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Synthesis of 7-alkylidene-7,12-dihydroindolo-[3,2-*d*]benzazepine-6-(5*H*)-ones (7-alkylidene-paullones) by N-cyclization–oxidative Heck cascade and characterization as sirtuin modulators†

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An extension of our reported protocol to benzofused heterocyclic derivatives (benzofurans, indoles, isochromeneimines), involving a palladium-induced cascade of N-cyclization and oxidative Heck reactions of *o*-alkynylanilines, has allowed the preparation of indolobenzazepinones (paullones) with an alkylidene group at C7 in just 3–4 steps from *ortho*-iodoanilines. Some of these compounds behave as Sirt1 activators in biochemical assays.

Introduction

Compounds with the 7,12-dihydroindolo[3,2-*d*]benzazepine-6(5*H*)-one scaffold represented by **1a**, collectively known as paullones, are endowed with a broad range of biological activities. They have been characterized as inhibitors of several kinases,[1] and of mitochondrial malate dehydrogenase (mMDH).[2] Some of the members of the group, in particular the C9-Br derivative (kenpaullone, **1b**) and analogues **2** and **3** have been reported to also target the NAD^+-dependent class of histone deacetylases (sirtuins, Sirt).[3] In addition, kenpaullone **1b** has been established as a chemical probe in stem-cell research.[4] Cytotoxic,[5] antiproliferative,[6] and pro-apoptotic[1b,7] effects of paullones have been noted in human cancer cell lines, rendering these compounds as promising antitumor agents.[8] Additionally, paullones have been considered as therapeutic agents for trypanosomiasis and leishmaniasis,[9] and selected members of the family (cazpaullone **1c** and alsterpaullone **1d**)[10] for the treatment of diabetes since they suppress cytokine induced β-cell apoptosis.[11]

These promising biological activities have raised interest in these compounds and have stimulated the development of synthetic methodologies to prepare analogues retaining the basic 7,12-dihydroindolo[3,2-*d*]benzazepine-6(5*H*)-one scaffold. In addition to the classical construction of the fused 1*H*-indole moiety by Fischer indolization reactions,[1b,2,6,9b] a variety of other methods have been reported, among them the free radical cyclisation of indolyl iodoacetamide derivatives,[12] and the photocyclization of 2-(2-chloro-1*H*-indol-3-yl)-*N*-arylacetamides.[13] Transition-metal mediated processes have likewise provided solutions for some of the steps in the construction of the basic paullone skeleton. Notable among them are the intramolecular Heck reaction,[14] an oxidative coupling after rhodium(III)-catalyzed C–H functionalization of acetamides with alkynes,[15] the Pd-promoted borylation/Suzuki coupling and lactam formation,[16] the Cu(I)-catalyzed borylative cyclization of 2-alkenylphenyl isocyanides,[17] the free radical formation of stannylindoles from *o*-alkenyl arylisonitriles and subsequent Stille cross-coupling with *N*-Boc-*o*-iodoanilines,[18] the combined Heck and Stille reactions,[19] and the one-pot Suzuki–Miyaura cross-coupling of an *o*-aminoarylboronic acid and methyl 2-iodoindoleacetate followed by intramolecular amide formation reported by our group.[20]

We have developed a new synthetic methodology that streamlines the preparation of benzofurans,[21] indoles[22,21c] and other heterocyclic derivatives[21b–c,22,23] starting from the corresponding *o*-iodoaryl precursors. This sequential process com-

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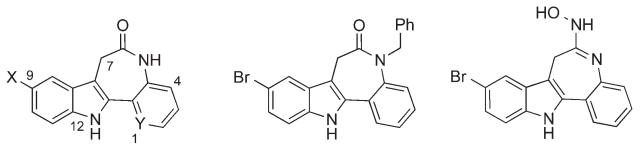
†Electronic supplementary information (ESI) available: ESI contains general experimental procedures, copies of the NMR spectra of the new compounds and X-ray diffraction data for **4ab** and **4bb**. CCDC 1036521 and 1036522. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob02493a

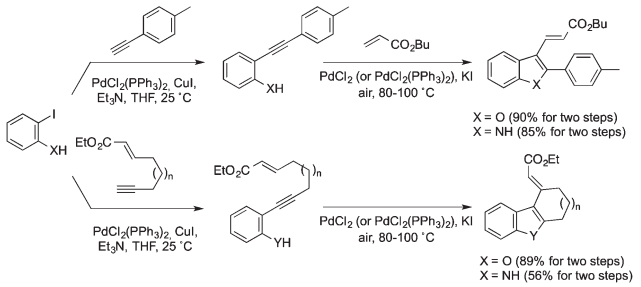


1a, X = H, Y = CH, Paullone
1b, X = Br, Y = CH, Kenpaullone
1c, X = CN, Y = N, Cazpaullone
1d, X = NO_2, Y = CH, Alsterpaullone

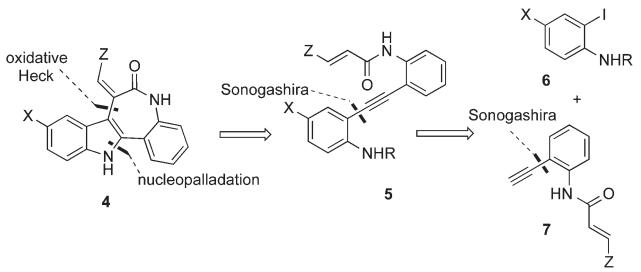
2, *N*-Benzylkenpaullone

3, Kenpaullone hydroxyamidine

Fig. 1 Biologically-relevant 7,12-dihydroindolo[3,2-*d*]benzazepine-6(5*H*)-ones (paullones).



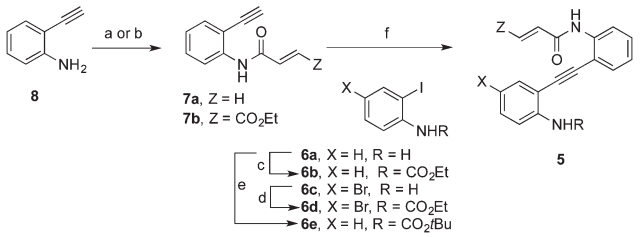
Scheme 1 Our synthetic approach to benzofurans and indoles, including the intramolecular version.



Scheme 2 Retrosynthetic analysis of C7-alkylidenepaullones using a Pd-catalyzed N-cyclization–intramolecular oxidative Heck cascade reaction.

bined a Pd-catalyzed Sonogashira cross-coupling and a nucleopalladation–Heck oxidative reaction (Scheme 1). Moreover, the protocol was also performed as a "one-pot" process where the Sonogashira and oxidative steps were combined in a three-component Sonogashira–heterocyclization–Heck-coupling cascade.[21c]

We envisioned that the intramolecular variant of this synthetic procedure[21b,c] could be extended to the preparation of additional paullone analogues featuring an exocyclic olefin at the C7 position (general structure **4**, Scheme 2) of the benzazepine-6(5*H*)-one ring, a modification that has no precedents to the best of our knowledge. To integrate this substitution pattern into the structures shown in Fig. 1, the precursor **5** containing an alkyne substituted with aryl rings that bear an *o*-amino and an *o*′-acylamino group was required. Two consecutive Sonogashira reactions *via* **7** would trace back the



Scheme 3 Reaction conditions: (a) acryloyl chloride, Et_3N, CH_2Cl_2, 25 °C (**7a**, 87%). (b) Ethyl (*E*)-4-chloro-4-oxobut-2-enoate, Py, Et_2O, 25 °C (**7b**, 99%). (c) $ClCO_2Et$, K_2CO_3, acetone, 25 °C (**6b**, 99%). (d) ClC(O)-OEt, Py, ether, 0–10 °C (**6d**, 91%). (e) $(Boc)_2O$, THF, reflux (**6e**, 97%). (f) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF or DMF, 60 °C (**5aa**, 98%; **5ab**, 99%; **5ac**, 99%; **5ae**, 92%; **5ba**, 76%; **5bb**, 92%; **5bd**, 90%; **5be**, 99%). See Table 1 for the structure of compounds **5**.

cyclising substrate **5** to simple, and in most cases commercial, *o*-haloanilines **6** (Scheme 2; for the meaning of X, R, Z, see Scheme 3).

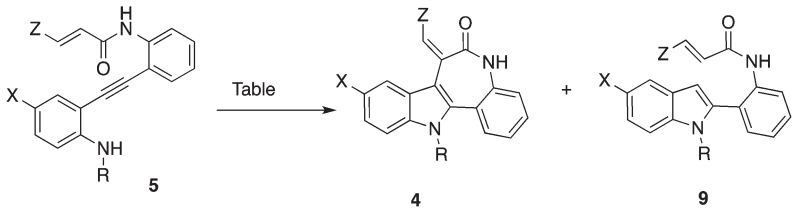
Results and discussion

After surveying all synthetic variants for the preparation of the N-differentiated *o*,*o*′-bisaniline-ethyne substrates **5** (see ESI†) we selected the order of steps shown in Scheme 3 comprising first the acylation of an *o*-alkynyl aniline and then the Sonogashira reaction with an appropriate *o*-iodoaniline. The condensation of 2-ethynylaniline **8** with acryloyl chloride,[24] was followed by the Sonogashira reaction[21,22] of product **7a** with commercial *o*-iodoaniline **6a** to afford in quantitative yield the corresponding internal alkyne **5aa**. Excellent yields were obtained in all steps of the synthetic route. The same sequence was used for the preparation of the remaining substrates **5** as shown in Scheme 3.

Acrylamide **5aa** was treated with 5 mol% $PdCl_2(PPh_3)_2$, 0.5 equivalents of KI and 1 equivalent of maleic anhydride (MA) in DMF under air, conditions previously developed for nucleopalladation–intramolecular Heck reactions.[21b,c] When these conditions were applied at 80 °C, only the 3*H*-indole product **9aa** could be isolated albeit in low yield (18%, Table 1, entry 1). Raising the temperature to 100 °C the desired product **4aa** was obtained in only 14% yield after heating for 24 h (entry 2), the 3*H*-indole product **9aa** being the major component (48%). Shortening the reaction time to 3 h increased the yield of **4aa** to 40% (entry 3), indicating that under the conditions of entry 2, with prolonged heating at high temperature, product degradation was taking place. The substrate with a bromine atom located at the aniline *para* position (compound **5ac**) showed somewhat higher reactivity, and the Pd-catalyzed cascade could be run at 80 °C, to yield **4ac** and **9ac** in a *ca.* 50 : 50 ratio (entry 4). Not surprisingly, a temperature increase (entry 5) resulted in a lower yield of **4ac**, again probably due to product degradation.

In the expected cascade reaction mechanism shown in Fig. 2, the initial coordination of the *o*-alkynylaniline to Pd(II)

Table 1 Nucleopalladation–oxidative Heck cascade for the synthesis of alkylidenepaullones[a]



Entry, substrate	X	R	Z	Reaction conditions			Yield (%)		
				T (°C)	t (h)	K_2CO_3[b]	**4**	**9**	**5**
1, **5aa**	H	H	H	80	24	—	—	18 (**9aa**)	—
2, **5aa**	H	H	H	100	24	—	14 (**4aa**)	48 (**9aa**)	—
3, **5aa**	H	H	H	100	3	—	40 (**4aa**)	37 (**9aa**)	—
4, **5ac**	Br	H	H	80	22	—	50 (**4ac**)	50 (**9ac**)	—
5, **5ac**	Br	H	H	100	22	—	25 (**4ac**)	50 (**9ac**)	—
6, **5aa**	H	H	H	100	3.5	0.25		28 (**9aa**)	28 (**5aa**)
7, **5aa**	H	H	H	100	3.5	0.50	65 (**4aa**)	20 (**9aa**)	—
8, **5aa**	H	H	H	100	3.5	1.00	22 (**4aa**)	<5 (**9aa**)	—
9, **5aa**	H	H	H	100	3.5	0.50[c]	34 (**4aa**)	30 (**9aa**)	—
10, **5ba**[d]	H	H	CO_2Et	100	24	—	—	70 (**9ba**)	—
11, **5ab**	H	CO_2Et	H	80	24	—	—	—	100 (**5ab**)
12, **5ab**	H	CO_2Et	H	100	24	—	52 (**4ab**)	—	—
13, **5bb**	H	CO_2Et	CO_2Et	100	24	—	65 (**4bb**)	—	—
14, **5bb**	H	CO_2Et	CO_2Et	120	24	—	80 (**4bb**) + 20 (**4ba**)	—	—
15, **5bd**	Br	CO_2Et	CO_2Et	120	20	—	60[e] (**4bd**)	—	—
16, **5ae**	H	CO_2t-Bu	H	120	20	—	25 (**4ae**) + 29 (**4aa**)	—	—
17, **5be**	H	CO_2t-Bu	CO_2Et	120	20	—	22 (**4be**) + 78 (**4ba**)	—	—

[a] Standard conditions: 5 mol% $PdCl_2(PPh_3)_2$, 0.5 equiv. KI, 1 equiv. MA under air in DMF. [b] Equivalents of K_2CO_3 used. [c] NaOAc was used as a base. [d] Using 0.5 equiv. of K_2CO_3, at 120 °C, the conjugate addition product was obtained (42%, see ESI). [e] Traces of the deprotected product were observed by ^{1}H-NMR.

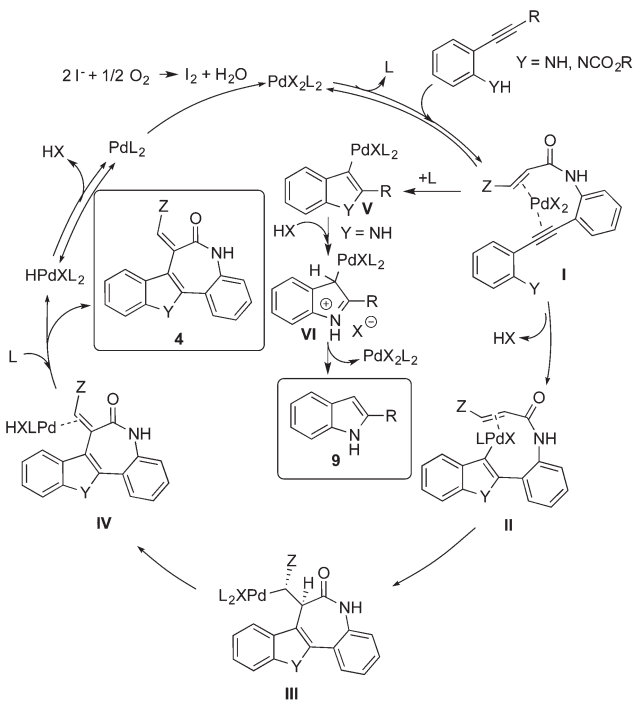


Fig. 2 Mechanistic proposal for the Pd-catalyzed N-cyclization–oxidative Heck cascade to alkylidenepaullones (Z = H or EWG; L = PPh_3; Y = NH or NCO_2R).

triggers nucleopalladation to afford the indole ring and then insertion of the heterocyclic C3-σ-Pd(II) complex into the pendant alkene leads to the olefin product, after β-hydride elimination. The resulting palladium hydride undergoes loss of HCl with the formation of Pd(0), which is finally oxidized to regenerate the Pd(II) species that starts the cycle.[21,22] The 3*H*-indole products **9** are considered to originate from a σ-indolylpalladium intermediate (**II** or **V**) that undergoes protonation to **VI** (Fig. 2).

Control experiments revealed that the 3*H*-indole product **9aa** did not undergo C–H activation to enter the catalytic cycle at the level of intermediate **II** (Fig. 2) under the reaction conditions. Therefore, it seems reasonable to assume that the product ratio results from a balance between the rates of carbopalladation with the pendant olefin and protonation of the σ-indolyl intermediate.[25] As a result, we tried to modulate the reactivity of the system through the addition of a base and the modification of the electronic nature of the olefin and aniline functionalization implicated in the cascade bond formation reactions.

The presence of K_2CO_3 was shown to have a beneficial effect (entries 6–9). Thus, the use of 0.5 mol equivalent induced the total consumption of the reactant and afforded a 76 : 24 ratio of the benzazepinone to 3*H*-indol (**4aa**/**9aa**) mixture in 85% overall yield (entry 7). Larger amounts of K_2CO_3 proved to be detrimental (entry 8) whereas smaller

quantities (entry 6) afforded an almost equal ratio of the reaction products in lower yields. The change to NaOAc had no effect (entry 7 *vs.* entry 9).

The introduction of carbonyl substituents at R and/or Z was examined next. Fumarate-derived substrate **5ba** led only to the 3*H*-indole derivative **9ba** in 70% yield (entry 10) under the standard conditions.

However, starting from the *N*-ethylcarbamate **5ab** the cascade product **4ab** was isolated in 52% yield under the same reaction conditions (entry 12) and, furthermore, the similar reactions of the carbamate–fumarate substrates **5bb** and **5bd** also afforded the desired alkylidenepaullones in good yields (entries 13–15). It is apparent that reducing the electron density at the palladium-substituted indole C3 position slows down protiodemetallation. As additional benefit, carbamates were expected to exhibit greater solubility thus facilitating the handling of the final product.

We also noticed that the indole carbamate underwent partial deprotection under the thermal conditions required for the Pd-catalyzed cascade reaction (see entries 14 and 15). Since *tert*-butylcarbamates are known to deprotect by thermal fragmentation reaction,[26] it was thought that they could directly provide the deprotected indolobenzazepine-6-one. However, this expectation was only partially realized, as the deprotection of the *N*-Boc-*o*,*o*′-bisaniline-ethynes **5ae** and **5be** (obtained from previously described[27] **6e**) to **4ae** and **4be** was incomplete after heating to 120 °C (**4ae**, 25%; **4aa**, 29%; **4ae**, 22%; **4ba**, 78%, Table 1, entries 16 and 17). Nevertheless, the use of *tert*-butylcarbamate **5be** allowed the isolation of **4ba** (a product that could not be obtained from fumarate **5ba**) in useful yield (78%).

The structures of indolobenzazepinones **4ab** and **4bb** were confirmed by X-ray analysis (see ESI†), which also corroborated the geometry of the exocyclic olefin, as anticipated from the stereospecific *syn*-β-elimination of PdL_2XH from intermediate **III** depicted in Fig. 2. As a result, it is confirmed that the products of this highly regio-, stereo- and chemoselective reaction indeed correspond to a 7-*exo* intramolecular Heck-type cyclization process, whereas the indolobenzazocinone products (originating from the alternative 8-*endo* cyclization manifold,[28,29] which have been observed in other substrates),[30] were not detected. Furthermore, the only products that were isolated originated from the manifold where the N further removed from the pendant alkenyl chain participated in the starting nucleopalladation step.

Biological evaluation

To explore the antitumor activities of the alkylidenepaullones, we first assessed their effects on cell cycle progression and cell death using the U937 leukaemia cell line (Fig. 3). As shown in Fig. 3A, the effect on the cell cycle of these compounds was not significant relative to the control, the Zn^{2+}-dependent histone deacetylase inhibitor suberoylanilide hydroxamic acid

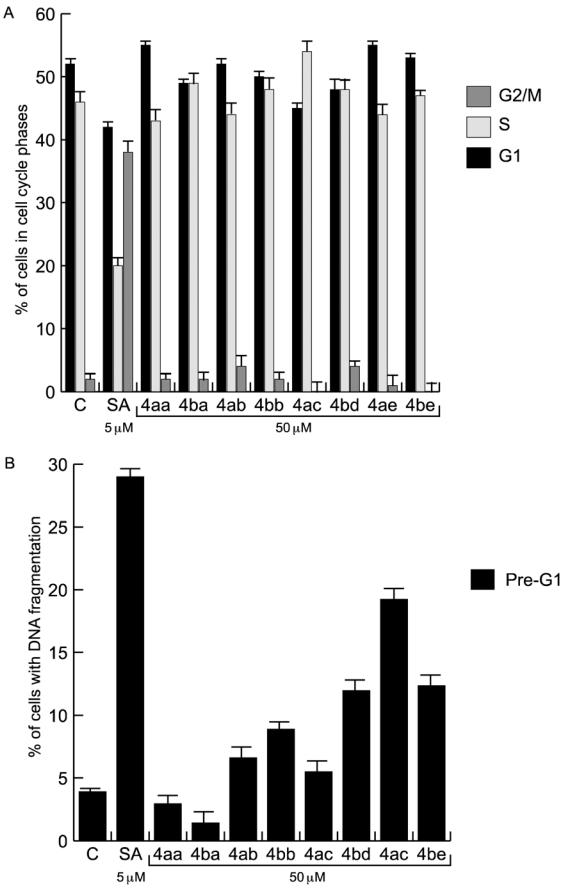


Fig. 3 Effects of alkylidenepaullones on cell cycle (A) and apoptosis (B) after treatment of U937 leukemia cells with the indicated compounds at 50 μM for 30 h. DMSO (0.1%) was used as the vehicle control and SAHA (SA) as the reference compound at 5 μM.

(SAHA) used at 5 μM. However, some compounds were able to induce cell death at the dose of 50 μM (Fig. 3B).

As second analysis, we checked by western blot the activity of the alkylidenepaullones on a recombinant Sirt1 enzyme.[20] Using a Sirt1 assay under conditions that detect both activation and inhibition, compounds **4aa** and **4ac** were found to display an apparent activating effect at 50 μM (compound STAC used as the reference[31] displayed activation in the same settings at the lower dose of 10 μM). On the other hand, compounds **4ba**, **4bb**, **4bd** and **4ae** displayed a low inhibitory effect under the same conditions (Fig. 4A). When compound **4ac** was tested in MCF7 cells for its ability to activate Sirt1 activity by causing deacetylation of p53 on K382 (a target of sirtuins[32,33]) after 30 h of treatment (Fig. 4B), a dose-dependent effect was noted, suggesting that the effective dose to obtain Sirt1 activation, in the cellular settings, is higher.

Conclusion

In conclusion, the Pd-catalyzed N-cyclization of *o*-alkynylanilines, combined with an intramolecular oxidative Heck reaction in a cascade process, allows the regioselective con-

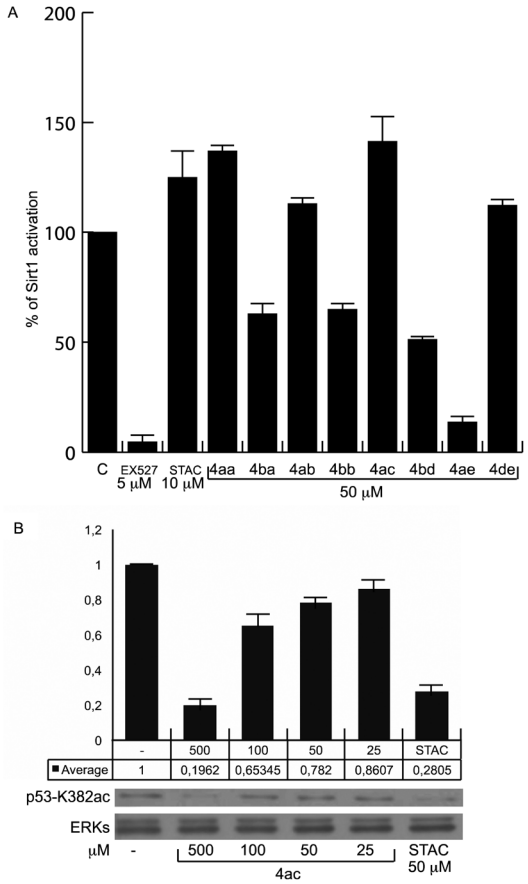


Fig. 4 Sirt1 activity assay. (A) The indicated compounds were tested at 50 μM. DMSO (0.1%) was used as the vehicle control. EX527 and STAC at 5 and 10 μM, respectively, were used as reference compounds. (B) Western blot analysis of p53K382 acetylation levels in MCF7 cells upon increasing concentrations of **4ac** for 30 h. DMSO (0.1%) and STAC (50 μM) were used as reference compounds. Signal quantitation was performed using the ImageJ software.

struction of the core indole and benzazepinone heterocycles of the polycyclic alkylidenepaullones. The scope of this methodology might be broadened with its application to other heterocyclic analogs (X = O, S in Scheme 1). Some of these compounds appear to activate Sirt1 in biochemical assays, and although at present the concentration required for their activity is higher than those of existing compounds, they represent a useful starting point for further additional structural studies aimed to improve their potencies as sirtuin activators.

Experimental section

Ethyl (2-iodophenyl)carbamate 6b.[34] 2-Iodoaniline **6a** (1.2 g, 5.478 mmol), ethylchloroformate (2.37 g, 21.916 mmol) and K_2CO_3 (4.54 g, 32.873 mmol) were stirred in 20 mL of acetone at room temperature for 18 h. The solution was diluted with H_2O. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3×). The organic layers were washed with brine and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 70 : 30 hexane–EtOAc) to afford 1.57 g (99%) of the title compound as a white solid. ^{1}H-NMR (400.16 MHz, $CDCl_3$) δ 8.06 (d, J = 8.1 Hz, 1H), 7.75 (dd, J = 7.9, 1.2 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 6.94 (s, 1H), 6.80 (t, J = 7.6 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H) ppm.^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 153.6, 138.9, 138.6, 129.4, 125.1, 120.4, 88.9, 61.7, 14.6 ppm.

***tert*-Butyl (2-iodophenyl)carbamate 6e.**[30] A solution of 2-iodoaniline **6a** (500 mg, 2.283 mmol) and $(Boc)_2O$ (797.2 mg, 3.653 mmol) in THF (4 mL) was refluxed for 4 days. Then H_2O was added and the mixture was extracted with AcOEt (3×) and the combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash chromatography (silica gel, 90 : 10 hexane–EtOAc) to afford 0.705 g (97%) of **6e** as white crystals. ^{1}H-NMR (400.16 MHz, $CDCl_3$) δ 8.05 (d, J = 8.2 Hz, 1H), 7.74 (dd, J = 7.9, 1.4 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 6.82 (s, 1H), 6.76 (ddd, J = 8.8, 7.6, 1.5 Hz, 1H), 1.54 (s, 9H) ppm.^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 152.7, 138.9, 138.9, 129.3, 124.8, 120.3, 88.9, 81.2, 28.4 ppm.

Ethyl (4-bromo-2-iodophenyl)-carbamate 6d. Ethyl chloroformate (115 μL, 1.217 mmol) was added to a solution of commercial 4-bromo-2-iodoaniline **6c** (250 mg, 0.839 mmol) in pyridine (1.13 mL) at 0–10 °C and the mixture was stirred for 3 h. The pyridine was evaporated and the residue was diluted with H_2O and extracted with Et_2O (3×). The combined organic layers were washed with a 3 M aqueous solution of HCl and a saturated aqueous solution of $NaHCO_3$ and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 95 : 5 hexane–EtOAc) to afford 282.1 mg (91%) of the title compound as a white solid. m.p.: 105–106 °C (CH_2Cl_2); ^{1}H-NMR (400.16 MHz, $CDCl_3$) δ 7.97 (d, J = 8.6 Hz, 1H, H_6), 7.87 (d, J = 2.3 Hz, 1H, H_3), 7.44 (dd, J = 8.8, 2.3 Hz, 1H, H_5), 6.91 (s, 1H, NH), 4.24 (q, J = 7.0 Hz, 2H, CH_2–CH_3), 1.34 (t, J = 7.0 Hz, 3H, CH_2–CH_3) ppm.^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 153.3, 140.6, 137.9, 132.2, 121.0, 116.3, 88.7, 61.9, 14.6 ppm. MS (EI): m/z (%) 370 (M^+, ^{81}Br, 37), 368 (M^+, ^{79}Br, 36), 324 (94), 322 (100), 298 (33), 296 (35), 215 (85), 213 (71), 170 (31), 169 (65), 167 (46), 63 (29). HRMS (EI): Calcd for $C_9H_9{}^{81}BrINO_2$ 370.8841; found, 370.8845. Calcd for $C_9H_9{}^{79}BrINO_2$ 368.8861; found, 368.8865. IR (neat): ν 3293 (w, N–H), 2980 (w, C–H), 2929 (w, C–H), 1730 (s, C=O) cm^{-1}.

***N*-(2-Ethynylphenyl)-acrylamide 7a.** Acryloyl chloride (79 μL, 0.971 mmol) was added to a solution of 2-ethynylaniline **8** (0.13 g, 0.883 mmol) in CH_2Cl_2 (8.8 mL) and Et_3N (0.14 mL) at 0 °C. After stirring for 30 min at 25 °C, an aqueous saturated solution of NH_4Cl was added and the mixture was extracted with Et_2O (3×). The combined organic combined layers were dried ($NaSO_4$) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 90 : 10 hexane–EtOAc) to afford 144 mg (87%) of the title compound as a white solid. m.p.: 91–92 °C (CH_2Cl_2). ^{1}H-NMR (400.16 MHz, $CDCl_3$): δ 8.46 (d, J = 8.4 Hz, 1H, ArH), 8.11 (s, 1H, NH), 7.42 (dd, J = 7.7, 1.6 Hz, 1H, ArH), 7.39–7.28 (m, 1H, ArH), 7.01 (td,

J = 7.6, 1.2 Hz, 1H, ArH), 6.40 (dd, J = 16.9, 1.4 Hz, 1H, H_2), 6.28 (dd, J = 16.9, 10.0 Hz, 1H, H_{3trans}), 5.74 (dd, J = 10.0, 1.4 Hz, 1H, H_{3cis}), 3.55 (s, 1H). ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 163.3, 139.2, 132.1, 131.2, 130.0, 127.8, 123.4, 119.5, 111.0, 84.7, 79.0 ppm. MS (EI): m/z (%) 171 (M^+, 46), 143 (11), 117 (100), 90 (19), 89 (21). HRMS (EI): Calcd for $C_{11}H_9NO$ 171.0684; found, 171.0689. IR (neat): ν 3379 (s, N–H), 3255 (s, Csp–H), 3209 (s, Csp^2–H), 2195 (w, C≡C), 1665 (s, C═O) cm^{-1}.

Ethyl (*E*)-4-(2-ethynylphenylamino)-4-oxobut-2-enoate 7b. To a solution of **8** (0.25 g, 1.552 mmol) in Et_2O (7.75 mL) was added pyridine (139 μL, 1.707 mmol). After cooling down to −78 °C, a solution of ethyl (*E*)-4-chloro-4-oxobut-2-enoate (0.25 g, 1.552 mmol) in Et_2O (2.35 mL) was added dropwise. The resulting suspension was warmed to 25 °C for 1 h and then partitioned between EtOAc (50 mL) and brine (50 mL). The layers were separated and the aqueous layers were extracted with EtOAc (3×) and the combined organic layers were washed with a 5% aqueous HCl solution (100 mL) and brine (100 mL) and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash chromatography (silica gel, 90 : 10 hexane–EtOAc) to afford 0.38 g (99%) of the title compound as white crystals. m.p.: 139 °C (Et_2O). ^{1}H-NMR (400.16 MHz, $CDCl_3$) δ 8.51 (d, J = 8.4 Hz, 1H, ArH), 8.19 (s, 1H, NH), 7.49 (dd, J = 7.8, 1.5 Hz, 1H, ArH), 7.40 (td, J = 8.0, 1.6 Hz, 1H, ArH), 7.10 (td, J = 7.6, 1.1 Hz, 1H, ArH), 7.07 (d, J = 15.3 Hz, 1H), 6.96 (d, J = 15.3 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H, CH_2–CH_3), 3.58 (s, 1H), 1.35 (t, J = 7.1 Hz, 3H, CH_2–CH_3) ppm. ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 165.4, 161.5, 139.0, 136.4, 132.4, 131.9, 130.4, 124.3, 119.7, 111.2, 85.3, 79.0, 61.5, 14.2 ppm. MS (EI): m/z (%) 243 (M^+, 52), 198 (13), 170 (43), 127 (23), 117 (100), 116 (17), 99 (19), 89 (20). HRMS (EI): Calcd for $C_{14}H_{13}NO_3$ 243.0895; found, 243.0893. IR (neat): ν 3289 (w, N–H), 3247 (s, ≡C–H), 1712 (s, C═O), 1641 (s, C═O) cm^{-1}.

***N*-[2-(2-Aminophen-1-ylethynyl)-phenyl]acrylamide 5aa.** General procedure for the Sonogashira reaction. To a solution of 2-iodoaniline **6a** (0.025 g, 1.141 mmol) in THF (12 mL) were added $PdCl_2(PPh_3)_2$ (0.016 g, 0.022 mmol), CuI (0.008 g, 0.045 mmol), Et_3N (2.96 mL) and *N*-(2-ethynylphenyl)-acrylamide **7a** (0.293 g, 1.712 mmol), and the reaction mixture was stirred at 25 °C for 4 h. The mixture was poured into H_2O and then extracted with EtOAc (3×). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 80 : 20 hexane–EtOAc) to afford the title compound (292.5 mg, 98%) as a yellowish-brown solid. m.p.: 94–95 °C (CH_2Cl_2). ^{1}H-NMR (400.16 MHz, $CDCl_3$) δ 8.49 (d, J = 6.7 Hz, 1H, ArH), 8.23 (s, 1H, NH), 7.49 (d, J = 7.7 Hz, 1H, ArH), 7.43–7.28 (m, 2H, ArH), 7.19 (t, J = 7.8 Hz, 1H, ArH), 7.09 (t, J = 7.6 Hz, 1H, ArH), 6.85–6.70 (m, 2H, ArH), 6.44 (dd, J = 17.0, 1.6 Hz, 1H, H_{3trans}), 6.31 (dd, J = 16.9, 10.1 Hz, 1H, H_2), 5.76 (dd, J = 10.2, 1.6 Hz, 1H, H_{3cis}), 4.32 (s, 2H, NH_2) ppm. ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 163.5, 148.0, 138.5, 132.0, 131.5, 131.4, 130.5, 129.7, 127.9, 123.8, 119.7, 118.3, 114.8, 112.6, 107.1, 93.4, 89.5 ppm. MS (EI): m/z (%) 262 (M^+, 5), 244 (64), 243 (100), 242 (27), 204 (11). HRMS (EI): Calcd for $C_{17}H_{14}N_2O$, 262.1106; found, 262.1097. IR (neat): ν 3436 (s, N–H), 3380–3350 (m, N–H), 3293 (w, Csp^2–H), 2210 (w, C≡C), 1659 (s, C═O) cm^{-1}.

***N*-{2-[(*N*-Ethoxycarbonyl-2-aminophenyl)-ethynyl]-phenyl}-acrylamide 5ab.** Following the general procedure for the Sonogashira reaction, the reaction of ethyl (4-bromo-2-iodophenyl)-formate **6b** (100 mg, 0.343 mmol), *N*-(2-ethynylphenyl)-acrylamide **7a** (88 mg, 0.515 mmol), $PdCl_2(PPh_3)_2$ (0.005 g, 0.007 mmol), CuI (0.003 g, 0.014 mmol) and Et_3N (0.89 mL) in THF (3.6 mL) afforded, after purification by column chromatography (silica gel, 80 : 20 hexane–EtOAc), 114.8 mg (100%) of the title compound as a white solid. m.p.: 158–159 °C (CH_2Cl_2). ^{1}H-NMR (400.16 MHz, $CDCl_3$) δ 8.51 (d, J = 8.4 Hz, 1H, ArH), 8.14 (d, J = 8.8 Hz, 1H), 8.08 (br, 1H, NH), 7.57–7.49 (m, 1H, ArH), 7.48 (ddd, J = 7.7, 1.6, 0.5 Hz, 1H, ArH), 7.46–7.35 (m, 2H, ArH), 7.30 (br, 1H, NH), 7.13 (td, J = 7.6, 1.2 Hz, 1H, ArH), 7.07 (td, J = 7.6, 1.1 Hz, 1H, ArH), 6.44 (dd, J = 16.9, 1.4 Hz, 1H, H_2), 6.31 (dd, J = 16.9, 10.1 Hz, 1H, H_{3A}), 5.78 (dd, J = 10.1, 1.4 Hz, 1H, H_{3B}), 4.23 (q, J = 7.1 Hz, 2H, CH_2), 1.31 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 163.5, 153.3, 139.1, 138.9, 132.1, 132.0, 131.4, 130.5, 130.4, 128.1, 123.9, 123.1, 120.1, 118.8, 111.9, 111.3, 91.6, 90.9, 61.7, 14.6 ppm. MS (EI): m/z (%) 334 (M^+, 4), 288 (27), 287 (21), 260 (14), 259 (12), 246 (24), 244 (71), 243 (100), 242 (23), 234 (76), 206 (24), 205 (30), 204 (16). HRMS (EI): Calcd for $C_{20}H_{18}N_2O_3$ 334.1337; found, 334.1331. IR (neat): ν 3307 (w, N–H), 2193 (w, C═C), 1705 (s, C═O), 1667 (s, C═O) cm^{-1}.

***N*-[2-((2-Amino-5-bromophenyl)-ethynyl)-phenyl]-acrylamide 5ac.** Following the general procedure for the Sonogashira reaction, the reaction of 4-bromo-2-iodoaniline **6c** (650 mg, 2.182 mmol), *N*-(2-ethynylphenyl)-acrylamide **7a** (560 mg, 2.273 mmol), $PdCl_2(PPh_3)_2$ (0.031 g, 0.044 mmol), CuI (0.017 g, 0.087 mmol) and Et_3N (5.7 mL) in DMF (23 mL) afforded, after purification by column chromatography (silica gel, 90 : 10 hexane–EtOAc), 744.4 mg (100%) of the title compound as a white solid. m.p.: 133–134 °C (CH_2Cl_2). ^{1}H-NMR (400.16 MHz, $CDCl_3$) δ 8.50 (d, J = 8.3 Hz, 1H, ArH), 8.08 (s, 1H, NH), 7.50 (ddd, J = 7.7, 1.6, 0.5 Hz, 1H, ArH), 7.47 (d, J = 2.3 Hz, 1H, ArH), 7.40 (ddd, J = 8.6, 7.5, 1.6 Hz, 1H, ArH), 7.30–7.27 (m, 1H, ArH), 7.11 (td, J = 7.6, 1.2 Hz, 1H, ArH), 6.66 (d, J = 8.7 Hz, 1H, ArH), 6.45 (dd, J = 16.9, 1.2 Hz, 1H, H_2), 6.31 (dd, J = 16.9, 10.1 Hz, 1H, H_{3A}), 5.81 (dd, J = 10.2, 1.2 Hz, 1H, H_{3B}), 4.30 (s, 2H, NH_2) ppm. ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 164.0, 147.5, 139.0, 134.4, 133.5, 132.1, 131.6, 130.5, 128.5, 124.2, 120.2, 116.5, 112.4, 109.5, 109.2, 91.9, 90.7 ppm. MS (EI): m/z (%) 342 (M^+, ^{81}Br, 20), 340 (M^+, ^{79}Br, 23), 325 (23), 324 (61), 323 (46), 322 (62), 321 (31), 243 (61), 242 (100), 206 (54), 205 (25). HRMS (EI): Calcd for $C_{17}H_{13}{}^{81}BrN_2O$, 342.0191; found, 342.0194. Calcd for $C_{17}H_{13}{}^{79}BrN_2O$, 340.0211; found, 340.0212. IR (neat): ν 3449 (w, N–H), 3256 (w, N–H), 3274 (w, N–H), 1654 (s, C═O) cm^{-1}.

***N*-{2-[(*N*-*tert*-Butoxycarbonyl-2-aminophenyl)-ethynyl]-phenyl}-acrylamide 5ae.** Following the general procedure for the Sonogashira reaction, the reaction of *tert*-butyl 2-iodophenyl formate **6e** (60 mg, 0.188 mmol), *N*-(2-ethynylphen-1-yl)-acrylamide **7a** (39 mg, 0.225 mmol), $PdCl_2(PPh_3)_2$ (0.003 g,

0.004 mmol), CuI (0.001 g, 0.07 mmol) and Et_3N (0.49 mL) in THF (2 mL) afforded, after purification by column chromatography (silica gel, 70 : 30 hexane–EtOAc), 62.4 mg (92%) of the title compound as a white solid. m.p.: 135–136 °C ($CDCl_3$). ^{1}H-NMR (400.16 MHz, $CDCl_3$) δ 8.53 (d, J = 8.3 Hz, 1H, ArH), 8.16 (d, J = 8.4 Hz, 1H, ArH), 8.07 (s, 1H, NH), 7.54 (dd, J = 7.7, 1.4 Hz, 1H, ArH), 7.47 (dd, J = 7.7, 1.3 Hz, 1H, ArH), 7.45–7.36 (m, 2H, ArH), 7.18 (s, 1H, NH), 7.14 (td, J = 7.6, 1.1 Hz, 1H, ArH), 7.05 (td, J = 7.6, 1.1 Hz, 1H, ArH), 6.45 (dd, J = 16.9, 1.2 Hz, 1H, $H_{3''A}$), 6.31 (dd, J = 16.9, 10.2 Hz, 1H, $H_{2''}$), 5.80 (dd, J = 10.2, 1.2 Hz, 1H, $H_{3''B}$), 1.52 (s, 9H, $C(CH_3)_3$) ppm. ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 163.6 (s), 152.6 (s), 139.7 (s), 139.0 (s), 132.2 (d), 132.1 (d), 131.6 (d), 130.7 (d), 130.5 (d), 128.4 (t), 124.1 (d), 122.9 (d), 120.1 (d), 118.7 (d), 111.9 (s), 111.0 (s), 92.0 (s), 90.8 (s), 81.4 (s), 28.5 (q) ppm. MS (ESI^+): m/z (%) 385 ([M + Na^+]), 363 [(M + H^+]). HRMS (ESI^+): Calcd for $C_{22}H_{23}N_2O_3$ 363.17032; found, 363.17033. IR (NaCl): ν 3400 (w, N–H), 3295 (w, N–H), 2978 (w, C–H), 1732 (s, C═O), 1688 (s, C═O) cm^{-1}.

Ethyl (*E*)-4-[(2-(2-aminophenylethynyl)-phenyl)amino]-4-oxobut-2-enoate 5ba. Following the general procedure for the Sonogashira reaction, the reaction of 2-iodoaniline **6c** (22 mg, 0.101 mmol), ethyl (*E*)-4-[(2-ethynylphenyl)-amino]-4-oxobut-2-enoate **7b** (37 mg, 0.152 mmol), $PdCl_2(PPh_3)_2$ (0.001 g, 0.002 mmol), CuI (0.001 g, 0.004 mmol) and Et_3N (0.26 mL) in DMF (1.06 mL) at 80 °C afforded, after purification by column chromatography (silica gel, 80 : 20 hexane–EtOAc), 25.8 mg (76%) of the title compound as a white solid. m.p.: 176–179 °C (CH_2Cl_2). ^{1}H-NMR (400.16 MHz, $CDCl_3$) δ 8.50 (d, J = 8.4 Hz, 1H, ArH), 8.41 (s, 1H, NH), 7.51 (dd, J = 7.7, 1.5 Hz, 1H, ArH), 7.43–7.33 (m, 2H, ArH), 7.20 (td, J = 7.6, 1.2 Hz, 1H, ArH), 7.18–7.07 (m, 2H, ArH + Csp^2–H), 6.96 (d, J = 15.3 Hz, 1H, Csp^2–H), 6.82–6.73 (m, 2H, ArH), 4.27 (q, J = 7.2 Hz, 2H, CH_2), 1.33 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 165.4, 161.6, 148.0, 138.0, 136.5, 132.1, 131.8, 131.7, 130.6, 129.8, 124.4, 120.0, 118.5, 115.0, 112.9, 107.2, 93.9, 89.3, 61.4, 14.2 ppm. MS (EI): m/z (%) 334 (M^+, 3), 317 (10), 316 (64), 288 (11), 244 (12), 243 (100), 242 (36). HRMS (EI): Calc. for $C_{20}H_{18}N_2O_3$, 334.1317; found, 334.1318. IR (neat): ν 3482 (w, N–H), 3385 (w, N–H), 3295 (w, N–H), 2204 (w, C═C), 1705 (s, C═O), 1666 (s, C═O) cm^{-1}.

Ethyl (*E*)-4-((2-((2-ethoxycarbonylamino-phenyl)-ethynyl)-phenyl)-amino)-4-oxobut-2-enoate 5bb. Following the general procedure for the Sonogashira reaction, the reaction of 2-iodophenyl-formate **6b** (500 mg, 1.718 mmol), ethyl (*E*)-4-(2-ethynylphenylamino)-4-oxobut-2-enoate **7b** (627 mg, 2.576 mmol), $PdCl_2(PPh_3)_2$ (0.024 g, 0.034 mmol), CuI (0.013 g, 0.069 mmol) and Et_3N (4.46 mL) in DMF (18 mL) at 60 °C afforded, after purification by column chromatography (silica gel, 80 : 20 hexane–EtOAc), 641.9 mg (92%) of the title compound as a white solid. m.p.: 168–169 °C (CH_2Cl_2). ^{1}H-NMR (400.16 MHz, $CDCl_3$) δ 8.52 (d, J = 8.4 Hz, 1H, ArH), 8.24 (s, 1H, NH), 8.12 (d, J = 8.4 Hz, 1H, ArH), 7.56 (dd, J = 7.8, 1.5 Hz, 1H, ArH), 7.51 (dd, J = 7.8, 1.6 Hz, 1H, ArH), 7.48–7.35 (m, 2H, ArH), 7.18 (td, J = 7.6, 1.1 Hz, 1H, ArH), 7.13–7.07 (m, 2H, ArH + Csp^2–H), 6.97 (d, J = 15.1 Hz, 1H, Csp^2–H), 4.35–4.15 (m, 4H, 2 × CH_2), 1.39–1.26 (m, 6H, 2 × CH_3) ppm. ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 165.3, 161.8, 153.3, 139.0, 138.2, 136.3, 132.2, 132.1, 131.8, 130.4, 130.1, 124.6, 123.1, 120.6, 118.9, 112.7, 111.5, 91.8, 90.5, 61.6, 61.3, 14.5, 14.1 ppm. MS (EI): m/z (%) 406 (M^+, 3), 360 (23), 318 (57), 316 (50), 288 (23), 287 (100), 259 (29), 243 (87), 242 (38), 234 (61), 206 (38), 205 (47). HRMS (EI): Calc. for $C_{23}H_{22}N_2O_5$, 406.1529; found, 406.1534. IR (neat): ν 3289 (w, N–H), 2978 (w, C–H), 1706 (s, C═O), 1672 (s, C═O) cm^{-1}.

Ethyl (*E*)-4-((2-((5-bromo-2-ethoxycarbonylaminophenyl)-ethynyl)-phenyl)-amino)-4-oxobut-2-enoate 5bd. Following the general procedure for the Sonogashira reaction, the reaction of ethyl (4-bromo-2-iodophenyl)-formate **6b** (100 mg, 0.265 mmol), ethyl (*E*)-4-(2-ethynylphenylamino)-4-oxobut-2-enoate **7b** (97 mg, 0.398 mmol), $PdCl_2(PPh_3)_2$ (0.004 g, 0.005 mmol), CuI (0.002 g, 0.011 mmol) and Et_3N (0.69 mL) in DMF (2.8 mL) at 60 °C afforded, after purification by column chromatography (silica gel, 90 : 10 hexane–EtOAc), 117.6 mg (90%) of the title compound as a white solid. m.p.: 215–216 °C (CH_2Cl_2). ^{1}H-NMR (400.16 MHz, DMSO-d_6) δ 10.23 (s, 1H, NH), 9.10 (s, 1H, NH), 7.91 (d, J = 8.3 Hz, 1H, ArH), 7.77 (d, J = 2.4 Hz, 1H, ArH), 7.70 (d, J = 8.9 Hz, 1H, ArH), 7.63 (dd, J = 7.8, 1.6 Hz, 1H, ArH), 7.58 (dd, J = 8.8, 2.4 Hz, 1H, ArH), 7.50–7.38 (m, 2H, ArH + Csp^2–H), 7.25 (t, J = 7.3 Hz, 1H, ArH), 6.78 (d, J = 15.4 Hz, 1H, Csp^2–H), 4.20 (q, J = 7.1 Hz, 2H, CH_2), 4.10 (q, J = 7.1 Hz, 2H, CH_2), 1.24 (t, J = 7.1 Hz, 3H, CH_3), 1.17 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100.62 MHz, DMSO-d_6) δ 164.9, 161.8, 153.6, 138.3, 138.1, 137.2, 134.5, 132.8, 132.3, 130.2, 129.7, 125.2, 123.7, 123.3, 116.6, 115.2, 115.0, 92.0, 89.9, 60.9, 60.8, 14.4, 14.0 ppm. MS (ESI^+): m/z (%) 509 (M + Na^+, ^{81}Br), 507 (M + Na^+, ^{79}Br), 487 (M + H^+, ^{81}Br), 485 (M + H^+, ^{79}Br), 340 (6), 318 (8), 290 (4), 262 (3). HRMS (ESI^+): Calc. for $C_{23}H_{22}{}^{79}BrN_2O_5$ ([M + H]$^+$) 485.07066; found, 485.07086. IR (neat): ν 3293 (m, N–H), 2981 (w, C–H), 1701 (m, C═O), 1671 (s, C═O) cm^{-1}.

Ethyl (*E*)-4-((2-((2-*tert*-butoxycarbonylamino-phenyl)-ethynyl)-phenyl)-amino)-4-oxobut-2-enoate 5be. Following the general procedure for the Sonogashira reaction, the reaction of *tert*-butyl 2-iodophenyl formate **6e** (76 mg, 0.238 mmol), ethyl (*E*)-4-(2-ethynylphenylamino)-4-oxobut-2-enoate **7b** (69 mg, 0.286 mmol), $PdCl_2(PPh_3)_2$ (0.003 g, 0.005 mmol), CuI (0.002 g, 0.009 mmol) and Et_3N (0.62 mL) in DMF (2.5 mL) at 80 °C afforded, after purification by column chromatography (silica gel, 85 : 15 hexane–EtOAc), 102.1 mg (99%) of the title compound as a white solid. m.p.: 127–128 °C ($CDCl_3$). ^{1}H-NMR (400.16 MHz, $CDCl_3$) δ 8.52 (d, J = 8.3 Hz, 1H, ArH), 8.21 (s, 1H, NH), 8.15 (d, J = 8.4 Hz, 1H, ArH), 7.56 (dd, J = 7.7, 1.2 Hz, 1H, ArH), 7.49 (td, J = 7.9, 1.6 Hz, 1H, ArH), 7.50–7.38 (m, 2H, ArH), 7.22–7.14 (m, 2H, ArH + NH), 7.12–7.02 (m, 2H, ArH + Csp^2–H), 6.97 (d, J = 15.3 Hz, 1H, Csp^2–H), 4.27 (q, J = 7.1 Hz, 2H, CH_2), 1.51 (s, 9H, $C(CH_3)_3$), 1.32 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 165.3, 161.7, 152.4, 139.7, 138.3, 136.3, 132.2, 132.1, 132.0, 130.5, 130.2, 124.6, 122.7, 120.5, 118.6, 112.7, 110.9, 92.2, 90.4, 81.2, 61.4, 27.3 (3×), 14.2 ppm. MS (ESI^+): m/z (%) 457 (M + Na^+), 435 (M + H^+). HRMS (ESI): Calcd for $C_{25}H_{27}N_2O_5$ ([M + H^+])

435.9145; found, 435.19132. IR (NaCl): ν 3207 (w, N–H), 3267 (w, N–H), 2978 (w, C–H), 1734 (s, C═O), 1666 (s, C═O) cm^{-1}.

7-Methylene-6-oxo-6,7-dihydrobenzo[*b*]azepino[4,5-*b*]indole 9aa and *N*-(2-indol-2-yl-phenyl)-acrylamide 4aa. General procedure for the N-cyclization–Heck reaction. To a solution of **5aa** (32 mg, 1.122 mmol) in DMF (3 mL) were added $PdCl_2(PPh_3)_2$ (4 mg, 0.006 mmol), KI (10 mg, 0.061 mmol), and MA (12 mg, 0.122 mmol) and the reaction was heated at 100 °C for 3 hours, under an air atmosphere. The reaction was cooled down to 25 °C and a saturated aqueous solution of NaCl (25 mL) was added. The mixture was extracted with EtOAc (3×), the combined organic layers were washed with water (15 mL) and dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash chromatography to afford 17.4 mg (37%) of **9aa** and 12.3 mg (40%) of **4aa**.

Data for **4aa**: m.p.: 180 °C (dec.) (CH_2Cl_2). ^{1}H-NMR (400.16 MHz, DMSO-d_6) δ 10.37 (s, 1H, NH), 7.79 (dd, J = 7.9, 1.5 Hz, 1H, ArH), 7.71 (d, J = 8.0 Hz, 1H, ArH), 7.48 (d, J = 8.0 Hz, 1H, ArH), 7.36 (ddd, J = 8.3, 7.1, 1.5 Hz, 1H, ArH), 7.30 (dd, J = 8.2, 1.4 Hz, 1H, ArH), 7.24 (ddd, J = 8.2, 6.9, 1.3 Hz, 2H, ArH), 7.12 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H, ArH), 6.12 (d, J = 1.7 Hz, 1H, Csp^2–H), 5.74 (d, J = 1.7 Hz, 1H, Csp^2–H) ppm. ^{13}C-NMR (100.62 MHz, DMSO-d_6) δ 170.6, 137.7, 135.7, 134.7, 132.4, 128.6, 126.6, 126.0, 123.6, 123.0, 121.6, 121.1, 120.5, 120.0, 118.6, 111.6, 110.7 ppm. HRMS (ESI^+): Calcd for $C_{17}H_{13}N_2O$ ($[M + 1]^+$) 261.10224; found, 261.10233. IR (neat): ν 3253 (s, C═H), 1644 (s, C═O) cm^{-1}.

Data for **9aa**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H, NH), 8.43 (d, J = 8.6 Hz, 1H, ArH), 8.06 (s, 1H, NH), 7.68 (dt, J = 7.9, 1.1 Hz, 1H, ArH), 7.49–7.40 (m, 2H, ArH), 7.36 (ddd, J = 8.7, 7.5, 1.6 Hz, 1H, ArH), 7.27 (ddd, J = 8.2, 6.0, 1.3 Hz, 1H, ArH), 7.22–7.16 (m, 2H, ArH), 6.66 (dd, J = 2.1, 1.0 Hz, 1H, ArH), 6.34 (dd, J = 16.9, 1.2 Hz, 1H, H_2), 6.11 (dd, J = 16.9, 10.3 Hz, 1H, H_{3trans}), 5.70 (dd, J = 10.2, 1.1 Hz, 1H, H_{3cis}) ppm. ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 163.9, 136.8, 135.2, 134.0, 131.3, 129.4, 129.3, 128.8, 128.0, 124.7, 123.5, 122.9, 121.6, 120.8, 120.6, 111.3, 102.6 ppm. MS (EI): m/z (%) 262 (M^+, 3), 244 (83), 243 (100), 242 (34). HRMS (EI): Calcd for $C_{17}H_{14}N_2O$ 262.1106; found, 262.1094. IR (neat): ν 3336 (m, N–H), 3209 (m, N–H), 2975 (w, C–H), 2927 (w, C–H), 1649 (s, C═O) cm^{-1}.

Ethyl 7-methylene-6-oxo-6,7-dihydrobenzo[2,3]azepino[4,5-*b*]-indole-12(5*H*)-carboxylate 4ab. Following the general procedure for N-cyclization–Heck reaction, the reaction of acrylamide **5ab** (25 mg, 0.075 mmol), $PdCl_2(PPh_3)_2$ (0.003 g, 0.004 mmol), KI (0.006 g, 0.037 mmol), and MA (7 mg, 0.075 mmol) in DMF (1.8 mL) at 100 °C afforded, after purification by column chromatography (silica gel, 80 : 20 hexane–EtOAc), 13.0 mg (52%) of the title compound as a white solid. m.p.: 205–208 °C (CH_2Cl_2). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H, NH), 8.12 (d, J = 8.4 Hz, 1H, ArH), 7.72 (d, J = 7.8 Hz, 1H, ArH), 7.49–7.43 (m, 1H), 7.40 (d, J = 7.9 1H, ArH), 7.39–7.33 (m, 2H), 7.28 (d, J = 7.3 Hz, 1H), 7.20–7.15 (m, 1H), 6.20 (d, J = 1.1 Hz, 1H, Csp^2–H), 5.87 (d, J = 1.1 Hz, 1H, Csp^2–H), 4.31 (q, J = 7.1 Hz, 2H, CH_2), 1.13 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100.62 MHz, DMSO-d_6) δ 172.2, 151.0, 137.7, 134.6, 134.0, 132.5, 129.8, 128.5, 126.6, 126.0, 124.5, 123.8, 123.1, 122.5, 122.2, 120.9, 119.0, 114.7, 63.7, 13.6 ppm. HRMS (ESI^+): Calcd for $C_{20}H_{17}N_2O_3$ ($[M + H]^+$) 333.12337; found, 333.12402. IR (neat): ν 3192 (w, N–H), 3068 (w, N–H), 2970 (w, C–H), 2923 (w, C–H), 1737 (s, C═O), 1660 (s, C═O) cm^{-1}. X-Ray: see ESI.†

9-Bromo-7-methylene-6-oxo-6,7-dihydrobenzo[*b*]azepino[4,5-*b*]indole 9ac and *N*-(2-(5-bromo-indol-2-yl)-phenyl)-acrylamide 4ac. Following the general procedure for N-cyclization–Heck reaction, the reaction of acrylamide **5ac** (32 mg, 0.094 mmol), $PdCl_2(PPh_3)_2$ (0.003 g, 0.005 mmol), KI (0.008 g, 0.047 mmol), and MA (9 mg, 0.094 mmol) in DMF (2.3 mL) at 80 °C afforded, after purification by column chromatography (silica gel, 80 : 20 hexane–EtOAc), 15.8 mg (50%) of **9ac** and 15.9 mg (50%) of **4ac** as a white solid.

Data for **4ac**: m.p.: 200 °C (dec.) (CH_2Cl_2). ^{1}H-NMR (400.16 MHz, DMSO-d_6) δ 10.40 (s, 1H, NH), 7.80 (d, J = 2.0 Hz, 1H, ArH), 7.77 (d, J = 8.0 Hz, 1H, ArH), 7.44 (dd, J = 8.6, 1.2 Hz, 1H, ArH), 7.41–7.22 (m, 4H, ArH), 6.12 (s, 1H, Csp^2–H), 5.75 (s, 1H, Csp^2–H) ppm. ^{13}C-NMR (100.62 MHz, DMSO-d_6) δ 170.5, 136.4, 135.1, 135.0, 133.8, 129.2, 127.8, 126.9, 125.5, 123.7, 121.8, 121.4, 120.7, 120.7, 113.7, 112.6, 110.1 ppm. HRMS (ESI^+): Calc. for $C_{17}H_{12}{}^{79}BrN_2O$ ($[M + H]^+$) 339.01275; found, 339.01264. IR (neat): ν 3256 (w, C–H), 3036 (w, C–H), 1648 (s, C═O) cm^{-1}.

Data for **9ac**: m.p.: 94–96 °C (CH_2Cl_2). ^{1}H-NMR (400.16 MHz, DMSO-d_6) δ 9.96 (s, 1H, NH), 7.93 (d, J = 1.9 Hz, 1H, ArH), 7.87 (dd, J = 7.8, 1.3 Hz, 1H, ArH), 7.63 (d, J = 8.1 Hz, 1H, ArH), 7.59 (d, J = 8.7 Hz, 1H, ArH), 7.46 (m, 2H, ArH), 7.38 (td, J = 7.7, 1.1 Hz, 1H, ArH), 6.53 (dd, J = 16.9, 10.2 Hz, 1H, H_2), 6.26 (dd, J = 17.1, 1.9 Hz, 1H, H_{3trans}), 5.80 (dd, J = 10.2, 1.6 Hz, 1H, H_{3cis}) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.7, 154.3, 152.7, 151.8, 134.6, 131.6, 131.0, 129.5, 128.1, 127.2, 127.2, 127.1, 126.1, 123.7, 115.4, 113.1, 104.5 ppm. MS (ESI^+): m/z (%) 343 ($[M + H]^+$, ^{81}Br), 341 ($[M + H]^+$, ^{79}Br). HRMS (ESI^+): Calcd for $C_{17}H_{14}{}^{79}BrN_2O$ ($[M + H]^+$) 341.02840; found, 341.02751. IR (neat): ν 3364 (s, N–H), 3265 (w, N–H), 1669 (s, C═O) cm^{-1}.

Ethyl (*E*)-4-(2-(1*H*-indol-2-yl)-phenylamino)-4-oxobut-2-enoate 9ba. Following the general procedure for N-cyclization–Heck reaction, the reaction of compound **5ba** (65 mg, 0.194 mmol), $PdCl_2(PPh_3)_2$ (0.007 g, 0.010 mmol), KI (0.016 g, 0.097 mmol), and MA (19 mg, 0.194 mmol) in DMF (4.75 mL) at 100 °C afforded, after purification by column chromatography (silica gel, 80 : 20 hexane–EtOAc), 45.1 mg (70%) of the title compound as a white solid. m.p.: 131 °C (CH_2Cl_2). ^{1}H-NMR (400.16 MHz, $CDCl_3$) δ 8.59 (s, 1H, NH), 8.46 (d, J = 8.3 Hz, 1H, ArH), 8.27 (s, 1H, NH), 7.70 (d, J = 7.9 Hz, 1H, ArH), 7.56–7.40 (m, 2H, ArH), 7.38 (t, J = 8.1 Hz, 1H, ArH), 7.28 (t, J = 8.1 Hz, 1H, ArH), 7.32–7.18 (m, 2H, ArH), 6.87 (app s, 2H, 2 × Csp^2–H), 6.67 (d, J = 0.9 Hz, 1H, ArH), 4.23 (q, J = 7.1 Hz, 2H, CH_2), 1.30 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 165.3, 161.9, 136.8, 136.2, 134.8, 133.6, 131.9, 129.5, 129.3, 128.8, 125.2, 123.6, 123.1, 121.6, 121.0, 120.8, 111.3, 102.8, 61.4, 14.2 ppm. MS (EI): m/z (%) 334 (M^+, 12), 317 (25), 316 (94), 288 (38), 244 (23), 243 (100), 242 (79). HRMS (EI): Calcd for $C_{20}H_{18}N_2O_3$ 334.1317; found, 334.1325.

IR (neat): ν 3216 (br, N–H), 3058 (w, C–H), 2925 (w, C–H), 1706 (s, C═O), 1670 (s, C═O) cm^{-1}.

Ethyl (*Z*)-7-(2-ethoxy-2-oxoethylene)-6-oxo-6,7-dihydrobenzo-[2,3]azepino[4,5-*b*]indole-12(5*H*)-carboxylate 4bb and (*Z*)-7-(2-ethoxy-2-oxoethylene)-6-oxo-6,7-dihydrobenzo[*b*]azepino[4,5-*b*]-indole 4ba. Following the general procedure for N-cyclization–Heck reaction, the reaction of compound **5bb** (35 mg, 0.861 mmol), $PdCl_2(PPh_3)_2$ (0.030 g, 0.043 mmol), KI (0.071 g, 0.430 mmol), and MA (84 mg, 0.861 mmol) in DMF (21 mL) at 110 °C afforded, after purification by column chromatography (silica gel, 70 : 30 hexane–EtOAc), 23.9 mg (80%) of **4bb** and 4.9 mg (20%) of **4ba** as a white solid.

Data for **4bb**. m.p.: 200 °C (dec.) (CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H, NH), 8.20 (d, J = 8.3 Hz, 1H, ArH), 7.79 (dd, J = 7.7, 1.2 Hz, 1H, ArH), 7.45 (ddd, J = 8.5, 7.3, 1.3 Hz, 1H, ArH), 7.41–7.31 (m, 3H, ArH), 7.28 (d, J = 7.9 Hz, 1H, ArH), 7.20 (td, J = 7.5, 1.4 Hz, 1H, ArH), 6.31 (s, 1H, Csp^2–H), 4.35 (q, J = 7.2 Hz, 2H, CH_2), 4.25 (q, J = 7.1 Hz, 2H, CH_2), 1.31 (t, J = 7.1 Hz, 3H, CH_3), 1.21 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 168.7, 164.7, 151.5, 139.0, 138.6, 133.9, 132.9 (2×), 129.9, 128.7, 126.4, 125.0 (2×), 124.1, 123.9, 122.8, 121.7, 119.2, 115.4, 63.8, 61.1, 13.9, 13.8 ppm. HRMS (ESI^+): Calc. for $C_{23}H_{21}N_2O_5$ ($[M + H]^+$) 405.14450; found, 405.14453. FTIR (neat): ν 3290 (w, N–H), 2922 (w, C–H), 1731 (s, C═O), 1712 (s, C═O) cm^{-1}. X-Ray: see ESI.†

Data for **4ba**. m.p.: 230–232 °C (CH_2Cl_2). ^{1}H-NMR (400.16 MHz, DMSO-d_6) δ 10.75 (s, 1H, NH), 7.78 (d, J = 7.9 Hz, 1H, ArH), 7.66 (d, J = 7.9 Hz, 1H, ArH), 7.50 (d, J = 8.1 Hz, 1H, ArH), 7.40 (t, J = 7.1 Hz, 1H, ArH), 7.34–7.22 (m, 3H, ArH), 7.16 (t, J = 7.5 Hz, 1H, ArH), 6.21 (s, 1H, Csp^2–H), 4.13 (q, J = 7.1 Hz, 2H, CH_2), 1.23 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100.62 MHz, DMSO-d_6) δ 166.1, 165.6, 139.8, 137.8, 134.2, 133.7, 128.9, 127.1, 125.1, 124.0, 123.4 (2×), 122.1, 121.3, 120.6, 118.2, 112.0, 110.4, 60.2, 13.9 ppm. HRMS (ESI^+): Calcd for $C_{20}H_{17}N_2O_3$ ($[M + H]^+$) 333.12337; found, 333.12361. IR (neat): ν 3333 (w, N–H), 3038 (w, C–H), 2921 (w, C–H), 1710 (s, C═O), 1618 (s, C═O) cm^{-1}.

(*Z*)-Ethyl 9-bromo-7-(2-ethoxy-2-oxoethylene)-6-oxo-6,7-dihydrobenzo[2,3]azepino[4,5-*b*]indole-12(5*H*)-carboxylate 4bd. Following the general procedure for N-cyclization–Heck reaction, the reaction of compound **5bd** (22 mg, 0.045 mmol), $PdCl_2(PPh_3)_2$ (2 mg, 0.002 mmol), KI (4 mg, 0.022 mmol), and MA (4 mg, 0.045 mmol) in DMF (1.2 mL) at 120 °C afforded, after purification by column chromatography (silica gel, 80 : 20 hexane–EtOAc), 13.0 mg (60%) of the title compound as a white solid. m.p.: 250 °C (CH_2Cl_2). ^{1}H-NMR (400.16 MHz, DMSO-d_6) δ 10.79 (s, 1H, NH), 8.10 (d, J = 8.8 Hz, 1H, ArH), 7.77 (d, J = 2.1 Hz, 1H, ArH), 7.65 (dt, J = 8.9, 1.7 Hz, 1H, ArH), 7.50 (dd, J = 8.0, 1.5 Hz, 1H, ArH), 7.42 (t, J = 7.6 Hz, 1H, ArH), 7.30 (d, J = 8.1 Hz, 1H, ArH), 7.22 (t, J = 7.6 Hz, 1H, ArH), 6.52 (s, 1H, Csp^2–H), 4.42–4.24 (br, 2H, CH_2), 4.15 (q, J = 7.0 Hz, 2H, CH_2), 1.25 (t, J = 7.1 Hz, 3H, CH_3), 1.14 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100.62 MHz, DMSO-d_6) δ 167.8, 164.8, 150.4, 137.8, 136.6, 134.7, 133.8, 130.3, 129.1, 128.8, 127.4, 125.4, 123.5, 122.7, 122.5, 121.0, 119.2, 117.1, 116.5, 64.2, 60.6, 13.8, 13.6 ppm. HRMS (ESI^+): Calc. mass for $C_{23}H_{20}{}^{79}BrN_2O_5$ ($[M + H]^+$) 483.05501; found, 483.05485. IR (neat): ν 3293 (w, N–H), 3070 (w, C–H), 2978 (w, C–H), 1731 (s, C═O), 1711 (s, C═O), 1665 (s, C═O) cm^{-1}.

***tert*-Butyl 7-methylene-6-oxo-6,7-dihydrobenzo[2,3]azepino-[4,5-*b*]indole-12(5*H*)-carboxylate 4ae and *N*-(2-indol-2-yl-phenyl)-acrylamide 4aa.** Following the general procedure for N-cyclization–Heck reaction, the reaction of compound **5ae** (20 mg, 0.055 mmol), $PdCl_2(PPh_3)_2$ (0.002 g, 0.003 mmol), KI (0.005 g, 0.028 mmol), and MA (5 mg, 0.055 mmol) in DMF (1.4 mL) at 110 °C afforded, after purification by column chromatography (silica gel, 70 : 30 hexane–EtOAc), 4.3 mg (22%) of **4ae** and 11.1 mg (78%) of **4aa** as a white solid.

Data for **4ae**. m.p.: >150 °C (dec.) ($CDCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H, NH), 8.20 (d, J = 8.4 Hz, 1H, ArH), 7.75 (d, J = 7.8 Hz, 1H, ArH), 7.46–7.38 (m, 2H, ArH), 7.32 (dd, J = 11.2, 4.6 Hz, 2H, ArH), 7.21 (td, J = 7.8, 1.1 Hz, 1H, ArH), 7.13 (d, J = 8.0 Hz, 1H, ArH), 6.39 (d, J = 1.0 Hz, 1H, Csp^2–H), 5.93 (s, 1H, Csp^2–H), 1.41 (s, J = 12.8 Hz, 9H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.7 (s), 150.8 (s), 139.4 (s), 135.0 (s), 133.8 (s), 133.3 (s), 130.8 (d), 128.9 (d), 127.7 (s), 126.4 (d), 125.6 (t), 124.1 (s), 124.0 (d), 124.0 (d), 122.2 (d), 121.8 (s), 119.5 (d), 115.3 (d), 84.6 (s), 27.4 (q) ppm. MS (ESI): m/z (%) 361 (M^+), 331, 305, 287, 233. HRMS (ESI): Calcd for $C_{22}H_{21}N_2O_3$ 361.15467; found, 361.15474. FTIR (NaCl): ν 3403 (w, N–H), 3311 (w, C–H), 2980 (w, C–H), 1726 (s, C═O), 1689 (s, C═O) cm^{-1}.

Ethyl (*Z*)-7-(2-*tert*-butoxy-2-oxoethylene)-6-oxo-6,7-dihydrobenzo[2,3]azepino[4,5-*b*]indole-12(5*H*)-carboxylate 4be and (*Z*)-7-(2-ethoxy-2-oxoethylene)-6-oxo-6,7-dihydrobenzo[*b*]azepino-[4,5-*b*]indole 4ba. Following the general procedure for N-cyclization–Heck reaction, the reaction of compound **5be** (34 mg, 0.078 mmol), $PdCl_2(PPh_3)_2$ (3 mg, 0.004 mmol), KI (6 mg, 0.039 mmol), and MA (8 mg, 0.078 mmol) in DMF (2 mL) at 120 °C afforded, after purification by column chromatography (silica gel, 60 : 40 hexane–EtOAc), 7.44 mg (22%) of **4be** and 20.3 mg (78%) of **4ba**.

Data for **4be**. m.p.: >250 °C (dec.) ($CDCl_3$). ^{1}H-NMR (400.16 MHz, $CDCl_3$) δ 9.85 (s, 1H, NH), 8.23 (d, J = 8.3 Hz, 1H, ArH), 7.81 (d, J = 7.8 Hz, 1H, ArH), 7.39 (m, 5H, ArH), 7.24–7.19 (m, 1H, ArH), 6.32 (s, 1H, Csp^2–H), 4.23 (q, J = 7.1 Hz, 2H, CH_2), 1.40 (s, 9H, $C(CH_3)_3$), 1.29 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 169.8, 165.5, 150.4, 139.8, 139.4, 134.6, 133.4, 130.6, 129.0, 126.6 (2×), 125.1, 124.5, 124.2, 124.2, 123.3, 121.6, 119.4, 115.5, 84.8, 61.1, 27.4, 13.7. MS (ESI^+): m/z (%) 433 ($[M + H]^+$), 387, 331, 287. HRMS (ESI^+): Calcd for $C_{25}H_{25}N_2O_5$ ($[M + H]^+$) 433.17580; found, 433.17562. IR (NaCl): ν 3190 (w, N–H), 2979 (w, C–H), 1735 (s, C═O), 1666 (s, C═O) cm^{-1}.

Biology

Cell lines. Human leukemia U937 cells were grown in RPMI medium with 10% fetal bovine serum (FBS) (Sigma), 2 mM L-glutamine (Euroclone) and antibiotics (100 U mL^{-1} penicillin, 100 μg mL^{-1} streptomycin and 250 ng mL^{-1} amphotericin-B). Human breast cancer MCF7 cells were propagated in DMEM medium with 10% fetal bovine serum (FBS) (Sigma),

2 mM L-glutamine (Euroclone) and antibiotics (100 U mL^{-1} penicillin, 100 μg mL^{-1} streptomycin and 250 ng mL^{-1} amphotericin-B) as previously reported.[35]

Cell cycle and cell death analysis. These assays were performed as described.[36]

Sirt1 assay. The Sirt1 assay was performed following the manufacturer's indications (Millipore). Briefly, this assay uses nicotinamidase to measure the nicotinamide produced upon cleavage of NAD^+ during the sirtuin-mediated deacetylation of a substrate providing a direct assessment of the activity. The use of an untagged acetylated peptide can eliminate part of the potential artifacts. Sirt1 recombinant human enzyme was produced in house following standard procedures.

Protein extraction. After the wash, cell pellets were resuspended in lysis buffer (50 mM Tris-HCl pH 7.4, 150 mM NaCl, 1% NP40, 10 mM NaF, 1 mM PMSF and protease inhibitor cocktail). The lysis reaction was carried out for 15 min at 4 °C. Finally, the samples were centrifuged at 13 000 rpm for 30 min at 4 °C and the protein concentration was quantified by the Bradford assay (Bio-Rad).

Western blot. 50 μg of proteins were loaded on 10% polyacrylamide gels. The nitrocellulose filters were stained with Ponceau red (Sigma) as the additional control for equal loading. ERK1 antibody was from Santa-Cruz and P53K382ac antibody was from Millipore.

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