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Allylation of isatin-derived N-Boc-hydrazones followed by Pd-catalyzed carboamination reaction: an entry to 3-spiro-pyrazolidyl-oxindoles†

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The indium-mediated allylation of novel 3-(2-Boc-hydrazono)indolin-2-one derivatives, followed by a palladium-catalysed carboamination reaction, is described to afford unprecedented spirocyclic oxindoles in good yields. The method provides an efficient access to both *cis* and *trans* diastereoisomers of highly functionalized compounds, bearing an N-Boc, 5-substituted pyrazolidine ring at the C3-oxindole spiro junction. The versatility of the method is fully demonstrated starting from a series of substituted isatins and employing a variety of aryl halides in the key cyclization step.

Introduction

The pyrazolidine five-membered ring, characterized by the presence of two adjacent nitrogen atoms, can be considered as a cyclic hydrazine moiety. Among natural products containing a nitrogen–nitrogen bond,[1] such a heterocycle is displayed by the highly unusual alkaloid garceine (**I**),[2] isolated from *Lotus garcinii* in 2001, but not investigated for biological properties because of insufficient material (Fig. 1).

Owing to their particular stability and, at the same time, peculiar electronic properties, pyrazolidines and their derivatives are potentially capable of providing improved physicochemical properties in their interaction with biological systems.[3] Indeed, this heterocyclic ring is present as a partial structure in a number of synthetic compounds, displaying a wide range of bioactivities, such as, for example, antibacterial (**II**),[4] anticancer (**III**)[5] and anticonvulsant (**IV**).[6]

In addition, pyrazolidine-amino acid derivatives, acting as azaproline analogues, have been shown to have application as peptidomimetics, displaying inhibitory activities against enzymes (serine peptidase dipeptidyl **IV** inhibitor, **V**)[7] and receptors (VLA-4 antagonist, **VI**).[8]

Despite a recurrent interest in pyrazolidine 3,5-diones[9–11] and N,N-disubstituted derivatives,[12] other kinds of pyrazolidine-based frameworks have received minor attention, and their application in the context of drug discovery has yet to be fully explored. Over the last decade the synthetic effort towards highly functionalized pyrazolidine derivatives has greatly increased, leading to the development of efficient protocols, such as cycloadditions of hydrazones and olefins,[13] 1,3-dipolar cycloadditions of azomethine imines,[14] carboamination reactions,[15] and amination reactions of allenes.[16]

As part of our interest in the synthesis of 3,3-disubstituted oxindole derivatives and related spirocompounds,[17] we looked into the biological significance of the pyrazolidine ring, conceiving its combination with the relevant oxindole nucleus, by means of a spiro arrangement of the two ring systems. The conjugation of privileged heterocycles into spiro structures is a challenging application of the molecular hybridization concept,[18] a viable and effective approach envisioning the rational design of new functional compounds through the structural fusion of two pharmacophoric subunits into one chemical entity. Since spiro compounds have an intrinsic three-dimensionality, they are able to access unexplored chemical space, often displaying improved biological interactions and being more likely to be successfully developed as drugs.[19]

At the best of our knowledge, only a recent work describes spirocyclic pyrazolidines, achieved by means of a gold-catalyzed

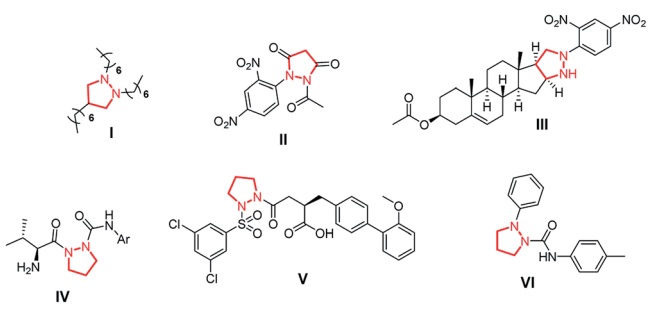

Fig. 1 Examples of natural products and bioactive agents containing the pyrazolidine ring.

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† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for all new compounds; ^{1}H–^{1}H ROESY NMR for compounds **6a** and **6a′**; full discussion of the crystallographic results, including information on crystal packing, for compound **6f′** (PDF). CCDC 1938731. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra07712j

three-component spirocyclization, starting from alkynols, hydrazines and carbonyl components, mainly aldehydes.[20]

No methods have been reported for the preparation of pyrazolidines derived from cyclic ketones and, of course, of oxindoles bearing an N-jointed pyrazolidine ring at the key C3 position.

Relying on our previous experience with isatin-derived ketimines and 3-amino substituted oxindoles,[17] we envisioned 3-allyl-3-hydrazinylindolin-2-ones **5**, obtainable from 3-hydrazonoindolin-2-ones **4**, as suitable substrates for a palladium-catalysed carboamination reaction, aimed to the synthesis of the unprecedented 1′,5′-disubstituted spiro[indoline-3,3′-pyrazolidin]-2-one scaffold **6** (Scheme 1).

Herein, we report the synthesis of a large family of highly functionalized 1′-Boc, 5′-arylmethyl spiro[indoline-3,3′-pyrazolidin]-2-ones, attainable as separable 3′-5′-*cis* and 3′-5′-*trans* diastereoisomers, thus demonstrating for the first time the suitability of the Pd-catalysed carboamination reaction of hydrazine derivatives for the synthesis of spiro compounds.

Results and discussion

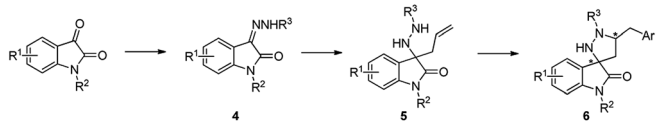
We started our investigation by taking into consideration the already known isatin-derived *N*-tosyl hydrazone **1** and the corresponding imino allylation product **2**,[21] besides 4-bromo-1,1′-biphenyl as aryl halide. We tested various reaction conditions for the Pd-catalysed carboamination step. However, treatment of compound **2** with different Pd catalysts ($Pd(OAc)_2$, $Pd_2(dba)_3$) in presence of various ligands (dppe, dpe-phos, BINAP) afforded high amounts of compounds **3a** and **3b**, instead of the expected spiro compound (Scheme 2).

Likely, *N*-tosyl hydrazine **2** is not stable in the basic reaction conditions employed and, due to the presence of NaO^{t}Bu, it easily decomposes, ejecting the tosyl anion and forming a diazonium anion. Loss of molecular nitrogen results in protonation of the substrate, affording the already known compound **3a**.[22] The formation of moderate amounts of compound **3b** can be explained as the result of a standard Heck reaction between **3a** and the 4-bromo-1,1′-biphenyl.

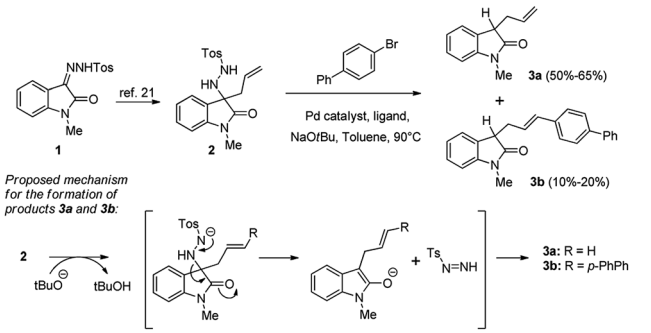
Thinking about more appropriate hydrazone N-substituents, we turned our attention to reaction of *N*-benzyl isatin with *tert*-butyl carbazate. After refluxing for two hours in ethanol, the unprecedented N-Boc hydrazone **4a** was obtained in nearly quantitative yield (Table 1, reaction). For the subsequent allylation reaction of **4a**, we initially explored the cheap tin powder, in combination with allyl bromide in a simple Barbier-type one-pot procedure, which avoids the use of the toxic allylic tributyltin reagent.[23] The reaction proved to be unsuccessful in MeOH (Table 1, entry 1), while it afforded the desired N-Boc allyl hydrazine derivative **5a** when the solvent was changed to THF (entry 2).

Aiming at improving the yield and, at the same time, at experimenting an environmentally benign chemical process, we then looked at the indium-promoted allylation in aqueous media.[21] Unlike most Barbier-type allylation methods, indium-mediated reactions are insensitive to moisture, relying on facile and practical reaction conditions coupled with minimal side reactions. Treatment of a THF/NH_4Cl (aq. saturated) solution of hydrazone **4a** with allyl bromide in the presence of indium afforded compound **5a** only in traces (entry 3). The yield improved when the reaction was conducted in a 3/1 MeOH/NH_4Cl (aq. saturated) solution (entry 4) and it was ultimately satisfying when only MeOH was adopted as a solvent (entry 5). An excess of allyl bromide and indium powder proved to be necessary for an almost quantitative yield, probably due to progressive metal inactivation.

Once a multi-gram scale procedure for the preparation of the hydrazine substrate **5a** was achieved, we moved our attention on the key Pd-catalysed carboamination reaction. Among all possible variables that can be considered for the screening of

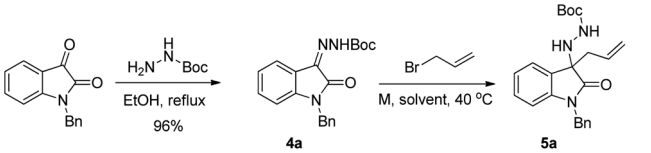


Scheme 1 Aim of the work.



Scheme 2 Reaction studies on *N*-tosyl hydrazone **1**.

Table 1 Synthesis of N-Boc hydrazine derivative **5a**[a]



Entry	M (powder)	Solvent	*T* (h)	Yield[b] (%)
1	Sn	MeOH	48	<5
2	Sn	THF	48	70
3	In	THF/NH_4Cl sat 1 : 1	6	<5
4	In	MeOH/NH_4Cl sat 3 : 1	72	40
5	In	MeOH	3	94

[a] Compound **4a** was prepared starting from *N*-benzyl isatin (2 mmol), *tert*-butyl carbazate (2 mmol), in ethanol (0.3 M), at reflux for two hours. All allylation reactions were conducted with **4a** (0.25 mmol), allyl bromide (0.5 mmol) and metal powder (0.5 mmol). [b] Isolated yields.

the reaction conditions, we chose to focus preliminary on Pd complexes and ligand additives. We investigated the effect of Pd(0)- and Pd(II)-based complexes and of several phosphines, at various degrees of basicity and steric encumbrance. After some preliminary screening on solvent and temperature, all reactions were carried out in toluene, at 90 °C, using NaO^{t}Bu as the base and 4-bromo-1,1′-biphenyl as reference aryl halide (Table 2).

We started our investigation from $Pd(OAc)_2$ catalyst, coupled with various phosphine-based ligands. Reaction employing dpe-phos failed to give the desired spiro products, affording only compound **7** from the competing Heck arylation, and compound **8**, from the Pd-promoted isomerization of the substrate **5a** double bond (entry 1). Switching to triscyclohexylphospine (TCP), we were pleased to observe the formation of diastereoisomeric **6a** and **6a′** target compounds (dr 1 : 2), together with a considerable amount of byproduct **9**,[24] deriving from decomposition of the starting N-Boc-hydrazine (entry 2). A significant yield improvement and reduction of reaction times was achieved exploiting tris(*o*-tolyl)phosphine (TTP) or tris(2-furyl)phosphine (TFP), but without any increase of diastereoisomeric ratios (entries 3 and 4). Switching to $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ complexes did not lead to any contribution, in terms of better yield or dr (entries 5–9). On the other hand, $Pd_2(dba)_3$ proved to be the catalyst of choice, both when paired with TTP or with X-phos, affording the desired 3-spiro-pyrazolidyl-oxindoles **6a** and **6a′** in excellent yield, albeit in negligible dr (entries 10–11). The known propensity of the $Pd_2(dba)_3$ complex to reduce the rate of β-hydrogen elimination in "PdII-σ-alkyl" complexes,[25] can likely explain the ability of this catalyst to drive the reaction towards the intramolecular key carboamination, rather than towards the competing standard intermolecular Heck reaction.

Diastereoisomeric 3-spiro-pyrazolidyl-oxindoles **6a** and **6a′** proved to be easily separable by flash chromatography, allowing a full mono- and bidimensional NMR characterization, including determination of the relative stereochemistry. In particular, NOESY experiments allowed assigning the 3′-5′-*trans* configuration to diastereoisomer **6a** and the 3′-5′-*cis* configuration to diastereoisomer **6a′**. Diagnostic NOE interactions between oxindole H-4 and selected pyrazolidine protons were identified for both diastereoisomers (Fig. 2).

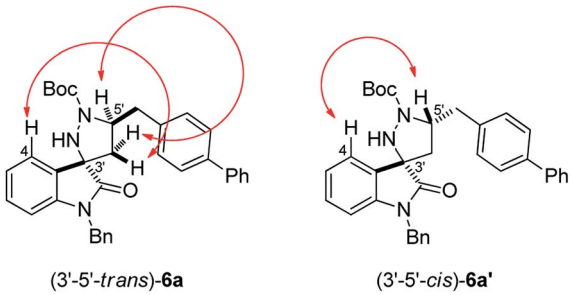
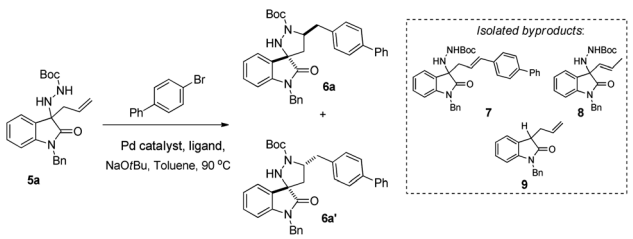


Fig. 2 Diagnostic NOE contacts for compounds **6a** and **6a′**.

Table 2 Screening of the Pd-catalysed carboamination reaction conditions on hydrazine derivative **5a**[a]

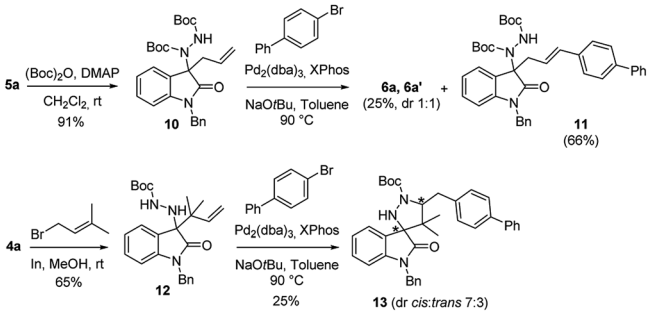


				Target spiro compounds		Isolated byproducts		
Entry	Pd cat	L[b]	*T* (h)	Yield[c] (**6a** + **6a′**%)	dr[d] (**6a** : **6a′**)	**7** (%)	**8** (%)	**9** (%)
1	$Pd(OAc)_2$	dpe-phos	12	0	—	32	53	
2	$Pd(OAc)_2$	TCP	12	45	1 : 2			49
3	$Pd(OAc)_2$	TTP	3	87	1 : 1			
4	$Pd(OAc)_2$	TFP	3	87	1 : 1.5			13
5	$PdCl_2(MeCN)_2$	TFP	24	79	1 : 2			14
6	$PdCl_2(MeCN)_2$	BINAP	24	44	1 : 1	44		3
7	$PdCl_2(MeCN)_2$	PPh_3	24	50	1 : 2			21
8	$PdCl_2(PPh_3)_2$	—	24	25	1 : 1			29
9	$Pd(PPh_3)_4$	—	24	69	1 : 1.6	19		
10	$Pd_2(dba)_3$	TTP	3	96	1.4 : 1			4
11	$Pd_2(dba)_3$	X-phos	3	98	1 : 1			

[a] Reactions were carried out on a 0.25 mmol scale, with 1.0 equiv. of **5a**, 1.3 equiv. of 4-bromo-1,1′-biphenyl, 1.3 equiv. of NaO^{t}Bu, 4 mol% of Pd catalyst, 4 mol% of ligand, toluene (0.20 M). [b] Dpe-phos = bis[(2-diphenylphosphino)phenyl]ether; BINAP= (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene; TFP = tris(2-furyl)phosphine; TCP = triscyclohexylphospine; TTP = tris(*o*-tolyl)phosphine; X-phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. [c] Sum of the isolated yields for each diastereoisomer. [d] Determined by ^{1}H NMR of the crude reaction product.

In order to evaluate possible improvements in dr, we made some focused modifications to the N-Boc hydrazine substrate. Aiming at exploring the effects of more steric constraints in the transition states, we selected N,N^2-Boc hydrazine **10** and 2,2-dimethylbut-3-en-1-yl hydrazine **12**, easily prepared from compounds **5a** and **4a**, respectively (Scheme 3).

From the Pd-catalysed reaction on substrate **10**, the mono-Boc spiro derivatives **6a** and **6a′** could be recovered in the usual dr, together with a substantial amount of the Heck product **11**. Reaction of **12** afforded the desired 4-dimethyl ethyl spiropyrazolidine **13**, in modest yield and only slightly higher dr.

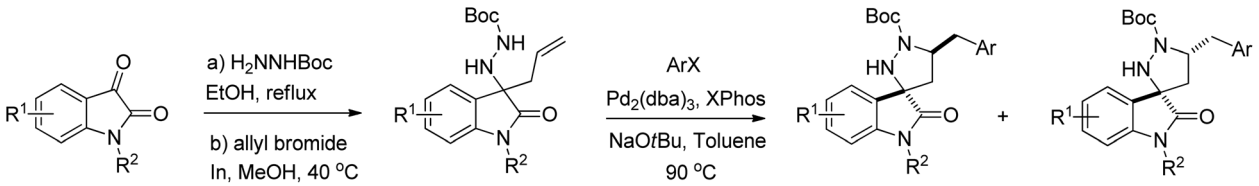


Scheme 3 Pd-catalysed carboamination reaction on hydrazine derivatives **10** and **12**.

With the best conditions in hand, we proceeded with the investigation of the reaction scope, varying R^1 and R^2 substituents in the starting isatin and ArX in the carboamination step (Table 3).

In reactions with **5a**, most of aryl halides are tolerated in the Pd-catalysed step (entries 1–8). The target spiro compounds are generally obtained in high yields, in the presence of either electron-withdrawing, -donating or bulky substituents on the aromatic Ar-X ring. On the other hand, the electronic characteristics and positions of the substituents at the isatin starting compounds affected more heavily the outcome of the synthetic process. To this regard, the allylation step appeared to be troublesome in two cases (entries 13, 16), affording the intermediate hydrazines derivatives **5f** and **5i** in modest yields, likely for electronic reasons. Starting from *N*-benzyl, 4-Cl-isatin (entry 17), the corresponding hydrazine derivative **5j** could not be achieved, probably because of the steric hindrance at the oxindole C3-position, due to the presence of the C4-substituent. Finally, the presence of a 5-NO_2 substituent on the substrate **5h** (entry 15) proved to be incompatible with a successful Pd-

Table 3 Generality of the substrate scope[a]



Entry	5 (R^1, R^2)	Yield (5%)[b]	ArX	T (h)	6	Yield (6%)[c]	dr (6 : 6′)[d]
1	**5a** (H, Bn)	94	*p*-Br-biphenyl	3	**6a**, **6a′**	98	1 : 1
2	**5a** (H, Bn)	94	*p*-Br-anisole	6	**6b**, **6b′**	98	1.4 : 1
3	**5a** (H, Bn)	94	*p*-Br-nitrobenzene	12	**6c**, **6c′**	53	1 : 1
4	**5a** (H, Bn)	94	*p*-Br-benzophenone	4	**6d**, **6d′**	92	1 : 1
5	**5a** (H, Bn)	94	*p*-Br-acetophenone	3	**6e**, **6e′**	98	1 : 1
6	**5a** (H, Bn)	94	*o*-Br-toluene	10	**6f**, **6f′**	98	1 : 1.6
7	**5a** (H, Bn)	94	2-Br-1,3,5-trimethylbenzene	5	**6g**, **6g′**	70	1 : 1.7
8	**5a** (H, Bn)	94	*p*-I-toluene	6	**6h**, **6h′**	63	1 : 1
9	**5b** (H, Me)	82	*p*-Br-biphenyl	12	**6i**, **6i′**	53	1.5 : 1
10	**5c** (H, 3,4-diCl-Ph(CH)$_2$CH$_2$)	93	*p*-Br-biphenyl	12	**6j**, **6j′**	69	1 : 1
11	**5d** (5-Me, Bn)	98	*p*-Br-biphenyl	12	**6k**, **6k′**	50	1.4 : 1
12	**5e** (5-Br, Bn)	82	*p*-Br-biphenyl	12	**6l**, **6l′**	34	2.3 : 1
13	**5f** (6-Cl, Bn)	25	*p*-Br-biphenyl	12	**6m**, **6m′**	72	1.5 : 1
14	**5g** (7-CF_3, Bn)	75	*p*-Br-biphenyl	12	**6n**, **6n′**	47	1.4 : 1
15	**5h** (5-NO_2, Bn)	71	*p*-Br-biphenyl	24	**6o**, **6o′**	nr[e]	
16	**5i** (5-OMe, Bn)	15					
17	**5j** (4-Cl, Bn)	nr[e]					

[a] Compounds **5** were prepared on a 0.3 mmol scale, starting from the proper R^1,R^2-substituted isatin (1.0 equiv.), *tert*-butyl carbazate (1 equiv.), in ethanol (0.3 M), at reflux for two hours, to give the corresponding N-Boc hydrazone intermediates **4**. Allylation reactions were conducted on **4** (1 equiv.), allyl bromide (2 equiv.) and metal powder (2 equiv.), in methanol (0.1 M), at 40 °C for 3 hours. Carboamination reactions were carried out on a 0.2 mmol scale, with 1.0 equiv. of **5**, 1.3 equiv. of aryl halide, 1.3 equiv. of NaO^{t}Bu, 4 mol% of $Pd_2(dba)_3$, 4 mol% of XPhos, toluene (0.2 M). [b] Isolated yields. [c] Sum of the isolated yields for each diastereoisomer. [d] Determined by ^{1}H NMR of the crude reaction product. [e] No reaction.

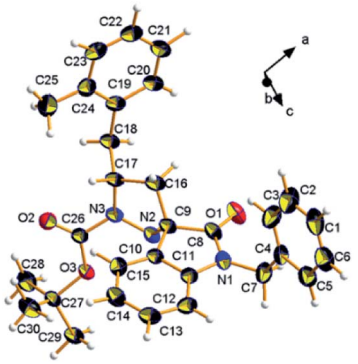


Fig. 3 ORTEP view of compound **6f′** at room temperature, with the atom-numbering scheme and the crystallographic reference system highlighted. Thermal ellipsoids of non-H atoms were drawn at the 30% probability level.

catalysed reaction, probably due to the instability of the nitro group in basic conditions.

In order to further confirm the relative stereochemistry of the two diastereoisomeric series of products **6**, as determined by NMR, a single crystal of the diastereoisomer **6f′** was subjected to single-crystal X-ray diffraction analysis. The experiment unambiguously assigns the *3′S*,5′R** (*cis*) relative configuration, highlighting at the same time the preferred solid-state conformation (Fig. 3. For a full discussion of the crystallographic results, see the ESI†).

Conclusion

We developed an efficient strategy for the synthesis of a novel class of oxindole-based spiro compounds, bearing the unusual pyrazolidine ring at the C3 stereogenic center. The reactivity of 3-hydrazonoindolin-2-ones under various allylation conditions was explored, developing a robust protocol for the multi-gram conversion of variously substituted isatins into the corresponding N-Boc allyl hydrazine derivatives. Through a screening of the carboamination reaction conditions, it was possible to react effectively such intermediates with a variety of aryl halides, affording the cyclized spiro compounds in satisfactory yields. Both *cis* and *trans* diastereoisomers, with respect to the pyrazolidine ring, were obtained. Further work is currently underway, aimed at establishing spirooxindole-fused pyrazolidines as possible lead compounds for drug discovery programs.

Experimental section

General procedures

All commercial materials (Aldrich, Fluorochem) were used without further purification. All solvents were of reagent grade or HPLC grade. Reactions requiring anhydrous conditions were performed under nitrogen atmosphere. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel Merck 60 F254; spots were visualized with UV light (254 nm) or by treatment with $KMnO_4$ solution in water or ninhydrin solution in ethanol. Products were purified by flash chromatography (FC) on silica gel 60 (230–400 mesh). Yields refer to isolated compounds estimated to be >95% pure as determined by ^{1}H NMR. NMR spectra were recorded on Bruker 300 or Advance 400 spectrometers, using TMS as an internal standard. ^{13}C NMR spectra have been recorded using the APT pulse sequence. Chemical shifts are reported in parts per million relative to the residual solvent, coupling constants (J) are given in Hz. Multiplicities in ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. High-resolution MS spectra (HRMS) were recorded with a Thermo Fisher LCQ Fleet ion trap mass spectrometer, equipped with an ESI source.

Typical procedure (TP-A) for the synthesis of *N*-Boc hydrazone derivatives (4a–4j)

A mixture of R^1,R^2-substituted isatin (0.3 mmol) and *tert*-butyl carbazate (0.3 mmol) were suspended in ethanol (0.3 M) and the reaction was stirred at reflux for 2 hours. The reaction was cooled down to room temperature, and then the solid was filtered and washed with cold ethanol. The pure product was obtained without need of purification.

Typical procedure (TP-B) for the synthesis of *N*-Boc hydrazine derivatives (5a–5j)

To a suspension of *N*-Boc hydrazone derivative (0.3 mmol) in methanol (0.1 M), indium (0.6 mmol) and allyl bromide (0.6 mmol) were added. After stirring at 40 °C for three hours, saturated aqueous NH_4Cl solution was added and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by FC as indicated below.

Typical procedure (TP-C) for the synthesis of 3-spiro-Pyrazolidyl-Oxindoles derivatives (6a,6a′–6n,6n′)

The N-Boc hydrazine derivative (0.2 mmol), the aryl halide (0.26 mmol), sodium *tert*-butoxide (0.26 mmol), $Pd_2(dba)_3$ (4 mol%) and XPhos (4 mol%) were suspended in anhydrous toluene (0.2 M) and the reaction was stirred at 90 °C. After the completion of reaction (monitored by TLC), saturated aqueous NH_4Cl solution was added and the reaction was extracted twice with ethyl acetate. The combined organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product. This was purified by FC (hexane : ethyl acetate, as described below), affording the desired product, as separated (3′-5′-*trans*) and (3′-5′-*cis*) diastereoisomers (except for **6l**, **6l′**).

Analytical data of products (4a–4j, 5a–5i, 6a,6a′–6n,6n′, 3b, 7–13)

(*Z*)-*tert*-Butyl 2-(1-benzyl-2-oxoindolin-3-ylidene) hydrazine carboxylate (4a). Prepared according to TP-A, starting from *N*-benzyl isatin. Yellow solid (96% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.32 (m, br, 1H), 7.74 (d, br, J = 7.8 Hz, 1H), 7.37–7.20

(m, 6H), 7.08 (t, J = 7.8 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 4.94 (s, 2H), 1.56 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 152.3, 142.1, 135.1, 133.8 (br), 130.6, 129.0 (2C), 128.0, 127.4 (2C), 123.4, 121.3, 120.2, 109.7, 82.6, 43.4, 28.2 (3C). HRMS (ESI) m/z: 352.1661 $[M + H]^+$; calcd for $C_{20}H_{22}N_3O_3^+$, 352.1656.

***tert*-Butyl 2-(1-methyl-2-oxoindolin-3-ylidene)hydrazinecarboxylate (4b).** Prepared according to TP-A, starting from *N*-methyl isatin. Light yellow solid (72% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 1.5 : 1 Z : E mixture) δ 12.27 (m, br, 0.6H), 8.79 (m, br, 0.4H), 7.71 (d, br, J = 7.8 Hz, 0.6H), 7.56 (d, br, J = 7.8 Hz, 0.4H), 7.42 (t, J = 7.8 Hz, 0.4H), 7.35 (t, J = 7.8 Hz, 0.6H), 7.10 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 7.8 Hz, 0.4H), 6.85 (d, J = 7.8 Hz, 0.6H), 3.25 (s, 1.8H), 3.24 (s, 1.2H), 1.57 (s, 3.6H), 1.55 (s, 5.4H). ^{13}C NMR (100 MHz, $CDCl_3$, 1.5 : 1 Z : E mixture) δ 160.8 and 160.7 (1C), 155.6 and 155.2 (1C), 152.4, 145.6 and 135.1 (1C), 136.0 and 116.2 (1C), 133.0 and 131.3 (1C), 124.6 and 123.8 (1C), 123.3 and 121.8 (1C), 110.0 and 109.4 (1C), 84.2 and 83.8 (1C), 29.0 and 28.8 (3C), 26.9. HRMS (ESI) m/z: 276.1349 $[M + H]^+$; calcd for $C_{14}H_{18}N_3O_3^+$, 276.1343.

(*Z*)-*tert*-Butyl 2-(1-((*E*)-3-(3,4-dichlorophenyl)allyl)-2-oxoindolin-3-ylidene)hydrazinecarboxylate (4c). Prepared according to TP-A, starting from *N*-((3,4-dichlorophenyl)allyl) isatin. Yellow solid (93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.25 (m, br, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.45–7.28 (m, 3H), 7.19–7.07 (m, 2H), 6.87 (d, J = 7.8 Hz, 1H), 6.48 (d, J = 15.6 Hz, 1H), 6.20 (dt, J = 15.6 and 5.8 Hz, 1H), 4.42 (d, J = 5.8 Hz, 2H), 1.55 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 155.1, 152.2, 141.9, 136.0, 132.8, 132.3, 131.8, 131.0, 130.7, 128.3, 125.7, 124.2, 123.5, 121.4, 120.2, 109.3, 82.7, 41.3, 28.1 (3C). HRMS (ESI) m/z: 446.1027 $[M + H]^+$; calcd for $C_{22}H_{22}N_3O_3^+$, 446.1033.

***tert*-Butyl 2-(1-benzyl-5-methyl-2-oxoindolin-3-ylidene)hydrazinecarboxylate (4d).** Prepared according to TP-A, starting from *N*-benzyl, 5-methyl isatin. Yellow solid (70% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 7 : 3 tautomer mixture) δ 12.29 (m, br, 0.7H), 8.05 (s, br, 0.3H), 7.57 (s, br, 0.7H), 7.37–7.23 (m, 3.7H), 7.16–7.00 (m, 2H), 6.84 (d, br, J = 7.8 Hz, 0.3H), 6.65 (d, J = 7.8 Hz, 0.7H), 6.50 (d, J = 7.8 Hz, 0.3H), 4.91 (s, 1.4H), 4.70 (s, br, 0.6H), 2.40–1.89 (m, br, 0.3H), 2.29 (s, 3H), 1.55 (s, 6.3H), 1.51 (s, 2.7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4 and 161.6 (1C), 168.3 and 154.9 (1C), 152.4 and 58.2 (1C), 139.9 and 137.9 (1C), 136.7 and 135.2 (1C), 133.1 and 131.9 (1C), 131.9–121.9 (7C), 120.0 and 118.2 (1C), 109.4 and 107.9 (1C), 82.6 and 78.6 (1C), 43.4 and 43.1 (1C), 28.6 and 28.2 (3C), 21.1 and 21.0 (1C). HRMS (ESI) m/z: 366.1804 $[M + H]^+$; calcd for $C_{21}H_{24}N_3O_3^+$, 366.1812.

(*Z*)-*tert*-Butyl 2-(1-benzyl-5-bromo-2-oxoindolin-3-ylidene)hydrazinecarboxylate (4e). Prepared according to TP-A, starting from *N*-benzyl, 5-bromo isatin. Yellow solid (84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.23 (m, br, 1H), 7.87 (d, br, J = 2.0 Hz, 1H), 7.40–7.22 (m, 6H), 6.64 (d, J = 7.8 Hz, 1H), 4.92 (s, 2H), 1.56 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 154.7, 151.7, 1342.8, 135.0, 134.6, 133.5, 128.9 (2C), 128.0, 127.4 (2C), 126.8, 117.1, 111.7, 84.1, 43.9, 28.1 (3C). HRMS (ESI) m/z: 430.0765 $[M + H]^+$; calcd for $C_{20}H_{21}BrN_3O_3^+$, 430.0761.

(*Z*)-*tert*-Butyl 2-(1-benzyl-6-chloro-2-oxoindolin-3-ylidene)hydrazinecarboxylate (4f). Prepared according to TP-A, starting from *N*-benzyl, 6-chloro isatin. Yellow solid (93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (m, br, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.42–7.27 (m, 5H), 7.09 (dd, br, J = 7.8 and 1.9 Hz, 1H), 6.80 (d, J = 1.9 Hz, 1H), 4.94 (s, 2H), 1.59 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 155.6, 152.7, 143.7, 137.0, 135.3, 129.8 (2C), 128.9, 128.0 (2C), 124.2, 122.8, 119.3, 111.0, 83.5, 44.3, 28.8 (3C). HRMS (ESI) m/z: 386.1259 $[M + H]^+$; calcd for $C_{20}H_{21}ClN_3O_3^+$, 386.1266.

(*Z*)-*tert*-Butyl 2-(1-benzyl-2-oxo-7-(trifluoromethyl)indolin-3-ylidene)hydrazinecarboxylate (4g). Prepared according to TP-A, starting from *N*-benzyl, 7-trifluoromethyl isatin. Yellow solid (64% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.23 (m, br, 1H), 8.01 (d, br, J = 7.6 Hz, 1H), 7.63 (d, br, J = 8.6 Hz, 1H), 7.34–7.17 (m, 4H), 7.10 (d, br, J = 6.9 Hz, 2H), 5.23 (s, 2H), 1.54 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 156.7, 151.9, 139.6, 135.7, 128.6 (2C), 128.3 (q, J = 7.4 Hz), 127.3, 125.7 (2C), 124.5, 122.9, 123.1 (q, J = 272.7 Hz), 122.8, 113.8 (q, J = 28.2 Hz), 83.1, 45.6, 28.1 (3C). HRMS (ESI) m/z: 420.1524 $[M + H]^+$; calcd for $C_{21}H_{21}F_3N_3O_3^+$, 420.1530.

(*Z*)-*tert*-Butyl 2-(1-benzyl-5-nitro-2-oxoindolin-3-ylidene)hydrazinecarboxylate (4h). Prepared according to TP-A, starting from *N*-benzyl, 5-nitro isatin. Yellow solid (87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.22 (m, br, 1H), 8.66 (d, J = 1.8 Hz, 1H), 8.22 (dd, J = 8.4 and 1.9 Hz, 1H), 7.42–7.27 (m, 5H), 6.91 (d, J = 8.4 Hz, 1H), 5.05 (s, 2H), 1.62 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 156.0, 1151.6, 146.2, 144.2, 134.1, 129.2 (2C), 128.5, 127.3 (2C), 126.4, 120.9, 116.8, 109.5, 83.5, 43.9, 28.1 (3C). HRMS (ESI) m/z: 397.1500 $[M + H]^+$; calcd for $C_{20}H_{21}N_4O_5^+$, 397.1506.

(*Z*)-*tert*-Butyl 2-(1-benzyl-5-methoxy-2-oxoindolin-3-ylidene) hydrazinecarboxylate (4i). Prepared according to TP-A, starting from *N*-benzyl, 5-methoxy isatin. Yellow solid (96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.38 (m, br, 1H), 7.37–7.23 (m, 6H), 6.80 (dd, J = 8.6 and 2.9 Hz, 1H), 6.66 (d, J = 8.6 Hz, 1H), 4.90 (s, 2H), 3.76 (s, 3H), 1.58 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 156.4, 155.6, 152.3, 135.8, 135.2, 130.9, 129.0 (2C), 128.0, 127.4 (2C), 117.4, 110.6, 106.0, 82.6, 55.9, 43.4, 28.2 (3C). HRMS (ESI) m/z: 382.1767 $[M + H]^+$; calcd for $C_{21}H_{24}N_3O_4^+$, 382.1761.

(*Z*)-*tert*-Butyl 2-(1-benzyl-4-chloro-2-oxoindolin-3-ylidene)hydrazinecarboxylate (4j). Prepared according to TP-A, starting from *N*-benzyl, 4-chloro isatin. Yellow solid (84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.49 (m, br, 1H), 7.41–7.25 (m, 5H), 7.17 (*t*, br, J = 7.8 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H),4.97 (s, 2H), 1.60 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 154.8, 151.8, 143.1, 134.8, 130.7, 129.5, 129.0 (2C), 128.1, 127.3 (2C), 125.0, 117.2, 108.0, 82.7, 43.6, 28.2 (3C). HRMS (ESI) m/z: 386.1261 $[M + H]^+$; calcd for $C_{20}H_{21}ClN_3O_3^+$, 386.1266.

***tert*-Butyl 2-(3-allyl-1-benzyl-2-oxoindolin-3-yl)hydrazinecarboxylate (5a).** Prepared according to TP-B starting from compound **4a**, and purified by FC (hexane : ethyl acetate from 7 : 3 to 3 : 7). Yellow foam (94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, br, J = 7.2 Hz, 1H), 7.34–7.22 (m, 5H), 7.17 (*t*, br, J = 7.5 Hz, 1H), 7.04 (*t*, br, J = 7.5 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 6.08 (m, br, 1H), 5.52 (m, 1H), 5.09 (d, br, J = 17.0 Hz, 1H), 5.00 (d, br, J = 10.2 Hz, 1H), 4.94 (d, br, J = 16.0 Hz, 1H), 4.87 (d, br, J = 16.0 Hz, 1H), 4.81–4.47 (m, br, 1H), 2.73 (dd, br, J = 13.3 and 6.2 Hz, 1H), 2.64 (dd, br, J = 13.3 and 8.5 Hz, 1H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 156.0, 143.2, 135.6, 130.7, 129.2, 128.7 (2C), 127.8, 127.6, 127.2 (2C), 125.2, 122.6, 120.1, 109.1, 80.5, 68.6, 43.8, 39.6, 28.1 (3C). HRMS (ESI) m/z: 416.1938 $[M + Na]^+$; calcd for $C_{23}H_{27}N_3NaO_3^+$, 416.1945.

***tert*-Butyl 2-(3-allyl-1-methyl-2-oxoindolin-3-yl)hydrazinecarboxylate (5b).** Prepared according to TP-B starting from compound **4b**, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 7.8 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 5.98 (m, br, 1H), 5.48 (m, 1H), 5.08–4.94 (m, 2H), 3.18 (s, 3H), 3.18–2.77 (m, br, 1H), 2.67 (dd, J = 15.6 and 6.8 Hz, 1H), 2.55 (dd, J = 15.6 and 8.8 Hz, 1H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 156.1, 143.9, 130.6, 129.2, 127.7, 125.2, 122.5, 119.8, 107.9, 80.3, 68.6, 39.5, 28.1 (3C), 26.1. HRMS (ESI) m/z: 340.1636 [M + Na]$^+$; calcd for $C_{17}H_{23}N_3NaO_3^+$, 340.1632.

(*E*)-*tert*-Butyl 2-(3-allyl-1-(3-(3,4-dichlorophenyl)allyl)-2-oxoindolin-3-yl)hydrazinecarboxylate (5c). Prepared according to TP-B starting from compound **4c**, and purified by FC (hexane : ethyl acetate 1 : 1). Dark yellow foam (93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, br, J = 7.8 Hz, 1H), 7.42–7.19 (m, 3H), 7.17–7.03 (m, 2H), 6.79 (d, br, J = 7.8 Hz, 1H), 6.41 (d, br, J = 15.6 Hz, 1H), 6.16 (dt, br, J = 15.6 and 4.9 Hz, 1H), 5.98 (m, br, 1H), 5.50 (m, br, 1H), 5.07 (d, J = 17.6 Hz, 1H), 5.01 (d, J = 10.8 Hz, 1H), 5.46 (d, br, J = 4.9 Hz, 2H), 2.81–2.50 (m, br, 1H), 2.71 (dd, J = 13.7 and 6.8 Hz, 1H), 2.60 (dd, J = 13.7 and 8.8 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 156.2, 143.0, 136.4, 132.7, 131.5, 130.7, 130.4, 129.9, 129.3, 128.2, 127.8, 125.6, 125.4, 124.9, 122.7, 120.1, 108.7, 80.5, 68.6, 41.5, 39.7, 28.1 (3C). HRMS (ESI) m/z: 510.1028 [M + Na]$^+$; calcd for $C_{25}H_{27}Cl_2N_3NaO_3^+$, 510.1322.

***tert*-Butyl 2-(3-allyl-1-benzyl-5-methyl-2-oxoindolin-3-yl)hydrazinecarboxylate (5d).** Prepared according to TP-B starting from compound **4d**, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.20 (m, 6H), 6.95 (d, br, J = 7.8 Hz, 1H), 6.53 (d, br, J = 7.8 Hz, 1H), 5.98 (m, br, 1H), 5.50 (m, 1H), 5.08 (d, br, J = 17.6 Hz, 1H), 4.99 (d, br, J = 10.7 Hz, 1H), 4.92 (d, br, J = 15.6 Hz, 1H), 4.81 (d, br, J = 15.6 Hz, 1H), 3.72 (m, br, 1H), 2.71 (dd, J = 12.7 and 5.8 Hz, 1H), 2.62 (dd, J = 12.7 and 8.8 Hz, 1H), 2.29 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 156.0, 140.8, 135.7, 132.0, 130.8, 129.4, 128.7 (2C), 127.8, 127.5, 127.2 (2C), 125.9, 120.0, 108.9, 80.5, 68.6, 43.8, 39.6, 28.1 (3C), 21.1. HRMS (ESI) m/z: 430.2096 [M + Na]$^+$; calcd for $C_{24}H_{29}N_3NaO_3^+$, 430.2101.

***tert*-Butyl 2-(3-allyl-1-benzyl-5-bromo-2-oxoindolin-3-yl)hydrazinecarboxylate (5e).** Prepared according to TP-B starting from compound **4e**, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 1.8 Hz, 1H), 7.35–7.17 (m, 6H), 6.51 (d, J = 7.8 Hz, 1H), 5.91 (m, br, 1H), 5.50 (m, 1H), 5.10 (d, br, J = 16.6 Hz, 1H), 5.03 (d, br, J = 9.8 Hz, 1H), 4.91(d, br, J = 15.0 Hz, 1H), 4.83 (d, br, J = 15.0 Hz, 1H), 3.04–2.71 (m, br, 1H), 2.69 (dd, J = 13.7 and 6.8 Hz, 1H), 2.61 (dd, J = 13.7 and 8.8 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 156.2, 142.3, 135.1, 131.9, 130.2, 130.1, 128.8 (2C), 128.5, 127.7, 127.1 (2C), 120.5, 115.3, 110.6, 80.6, 69,1, 43.9, 39.6, 28.1 (3C). HRMS (ESI) m/z: 494.1055 [M + Na]$^+$; calcd for $C_{23}H_{26}BrN_3NaO_3^+$, 494.1050.

***tert*-Butyl 2-(3-allyl-1-benzyl-6-chloro-2-oxoindolin-3-yl)hydrazinecarboxylate (5f).** Prepared according to TP-B starting from compound **4f**, and purified by FC (hexane : ethyl acetate from 8 : 2 to 4 : 6). Dark yellow foam (25% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.20 (m, 6H), 7.01 (d, br, J = 7.8 Hz, 1H), 6.33 (m, 1H), 5.92 (m, br, 1H), 5.50 (m, 1H), 5.07 (d, br, J = 16.6 Hz, 1H), 5.01 (d, br, J = 9.8 Hz, 1H), 4.89 (d, J = 15.6 Hz, 1H), 4.82 (d, J = 15.6 Hz, 1H), 3.35–2.84 (m, br, 1H), 2.69 (dd, J = 13.7 and 6.8 Hz, 1H), 2.60 (dd, J = 13.7 and 8.8 Hz, 1H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 156.1, 144.4, 135.1, 134.9, 130.3, 128.9 (2C), 127.8, 127.1 (2C), 126.3, 126.2, 122.5, 120.5, 109.7, 80.6, 68.5, 43.9, 39.6, 28.1 (3C). HRMS (ESI) m/z: 450.1560 [M + Na]$^+$; calcd for $C_{23}H_{26}ClN_3NaO_3^+$, 450.1555.

***tert*-Butyl 2-(3-allyl-1-benzyl-2-oxo-7-(trifluoromethyl)indolin-3-yl)hydrazinecarboxylate (5g).** Prepared according to TP-B starting from compound **4g**, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, br, J = 6.9 Hz, 1H), 7.56 (d, br, J = 7.9 Hz, 1H), 7.33–7.07 (m, 6H), 5.91 (m, br, 1H), 5.48 (m, 1H), 5.20 (d, J = 16.6 Hz, 1H), 5.13 (d, J = 16.6 Hz, 1H), 5.06 (d, br, J = 17.6 Hz, 1H), 5.05 (d, br, J = 10.8 Hz, 1H), 3.34 (m, br, 1H), 2.74–2.56 (m, 2H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 156.0, 141.5, 136.3, 130.9, 129.8, 129.1, 128.3 (2C), 127.5 (q, J = 5.9 Hz), 126.9, 125.8 (2C), 123.3 (q, J = 271.3 Hz), 122.2, 120.8, 112.8 (q, J = 33.9 Hz), 80.7, 67.0, 45.7, 40.0, 28.1 (3C). HRMS (ESI) m/z: 484.1824 [M + Na]$^+$; calcd for $C_{24}H_{26}F_3N_3NaO_3^+$, 484.1818.

***tert*-Butyl 2-(3-allyl-1-benzyl-5-nitro-2-oxoindolin-3-yl)hydrazinecarboxylate (5h).** Prepared according to TP-B starting from compound **4h**, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (m, br, 1H), 8.13 (d, br, J = 8.7 Hz, 1H), 7.36–7.17 (m, 5H), 6.71 (d, J = 8.7 Hz, 1H), 6.00 (m, 1H), 5.49 (m, 1H), 5.15–5.00 (m, 2H), 4.97 (d, J = 15.6 Hz, 1H), 4.91 (d, J = 15.6 Hz, 1H), 3.54–2.87 (m, br, 1H), 2.75 (dd, J = 13.0 and 5.8 Hz, 1H), 2.56 (dd, J = 13.0 and 7.8 Hz, 1H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 156.4, 148.9, 143.4, 134.5, 129.6, 129.1, 129.0 (2C), 127.2 (2C), 126.2, 121.2, 121.0, 120.0, 108.8, 81.3, 68.7, 44.2, 39.6, 28.0 (3C). HRMS (ESI) m/z: 461.1791 [M + Na]$^+$; calcd for $C_{23}H_{26}N_4NaO_5^+$, 461.1795.

***tert*-Butyl 2-(3-allyl-1-benzyl-5-methoxy-2-oxoindolin-3-yl)hydrazinecarboxylate (5i).** Prepared according to TP-B starting from compound **4i**, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (15% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.20 (m, 5H), 7.09 (d, br, J = 2.9 Hz, 1H), 6.69 (dd, J = 8.7 and 2.9 Hz, 1H), 6.52 (d, J = 8.7 Hz, 1H), 6.00 (m, br, 1H), 5.51 (m, 1H), 5.08 (d, br, J = 17.6 Hz, 1H), 5.00 (d, br, J = 11.7 Hz, 1H), 4.91 (d, J = 15.6 Hz, 1H), 4.82 (d, J = 15.6 Hz, 1H), 3.75 (s, 3H), 2.71 (dd, J = 12.7 and 5.8 Hz, 1H), 2.62 (dd, J = 12.7 and 7.8 Hz, 1H), 2.52 (m, br, 1H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 156.7 (2C), 137.1, 136.3, 131.3, 129.7, 129.4 (2C), 128.2, 127.9 (2C), 120.8, 114.8 (br), 112.8 (br), 110.2, 81.1, 69.6, 56.5, 44.5, 40.3, 28.8 (3C). HRMS (ESI) m/z: 446.2056 [M + Na]$^+$; calcd for $C_{24}H_{29}N_3NaO_4^+$, 446.2050.

(3*S,5′*S**)-*tert*-Butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-benzyl-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6a) and (3*S**,5′*R**)-*tert*-butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-benzyl-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6a′).** Prepared according to TP-C starting from compound **5a** and *p*-Br-biphenyl, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (98% yield, separated diastereoisomers, 1 : 1 dr). Diastereoisomer **6a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.57 (m, 4H), 7.48 (t, br, J = 7.7 Hz, 2H), 7.44–7.22 (m, 9H), 7.16 (t, br, J = 7.8 Hz, 1H), 6.93 (t, br, J = 7.8 Hz, 1H), 6.85 (m, br, 1H), 6.65 (d, br, J = 7.8 Hz, 1H),

5.07–4.71 (m, br, 3H), 3.23 (dd, J = 13.2 and 3.8 Hz, 1H), 3.15 (dd, J = 13.2 and 7.0 Hz, 1H), 2.60 (dd, J = 12.8 and 8.2 Hz, 1H), 2.25 (dd, J = 12.8 and 7.9 Hz, 1H), 1.56 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 156.7 (br), 144.4, 141.5, 140.4, 137.5, 136.3, 131.1 (2C), 130.6, 129.5 (2C), 129.4 (2C), 128.3, 128.0 (3C), 127.9 (2C), 127.7 (2C), 126.2, 123.4, 123.2, 110.0, 81.4, 67.3, 61.0, 44.0 (2C), 41.1, 29.1 (3C). HRMS (ESI) m/z: 568.2566 $[M + Na]^+$; calcd for $C_{35}H_{35}N_3NaO_5^+$, 568.2571. Diastereoisomer **6a′**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.53 (m, 4H), 7.45 (t, br, J = 7.7 Hz, 2H), 7.41–7.24 (m, 9H), 7.17 (t, br, J = 7.8 Hz, 1H), 7.05 (d, br, J = 7.8 Hz, 1H), 7.00 (t, br, J = 7.8 Hz, 1H), 6.74 (d, br, J = 7.8 Hz, 1H), 5.01 (d, J = 15.6 Hz, 1H), 4.82 (d, J = 15.6 Hz, 1H), 4.75 (m, br, 1H), 3.46 (dd, J = 13.2 and 4.4 Hz, 1H), 2.96 (dd, J = 13.2 and 9.0 Hz, 1H), 2.44 (dd, J = 12.3 and 8.5 Hz, 1H), 2.35 (dd, J = 12.3 and 7.3 Hz, 1H), 1.54 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 156.4 (br), 142.5, 141.6, 140.3, 137.7, 135.8, 132.3, 130.5 (2C), 129.6 (2C), 129.4 (2C), 128.5, 128.0 (4C), 127.9 (2C), 127.7 (2C), 124.0, 123.4, 110.4, 81.8, 68.7, 61.8, 45.4, 44.9, 41.6, 29.1 (3C). HRMS (ESI) m/z: 568.2576 $[M + Na]^+$; calcd for $C_{35}H_{35}N_3NaO_5^+$, 568.2571.

(3*S,5′*S**)-*tert*-Butyl 1-benzyl-5′-(4-methoxybenzyl)-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6b) and (3*S**,5′*R**)-*tert*-butyl 1-benzyl-5′-(4-methoxybenzyl)-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6b′).** Prepared according to TP-C starting from compound **5a** and *p*-Br-anisole, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (98% yield, separated diastereoisomers, 1 : 1 dr). Diastereoisomer **6b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.18 (m, 7H), 7.14 (d, br, J = 7.8 Hz, 1H), 6.92 (t, br, J = 7.8 Hz, 1H), 6.89 (d, br, J = 8.8 Hz, 2H), 6.74 (d, br, J = 7.8 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H), 5.00–4.97 (m, br, 3H), 4.11 (m, br, 1H), 3.81 (s, 3H), 3.11–2.97 (m, 2H), 2.51 (dd, J = 12.7 and 7.8 Hz, 1H), 2.13 (dd, J = 12.7 and 7.8 Hz, 1H), 1.53 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 159.2, 157.4 (br), 144.3, 136.3 (2C), 131.6 (2C), 130.7, 130.3, 129.5 (3C), 128.3, 127.9 (2C), 123.5, 114.7 (2C), 110.0, 81.7, 68.3, 61.1, 56.0, 44.1 (2C), 40.4, 29.1 (3C). HRMS (ESI) m/z: 522.2368 $[M + Na]^+$; calcd for $C_{30}H_{33}N_3NaO_4^+$, 522.2363. Diastereoisomer **6b′**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.09 (m, 9H), 7.03–6.92 (m, 2H), 6.84 (d, br, J = 7.7 Hz, 1H), 6.70 (d, br, J = 7.8 Hz, 1H), 4.97 (d, J = 15.6 Hz, 1H), 4.77 (d, J = 15.6 Hz, 1H), 4.71–4.57 (m, br, 2H), 3.77 (s, 3H), 3.30 (dd, J = 13.7 and 4.9 Hz, 1H), 2.84 (dd, J = 13.7 and 9.8 Hz, 1H), 2.35 (dd, J = 12.7 and 8.8 Hz, 1H), 2.24 (dd, J = 12.7 and 7.8 Hz, 1H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 159.1, 152.9 (br), 142.5, 135.8, 132.3, 131.0 (2C), 130.5, 129.5 (3C), 128.4, 127.9 (2C), 124.0, 123.4, 114.7 (2C), 110.3, 81.6, 68.6, 61.8, 55.9, 45.1, 44.9, 40.8, 29.1 (3C). HRMS (ESI) m/z: 522.2367 $[M + Na]^+$; calcd for $C_{30}H_{33}N_3NaO_4^+$, 522.2363.

(3*S,5′*S**)-*tert*-Butyl 1-benzyl-5′-(4-nitrobenzyl)-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6c) and (3*S**,5′*R**)-*tert*-butyl 1-benzyl-5′-(4-nitrobenzyl)-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6c′).** Prepared according to TP-C starting from compound **5a** and *p*-Br-nitrobenzene, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (53% yield, separated diastereoisomers, 1.5 : 1 dr).

Diastereoisomer **6c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, br, J = 8.8 Hz, 2H), 7.47 (d, br, J = 8.8 Hz, 2H), 7.33–7.09 (m, 7H), 7.06–6.94 (m, 2H), 6.66 (d, br, J = 7.7 Hz, 1H), 4.93 (m, br, 1H), 4.84 (d, br, J = 15.5 Hz, 1H), 4.76 (d, br, J = 15.5 Hz, 1H), 3.35 (dd, J = 13.2 and 5.8 Hz, 1H), 3.09 (dd, J = 13.2 and 7.8 Hz, 1H), 2.54 (dd, J = 12.7 and 7.8 Hz, 1H), 2.09 (dd, J = 13.2 and 8.8 Hz, 1H), 1.47 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 156.9 (br), 146.9, 145.9, 143.8, 135.6, 130.5 (2C), 130.2, 130.0, 128.8 (2C), 127.7, 127.2 (2C), 123.7 (2C), 122.8, 122.4, 109.6, 81.1, 66.4, 60.2, 43.4, 42.3, 41.2, 28.3 (3C). HRMS (ESI) m/z: 537.2113 $[M + Na]^+$; calcd for $C_{29}H_{30}N_4NaO_5^+$, 537.2108. Diastereoisomer **6c′**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, br, J = 8.8 Hz, 2H), 7.48 (d, br, J = 8.8 Hz, 2H), 7.38–7.15 (m, 7H), 7.04–6.97 (m, 2H), 6.76 (d, br, J = 7.7 Hz, 1H), 5.01 (d, J = 15.5 Hz, 1H), 4.80 (d, J = 15.5 Hz, 1H), 4.74 (m, br, 1H), 3.47 (dd, J = 13.2 and 5.0 Hz, 1H), 3.06 (dd, J = 13.2 and 8.5 Hz, 1H), 2.41–2.30 (m, 2H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 153.1 (br), 147.6, 146.3, 142.5, 135.7, 132.1, 130.9 (2C), 129.8, 129.6 (2C), 128.6, 128.0 (2C), 124.5 (2C), 124.1, 123.4, 110.5, 82.1, 68.8, 61.3, 45.2, 45.0, 41.6, 29.0 (3C). HRMS (ESI) m/z: 537.2102 $[M + Na]^+$; calcd for $C_{29}H_{30}N_4NaO_5^+$, 537.2108.

(3*S,5′*S**)-*tert*-Butyl 5′-(4-benzoylbenzyl)-1-benzyl-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6d) and (3*S**,5′*R**)-*tert*-butyl 5′-(4-benzoylbenzyl)-1-benzyl-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6d′).** Prepared according to TP-C starting from compound **5a** and *p*-Br-benzophenone, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (92% yield, separated diastereoisomers, 1 : 1 dr). Diastereoisomer **6d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.62–7.18 (m, 12H), 7.07 (td, J = 7.8 and 1.9 Hz, 1H), 6.95 (t, br, J = 7.8 Hz, 1H), 6.88 (m, br, 1H), 6.65 (d, J = 7.8 Hz, 1H), 4.99 (m, br, 1H), 4.84 (d, br, J = 15.6 Hz, 1H), 4.76 (d, br, J = 15.6 Hz, 1H), 4.49–4.15 (m, br, 1H), 3.30 (dd, J = 13.7 and 4.9 Hz, 1H), 3.11 (dd, J = 13.7 and 7.8 Hz, 1H), 2.56 (dd, J = 13.7 and 8.8 Hz, 1H), 2.15 (dd, J = 13.7 and 8.8 Hz, 1H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 177.1, 157.4 (br), 144.4, 144.2, 143.6, 138.4, 136.8, 136.3, 133.1, 131.1 (2C), 130.7, 130.6 (2C), 130.4 (2C), 129.5 (2C), 129.0 (2C), 128.3, 127.9 (2C), 123.4, 123.1, 110.1, 81.6, 67.2, 60.9, 44.1 (2C), 41.8, 29.1 (3C). HRMS (ESI) m/z: 596.2526 $[M + Na]^+$; calcd for $C_{36}H_{35}N_3NaO_4^+$, 596.2520. Diastereoisomer **6d′**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.20 (m, 15H), 7.15 (td, J = 7.8 and 1.9 Hz, 1H), 6.97 (t, br, J = 7.8 Hz, 1H), 6.73 (d, J = 7.7 Hz, 1H), 4.99 (d, J = 15.6 Hz, 1H), 4.78 (d, J = 15.6 Hz, 1H), 4.78–4.66 (m, br, 2H), 3.46 (dd, J = 12.7 and 4.9 Hz, 1H), 2.99 (dd, J = 12.7 and 8.5 Hz, 1H), 2.36 (dd, J = 12.7 and 7.8 Hz, 1H), 2.30 (dd, J = 12.7 and 7.8 Hz, 1H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 174.8, 156.7 (br), 143.5, 142.5, 138.4, 136.8, 135.8, 133.0, 132.2, 131.2 (2C), 130.6 (2C), 130.0 (2C), 129.7, 129.6 (2C), 128.9 (2C), 128.5, 127.9 (2C), 124.0, 123.4, 110.4, 81.9, 68.7, 61.5, 45.3, 45.0, 41.9, 29.1 (3C). HRMS (ESI) m/z: 596.2527 $[M + Na]^+$; calcd for $C_{36}H_{35}N_3NaO_4^+$, 596.2520.

(3*S,5′*S**)-*tert*-Butyl 5′-(4-acetylbenzyl)-1-benzyl-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6e) and (3*S**,5′*R**)-*tert*-butyl 5′-(4-acetylbenzyl)-1-benzyl-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6e′).** Prepared according to TP-C starting from compound **5a** and *p*-Br-acetophenone, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (98% yield, separated diastereoisomers, 1 : 1 dr). Diastereoisomer **6e**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.33–7.21 (m, 5H), 7.15 (t, J = 7.8 Hz, 1H), 6.94 (t, J =

7.8 Hz, 1H), 6.85 (d, br, J = 7.8 Hz, 1H), 6.64 (d, J = 7.8 Hz, 1H), 4.95 (m, br, 1H), 4.83 (d, br, J = 15.6 Hz, 1H), 4.75 (d, br, J = 15.6 Hz, 1H), 4.27 (m, br, 1H), 3.26 (dd, J = 13.7 and 4.9 Hz, 1H), 3.07 (dd, J = 13.7 and 7.8 Hz, 1H), 2.60 (s, 3H), 2.52 (dd, J = 12.7 and 7.8 Hz, 1H), 2.10 (dd, J = 12.7 and 8.8 Hz, 1H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 176.3, 156.8 (br), 143.6 (2C), 135.7, 135.6, 130.1 (3C), 128.8 (2C), 128.6 (2C), 127.6, 127.2 (2C), 125.2, 122.8, 122.5, 109.4, 80.9, 66.4, 60.2, 43.4, 41.9 (br), 41.0, 28.4 (3C), 26.7. HRMS (ESI) m/z: 534.2355 $[M + Na]^+$; calcd for $C_{31}H_{33}N_3NaO_4^+$, 534.2363. Diastereoisomer **6e′**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.8 Hz, 2H), 7.44–7.20 (m, 7H), 7.14 (t, J = 7.8 Hz, 1H), 7.01–6.92 (m, 2H), 6.71 (d, J = 7.8 Hz, 1H), 4.97 (d, J = 15.6 Hz, 1H), 4.76 (d, J = 15.6 Hz, 1H), 4.70 (m, br, 1H), 4.65 (s, br, 1H), 3.42 (dd, J = 13.7 and 4.9 Hz, 1H), 2.95 (dd, J = 13.7 and 8.8 Hz, 1H), 2.57 (s, 3H), 2.32 (dd, J = 12.7 and 8.8 Hz, 1H), 2.26 (dd, J = 12.7 and 7.8 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 174.1, 156.2 (br), 143.5, 141.8, 135.7, 135.1, 131.4, 129.6 (2C), 129.0, 128.9, 128.7 (2C), 127.9 (2C), 127.3 (2C), 123.4, 122.7, 109.8, 81.2, 68.0, 60.7, 44.5, 44.2, 41.0, 28.3 (3C), 26.6. HRMS (ESI) m/z: 5342.358 $[M + Na]^+$; calcd for $C_{31}H_{33}N_3NaO_4^+$, 534.2363.

(3*S,5′*S**)-*tert*-Butyl 1-benzyl-5′-(2-methylbenzyl)-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6f) and (3*S**,5′*R**)-*tert*-butyl 1-benzyl-5′-(2-methylbenzyl)-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6f′).** Prepared according to TP-C starting from compound **5a** and o-Br-toluene, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (98% yield, separated diastereoisomers, 1 : 1.6 dr). Diastereoisomer **6f**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.10 (m, 10H), 7.01–6.89 (m, 2H), 6.63 (d, J = 7.8 Hz, 1H), 4.95 (m, 1H), 4.88 (d, br, J = 15.6 Hz, 1H), 4.73 (d, br, J = 15.6 Hz, 1H), 4.41 (m, br, 1H), 3.28 (dd, J = 13.7 and 4.9 Hz, 1H), 2.98 (dd, J = 13.7 and 7.8 Hz, 1H), 2.50 (dd, J = 12.7 and 7.8 Hz, 1H), 2.42 (s, 3H), 2.13 (dd, J = 12.7 and 7.8 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 156.7 (br), 143.7, 137.0, 136.3, 135.7, 130.5 (2C), 129.9, 128.8 (2C), 127.6, 127.2 (2C), 126.8, 126.0, 125.7, 122.7, 122.6, 109.4, 80.7, 66.5, 59.3, 43.3, 42.0, 38.5, 28.4 (3C), 19.9. HRMS (ESI) m/z: 506.2411 $[M + Na]^+$; calcd for $C_{30}H_{33}N_3NaO_3^+$, 506.2414. Diastereoisomer **6f′**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.08 (m, 10H), 7.03–6.92 (m, 2H), 6.70 (d, J = 7.8 Hz, 1H), 4.98 (d, J = 15.6 Hz, 1H), 4.84–4.67 (m, 3H), 3.41 (dd, J = 12.7 and 4.9 Hz, 1H), 2.87 (dd, J = 12.7 and 8.8 Hz, 1H), 2.45 (s, 3H), 2.37 (dd, J = 12.7 and 7.8 Hz, 1H), 2.25 (dd, J = 12.7 and 7.8 Hz, 1H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 156.1 (br), 141.8, 136.6, 136.2, 135.1, 131.7, 130.4 (2C), 128.9 (3C), 127.8, 127.3 (2C), 126.8, 126.1, 123.3, 122.7, 109.7, 81.1, 68.2, 59.6, 44.7, 44.2, 38.8, 28.4 (3C), 19.8. HRMS (ESI) m/z: 506.2419 $[M + Na]^+$; calcd for $C_{30}H_{33}N_3NaO_3^+$, 506.2414.

(3*S,5′*S**)-*tert*-Butyl 1-benzyl-2-oxo-5′-(2,4,6-trimethylbenzyl)spiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6g) and (3*S**,5′*R**)-*tert*-butyl 1-benzyl-2-oxo-5′-(2,4,6-trimethylbenzyl)spiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6g′).** Prepared according to TP-C starting from compound **5a** and 2-Br-1,3,5-trimethylbenzene, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (70% yield, separated diastereoisomers, 1 : 1 dr). Diastereoisomer **6g**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.20 (m, 6H), 7.09–6.98 (m, 2H), 6.84 (s, 2H), 6.65 (d, J = 7.8 Hz, 1H), 5.01–4.86 (m, 3H), 4.69 (d, J = 15.6 Hz, 1H), 3.28 (dd, J = 13.7 and 7.8 Hz, 1H), 3.04 (dd, J = 13.7 and 6.8 Hz, 1H), 3.28 (dd, J = 12.7 and 7.8 Hz, 1H), 2.40 (s, 6H), 2.38–2.29 (m, 1H), 2.24 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 157.0, 144.4, 137.5, 136.4, 136.2, 133.0, 130.6, 129.8 (3C), 129.6 (2C), 129.1, 128.3, 127.9, 126.6, 123.5, 123.4, 110.1, 81.2, 67.2, 59.4, 44.4, 44.1, 35.7, 28.8 (3C), 21.5, 21.4 (2C). HRMS (ESI) m/z: 534.2721 $[M + Na]^+$; calcd for $C_{32}H_{37}N_3NaO_3^+$, 534.2727. Diastereoisomer **6g′**. 1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.21 (m, 5H), 7.14 (td, J = 7.8 and 2.9 Hz, 1H), 7.02–6.92 (m, 2H), 6.83 (s, 2H), 6.70 (d, J = 7.8 Hz, 1H), 4.96 (d, J = 15.6 Hz, 1H), 4.93–4.76 (m, 3H), 3.29 (dd, J = 13.7 and 6.8 Hz, 1H), 2.96 (dd, J = 13.7 and 6.8 Hz, 1H), 2.41 (s, 6H), 2.38–2.29 (m, 2H), 2.23 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 156.5 (br), 142.5, 137.5 (2C), 136.3, 135.8, 132.8, 132.6, 129.8 (3C), 129.6 (3C), 128.5, 128.0, 124.0, 123.4, 110.4, 81.5, 69.0, 59.7, 45.3, 44.9, 35.4, 28.8 (3C), 21.5, 21.4 (2C). HRMS (ESI) m/z: 534.2719 $[M + Na]^+$; calcd for $C_{32}H_{37}N_3NaO_3^+$, 534.2727.

(3*S,5′*S**)-*tert*-Butyl 1-benzyl-5′-(4-methylbenzyl)-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6h) and (3*S**,5′*R**)-*tert*-butyl 1-benzyl-5′-(4-methylbenzyl)-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6h′).** Prepared according to TP-C starting from compound **5a** and *p*-I-toluene, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (63% yield, separated diastereoisomers, 1 : 1 dr). Diastereoisomer **6h**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.10 (m, 10H), 6.92 (t, J = 7.8 Hz, 1H), 6.77 (m, br, 1H), 6.61 (d, J = 7.8 Hz, 1H), 4.98–4.67 (m, br, 4H), 3.12 (dd, J = 13.6 and 3.9 Hz, 1H), 3.03 (dd, J = 13.6 and 6.8 Hz, 1H), 2.51 (dd, J = 12.7 and 7.8 Hz, 1H), 2.34 (s, 3H), 2.17 (dd, J = 12.7 and 7.8 Hz, 1H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 157.3, 144.3, 136.9, 136.3, 135.2, 130.6, 130.5 (2C), 130.0 (2C), 129.5 (2C), 128.3, 127.9 (2C), 122.3 (2C), 121.3, 110.0, 81.5, 67.3, 61.0, 44.5, 44.0, 41.0, 29.1 (3C), 21.7. HRMS (ESI) m/z: 506.2410 $[M + Na]^+$; calcd for $C_{30}H_{33}N_3NaO_3^+$, 506.2414. Diastereoisomer **6h′**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.10 (m, 10H), 7.05–6.95 (m, 2H), 6.73 (d, J = 7.8 Hz, 1H), 5.00 (d, J = 15.6 Hz, 1H), 4.81 (d, J = 15.6 Hz, 1H), 4.73–4.62 (m, br, 2H), 3.37 (dd, J = 12.7 and 3.9 Hz, 1H), 2.88 (dd, J = 12.7 and 8.8 Hz, 1H), 2.39 (dd, J = 12.7 and 8.8 Hz, 1H), 2.34 (s, 3H), 2.28 (dd, J = 12.7 and 7.8 Hz, 1H), 1.55 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 156.5, 142.5, 136.9, 135.8, 135.3, 132.3, 130.0 (4C), 129.5 (3C), 128.5, 127.9 (2C), 124.0, 123.4, 110.3, 81.7, 68.6, 61.8, 45.2, 44.9, 41.3, 29.1 (3C), 21.7. HRMS (ESI) m/z: 506.2409 $[M + Na]^+$; calcd for $C_{30}H_{33}N_3NaO_3^+$, 506.2414.

(3*S,5′*S**)-*tert*-Butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-methyl-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6i) and (3*S**,5′*R**)-*tert*-butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-methyl-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6i′).** Prepared according to TP-C starting from compound **5b** and *p*-Br-biphenyl, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (53% yield, separated diastereoisomers, 1.5 : 1 dr). Diastereoisomer **6i**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62–7.52 (m, 4H), 7.49–7.22 (m, 7H), 6.96 (t, br, J = 7.8 Hz, 1H), 6.88 (m, br, 1H), 6.74 (d, br, J = 7.8 Hz, 1H), 4.88 (m, br, 1H), 3.24–3.12 (m, 2H), 3.10 (s, 3H), 2.49 (dd, J = 12.7 and 6.8 Hz, 1H), 2.17 (dd, J = 12.7 and 7.8 Hz, 1H), 1.53 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 156.7 (br), 144.6, 140.9, 139.7, 136.9, 130.3 (2C), 130.0, 128.8 (2C), 127.3

(3C), 127.0 (2C), 125.6, 122.7, 122.4, 108.3, 80.8, 66.4, 60.2, 41.9, 40.5, 28.5 (3C), 26.0. HRMS (ESI) *m*/*z*: 492.2262 [M + Na]$^+$; calcd for $C_{29}H_{31}N_3NaO_3^+$, 492.2258. Diastereoisomer **6i′**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.47 (m, 4H), 7.46–7.28 (m, 5H), 7.09 (t, br, J = 7.8 Hz, 1H), 6.99 (d, br, J = 6.8 Hz, 2H), 6.83 (d, br, J = 7.8 Hz, 2H), 4.70 (m, br, 1H), 3.40 (dd, J = 12.7 and 4.9 Hz, 1H), 3.17 (s, 3H), 2.89 (dd, J = 12.7 and 9.8 Hz, 1H), 2.33 (dd, J = 12.7 and 8.8 Hz, 1H), 2.24 (dd, J = 12.7 and 7.8 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 153.8 (br), 145.8, 140.9, 139.6, 137.0, 131.5, 130.7, 129.8 (2C), 128.8 (2C), 127.3 (2C), 127.2, 127.0 (2C), 123.3, 123.0, 108.7, 81.0, 68.1, 61.1, 44.4, 40.9, 28.4 (3C), 26.1. HRMS (ESI) *m*/*z*: 492.2253 [M + Na]$^+$; calcd for $C_{29}H_{31}N_3NaO_3^+$, 492.2258.

(3*S,5′*S**)-*tert*-Butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-((*E*)-3-(3,4-dichlorophenyl)allyl)-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6j) and (3*S**,5′*R**)-*tert*-butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-((*E*)-3-(3,4-dichlorophenyl)allyl)-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6j′).** Prepared according to TP-C starting from compound **5c** and *p*-Br-biphenyl, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (69% yield, separated diastereoisomers, 1 : 1 dr). Diastereoisomer **6j**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62–7.54 (m, 4H), 7.48–7.28 (m, 8H), 7.23 (t, br, J = 7.8 Hz, 1H), 7.12 (dd, J = 8.7 and 1.9 Hz, 1H), 6.95 (t, br, J = 7.8 Hz, 1H), 6.84–6.83 (m, 2H), 6.44 (d, br, J = 15.6 Hz, 1H), 6.14 (dt, J = 15.6 and 4.9 Hz, 1H), 4.93 (m, br, 1H), 4.45 (dd, br, J = 16.6 and 4.9 Hz, 1H), 4.31 (dd, br, J = 16.6 and 4.9 Hz, 1H), 3.19 (dd, J = 13.7 and 3.9 Hz, 1H), 3.10 (dd, J = 13.7 and 6.8 Hz, 1H), 2.54 (dd, J = 12.7 and 7.8 Hz, 1H), 2.17 (dd, J = 12.7 and 7.8 Hz, 1H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 154.4 (br), 143.6, 140.9, 139.8, 136.9, 136.3, 132.7, 131.6, 130.5 (2C), 130.4 (2C), 130.0, 128.9 (2C), 128.2, 127.3 (4C), 127.0, 125.7, 125.6, 125.0, 122.8, 122.6, 109.0, 80.8, 66.4, 60.3, 41.4 (2C), 40.5, 28.5 (3C). HRMS (ESI) *m*/*z*: 662.1956 [M + Na]$^+$; calcd for $C_{37}H_{35}Cl_2N_3NaO_3^+$, 662.1948. Diastereoisomer **6j′**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.20 (m, 13H), 7.15 (d, br, J = 8.7 Hz, 1H), 7.06–6.97 (m, 2H), 6.85 (d, J = 7.8 Hz, 1H), 6.48 (d, br, J = 15.6 Hz, 1H), 6.15 (dt, J = 15.6 and 5.9 Hz, 1H), 4.71 (m, br, 1H), 4.57–4.37 (m, 2H), 3.42 (dd, J = 12.7 and 3.9 Hz, 1H), 2.90 (dd, J = 12.7 and 8.8 Hz, 1H), 2.43–2.24 (m, 2H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 151.0 (br), 141.7, 140.9, 139.6, 136.9, 136.1, 132.8, 131.7, 131.6, 131.0, 130.5, 129.8 (2C), 129.1, 128.8 (2C), 128.3, 127.3 (2C), 127.2, 127.0 (2C), 125.6, 124.5, 123.5, 122.9, 109.3, 81.1, 68.0, 61.2, 44.6, 42.2, 40.9, 28.4 (3C). HRMS (ESI) *m*/*z*: 662.1954 [M + Na]$^+$; calcd for $C_{37}H_{35}Cl_2N_3NaO_3^+$, 662.1948.

(3*S,5′*S**)-*tert*-Butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-benzyl-5-methyl-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6k) and (3*S**,5′*R**)-*tert*-butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-benzyl-5-methyl-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6k′).** Prepared according to TP-C starting from compound **5d** and *p*-Br-biphenyl, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (50% yield, separated diastereoisomers, 1 : 1 dr). Diastereoisomer **6k**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, br, J = 7.8 Hz, 4H), 7.49–7.20 (m, 12H), 6.90 (d, br, J = 7.8 Hz, 1H), 6.49 (d, J = 7.8 Hz, 1H), 5.02 (m, br, 1H), 4.99–4.71 (m, br, 2H), 3.19 (dd, J = 12.7 and 3.9 Hz, 1H), 3.11 (dd, J = 12.7 and 6.8 Hz, 1H), 2.56 (dd, J = 12.7 and 7.8 Hz, 1H), 2.19 (dd, J = 12.7 and 7.8 Hz, 1H), 2.14 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 158.5, 141.2, 140.8, 139.8, 137.0, 135.8, 132.3, 130.5 (2C), 130.1, 128.8 (2C), 128.7 (2C), 127.5, 127.3 (5C), 127.2, 127.0, 125.7, 123.3, 109.1, 80.7, 66.7, 60.3, 43.4 (2C), 40.6, 28.4 (3C), 20.9. HRMS (ESI) *m*/*z*: 582.2723 [M + Na]$^+$; calcd for $C_{36}H_{37}N_3NaO_3^+$, 582.2727. Diastereoisomer **6k′**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.54 (m, 4H), 7.45 (t, br, J = 7.8 Hz, 2H), 7.42–7.23 (m, 9H), 6.97 (d, br, J = 7.8 Hz, 1H), 6.85 (s, br, 1H), 6.62 (d, J = 7.8 Hz, 1H), 4,98 (d, J = 15.8 Hz, 1H), 4,80 (d, J = 15.8 Hz, 1H), 4.75 (m, br, 1H), 3.44 (dd, J = 12.7 and 4.9 Hz, 1H), 2.96 (dd, J = 12.7 and 8.8 Hz, 1H), 2.43 (dd, J = 12.7 and 8.5 Hz, 1H), 2.35 (dd, J = 12.7 and 7.6 Hz, 1H), 2.26 (s, 3H), 1.55 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 158.0 (br), 142.4, 139.6, 139.4, 137.0, 135.3, 132.9, 131.7, 129.9 (2C), 129.1, 128.8 (2C), 128.7, 127.8, 127.3 (4C), 127.3, 127.2, 127.0 (2C), 123.6, 109.4, 81.0, 68.7, 61.2, 44.8, 44.2, 41.0, 28.4 (3C), 21.0. HRMS (ESI) *m*/*z*: 582.2720 [M + Na]$^+$; calcd for $C_{36}H_{37}N_3NaO_3^+$, 582.2727.

(3*S)-*tert*-Butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-benzyl-5-bromo-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6l and 6l′).** Prepared according to TP-C starting from compound **5e** and *p*-Br-biphenyl, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (34% yield, unseparable diastereoisomers, 1 : 1 dr). ^{1}H NMR (400 MHz, $CDCl_3$, 7 : 3 mixture of diastereoisomers) δ 7.67–7.20 (m, 16H), 7.13 (d, J = 2.1 Hz, 0.7H), 6.85 (m, br, 0.3H), 6.61 (d, J = 8.4 Hz, 0.7H), 6.50 (d, J = 8.4 Hz, 0.3H), 5.07–4.93 (m, br, 1.3H), 4.85–4.64 (m, br, 1.7H), 3.21 (dd, J = 13.2 and 5.0 Hz, 0.7H), 3.29 (dd, J = 13.1 and 4.4 Hz, 0.3H), 3.14 (dd, J = 13.1 and 6.7 Hz, 0.3H), 2.97 (dd, J = 13.2 and 8.8 Hz, 0.7H), 2.61 (dd, J = 13.2 and 8.2 Hz, 0.3H), 2.42 (dd, J = 12.6 and 8.2 Hz, 0.7H), 2.37 (dd, J = 12.6 and 7.6 Hz, 0.7H), 2.21 (dd, J = 13.2 and 7.6 Hz, 0.3H), 1.56 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 7 : 3 mixture of diastereoisomers) δ 175.7 and 173.7 (1C), 159.0 (br), 146.1 and 142.2 (1C), 140.9 and 140.2 (1C), 139.7 and 138.7 (1C), 137.0 and 136.8 (1C), 136.0 and 135.1 (1C), 134.6 and 134.2 (1C), 133.7 and 120.7 (1C), 132.7–126.0 (16C), 112.2 and 110.8 (1C), 81.5, 68.3 and 68.1 (1C), 61.1 and 60.1 (1C), 44.4 and 43.5 (1C), 43.9 and 41.3 (1C), 43.5 and 41.0 (1C), 28.4 and 28.1 (3C). HRMS (ESI) *m*/*z*: 646.1676 [M + Na]$^+$; calcd for $C_{35}H_{34}BrN_3NaO_3^+$, 646.1676.

(3*S,5′*S**)-*tert*-Butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-benzyl-6-chloro-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6m) and (3*S**,5′*R**)-*tert*-butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-benzyl-6-chloro-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6m′).** Prepared according to TP-C starting from compound **5f** and *p*-Br-biphenyl, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (72% yield, separated diastereoisomers, 1.5 : 1 dr).

Diastereoisomer **6m**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, br, J = 7.9 and 1.5 Hz, 4H), 7.48 (t, J = 7.8 Hz, 2H), 7.44–7.23 (m, 9H), 6.90 (dd, br, J = 7.8 and 1.2 Hz, 1H), 6.75–6.65 (m, br, 1H), 6.65 (d, br, J = 1.5 Hz, 1H), 5.02 (m, br, 1H), 4,91–4.68 (m, br, 2H), 3.21 (dd, J = 13.5 and 4.4 Hz, 1H), 3.16 (dd, J = 13.5 and 7.0 Hz, 1H), 2.59 (dd, J = 12.9 and 7.9 Hz, 1H), 2.20 (dd, J = 12.9 and 7.9 Hz, 1H), 1.57 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 157.3, 145.6, 141.4, 140.5, 137.4 (2C), 136.4, 135.8, 131.1 (2C), 129.6 (2C), 129.5 (2C), 128.5, 128.0 (3C), 127.8 (2C), 127.7 (2C), 124.3, 123.3, 110.6, 81.6, 66.9, 60.9, 44.2, 41.1 (2C), 29.1 (3C).

HRMS (ESI) *m*/*z*: 602.2189 [M + Na]$^+$; calcd for $C_{35}H_{34}ClN_3NaO_3^+$, 602.2181. Diastereoisomer **6m′**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (t, br, J = 7.9 Hz, 4H), 7.42 (t, br, J = 7.8 Hz, 2H), 7.37–7.20 (m, 9H), 6.95 (d, br, J = 7.8 Hz, 1H), 6.91 (t, br, J = 7.8 Hz, 1H), 6.70 (s, br, 1H), 4,94 (d, J = 15.6 Hz, 1H), 4,75 (d, J = 15.6 Hz, 1H), 4.69 (m, br, 1H), 3.39 (dd, J = 12.7 and 4.9 Hz, 1H), 2.91 (dd, J = 12.7 and 8.8 Hz, 1H), 2.39 (dd, J = 12.7 and 8.8 Hz, 1H), 2.29 (dd, J = 12.7 and 7.8 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 156.0, 143.2, 140.9, 139.7, 136.8 (2C), 134.8, 134.6, 129.9 (2C), 129.1 (2C), 128.8 (2C), 128.1, 127.4 (2C), 127.3 (3C), 127.1 (2C), 123.7, 123.2, 110.4, 81.2, 67.8, 61.1, 44.6, 44.4, 40.8, 28.4 (3C). HRMS (ESI) *m*/*z*: 602.2188 [M + Na]$^+$; calcd for $C_{35}H_{34}ClN_3NaO_3^+$, 602.2181.

(3*S,5′*S**)-*tert*-Butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-benzyl-2-oxo-7-(trifluoromethyl)spiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6n) and (3*S**,5′*R**)-*tert*-butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-benzyl-2-oxo-7-(trifluoromethyl)spiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (6n′).** Prepared according to TP-C starting from compound **5g** and *p*-Br-biphenyl, and purified by FC (hexane : ethyl acetate 7 : 3). Yellow foam (47% yield, separated diastereoisomers, 1.4 : 1 dr).

Diastereoisomer **6n**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66–7.54 (m, 4H), 7.54–7.33 (m, 6H), 7.31–6.93 (m, 7H), 6.83 (m, br, 1H), 5.15 (d, br, J = 16.6 Hz, 1H), 5.10–4.94 (m, 2H), 3.24–3.08 (m, 2H), 2.59 (dd, J = 12.7 and 7.8 Hz, 1H), 2.20 (dd, J = 12.7 and 7.8 Hz, 1H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 156.9 (br), 142.0, 140.8, 136.7, 136.2, 132.6, 130.6 (2C), 128.9 (2C), 128.4 (2C), 128.0 (q, J = 5.9 Hz), 127.4 (4C), 127.0 (2C), 126.9, 126.2, 125.7 (2C), 123.0 (q, J = 272.8 Hz), 122.3, 113.2 (q, J = 33.9 Hz), 81.0, 64.7, 60.1, 45.7, 45.0, 40.2, 28.3 (3C). HRMS (ESI) *m*/*z*: 636.2448 [M + Na]$^+$; calcd for $C_{36}H_{34}F_3N_3NaO_3^+$, 636.2444. Diastereoisomer **6n′**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.52 (m, 5H), 7.43 (t, br, J = 7.8 Hz, 2H), 7.37–7.02 (m, 11H), 5.22 (d, J = 16.6 Hz, 1H), 5.17 (d, J = 16.6 Hz, 1H), 4.77 (m, br, 1H), 3.40 (dd, J = 12.7 and 4.9 Hz, 1H), 2.94 (dd, J = 12.7 and 8.8 Hz, 1H), 2.45 (dd, J = 12.7 and 7.8 Hz, 1H), 2.37 (dd, J = 12.7 and 7.8 Hz, 1H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 150.5 (br), 140.9, 140.1, 139.7, 136.7, 135.6, 134.8, 129.9 (2C), 128.8 (2C), 128.5 (2C), 127.4–127.0 (7C), 126.5, 125.6 (2C), 123.2 (q, J = 272.8 Hz), 123.1, 113.6 (q, J = 33.9 Hz), 81.3, 66.3, 61.2, 46.0, 44.9, 40.7, 28.4 (3C). HRMS (ESI) *m*/*z*: 636.2449 [M + Na]$^+$; calcd for $C_{36}H_{34}F_3N_3NaO_3^+$, 636.2444.

Analytical data of other new compounds

(*E*)-3-(3-([1,1′-Biphenyl]-4-yl)allyl)-1-methylindolin-2-one (3b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.15 (m, 11H), 7.03 (t, J = 7.8 Hz, 1H), 6.82 (d, br, J = 7.8 Hz, 1H), 6.49 (d, J = 15.6 Hz, 1H), 6.22 (ddd, J = 15.6, 7.8 and 5.8 Hz, 1H), 3.57 (dd, J = 7.8 and 4.9 Hz, 1H), 3.14 (s, 3H), 3.03 (dt, br, J = 14.7 and 5.4 Hz, 1H), 2.68 (dt, J = 14.7 and 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 144.3, 140.7, 140.1, 137.8, 136.2, 128.8 (4C), 128.1, 127.2 (4C), 127.0 (2C), 126.1, 124.3, 122.4, 108.1, 45.6, 34.4, 26.2. HRMS (ESI) *m*/*z*: 362.1519 [M + Na]$^+$; calcd for $C_{24}H_{21}NNaO^+$, 362.1515.

(*E*)-*tert*-Butyl 2-(3-(3-([1,1′-biphenyl]-4-yl)allyl)-1-benzyl-2-oxo indolin-3-yl)hydrazinecarboxylate (7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.21 (m, 15H), 7.18 (t, br, J = 7.2 Hz, 1H), 7.05 (t, br, J = 7.5 Hz, 1H), 6.66 (d, J = 7.6 Hz, 1H), 6.46 (d, br, J = 16.0, 1H), 6.04 (m, br, 1H), 5.96 (m, br, 1H), 5.90 (ddd, J = 16.0, 8.9 and 6.5 Hz, 1H), 5.10 (d, br, J = 15.7 Hz, 1H), 4.70 (d, br, J = 15.7 Hz, 1H), 2.94 (dd, J = 12.6 and 5.8 Hz, 1H), 2.86 (dd, J = 12.6 and 8.5 Hz, 1H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 156.0, 144.2, 143.1, 141.9, 137.9, 136.8, 134.5, 129.2, 128.8 (2C), 128.7 (2C), 127.6–126.8 (9C), 125.2, 125.1, 122.8, 122.1, 109.3, 83.8, 68.5, 43.9, 38.9, 28.2 (3C). HRMS (ESI) *m*/*z*: 568.2177 [M + Na]$^+$; calcd for $C_{35}H_{35}N_3NaO_3^+$, 568.2571.

(*E*)-*tert*-Butyl 2-(1-benzyl-2-oxo-3-(prop-1-en-1-yl)indolin-3-yl) hydrazinecarboxylate (8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.8 Hz, 1H), 7.35–7.19 (m, 5H), 7.15 (t, J = 7.8 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H)), 6.65 (d, J = 7.8 Hz, 1H), 6.16–5.87 (m, br, 2H), 5.78 (dq, J = 15.6 and 5.9 Hz, 1H), 5.71 (d, J = 15.6 Hz, 1H), 4.91 (m, 2H), 1.69 (d, J = 5.9 Hz, 3H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 156.1, 143.2, 142.8, 135.7, 130.9, 129.1, 128.8 (2C), 127.6, 127.2 (2C), 127.0, 125.7, 122.7, 109.2, 80.5, 70.0, 43.8, 28.1 (3C), 18.1. HRMS (ESI) *m*/*z*: 416.1941 [M + Na]$^+$; calcd for $C_{23}H_{27}N_3NaO_3^+$, 416.1945.

3-Allyl-1-benzylindolin-2-one (9). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.21 (m, 6H), 7.15 (t, br, J = 7.8 Hz, 1H), 7.00 (t, br, J = 7.8 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 5.75 (m, 1H), 5.13 (d, br, J = 15.6 Hz, 1H), 5.05 (d, br, J = 10.7 Hz, 1H), 4.99 (d, J = 15.6 Hz, 1H), 4.82 (d, J = 15.6 Hz, 1H), 3.60 (m, 1H), 2.88 (m, 1H), 2.65 (dt, J = 14.6 and 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 143.5, 135.9, 133.9, 128.8 (2C), 128.6, 127.9, 127.6 (2C), 127.4, 124.2, 122.3, 118.2, 109.0, 45.2, 43.7, 35.0. HRMS (ESI) *m*/*z*: 286.1200 [M + Na]$^+$; calcd for $C_{18}H_{17}NNaO^+$, 286.1202.

Di-*tert*-butyl 1-(3-allyl-1-benzyl-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (10). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.19 (m, 6H), 7.13 (t, br, J = 7.8 Hz, 1H), 6.97 (t, br, J = 7.8 Hz, 1H), 6.59 (d, br, J = 7.8 Hz, 1H), 5.46 (m, 1H), 5.34 (m, br, 1H), 5.02 (d, br, J = 16.6 Hz, 1H), 4.93 (d, br, J = 10.0 Hz, 1H), 4.88(d, br, J = 15.6 Hz, 1H), 4.79 (d, br, J = 15.6 Hz, 1H), 2.86 (dd, br, J = 13.7 and 6.8 Hz, 1H), 2.75 (dd, br, J = 13.7 and 7.8 Hz, 1H), 1.39 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 153.3 (2C), 143.5, 135.8, 131.4, 129.2, 128.6 (2C), 127.4 (3C), 126.7, 125.5, 122.2, 119.8, 109.1, 83.3 (2C), 67.5, 43.8, 40.8, 27.9 (6C). HRMS (ESI) *m*/*z*: 516.2473 [M + Na]$^+$; calcd for $C_{28}H_{35}N_3NaO_5^+$, 516.2469.

(*E*)-Di-*tert*-butyl 1-(3-(3-([1,1′-biphenyl]-4-yl)allyl)-1-benzyl-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (11). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, br, J = 8.4 Hz, 2H), 7.51–6.96 (m, 16H), 6.59 (d, J = 7.8 Hz, 1H), 6.44 (d, J = 15.8 Hz, 1H), 5.87 (ddd, J = 15.8, 8.5 and 6.4 Hz, 1H), 5.10 (d, J = 16.1 Hz, 1H), 4.63 (d, J = 16.1 Hz, 1H), 3.10 (dd, J = 13.2 and 6.4 Hz, 1H), 3.01 (dd, J = 13.2 and 8.5 Hz, 1H), 1.46 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 154.0 (2C), 144.2, 141.5, 140.7, 136.9, 136.2, 134.9, 130.1, 129.4 (2C), 129.2 (2C), 127.9 (2C), 127.8 (4C), 127.6 (2C), 127.4 (2C), 126.1, 124.5, 123.7, 123.0, 109.9, 84.1 (2C), 68.5, 44.5, 40.9, 28.6 (6C). HRMS (ESI) *m*/*z*: 668.3097 [M + Na]$^+$; calcd for $C_{40}H_{43}N_3NaO_5^+$, 668.3095.

***tert*-Butyl 2-(1-benzyl-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)hydrazinecarboxylate (12).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.7 Hz, 1H), 7.37–7.24 (m, 5H), 7.18 (t, J = 7.8 Hz, 1H), 7.01 (t, J = 7.8 Hz, 1H), 6.66 (d, J = 7.7 Hz, 1H), 6.26 (dd, J = 17.5 and 10.8 Hz, 1H), 5.60 (m, br, 1H), 5.19 (d, J = 10.8 Hz, 1H),

5.14 (d, br, $J = 17.5$ Hz, 1H), 5.02–4.78 (m, 3H), 1.26 (s, br, 9H), 1.24 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 156.4, 144.9, 142.7, 136.5, 129.6, 129.4 (2C), 128.2, 128.1, 127.9 (2C), 127.3, 122.4, 115.7, 109.3, 80.9, 74.9, 44.6, 43.0, 28.7 (3C), 23.7, 21.4. HRMS (ESI) *m*/*z*: 444.2261 $[M + Na]^+$; calcd for $C_{25}H_{31}N_3NaO_3^+$, 444.2258.

(3*S,5′*R**)- and (3*S**,5′*S**)-*tert*-Butyl 5′-([1,1′-biphenyl]-4-ylmethyl)-1-benzyl-4′,4′-dimethyl-2-oxospiro[indoline-3,3′-pyrazolidine]-1′-carboxylate (13).** ^{1}H NMR (300 MHz, $CDCl_3$, *cis* : *trans* 7 : 3 diastereoisomeric mixture) δ 7.64–7.11 (m, 16H), 7.01 (t, br, $J = 7.8$ Hz, 0.3H), 6.98 (t, br, $J = 7.8$ Hz, 0.7H), 6.65 (d, $J = 7.8$ Hz, 0.7H), 6.61 (d, $J = 7.8$ Hz, 0.3H), 5.27–5.02 (m, 2H), 4.81 (m, 0.3H), 4.77 (dd, $J = 10.7$ and 3.9 Hz, 0.7H), 4.66 (d, br, $J = 15.6$ Hz, 0.3H), 4.46 (d, br, $J = 15.6$ Hz, 0.7H), 3.69 (dd, $J = 13.7$ and 3.9 Hz, 0.7H), 2.86 (dd, $J = 13.7$ and 10.7 Hz, 0.7H), 2.74–2.56 (m, 0.6H), 1.57 (s, 6.3H), 1.55 (s, 0.9H), 1.50 (s, 0.9H), 1.38 (s, 2.1H), 1.31 (s, 2.7H), 1.25 (s, 2.1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5 and 169.6 (1C), 157.8 and 156.0 (1C), 144.6 and 143.3 (1C), 140.8, 139.1, 137.7 and 136.7 (1C), 135.8 and 123.1 (2C), 129.8–125.2 (*x*C), 122.6 and 121.9 (1C), 109.3 and 109.0 (1C), 81.1 and 80.4 (1C), 73.2 and 69.4 (1C), 67.0, 49.3, 43.7 and 43.6 (1C), 36.4 and 34.1 (1C), 28.5 and 28.1 (3C), 25.9 and 20.4 (1C), 22.2 and 18.0 (1C). HRMS (ESI) *m*/*z*: 596.2888 $[M + Na]^+$; calcd for $C_{37}H_{39}N_3NaO_3^+$, 596.2884.

Conflicts of interest

The authors declare no competing financial interest.

References

1 L. M. Blair and J. Sperry, Natural Products Containing a Nitrogen–Nitrogen Bond, *J. Nat. Prod.*, 2013, **76**, 794–812.
2 M. S. Ali, F. Ahmad, V. U. Ahmad, I. Azhar and K. Usmanghani, Unusual Chemical Constituents of Lotus garcinia (Fabaceae), *Turk. J. Chem.*, 2001, **25**, 107–112.
3 D. Secci, A. Bolasco, P. Chimenti and S. Carradori, The State of the Art of Pyrazole Derivatives as Monoamine Oxidase Inhibitors and Antidepressant/Anticonvulsant Agents, *Curr. Med. Chem.*, 2011, **18**, 5114–5144.
4 B. Parashar, A. Jain, S. Bharadwaj and V. K. Sharma, Synthesis and pharmacological properties of some novel pyrazolidine and pyrazole derivatives, *Med. Chem. Res.*, 2012, **21**, 1692–1699.
5 E. Frank, Z. Mucsi, I. Zupko, B. Rethy, G. Falkay, G. Schneider and J. Wolfling, Efficient Approach to Androstene-Fused Arylpyrazolines as Potent Antiproliferative Agents. Experimental and Theoretical Studies of Substituent Effects on BF3-Catalyzed Intramolecular [3+2] Cycloadditions of Olefinic Phenylhydrazones, *J. Am. Chem. Soc.*, 2009, **131**, 3894–3904.
6 M. J. Kornet and R. J. Garrett, Synthesis of 1-phenyl-2-(phenylcarbamoyl)pyrazolidines as potential anticonvulsant agents, *J. Pharm. Sci.*, 1979, **68**, 377–378.
7 (*a*) J. H. Ahn, J. A. Kim, H. M. Kim, H. M. Kwon, S. C. Huh, S. D. Rhee, K. R. Kim, S. D. Yang, S. D. Park, J. M. Lee, S. S. Kim and H. G. Cheon, Synthesis and evaluation of pyrazolidine derivatives as dipeptidyl peptidase IV (DP-IV) inhibitors, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1337–1340; (*b*) H. G. Cheon, S. S. Kim, K. R. Kim, S. D. Rhee, S. D. Yang, J. H. Ahn, S. D. Park, J. M. Lee, W. H. Jung, H. S. Lee and H. Y. Kim, Inhibition of dipeptidyl peptidase IV by novel inhibitors with pyrazolidine scaffold, *Biochem. Pharmacol.*, 2005, **70**, 22–29.
8 G. X. Yang, L. L. Chang, Q. Truong, G. A. Doherty, P. A. Magriotis, S. E. de Laszlo, B. Li, M. MacCoss, U. Kidambi, L. A. Egger, E. McCauley, G. V. Riper, R. A. Mumford, J. A. Schmidt and W. K. Hagmann, *N*-Tetrahydrofuroyl-(L)-phenylalanine derivatives as potent VLA-4 antagonists, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1497–1500.
9 S. H. Ahmed, H. Ahmed, S. H. Ali, S. Fatima, S. Hyder and A. Pasha, Synthesis and anti-bacterial activity of some novel pyrazolidinedione substituted derivatives of 2-quinolones, *Indo Am. J. Pharm. Res.*, 2017, **7**, 801–823.
10 K. A. Koo, N. D. Kim, Y. S. Chon, M. S. Jung, B. J. Lee, J. H. Kim and W. J. Song, QSAR analysis of pyrazolidine-3,5-diones derivatives as Dyrk1A inhibitors, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2324–2328.
11 K. Singh, R. S. N. Munuganti, E. Leblanc, Y. L. Lin, E. Leung, N. Lallous, M. Butler, A. Cherkasov and P. S. Rennie, In silico discovery and validation of potent small-molecule inhibitors targeting the activation function 2 site of human oestrogen receptor α, *Breast Cancer Res.*, 2015, **17**, 1–17.
12 J. Velcicky, U. Bodendorf, P. Rigollier, R. Epple, D. R. Beisner, D. Guerini, *et al.*, Discovery of the First Potent, Selective, and Orally Bioavailable Signal Peptide Peptidase-Like 2a (SPPL2a) Inhibitor Displaying Pronounced Immunomodulatory Effects In Vivo, *J. Med. Chem.*, 2018, **61**, 865–880.
13 Y. Yamashita and S. Kobayashi, Zirconium-Catalyzed Enantioselective [3+2] Cycloaddition of Hydrazones to Olefins Leading to Optically Active Pyrazolidine, Pyrazoline, and 1,3-Diamine Derivatives, *J. Am. Chem. Soc.*, 2004, **126**, 11279–11282.
14 (*a*) F. Požgan, H. AlMamari, U. Grošelj, J. Svete and B. Štefane, Synthesis of Non-Racemic Pyrazolines and Pyrazolidines by [3+2] Cycloadditions of Azomethine Imines, *Molecules*, 2018, **23**, 3; (*b*) U. Grošelj, J. Svete, H. Al Mamari, F. Požgan and B. Štefane, Metal-catalyzed [3+2] cycloadditions of azomethine imines, *Chem. Heterocycl. Compd.*, 2018, **54**, 214–240.
15 (*a*) B. R. Rosen, J. E. Ney and J. P. Wolfe, Use of Aryl Chlorides as Electrophiles in Pd-Catalyzed Alkene Difunctionalization Reactions, *J. Org. Chem.*, 2010, **75**, 2756–2759; (*b*) J. P. Wolfe and N. C. Giampietro, Stereoselective Synthesis of *cis*- or *trans*-3,5-Disubstituted Pyrazolidines *via* Pd-Catalyzed Carboamination Reactions: Use of Allylic Strain to Control Product Stereochemistry Through N-Substituent Manipulation, *J. Am. Chem. Soc.*, 2008, **130**, 12907–12911.
16 L. O. Davis, Recent Developments in the Synthesis and Applications of Pyrazolidines. A Review, *Org. Prep. Proced. Int.*, 2013, **45**, 437–464.
17 (*a*) G. Rainoldi, F. Begnini, M. de Munnik, L. Lo Presti, C. M. L. Vande Velde, R. Orru, G. Lesma, E. Ruijter and

A. Silvani, Sequential Multicomponent Strategy for the Diastereoselective Synthesis of Densely Functionalized Spirooxindole-Fused Thiazolidines, *ACS Comb. Sci.*, 2018, **20**, 98–105; (*b*) G. Rainoldi, M. Faltracco, C. Spatti, A. Silvani and G. Lesma, Organocatalytic Access to Enantioenriched Spirooxindole-Based 4-Methyleneazetidines, *Molecules*, 2017, **22**, 2016; (*c*) G. Rainoldi, M. Faltracco, L. Lo Presti, A. Silvani and G. Lesma, Highly diastereoselective entry into chiral spirooxindole-based 4-methyleneazetidines *via* formal [2 + 2] annulation reaction, *Chem. Commun.*, 2016, **52**, 11575–11578; (*d*) G. Rainoldi, F. Begnini, A. Silvani and G. Lesma, Efficient Synthesis of Spirooxindole-fused 3-Thiazoline Derivatives by a One-Pot Asinger-Type Reaction, *Synlett*, 2016, **27**, 2831–2835; (*e*) G. Rainoldi, A. Sacchetti, A. Silvani and G. Lesma, Organocatalytic vinylogous Mannich reaction of trimethylsiloxyfuran with isatin-derived benzhydryl-ketimines, *Org. Biomol. Chem.*, 2016, **14**, 7768–7776; (*f*) G. Lesma, F. Meneghetti, A. Sadcchetti, M. Stucchi and A. Silvani, Asymmetric Ugi 3CR on isatin-derived ketimine: synthesis of chiral 3,3-disubstituted 3-aminooxindole derivatives, *Beilstein J. Org. Chem.*, 2014, **10**, 1383–1389; (*g*) G. Lesma, N. Landoni, T. Pilati, A. Sacchetti and A. Silvani, Grignard Addition to Imines Derived from Isatine: A Method for the Asymmetric Synthesis of Quaternary 3-Aminooxindoles, *J. Org. Chem.*, 2009, **74**, 4537–4541.

18 *Design of Hybrid Molecules for Drug Development*. ed. M. Decker, Elsevier Ed, 2017.

19 (*a*) G.-J. Mei and F. Shi, Catalytic asymmetric synthesis of spirooxindoles: recent developments, *Chem. Commun.*, 2018, **54**, 6607–6621; (*b*) G. Meller, T. Berkenbosch, J. C. J. Benningshof, D. Stumpfe and J. Bajorath, Charting Biologically Relevant Spirocyclic Compound Space, *Chem.–Eur. J.*, 2017, **23**, 703–71; (*c*) V. Pace, L. Castoldi, A. D. Mamuye, T. Langer and W. Holzera, Chemoselective Addition of Halomethyllithiums to Functionalized Isatins: A Straightforward Access to Spiro-Epoxyoxindoles, *Adv. Synth. Catal.*, 2016, **358**, 172–177.

20 B. Wagner, W. Hiller, H. Ohno and N. Krause, Gold-catalyzed three-component spirocyclization: a one-pot approach to functionalized pyrazolidines, *Org. Biomol. Chem.*, 2016, **14**, 1579–1583.

21 (*a*) N. A. Aslam, S. A. Babu, S. Rani, S. Mahajan, J. Solanki, M. Yasuda and A. Baba, Diastereoselective Construction of 3-Aminooxindoles with Adjacent Stereocenters: Stereocontrolled Addition of γ-Substituted Allylindiums to Isatin Ketimines, *Eur. J. Org. Chem.*, 2015, 4168–4189; (*b*) B. Alcaide, P. Almendros and C. Aragoncillo, Indium-Promoted Allylation Reaction of Imino-Isatins in Aqueous Media: Synthesis of Quaternary 3-Aminooxindoles, *Eur. J. Org. Chem.*, 2010, 2845–2848.

22 P. D. Chaudhari, B. C. Hong and G. H. Lee, Organocatalytic Enantioselective Michael-Michael-Michael-Aldol Condensation Reactions: Control of Six Stereocenters in a Quadruple-Cascade Asymmetric Synthesis of Polysubstituted Spirocyclic Oxindoles, *Org. Lett.*, 2017, **19**, 6112–6115.

23 D. Ganggang, H. Danfeng, W. Ke-Hu, C. Xiaowei, X. Yanli, M. Junyan, S. Yingpeng, F. Ying and H. Yulai, One-pot preparation of trifluoromethylated homoallylic N-acylhydrazines or α-methylene-γ-lactams from acylhydrazines, trifluoroacetaldehyde methyl hemiacetal, allyl bromide and tin, *Org. Biomol. Chem.*, 2016, **14**, 1492–1500.

24 J. E. Thomson, A. F. Kyle, K. B. Ling, S. R. Smith, A. M. Z. Slawin and A. D. Smith, Applications of NHC-mediated O- to C-carboxyl transfer: synthesis of (±)-N-benzyl-coerulescine and (±)-horsfiline, *Tetrahedron*, 2010, **66**, 3801–3813.

25 L. Firmansjah and G. C. Fu, Intramolecular Heck Reactions of Unactivated Alkyl Halides, *J. Am. Chem. Soc.*, 2007, **129**, 11340–11341.