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INTRAMOLECULAR BENZYLIC CYCLIZATION WITH NITRENIUM IONS GENERATED FROM *N*-ACYLAMINOPHTHALIMIDES USING PHENYLIODINE(III) BIS(TRIFLUOROACETATE): FORMATION OF PHENYL SUBSTITUTED LACTAMS

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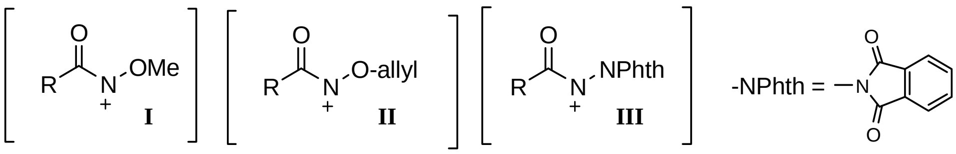
Abstract – *N*-Phthalimido-*N*-acylnitrenium ions generated from *N*-acylaminophthalimides using phenyliodine(III) bis(trifluoroacetate) in polyfluoro alcohols do not undergo intramolecular aromatic substitution reactions. Instead, intramolecular cyclization to the benzylic position occurs to afford lactams having a phenyl group substituted at the α-position to the ring nitrogen. These reactions proceed in moderate to good yields.

Nitrenium ions continue to receive increasing attention from synthetic, theoretical, and biological perspectives.[1] However, synthetic applications of nitrenium ions remain limited, primarily because they exist only as short-lived reaction intermediates. We have been exploring strategies to increase the lifetime of the ion in order to enhance the synthetic value of this species.

In previous work, we have reported that *N*-methoxy- and *N*-allyloxy-*N*-acylnitrenium ions (**I** and **II**) can be generated from the corresponding *N*-chloro-*N*-methoxyamides[2] and *N*-chloro-*N*-allyloxyamides,[3] respectively, by the action of silver or zinc ion. We have also reported that **I**[4] and *N*-phthalimido-*N*-acylnitrenium ions (**III**)[5] can be generated directly from the corresponding *N*-methoxyamides and *N*-acylaminophthalimides, respectively, by the action of phenyliodine(III) bis(trifluoroacetate) (PIFA). These nitrenium ions are stabilized by adjacent methoxy, allyloxy and phthalimido groups, respectively, attached to the nitrogen, and are able to undergo intramolecular substitution reactions with a range of aromatic compounds. PIFA is the most frequently used and easily available reagent in the family of hypervalent iodine compounds, and Wardrop et al. recently utilized PIFA for the generation of **I** in the synthesis of biologically active compounds.[6]

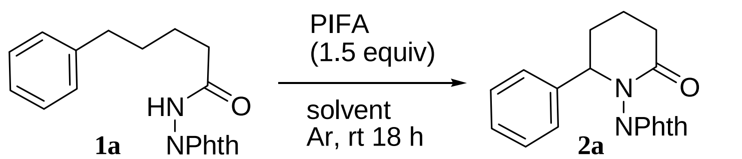
This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.



Herein, we report that **III**, having a pendant phenyl group suitably located in a molecule, do not undergo intramolecular aromatic substitution reactions, but instead intramolecular cyclization to the benzylic position occurs to give phenyl substituted lactams in moderate to good yields.

Previously we had examined PIFA-mediated cyclization of *N*-methoxy-5-phenylpentanamide in hexafluoroisopropanol and obtained the benzannulated compound, 1-methoxy-3,4,5,6-tetrahydro-1-benzoazocin-2(1*H*)-one in 72% yield.[7] We undertook preliminary experiments to examine intramolecular cyclization of *N*-(5-phenylpentanamido)phthalimide (**1a**) with PIFA in various solvents, anticipating a similar benzannulation to occur. However, treatment of **1a** with PIFA for 18 h at room temperature afforded 5-phenyl-*N*-phthalimido-δ-lactam (**2a**), the product of cyclization to the benzylic position, in 46% yield in 2,2,3,3-tetrafluoro-1-propanol and in 36% yield in 2,2,2-trifluoroethanol. In contrast to the previous work, the reaction produced only small amounts of the benzannulated compound, 1-phthalimido-3,4,5,6-tetrahydro-1-benzoazocin-2(1*H*)-one (**3**). Thus, the nitrenium ion generated by PIFA attacks the benzylic position, presumably because formation of an eight-membered ring required for benzannulation is unfavorable. We believe that this is the first case wherein a nitrenium ion attack at an aliphatic carbon is preferred over aromatic substitution. We examined this unprecedented reaction further with substrates **1b-j**. Initially, the effects of solvent on the reaction were studied. The results are presented in Table 1.

Table 1. Benzylic cyclization of **1a** with PIFA in various solvents



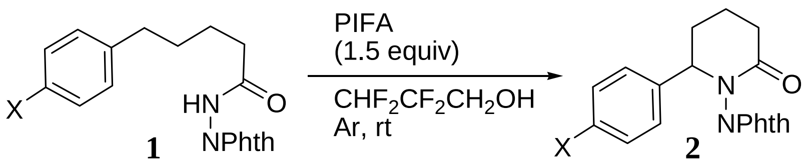
Entry	Solvent	Product (**2a**) Yield (%)
1	CH_2Cl_2	9
2	$CHCl_3$	trace
3	CF_3CH_2OH	11
4	$(CF_3)_2CHOH$	36 + trace[a]
5	$CHF_2CF_2CH_2OH$	46 + trace[a]

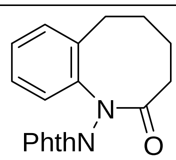
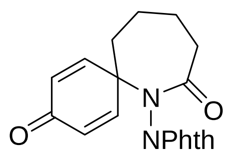
6	$H(CF_2)_6CH_2OH$	2
7	$CF_3(CF_2)_2OCF(CF_3)CH_2OH$	7

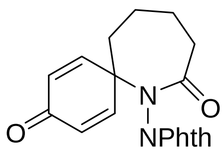
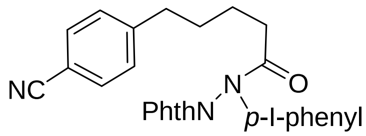
[a] Yield of compound **3**.

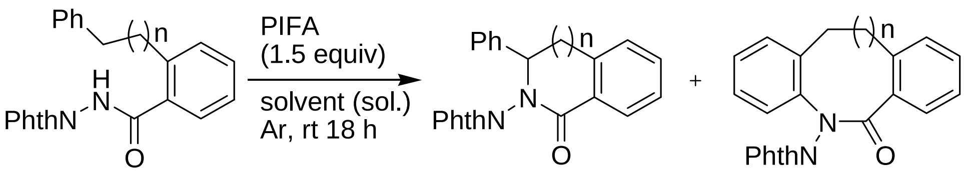
The yield of **2a** is slightly better in 2,2,3,3-tetrafluoro-1-propanol than in 2,2,2-trifluoroethanol. In the case of long chain fluorinated solvents the reaction proceeds unsatisfactorily probably because of poor solubility of **1a** in these solvents (entries 6 and 7). Generally reactions in poorly nucleophilic polar solvents gave good results, while use of other polar solvents such as dichloromethane and chloroform did not give satisfactory results. The combination of the phthalimido group and fluorinated solvents plays an important role for the stabilization of the acyl nitrenium ion and for its further reaction. Several *N*-(phenylpentanamido)phthalimides (**1a-h**) and the similar compounds (**1i** and **1j**) reacted in a similar way and the results are presented in Table 2.

Table 2. Benzylic cyclization of *N*-(5-phenylpentanamido)phthalimides (**1**) with PIFA



Entry	Starting Material	Reaction Time (h)	Product Yield (%)		
1	**1a** (X = H)	18	**2a** (46)		**3** (10)
2	**1b** (X = F)	5	**2b** (73)		
3	**1c** (X = Cl)	18	**2c** (56)		
4	**1d** (X = Br)	18	**2d** (71)		
5	**1e** (X = I)	18	**2e** (72)		
6	**1f** (X = OMe)	4			**4** (54)

7	**1g** (X = OCH_2CF_3)	4		**4** (22)
8	**1h** (X = CN)	18		**5** (70)



1i; n = 0 (sol: $(CF_3)_2CHOH$) **2i**; n = 0 (37%) **6**; n = 0 (59%)
1j; n = 1 (sol: CF_3CH_2OH) **2j**; n = 1 (27%) **7**; n = 1 (52%)

These results show that benzylic cyclization occurs in good yields with compounds having a 4-halogenophenyl group (Table 2, entries 1-5) and that seven membered spirodienones are formed from compounds having 4-alkoxyphenyl groups (Table 2, entries 6 and 7). Compound **1h**, which has an electron-withdrawing cyano group in the *para*-position, did not give rise to either the benzannulated and spirobenzannulated products. Instead, the 4-iodophenyl group was transferred from PIFA to the amide nitrogen to afford the acyldiarylamine **5** in 70% yield.[8]

The nitrenium ions formed from **1i** and **1j**, which have two reaction sites in a molecule, gave rise to both the benzannulated and the benzylic cyclization compounds.

As for the reaction mechanism it is assumed from the by-products that initially PIFA attacks the amide moiety of **1** to afford an electron deficient nitrogen that behaves as a nitrenium ion; however, the precise reaction mechanism, especially the reason for the benzylic carbon-nitrogen bond formation, remains unclear.

In summary, we have developed a new method for the synthesis of phenyl substituted lactams from *N*-acylaminophthalimides using PIFA in 2,2,3,3-tetrafluoro-1-propanol. PIFA reacts with the amide nitrogen to form an intermediate, which is decomposed to generate an electron deficient nitrogen ion (**III**). When the phenyl group is not suitably located in a molecule, the benzyl position is attacked by this electron deficient nitrogen to form phenyl substituted lactams in moderate to good yields.

EXPERIMENTAL

All the melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H NMR (270 MHz) spectra and ^{13}C NMR spectra (68 MHz) were measured on a JEOL JNM-EX270 spectrometer with tetramethylsilane ($MeSi_4$) as an internal reference. ^{1}H NMR and ^{13}C

NMR spectral data are reported in parts per million (δ) relative to $MeSi_4$. IR spectra were recorded on a JASCO IR 810 spectrophotometer. MS spectra were obtained with a JEOL JMX-DX 300 spectrometer with a direct inlet system at 70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this University.

All the starting materials **1a-j** were prepared by the reaction of the corresponding acid chlorides with *N*-aminophthalimide in dry pyridine.[2d] 5-Arylpentanoic acids were synthesized by the literature method.[9] 2-Benzylbenzoic acid and 2-phenethylbenzoic acids were commercially available.

***N*-(1,3-Dioxoisoindolin-2-yl)-5-phenylpentanamide (1a).** Colorless crystals: mp 132-134 ºC (AcOEt/*n*-hexane); IR (KBr) 3250, 1805, 1750, 1670, 1525, 710cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.72-1.82 (m, 4H), 2.43 (t, *J* = 7.1 Hz, 2H), 2.67 (t, *J* = 6.8 Hz, 2H), 7.14-7.33 (m, 6H), 7.77-7.83 (m, 2H), 7.87-7.94 (m, 2H); EI-MS *m/z* 332 (M^+, 0.6), 162 (100), 117 (16.7), 91 (39.8); FAB-MS *m/z* 333 (M^+ + 1). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.74; H, 5.60; N, 8.68.

***N*-(1,3-Dioxoisoindolin-2-yl)-5-(4-fluorophenyl)pentanamide (1b).** Colorless crystals: mp 132-133 ºC (AcOEt-*n*-hexane); IR (KBr) 3170, 3000, 1790, 1750, 1670, 1510, 1220, 710 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.61-1.87 (m, 4H), 2.43 (t, *J* = 7.0 Hz, 2H), 2.63 (t, *J* = 6.9 Hz, 2H), 6.90-7.01 (m, 2H), 7.08-7.19 (m, 2H), 7.37 (br s, 1H), 7.74-7.83 (m, 2H), 7.86-7.96 (m, 2H); EI-MS *m/z* 340 (M^+, 0.4), 162 (100), 109 (48.6) ; FAB-MS *m/z* 341 (M^+ + 1, 48.8). Anal Calcd for $C_{19}H_{17}FN_2O_3$: C, 67.05; H, 5.03; N, 8.23. Found: C, 67.17; H, 5.12; N, 8.26.

***N*-(1,3-Dioxoisoindolin-2-yl)-5-(4-chlorophenyl)pentanamide (1c).** Colorless crystals: mp 148-149 ºC (AcOEt-*n*-hexane); IR (KBr) 3250, 1790, 1750, 1685, 1490, 1420, 1210, 880, 710 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.65-1.85 (m, 4H), 2.43 (t, *J* = 6.8 Hz, 2H), 2.63 (t, *J* = 6.9 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.43 (br s, 1H), 7.73-7.84 (m, 2H), 7.85-7.98 (m, 2H); EI-MS *m/z* 358 (M^+ + 2, 0.1), 356 (M^+, 0.3), 194 (8.7), 162 (100), 151 (12.5), 125 (28.7). Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; N, 7.85. Found: C, 63.93; H, 4.85; N, 7.83.

***N*-(1,3-Dioxoisoindolin-2-yl)-5-(4-bromophenyl)pentanamide (1d).** Colorless crystals: mp 165-167 ºC (AcOEt-*n*-hexane); IR (KBr) 3260, 1800, 1755, 1675, 710 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.65-1.85 (m, 4H), 2.43 (t, *J* = 6.9 Hz, 2H), 2.62 (t, *J* = 6.9 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.29 (br s, 1H), 7.74-7.84 (m, 2H), 7.86-7.96 (m, 2H); EI-MS *m/z* 402 (M^+ + 2, 0.3), 400 (M^+, 0.3), 292 (2.1), 238 (7.5), 171 (19.5), 169 (19.9), 162 (100), 104 (15.0). Anal Calcd for $C_{19}H_{17}BrN_2O_3$: C, 56.87; H, 4.27; N, 6.98. Found: C, 57.06; H, 4.04; N, 6.97.

***N*-(1,3-Dioxoisoindolin-2-yl)-5-(4-iodophenyl)pentanamide (1e).** Colorless crystals: mp 178-179 ºC ($CHCl_3$-*n*-hexane); IR (KBr) 3250, 1800, 1750, 1670, 710 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.67-1.87 (m, 4H), 2.43 (t, *J* = 7.0 Hz, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 7.40 (br s, 1H), 7.60

(d, J = 8.4 Hz, 2H), 7.74-7.83 (m, 2H), 7.87-7.96 (m, 2H); EI-MS m/z 448 (M^+, 3.1), 286 (50.2), 162 (100) ; FAB-MS m/z 449 (M^+ + 1, 27.7). Anal Calcd for $C_{19}H_{17}IN_2O_3$: C, 50.91; H, 3.82; N, 6.25. Found: C, 50.95; H, 3.85; N, 6.28.

***N*-(1,3-Dioxoisoindolin-2-yl)-5-(4-methoxyphenyl)pentanamide (1f).** Colorless crystals: mp 134-135 ºC (AcOEt-*n*-hexane); IR (KBr) 3250, 1800, 1750, 1675, 1515, 1250, 710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.62-1.76 (m, 4H, CH), 2.42 (t, J = 6.9 Hz, 2H), 2.61 (t, J = 7.3 Hz, 2H), 3.78 (s, 3H), 6.82 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 7.35 (br s, 1H), 7.74-7.83 (m, 2H), 7.86-7.96 (m, 2H); EI-MS m/z 352 (M^+, 11.0), 190 (100), 162 (15.4), 147 (46.1), 134 (47.5), 121 (61.2). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.05; H, 5.66; N, 7.84.

***N*-(1,3-Dioxoisoindolin-2-yl)-5-(4-(2,2,2-trifluoroethoxy)phenyl)pentanamide (1g).** Colorless crystals: mp 144-145 ºC (AcOEt-*n*-hexane); IR (KBr) 3450, 1800, 1750, 1675, 1510, 1235 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.64-1.86 (m, 4H), 2.43 (t, J = 6.9 Hz, 2H), 2.62 (t, J = 6.8 Hz, 2H), 4.32 (q, $J_{H\text{-}F}$ = 7.2 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 7.35 (br s, 1H), 7.74-7.83 (m, 2H), 7.86-7.95 (m, 2H); EI-MS m/z 420 (M^+, 0.6), 258 (100), 215 (40.4), 209 (49.3), 189 (56.2), 162 (31.1). Anal. Calcd for $C_{21}H_{19}F_3N_2O_4$: C, 60.00; H, 4.56; N, 6.66. Found: C, 59.77; H, 4.50; N, 6.76.

5-(4-Cyanophenyl)-*N*-(1,3-dioxoisoindolin-2-yl)pentanamide (1h). Colorless crystals: mp 165-166 ºC (AcOEt-*n*-hexane); IR (KBr) 3250, 2220, 1790, 1740, 1670, 710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.73-1.83 (m, 4H), 2.41-2.49 (m, 2H), 2.67-2.77 (m, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.42 (br s, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.77-7.83 (m, 2H), 7.89-7.94 (m, 2H); EI-MS m/z 347 (M^+, 0.04), 162 (100), 116 (33.9); FAB-MS m/z 348 (M^+ + 1, 48.5). Anal Calcd for $C_{20}H_{17}IN_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.15; H, 5.00; N, 12.14.

2-Benzyl-*N*-(1,3-dioxoisoindolin-2-yl)benzamide (1i). Colorless crystals: mp 198-201 ºC (AcOEt/*n*-hexane); IR (KBr) 3280, 1795, 1725, 1700, 1425, 1125, 715, 705 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.27 (s, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.32-7.40 (m, 4H), 7.45 (td, J = 7.7, 1.3 Hz, 1H), 7.69 (d, J = 7.7 Hz, 2H), 7.91-8.02 (m, 4H); EI-MS m/z 356 (M^+, 2.9), 195 (100), 165 (21.1). Anal. Calcd for $C_{22}H_{16}N_2O_3$: C, 74.15; H, 4.53; N, 7.86. Found: C, 74.18; H, 4.49; N, 7.85.

***N*-(1,3-Dioxoisoindolin-2-yl)-2-phenethylbenzamide (1j).** Colorless crystals: mp 189-192 ºC (AcOEt); IR (KBr) 3290, 1795, 1730, 1705, 765, 715, 710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.02 (t, J =7.5 Hz, 2H), 3.19 (t, J =7.5 Hz, 2H), 7.11-7.34 (m, 8H), 7.44 (t, J =7.2 Hz, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.78-7.88 (m, 2H), 7.91-7.99 (m, 2H); EI-MS m/z 370 (M^+, 0.1), 209 (100), 131 (34.9); FAB-MS m/z 371 (M^+ + 1). Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.59; H, 4.81; N, 7.53.

Reaction of *N*-(1,3-Dioxoisoindolin-2-yl)-5-(4-bromophenyl)pentanamide (1d) with PIFA in 2,2,3,3-Tetrafluoro-1-propanol. A Typical Experimental Procedure for Table 2

PIFA (161 mg, 0.37 mmol) was added to a solution of **1d** (100 mg, 0.25 mmol) in 2,2,3,3-tetrafluoro-1-propanol (20 mL). The reaction mixture was stirred at room temperature for 22 h under argon atomosphere. After the reaction, the mixture was evaporated and the residue was diluted with EtOAc (40 mL). The organic layer was washed with 10% Na_2CO_3 aq. (15 mL x 2), brine, and dried over Na_2SO_4. After removal of solvent, the residue was purified by column chromatography, eluting with EtOAc/toluene (1:10), to give **2d** (71 mg, 71%).

2-(2-Oxo-6-phenylpiperidin-1-yl)isoindoline-1,3-dione (2a). Colorless crystals: mp 170-173 ºC (AcOEt/*n*-hexane); IR (KBr) 1795, 1740, 1680, 1380, 715, 705 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.00-2.20 (m, 3H), 2.29-2.39 (m, 1H), 2.72-2.81 (m, 2H), 5.08-5.19 (m, 1H), 7.19-7.32 (m, 3H), 7.43 (d, *J* = 6.4 Hz, 2H), 7.64-7.74 (m, 3H), 7.76-7.82 (m, 1H); EI-MS *m/z* 320 (M^+, 0.3), 251 (7.1), 173 (82.1), 145 (100), 130 (41.6), 104 (25.9); FAB-MS *m/z* 321 (M^+ + 1). Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.22; H, 4.77; N, 8.74.

2-(2-(4-Fluorophenyl)-6-oxopiperidin-1-yl)isoindoline-1,3-dione (2b). Colorless crystals: mp 220-222 ºC ($CHCl_3$-*n*-hexane); IR (KBr) 2950, 1790, 1730, 1680, 700 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.00-2.16 (m, 3H), 2.26-2.37 (m, 1H), 2.75 (t, *J* = 5.9 Hz, 2H), 5.06-5.15 (m, 1H), 6.92-7.01 (m, 2H), 7.37-7.45 (m, 2H), 7.66-7.83 (m, 4H); EI-MS *m/z* 338 (M^+ , 0.1), 192 (43.7), 191 (48.0), 163 (100), 148 (42.8); FAB-MS *m/z* 339 (M^+ +1, 80.6). Anal. Calcd for $C_{19}H_{15}FN_2O_3$: C, 67.45; H, 4.47; N, 8.28. Found: C, 67.72; H, 4.61; N, 8.34.

2-(2-(4-Chlorophenyl)-6-oxopiperidin-1-yl)isoindole-1,3-dione (2c). Colorless crystals: mp 217-219 ºC (AcOEt-*n*-hexane); IR (KBr) 1795, 1735, 1685, 1380, 1190, 880, 710 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.96-2.14 (m, 3H), 2.23-2.38 (m, 1H), 2.74 (t, *J* = 5.5 Hz, 2H), 5.06-5.14 (m, 1H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.64-7.83 (m, 4H); EI-MS *m/z* 357 (M^+ + 2 + H, 2.5), 355 (M^+ + H, 7.6), 319 (8.3), 308 (14.9), 208 (40.6), 179 (77.2), 172 (100); FAB-MS *m/z* 355 (M^+ + 1, 67.5). Anal. Calcd for $C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.35; H, 4.02; N, 7.93.

2-(2-(4-Bromophenyl)-6-oxopiperidin-1-yl)isoindole-1,3-dione (2d). Colorless crystals: mp 195-196 ºC (AcOEt-*n*-hexane); IR (KBr) 1795, 1735, 1685, 1380, 1290, 885, 710 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.95-2.16 (m, 3H), 2.22-2.40 (m, 1H), 2.74 (t, *J* = 5.4 Hz, 2H), 5.10-5.18 (m, 1H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.66-7.85 (m, 4H); EI-MS *m/z* 401 (M^+ + 2 + H, 1.5), 399 (M^+ + H, 1.9) 254 (27.4), 252 (30.1), 225 (50.5), 223 (50.9), 172 (100); FAB-MS *m/z* 399 (M^+ + 1, 38.9). Anal. Calcd for $C_{19}H_{15}BrN_2O_3$: C, 57.16; H, 3.79; N, 7.02. Found: C, 57.20; H, 3.68; N, 6.94.

2-(2-(4-Iodophenyl)-6-oxopiperidin-1-yl)isoindole-1,3-dione (2e). Colorless crystals: mp 190-193 ºC ($CHCl_3$-AcOEt-*n*-hexane); IR (KBr) 2950, 1790, 1730, 1690, 720 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.95-2.12 (m, 3H), 2.25-2.39 (m, 1H), 2.74 (t, *J* = 5.4 Hz, 2H), 5.00-5.13 (m, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.69-7.87 (m, 4H); EI-MS *m/z* 446 (M^+, 0.5), 300 (49.4), 271 (74.8), 172

(100). Anal. Calcd for $C_{19}H_{15}IN_2O_3$: C, 51.14; H, 3.39; N, 6.28. Found: C, 51.30; H, 3.44; N, 6.20.

3'-Phenyl-3'*H*-2,2'-biisoindolyl-1,1',3-trione (2i). Colorless crystals: mp 218-221 ºC (AcOEt/*n*-hexane); IR (KBr) 1805, 1740, 1715, 710 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6) δ 6.12 (s, 1H), 7.34-7.39 (m, 4H), 7.47-7.51 (m, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.73 (dt, *J* = 7.4, 1.2 Hz, 2H), 7.87-7.90 (m, 1H), 7.92-7.99 (m, 4H); EI-MS *m/z* 354 (M^+, 25.9), 208 (100), 195 (54.5), 165 (53.1). Anal. Calcd for $C_{22}H_{14}N_2O_3$: C, 74.57; H, 3.98; N, 7.91. Found: C, 74.43; H, 3.83; N, 7.87.

2-(1-Oxo-3-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl)isoindoline-1,3-dione (2j) Colorless crystals: mp 173-175 ºC (benzne/*n*-hexane); IR (KBr) 1790, 1735, 1690, 1300, 725, 710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.34 (dd, *J* = 16.0, 4.3 Hz, 1H), 3.59 (dd, *J* = 16.0, 11.7 Hz, 1H), 5.50 (dd, *J* = 11.7, 4.3 Hz, 1H), 7.72-7.32 (m, 4H), 7.38-7.50 (m, 3H), 7.54 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.66-7.72 (m, 2H), 7.73-7.80 (m, 2H), 8.16 (dd, *J* = 7.6, 1.3 Hz, 1H); EI-MS *m/z* 368 (M^+, 1.7), 221 (100), 118 (89.7). Anal. Calcd for $C_{23}H_{16}N_2O_3$: C, 74.99; H, 4.38; N, 7.60. Found: C, 74.99; H, 4.28; N, 7.58.

2-(2-Oxo-3,4,5,6-tetrahydrobenzo[*b*]azocin-1(2*H*)-yl)isoindoline-1,3-dione (3). Colorless crystals: mp 278-282 ºC (EtOH); IR (KBr) 1795, 1740, 1685, 715 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.38-1.55 (m, 2H) 1.77-2.10 (m, 2H), 2.25 (d, *J* = 11.9 Hz, 1H), 2.53 (q, *J* = 7.2 Hz, 1H), 2.95 (q, *J* = 7.2 Hz, 1H), 3.34 (t, *J* = 13.0 Hz, 1H), 7.19-7.25 (m, 1H), 7.33 (d, *J* = 3.7 Hz, 2H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.76-7.87 (m, 3H), 7.94-7.99 (m, 1H); EI-MS *m/z* 320 (M^+, 100), 174 (33.1), 104 (35.1). Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.00; H, 4.90; N, 8.61.

7-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-7-aza-spiro[5.6]dodeca-1,4-diene-3,8-dione (4). Colorless crystals: mp 197-198 ºC (AcOEt-*n*-hexane); IR (KBr) 1790, 1740, 1680, 1670 710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.94-2.13 (m, 4H), 2.24-2.38 (m, 2H), 2.80-2.94 (m, 2H), 6.17 (d, *J* = 10.1 Hz, 2H), 7.24 (d, *J* = 10.1 Hz, 2H), 7.71-7.89 (m, 4H); EI-MS *m/z* 33.6 (M^+, 10.8), 252 (44.4), 229 (100), 146 (60.9), 133 (40.9), 104 (11.3). Anal Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.75; H, 4.75; N, 8.05.

5-(4-Cyanophenyl)-*N*-(1,3-dioxoisoindolin-2-yl)-*N*-(4-iodophenyl)pentanamide (5). Colorless crystals: mp 173-174 ºC (toluene); IR (KBr) 2230, 1750, 1740, 1690, 730, 710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.62-1.74 (m, 4H), 2.32 (t, *J* = 6.5 Hz, 2H), 2.64 (t, *J* = 6.5 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.74-7.92 (m, 6H); EI-MS *m/z* 549 (M^+, 1.6), 364 (100), 116 (26.5) ; FAB-MS *m/z* 550 (M^+ + 1, 20.0). Anal Calcd for $C_{26}H_{20}IN_3O_3$: C, 56.84; H, 3.67; N, 7.65. Found: C, 57.10; H, 3.54; N, 7.76.

2-(6-Oxo-6,11-dihydro-dibenzo[*b*,*e*]azepin-5-yl)-isoindole-1,3-dione (6). Colorless crystals: mp 235-237 ºC (AcOEt/*n*-hexane); IR (KBr) 1800, 1745, 1665, 1315, 710 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6) δ 3.98 (d, *J* = 13.1 Hz, 1H), 4.64 (d, *J* = 13.1 Hz, 1H), 7.22-7.28 (m, 4H), 7.37 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.40-7.43 (m, 1H), 7.47-7.50 (m, 2H), 7.54 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.76 (dd, *J* = 7.9, 1.2

Hz, 1H), 7.97-8.15 (m, 2H); EI-MS *m/z* 354 (M^+, 64.6), 208 (100), 179 (43.9). Anal. Calcd for $C_{22}H_{14}N_2O_3$: C, 74.57; H, 3.98; N, 7.91. Found: C, 74.39; H, 3.96; N, 7.88.

2-(6-Oxo-11,12-dihydro-6*H*-dibenzo[*b*,*f*]azocin-5-yl)-isoindole-1,3-dione (7). Colorless crystals: mp 224-227 ºC (AcOEt/*n*-hexane); IR (KBr) 1800, 1745, 1690, 1320, 710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.96-3.15 (m, 2H), 3.34-3.79 (m, 1H), 4.05-4.18 (m, 1H), 7.02-7.29 (m, 6H), 7.39 (dd, J = 9.6, 1.5 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.76-7.94 (m, 2H), 7.96-8.04 (m, 2H); EI-MS *m/z* 368 (M^+, 63.3), 356 (17.3), 222 (100), 204 (29.8), 193 (78.1). Anal. Calcd for $C_{23}H_{16}N_2O_3$: C, 74.99; H, 4.38; N, 7.60. Found: C, 75.03; H, 4.34; N, 7.56.

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