Synthesis of new oxindole derivatives containing an oxazolidin-2-one

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Abstract

The reactions of *bis*(2-chloroethyl)amine in presence of potassium carbonate with substituted isatins afforded the corresponding 1-[2-(2-oxo-1,3-oxazolidin-3-yl)ethyl)indoline-2,3-diones, which are used as starting materials for the preparation of new heterocyclic systems containing quinoxaline, oxazolidine, benzimidazoquinazoline and oxindole nuclei. The structures of the products were established by NMR spectroscopy, mass spectra and X-ray diffraction analysis.

Keywords: Oxindole, oxazolidine, potassium carbonate, spiro[benzimidazo[1,2-c]quinazoline], oxindole, quinoxaline

Introduction

Heterocyclic compounds containing 5- or 6-membered ring are important for their diverse biological activities.[1] For example, indole-2,3-diones, which represent a large family of heterocyclic compounds, have been extensively explored for developing pharmaceutically important molecules. *N*-Substituted isatins[2] especially are reported to show a wide range of biological activities such as antibacterial,[3] anti-fungal[4,5] antiviral[6] and anti-HIV,[7,8] antileukemia.[9] These compounds were also reported to have effects on central nervous system.[10,11]

The chemistry of oxazolidinone and its derivatives has received considerable attention owing to their synthetic and biological importance.[12] The oxazolidinone moiety has been incorporated into a wide variety of therapeutically interesting compounds that have antibacterial, antifungal (Streptazoline);[13,14] immunodulatory activity (Cytotoxane).[15] Oxindoles containing an oxazolidinone nucleus (I and II) have been shown to have antibacterial activity and MAO-A and B inhibitory property.[16]

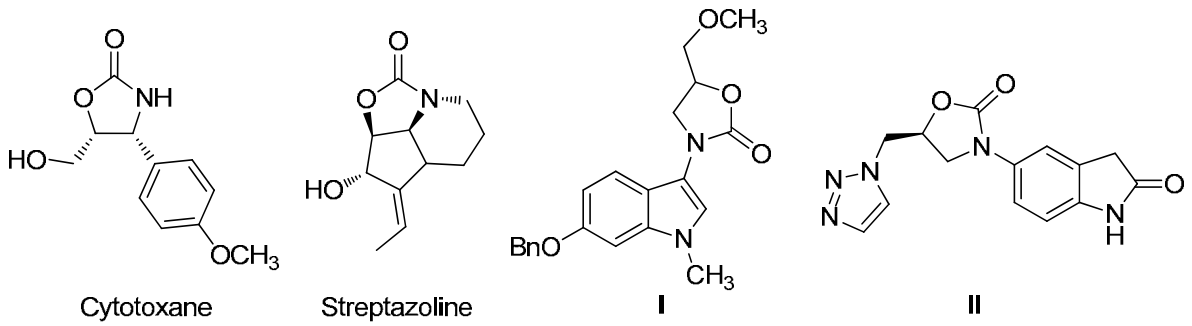
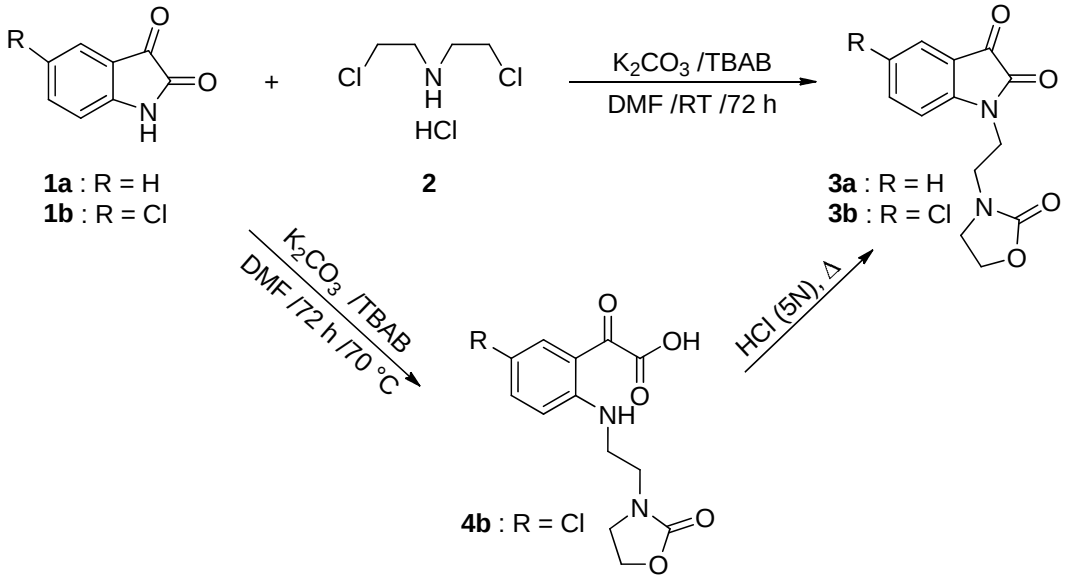


Figure 1

Generally, oxazolidinones aare prepared from amino alcohols, which in turn are prepared from amino acids by reduction with a metal hydride. Reaction of amino alcohols with phosgene and related compounds furnishes oxazolidinones.[17-19] Also, treatment of amino alcohols with ethyl chloroformate produced carbamates which in turn can be cyclized to 2-oxazolidinones.[20]
In continuation of our work on the synthesis of *N*-substituted isatins,[3,21,22] we herein report the synthesis and characterization of new oxindole derivatives bearing an oxazolidin-2-one sub-unit.

Results and Discussion

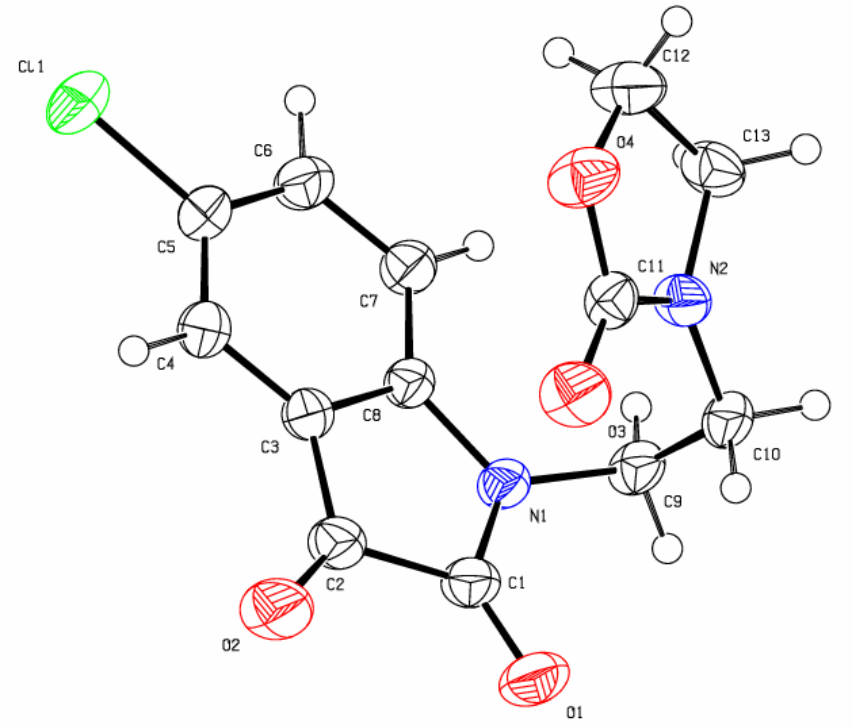
The alkylation of isatins **1a-b** with *bis*(chloroethyl)amine dihydrochloride **2** at room temperature, using phase transfer catalysis conditions, yielded a one-pot synthesis of oxindoles **3a-b**, containing an oxazolidinone nucleus (Scheme 1). It is worth mentioning that heating compounds **1b** and **2** at 70 °C for 72 hours with similar reaction condition yielded compound **4b** due to ring opening. However, heating **4b** in presence of 5N HCl led to compound **3b**.



Scheme 1

The structures of isolated products were confirmed by ^{1}H, ^{13}C NMR spectroscopy and mass spectrometry. For example the ^{1}H NMR spectrum of **3b** exhibited four triplets, arising from the methylene groups (δ 3.86, 3.62, 3.42 NCH_2, 4.16 OCH_2). The aromatic protons of the indole ring system showed a multiplet in the region (7.28-7.72 ppm). The ^{13}C NMR spectrum of **3b**, exhibited three signals at 182.6, 158.6, 158.5 ppm for the carbonyl carbons of isatin and oxazolidine ring respectively and four signals at 37.95, 41.49, 44.54, 62.36 ppm for the methylene groups. The mass spectrum (APCI) of **3b** displayed the pseudo molecular ion peak at *m/z* = 295 ($M+H^+$). A single crystal X-ray analysis of **3b** confirmed its structure and by extrapolation, those of the analogues. An ORTEP diagram of **3b** is shown in Figure 2.

For compound **4b**, the ^{1}H NMR specrum of **4b** exhibited four triplets, arising from the methylene groups (δ 3.43, 3.38, 3.57 NCH_2, 4.24 OCH_2). The aromatic protons of the indole ring system showed a multiplet in the region (6.85-7.56 ppm). The ^{13}C NMR spectrum of **4b**, exhibited three peaks at 199.9, 169.3, 158.6 ppm for the carbonyl carbons of isatin and oxazolidine ring respectively, four peaks at 40.1, 43.2, 44.9, 62.3 ppm for the methylene groups and (113.7, 133.8, 134.3) for aromatic carbons. The structure of this molecule was also confirmed by single-crystal X-ray data (Figure 2).



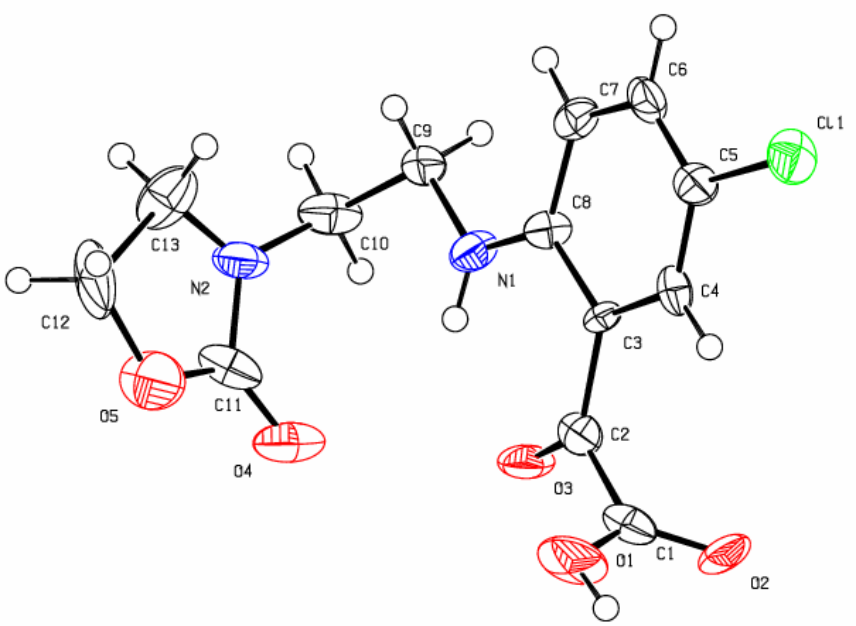


Figure 2. Molecular structure of **3b** and **4b**, with 30% probability displacement ellipsoids.

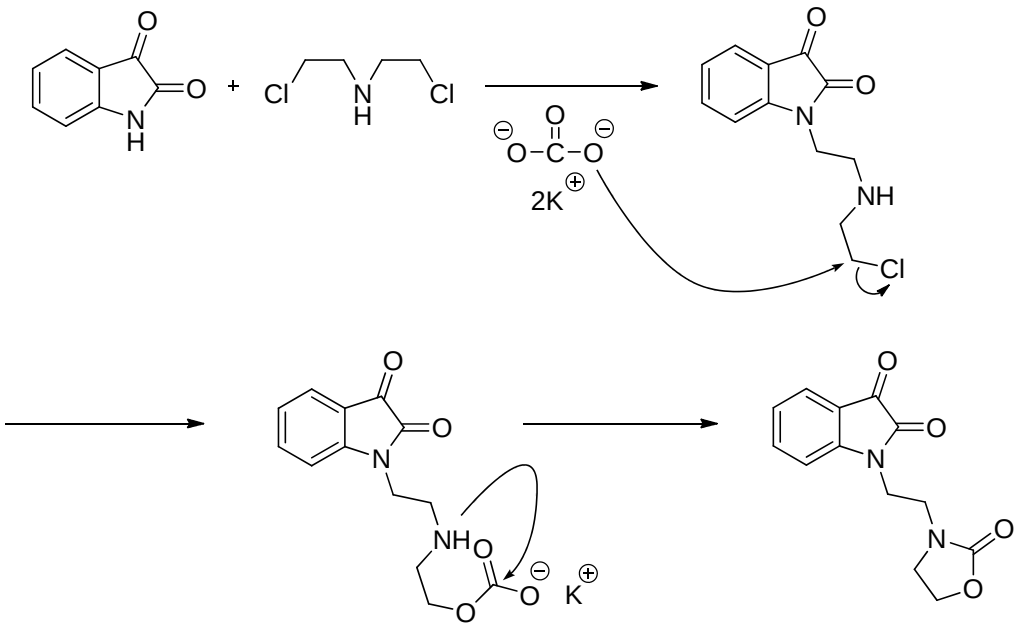
Table 1. Crystal data and structure refinement for **3b** and **4b**

	3b	**4b**
Crystal data		
Formula	$C_{13}H_{11}ClN_2O_4$	$C_{13}H_{13}ClN_2O_5$
Formula Weight	294.69	312.70
Crystal System	triclinic	triclinic
Space group	P-1	P-1
a, b, c [Å]	a = 5.99770(10)	8.9616(3)
	b = 8.3572(2)	13.5680(4)
	c = 13.2865(2)	15.0874(4)
α, β, γ [°]	82.7880(10)	113.126(1)
	88.4750(10)	94.855(2)
	73.8400(10)	94.104(2)
V [Å^3]	634.57(2)	1669.99(9)
Z	4	4
D(calc) [g/cm^3]	1.542	1.24_
Mu(MoKα) [mm^{-1}]	0.633	0.124
F(000)	304	648
Data Collection		
Temperature (K)	298(2)	298
Radiation [Å]	0.71073	0.71073

Table 1. Continued

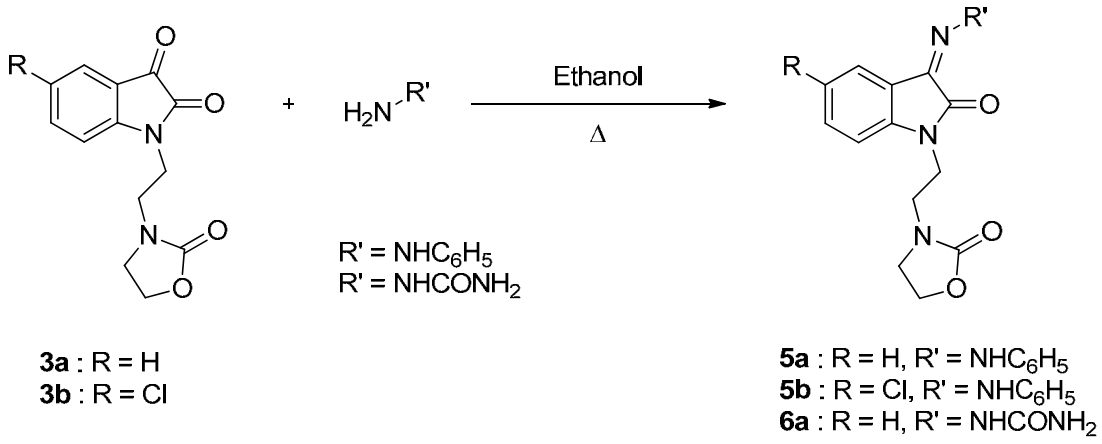
	3b	**4b**
Theta Min-Max [°]	1.54, 34.96	1.5, 30.3
Dataset	-9: 9; -13: 13; -21: 21	-12: 12 ; -18: 19 ; -21: 21
Tot., Uniq. Data, R(int)	24424, 5570, 0.0287	44215, 9827, 0.030
Refinement		
Nref, Npar	5570, 188	9827, 379
R, wR2, S	0.0420, 0.1084	0.0912, 0.2487, 1.04
Max. and Av. Shift/Error	0.0731, 0.1251	1.52, 0.05
Min. and Max. Resd. Dens. [e/Å^3]	-0.278, 0.338	-0.71, 0.98
CCDC number[23]	691519	691520

According to these results, we propose a mechanism for the formation of compounds **3a-b**. It is postulated that initial alkylation of the nitrogen atom of the lactam functionality gave intermediates that underwent a nucleophilic reaction involving potassium carbonate. Cyclisation of these intermediates led to the formation of **3a-b** (Scheme 2).

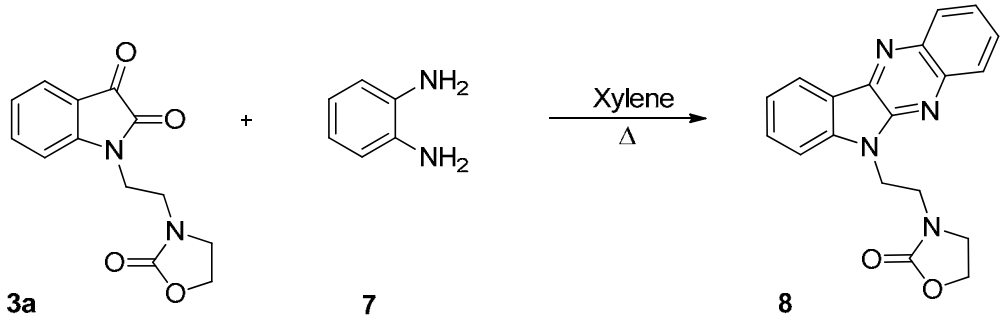


Scheme 2

In order to explore the reactivity of carbonyl group at position 3 of compounds **3a-b**, we carried out the reactions of compounds **3a-b** with phenylhydrazine, semicarbazide and *o*-phenylenediamine. The corresponding products: phenylhydrazones **5a-b**, semicarbazone **6a** and indoloquinoxaline **8**, were obtained in good yields (Schemes 3 and 4).



Scheme 3

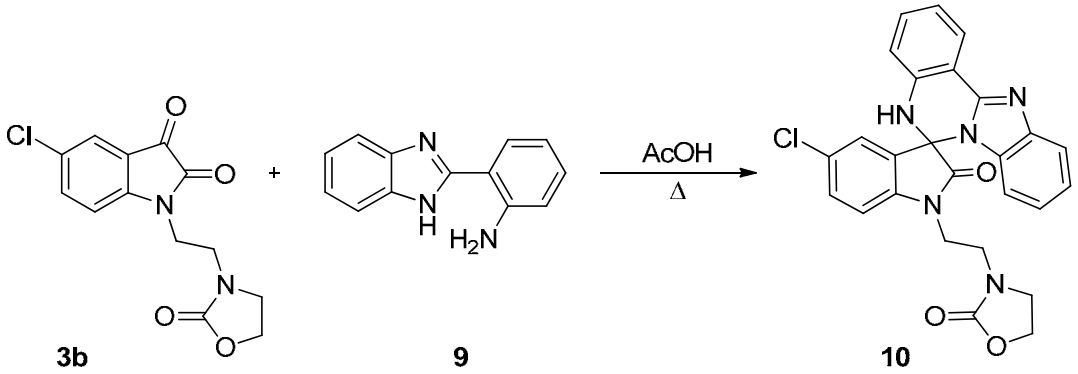


Scheme 4

The ^{1}H NMR spectrum of **5a** exhibited four triplets (δ 3.50, 3.63, 3.99 and 4.17) readily recognized to arise from the methylene CH_2 protons, along with multiplets (δ 7.06-7.70) for the aromatic protons. The ^{13}C NMR spectrum of **5a** showed 17 distinct resonances in agreement with the proposed structure. The carbonyl carbon resonated at δ 162.1 ppm and C=N carbon at 142.9 ppm.

Recently, studies of spiro-oxindoles have been carried out due to an increased interest in their biological activities. The oxindole ring, linked to other heterocyclic system through the spiro carbon at C-3, is of interest. In addition, various pharmacological properties are also associated with benzimidazo[1,2-*c*]quinazoline.[24] Thus, it is possible that a benzimidazo[1,2-*c*]quinazoline moiety at C-3 of the oxindole, containing an oxazolidinone sub-unit, could show biological activity.

Spiro[benzimidazo[1,2-*c*]quinazoline-6,3'-oxindole] **10** was obtained by the reaction of indoline-2,3-dione derivative **3b** with 2-(2-aminophenyl)benzimidazole **9** in refluxing acetic acid. The structure of compound **10** was confirmed on the basis of its ^{1}H, ^{13}C NMR and mass spectral analysis.



Scheme 5

The ^{1}H NMR spectrum of **10** shows a multiplet in the region δ 6.09-7.71 for the aromatic protons. The methylene protons of the oxazolidine ring resonate as two triplets at δ 3.72, 4.04 (J = 7.5 Hz) while the methylene protons of the alkyl chain linked to nitrogen atom of the oxindole ring appear as two triplets at δ 3.47, 3.87 (J = 6 Hz). The NH proton of quinazoline ring exhibits a peak at δ 5.63 as a singlet. In the ^{13}C NMR spectrum of **10** the signals were observed at δ 73.3 (spiro carbon), 38.1, 41.4, 44.6, 62.2 (methylene carbons), 158.7, 172.1 (both C=O).

Conclusions

In summary, we have successfully synthesized isatin derivatives bearing oxazolidin-2-one rings.

Experimental Section

General. Melting points were determined in one-end-open capillary tubes on a Büchi melting point apparatus and are uncorrected. ^{1}H NMR, ^{13}C NMR spectra were recorded on a Bruker Avance (300MHz) Spectrometer. Chemical shifts are reported in parts per million (ppm) using tetramethyl silane (TMS) as the internal standard, multiplicities were determined by the DEPT 135 sequence. Coupling constants were reported in Hertz (Hz). Splitting patterns were designated as s: singlet; d: doublet, t: triplet. Mass spectra were recorded on VARIAN MAT 311A Spectrometer.

1-(2-(2-Oxooxazolidin-3-yl)ethyl)indoline-2,3-dione 3a. To a stirred mixture of isatin **1a** (6.8 mmol) and K_2CO_3 (8.16 mmol) in dimethylformamide (30 mL) at room temperature, was added tetra-*n*-butylammonium bromide (0.1 mmol) and bis(chloroethyl)amine dihydrochloride (8.16 mmol). The mixture was stirred at room temperature for 72 h. The white solid formed was filtered off and the solvent was evaporated under vacuum and the remaining foam was dissolved

in CH_2Cl_2 and filtered. The CH_2Cl_2 was removed and the residue was recrystallized in ethanol to offer the pure product. Mp: 131 °C. Yield: 60%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.56 (t, 2H, NCH_2, ^3J = 6.0 Hz); 3.70 (t, 2H, NCH_2, ^3J= 7.5 Hz); 3.92 (t, 2H, NCH_2, ^3J= 6.0 Hz); 4.26 (t, 2H, OCH_2, ^3J= 7.5 Hz); 7.02-7.62 (m, 4H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.7, 41.7, 45.0 3(NCH_2); 62.1 (OCH_2); 110.1, 124.1, 125.6, 138.6 (CH_{Ar}); 182.7 ($C{=}O_{ketone}$); 158.6 (2)($C{=}O_{amide}$); 150.3 (O-C=O) 117.7 (Cq-N); Mass spectra (CI, [MH^+] *m/z*): 261. Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76% Found: C, 60.07; H, 4.55; N, 10.70%.

5-Chloro-1-(2-(2-oxooxazolidin-3-yl)ethyl)indoline-2,3-dione 3b. Preparation as described for **3a** starting from **1b**. Mp: 194 °C. Yield: 65%. ^{1}H NMR (300 MHz, DMSO-d_6): δ= 3.42 (t, 2H, NCH_2, ^3J= 6 Hz); 3.62 (t, 2H, NCH^2, ^3J = 7.5 Hz); 3.86 (t, 2H, NCH_2, ^3J= 6 Hz); 4.16 (t, 2H, OCH_2, ^3J= 7.5 Hz); 7.28-7.72 (m, 3H, H_{Ar}). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 62.4 (OCH_2); 38.0, 41.5, 44.5 (NCH_2); 112.8, 124.5, 137.7 (CH_{Ar}); 119.2, 128.1, 149.6 (Cq); 158.5 ($C{=}O_{oxazolidine}$); 158.6 ($C{=}O_{amide}$); 182.6 ($C{=}O_{ketone}$); Mass spectra (CI, [MH^+] *m/z*: 295). Anal. Calcd for $C_{13}H_{11}ClN_2O_4$: C, 52.98; H, 3.76; N, 9.51% Found: C, 53.05; H, 3.83; N, 9.45%.

2-(5-Chloro-2-(2-(2-oxooxazolidin-3-yl)ethylamino)phenyl)-2-oxoacetic acid 4b. Similar to **3a**, the mixture was heated at 70 °C for 72 h. Mp: 96 °C. Yield: 20%. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 4.26 (t, 2H, OCH_2, ^3J= 1.12 Hz); 3.57 (t, 2H, $NHCH_2$, ^3J= 1.66 Hz); 3.44, 3.36 (2xt, 4H, CH_2-N-CH_2); 9.98 (1H, CO_2H); 8.62 (1H, NH); 6.82-7.57 (m, 4H, H_{Ar}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ= 62.8 (OCH_2); 38.2, 41.5 (CH_2NCH_2); 43.6 ($NHCH_2$); 112.4,124,O8 125,56, 136.62 (CH_{Ar}); 199.9 ($C{=}O_{ketone}$); 168.2 ($C{=}O_{amide}$); 157.4 (CO_2H); 153.2 (Cq-NH); 138.9 (Cq-Cl); 116.5 (Cq-C=O). Mass spectra (CI, [MH^+] *m/z*): 313. Anal. Calcd for $C_{13}H_{13}ClN_2O_5$: C, 49.93; H, 4.19; N, 8.96% Found: C, 50.01; H, 4.11; N, 9.07%.

3-(2-(2-Oxo-3-(2-phenylhydrazono)indolin-1-yl)ethyl)oxazolidin-2-one 5a. A mixture of isatin (1.00 g, 6.8 mmol) and aniline (0.62 mL, 6.8 mmol) in absolute ethanol (20 mL) was heated at reflux for 5 h. The reaction mixture was allowed to cool and the resulting precipitate filtered from the solution. The crude product was recrystallized in ethanol. Mp: 192 °C. Yield: 89%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.50 (t, 2H, NCH_2, ^3J = 6 Hz); 3.63 (t, 2H, NCH_2, ^3J= 7.2 Hz); 3.99 (t, 2H, NCH_2, ^3J= 6 Hz); 4.17 (t, 2H, OCH_2, ^3J= 7.2 Hz); 7.06-7.70 (m, 9H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.4, 42.1, 44.7 3(NCH_2); 62.3 (OCH_2); 109.5, 2×114.7, 118.9, 122.8, 123.6, 128.8, 2×129.9 (CH_{Ar}); 121.1, 127.3, 140.7 (Cq); 142.9 (C=N); 158.3, 162.1 ($C{=}O_{amide}$);. Mass spectra (CI, [MH^+] *m/z*): 351. Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found : C, 65.05; H, 5.25; N, 16.07%.

3-(2-(5-Chloro-2-oxo-3-(2-phenylhydrazono)indolin-1-yl)ethyl)oxazolidin-2-one 5b. This compound was made using the method for **5a**. Mp : 210 °C. Yield: 84%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.48 (t, 2H, NCH_2, ^3J = 6 Hz); 3.63 (t, 2H, NCH_2, ^3J= 7.2 Hz); 3.98 (t, 2H, NCH_2, ^3J= 6 Hz); 4.17 (t, 2H, OCH_2, ^3J = 7.2 Hz); 7.09-7.60 (m, 8H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.4, 42.0, 44.6 3×(NCH_2); 62.3 (OCH_2); 111.1, 2×115.1, 115.1, 118.5, 124.1, 128.1, 2×129.9 (CH_{Ar}); 122.8, 125.9, 127.2, 139.2, (Cq); 142.7 (C=N); 158.3, 161.7 ($C{=}O_{amide}$). Mass spectra (CI, [MH^+] *m/z*): 385. Anal. Calcd for $C_{19}H_{17}ClN_4O_3$: C, 59.30; H, 4.45; N, 14.56% Found: C, 59.41; H, 4.33; N, 14.59%.

2-(2-Oxo-1-(2-(2-oxooxazolidin-3-yl)ethyl)indolin-3-ylidene)hydrazinecarboxamide 6a. This compound was made using the method for **5a**. Mp : 163 °C. Yield: 86%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.47 (t, 2H, NCH_2, ^3J = 6 Hz); 3.63 (t, 2H, NCH_2, ^3J = 7.2 Hz); 3.94 (t, 2H, NCH_2, ^3J = 6 Hz); 4.16 (t, 2H, OCH_2, ^3J = 7.2 Hz); 7.10-7.66 (m, 4H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.4, 41.8, 44.5 3×(NCH_2); 62.3 (OCH_2); 109.9, 120.9, 123.2, 130.7 (CH_{Ar}); 120.2, 130.4 (Cq); 141.4 (C=N); 155.3, 158.4, 161.6 ($C{=}O_{amide}$). Mass spectra (CI, [MH^+] *m/z*): 318. Anal. Calcd for $C_{14}H_{15}N_5O_4$: C, 52.99; H, 4.76; N, 22.07% Found: C, 53.10; H, 4.69; N, 22.15%.

3-(2-(6*H*-Indolo[2,3-b]quinoxalin-6-yl)ethyl)oxazolidin-2-one 8. A mixture of oxindole **3a** (0.5 g, 3.84 mmole) and *o*-phenylenediamine **7** (0.41 g, 3.84 mmole) in xylene (30 mL) was refluxed for 12 h. The reaction mixture was evaporated under reduce pressure. The residue was recrystallized in ethanol. Mp : 202 °C. Yield: 62%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.63 (t, 2H, NCH_2, ^3J = 6 Hz); 3.74 (t, 2H, NCH_2, ^3J = 7.2 Hz); 4.02 (t, 2H, NCH_2, ^3J = 6 Hz); 4.62 (t, 2H, OCH_2, ^3J = 7.2 Hz); 7.39-8.40 (m, 8H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.2, 42.8, 44.5 3×(NCH_2); 62.1 (OCH_2); 110.5, 121.5, 122.6, 126.5, 127.9, 129.4, 129.5, 131.8 (CH_{Ar}); 119.2, 139.2, 140.1, 140.3 (Cq); 144.7, 145.9 (C=N); 158.4 ($C{=}O_{amide}$). Mass spectra (CI, [MH^+] *m/z*): 333. Anal. Calcd for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86% Found: C, 68.75; H, 4.78; N, 16.94%.

Spiro[benzimidazo[1,2-c]quinazoline-6,3'-oxindole] 10. A mixture of oxindole **3b** (3.84 mmole) and 2-(2-aminophenyl)benzimidazole **9** (3.84 mmole) in acetic acid (30 mL) was refluxed for 12 h. The reaction mixture was evaporated under reduce pressure. The residue was recrystallized in methylenechloride. Mp > 300 °C. Yield: 85%. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.47 (t, 2H, NCH_2, ^3J = 6 Hz); 3.72 (t, 2H, NCH_2, ^3J = 7.5 Hz); 3.87 (t, 2H, NCH_2, ^3J = 6 Hz); 4.04 (t, 2H, OCH_2, ^3J = 7.5 Hz); 6.09-8.05 (m, 3H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 38.1, 41.4, 44.6, 62.2 (CH_2); 73.3 (C_{spiro}); 110.1, 112.4, 115.1, 119.6, 123.2, 123.4, 125.1, 126.6, 132.1, 132.7 (CH_{Ar}); 112.1, 127.9, 128.5, 142.2, 142.4, 144.5, 148.2, 158.7, 172.1 (Cq). Mass spectra (CI, [MH^+] *m/z*):486. Anal. Calcd for $C_{26}H_{20}ClN_5O_3$: C, 64.27; H, 4.15; N, 14.41% Found: C, 64.33; H, 4.19; N, 14.29%.

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