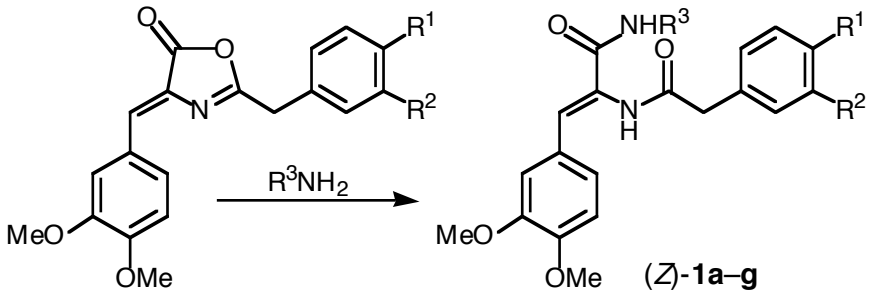
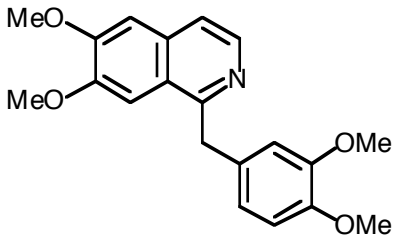
Abstract–Photochemical cyclizations of (*Z*)-*N*-(substituted phenylacetyl)-α-dehydro(3,4-dimethoxyphenyl)alaninamides in methanol were found to proceed regioselectively giving papaverine analogs in satisfactory yields, irrespective of the substituent introduced. MM2 and PM5 calculations revealed that steric hindrance of the methoxy group introduced at the *meta*-position on the styryl benzene ring is responsible for the regioselective photocyclization observed.

Photochemistry has continued to contribute to the development of efficient and selective transformations of organic materials into pharmaceutically important heterocyclic compounds.[1] It is well-known that numerous biomolecules and natural products contain various types of heterocyclic rings as their principal constituents. We have been interested in exploring the excited-state reactivities of α-dehydroamino acid derivatives, one of the main constituents of some antibiotics,[2] as well as in demonstrating the synthetic utility of these photochemical reactions. Taking into account that α-dehydroamino acid-derived products may possess high biological activities, we embarked on a systematic study regarding photochemical reactivities of aryl-substituted α-dehydroalanine derivatives and discovered novel photocyclization reactions forming pharmaceutically useful products.[3,4] One of the important findings is that the photocyclization of substituted (*Z*)-*N*-acetyl-α-dehydrophenylalaninamides in methanol and acetonitrile constitutes a useful method for constructing the isoquinoline skeleton.[3] Very recently, we found that the introduction of a methoxy group at the *meta*-position on the styryl benzene ring accomplishes regioselective photocyclization to give 6-methoxyisoquinoline derivative in a reasonable yield without forming any 8-methoxy derivative.[5] These findings stimulated us to photochemically synthesize analogs of papaverine, one of the isoquinoline alkaloids, as an extension of our study on the photocyclization of *N*-acyl-α- dehydroamino acid derivatives. A careful literature survey demonstrates that although there are many synthetic routes to papaverine and its analogs, no convenient photochemical route to these analogs is known.[6] Thus, it is of significance to develop a photochemical method for synthesizing papaverine analogs. To this end we designed and synthesized (*Z*)-*N*-(substituted phenylacetyl)-α-dehydro(3,4-dimethoxyphenyl)alaninamides [(*Z*)-**1a**–**g**], hoping to establish a new route to analogs of pharmaceutically important papaverine.

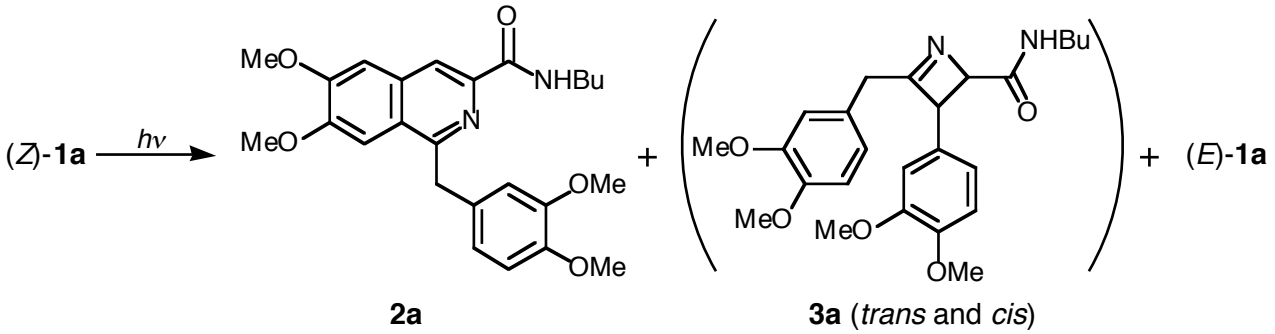


	1a	1b	1c	1d	1e	1f	1g
R^1:	OMe	OMe	OMe	H	Cl	Cl	F
R^2:	OMe	OMe	H	H	Cl	H	H
R^3:	Bu	CH_2Ph	Bu	Bu	Bu	Bu	Bu



Scheme 1

The starting (*Z*)-isomers were prepared in high yields (>80%) by the ring opening reactions of (*Z*)-2-(substituted benzyl)-4-(methoxy-substituted benzylidene)-5(4*H*)-oxazolones with butylamine [for (*Z*)-**1a**,**c**–**g**] or benzylamine [for (*Z*)-**1b**] in the presence of triethylamine (Scheme 1).[7] The synthesis of these oxazolones was achieved by the Knoevenagel-type condensation and ring closure reactions between methoxy-substituted benzaldehydes and *N*-(substituted phenylacetyl)glycines,[7] though their yields were not so high (20–27%). After a nitrogen purged methanol solution of (*Z*)-**1a** (1.0×10^{-3} mol dm^{-3}) was irradiated with Pyrex-filtered light (>280 nm) from a 400 W high pressure Hg lamp for 360 min at room temperature, the product mixture obtained was subjected to column or preparative thin layer chromatography over silica gel (ethyl acetate-chloroform), which allowed us to isolate papaverine analog (**2a**, 46%) as shown in Scheme 2. In addition, (*E*)-**1a** could be isolated in 33% yield from the mixture obtained by the 60 min irradiation of the same solution. The structures of (*E*)-**1a** and **2a** were determined based on their spectroscopic and physical properties. A ^{1}H NMR spectral analysis of the product mixture showed that there is formation of *trans*-1-azetine [*trans*-**3a**; δ= 4.37 and 5.45 ppm, *J*= 6.7 Hz (azetine ring-proton signals)] and *cis*-**3a** [δ= 4.82 and 5.69 ppm, *J*= 10.4 Hz (azetine ring-proton signals)], as predicted from the previous studies (Scheme 2).[3] However, any attempts to isolate these azetine derivatives were unsuccessful, probably because of the much lower stability of **3a** as compared to that of 1-azetines previously isolated.



Scheme 2

Since the photocyclization of (*Z*)-**1a** accompanies side reactions to some extent, the sum of composition for

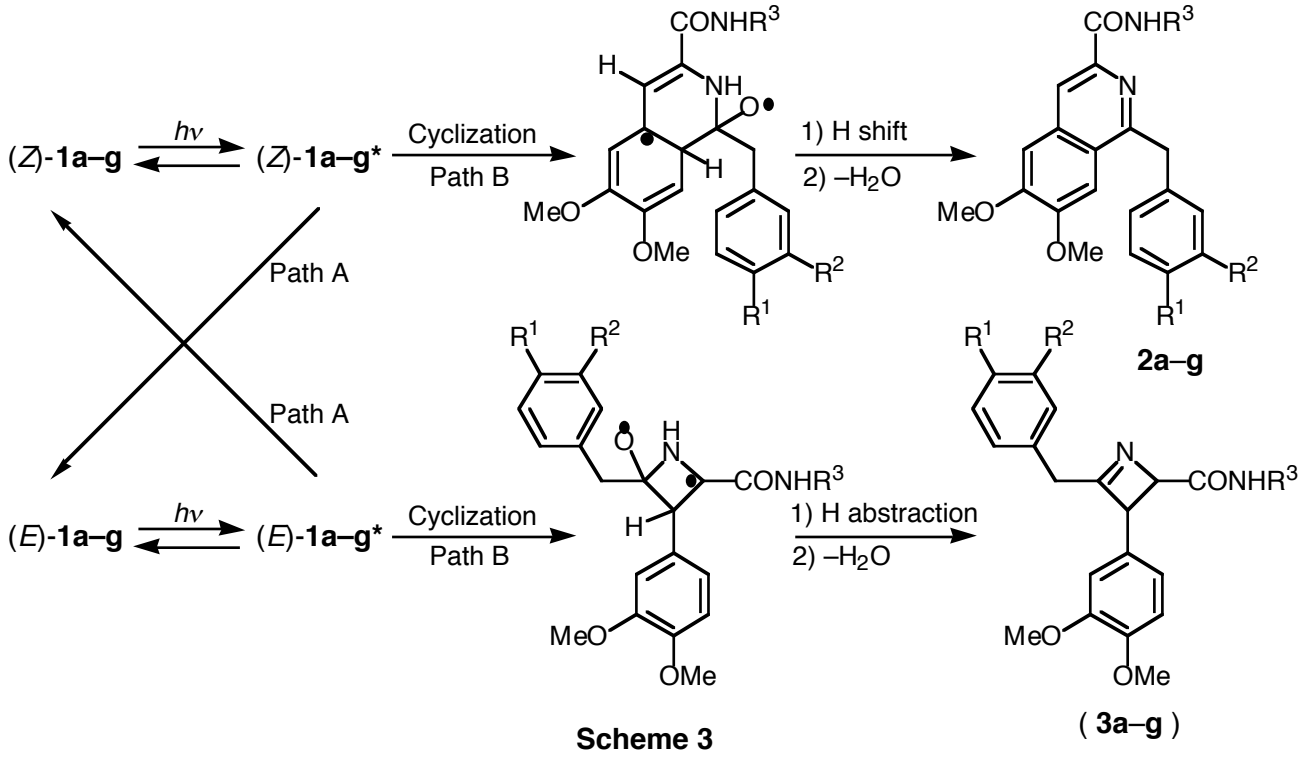
(*Z*)-**1a**, (*E*)-**1a**, **2a**, and **3a** was regarded as 100% for estimating the compositions of these compounds based on the area ratio of given ^{1}H NMR signals (Table 1). The photocyclization of (*Z*)-**1a** in methanol gave the same product distribution as that derived from the cyclization of substituted *N*-acetyl-α-dehydrophenylalaninamides, thus allowing us to discuss the rate of the isomerization relative to the rate of the cyclization on the basis of the same reaction scheme as that previously proposed (Scheme 3).[3] The result obtained for (*Z*)-**1a** demonstrates the rapid production of (*E*)-**1a** and the subsequent increase in a composition for **2a** and **3a** with the decrease of (*Z*)- and (*E*)-isomer compositions. In addition, the use of (*E*)-**1a** (1.0×10^{-3} mol dm^{-3}) as the starting isomer gave almost the same isomer composition as that derived from (*Z*)-**1a** at the early stage of the reaction (Table 1), confirming that the rate of the photoisomerization (Path A in Scheme 3) is much faster than that of the subsequent photocyclization process (Path B). The

Table 1. Relation between irradiation time and composition (%) of each compound obtained by the irradiation of (*Z*)-**1a** and (*E*)-**1a** in methanol

Compound	Irradiation time (min)						
	0	30	60	90	120	240	360
(Z)-**1a**	100	39.6	38.6	36.2	34.1	18.4	3.5
	(0)[a]	(38.9)[a]	(38.0)[a]				
(E)-**1a**	0	57.3	53.5	50.2	46.4	25.9	4.3
	(100)[a]	(58.0)[a]	(54.5)[a]				
2a	0	1.8	4.6	8.0	12.5	38.0	63.9
	(0)[a]	(1.5)[a]	(4.0)[a]				
trans-**3a**	0	0.8	2.0	3.2	4.4	12.0	19.6
	(0)[a]	(1.0)[a]	(2.0)[a]				
cis-**3a**	0	0.5	1.3	2.4	2.6	5.7	8.7
	(0)[a]	(0.6)[a]	(1.5)[a]				

a) Composition obtained by the irradiation of (*E*)-**1a**.

data in Table 1 also show that selectivity for **2a** [defined as the product-composition ratio, namely, **2**/(**2** + **3**)] is in the range of 60–70% and comparable to that (69%) for isoquinoline derivative generated by the irradiation of *N*-acetyl-α-dehydro(4-methoxyphenyl)alaninamide in methanol.[3] This finding strongly suggests that the methoxy-substituted phenylacetyl carbonyl in the excited-state (*Z*)- and (*E*)-isomers possesses the reactivity comparable to that of the acetyl carbonyl. A careful analysis of the ^{1}H NMR spectrum recorded after 360 min irradiation revealed negligible formation of 7,8-dimethoxyisoquinoline derivative. In order to confirm whether the methoxy group introduced at the 3-position on the styryl benzene ring exerts a large steric effect on the cyclization proceeding at the 2-position, conformational energy of the (*Z*)-isomer was minimized by MM2 and PM5 calculations (Figure 1).[8] An examination of the energy-minimized conformation revealed that the 3-methoxy methyl group is directed toward the hydrogen atom attached to the 2-position and, hence, the cyclization process taking place at this position experiences a



Scheme 3

great steric hindrance of the methoxy group. Therefore, we were led to conclude that the 3-methoxy substituent plays a decisive role in constructing the papaverine skeleton.

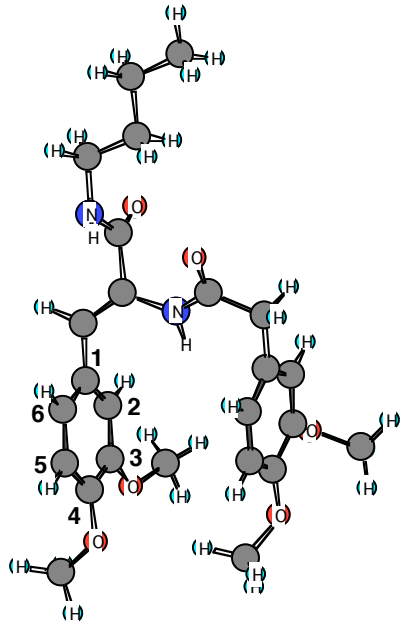


Figure 1. Energy-minimized conformation of (*Z*)-**1a**.

Table 2. Relation between irradiation time and composition (%) of each compound obtained by the irradiation of (*Z*)-**1a** in acetonitrile

Compound	Irradiation time (min)				
	0	30	60	90	120
(Z)-**1a**	100	69.7	66.0	62.5	57.3
(E)-**1a**	0	30.3	32.0	33.4	35.2
2a	0	0	2.0	3.5	6.3
trans-**3a**	0	0	0	0.6	1.2
cis-**3a**	0	0	0	0	0

In Table 2 are shown solvent effects on the photoreactivity of **1a** and the product composition. A comparison of the data given in Tables 1 and 2 clearly indicates that the use of aprotic polar solvent, acetonitrile, lowers the reactivity of each isomer in the excited state whereas the (*Z*)-isomer composition is increased by a factor of about 2 at photostationary state in this solvent. It was previously found that methanol is able to form a hydrogen bond to the amide carbonyl oxygen of *N*-acetyl-α-

dehydronaphthylalaninamide derivative in the ground and excited states.[4] In addition to the fact that methanol and acetonitrile have comparable polarities,[9] this finding allowed us to propose that hydrogen-bonding solvation of (*Z*)- and (*E*)-isomers in the excited state greatly affects not only the relative rate for the isomerization but also the rate for the cyclization from a given isomer. Interestingly, the change in solvent from methanol to acetonitrile resulted in an increase of the selectivity for **2a** (64→84% at 120 min irradiation) with a decrease of that for **3a** (36→16%). However, on prolonged irradiation (>240 min) in acetonitrile side reactions took place to an appreciable extent, making methanol better solvent for the reaction.

Table 3. Substituent effects on the composition of each compound obtained by the irradiation of *(Z)*-**1a** in methanol and the selectivity of **2a**

Compound	Irradiation time (min)	Composition (%)				Selectivity of **2** (%)
		(Z)-**1**	*(E)*-**1**	**2**	**3**[a)]	
1a	60	38.6	53.5	4.6	3.3	
	360	3.5	4.3	63.9 (46)[b)]	28.3	69
1b	60	39.9	55.5	2.6	2.0	
	360	4.3	5.7	60.7 (45)[b)]	29.3	67
1c	60	36.7	55.0	5.2	3.1	
	240	0.7	0.9	68.6 (43)[b)]	29.8	70
1d	60	36.9	56.1	3.7	3.3	
	360	3.0	4.0	61.5 (48)[b)]	31.5	66
1e	60	34.8	59.7	3.8	1.7	
	360	2.7	3.6	75.6 (50)[b)]	18.1	81
1f	60	36.5	59.6	2.9	1.0	
	360	3.2	4.2	62.6 (42)[b)]	30.0	68
1g	60	36.1	57.8	4.2	1.9	
	360	2.5	3.7	70.4 (46)[b)]	23.4	75

a) The sum of *cis*- and *trans*-isomers. b) Isolated yield (%).

In order to shed light on the scope and limitations of the photoinduced cyclization of (*Z*)-**1a** that provides a new route to papaverine analog (**2a**), we investigated substituent effects on the composition of each compound obtained at a given irradiation time. As demonstrated in Table 3, both the conversion of **1a** and the selectivity of **2a** were only sightly affected by the replacement of two methoxy groups on the benzene ring of the phenylacetyl moiety (R^1 and R^2) by two chlorine atoms (**1e**), as well as by the introduction of benzyl group (R^3) instead of butyl one (**1b**). A comparison of the data for **1c** (R^1= OMe, R^2= H, R^3= Bu), **1d** (R^1= R^2= H, R^3= Bu), **1f** (R^1= Cl, R^2= H, R^3= Bu), and **1g** (R^1= F, R^2= H, R^3= Bu) confirmed that the electron-donating methoxy group has a clear tendency to increase the conversion of **1** at a given irradiation time. It is likely that the methoxy group as substituent R^1 (**1c**) results in an enhancement in the reactivity of the phenylacetyl carbonyl in the excited state (Scheme 3). Thus, the observed substituent effects allow us to predict that the regioselective photocyclization of (*Z*)-**1** would be

applicable to the synthesis of various kinds of papaverine analogs.

The procedure for preparing the starting α-dehydroamino acids [(*Z*)-**1**] is very simple and easily applicable to its related compounds. In addition, column chromatography on silica gel enables rapid separation of **2**, the R_f value of which is much larger than that of (*Z*)-**1**, (*E*)-**1**, and **3**. The photocyclization of (*Z*)-*N*-(substituted phenylacetyl)-α-dehydro(3,4-dimethoxy)phenylalaninamides described above, therefore, provides a new synthetic route to papaverine analogs.

EXPERIMENTAL

General

^{1}H and ^{13}C NMR and IR spectra were taken with a JEOL JNM-A500 spectrometer and a Hitachi 270-30 infrared spectrophotometer, respectively. Chemical shifts were determined using tetramethylsilane as an internal standard. Methanol and acetonitrile were purified according to the standard procedures[9] and freshly distilled prior to use. All other reagents used were obtained from commercial sources and were of the highest grade available. MM2 and PM5 calculations were accomplished by using CAChe 5.0 for Windows available from Fujitsu Ltd, 2002.

General Procedure for the Synthesis of (*Z*)-2-(Substituted benzyl)-4-(methoxy-substituted benzylidene)-5(4*H*)-oxazolones. *N*-(Substituted phenylacetyl)glycine (0.10 mol), methoxy-substituted benzaldehyde (0.11 mol) and sodium acetate (8.2 g, 0.10 mol) were added to acetic anhydride (100 mL) and the resulting mixture was heated at 70–80 °C for 5–10 h with stirring. The mixture was cooled with ice and then poured into ice-water (200 mL). The solid separated out was collected by filtration with suction and washed with small amounts of cold ethanol. After the crude product had been air-dried at rt, it was recrystallized from chloroform–hexane to give yellow crystals (20–27%).

(*Z*)-2-(3,4-Dimethoxybenzyl)-4-(3,4-dimethoxybenzylidene)-5(4*H*)-oxazolone: yield 24%; mp 157.0–158.0 °C; IR (KBr): 1794, 1770, 1650 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.85 (3H, s), 3.87 (3H,s), 3.89 (3H, s), 3.91 (2H, s), 3.93 (3H, s), 6.84 (1H, d, *J*= 8.3 Hz), 6.88 (1H, d, *J*= 2.0 Hz), 6.89 (1H, d, *J*= 8.3 Hz), 6.92 (1H, dd, *J*= 2.0, 8.3 Hz), 7.10 (1H, s), 7.46 (1H, dd, *J*= 2.0, 8.3 Hz), 7.97 (1H, d, *J*= 2.0 Hz), 8.01 (1H, d, *J*= 2.0 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 35.7, 55.8, 56.0 (3C), 110.8, 111.3, 112.6, 113.9, 121.7, 125.4, 126.5, 127.5, 130.4, 132.3, 148.6, 149.1 (2C), 152.0, 166.2, 168.0.

(*Z*)-2-Benzyl-4-(3,4-dimethoxybenzylidene)-5(4*H*)-oxazolone: yield 23%; mp 152.0–153.0 °C; IR (KBr): 1839, 1797, 1650 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.81 (3H, s), 3.93 (3H,s), 3.97 (2H, s), 6.88 (1H, d, *J*= 8.6 Hz), 7.11 (1H, s), 7.27–7.39 (5H, m), 7.40 (1H, dd, *J*= 2.0, 8.6 Hz), 8.01 (1H, d, *J*= 2.0 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 36.0, 55.8, 56.0, 110.7, 113.8, 126.5, 127.5, 127.6, 128.7 (2C), 129.5 (2C), 130.3, 132.3, 133.1, 149.1, 152.0, 166.0, 167.9.

(*Z*)-4-(3,4-Dimethoxybenzylidene)-2-(4-methoxybenzyl)-5(4*H*)-oxazolone: yield 22%; mp 128.0–

129.0 °C; IR (KBr): 1834, 1796, 1696, 1656 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.80 (3H, s), 3.84 (3H,s), 3.91 (2H, s), 3.93 (3H, s), 6.85–6.90 (3H, m), 7.09 (1H, s), 7.29 (2H, d, *J*= 8.6 Hz), 7.42 (1H, dd, *J*= 2.0, 8.6 Hz), 8.01 (1H, d, *J*= 2.0 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 35.2, 55.3, 55.8, 56.0, 110.8, 113.8, 114.1 (2C), 125.0, 126.5, 127.6, 130.4, 130.5 (2C), 132.2, 149.1, 152.0, 159.1, 166.3, 168.0.

(*Z*)-2-(3,4-Dichlorobenzyl)-4-(3,4-dimethoxybenzylidene)-5(4*H*)-oxazolone: yield 20%; mp 132.5–133.5 °C; IR (KBr): 1786, 1651 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.84 (3H, s), 3.94 (2H,s), 3.94 (3H, s), 6.90 (1H, d, *J*= 8.2 Hz), 7.14 (1H, s), 7.22 (1H, dd, *J*= 2.1, 8.2 Hz), 7.41 (1H, dd, *J*= 1.4, 8.2 Hz), 7.44 (1H, d, *J*= 8.2 Hz), 7.50 (1H, d, *J*= 2,1 Hz), 7.96 (1H, d, *J*= 1.4 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 35.0, 55.7, 56.0, 110.8, 113.7, 126.3, 127.9, 128.9, 129.8, 130.6, 131.5, 131.9, 132.8, 133.07, 133.11, 149.2, 152.3, 164.8, 167.5.

(*Z*)-2-(4-Chlorobenzyl)-4-(3,4-dimethoxybenzylidene)-5(4*H*)-oxazolone: yield 20%; mp 144.5–146.0 °C; IR (KBr): 1800, 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.82 (3H, s), 3.94 (2H,s), 3.94 (3H, s), 6.89 (1H, d, *J*= 8.6 Hz), 7.11 (1H, s), 7.31 (2H, d, *J*= 8.6 Hz), 7.33 (2H, d, *J*= 8.6 Hz), 7.41 (1H, d, *J*= 8.6 Hz), 7.97 (1H, s); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 35.4, 55.7, 56.0, 110.8, 113.8, 126.4, 127.7, 128.9 (2C), 130.1, 130.9 (2C), 131.6, 132.7, 133.6, 149.2, 152.2, 165.7, 167.7.

(*Z*)-4-(3,4-Dimethoxybenzylidene)-2-(4-fluorobenzyl)-5(4*H*)-oxazolone: yield 27%; mp 134.0–135.0 °C; IR (KBr): 1744, 1653 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.83 (3H, s), 3.94 (3H,s), 3.95 (2H, s), 6.89 (1H, d, *J*= 8.3 Hz), 7.04 (2H, dd, *J*= 8.3, 8.9 Hz), 7.11 (1H, s), 7.34 (2H, dd, *J*= 5.5, 8.3 Hz), 7.42 (1H, dd, *J*= 2.1, 8.3 Hz), 7.98 (1H, d, *J*= 2.1 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 35.2, 55.7, 56.0, 110.7, 113.7, 115.6 (2C, d, *J*= 22 Hz), 126.4, 127.7, 128.7 (1C, d, *J*= 3 Hz), 130.1, 131.1 (2C, d, *J*= 9 Hz), 132.5, 149.1, 152.1, 162.4 (1C, d, *J*= 247 Hz), 165.7, 167.8.

General Procedure for the Synthesis of (*Z*)-*N*-Alkyl-3-(methoxy-substituted phenyl)-2-(substituted phenylacetylamino)-2-propenamides [(*Z*)-1a–g]. (*Z*)-2-(Substituted benzyl)-4-(methoxy-substituted benzylidene)-5(4*H*)-oxazolone (0.010 mol) was added to dry chloroform (20 mL) containing alkylamine (0.011 mol) and a small amount of triethylamine and the resulting mixture was refluxed for 2–3 h. The reaction mixture was concentrated to dryness and the residual solid was dissolved in ethanol (20 mL) and then treated with activated charcoal powder. After removal of the solvent under reduced pressure, the crude product obtained was recrystallized from ethanol-hexane affording colorless crystals (80–90%).

(*Z*)-*N*-Butyl-3-(3,4-dimethoxyphenyl)-2-(3,4-dimethoxyphenylacetylamino)-2-propenamide [(*Z*)-1a]: yield 80%; mp 140.0–141.0 °C; IR (KBr): 3272, 1644, 1620 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.87 (3H, t, *J*= 7.3 Hz), 1.27 (2H, tq, *J*= 7.3, 7.3 Hz), 1.40 (2H, tt, *J*= 7.3, 7.3 Hz), 3.11 (2H, dt, *J*= 5.5, 7.3 Hz), 3.55 (2H, s), 3.64 (3H, s), 3.71 (3H, s), 3.74 (3H, s), 3.75 (3H, s), 6.76 (1H, d, *J*= 8.5 Hz), 6.84 (1H, dd, *J*= 1.8, 7.9 Hz), 6.90 (1H, d, *J*= 7.9 Hz), 6.94 (1H, br s), 6.95 (1H, dd, *J*= 1.8, 8.5 Hz), 6.97 (1H, s), 7.12 (1H, d, *J*= 1.8 Hz), 7.71 (1H, t, *J*= 5.5 Hz), 9.43 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.5, 31.2,

38.7, 41.9, 55.2, 55.3 (2C), 55.5, 111.2, 111.8, 113.0, 113.1, 121.2, 122.7, 126.7, 127.7, 128.0, 128.2, 147.6, 148.2, 148.5, 149.1, 164.9, 169.9; *Anal*. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.06; N, 6.14. Found: C, 65.91; H, 7.03; N, 6.35.

(*Z*)-*N*-Benzyl-3-(3,4-dimethoxyphenyl)-2-(3,4-dimethoxyphenylacetylamino)-2-propenamide [(*Z*)-1b]: yield 81%; mp 185.0–186.0 °C; IR (KBr): 3316, 3208, 1731, 1653, 1614 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 3.35 (2H, s), 3.64 (3H, s), 3.69 (3H, s), 3.74 (3H, s), 3.75 (3H, s), 4.38 (2H, d, *J*= 6.1 Hz), 6.74 (1H, d, *J*= 8.6 Hz), 6.84 (1H, dd, *J*= 1.8, 8.6 Hz), 6.89 (1H, d, *J*= 8.6 Hz), 6.94 (1H, d, *J*= 1.8 Hz), 6.96 (1H, dd, *J*= 1.8, 8.6 Hz), 7.08 (1H, s), 7.13 (1H, d, *J*= 1.8 Hz), 7.21–7.25 (1H, m), 7.27–7.32 (4H, m), 8.44 (1H, t, *J*= 6.1 Hz), 9.51 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 41.9, 42.5, 55.28, 55.34 (2C), 55.5, 111.2, 111.7, 113.1, 113.2, 121.3, 122.8, 126.5, 126.6, 127.0 (2C), 127.96, 127.99, 128.1 (2C), 128.5, 139.7, 147.6, 148.2, 148.5, 149.2, 165.2, 170.1; *Anal*. Calcd for $C_{28}H_{30}N_2O_6$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.21; H, 6.09; N, 5.62.

(*Z*)-*N*-Butyl-3-(3,4-dimethoxyphenyl)-2-(4-methoxyphenylacetylamino)-2-propenamide [(*Z*)-1c]: yield 80%; mp 161.0–161.5 °C; IR (KBr): 3214, 1650, 1605 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.87 (3H, t, *J*= 7.3 Hz), 1.27 (2H, tq, *J*= 7.3, 7.3 Hz), 1.40 (2H, tt, *J*= 7.3, 7.3 Hz), 3.11 (2H, dt, *J*= 6.1, 7.3 Hz), 3.56 (2H, s), 3.64 (3H, s), 3.74 (3H, s), 3.75 (3H, s), 6.79 (1H, d, *J*= 8.6 Hz), 6.89 (2H, d, *J*= 8.6 Hz), 6.965 (1H, dd, *J*= 1.8, 8.6 Hz), 6.969 (1H, s), 7.12 (1H, d, *J*= 1.8 Hz), 7.24 (2H, d, *J*= 8.6 Hz), 7.71 (1H, t, *J*= 6.1 Hz), 9.45 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.5, 31.2, 38.7, 41.4, 55.0, 55.3, 55.4, 111.3, 112.9, 113.6 (2C), 122.7, 126.7, 127.6, 127.7, 128.2, 130.2 (2C), 148.2, 149.1, 158.0, 164.9, 170.1; *Anal*. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.69; H, 7.00; N, 6.54.

(*Z*)-*N*-Butyl-3-(3,4-dimethoxyphenyl)-2-phenylacetylamino-2-propenamide [(*Z*)-1d]: yield 90%; mp 170.0–171.0 °C; IR (KBr): 3224, 1648, 1604 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.88 (3H, t, *J*= 7.3 Hz), 1.28 (2H, tq, *J*= 7.3, 7.3 Hz), 1.41 (2H, tt, *J*= 6.7, 7.3 Hz), 3.12 (2H, dt, *J*= 5.5, 6.7 Hz), 3.63 (3H, s), 3.65 (2H, s), 3.76 (3H, s), 6.80 (1H, d, *J*= 8.5 Hz), 6.97 (1H, s), 6.98 (1H, dd, *J*= 1.8, 8.5 Hz), 7.13 (1H, d, *J*= 1.8 Hz), 7.26 (1H, dd, *J*= 8.5, 8.5 Hz), 7.30–7.33 (4H, m), 7.77 (1H, t, *J*= 5.5 Hz), 9.53 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.4, 31.2, 38.7, 42.1, 55.2, 55.3, 111.3, 112.8, 122.7, 126.3, 126.6, 127.6, 128.1 (2C), 128.2, 129.2 (2C), 135.6, 148.2, 149.0, 164.8, 169.6; *Anal*. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.95; H, 7.13; N, 6.97.

(*Z*)-*N*-Butyl-2-(3,4-dichlorophenylacetylamino)-3-(3,4-dimethoxyphenyl)-2-propenamide [(*Z*)-1e]: yield 82%; mp 202.0–203.0 °C; IR (KBr): 3302, 1653, 1647 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.87 (3H, t, *J*= 7.6 Hz), 1.27 (2H, tq, *J*= 7.6, 7.6 Hz), 1.41 (2H, tt, *J*= 6.9, 7.6 Hz), 3.13 (2H, dt, *J*= 6.2, 6.9 Hz), 3.67 (2H, s), 3.68 (3H, s), 3.76 (3H, s), 6.79 (1H, d, *J*= 8.3 Hz), 6.97 (1H, dd, *J*= 2.1, 8.3 Hz), 7.00 (1H, s), 7.12 (1H, d, *J*= 2.1 Hz), 7.31 (1H, dd, *J*= 2.1, 8.3 Hz), 7.59 (1H, d, *J*= 2.1 Hz), 7.60 (1H, d, *J*= 8.3 Hz), 7.89 (1H, t, *J*= 6.2 Hz), 9.58 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.5, 31.3, 38.8, 41.0, 55.3, 55.4, 111.2, 113.0, 122.6, 126.6, 127.99, 128.03, 129.2, 129.8, 130.3, 130.7, 131.3, 136.9, 148.3, 149.2,

164.8, 168.9; *Anal*. Calcd for $C_{23}H_{26}N_2O_4Cl_2$: C, 59.36; H, 5.63; N, 6.02. Found: C, 59.33; H, 5.45; N, 5.88.

(*Z*)-*N*-Butyl-2-(4-chlorophenylacetylamino)-3-(3,4-dimethoxyphenyl)-2-propenamide [(*Z*)-1f]: yield 90%; mp 187.0–188.0 °C; IR (KBr): 3310, 3136, 1671, 1647 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.88 (3H, t, *J*= 7.3 Hz), 1.27 (2H, tq, *J*= 6.7, 7.3 Hz), 1.41 (2H, tt, *J*= 6.7, 7.3 Hz), 3.13 (2H, dt, *J*= 5.5, 7.3 Hz), 3.65 (2H, s), 3.66 (3H, s), 3.76 (3H, s), 6.80 (1H, d, *J*= 8.6 Hz), 6.96 (1H, dd, *J*= 1.8, 8.6 Hz), 6.99 (1H, s), 7.12 (1H, d, *J*= 1.8 Hz), 7.34 (2H, d, *J*= 8.6 Hz), 7.39 (2H, d, *J*= 8.6 Hz), 7.83 (1H, t, *J*= 5.5 Hz), 9.55 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.5, 31.2, 38.7, 41.4, 55.3, 55.4, 111.3, 113.0, 122.7, 126.6, 127.9, 128.1 (3C), 131.15, 131.23 (2C), 134.7, 148.3, 149.1, 164.9, 169.4; *Anal*. Calcd for $C_{23}H_{27}N_2O_4Cl$: C, 64.11; H, 6.32; N, 6.50. Found: C, 63.77; H, 6.29; N, 6.40.

(*Z*)-*N*-Butyl-3-(3,4-dimethoxyphenyl)-2-(4-fluorophenylacetylamino)-2-propenamide [(*Z*)-1g]: yield 85%; mp 175.0–175.5 °C; IR (KBr): 3296, 3136, 1668, 1648 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.87 (3H, t, *J*= 7.4 Hz), 1.27 (2H, tq, *J*= 6.9, 7.4 Hz), 1.41 (2H, tt, *J*= 6.9, 7.4 Hz), 3.12 (2H, dt, *J*= 5.7, 6.9 Hz), 3.64 (2H, s), 3.66 (3H, s), 3.76 (3H, s), 6.82 (1H, d, *J*= 8.6 Hz), 6.98 (1H, s), 7.00 (1H, dd, *J*= 1.7, 8.6 Hz), 7.12 (1H, d, *J*= 1.7 Hz), 7.15 (2H, dd, *J*= 8.6, 9.1 Hz), 7.35 (2H, dd, *J*= 5.7, 8.6 Hz), 7.79 (1H, t, *J*= 5.7 Hz), 9.52 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.6, 19.4, 31.2, 38.6, 41.1, 55.2, 55.3, 111.3, 112.8, 114.8 (2C, d, *J*= 20 Hz), 122.7, 126.6, 127.8, 128.1, 131.0 (2C, d, *J*= 9 Hz), 131.8, 148.2, 149.1, 161.2 (1C, d, *J*= 243 Hz), 164.8, 169.6; *Anal*. Calcd for $C_{23}H_{27}N_2O_4F$: C, 66.65; H, 6.57; N, 6.76. Found: C, 66.40; H, 6.28; N, 6.83.

General Procedure for the Irradiation of (*Z*)-1a–g. A methanol solution of (*Z*)-**1** (1.0×10^{-3} mol dm^{-3}, 500 mL), placed in a Pyrex vessel, was irradiated for a given period of time under nitrogen with Pyrex-filtered light from a 400 W high pressure Hg lamp at rt. At a given irradiation time, an appropriate amount of the solution (5 mL) was pipetted off and concentrated to dryness *in vacuo* giving the residue which was subjected to ^1H NMR spectral analysis in dimethyl-d_6 sulfoxide. The composition was estimated from the area ratio of a given ^1H NMR signal for each compound. The remaining solution irradiated for 360 min was concentrated to dryness under reduced pressure and the resulting residue was subjected to preparative thin-layer chromatography over silica gel (developing solvent: ethyl acetate-hexane or ethyl acetate-chloroform). In order to isolate (*E*)-**1**, a methanol solution of (*Z*)-**1** (1.0×10^{-3} mol dm^{-3}, 500 mL) was independently irradiated for 60 min under the same conditions. For the purpose of isolating and purifying the photoproducts, column chromatography over silica gel (230 mesh, Merck) was also used. Physical and spectroscopic properties of the (*E*)-isomers and isoquinoline derivatives (papaverine analogs, **2**) isolated are as follows.

(*E*)-1a: yield 33%; mp 139.0–140.0 °C (EtOAc-hexane); IR (KBr): 3310, 1641 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.79 (3H, t, *J*= 7.3 Hz), 1.13 (2H, tq, *J*= 7.3, 7.3 Hz), 1.30 (2H, tt, *J*= 6.7, 7.3 Hz), 3.02 (2H, dt, *J*= 6.1, 6.7 Hz), 3.47 (2H, s), 3.69 (3H, s), 3.72 (3H, s), 3.73 (3H, s), 3.75 (3H, s), 6.76 (1H, dd, *J*= 1.8, 8.5 Hz), 6.80 (1H, s), 6.81 (1H, dd, *J*= 1.8, 8.5 Hz), 6.84 (1H, d, *J*= 8.5 Hz), 6.86 (1H, d, *J*= 1.8 Hz), 6.88

(1H, d, *J*= 8.5 Hz), 6.92 (1H, d, *J*= 1.8 Hz), 7.99 (1H, t, *J*= 6.1 Hz), 9.63 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.6, 19.5, 30.4, 38.6, 42.2, 55.2, 55.4 (2C), 55.5, 111.5, 111.6, 111.8, 113.1, 115.5, 120.8, 121.1, 128.0, 128.3, 132.2, 147.6, 147.8, 148.2, 148.5, 164.8, 169.1; *Anal*. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.06; N, 6.14. Found: C, 65.46; H, 6.84; N, 5.99.

(*E*)-1b: yield 30%; mp 125.0–126.0 °C (EtOAc-hexane); IR (KBr): 3262, 1653, 1605 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.49 (2H, s), 3.57 (3H, s), 3.72 (3H, s), 3.73 (3H, s), 3.75 (3H, s), 4.27 (2H, d, *J*= 6.1 Hz), 6.71–6.75 (2H, m), 6.76 (1H, s), 6.82 (1H, dd, *J*= 1.8, 8.5 Hz), 6.84 (1H, s), 6.89 (1H, d, *J*= 8.5 Hz), 6.93 (1H, d, *J*= 1.8 Hz), 7.16–7.23 (5H, m), 8.54 (1H, t, *J*= 6.1 Hz), 9.73 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 42.1, 42.4, 55.2, 55.4 (2C), 55.6, 111.5, 111.7, 111.8, 113.1, 116.4, 120.8, 121.1, 126.6, 127.5 (2C), 127.7, 127.9 (2C), 128.3, 131.8, 138.6, 147.6, 147.9, 148.2, 148.5, 165.0, 169.2; *Anal*. Calcd for $C_{28}H_{30}N_2O_6$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.88; H, 5.98; N, 5.91.

(*E*)-1c: yield 36%; mp 153.0–154.0 °C (EtOAc-hexane); IR (KBr): 3238, 1641 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.79 (3H, t, *J*= 7.3 Hz), 1.12 (2H, tq, *J*= 7.3, 7.3 Hz), 1.29 (2H, tt, *J*= 7.3, 7.3 Hz), 3.02 (2H, dt, *J*= 5.5, 7.3 Hz), 3.47 (2H, s), 3.69 (3H, s), 3.72 (3H, s), 3.73 (3H, s), 6.76 (1H, dd, *J*= 1.8, 8.5 Hz), 6.79 (1H, br s), 6.84 (1H, d, *J*= 8.5 Hz), 6.85 (1H, s), 6.88 (2H, d, *J*= 8.5 Hz), 7.21 (2H, d, *J*= 8.5 Hz), 7.99 (1H, t, *J*= 5.5 Hz), 9.65 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.6, 19.5, 30.4, 38.6, 41.7, 55.0, 55.2, 55.4, 111.5, 111.6, 113.6 (2C), 115.4, 120.7, 127.8, 128.0, 130.0 (2C), 132.2, 147.8, 148.2, 158.0, 164.8, 169.2; *Anal*. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.70; H, 6.82; N, 6.48.

(*E*)-1d: yield 39%; mp 148.0–149.0 °C (EtOAc-hexane); IR (KBr): 3238, 3028, 1660, 1644 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.79 (3H, t, *J*= 7.3 Hz), 1.12 (2H, tq, *J*= 7.3, 7.3 Hz), 1.30 (2H, tt, *J*= 7.3, 7.3 Hz), 3.02 (2H, dt, *J*= 5.5, 7.3 Hz), 3.56 (2H, s), 3.69 (3H, s), 3.72 (3H, s), 6.77 (1H, dd, *J*= 1.8, 8.5 Hz), 6.80 (1H, s), 6.84 (1H, d, *J*= 8.5 Hz), 6.86 (1H, d, *J*= 1.8 Hz), 7.22–7.25 (1H, m), 7.29–7.33 (4H, m), 8.00 (1H, t, *J*= 5.5 Hz), 9.72 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.6, 19.5, 30.4, 38.6, 42.6, 55.2, 55.4, 111.5, 111.6, 115.5, 120.7, 126.4, 127.9, 128.2 (2C), 129.1 (2C), 132.2, 135.9, 147.8, 148.2, 164.8, 168.8; *Anal.* Calcd for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.30; H, 7.18; N, 6.90.

(*E*)-1e: yield 38%; mp 177.0–178.0 °C (EtOAc-hexane); IR (KBr): 3421, 1655, 1637 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.84 (3H, t, *J*= 6.9 Hz), 1.18 (2H, tq, *J*= 6.9, 7.4 Hz), 1.33 (2H, tt, *J*= 6.9, 7.4 Hz), 3.08 (2H, dt, *J*= 5.7, 6.9 Hz), 3.65 (2H, s), 3.74 (3H, s), 3.78 (3H, s), 6.82 (1H, d, *J*= 1.7 Hz), 6.84 (1H, s), 6.90 (1H, d, *J*= 8.6 Hz), 6.91 (1H, dd, *J*= 1.7, 8.6 Hz), 7.34 (1H, dd, *J*= 1.7, 8.0 Hz), 7.62 (1H, d, *J*= 1.7 Hz), 7.64 (1H, d, *J*= 8.0 Hz), 8.11 (1H, t, *J*= 5.7 Hz), 9.85 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.6, 30.4, 38.6, 41.4, 55.3, 55.5, 111.5, 111.6, 116.0, 120.8, 127.8, 129.2, 129.6, 130.3, 130.7, 131.1, 132.0, 137.0, 147.9, 148.2, 164.7, 168.0; *Anal*. Calcd for $C_{23}H_{26}N_2O_4Cl_2$: C, 59.36; H, 5.63; N, 6.02. Found: C, 59.28; H, 5.37; N, 5.76.

(*E*)-1f: yield 42%; mp 155.0–156.0 °C (EtOAc-hexane); IR (KBr): 3397, 1676, 1657 cm^{-1}; ^{1}H NMR (500

MHz, DMSO-d_6): δ 0.79 (3H, t, *J*= 7.4 Hz), 1.12 (2H, tq, *J*= 6.9, 7.4 Hz), 1.29 (2H, tt, *J*= 6.9, 6.9 Hz), 3.02 (2H, dt, *J*= 5.7, 6.9 Hz), 3.56 (2H, s), 3.68 (3H, s), 3.72 (3H, s), 6.77 (1H, dd, *J*= 1.7, 8.6 Hz), 6.79 (1H, s), 6.85 (1H, d, *J*= 8.6 Hz), 6.86 (1H, d, *J*= 1.7 Hz), 7.32 (2H, d, *J*= 8.6 Hz), 7.38 (2H, d, *J*= 8.6 Hz), 8.03 (1H, t, *J*= 5.7 Hz), 9.75 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.6, 19.6, 30.4, 38.6, 41.7, 55.3, 55.4, 111.5, 111.6, 115.7, 120.8, 127.8, 128.1 (2C), 131.0 (2C), 131.2, 132.1, 134.9, 147.9, 148.2, 164.7, 168.5; *Anal*. Calcd for $C_{23}H_{27}N_2O_4Cl$: C, 64.11; H, 6.32; N, 6.50. Found: C, 64.07; H, 6.15; N, 6.28.

(*E*)-1g: yield 35%; mp 148.5–149.0 °C (EtOAc-hexane); IR (KBr): 3435, 1655, 1638 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.79 (3H, t, *J*= 7.6 Hz), 1.13 (2H, tq, *J*= 7.6, 7.6 Hz), 1.30 (2H, tt, *J*= 6.9, 7.6 Hz), 3.02 (2H, dt, *J*= 6.2, 6.9 Hz), 3.55 (2H, s), 3.69 (3H, s), 3.72 (3H, s), 6.77 (1H, dd, *J*= 2.1, 8.3 Hz), 6.80 (1H, s), 6.85 (1H, d, *J*= 8.3 Hz), 7.15 (2H, dd, *J*= 8.9, 8.9 Hz), 7.16 (1H, d, *J*= 2.1 Hz Hz), 7.33 (2H, dd, *J*= 5.5, 8.9 Hz), 8.03 (1H, t, *J*= 6.2 Hz), 9.74 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.6, 30.4, 38.6, 41.6, 55.3, 55.5, 111.5, 111.6, 114.8 (2C, d, *J*= 22 Hz), 115.6, 120.8, 127.9, 130.9 (2C, d, *J*= 7 Hz), 132.10, 132.14, 147.9, 148.2, 161.0 (1C, d, *J*= 246 Hz), 164.8, 168.8; *Anal*. Calcd for $C_{23}H_{27}N_2O_4F$: C, 66.65; H, 6.57; N, 6.76. Found: C, 66.47; H, 6.42; N, 6.75.

3-Butylaminocarbonyl-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline (2a): yield 46%; mp 140.0–140.5 °C (EtOAc); IR (KBr): 3388, 1743, 1665 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.92 (3H, t, *J*= 7.3 Hz), 1.33 (2H, tq, *J*= 7.3, 7.3 Hz), 1.54 (2H, tt, *J*= 6.7, 7.3 Hz), 3.36 (2H, dt, *J*= 6.1, 6.7 Hz), 3.67 (3H, s), 3.69 (3H, s), 3.92 (3H, s), 3.92 (3H, s), 4.56 (2H, s), 6.82 (1H, d, *J*= 7.9 Hz), 6.83–6.85 (1H, m), 7.12 (1H, br s), 7.56 (1H, s), 7.60 (1H, s), 8.25 (1H, s), 8.68 (1H, t, *J*= 6.1 Hz); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.6, 31.5, 38.3, 40.4, 55.3, 55.4, 55.77, 55.82, 104.5, 107.1, 111.8, 112.9, 117.2, 120.7, 123.3, 131.6, 133.0, 141.4, 147.2, 148.6, 150.7, 152.5, 157.0, 164.3; *Anal*. Calcd for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39. Found: C, 68.14; H, 6.82; N, 6.19.

3-Benzylaminocarbonyl-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline (2b): yield 45%; mp 174.0–175.0 °C (EtOAc); IR (KBr): 3370, 3064, 1677, 1600 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.64 (3H, s), 3.65 (3H, s), 3.92 (3H, s), 3.92 (3H, s), 4.57 (2H, s), 4.58 (2H, d, *J*= 6.1 Hz), 6.80 (1H, d, *J*= 8.5 Hz), 6.86 (1H, dd, *J*= 1.8, 8.5 Hz), 7.13 (1H, d, *J*= 1.8 Hz), 7.25 (1H, dd, *J*= 7.3, 7.3 Hz), 7.33 (2H, dd, *J*= 7.3, 7.3 Hz), 7.36 (2H, d, *J*= 7.3 Hz), 7.57 (1H, s), 7.61 (1H, s), 8.29 (1H, s), 9.29 (1H, t, *J*= 6.1 Hz); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 40.4, 42.3, 55.3, 55.4, 55.79, 55.84, 104.5, 107.1, 111.8, 112.8, 117.6, 120.6, 123.4, 126.7, 127.3 (2C), 128.3 (2C), 131.6, 133.0, 139.7, 141.3, 147.2, 148.6, 150.8, 152.6, 157.1, 164.5; *Anal*. Calcd for $C_{28}H_{28}N_2O_5$: C, 71.17; H, 5.97; N, 5.93. Found: C, 71.33; H, 5.90; N, 5.96.

3-Butylaminocarbonyl-6,7-dimethoxy-1-(4-methoxybenzyl)isoquinoline (2c): yield 43%; mp 152.0–153.0 °C (EtOAc); IR (KBr): 3340, 1656, 1617 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.93 (3H, t, *J*= 7.3 Hz), 1.34 (2H, tq, *J*= 7.3, 7.3 Hz), 1.54 (2H, tt, *J*= 7.3, 7.3 Hz), 3.34 (2H, dt, *J*= 6.1, 7.3 Hz), 3.68 (3H, s), 3.90 (3H, s), 3.92 (3H, s), 4.56 (2H, s), 6.83 (2H, d, *J*= 8.5 Hz), 7.30 (2H, d, *J*= 8.5 Hz), 7.56 (1H, s), 7.56 (1H, s), 8.24 (1H, s), 8.62 (1H, t, *J*= 6.1 Hz); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.6, 31.4,

38.4, 39.8, 54.9, 55.75, 55.82, 104.5, 107.1, 113.7 (2C), 117.2, 123.2, 129.8 (2C), 131.1, 133.0, 141.4, 150.7, 152.5, 157.0, 157.6, 164.2; *Anal*. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.17; H, 6.89; N, 6.79.

1-Benzyl-3-butylaminocarbonyl-6,7-dimethoxyisoquinoline (2d): yield 48%; mp 137.0–138.0 °C (EtOAc); IR (KBr): 3394, 3322, 1653 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.87 (3H, t, *J*= 7.3 Hz), 1.33 (2H, tq, *J*= 7.3, 7.3 Hz), 1.54 (2H, tt, *J*= 7.3, 7.3 Hz), 3.35 (2H, dt, *J*= 5.5, 7.3 Hz), 3.89 (3H, s), 3.92 (3H, s), 4.64 (2H, s), 7.18 (1H, dd, *J*= 7.3, 7.3 Hz), 7.27 (2H, dd, *J*= 7.3, 7.3 Hz), 7.38 (2H, d, *J*= 7.3 Hz), 7.557 (1H, s), 7.563 (1H, s), 8.26 (1H, s), 8.61 (1H, t, *J*= 5.5 Hz); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.6, 31.4, 38.4, 40.9, 55.7, 55.8, 104.4, 107.1, 117.3, 123.3, 126.1, 128.3 (2C), 128.8 (2C), 133.0, 139.2, 141.4, 150.8, 152.6, 156.7, 164.2; *Anal*. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.63; H, 6.81; N, 7.75.

3-Butylaminocarbonyl-1-(3,4-dichlorobenzyl)-6,7-dimethoxyisoquinoline (2e): yield 50%; mp 174.0–175.0 °C (EtOAc); IR (KBr): 3375, 1654 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.92 (3H, t, *J*= 7.6 Hz), 1.31 (2H, tq, *J*= 7.6, 7.6 Hz), 1.51 (2H, tt, *J*= 6.9, 7.6 Hz), 3.33 (2H, dt, *J*= 6.2, 6.9 Hz), 3.93 (3H, s), 3.95 (3H, s), 4.66 (2H, s), 7.38 (1H, dd, *J*= 2.1, 8.3 Hz), 7.55 (1H, d, *J*= 8.3 Hz), 7.59 (1H, s), 7.60 (1H, s), 7.75 (1H, d, *J*= 2.1 Hz), 8.27 (1H, s), 8.53 (1H, t, *J*= 6.2 Hz); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.6, 31.4, 38.3, 39.5, 55.8, 55.9, 104.1, 107.2, 117.4, 123.3, 128.8, 129.5, 130.4, 130.7, 131.1, 133.0, 140.4, 141.3, 151.0, 152.7, 155.7, 164.1; *Anal*. Calcd for $C_{23}H_{24}N_2O_3Cl_2$: C, 61.75; H, 5.41; N, 6.26. Found: C, 61.41; H, 5.20; N, 5.95.

3-Butylaminocarbonyl-1-(4-chlorobenzyl)-6,7-dimethoxyisoquinoline (2f): yield 42%; mp 206.0–206.5 °C (EtOAc); IR (KBr): 3362, 1663 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.93 (3H, t, *J*= 7.4 Hz), 1.32 (2H, tq, *J*= 7.4, 7.4 Hz), 1.52 (2H, tt, *J*= 6.9, 7.4 Hz), 3.34 (2H, dt, *J*= 5.7, 6.9 Hz), 3.92 (3H, s), 3.93 (3H, s), 4.64 (2H, s), 7.32 (2H, d, *J*= 8.6 Hz), 7.42 (2H, d, *J*= 8.6 Hz), 7.55 (1H, s), 7.58 (1H, s), 8.27 (1H, s), 8.57 (1H, t, *J*= 5.7 Hz); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.6, 31.4, 38.4, 40.0, 55.8, 55.9, 104.2, 107.1, 117.4, 123.3, 128.2 (2C), 130.77 (2C), 130.81, 133.0, 138.2, 141.4, 150.9, 152.7, 156.2, 164.2; *Anal*. Calcd for $C_{23}H_{25}N_2O_3Cl$: C, 66.90; H, 6.10; N, 6.78. Found: C, 66.52; H, 6.32; N, 6.72.

3-Butylaminocarbonyl-6,7-dimethoxy-1-(4-fluorobenzyl)isoquinoline (2g): yield 46%; mp 166.0–167.0 °C (EtOAc); IR (KBr): 3347, 1659 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.92 (3H, t, *J*= 7.6 Hz), 1.32 (2H, tq, *J*= 7.6, 7.6 Hz), 1.53 (2H, tt, *J*= 6.9, 7.6 Hz), 3.35 (2H, dt, *J*= 6.2, 6.9 Hz), 3.92 (3H, s), 3.92 (3H, s), 4.63 (2H, s), 7.11 (2H, dd, *J*= 9.0, 9.0 Hz), 7.43 (2H, dd, *J*= 5.5, 9.0 Hz), 7.56 (1H, s), 7.57 (1H, s), 8.26 (1H, s), 8.59 (1H, t, *J*= 6.2 Hz); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.6, 31.4, 38.4, 40.0, 55.8, 55.9, 104.3, 107.1, 115.0 (2C, d, *J*= 20 Hz), 117.4, 123.3, 130.7 (2C, d, *J*= 9 Hz), 133.0, 135.3, 141.4, 150.9, 152.6, 156.5, 160.8 (1C, d, *J*= 243 Hz), 164.2; *Anal*. Calcd for $C_{23}H_{25}N_2O_3F$: C, 69.68; H, 6.36; N, 7.07. Found: C, 69.60; H, 6.11; N, 6.93.

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