

Cite this: *RSC Adv.*, 2018, 8, 34903Received 2nd October 2018
Accepted 4th October 2018

DOI: 10.1039/c8ra08165d

rsc.li/rsc-advances

One step access to oxindole-based β -lactams through Ugi four-center three-component reaction†

Giulia Rainoldi,^a Giordano Lesma,^a Claudia Picozzi,^b Leonardo Lo Presti^a and Alessandra Silvani^{b*}

A multicomponent Ugi reaction involving isatin, isocyanide and β -amino acid components has been developed. The reactions proceeded smoothly to give β -lactam-containing 3,3-disubstituted oxindoles in only one step and generally high yields. When chiral, non racemic, β -amino acids were used, products were obtained as enantiomerically pure β -lactams diastereoisomers, whose relative stereochemistry was determined by X-ray analysis. For one compound, a weak antibacterial activity has been preliminarily highlighted.

Introduction

The β -lactam fragment constitutes a part of various naturally occurring compounds, a number of which exhibit pronounced biological activity. Despite many decades of clinical significance from the discovery of penicillin forward, it remains an interesting pharmacophore for medicinal chemistry and novel applications of β -lactam derivatives continue to be developed.¹ On the other hand, 3-substituted-3-amino-2-oxindoles are also recurring core structures, that can be found in drug molecules and biologically active compounds acting on different targets² (Fig. 1). Since the manifold biological activities of 3-substituted-3-amino-2-oxindoles are strongly influenced by the type of substitution at C3 position, the rapid construction of such privileged compounds, displaying complex and varied architectures, is a valuable way to contribute to drug discovery.³

As part of our interest in the synthesis of aminooxindoles and related spiro-compounds,⁴ we recently turned our attention to the molecular hybridization concept, a viable and effective approach envisioning the rational design of new functional compounds through the structural fusion of two pharmacophoric subunits from known structures into one chemical entity. Until now, several new chemical classes have been discovered by the combination of pharmacophoric moieties of

known molecules, resulting often in novel and more potent hybrid derivatives.⁵ As, to the best of our knowledge, no methods have been reported for the preparation of oxindoles bearing a *N*-jointed β -lactam ring at the key C3 position, we envisioned the first construction of such hybrid molecules, selecting in particular, a peptidomimetic scaffold as the privileged target. New peptidomimetic small molecules are indeed desirable, particularly in the highly challenging fields of protein–protein interactions targeting and of antimicrobial drug discovery research.⁶ Among strategies to the β -lactam ring, Staudinger reaction involving [2 + 2] cycloaddition of ketenes and imines has been the most widely used protocol.⁷ Considering a multicomponent approach more suitable for the rapid generation of peptidomimetic backbones containing the β -lactam ring, we looked at the Ugi four-center three-component reaction (Ugi-4C-3CR),⁸ using easily accessible β -amino acids,

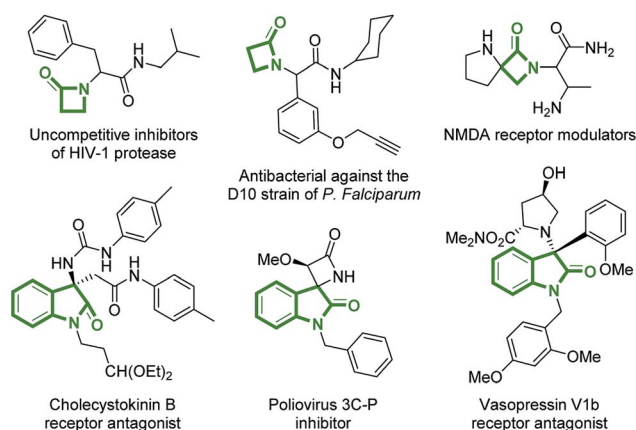


Fig. 1 Examples of biologically relevant compounds containing β -lactam or 3-substituted-3-amino-2-oxindole fragments.

^aDipartimento di Chimica, Università degli Studi di Milano, Via Golgi 19, Milano, 20133, Italy. E-mail: alessandra.silvani@unimi.it

^bDepartment of Food, Environmental and Nutritional Sciences (DeFENS), Division of Food Microbiology and Bioprocessing, Via Celoria 2, 20133 Milan, Italy

† Electronic supplementary information (ESI) available: ¹H NMR and ¹³C NMR spectra for all new compounds, X-ray data, table of physicochemical properties. CCDC 1849730. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ra08165d

isocyanides and isatins. Apart a single example reported,⁹ this is the first wide application of such reaction involving a ketone as the carbonyl component and following the complete Ugi pathway, including the final rearrangement, leading to β -lactam derivatives.

Herein, we report the high yield, single step synthesis of a variety of oxindole-based β -lactams, bearing a peptidomimetic backbone, some their post-transformations and they evaluation according to the Lipinski rule of five and against a set of bacterial strains.

Results and discussion

Initially, *N*-Bn isatin **1a**, *tert*-butyl isocyanide **2a** and β -alanine **3a** were selected to optimize the conditions for the Ugi-4C-3CR (Table 1). We started our investigation considering aprotic solvents such as dichloromethane and toluene (entries 1–2),

Table 1 Optimization of the reaction conditions^a

Entry	Solvent	Conc. [M]	Time [h]	Yield ^b (%)
1	CH ₂ Cl ₂	0.25	24	<5
2	Toluene	0.25	24	<5
3	MeOH	0.25	18	15
4	TFE	0.25	6	61
5	TFE	0.5	6	95
6	TFE	1.0	6	87

^a Reactions were performed on a 0.3 mmol scale, with **1a** : **2a** : **3a** in a 1 : 1 : 1 ratio, at room temperature. ^b Isolated yields.

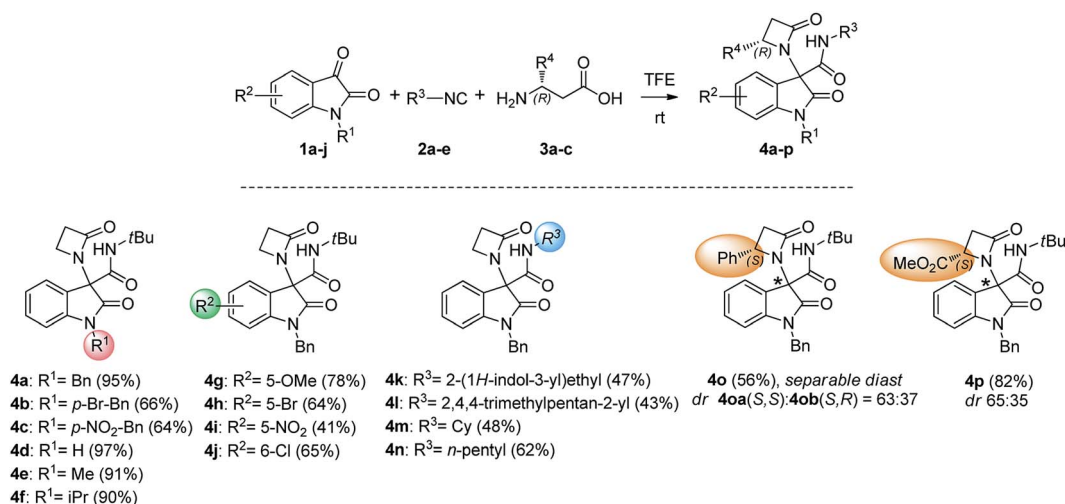
but the reaction was found to be sluggish. Working in MeOH (entry 3), the same reaction afforded the desired β -lactam **4a** in low yield. When we switched to the more acidic tri-fluoroethanol (TFE), following our recent achievements in different Ugi-type reactions,¹⁰ both the reaction rate and yield definitely increased (entries 4–6). With satisfactory conditions in hand, a variety of substituted isatins **1a–j** were next explored to investigate the carbonyl component scope of the Ugi-4C-3CR (Scheme 1). Working with *tert*-butyl isocyanide (**2a**) and β -alanine **3a**, the protecting group on the oxindole nitrogen atom was found to have a moderate influence on the reaction, with compounds **4a–f** obtained in substantial yields, up to 97%.

Next, *N*-benzyl-isatins bearing various substituents on the aromatic ring were explored. Good yields of the corresponding β -lactams derivatives were obtained in the presence of a variety of substituents, including electron-donating group (**4g**) and halogen substituents at either the 5- or 6-position (**4h** and **4j**), whereas the reaction proved to be moderately inhibited when a strongly electron-withdrawing group was present (**4i**).

Investigation of the isocyanide component (**2a–e**) scope was also conducted. Expected β -lactams **4k–n** were readily obtained, both with aliphatic and heteroaromatic isocyanides, although in a generally bit lower yield.

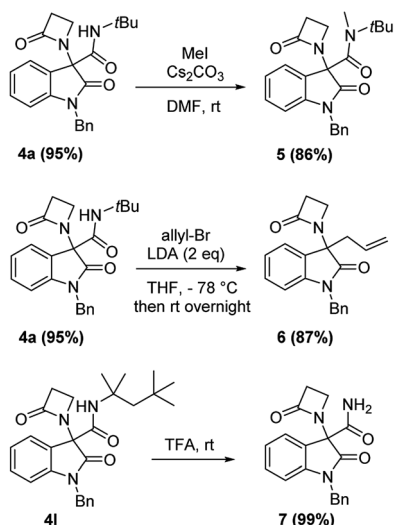
Finally, two enantiomerically pure β -amino acids, namely (*S*)-3-amino-3-phenylpropanoic acid and (*S*)-3-amino-4-methoxy-4-oxobutanoic acid (**3b**, **c**), were tested in the reaction. Compounds **4o** and **4p** were easily obtained as mixtures of enantiomerically pure β -lactams diastereoisomers.

Chromatographic separation on compound **4o** allowed to obtain crystals of diastereoisomers **4oa** and **4ob**, suitable for determination of relative (and absolute) stereochemistry. By means of X-ray analysis of the major diastereoisomer **4oa**, given the fixed *S* configuration at the β -lactam stereocenter, the configuration at the oxindole ring stereocenter was found to be



Scheme 1 Components scope of the Ugi-4C-3CR.^a Reaction conditions: isatin **1** (0.5 mmol), isocyanide **2** (0.5 mmol) and β -amino acid **3** (0.5 mmol) in TFE (1 mL), stirred at room temperature. Isolated yields are reported. PBB = *p*-bromobenzyl, PNB = *p*-nitrobenzyl.





Scheme 2 Post-transformation reactions performed on selected compounds.

S (Fig. 2; see ESI† for full crystallographic details). Considering the quite similar chemical shifts trend in NMR spectra of **4o** and **4p**, the same *S,S*-configuration could be conceivably assigned also to the **4p** major diastereoisomer. Having established the scope of the method, some post-transformations were performed on selected derivatives (Scheme 2). The reaction of β -lactam **4a** with methyl iodide under basic conditions gave the alkylated amide **5** in high yield. Aiming to obtain the double functionalization on both the NH and at the α -position on the lactam moiety, compound **4a** was also treated with two equivalents of LDA followed by the addition of allyl bromide.

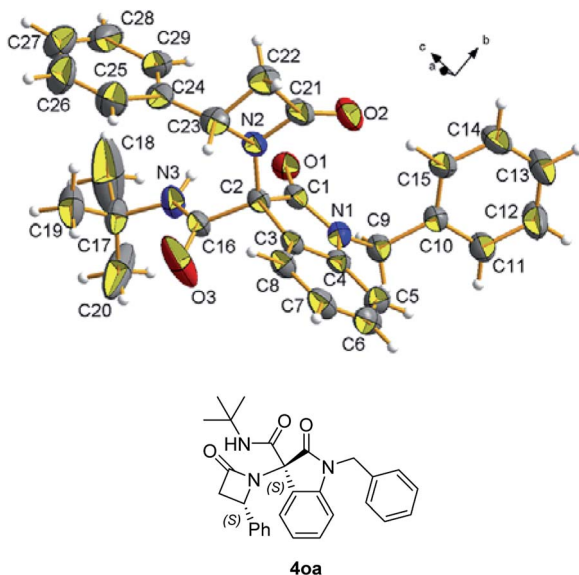
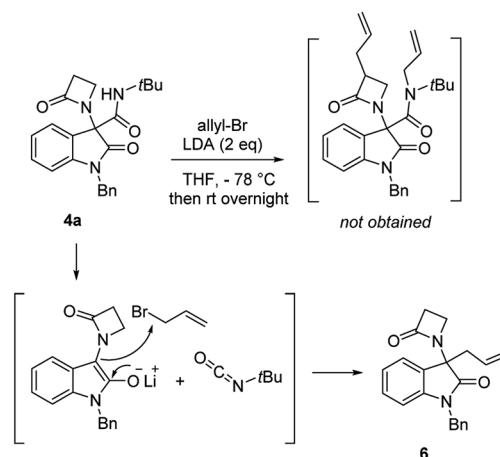


Fig. 2 ORTEP view of compound **4oa** with the atom-numbering scheme. The crystallographic reference system is also highlighted. Thermal ellipsoids of non-H atoms at RT were drawn at the 30% probability level.

However, in this condition, only the unprecedented product **6** was obtained in good yield, likely deriving from a retro-condensation process, followed by irreversible allylation. This outcome discloses an effective deacylative alkylation strategy,¹¹ that could be useful for the construction of a variety of 3,3-disubstituted 2-oxindoles. A proposed mechanism for this reaction is reported in Scheme 3. Finally, starting from compound **4l**, the secondary amido group was easily dealkylated under acid conditions to give the primary amide **7** in quantitative yield, fully demonstrating the high versatility of 2-isocyanato-2,4,4-trimethylpentane as cleavable isocyanide. To evaluate the suitability of the obtained compounds in drug discovery programs, their physico-chemical properties have been calculated using DruLiTo¹² (calculation details are provided in the ESI†). All compounds proved to be drug-like according to the rule of five (Ro5) proposed by Lipinski, having a calculated octanol/water partition ($\log P$) lower than 3, therefore positioning themselves in the highly hydrophilic area (Fig. 3). Regarding the other Ro5 properties, all the synthesized compounds have hydrogen bonding donor groups (HBD) lower than five and hydrogen bonding acceptor groups (HBA) lower than ten (Fig. 4). Further, the presence of rotational bonds (RB) lower than ten and the polar surface area prediction (TPSA) lower than 140 Å² (see ESI†) show that all compounds also meet the more recent Veber's rule¹³ on good oral bioavailability, making them definitively of potential interest from the pharmacological point of view.

Lastly, a preliminary biological evaluation was also performed. The antibacterial activity was tested by the disc diffusion method¹⁴ using Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus* and *Streptococcus mutans*) bacteria. The results show that one of the synthesised compounds, namely **4e**, gives rise to a slight inhibition zone (9.5 ± 0.7 mm) on *St. mutans* at a concentration of 0.81 mM. None of the other compounds displayed activity at concentrations less than 1 mM.



Scheme 3 Proposed mechanism for compound **6**.



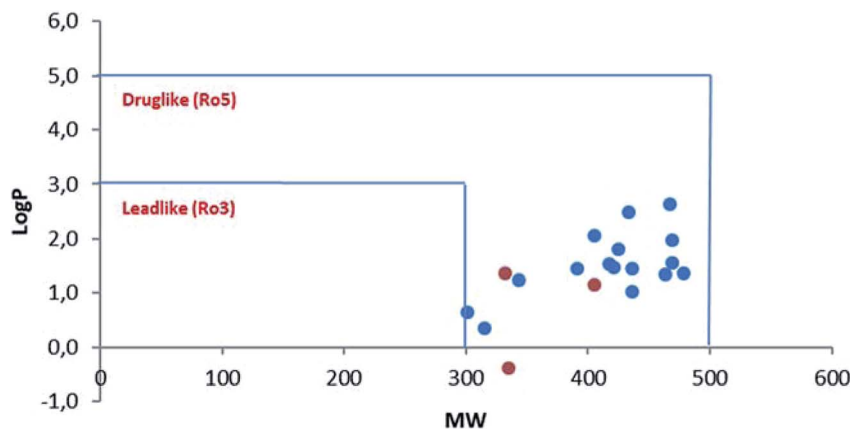


Fig. 3 Drug- and lead-likeness (MW/log *P*) of all the products obtained in this work. Blue-spots: β -lactams derivatives 4a–p. Red-spots: post-transformation derivatives 5–7.

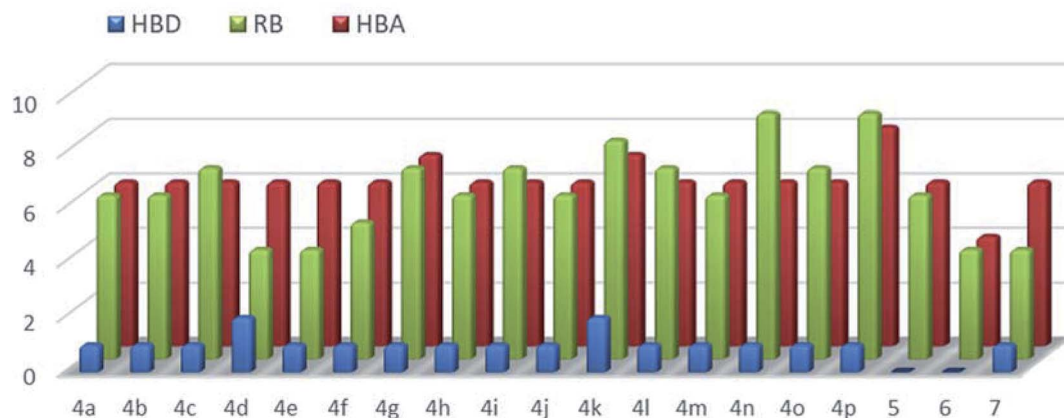


Fig. 4 Calculated hydrogen bonding donors (HBD, blue-bars), hydrogen bonding acceptors (HBA, red-bars), and rotational bonds (RB, greenbars) for all the synthesized compounds.

Conclusions

In conclusion, we have achieved the one-step synthesis of new β -lactam-containing 3,3-disubstituted oxindole derivatives, relying on the Ugi four-center three-component reaction applied to isatin as the oxo component. The reaction conditions were optimized and adopted for a variety of substituted isatins and isocyanides, employing β -alanine or chiral, non racemic, β -amino acids as bifunctional components. Based on their calculated physicochemical properties, all compounds are eligible for being drug-like and therefore potentially suitable in drug discovery programs. Preliminary evaluation against selected bacterial strains highlighted compound 4e as the more promising for future tuning of functional groups on the β -lactam-oxindole scaffold.

Experimental

General

All commercial materials (Aldrich, Fluka) were used without further purification. All solvents were of reagent grade or HPLC

grade. All reactions were carried out under a nitrogen atmosphere unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light or by treatment with suitable TLC visualization reagents. Products were purified by flash chromatography (FC) on silica gel 60 (230–400 mesh). ^1H NMR spectra and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers. Chemical shifts are reported in parts per million relative to the residual solvent. ^{13}C NMR spectra have been recorded using the APT pulse sequence. Multiplicities in ^1H NMR are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. High-resolution MS spectra were recorded with a LCQ Fleet ion trap mass spectrometer, equipped with an ESI source. All the *N*-substituted isatins were synthesized according to reported literature.¹⁵

General procedure for the Ugi-4C-3CR. To a solution of isatin (0.5 mmol) and β -amino acid (0.5 mmol) in TFE (1 mL), isocyanide (0.5 mmol) was added. The mixture was stirred at room temperature and the conversion was monitored by TLC. The solvent was evaporated *in vacuo* and the crude was purified by flash chromatography (FC) as reported below.



1-Benzyl-*N*-(*tert*-butyl)-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (4a). Prepared using *N*-benzyl isatin, β -alanine and *tert*-butyl isocyanide. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 95%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 7.72 (d, J = 7.6 Hz, 1H), 7.40–7.19 (m, 7H), 7.11 (t, J = 7.6 Hz, 1H), 6.73 (d, J = 7.6 Hz, 1H), 5.05 (d, J = 15.8 Hz, 1H), 4.90 (d, J = 15.8 Hz, 1H), 3.62–3.52 (m, 1H), 3.40–3.32 (m, 1H), 2.97–2.87 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.2, 167.7, 162.7, 143.0, 135.6, 130.7, 129.5 (2C), 128.5, 127.8 (2C), 127.3, 126.3, 124.3, 110.5, 68.9, 52.9, 45.0, 40.0, 36.7, 29.2 (3C); HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{26}\text{N}_3\text{O}_3^+$ $[\text{MH}]^+$ 392.1969, found 392.1971.

1-(4-Bromobenzyl)-*N*-(*tert*-butyl)-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (4b). Prepared using *N*-*p*-Br-benzyl isatin, β -alanine and *tert*-butyl isocyanide FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 66%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, J = 7.4 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.31 (br s, 1H), 7.29–7.19 (m, 3H), 7.10 (t, J = 7.4 Hz, 1H), 6.67 (d, J = 7.4 Hz, 1H), 5.00 (d, J = 15.9 Hz, 1H), 4.79 (d, J = 15.9 Hz, 1H), 3.63–3.53 (m, 1H), 3.43–3.31 (m, 1H), 2.98–2.86 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.5, 167.0, 161.9, 142.0, 134.0, 132.0 (2C), 130.1, 129.0 (2C), 126.6, 125.7, 123.8, 121.8, 109.7, 68.2, 52.3, 43.7, 39.4, 36.1, 28.5 (3C); HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{24}\text{BrN}_3\text{NaO}_3^+$ $[\text{MNa}]^+$ 494.0893, found 494.0899.

***N*-(*tert*-Butyl)-1-(4-nitrobenzyl)-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (4c).** Prepared using *N*-*p*- NO_2 -benzyl isatin, β -alanine and *tert*-butyl isocyanide. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 64%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 8.20 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.36 (br s, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 6.63 (d, J = 7.8 Hz, 1H), 5.20 (d, J = 16.5 Hz, 1H), 4.93 (d, J = 16.5 Hz, 1H), 3.68–3.60 (m, 1H), 3.47–3.40 (m, 1H), 3.00–2.94 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.6, 167.0, 161.7, 147.6, 142.2, 141.7, 130.1, 128.0 (2C), 126.8, 125.7, 124.1 (3C), 109.4, 68.1, 52.4, 43.7, 39.5, 36.1, 28.5 (3C); HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{NaO}_5^+$ $[\text{MNa}]^+$ 459.1639, found 459.1642.

***N*-(*tert*-Butyl)-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (4d).** Prepared using isatin, β -alanine and *tert*-butyl isocyanide. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 97%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 9.47 (br s, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.35 (br s, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 3.65–3.50 (m, 1H), 3.45–3.30 (m, 1H), 2.99–2.81 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.8, 167.5, 162.3, 141.2, 130.1, 126.3, 126.0, 123.2, 111.1, 68.5, 52.2, 39.5, 35.8, 28.4 (3C); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{NaO}_3^+$ $[\text{MNa}]^+$ 324.1319, found 324.1325.

***N*-(*tert*-Butyl)-1-methyl-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (4e).** Prepared using *N*-methyl isatin, β -alanine and *tert*-butyl isocyanide. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 91%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, J = 7.5 Hz, 1H), 7.40–7.25 (m, 2H), 7.12 (td, J = 7.5, 0.9 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H), 3.64–3.45 (m, 1H), 3.41–3.29 (m, 1H), 3.24 (s, 3H), 2.95–2.80 (m, 2H), 1.35 (s, 9H); ^{13}C

NMR (101 MHz, CDCl_3) δ 171.3, 167.1, 162.1, 143.3, 130.1, 126.6, 125.3, 123.6, 108.9, 68.1, 52.2, 39.2, 36.0, 32.6, 28.4 (3C); HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{21}\text{N}_3\text{NaO}_3^+$ $[\text{MNa}]^+$ 338.1475, found 338.1480.

***N*-(*tert*-Butyl)-1-isopropyl-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (4f).** Prepared using *N*-isopropyl isatin, β -alanine and *tert*-butyl isocyanide. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 90%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 7.72 (d, J = 7.6 Hz, 1H), 7.42–7.24 (m, 2H), 7.11 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 4.59 (hept, J = 7.0 Hz, 1H), 3.62–3.46 (m, 1H), 3.38–3.22 (m, 1H), 3.00–2.75 (m, 2H), 1.52 (d, J = 7.0 Hz, 6H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.9, 166.9, 162.2, 142.2, 129.8, 126.9, 126.0, 123.0, 110.3, 67.9, 52.1, 44.9, 39.0, 35.9, 28.5 (3C), 19.2 (2C); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{25}\text{N}_3\text{NaO}_3^+$ $[\text{MNa}]^+$ 366.1788, found 366.1790.

1-Benzyl-*N*-(*tert*-butyl)-5-methoxy-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (4g). Prepared using *N*-benzyl, 5-OMe isatin, β -alanine and *tert*-butyl isocyanide. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 78%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 7.64–7.12 (m, 8H), 6.73 (dd, J = 8.6, 2.6 Hz, 1H), 6.60 (d, J = 8.6 Hz, 1H), 4.98 (d, J = 15.7 Hz, 1H), 4.85 (d, J = 15.8 Hz, 1H), 3.74 (s, 3H), 3.60–3.45 (m, 1H), 3.40–3.25 (m, 1H), 3.00–2.85 (m, 1H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.4, 167.0, 161.8, 156.5, 135.5, 135.0, 128.8 (2C), 127.8, 127.2 (2C), 126.6, 115.0, 113.4, 110.4, 68.4, 55.8, 52.2, 44.3, 39.3, 36.1, 28.5 (3C); HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{27}\text{N}_3\text{NaO}_4^+$ $[\text{MNa}]^+$ 444.1894, found 444.1899.

1-Benzyl-5-bromo-*N*-(*tert*-butyl)-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (4h). Prepared using *N*-benzyl, 5-Br isatin, β -alanine and *tert*-butyl isocyanide. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 64%; yellow foamy solid; ^1H NMR (300 MHz, CDCl_3) δ 7.83 (d, J = 1.0 Hz, 1H), 7.50–7.20 (m, 7H), 6.58 (d, J = 8.4 Hz, 1H), 5.04 (d, J = 15.8 Hz, 1H), 4.86 (d, J = 15.8 Hz, 1H), 3.71–3.50 (m, 1H), 3.50–3.30 (m, 1H), 3.16–2.83 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.3, 166.8, 161.0, 141.3, 134.4, 132.9, 129.8, 129.0 (2C), 128.0, 127.3, 127.1 (2C), 116.5, 111.0, 67.7, 52.4, 44.5, 39.5, 36.2, 28.5 (3C); HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{24}\text{BrN}_3\text{NaO}_3^+$ $[\text{MNa}]^+$ 492.0893, found 492.0899.

1-Benzyl-*N*-(*tert*-butyl)-5-nitro-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (4i). Prepared using *N*-benzyl, 5- NO_2 isatin, β -alanine and *tert*-butyl isocyanide. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 41%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 8.55 (d, J = 2.3 Hz, 1H), 8.18 (dd, J = 8.7, 2.3 Hz, 1H), 7.45–7.23 (m, 6H), 6.80 (d, J = 8.7 Hz, 1H), 5.14 (d, J = 15.9 Hz, 1H), 4.94 (d, J = 15.9 Hz, 1H), 3.73–3.62 (m, 1H), 3.55–3.48 (m, 1H), 3.07–2.97 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.2, 166.8, 160.1, 147.7, 144.2, 133.7, 129.1 (2C), 128.3, 127.1, 126.7 (2C), 126.3, 122.5, 109.7, 67.0, 52.7, 44.8, 39.7, 36.3, 28.5 (3C); HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{NaO}_5^+$ $[\text{MNa}]^+$ 459.1639, found 459.1641.

1-Benzyl-*N*-(*tert*-butyl)-6-chloro-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (4j). Prepared using *N*-benzyl, 6-Cl isatin, β -alanine and *tert*-butyl isocyanide. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 65%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 7.64 (d, J = 8.0 Hz, 1H), 7.42–7.27 (m, 5H), 7.23 (br s, 1H), 7.09 (dd, J = 8.0, 1.8 Hz, 1H), 6.73 (d, J = 1.8 Hz,



1H), 5.00 (d, $J = 15.8$ Hz, 1H), 4.87 (d, $J = 15.8$ Hz, 1H), 3.64–3.54 (m, 1H), 3.42–3.35 (m, 1H), 3.25–2.75 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.7, 167.0, 161.5, 143.5, 136.0, 134.3, 129.0 (2C), 128.1, 127.7, 127.1 (2C), 123.9, 123.7, 110.6, 67.7, 52.4, 44.4, 39.5, 36.1, 28.5 (3C); HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{24}\text{ClN}_3\text{NaO}_3^+ [\text{MNa}]^+$ 448.1398, found 448.1400.

***N*-(2-(1*H*-Indol-3-yl)ethyl)-1-benzyl-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (4k).** Prepared using *N*-benzyl isatin, β -alanine and 3-(2-isocyanoethyl)-1*H*-indole. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 47%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 8.32 (br s, 1H), 7.79 (d, 7.9 Hz, 1H), 7.61 (d, 7.9 Hz, 1H), 7.50–6.90 (m, 12H), 6.71 (d, $J = 7.9$ Hz, 1H), 4.95 (d, $J = 15.8$ Hz, 1H), 4.87 (d, $J = 15.8$ Hz, 1H), 3.75–3.57 (m, 2H), 3.56–3.44 (m, 1H), 3.30–3.18 (m, 1H), 3.20–2.80 (m, 2H), 2.82 (t, $J = 3.6$ Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.0, 167.4, 163.8, 142.5, 136.4, 135.0, 130.2, 128.9 (2C), 127.9, 127.1 (2C), 126.6, 125.4, 123.7, 122.5, 122.0, 119.4, 118.6, 112.2, 111.3, 109.9, 60.4, 44.3, 40.5, 39.5, 36.0, 29.7, 24.9; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{26}\text{N}_4\text{NaO}_3^+ [\text{MNa}]^+$ 501.1897, found 501.1900.

1-Benzyl-2-oxo-3-(2-oxoazetidin-1-yl)-*N*-(2,4,4-trimethylpentan-2-yl)indoline-3-carboxamide (4l). Prepared using 1-benzyl isatin, β -alanine and 2-isocyano-2,4,4-trimethylpentane. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 43%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, $J = 7.8$ Hz, 1H), 7.42–7.20 (m, 6H), 7.20–7.13 (m, 2H), 6.75 (d, $J = 7.8$ Hz, 1H), 5.00 (d, $J = 15.7$ Hz, 1H), 4.93 (d, $J = 15.7$ Hz, 1H), 3.75–3.50 (m, 1H), 3.50–3.25 (m, 1H), 3.02–2.85 (m, 2H), 1.86 (d, $J = 15.0$ Hz, 1H), 1.55 (d, $J = 15.0$ Hz, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 0.94 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.0, 167.7, 162.4, 143.0, 135.6, 130.7, 129.5 (2C), 128.5, 127.9 (2C), 127.5, 126.2, 124.3, 110.4, 69.0, 56.9, 52.9, 45.0, 40.1, 36.8, 32.2, 32.0 (3C), 29.2 (2C); HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{33}\text{N}_3\text{NaO}_3^+ [\text{MNa}]^+$ 470.2414, found 470.2419.

1-Benzyl-*N*-cyclohexyl-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (4m). Prepared using 1-benzyl isatin, β -alanine and cyclohexyl isocyanide. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 48%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 7.4$ Hz, 1H), 7.45–7.18 (m, 7H), 7.11 (t, $J = 7.4$ Hz, 1H), 6.73 (d, $J = 7.4$ Hz, 1H), 5.03–4.92 (m, 2H), 3.82 (m, br, 1H), 3.60 (q, $J = 4.7$ Hz, 1H), 3.36 (q, $J = 4.7$ Hz, 1H), 2.95 (t, br, $J = 4.4$ Hz, 2H), 1.98 (m, br, 1H), 1.86 (m, br, 1H), 1.79–1.65 (m, 2H), 1.60 (m, br, 1H), 1.44–1.11 (m, 5H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.3, 167.3, 162.6, 142.4, 134.9, 130.1, 128.9 (2C), 127.8, 127.1 (2C), 126.5, 125.6, 123.7, 109.9, 68.1, 49.0, 44.3, 39.4, 36.1, 32.6, 32.5, 25.5, 24.5 (2C); HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{27}\text{N}_3\text{NaO}_3^+ [\text{MNa}]^+$ 440.1945, found 440.1943.

1-Benzyl-2-oxo-3-(2-oxoazetidin-1-yl)-*N*-pentylindoline-3-carboxamide (4n). Prepared using 1-benzyl isatin, β -alanine and *n*-pentyl isocyanide. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 62%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 7.74 (d, $J = 7.3$ Hz, 1H), 7.42 (br m, 1H), 7.40–7.20 (m, 6H), 7.11 (t, $J = 7.3$ Hz, 1H), 6.73 (d, $J = 7.3$ Hz, 1H), 5.05–4.91 (m, 2H), 3.60 (q, $J = 4.7$ Hz, 1H), 3.35–3.20 (m, 3H), 3.00–2.90 (m, 2H), 1.56 (quint, $J = 7.1$ Hz, 2H), 1.42–1.21 (m, 4H), 0.90 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.2, 167.4, 163.7, 142.5, 134.8, 130.2, 128.9 (2C), 127.9, 127.2 (2C), 126.6, 125.6, 123.7, 109.9, 68.2,

44.3, 40.2, 39.4, 36.1, 29.0, 28.9, 22.3, 14.0; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{27}\text{N}_3\text{NaO}_3^+ [\text{MNa}]^+$ 428.1945, found 428.1943.

(*S*)-1-Benzyl-*N*-(*tert*-butyl)-2-oxo-3-((*S*)-2-oxo-4-henylazetidin-1-yl)indoline-3-carboxamide (4o). Prepared using 1-benzyl isatin, (*S*)-3-amino-3-phenylpropanoic acid and *tert*-butyl isocyanide. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 56%. Major diastereoisomer (*S,S*) (**4oa**): yellow foamy solid; $[\alpha]_{\text{D}} = -179.1$ (c. 0.6, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.81 (d, $J = 7.4$ Hz, 1H), 7.33–7.12 (m, 12H), 7.10 (t, $J = 7.4$ Hz, 1H), 6.51 (d, $J = 7.4$ Hz, 1H), 5.17 (dd, $J = 5.5$ and 2.4 Hz, 1H), 4.83 (d, $J = 15.9$ Hz, 1H), 4.47 (d, $J = 15.9$ Hz, 1H), 3.44 (dd, $J = 15.0$ and 5.5 Hz, 1H), 2.81 (dd, $J = 15.0$ and 2.4 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.3, 168.8, 163.0, 143.0, 139.1, 135.4, 130.5, 129.5 (2C), 129.2 (2C), 129.1, 128.3, 127.8, 127.6 (2C), 127.5 (2C), 126.7, 124.3, 110.2, 69.5, 56.5, 52.7, 47.3, 44.8, 28.9 (3C); HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{29}\text{N}_3\text{NaO}_3^+ [\text{MNa}]^+$ 490.2101, found 490.2105. Minor diastereoisomer (*R,S*) (**4ob**): yellow foamy solid; $[\alpha]_{\text{D}} = -39.8$ (c. 0.2, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.50 (d, $J = 7.8$ Hz, 1H), 7.35–7.02 (m, 13H), 6.48 (d, $J = 7.8$ Hz, 1H), 4.82 (d, $J = 15.8$ Hz, 1H), 4.73 (dd, $J = 5.5$ and 2.5 Hz, 1H), 4.38 (d, $J = 15.8$ Hz, 1H), 3.43 (dd, $J = 15.0$ and 5.5 Hz, 1H), 2.93 (dd, $J = 15.0$ and 2.5 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.5, 168.5, 166.9, 142.5, 137.6, 134.8, 130.0, 128.8 (2C), 128.6, 128.5 (2C), 127.7, 127.2, 127.1 (4C), 123.8, 123.3, 109.5, 69.5, 55.3, 52.2, 45.8, 44.0, 28.3 (3C); HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{29}\text{N}_3\text{NaO}_3^+ [\text{MNa}]^+$ 490.2101, found 490.2108.

Methyl

(2*S*)-1-(1-benzyl-3-(*tert*-butylcarbamoyl)-2-oxoindolin-3-yl)-4-oxoazetidine-2-carboxylate (4p). Prepared using 1-benzyl isatin, (*S*)-3-amino-4-methoxy-4-oxobutanoic acid and *tert*-butyl isocyanide. FC: hexane : EtOAc, from 1.5 : 1 to 1 : 1.5; yield 82%; yellow foamy solid; ^1H NMR (400 MHz, CDCl_3 , 7 : 3 mixture of diastereoisomers) δ 7.85 (d, $J = 7.5$ Hz, 0.7H), 7.44–7.20 (m, 6.6H), 7.12 (t, $J = 7.6$ Hz, 1H), 6.77 (d, $J = 7.8$ Hz, 0.7H), 6.73 (d, $J = 7.9$ Hz, 0.3H), 6.36 (s, br, 0.7H), 5.02 (d, $J = 15.7$ Hz, 0.7H), 4.93 (s, 0.6H), 4.85 (d, $J = 15.7$ Hz, 0.7H), 4.75 (dd, $J = 6.0$ and 2.7 Hz, 0.7H), 4.37 (dd, $J = 5.7$ and 2.3 Hz, 0.3H), 3.84 (s, 0.9H), 3.58 (s, 2.1H), 3.33 (dd, $J = 14.7$ and 6.1 Hz, 0.7H), 3.22 (dd, $J = 14.6$ and 5.8 Hz, 0.3H), 3.00–2.80 (m, 1H), 1.38 (s, 2.7H), 1.31 (s, 6.3H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.7, 170.9 and 170.3 (1C), 166.9 and 166.6 (1C), 163.9 and 163.1 (1C), 143.4, 135.7, 130.9 and 130.8 (1C), 129.6 (2C), 128.5, 128.0 (2C), 127.7, 126.8 and 126.5 (1C), 124.4, 110.4 and 110.3 (1C), 69.6, 53.4 and 53.0 (1C), 52.9, 52.7 and 51.8 (1C), 45.0, 42.3 and 42.0 (1C), 29.1 (3C); HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{27}\text{N}_3\text{NaO}_5^+ [\text{MNa}]^+$ 472.1843, found 472.1840.

Post-transformation reactions

1-Benzyl-*N*-(*tert*-butyl)-*N*-methyl-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (5). To a solution of compound **4a** (0.30 mmol) in anhydrous dimethylformamide (1 mL), Cs_2CO_3 (0.35 mmol) was added and the mixture was stirred for 1 h at room temperature. Then, methyl iodide (0.40 mmol) was slowly added, and the mixture was stirred overnight. After the completion of the reaction (monitored by TLC), saturated aq. NaCl was added. The reaction mixture was extracted with EtOAc



twice, then the combined organic layers were washed with water, followed by brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude was purified by FC (hexane : EtOAc, from 1.5 : 1 to 1 : 1.5) affording the desired product **5** (86% yield) as a yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 7.44 (d, J = 7.3 Hz, 1H), 7.39–7.26 (m, 5H), 7.22 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 4.99 (d, J = 15.8 Hz, 1H), 4.90 (d, J = 15.7 Hz, 1H), 3.35 (m, br, 1H), 3.28–3.12 (m, 6H), 1.33 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.6, 168.0, 163.3, 142.3, 136.1, 130.0, 129.6 (2C), 128.4, 127.9 (2C), 127.5, 124.5, 124.0, 110.4, 69.8, 57.0, 44.6, 38.3, 36.8, 30.4 (3C), 22.4; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{27}\text{N}_3\text{NaO}_3^+ [\text{MNa}]^+$ 428.1945, found 428.1940.

3-Allyl-1-benzyl-3-(2-oxoazetidin-1-yl)indolin-2-one (6). To a solution of compound **4a** (0.1 mmol) in THF (0.5 mL) cooled at -78°C , LDA (0.2 mmol) was added. After 1 h of stirring at -78°C , allyl bromide (0.25 mmol) was added and the mixture was slowly warmed to 20°C , and further left for 15 h at 20°C . 10% saturated aqueous NH_4Cl and CH_2Cl_2 were added. The organic phase was recovered, washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by FC (hexane : EtOAc, from 1.5 : 1 to 1 : 1.5) obtaining compound **6** (87% yield) as a white foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 7.50 (dd, J = 7.2 and 1.0 Hz, 1H), 7.37–7.23 (m, 5H), 7.21 (td, J = 7.2 and 1.0 Hz, 1H), 7.07 (td, J = 7.2 and 1.0 Hz, 1H), 6.70 (d, J = 7.2 Hz, 1H), 5.41 (dddd, J = 16.5, 10.1, 8.2 and 6.4 Hz, 1H), 5.11 (dq, J = 16.5 and 1.4 Hz, 1H), 5.00 (d, br, J = 10.1 Hz, 1H), 4.95 (d, J = 15.7, 1H), 4.86 (d, J = 15.7, 1H), 3.36 (td, J = 5.5 and 3.0 Hz, 1H), 3.22 (td, J = 5.5 and 3.1 Hz, 1H), 3.20 (ddt, J = 13.3, 6.5 and 1.0 Hz, 1H), 3.05 (dd, J = 13.3, 8.2 Hz, 1H), 2.93 (ddd, J = 14.7, 5.8 and 3.1 Hz, 1H), 2.86 (ddd, J = 14.7, 5.8 and 3.1 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 173.7, 167.2, 142.3, 135.4, 130.1, 129.5, 128.8 (2C), 127.7, 127.3 (2C), 124.8, 123.1, 120.7, 115.2, 109.5, 65.1, 44.0, 39.2, 37.9, 36.1; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{NaO}_2^+ [\text{MNa}]^+$ 355.1417, found 355.1420.

1-Benzyl-2-oxo-3-(2-oxoazetidin-1-yl)indoline-3-carboxamide (7). Compound **4l** (0.1 mmol) was dissolved in TFA (0.5 mL) and stirred overnight at room temperature. The mixture was diluted in EtOAc and washed with water and then brine. The solvent was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure affording product **7** (99% yield). Yellow foamy solid; ^1H NMR (400 MHz, CDCl_3) δ 7.83 (d, J = 7.2 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.43–7.18 (m, 7H), 7.01 (d, J = 7.2 Hz, 1H), 5.61 (br s, 1H), 5.20 (d, J = 15.3 Hz, 1H), 4.73 (d, J = 15.3 Hz, 1H), 3.20–3.07 (m, 1H), 3.07–2.87 (m, 2H), 2.85–2.69 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.0, 169.4, 162.0, 144.4, 135.2, 133.3, 129.9 (2C), 129.2, 128.4 (2C), 127.4, 125.8, 120.0, 111.8, 57.8, 53.6, 45.4, 40.7; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{NaO}_3^+ [\text{MNa}]^+$ 358.1162, found 358.1160.

Antibacterial activity. The antibacterial activity was evaluated by the disc diffusion method¹² using Gram-negative (*Escherichia coli* ATCC25922 and *Pseudomonas aeruginosa* DSM22644) and Gram-positive (*Staphylococcus aureus* ATCC25923 and *Streptococcus mutans* ATCC35668) bacteria. Several morphologically similar colonies for each microorganism, grown overnight at 37°C or 30°C (*P. aeruginosa*) on Tryptic Soy Agar (TSA, Scharlab, Barcelona, Spain), were selected and suspended in sterile saline

solution (0.85% NaCl w/v) to a turbidity of 0.5 McFarland standard, approximately corresponding to $1\text{--}2 \times 10^8$ CFU mL^{-1} . Each bacterial suspension was then spread over Mueller–Hinton Agar (MHA, Merck KGaA, Darmstadt, Germany) plates by swabbing in three directions. Solutions were prepared in an initial concentration of approximately $500 \mu\text{g mL}^{-1}$ and then serially diluted two-fold for three times. Sterile discs (6 mm diameter) were then placed on agar plates and loaded with $50 \mu\text{L}$ of each dilution. After incubation at 37°C or 30°C for 18–24 h, plates were checked to evaluate the presence of inhibition zones.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- Reviews: (a) A. V. Sklyarenko, M. A. El'darov, V. B. Kurochkina and S. V. Yarotsky, Enzymatic synthesis of β -lactam acids (review), *Appl. Biochem. Microbiol.*, 2015, **51**, 627–640; (b) B. K. Banik, Novel synthesis of β -lactams and their biological evaluation, *J. Indian Chem. Soc.*, 2014, **91**, 1837–1860; (c) G. S. Singh, β -Lactams in the new millenium. Part-II: Cephems, oxacephems, penams and sulbactam, *Mini-Rev. Med. Chem.*, 2004, **4**, 93–109. Selected examples: ; (d) T. Sperka, J. Pitlik, P. Bagossi and J. Tozser, Beta-lactam compounds as apparently uncompetitive inhibitors of HIV-1 protease, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3086–3090; (e) M. A. L. Blackie, F. Tzu-Shean, P. J. Smith and K. Chibale, Synthesis of novel β -lactams and *in vitro* evaluation against the human malaria parasite *Plasmodium falciparum*, *ARKIVOC*, 2016, **iii**, 214–235; (f) A. Khan, J. Moskal and P. Wood, NMDA receptor modulators and uses thereof for the treatment of cognitive and other conditions, PCT Int. Appl., WO 2010033757 A1 20100325, 2010.
- (a) T. Oost, G. Backfisch, S. Bhowmik, M. M. van Gaalen, H. Geneste, W. Hornberger, W. Lubisch, A. Netz, L. Unger and W. Wernet, Potent and selective oxindole-ased vasopressin 1b receptor antagonists with improved pharmacokinetic properties, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3828–3831; (b) K. Ding, Y. Lu, Z. Nikolovska-Coleska, G. Wang, S. Qiu, S. Shangary, W. Gao, D. Qin, J. Stuke, K. Krajewski, P. P. Roller and S. Wang, Structure-based design of spiro-oxindoles as potent, specific small-molecule inhibitors of the MDM2-p53 interaction, *J. Med. Chem.*, 2006, **49**, 3432–3435; (c) T. Emura, T. Esaki, K. Tachibana and M. Shimizu, Efficient Asymmetric Synthesis of Novel Gastrin Receptor Antagonist AG-041R *via* Highly Stereoselective Alkylation of Oxindole Enolates, *J. Org. Chem.*, 2006, **71**, 8559–8564.
- (a) J. –S. Yu, F. Zhou, Y. –L. Liu and J. Zhou, A Journey in the Catalytic Synthesis of 3-Substituted 3-Aminooxindoles, *Synlett*, 2015, **26**, 2491–2504; (b) J. Kaur, S. Singh Chimni, S. Mahajan and A. Kumar, Stereoselective synthesis of 3-amino-2-oxindoles from isatin imines: new scaffolds for



- bioactivity evaluation, *RSC Adv.*, 2015, **5**, 52481–52496; (c) P. Chauhan and S. Singh Chimni, Organocatalytic asymmetric synthesis of 3-amino-2-oxindole derivatives bearing a tetra-substituted stereocenter, *Tetrahedron: Asymmetry*, 2013, **24**, 343–356.
- 4 (a) 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; (b) 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; (c) M. Stucchi, G. Lesma, F. Meneghetti, G. Rainoldi, A. Sacchetti and A. Silvani, Organocatalytic Asymmetric Biginelli-like Reaction Involving Isatin, *J. Org. Chem.*, 2016, **81**, 1877–1884; (d) G. Lesma, F. Meneghetti, A. Sacchetti, 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; (e) A. Sacchetti, A. Silvani, F. G. Gatti, G. Lesma, T. Pilati and B. Trucchi, Addition of TMSCN to chiral ketimines derived from isatin. Synthesis of an oxindole-based peptidomimetic and a bioactive spirohydantoin, *Org. Biomol. Chem.*, 2011, **9**, 5515–5522; (f) 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.
- 5 *Design of Hybrid Molecules for Drug Development*, ed. M. Decker, Elsevier Ed, 2017.
- 6 S. Lohan and G. T. Bisht, Recent approaches in design of peptidomimetics for antimicrobial drug discovery research, *Mini-Rev. Med. Chem.*, 2013, **13**, 1073–1088.
- 7 R. Tuba, Synthesis of β -actams by transition metal promoted Staudinger reactions: alternative synthetic approaches from transition metal enhanced organocatalysis to *in situ*, highly reactive intermediate synthesis and catalytic tandem reactions, *Org. Biomol. Chem.*, 2013, **11**, 5976–5988.
- 8 Review: (a) S. S. van Berkel, B. G. M. Bögels, M. A. Wijdeven, B. Westermann and F. P. J. T. Rutjes, Recent Advances in Asymmetric Isocyanide-Based Multicomponent Reactions, *Eur. J. Org. Chem.*, 2012, 3543–3559. Selected examples: ; (b) C. C. Răzvan, L. Schaepkens van Riepst, P. Schuckman, E. Ruijter and R. V. A. Orru, Ugi Four-Center Three-Component Reaction as a Direct Approach to Racetams, *Synthesis*, 2017, **49**, 1664–1674; (c) T. M. Vishwanatha, N. Narendra and V. V. Sureshbabu, Synthesis of β -lactam peptidomimetics through Ugi MCR: first application of chiral N β -Fmoc amino alkyl isonitriles in MCRs, *Tetrahedron Lett.*, 2011, **52**, 5620–5624.
- 9 M. A. Mironov, M. I. Tokarev, M. N. Ivantsova and V. S. Mokrushin, Ugi reaction with isocyanindoles, *Russ. J. Org. Chem.*, 2004, **40**, 847–853.
- 10 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.
- 11 N. Kumar, M. Kanti Das, S. Ghosh and A. Bisai, Development of catalytic deacylative alkylations (DaA) of 3-acyl-2-oxindoles: total synthesis of meso-chimonanthine and related alkaloids, *Chem. Commun.*, 2017, **53**, 2170–2173.
- 12 DruLiTo, https://www.niper.gov.in/pi_dev_tools/DruLiToWeb/DruLiTo_index.html.
- 13 D. F. Veber, S. R. Johnson, H. Y. Cheng, B. R. Smith, K. W. Ward and K. D. Kopple, Molecular properties that influence the oral bioavailability of drug candidates, *J. Med. Chem.*, 2002, **45**, 2615–2623.
- 14 E. Matuschek, D. F. J. Brown and G. Kahlmeter, Development of the EUCAST disk diffusion antimicrobial susceptibility testing method and its implementation in routine microbiology laboratories, *Clin. Microbiol. Infect.*, 2014, **20**, 255–266.
- 15 (a) M. Ganga, N. Kashyap, K. Kumar, S. Goyal and V. A. Nair, Imidazolidinone based chiral auxiliary mediated acetate aldol reactions of isatin derivatives and stereoselective synthesis of 3-substituted-3-hydroxy-2-oxindoles, *Tetrahedron Lett.*, 2015, **56**, 7074–7081; (b) G. C. Senadi, H. W. Chandru, S. S. K. Boominathan and J. J. Wang, Palladium (0)-Catalyzed Single and Double Isonitrile Insertion: A Facile Synthesis of Benzofurans, Indoles, and Isatins, *Chem.-Eur. J.*, 2015, **21**, 998–1003.

