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ARTICLE TYPE

Regio- and stereoselective synthesis of novel spiropyrrolidines through 1,3-dipolar cycloaddition reactions of azomethine ylides and 2-styrylquinazolin-4(3*H*)-ones

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Efficient regio- and stereoselective synthesis of novel of spiropyrrolidines was achieved through 1,3-dipolar cycloaddition reaction of 2-styrylquinazolin-4(3*H*)-ones with azomethine ylides generated in-situ from decarboxylative coupling of L-proline and isatin. The present approach offers the advantages of a clean and simple methodology, high atom economy, short reaction time, wide substrate scope, and a high yielding protocol for spiropyrrolidines.

Introduction

Novel hereocyclic libraries are very important in drug discovery for screening new hits against biological targets.[1] However, efficient construction of complex heterocyclic scaffolds from simple building blocks remains a great challenge in organic chemistry. Spiro-fused pyrrolidines, which have brought considerable attention due to their widespread biological activities, are particularly noteworthy in this concern.[2] These spiro-heterocycles possess anticonvulsant, potential antileukaemic, local anaesthetic, antidiabetic, antibacterial and antiviral activity.[3] The spiropyrrolidine core unit has been found in numerous biologically important alkaloids such as spirotryprostatin A **I,** isopteropodine **II,** elacomine **III** and horsfiline **IV** (Figure 1). Spirotryprostatin A **I,** and its related alkaloids, which have been identified as novel inhibitors of microtubule assembly, have led to the development of many synthetic spiropyrrolidines with potential anticancer activity.[4]

On the other hand, quinazolinones **V** have been associated with a wide spectrum of biological activities ranging from inhibitory effect on tubulin polymerization to anticonvulsant.[5] Recently we reported quinazolinone-podophyllotoxin conjugates showing promising anticancer activity.[6] Constructing conjugates/hybrids of two active pharmacophores has been considered as an alternative approach to achieve better hits against biological targets.[7] Therefore, development of novel spiropyrrolidines containing quinazolinone and indoline scaffolds could be promising from a medicinal chemistry perspective.

1,3-Dipolar cycloaddition reactions of alkenes with azomethine ylides, generated in-situ from decarboxylative coupling of α-amino acids and carbonyls, have been found amongst the most efficient synthetic routes for the construction of pyrrolidines. Consequently, many 1,3-dipolar cycloaddition reactions of isatin derived azomethine ylides were reported for the synthesis of spiropyrrolidines with a varying degree of regioselectivity.[8] Presented in this letter are the results of a region and stereoselective construction of novel spiropyrrolidines containing quinazolinone scaffold through 1,3-dipolar cycloaddition reaction of 2-styryl quinazolinones and azomethine ylides generated in situ from isatin/acenaphthoquinones with L-proline.

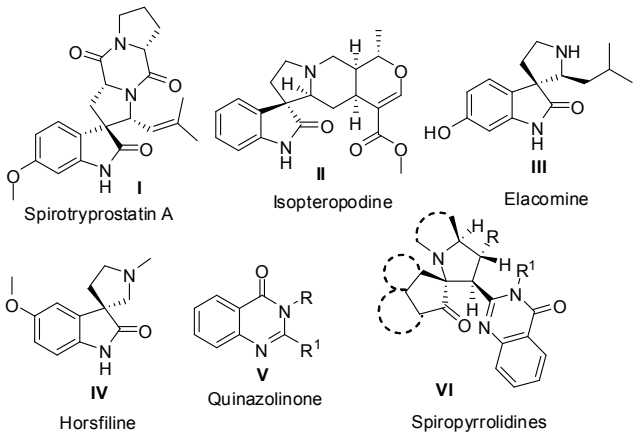


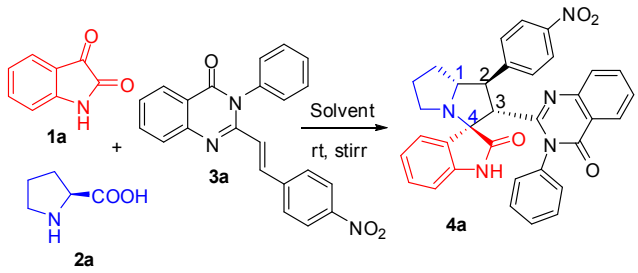
Figure 1. Natural (**I, II, III** & **IV**) biologically important spiropyrrolidine, quinazolinone **V** and spiropyrrolidines- quinazolinone conjugates **VI**

Results and discussion

At the onset, a three-component reaction of isatin **1a** (0.5 mmol), L-proline **2a** (0.55 mmol) and 2-(*p*-nitrostyryl)quinazolinone **3a** (0.5 mmol) was taken as a model reaction to establish the feasibility of the strategy and optimize the reaction conditions (Scheme 1). Firstly, we sought to optimize the reaction solvent as it is of much importance for a successful organic synthesis. Therefore, we investigated the reaction in various solvents including acetonitrile, methanol, ethanol, DMF, 1,4-dioxane,

THF and dichloromethane (Table 1, entry 1-7). The reaction proceeded smoothly at ambient temperature. Among the several solvents screened, methanol was found the best in terms of reaction time and product yield. In other solvents such as CH_2Cl_2, THF, 1,4-dioxane, and DMF, the reaction took longer time to complete yet the yields were fairly good. Moreover, the product selectivity was not influenced by the nature of the solvents as the same single diastereomer of the product was obtained in all the solvents screened (determined by ^{1}H NMR spectrum of the crude reaction product).

Table1. Solvent screening for the three-component reaction of isatin **1a**, L-proline **2a** and 2-(*p*-nitrostyryl)-quinazolinone **3a** [a]



Entry	Solvent	Reaction time (h)	Conversion[b] (Yield of **4a** %)[c]	Selectivity [d]
1	CH_2Cl_2	24	100 (78)	SD
2	THF	24	100 (75)	SD
3	1,4-Dioxane	24	100 (79)	SD
4	DMF	24	100 (73)	SD
5	CH_3CN	6	100 (84)	SD
6	Methanol	2	100 (87)	SD
7	Ethanol	3	100 (86)	SD

[a] Reaction conditions: Isatin **1a** (0.5 mmol), L-proline **2a** (0.55 mmol), quinazolinone **3a** (0.5 mmol), solvent 5 ml, rt, stir. [b] Conversion was assumed 100% when both the substrates **1a** and **3a** were completely consumed (monitored by TLC). [c] Yields refer to isolated yield which are not optimized. [d] Determined from the ^{1}H NMR spectrum of the crude reaction product. SD = Single Diastereomer.

The chemical structure of the cycloadduct **4a** was confirmed by spectroscopic analysis. A peak at *m/z* = 570 (M+H) in the ESI-mass spectrum of **4a** confirmed the formation of a cycloadduct derived from isatin **1a**, L-proline **2a**, and quinazolinone **3a**. The high resolution mass spectrum (HRMS) of **4a** confirmed its elemental composition. The infra-red (IR) spectrum of **4a** showed two bands at 1712 and 1681 cm^{-1} corresponding to the oxindole ring carbonyl and the quinazolinone ring carbonyl respectively. The ^{1}H NMR spectrum of **4a** showed a 1H doublet at 4.00 ppm (J = 9.5 Hz), a 1H multiplet at 4.18 ppm and a 1H triplet at 4.53 ppm (J = 10.0 Hz) corresponding to the CHs of the newly constructed pyrrolidine ring. The ^{13}C NMR spectrum of **4a** had a peak at 70.8 ppm corresponding to the spiro carbon and peaks at 177.2, 159.4 ppm corresponding to the carbonyls of oxindole and quinazolinone ring. Finally, the relative stereochemistry of the cycloadduct **4a** was determined unambiguously from single crystal X-ray analysis (Figure 2).

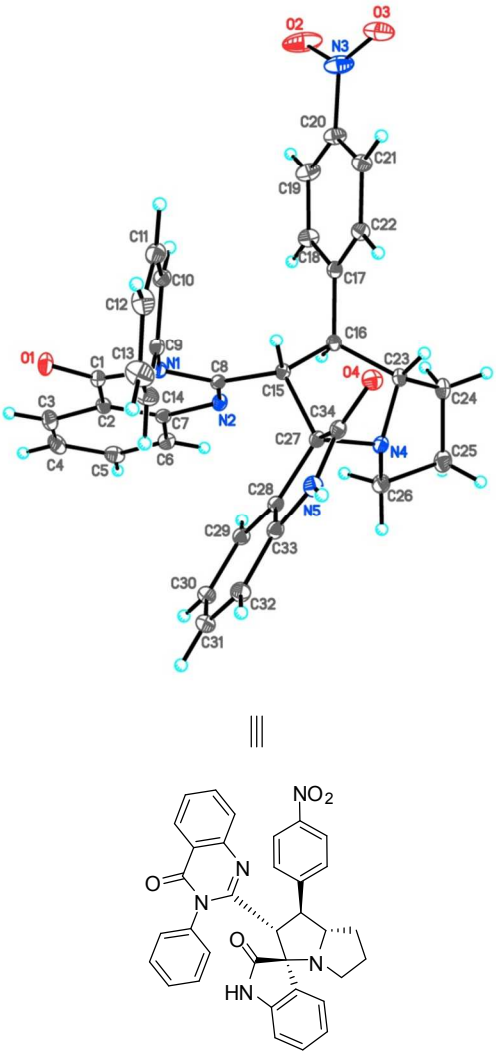
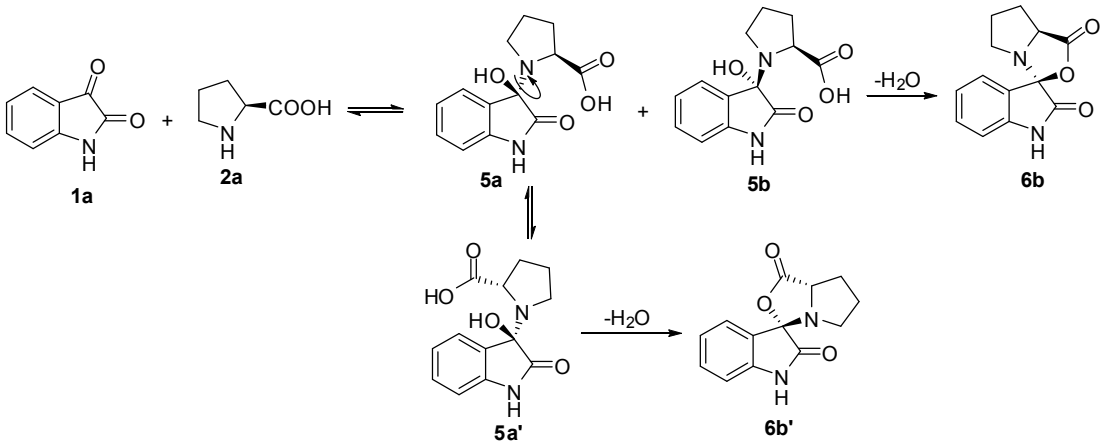


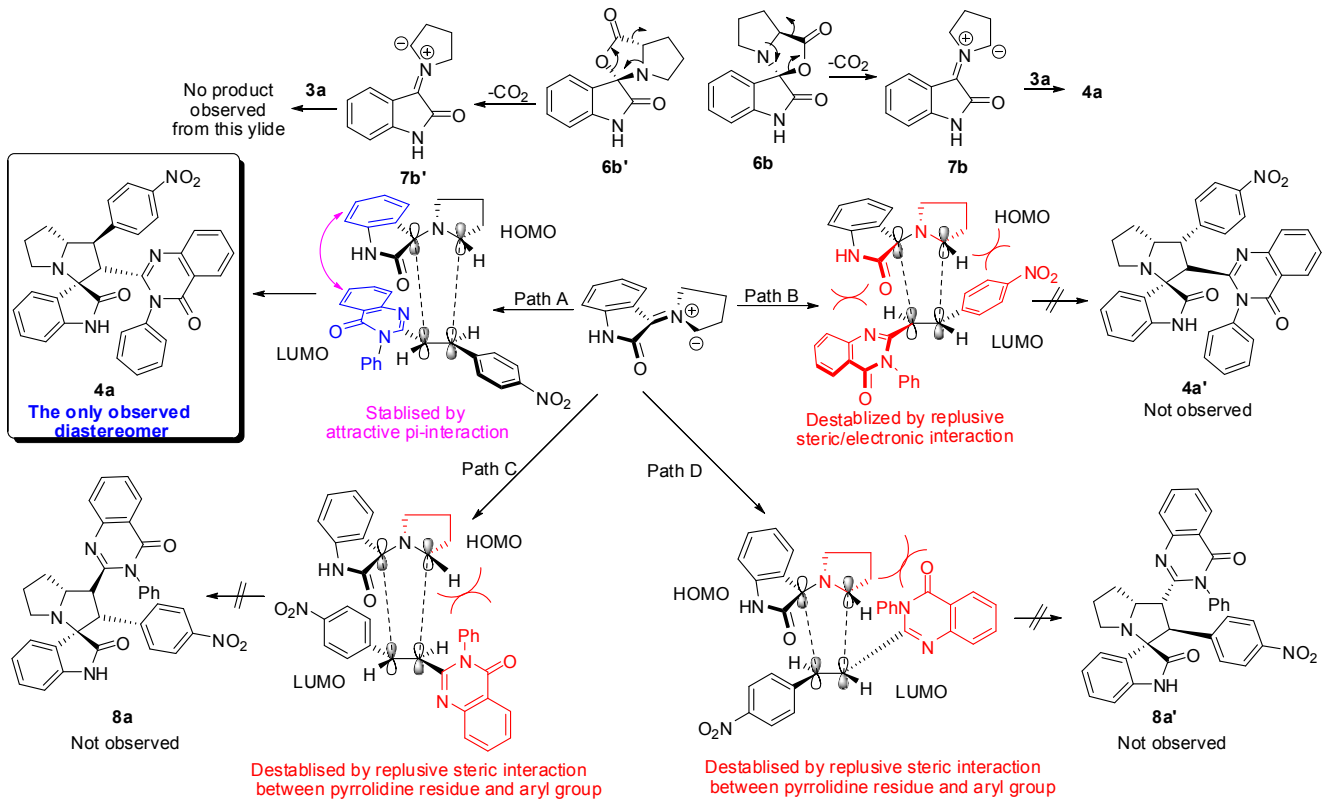
Figure 2. Stereochemical assignment of the cycloadduct **4a** by single crystal X-ray analysis (CCDC ref. no. 994872)

Compound **4a** has 4 stereocenters thereby indicating the possibility of (2^4 = 16 stereoisomers) eight pairs of diastereoisomers. It should be noted here that the *trans*-geometry of the alkene **3a** was preserved in the final product **4a**. 1,3-Dipolar cycloaddition reactions of the azomethine ylide (from isatin and L-proline) with alkenes are believed to proceed in a concerted manner rather than a step-wise diradical transition state.[8] Therefore the reaction is stereospecific and the relative stereochemistry of L-proline **2a** and *trans*-alkene (quinazolinone **3a**) would influence the stereochemistry at 1st, 2nd, and 3rd stereocenteres (the stereocenters of **4a** are marked as 1, 2, 3, & 4 in Table 1). In order to understand the stereochemical outcome at the spiro-carbon (4th stereocenter of compound **4a**, see table 1), we needed to look at the first step of the reaction, which is coupling of isatin **1a** and L-proline **2a** to yield an azomethine ylide intermediate (Scheme 1) that further undergoes a [3+2] dipolar cycloaddition with quinazolinone **3a** to afford **4a**. In this context, a recent report from Kouznetsov's group proposed selective formation of spiro-lactone **6b** and is particularly noticeable.[9] It should be noted that despite reasonable

explanations some chemical structures are incorrectly drawn in Kouznetsov's report. Nevertheless, the same explanation works for our observation about the stereochemical outcome of the three-component reaction (Scheme 2). Since no stereoisomer of **4** originating from azomethine ylide **7b'** was observed, it was assumed that **6b** was formed exclusively possibly due to some kind of attractive interaction or hydrogen bonding between amide oxygen of isatin and carboxylic acid group of L-proline.



Scheme 1. Plausible intermediates **6b** and **6b'** prior to the formation of the azomethine ylide



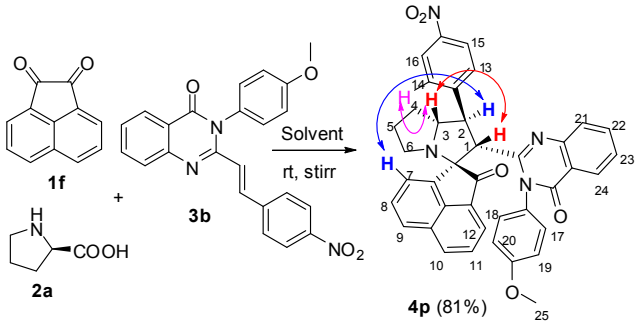
Scheme 2. Plausible transition state for the formation of **4a, 4a', 8a** and **8a'**

The reaction of **3a** with the ylide **7b** might lead to the formation of two different diastereomers **4a** and **4a'**depending upon how the ylide **7b** is approached to alkene **3a** (Path A and Path B of Scheme 2). Here we assume that reaction proceeds through interactions of highest occupied molecular orbital (HOMO) of azomethine **7b** with lowest unoccupied molecular orbital (LUMO) of alkene **3a**. The approach of **7b** to **3a** according path A (Scheme 2) would lead to the formation of **4a**. Path A is plausibly favoured by attractive *pi*-interaction between aromatic rings as depicted in Scheme 2. Following path A, the alkene **3a**

can approach **7a** from both its faces with equal feasibility hence compound **4a** should be a recemic mixture and indeed it was. The observation that **4a'** was not formed can be explained by the plausible transition state as depicted in path B of Scheme 2. The approach of **7b** to **3a** through path B appears to be hindered by steric crowding between *p*-nitroaryl and pyrrolidine reside of **7b** as well as electrostatic repulsion between indole amide and quinazolinone ring.

The observed regioselectivity can be explained in the same way by considering HOMO-LUMO interactions of **7b** and **3a**. As depicted in Scheme 2, either of the two possible pathways (Path C & D) lead to strong steric crowding between the pyrrolidine residue of **7b** and the quinazolinone part of **3a** in the transition states and agree well with the non-observation of regioisomers **8a** and **8a'**.

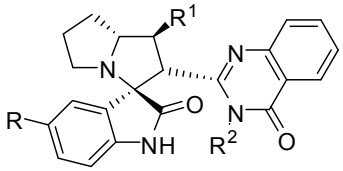
Having optimized the reaction conditions at hand, a series of spiropyrrolidine-quinazolinones was synthesized using the same protocol (Table 2). The reaction worked well with a variety of substituted isatins and 2-styryl-quinazolinones leading to good yields of cycloadducts **4a-o** (75-89%). The reaction time and yields had little dependence on the styryl group (R^1 in Table 2). The ^{1}H NMR spectra of **4a-o**, showed different chemical shifts for the *ortho* and *meta*-H atoms of the symmetrically substituted N-aryl residue (NR^2, Table 2) in the quinazolinone part of the cycloadducts (**4a-o**). It indicated that the rotation of aryl group (R^2) around N-C (N-R^2) bond is restricted plausibly due to the presence of sterically demanding spiroindoline residue at C-2 carbon of quinazolinone. In some cases (**4g, 4i, 4j, 4k and 4l),** the main product was obtained along with the impurity of a minor isomer (10-33%) which was inseparable from column chromatography. Chemical-exchange NMR experiments[10] of such a mixture (**4i**) was carried out and its results ruled out the possibility of the existence of a rotameric mixture. However the correct stereochemical assignment of the inseparable minor isomer could not be established.



Scheme 3. A three-component reaction of acenaphthaquinone **1f**, L-proline **2a**, and quinazolinones **3**

Similarly, a three-component reaction of acenaphthaquinone **1f**, L-proline **2a**, and quinazolinones **3b** was successfully performed (Scheme 3). The product (**4p**), obtained in high yield (81%), was diasteromerically pure. Replacing the isatin with acenaphthoquinone in the three-component coupling reaction further allows diversification of the products. The structure of the cycloadduct (**4p**) was confirmed by MS, HRMS, IR, ^{1}H NMR, ^{13}C NMR and NOESY spectroscopy. Characteristic NOE's of **4p** are shown in Scheme 3. The regio- and diastereoselective formation of **4p** can be explained in the same way as for **4a** by considering HOMO (azomithine) and LUMO (alkene) interactions.

Table 2. Synthesis of spiropyrrolidine-quinazolinones via a three-component coupling reaction of isatin, L-proline and 2-styryl-quinazolinones [a]



Entry	R	R^1	R^2	Product (Yield %)[d]
1	H	4-NO_2-C_6H_4	C_6H_5	**4a** (87)
2	H	4-NO_2-C_6H_4	4-MeO-C_6H_4	**4b** (89)
3	H	4-NO_2-C_6H_4	3,4,5-$(MeO)_3$-C_6H_2	**4c** (85)
4	H	C_6H_5	3,5-$(MeO)_2$-C_6H_3	**4d** (80)
5	H	4-MeO-C_6H_4	C_6H_5	**4e** (77)
6	Cl	4-NO_2-C_6H_4	4-MeO-C_6H_4	**4f** (86)
7	Cl	4-NO_2-C_6H_4	3,4,5-$(MeO)_3$-C_6H_2	**4g** (83)
8	Cl	4-NO_2-C_6H_4	C_6H_5	**4h** (81)
9	Br	4-NO_2-C_6H_4	3,4,5-$(MeO)_3$-C_6H_2	**4i** (82)
10	Br	4-NO_2-C_6H_4	C_6H_5	**4j** (83)
11	Br	4-NO_2-C_6H_4	4-MeO-C_6H_4	**4k** (88)
12	Br	4-MeO-C_6H_4	C_6H_5	**4l** (75)
13	Me	4-NO_2-C_6H_4	C_6H_5	**4m** (85)
14	Me	4-NO_2-C_6H_4	4-MeO-C_6H_4	**4n** (85)
15	MeO	4-NO_2-C_6H_4	C_6H_5	**4o** (81)

[a] Reaction conditions: Isatin **1** (0.5 mmol), L-proline **2** (0.55 mmol), quinazolinone **3** (0.5 mmol), methanol 5 ml, rt, stir. [c] Yields refer to isolated yield which are not optimized.

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Conclusions

An efficient and atom economical protocol for the synthesis of novel spiropyrrolidine-quinazolinones has been developed using a three-component reaction of isatin/acenaphthoquinone, L-proline, and 2-styryl quinazolinones. The reaction proceeds through a regio- and stereoselective 1,3-dipolar cycloaddition of azomethine ylides with 2-styryl quinazolinones. The clean and simple high yielding protocol provides efficient access to novel spiropyrrolidine-quinazolinones which could be of potential biological and pharamacological interest.

Experimental

General information

All reagents and chemicals were purchased from commercial sources and used without further purification. Common laboratory solvents (LR grade) were purchased from domestic suppliers. Analytical thin layer chromatography was performed with E. Merck silica gel 60 F aluminium plates and visualized under UV 254 nm. NMR spectra were measured with Brucker 300, 500, and 600 MHz, and Varian 400 MHz instruments. Chemical shifts are reported in δ units, parts per million (ppm) downfield from TMS. Coupling constants (*J*) are in hertz (Hz) and are unadjusted; therefore, due to limits in resolution, in some cases there are small differences (<1 Hz) in the measured J value of the same coupling constant determined from different signals. Splitting patterns are designed as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; tt, triplet of triplets; m, multiplet; br, broad. IR spectra were recorded on a Perkin–Elmer FT-IR RXI spectrophotometer and values reported in cm^{-1}. ESI-MS spectra were obtained on a LCQ Advantage Ion trap mass spectrometer (Finnigan thermo fischer scientific) and High-resolution mass spectra (ESI-HRMS) were recorded on Agilent 6520 ESI-QTOP mass spectrometer. Melting points were determined on a Kofler block and are uncorrected. All the new compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS, IR, and HRMS analysis. The chromatographic solvents are in v/v ratios. The 2-styrylquinazolin-4(3*H*)-ones were synthesized according to the literature procedure.[11]

General experimental procedure for the synthesis of spiropyrrolidine 4a-4p

To a 25 ml round bottom flask was added isatin/ acenaphthoquinone (0.5 mmol), L-proline (0.55 mmol), quinazolinone (0.5 mmol), and 5 ml of methanol. The reaction mixture was stirred at ambient temperature until the starting materials were completely consumed (TLC). Then methanol was evaporated under reduced pressure and the residue was purified from silica-gel column chromatography to yield compound **4a-p.**

1'-(4-nitrophenyl)-2'-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4a*)

Compound **4a** (248 mg, 87%) was obtained as a light yellow coloured solid, R_f = 0.29 (ethyl acetate-*n*-hexane; 1/1); Mp. 210-211 ^{0}C; IR $^{\nu}$max (KBr): 3180, 3080, 2952, 1712, 1681, 1603, 1587, 1518, 1472, 1346 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + $DMSOd_6$): δ 10.10 (1H, bs, NH), 8.14 (2H, d, *J* = 8.7 Hz, two *ortho*-H of nitroaryl residue), 8.04 (1H, d, *J* = 7.9 Hz, C5-H of quinazolinone residue), 7.93-7.85 (2H, m, two ArH of quinazolinone residue), 7.62 (2H, d, *J* = 8.7 Hz, two *meta*-H of nitroaryl residue), 7.53-7.31 (4H, m, ArH of isatin and quinazolinone residue), 7.17 (1H, d, *J* = 7.6 Hz, ArH of isatin residue), 6.99 (1H, d, *J* = 7.6 Hz, ArH of N-Aryl residue), 6.87 (1H, d, *J* = 7.7 Hz, ArH of N-Aryl residue), 6.60 (1H, t, *J* = 7.5 Hz, ArH of N-Aryl residue), 6.52 (1H, d, *J* = 7.6 Hz, ArH of N-Aryl residue), 5.87 (1H, d, *J* = 7.9 Hz, ArH of N-Aryl residue), 4.53 (1H, t, *J* = 10.0 Hz, CH), 4.24-4.18 (1H, m, CH), 4.00 (1H, d, *J* = 9.5 Hz, CH), 3.56-3.47 (1H, m, one hydrogen of NCH_2), 2.62 (1H, m, one hydrogen of NCH_2), 2.13-1.92 (2H, m, CH_2), 1.85-1.74 (2H, m, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$ + $DMSOd_6$): δ 177.2, 159.4, 153.6, 147.0, 144.8, 144.6, 142.0, 134.0, 133.0, 128.0, 127.8, 127.7, 127.3, 126.7, 126.0, 125.4, 125.2, 124.6, 124.1, 121.9, 119.1, 118.4, 108.2, 70.8, 67.5, 58.4, 54.1, 47.4, 25.2, 22.3; HRMS (ESI, Orbitrap): calcd for $C_{34}H_{28}N_5O4$:$[M+H]^+$ 570.21358; found 570.21270.

2'-(3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-1'-(4-nitrophenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4b*)

Compound **4b** (267 mg, 89%) was obtained as a light yellow coloured solid, R_f = 0.47 (ethyl acetate-*n*-hexane; 1/1); Mp. 194-195 ^{0}C; IR $^{\nu}$max (KBr): 3410, 3141, 2957, 2873, 1716,1685, 1616, 1599, 1587, 1569, 1527, 1471, 1431, 1338 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+$DMSOd_6$): δ 10.22 (1H, bs, NH), 8.16 (2H, d, *J* = 8.7 Hz, two *ortho*-H of nitroaryl residue), 8.01 (1H, d, *J* = 7.9 Hz, C5-H of quinazolinone residue), 7.92-7.85 (2H, m, two ArH of quinazolinone residue), 7.64 (2H, d, *J* = 8.7 Hz, two *meta*-H of nitroaryl residue), 7.53-7.47 (1H, m, ArH of quinazolinone residue), 7.17 (1H, t, *J* = 7.7 Hz, ArH of isatin residue), 6.95 (1H, d, *J* = 7.7 Hz, ArH of isatin residue), 6.93-6.86 (2H, m, ArH of isatin residue), 6.78 (1H, dd, *J* = 2.8, 8.7 Hz, ArH of N-Aryl residue), 6.59 (1H, t, *J* = 7.6 Hz, ArH of N-Aryl residue), 6.46 (1H, dd, *J* = 2.5, 8.7 Hz, ArH of N-Aryl residue), 5.66 (1H, dd, *J* = 2.2, 8.7 Hz, ArH of N-Aryl residue), 4.55 (1H, t, *J* = 10.0 Hz, CH), 4.23-4.17 (1H, m, CH), 4.07 (1H, d, *J* = 9.5 Hz. CH), 3.87 (3H, s, OCH_3), 3.53-3.45 (1H, m, one hydrogen of NCH_2), 2.55-2.54 (1H, m, one hydrogen of NCH_2), 2.14-1.90 (2H, m, CH_2), 1.86-1.73 (2H, m, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$ + $DMSOd_6$): δ 177.7, 160.0, 158.0, 154.1, 147.3, 145.0, 144.8, 142.2, 133.0, 128.1, 128.0, 127.5, 127.0, 126.4, 125.6, 125.4, 124.8, 124.4, 122.1, 119.3, 118.7, 113.1, 108.4, 71.0, 67.8, 58.6, 54.3, 53.8, 47.6, 25.5, 22.5; HRMS (ESI, Orbitrap): calcd for $C_{35}H_{30}N_5O_5$:$[M+H]^+$ 600.2247; found 600.22303.

1'-(4-nitrophenyl)-2'-(4-oxo-3-(3,4,5-trimethoxyphenyl)-3,4-dihydroquinazolin-2-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4c*)

Compound **4c** (281 mg, 85%) was obtained as a red coloured solid, R_f = 0.31 (ethyl acetate-*n*-hexane; 1/1); Mp. 220-221 ^{0}C; IR $^{\nu}$max (KBr): 3318, 3145, 2953, 1719, 1697, 1617, 1597, 1567, 1521, 1503, 1473, 1349 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.44 (1H, bs, NH), 8.20-8.17 (3H, m, two *ortho*-H of nitroaryl residue + C5-H of quinazolinone residue), 7.93-7.86 (2H, m, two ArH of quinazolinone residue), 7.67 (2H, d, *J* = 8.7 Hz, two *meta*-H of nitroaryl residue), 7.52 (1H, dt, *J* = 1.3, 7.5 Hz, ArH of quinazolinone residue), 7.19 (1H, dt, *J* = 1.0, 7.6 Hz, ArH of isatin residue), 7.11 (1H, d, *J* = 7.6 Hz, ArH of isatin residue), 7.06-7.03 (1H, m, ArH of isatin residue), 6.63 (1H, t, *J* = 7.6 Hz, ArH of isatin residue), 5.68 (1H, d, *J* = 2.2 Hz, ArH of N-Aryl residue), 5.50 (1H, d, *J* = 2.2 Hz, ArH of N-Aryl residue), 4.50 (1H, t, *J* = 9.9 Hz, CH), 4.36-4.32 (1H, m, CH), 4.20 (1H, d, *J* = 9.5 Hz. CH), 3.83 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.60-3.55 (1H, m, one hydrogen of NCH_2), 3.49 (3H, s, OCH_3), 2.68 (1H, t, *J* = 7.9 Hz, one hydrogen of NCH_2), 2.19-1.99 (2H, m, CH_2), 1.93-1.77 (m, 2H, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$ + $DMSOd_6$): δ 179.1, 161.3, 155.1, 153.1, 148.6, 146.2, 145.9, 142.8, 137.8, 134.1, 130.9, 128.9, 128.8, 127.1, 126.5, 126.2, 125.2, 123.1, 120.7, 119.8, 109.3, 105.3, 103.8, 72.6, 69.3, 60.1, 59.8, 56.5, 55.4, 55.0, 48.8, 26.7, 23.6; HRMS (ESI, Orbitrap): calcd for $C_{37}H_{34}O_7N_5$ $[M+H]^+$ 660.2453; found 660.2460.

2'-(3-(3,5-dimethoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4d*)

Compound **4d** (234 mg, 80%) was obtained as a cream coloured solid, R_f = 0.32 (ethyl acetate-*n*-hexane; 1/1); Mp. 195-196 ^{0}C; IR $^{\nu}$max (KBr): 3144, 1710, 1690, 1650, 1584, 1566, 1471, 1400 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (1H, d, *J* = 7.6 Hz, C5-H of quinazolinone residue), 7.86 (1H, d, *J* = 7.9 Hz, ArH of quinazolinone residue), 7.84-7.80 (m, 1H, ArH of quinazolinone residue), 7.60 (1H, bs, NH), 7.45 (1H, t, *J* = 7.3 Hz, ArH of quinazolinone residue), 7.41 (2H, d, *J* = 7.3 Hz, 2H of phenyl residue), 7.28 (2H, d, *J* = 7.3 Hz, 2H of phenyl residue), 7.22-7.18 (2H, m, ArH of isatin residue + 1H of phenyl residue), 7.13 (1H, t, *J* = 7.6 Hz, ArH of isatin residue), 6.82 (1H, d, *J* = 7.6 Hz, ArH of isatin residue), 6.63 (1H, t, *J* = 7.6 Hz, ArH of isatin residue), 6.46 (1H, s, ArH of N-Aryl residue), 5.62 (1H, s, ArH of N-Aryl residue), 5.32 (1H, s, ArH of N-Aryl residue), 4.36-4.28 (2H, m, 2CH), 4.24-4.19 (1H, m, CH), 4.15 (1H, d, *J* = 9.3 Hz. CH), 3.72 (3H, s, OCH_3), 3.52 (3H, s, OCH_3), 2.65- 2.62 (1H, m, CH), 2.14-1.96 (2H, m, CH_2), 1.91-1.76 (2H, m, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$ + $DMSOd_6$): δ 177.8, 159.5, 159.4, 154.4, 145.0, 141.9, 138.9, 136.0, 133.1, 127.7, 126.9, 126.5, 125.9, 125.6, 125.3, 124.9, 124.5, 119.2, 118.6, 108.3, 105.4, 102.9, 100.4, 71.1, 67.6, 58.4, 55.1, 53.9, 53.6, 47.6, 25.6, 22.7; HRMS (ESI, Orbitrap): calcd for $C_{36}H_{33}O_4N_4$ $[M+H]^+$ 585.2496; found 585.2498.

1'-(4-methoxyphenyl)-2'-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4e*)

Compound **4e** (214 mg, 77%) was obtained as a white coloured solid, R_f = 0.29 (ethyl acetate-*n*-hexane; 1/1); Mp. 195-196 ^{0}C; IR $^{\nu}$max (KBr): 3280, 2972, 1725, 1692, 1665, 1614, 1583, 1485, 1471, 1399 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (1H, d, *J* = 7.6 Hz, C5-H of quinazolinone residue), 7.84-7.79 (2H, m, ArH of quinazolinone residue), 7.71 (1H, bs, NH), 7.44 (1H, dt, *J* = 1.6 & 7.3 Hz, ArH of quinazolinone residue), 7.36-7.33 (2H, m, ArH of isatin residue), 7.30 (2H, d, *J* = 8.7 Hz, ArH of 4-methoxyphenyl residue), 7.27-7.23 (1H, m, ArH of isatin residue), 7.21 (1H, d, *J* = 7.5 Hz, 1H of isatin residue), 7.14 (1H, dt, *J* = 0.8, 7.6 Hz, 1H N-aryl residue), 6.84 (2H, d, *J* = 8.7 Hz, ArH of 4-methoxyphenyl residue), 6.79 (1H, d, *J* = 7.6 Hz, ArH of N-Aryl residue), 6.87 (1H, dt, *J* = 0.6, 7.6 Hz, ArH of N-Aryl residue), 6.51-6.48 (1H, m, ArH of N-Aryl residue), 6.14 (1H, d, *J* = 7.5 Hz, ArH of N-Aryl residue), 4.29 (1H, t, *J* = 10.0 Hz, CH), 4.23-4.18 (1H, m, CH), 4.08 (1H, d, *J* = 10.0 Hz. CH), 3.79 (3H, s, OCH_3), 3.42-3.37 (1H, m, one hydrogen of NCH_2), 2.63-2.59 (1H, m, one hydrogen of NCH_2), 2.12-1.96 (2H, m, CH_2), 1.90-1.75 (2H, m, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 180.3, 162.3, 158.6, 154.8, 146.8, 142.1, 135.9, 134.4, 131.8, 129.6, 129.3, 129.2, 128.6, 128.3, 128.1, 127.2, 126.9, 126.8, 126.2, 121.7, 120.6, 114.0, 110.0, 73.0, 69.5, 60.5, 55.8, 55.2, 49.3, 27.8, 25.0; HRMS (ESI, Orbitrap): calcd for $C_{35}H_{31}O_3N_4$ $[M+H]^+$ 555.2391; found 555.2376.

5-chloro-2'-(3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-1'-(4-nitrophenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4f*)

Compound **4f** (273 mg, 86%) was obtained as a light yellow coloured solid, R_f = 0.35 (ethyl acetate-*n*-hexane; 1/1); Mp. 192-193 ^{0}C; IR $^{\nu}$max (KBr): 3159, 2924, 1716, 1684, 1608, 1593, 1473, 1347, 1299, 1249, 1222 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (2H, d, *J* = 8.9 Hz, two *ortho*-H of nitroaryl residue), 8.15 (1H, d, *J* = 7.6 Hz, C5-H of quinazolinone residue), 7.86-7.80 (2H, m, ArH of quinazolinone residue), 7.59 (2H, d, *J* = 8.9 Hz, two *meta*-H of nitroaryl residue), 7.53 (1H, bs, NH), 7.50-7.46 (1H, m, ArH of quinazolinone residue), 7.19 (1H, d, *J* = 2.1 Hz, ArH of isatin residue), 7.16 (1H, dd, J = 2.1, 8.2 Hz, ArH of isatin residue), 6.86 (1H, dd, *J* = 2.9, 8.6 Hz, ArH of N-aryl residue), 6.79 (1H, dd, *J* = 2.9, 8.6 Hz, ArH of N-aryl residue), 6.75 (1H, d, *J* = 8.2 Hz, ArH of isatin residue), 6.36 (1H, dd, *J* = 2.7, 8.7 Hz, ArH of N-aryl residue), 6.15 (1H, dd, *J* = 2.7, 8.7 Hz, ArH of N-aryl residue), 4.46 (1H, t, *J* = 10.2 Hz, CH), 4.26-4.21 (1H, m, CH), 4.20 (1H, d, *J* = 10.0 Hz. CH), 3.80 (3H, s, OCH_3), 3.36-3.31 (1H, m, one hydrogen of NCH_2), 2.66-2.63 (1H, m, one hydrogen of NCH_2), 2.16-1.98 (2H, m, CH_2), 1.93-1.73 (2H, m, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 179.1, 161.7, 159.5, 154.5, 148.0, 146.5, 145.9, 141.6, 134.2, 129.2, 129.0, 128.8, 128.2, 127.7, 127.1, 126.7, 126.4, 125.9, 123.3, 120.0, 115.0, 114.1, 110.5, 72.6, 69.6, 60.5, 55.8, 55.0, 48.7, 26.9, 24.2; HRMS (ESI, Orbitrap): calcd for $C_{35}H_{29}O_5N_5Cl$ $[M+H]^+$ 634.18517; found 634.18499.

5-chloro-1'-(4-nitrophenyl)-2'-(4-oxo-3-(3,4,5-trimethoxyphenyl)-3,4-dihydroquinazolin-2-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4g*)

Compound **4g** (288 mg, 83%) was obtained as an inseparable mixture of two stereoisomers (2:1) as yellow coloured solid, R_f = 0.40 (ethyl acetate-*n*-hexane; 1/1); Mp. 239-240 ^{0}C; IR $^{\nu}$max (KBr): 3300, 2964, 1725, 1697, 1599, 1569, 1519, 1503, 1474, 1429, 1400, 1346, 1226, 1128 cm^{-1}; ^{1}H NMR of the major stereoisomer (500 MHz, $CDCl_3$): 8.28 (1H, bs, NH), 8.20 (3H, d, *J* = 8.5 Hz, two *ortho*-H of nitroaryl residue + C5-H of quinazolinone residue), 7.96-7.88 (2H, m, ArH of quinazolinone residue), 7.84 (2H, d, *J* = 8.6 Hz, two *meta*-H of nitroaryl

residue), 7.56 (1H, dt, *J* = 1.4, 7.4 Hz, ArH of quinazolinone residue), 7.18-7.16 (2H, m, ArH of isatin residue), 6.93 (1H, d, *J* = 8.8 Hz, ArH of isatin residue), 5.68 (1H, d, *J* = 2.1 Hz, ArH of N-aryl residue), 5.55 (1H, d, *J* = 2.1 Hz, ArH of N-aryl residue), 4.46-4.42 (1H, m, CH), 4.35-4.28 (1H, m, CH), 4.17 (1H, d, *J* = 9.6 Hz, CH), 3.85 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.51-3.47 (4H, m, OCH_3 + one H of NCH_2), 2.71-2.63 (1H, m, one H of NCH_2), 2.18-2.00 (2H, m, CH_2), 1.93-1.75 (2H, m, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 179.1, 161,6, 154.7, 153.4, 148.2, 146.5, 145.9, 141.5, 137.9, 134.5, 131.0, 128.9, 128.0, 126.9, 126.6, 126.5, 126.0, 123.3, 119.9, 110.3, 105.2, 104.0, 72.9, 69.8, 60.3, 56.6, 55.7, 55.2, 48.7, 26.9, 24.9, 24.1; HRMS (ESI, Orbitrap): calcd for $C_{37}H_{33}O_7N_5Cl$ $[M+H]^+$ 694.20630; found 694.20760.

5-chloro-1'-(4-nitrophenyl)-2'-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4h*)

Compound **4h** (244 mg, 81%) was obtained as a light orange coloured solid, R_f = 0.45 (ethyl acetate-*n*-hexane; 1/1); Mp. 196-197 ^{0}C; IR $^{\nu}$max (KBr): 3093, 2924, 1731, 1688, 1603, 1585, 1568, 1518, 1473, 1384, 1346, 1187 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + $DMSOd_6$): 9.92 (1H, bs, NH), 8.10-8.04 (3H, m, two *ortho*-H of nitroaryl residue + C5-H of quinazolinone residue), 7.86-7.77 (2H, m, ArH of quinazolinone residue), 7.53 (2H, d, *J* = 8.7 Hz, two *meta*-H of nitroaryl residue), 7.46-7.38 (2H, m, 1H of quinazolinone residue + 1H of isatin residue), 7.35-7.24 (2H, m, ArH of isatin residue), 7.06-7.00 (2H, m, ArH of N-aryl residue), 6.75 (1H, d, *J* = 7.9 Hz, ArH of N-aryl residue), 6.40 (1H, d, *J* = 9.0 Hz, ArH of N-aryl residue), 6.10 (1H, d, *J* = 9.0 Hz, ArH of N-aryl residue), 4.40 (1H, t, *J* = 10 Hz, CH), 4.21-4.11 (1H, m, CH), 3.97 (1H, d, *J* = 9.8 Hz, CH), 3.41-3.32 (1H, m, one H of NCH_2), 2.57-2.49 (1H, m, one H of NCH_2), 2.11-1.70 (4H, m, CH_2CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$ + $DMSOd_6$): δ 178.3, 160.8, 153.7, 147.4, 145.9, 145.4, 141.2, 134.9, 133.8, 129.0, 128.7, 128.6, 128.4, 127.6, 127.1, 126.7, 126.5, 126.3, 125.7, 125.2, 122.8, 119.4, 110.1, 72.0, 69.1, 59.8, 55.3, 48.1, 26.3, 23.7; HRMS (ESI, Orbitrap): calcd for $C_{34}H_{27}O_4N_5Cl$ $[M+H]^+$ 604.17461; found 604.17543.

5-bromo-1'-(4-nitrophenyl)-2'-(4-oxo-3-(3,4,5-trimethoxyphenyl)-3,4-dihydroquinazolin-2-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4i*)

Compound **4i** (303 mg, 82%) was obtained as an inseparable mixture of two stereoisomers (10:1) as orange coloured solid, R_f = 0.33 (ethyl acetate-*n*-hexane; 1/1); Mp. 226-227 ^{0}C; IR $^{\nu}$max (KBr): 3299, 2941, 1725, 1697, 1599, 1519, 1502, 1430, 1227, 1185, 1128 cm^{-1}; ^1H NMR of the major stereoisomer (500 MHz, $CDCl_3$): δ 8.53 (1H, bs, NH), 8.22-8.17 (3H, m, two *ortho*-H of nitroaryl residue + C5-H of quinazolinone residue), 7.95-7.88 (2H, m, ArH of quinazolinone residue), 7.64 (2H, d, *J* = 8.7 Hz, two *meta*-H of nitroaryl residue), 7.56 (1H, dt, *J* = 1.4, 7.5 Hz, ArH of quinazolinone residue), 7.32-7.30 (2H, m, ArH of isatin residue), 6.91 (1H, d, *J* = 8.7 Hz, ArH of isatin residue), 5.67 (1H, d, *J* = 2.1 Hz, ArH of N-aryl residue), 5.56 (1H, d, *J* = 2.1 Hz, ArH of N-aryl residue), 4.47 (1H, t, *J* = 10.2 Hz, CH), 4.32-4.28 (1H, m, CH), 4.16 (1H, d, *J* = 9.6 Hz, CH), 3.83 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.50-3.48 (1H, m, one H of NCH_2), 3.47 (3H, s, OCH_3), 2.71-2.67 (1H, m, one H of NCH_2), 2.19-1.99 (2H, m, CH_2), 1.94-1.75 (2H, m, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$ + $DMSOd_6$): δ 178.4, 160.9, 154.3, 152.9, 147.8, 146.0, 145.4, 141.6, 137.4, 134.0, 131.3, 130.6, 130.4, 128.5, 126.8, 126.4, 126.2, 125.9, 122.9, 119.5, 112.7, 110.4, 104.7, 103.6, 72.5, 69.4, 59.8, 56.0, 55.2, 54.7, 48.2, 30.0, 26.4, 23.7; HRMS (ESI, Orbitrap): calcd for $C_{37}H_{33}O_7N_5Br$ $[M+H]^+$ 738.15579; found 738.15693.

5-bromo-1'-(4-nitrophenyl)-2'-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4j*)

Compound **4j** (269 mg, 83%) was obtained as an inseparable mixture of two stereoisomers (9:1) as white coloured solid, R_f = 0.44 (ethyl acetate-*n*-hexane; 1/1); Mp. 184-185 ^{0}C; IR $^{\nu}$max (KBr): 3077, 2925, 1731, 1687, 1603, 1586, 1518, 1473, 1346, 1188, 1111 cm^{-1}; ^1H NMR for the major stereoisomer (300 MHz, $CDCl_3$ + $DMSOd_6$): 10.20 (1H, bs, NH), 8.17 (2H, d, *J* = 8.7 Hz, two *ortho*-H of nitroaryl residue), 8.12 (1H, d, *J* = 7.6 Hz, C5-H of quinazolinone residue), 7.93-7.85 (2H, m, ArH of quinazolinone residue), 7.60 (2H, d, *J* = 8.7 Hz, two *meta*-H of nitroaryl residue), 7.54-7.48 (1H, m, ArH of quinazolinone residue), 7.46 (1H, d, *J* = 7.2 Hz, ArH of isatin residue), 7.40-7.35 (2H, m, ArH of isatin residue), 7.28-7.21 (2H, m, ArH of N-aryl residue), 6.80 (1H, d, *J* = 8.1 Hz, ArH of N-aryl residue), 6.48 (1H, d, *J* = 7.6 Hz, ArH of N-aryl residue), 6.15 (1H, d, *J* = 7.6 Hz, ArH of N-aryl residue), 4.47 (1H, t, *J* = 10.2 Hz, CH), 4.26-4.17 (1H, m, CH), 4.01 (1H, d, *J* = 9.6 Hz, CH), 3.49-3.39 (1H, m, one H of NCH_2), 2.65-2.61 (1H, m, one H of NCH_2), 2.16-1.73 (4H, m, CH_2CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$ + $DMSOd_6$): δ 178.5, 161.0, 153.9, 147.6, 146.2, 145.6, 141.8, 135.1, 134.0, 131.6, 130.23, 129.2, 128.9, 128.6, 128.5, 127.8, 127.0, 126.4, 126.0, 119.7, 123.0, 112.8, 110.8, 72.3, 69.4, 60.2, 55.5, 48.3, 26.6, 23.9; HRMS (ESI, Orbitrap): calcd for $C_{34}H_{27}O_4N_5Br$ $[M+H]^+$ 650.12464; found 650.12350.

5-bromo-2'-(3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-1'-(4-nitrophenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4k*)

Compound **4k** (299 mg, 88%) was obtained as an inseparable mixture of two stereoisomers (6:1) as an orange coloured solid, R_f = 0.41 (ethyl acetate-*n*-hexane; 1/1); Mp. 229-230 ^{0}C; IR $^{\nu}$max (KBr): 3074, 2923, 1717, 1686, 1607, 1592, 1570, 1550, 1508, 1471, 1389, 1342, 1246, 1167 cm^{-1}; ^1H NMR for the major stereoisomer (300 MHz, $CDCl_3$): 8.25 (1H, bs, NH), 8.20 (2H, d, *J* = 8.7 Hz, two *ortho*-H of nitroaryl residue), 8.15 (1H, d, *J* = 8.2 Hz, C5-H of quinazolinone residue), 7.87-7.80 (2H, m, ArH of quinazolinone residue), 7.59 (2H, d, *J* = 8.7 Hz, two *meta*-H of nitroaryl residue), 7.50-7.47 (1H, m, ArH of quinazolinone residue), 7.35 (1H, s, ArH of isatin residue), 7.39-7.27 (1H, m, ArH of isatin residue), 6.85(1H, dd, *J* = 2.8, 8.7 Hz, ArH of isatin residue), 6.78 (1H, dd, *J* = 2.4, 8.5 Hz, ArH of N-aryl residue), 6.70 (1H, d, *J* = 8.2 Hz, ArH of N-aryl residue),), 6.35 (1H, dd, *J* = 2.6, 8.7 Hz, ArH of N-aryl residue), 6.20 (1H, d, *J* = 8.3 Hz, ArH of N-aryl residue), 4.45 (1H, t, *J* = 10.3 Hz, CH), 4.25-4.21 (1H, m, CH), 4.20 (1H, d, *J* = 10.2 Hz, CH), 3.73 (3H, s, OCH_3), 3.34-3.29 (1H, m, one H of NCH_2), 2.67-2.62 (1H, m, one H of NCH_2), 2.16-1.80 (4H, m, CH_2CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$ + $DMSOd_6$): δ 178.9, 161.6, 159.4, 154.4, 147.9, 146.4, 145.8, 141.9, 134.1, 131.8, 130.4, 129.1, 128.7, 128.1, 127.6, 126.6, 126.3, 123.3, 119.9, 114.9, 114.0, 113.1, 111.0, 72.5, 69.5,

60.4, 55.6, 54.9, 48.6, 26.8, 24.2; HRMS (ESI, Orbitrap): calcd for $C_{35}H_{29}O_5N_5Br$ $[M+H]^+$ 680.13466; found 680.13223.

5-bromo-1'-(4-methoxyphenyl)-2'-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4l*)

Compound **4l** (238 mg, 75%) was obtained as an inseparable mixture of two stereoisomers (5:1) as a white coloured solid, R_f = 0.34 (ethyl acetate-*n*-hexane; 1/1); Mp. 170-171 ^{0}C; IR ^{v}max (KBr): 3417, 2958, 1738, 1687, 1613, 1585, 1567, 1473, 1398, 1329, 1246, 1181 cm^{-1};^{1}H NMR for the major stereoisomer (500 MHz, $CDCl_3$): 8.41 (1H, bs, NH), 8.13 (1H, d, *J* = 7.6 Hz, ArH C5-H of quinazolinone residue), 7.83-7.80 (2H, m, ArH of quinazolinone residue), 7.51 (1H, d, *J* = 1.8 Hz, ArH of quinazolinone residue), 7.47-7.43 (1H, m, ArH of isatin residue), 7.34-7.30 (2H, m, ArH of 4-methoxyphenyl residue), 7.25-7.23 (4H, m, 2H of 4-methoxyphenyl residue +2H of isatin residue), 6.85 (2H, d, *J* = 8.7 Hz, ArH of N-aryl residue), 6.69 (1H, d, *J* = 8.2 Hz, ArH of N-aryl residue), 6.45 (1H, d, *J* = 7.8 Hz, ArH of N-aryl residue), 6.39-6.37 (1H, m, ArH of N-aryl residue), 4.23-4.12 (2H, m, 2CH), 4.05 (1H, d, *J* = 10.2 Hz, CH), 3.79 (3H, s, OCH_3), 3.26-3.20 (1H, m, one H of NCH_2), 2.65-2.59 (1H, m, one H of NCH_2), 2.12-1.80 (4H, m, CH_2CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$ + $DMSOd_6$): δ 178.9, 161.4, 157.9, 154.2, 145.9, 141.5, 135.4, 133.9, 131.4, 130.9, 129.1, 128.8, 128.5, 128.1, 127.9, 127.4, 126.6, 126.3, 126.0, 119.7, 113.3, 112.8, 110.7, 72.4, 69.1, 60.3, 55.3, 54.5, 48.3, 27.1, 25.5; HRMS (ESI, Orbitrap): calcd for $C_{35}H_{30}O_3N_4Br$ $[M+H]^+$ 635.15013; found 635.14870.

5-methyl-1'-(4-nitrophenyl)-2'-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4m*)

Compound **4m** (248 mg, 85%) was obtained as a light orange coloured solid, R_f = 0.30 (ethyl acetate-*n*-hexane; 1/1); Mp. 186-187 ^{0}C; IR ^{v}max (KBr): 3250, 2923, 1719, 1692, 1622, 1603, 1585, 1567, 1490, 1346, 1210 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (2H, d, *J* = 8.7 Hz, two *ortho*-H of nitroaryl residue), 8.16 (1H, dd, *J* = 0.9, 7.9 Hz, C5-H of quinazolinone residue), 7.91-7.84 (2H, m, ArH of quinazolinone residue), 7.62 (2H, d, *J* = 8.8 Hz, two *meta*-H of nitroaryl residue), 7.51 (1H, dd, *J* = 1.4, 7.2 Hz, ArH of quinazolinone residue), 7.46 (1H, bs, NH), 7.40-7.32 (2H, m, one H of N-aryl residue + one H of isatin residue), 7.29 (1H, dd, *J* = 1.5, 7.5Hz, ArH of isatin residue), 6.98 (1H, d, *J* = 7.8 Hz, ArH of N-aryl residue), 6.90 (1H, s, ArH of isatin residue), 6.72 (1H, d, *J* = 7.8 Hz, ArH of N-aryl residue), 6.68 (1H, d, *J* = 7.9 Hz, ArH of N-aryl residue), 6.07 (1H, d, *J* = 7.9 Hz, ArH of N-aryl residue), 4.53 (1H, t, *J* = 10.2 Hz, CH), 4.28-4.24 (1H, m, CH), 4.10 (1H, d, *J* = 9.6 Hz, CH), 3.51-3.46 (1H, m, one H of NCH_2), 2.67-2.63 (1H, m, one H of NCH_2), 2.16-1.98 (2H, m, CH_2), 1.90-1.77 (5H, m, CH_2 + CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$ + $DMSOd_6$): δ 179.0, 161.0, 154.7, 148.2, 146.1, 145.8, 140.2, 135.2, 133.9, 129.6, 129.1, 128.7, 128.5, 128.1, 127.8, 126.8, 126.3, 126.4, 125.9, 125.1, 122.9, 119.7, 108.9, 72.5, 69.3, 60.1, 55.4, 48.5, 26.5, 23.6, 19.8; HRMS (ESI, Orbitrap): calcd for $C_{35}H_{30}O_4N_5$ $[M+H]^+$ 584.22923; found 584.22845.

2'-(3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-5-methyl-1'-(4-nitrophenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4n*)

Compound **4n** (248 mg, 85%) was obtained as yellow coloured solid, R_f = 0.31 (ethyl acetate-*n*-hexane; 1/1); Mp. 213-214 ^{0}C; IR ^{v}max (KBr): 3166, 2923, 1711, 1689, 1608, 1592, 1568, 1514, 1490, 1345, 1299, 1250 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (2H, d, *J* = 8.6 Hz, two *ortho*-H of nitroaryl residue), 8.16 (1H, d, *J* = 7.9 Hz, C5-H of quinazolinone residue), 7.88-7.83 (2H, m, ArH of quinazolinone residue), 7.66 (1H, bs, NH), 7.64 (2H, d, *J* = 8.6 Hz, two *meta*-H of nitroaryl residue), 7.50 (1H, t, *J* = 6.9 Hz, ArH of quinazolinone residue), 6.96 (1H, d, *J* = 7.8 Hz, ArH of isatin residue), 6.88 (1H, s, ArH of isatin residue), 6.83 (1H, dd, *J* = 2.4, 8.6 Hz, ArH of N-aryl residue), 6.77 (1H, dd, *J* = 2.5, 8.7 Hz, ArH of N-aryl residue), 6.71 (1H, d, *J* = 7.8 Hz, ArH of isatin residue), 6.39 (1H, dd, *J* = 2.3, 8.6 Hz, ArH of N-aryl residue), 5.97 (1H, dd, *J* = 2.1, 8.6 Hz, ArH of N-aryl residue), 4.54 (1H, t, *J* = 10.2 Hz, CH), 4.31-4.27 (1H, m, CH), 4.19 (1H, d, *J* = 9.6 Hz, CH), 3.76 (3H, s, OCH_3), 3.50-3.44 (1H, m, one H of NCH_2), 2.67-2.64 (1H, m, one H of NCH_2), 2.15-1.99 (2H, m, CH_2), 1.92-1.78 (5H, m, CH_2 + CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$ + $DMSOd_6$): δ 180.3, 160.1, 155.1, 148.6, 147.1, 146.6, 139.6, 134.6, 131.4, 130.2, 129.8, 129.7, 129.3, 128.9, 128.7, 128.1, 127.2, 125.8, 123.9, 120.6, 115.3, 114.5, 109.7, 73.3, 70.2, 60.9, 56.1, 55.4, 49.4, 27.7, 24.8, 20.8; HRMS (ESI, Orbitrap): calcd for $C_{36}H_{32}O_5N_5$ $[M+H]^+$ 614.23980; found 614.23886.

5-methoxy-1'-(4-nitrophenyl)-2'-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (*4o*)

Compound **4o** (243 mg, 81%) was obtained as white coloured solid, R_f = 0.32 (ethyl acetate-*n*-hexane; 1/1); Mp. 189-190 ^{0}C; IR ^{v}max (KBr): 3281, 2925, 1720, 1691, 1602, 1585, 1518, 1487, 1473, 1347, 1206 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (2H, d, *J* = 8.8 Hz, two *ortho*-H of nitroaryl residue), 8.18-8.16 (1H, buried m, ArH C5-H of quinazolinone residue), 7.90 (1H, d, *J* = 8.0 Hz, of quinazolinone residue), 7.85 (1H, dt, *J* = 1.5, 7.2 Hz, ArH of quinazolinone residue), 7.62 (2H, d, *J* = 8.7 Hz, two *meta*-H of nitroaryl residue), 7.51 (1H, dt, *J* = 1.2, 7.6 Hz, ArH of quinazolinone residue), 7.42-7.35 (2H, m, ArH of isatin residue), 7.31 (1H, bs, NH), 7.28 (1H, dt, *J* = 1.8, 7.8 Hz, ArH of N-aryl residue), 6.77-6.72 (3H, m, 2H of N-aryl residue + 1H of isatin residue), 6.52 (1H, d, *J* = 7.6 Hz, ArH of N-aryl residue), 6.04 (1H, d, *J* = 7.8 Hz, ArH of N-aryl residue), 4.54 (1H, t, *J* = 10.2 Hz, CH), 4.28-4.24 (1H, m, CH), 4.13 (1H, d, *J* = 9.6 Hz, CH), 3.49-3.44 (1H, m, one H of NCH_2), 3.13 (3H, s, OCH_3), 2.67-2.63 (1H, m, one H of NCH_2), 2.17-1.98 (2H, m, CH_2), 1.92-1.75 (2H, m, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$ + $DMSOd_6$): δ 179.1, 161.3, 154.9, 154.0, 148.3, 146.3, 146.1, 136.3, 135.3, 134.0, 129.4, 128.9, 128.7, 128.1, 126.9, 126.6, 126.3, 126.2, 123.2, 120.0, 115.9, 112.4, 110.0, 72.5, 69.2, 60.1, 55.7, 54.4, 48.6, 26.6, 23.8; HRMS (ESI, Orbitrap): calcd for $C_{35}H_{30}O_5N_5$ $[M+H]^+$ 600.22469; found 600.22461.

2'-(3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-1'-(4-nitrophenyl)-1',2',5',6',7',7a'-hexahydro-2H-spiro[acenaphthylene-1,3'-pyrrolizin]-2-one (*4p*)

Compound **4p** (257 mg, 81%) was obtained as yellow coloured solid, R_f = 0.38 (ethyl acetate-*n*-hexane; 1/1); Mp. 220-221 ^{0}C; IR ^{v}max (KBr): 3132, 1723, 1681, 1609, 1509, 1400, 1346, 1250 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (2H, d, *J* = 8.7 Hz, H15, H16), 8.13 (2H, d, *J* = 8.1 Hz, H10, H24), 7.93 (1H, d, *J* =

7.9 Hz, H21), 7.87-7.82 (3H, m, H12, H22, H9), 7.77-7.74 (3H, m, H23, H13, H14), 7.50 (1H, t, J = 8.0 Hz, H11), 7.33-7.28 (2H, m, H7, H8), 6.81 (1H, dd, J = 2.9, 8.7 Hz, H20), 6.42 (1H, dd, J = 2.5, 8.7 Hz, H17), 5.67 (1H, dd, J = 2.9, 8.7 Hz, H19), 4.71 (1H, m, H18) 4.68 (1H, m, H2), 4.38 (1H, d, J = 9.8 Hz, H1), 4.26-4.23 (1H, m, H3), 3.69 (3H, s, OCH_3), 3.54-3.48 (1H, m, H6), 2.47-2.44 (1H, m, H6'), 2.14-1.98 (2H, m, H4, H5), 1.89-1.77 (2H, m, H4', H5') [The numbering of H atoms follows as depicted in Scheme 3]; ^{13}C NMR (125.8 MHz, $CDCl_3$ + $DMSOd_6$): δ 201.1, 161.9, 159.2, 155.4, 148.7, 146.7, 146.3, 142.3, 135.5, 134.4, 131.3, 130.7, 130.3, 129.0, 128.1, 127.8, 127.2, 126.9, 126.8, 126.7, 125.5, 123.7, 123.6, 122.5, 120.3, 114.8, 113.4, 75.9, 69.7, 59.1, 56.2, 55.1, 50.1, 27.0, 24.0; HRMS (ESI, Orbitrap): calcd for $C_{39}H_{31}O_5N_4$ $[M+H]^+$ 635.22890; found 635.23000.

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Regio- and stereoselective synthesis of novel spiropyrrolidines through 1,3-dipolar cycloaddition reactions of azomethine ylides and 2-styrylquinazolin-4(3*H*)-ones

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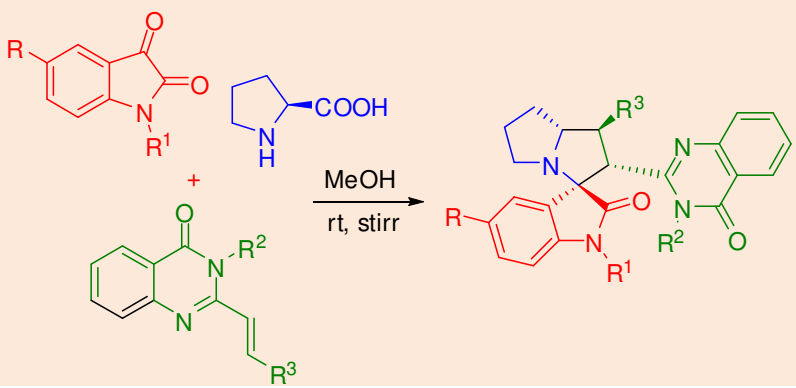

Efficient regio- and stereoselective synthesis of novel of spiropyrrolidines was achieved through 1,3-dipolar cycloaddition reaction of 2-styrylquinazolin-4(3*H*)-ones with azomethine ylides.