cis-Diastereoselective Synthesis of Spirooxindolo-β-Lactams by Staudinger Cycloaddition with TsCl as Activating Co-reagent

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ABSTRACT: A convenient and versatile one-pot method for synthesis of 1,3-bis-aryl spirooxindolo-β-lactams from isatin Schiff bases and substituted phenylacetic acids using ketene–imine cycloaddition reaction with TsCl for a ketene generation has been developed. The reaction procedure does not require absolute solvents and unstable starting reagents. The studied reactions lead to cis-diastereoselective β-lactam formation for all tested phenylacetic acids except 4-MeOC₆H₄CH₂COOH. An increase of trans-diastereomers yields with increasing temperature and solvent polarity was demonstrated.

INTRODUCTION

The research of small-molecule inhibitors (SMIs) for targeted therapy, despite being carried out for several decades, is a hot topic of organic and medicinal chemistry. Drugs based on SMIs using different means of delivery or specific mechanisms of action cause less or no harm to ordinary healthy cells compared to conventional chemotherapy. These agents are usually more potent since targeting specific protein targets critical for tumor survival is much more efficient than chemotherapy based on regular cytotoxic agents. In addition, this field of study is greatly expanded by a vast diversity of potential targets.

Among a great variety of targets, the MDM2 protein for over a decade has kept the attention of researchers engaged in design and synthesis of SMIs. This protein, being an endogenous inhibitor of the “genome guardian” cellular protein p53, regulates SMI levels, keeping it at moderate and thus preventing early cell aging. On the other hand, in cancer cells, the MDM2 protein can be overexpressed. This leads to a complete elimination of p53, which in turn leads to further breach of the cell cycle and provides a suitable environment for cancer proliferation. Consequently, blocking of p53–MDM2 interaction by inhibition of the MDM2 active site is considered a favorable therapeutic strategy. A released p53 is expected to restore the cell cycle or initiate an apoptotic sequence in cancer cells.

The most popular approach for design of MDM2 inhibitors is imitation of the structural fragment of the p52 protein responsible for complementary binding to MDM2. This fragment (Trp23) has led to the development of multiple classes of spirooxindoles since indoline-2-one has a good compatibility with the active site of MDM2, and spiroconjugation provides the capacity for further functionalization and conformational stability. For more than a decade, a large number of reports have been published presenting many novel classes of spirooxindoles derived through diverse synthesis pathways, including the reactions of 1,3-dipolar cycloaddition. However, there are only some cases of successful advances through clinical trials. For instance, the phase I study of spirooxindole SAR405838 (Figure 1a) developed by Sanofi in patients with solid tumours was recently reported by de

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Weger and co-workers. As another example of dispirooxindoles, APG-115 (Figure 1b) antitumor activity in patients with unresectable or metastatic melanomas and advanced solid tumors has been reported. Recently we have developed a new structure class of 1,3-diaryl-spiro[azetidine-2,3-indoline]-2,4-diones displaying a great potential as inhibitors of MDM2 in molecular docking studies. It was demonstrated that only cis-diastereomer shows a considerable affinity to the binding site of MDM2. We have also reported several synthesis methods for creation of the desired spiroconjugation including a novel one-pot reaction of imines with substituted phenylacetic acids activated by oxalyl chloride (Scheme 1). The conventional approach of imine’s reaction with ketene formed in situ from acylchloride has provided a series of designed spirooxindoles (Scheme 1, Path 1). Yet, the diastereoselectivity was inclined heavily towards...
the trans-diastereomer, which was less desirable according to molecular modeling. The one-pot approach (Scheme 1, Path 2) provided a favorable diastereoselectivity, but due to the high reactivity of oxalyl chloride, the applicability of these reactions was severely restricted.

**RESULTS AND DISCUSSION**

In our current study, we implemented TsCl as a substitute for oxalyl chloride. Since mixed anhydrides of 4-toluene sulfonic acid and carboxylic acids are known to be relatively stable,24−27 the formation of ketene is expected to proceed more slowly, providing a more simple procedure. TsCl is known as an activation co-reagent in \( \beta \)-lactam ring formation reactions.28−32

Our study commenced with application of the methodology previously used for reactions with oxalyl chloride.23 To derive a desired spirooxindol-\( \beta \)-lactam, we stirred a mixture of 4-chlorophenyl isatinimine, 4-chlorophenylacetic acid, TsCl, and diisopropyl ethyl amine in tetrahydrofuran (THF) at room temperature for 24 h (Scheme 2). Alternatively, we carried out the same procedure at reflux. It was found out that the reactions either proceed at a very slow rate or give a very low yield, or both. Thus, we carried out the preliminary formation of a mixed anhydride from 4-chlorophenylacetic acid and tosyl chloride in the presence of tertiary amine as a base at 120 °C, followed by cooling and addition of imine with another equivalent of base at room temperature. Thus, we were able to obtain the desired spiro-\( \beta \)-lactams 3i, although the reaction still proceeded with the formation of both cis- and trans-diastereomers.

To optimize the reaction in terms of better yield and diastereoselectivity, we carried out a series of reactions of 4-methoxyphenyl isatinimine with TsCl and 4-chlorophenylacetic acid in \( o \)-xylene at room temperature, at 110 °C and reflux. Each reaction yielded a mixture of diastereomers; yet, according to the NMR spectra of the reaction mixtures, depending on the temperature the isomer ratio shifted notably. At room temperature, the cis-isomer prevails over the trans-isomer. But at temperatures above 100 °C, the content of trans-isomers increases significantly. This could be easily traced by the change of intensities of the characteristic signals of amide protons of the isatin fragment, and the more distinct H-C(3)-protons of the azetidin ring in the corresponding NMR spectra (Figure 2). Additionally, we found that at the same temperature, the reaction carried out in more polar solvents,
such as 1,4-dioxane, yields a higher content of trans-isomers than observed in the less polar o-xylene. This tendency was observed for reactions in DCM, THF, and MeCN, though the low solubility of imine leads to slow kinetics and a high content of side products hinders quantitative NMR analysis of the reaction media.

A correlation between the structure of the isomers and NMR signals was confirmed by X-ray analysis of the compounds cis-3f, cis-3k, and trans-3i crystals (see the Supporting Information). Thus, further reactions for preferential formation of cis-spiro-β-lactams were carried out in o-xylene at room temperature.

For the synthesis of 1,3-diaryl-spiro[azetidine-2,3-indoline]-2,4-diones, we carried out reactions of different isatin Schiff bases 1a−g, substituted phenylacetic acids 2a−c. Schiff bases 1a−g as E/Z isomer mixtures were prepared according to previously published methods37,33−36 (Scheme 3).

For 4-hydroxyphenyl isatinimine, due to its bad solubility in xylenes, the reactions were carried out in 1,4-dioxane. In all cases, the mixtures of cis/trans-isomers of the desired spiro-β-lactams were obtained, with predominant or exclusive preparative release of cis-isomers from the reaction mixtures by column chromatography. The yields of the target spiro-β-lactams 3a−l varied from moderate for imines with more electron-withdrawing substituents to good for imines with electron-donating substituents.

To explain the formation of both diastereomers and the correlations between the isomer ratio and the reaction conditions, an analysis of the reaction mechanism may be considered (Scheme 4). The principles of Staudinger β-lactam synthesis have been recently thoroughly studied by Cossio and co-workers.37 First, the formation of both diastereomers is possible due to the existence of both isomers of the initial Schiff base and significantly depends on the Z/E-ratio of the starting imines. However, the cis/trans-ratio of the reaction products never directly correlated with the Z/E-ratio of the starting imines, meaning other factors were involved. For instance, a decrease of cis-diastereomer content with increase of temperature can be explained by the E/Z-wwitterionic intermediate gaining enough energy to proceed with cyclization into trans-β-lactam instead of isomerization into the ZZ-wwitterion cyclizing into cis-β-lactam. The solvent polarity dependence can be explained by the assumption that a more polar solvent better stabilizes wwitterionic intermediates, restricting the ZZ-wwitterion from spontaneous cyclization and thus enabling it to isomerize into the E/Z-wwitterion, which in turn can cyclize into trans-spiro-β-lactam. In addition, according to quantum calculations carried out in our previous work23 and the current experimental data, cis-diastereomer should be considered a kinetic product of E-imine. Meanwhile, for Z-imine, the kinetic product is the trans-diastereomer of spirooxindolo-β-lactam. An important point is that thermodynamic control is hardly applicable since the calculated difference between the free energies of cis/trans-diastereomers is less than 0.5 kcal/mol.

Note especially the results obtained for the reaction of 4-methoxyphenylacetic acid with the series of isatinimines, where the diastereoselectivity was inverse to that observed for reactions of other phenylacetic acids (Scheme 5). The obtaining of ketene-imine cycloaddition products for 4-
methoxyphenylacetic acid was a good result in itself since Staudinger synthesis of β-lactams involving 4-methoxyphenyl ketene previously required the use of α-diazoketone\(^ {37,38}\) or included an additional step of acyl halide formation,\(^ {39}\) or in the case of isatinimines, required a protective group on the amide nitrogen.\(^ {40}\) Still more important is the fact that the diastereoselectivity of the reactions surprisingly became completely the opposite of what we have observed for any other substituted phenylacetic acid since the trans-diastereomer was a major product even at room temperature. However, a tendency of increase of trans-isomer content with increase of temperature and solvent polarity still existed, similar to the pattern observed for other substituted phenylacetic acids.

**CONCLUSIONS**

Summing up, we developed an easy and convenient method for bis-aryl spirooxindolo-β-lactam synthesis suitable for starting izatines and phenylacetic acids with different substitutes. The proposed technique provides the target products with reasonable cis-diastereoselectivity for the most tested phenylacetic acids. A phenylacetic acid with electron-donating substituent (4-MeOC\(_6\)H\(_4\)CH\(_2\)COOH) was first employed in a one-pot Staudinger synthesis with β-lactam ring formation, and in this case, trans-spirooxindolo-β-lactams were obtained as the main products. The main advantages of the proposed synthesis technique include (1) the first proposed use of tosyl chloride instead of oxalyl chloride for the ketene generation in Staudinger reaction in the synthesis of spiro-β-lactams; (2) the course of this reaction with the predominant obtaining of 1,3-diaryl-spiro[azetidine-2,3-indoline]-2,4-diones with cis-configuration.

The developed technique may be useful as a method of diastereoselective synthesis of cis-spiro-β-lactams, complementing the previously known method of using trans-diastereoselective materials for such reactions.
EXPERIMENTAL SECTION

General Information. All solvents used were purified and dehydrated using the methods described in ref 41. All starting reagents were purchased from Sigma-Aldrich. Microwave-heated reactions were performed using a Monowave 300—Anton Paar reactor in sealed glass vessels with external temperature control. The reactions were analyzed by TLC analysis using silica plates with a fluorescent indicator (254 nm) and visualized with a UV lamp. 1H and 13C NMR spectra were recorded using a Bruker Avance spectrometer (400 MHz for 1H, 100 MHz for 13C) in DMSO-d6. Chemical shifts are reported in parts per million relative to TMS. Electrospray ionization high-resolution mass spectra were recorded in positive ion mode using a TripleTOF 5600+ quadrupole time-of-flight mass spectrometer (ABSciex, Concord, Canada) equipped with a DuoSpray ion source. The following MS parameters were applied: capillary voltage 5.5 kV; nebulizing and curtain gas pressure 15 and 25 psi, respectively; ion source temperature ambient; declustering potential 20 V; m/z range 100−1200. Elemental compositions of the detected ions were determined based on accurate masses and isotopic distributions using Formula Finder software (ABSciex, Concord, Canada). The maximum allowed deviation of the experimental molecular mass from the calculated one was 5 ppm.

The data of cis-3f, cis-3k, and trans-3i were collected at room temperature using an STOE diffractometer Pilatus100K detector, focusing on mirror collimation Cu Kα (1.4086 Å) radiation, in rotation method mode. STOE X-AREA software was used for cell refinement and data reduction. Data collection and image processing were performed with X-Area 1.67 (STOE & Cie GmbH, Darmstadt, Germany, 2013). Intensity data were scaled with LANA (part of X-Area) in order to minimize the differences in intensities of symmetry-equivalent reflections (multiscan method).

Structures were Solved with SHELXT and Refined with SHELX (14a). The non-hydrogen atoms (for both substances) were refined using the anisotropic full-matrix least-squares procedure. All hydrogen atoms were placed on their parent atoms [C−H 0.93−0.98; Uiso 1.2 Ueq (parent atom)].

CCDC-2084190 (cis-3f), 2084191 (cis-3k), and 2084193 (trans-3i) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif website.

Synthesis Procedures. General procedure for synthesis of isatinimines.

General Procedure A.36 Aromatic amine (11 mmol) was added into a boiling solution of isatin (10 mmol) in 25 mL of absolute ethanol containing a few drops of glacial acetic acid. The reaction mixture was refluxed for 3 h. The completion was checked by TLC. After the cooling of the reaction mixture to room temperature, it was filtered under reduced pressure. The precipitate was washed with cold EtOH (5 mL), then dried.

General Procedure B.35 A suspension of aromatic amine (11 mmol) and isatin (10 mmol) in 15 mL of absolute MeOH containing a few drops of glacial acetic acid was stirred under microwave irradiation for 15 min at 70 °C (the power is adjusted automatically). The reaction completion was checked by TLC. After the cooling of the reaction mixture to room temperature, it was filtered under reduced pressure. The precipitate was washed twice with cold Et2O (5 mL), then dried.

ACS Omega 2021, 6, 22740−22751
A reaction between p-toluidine (1178 mg, 11 mmol) and isatin (1471 mg, 10 mmol) yields 3-(p-tolylimino)indolin-2-one as a yellow solid (2066 mg, 86%, δ = 7.60 – 7.80 (m, 2H), 7.68 – 7.90 (m, 4H), 2.30 (s, 3H), 377 (s, 3H).

3-(p-Tolylimino)indolin-2-one (1b). A reaction between p-toluidine (1178 mg, 11 mmol) and isatin (1471 mg, 10 mmol) yields 3-(p-tolylimino)indolin-2-one as an orange solid (2055 mg, 87%, δ = 7.70 Hz, 1H), 2.35 (s, 3H).

3-(p-Methylphenylimino)indolin-2-one (1c). A reaction between m-toluidine (1178 mg, 11 mmol) and isatin (1471 mg, 10 mmol) yields 3-(m-tolylimino)indolin-2-one as a yellow solid (1914 mg, 81%, δ = 7.5(1-7.6) Hz, 1H), 6.88 – 7.0 (m, 2H), 7.08 – 7.27 (m, 2H), 7.39 (m, 1H), 7.01 (t, J = 7.71 Hz, 1H), 6.47 (d, J = 7.82 Hz, 1H), 6.84 (s, 1H), 2.30 (s, 2H).

3-(4-Fluorophenylimino)indolin-2-one (1d). A reaction between 4-fluoroaniline (1222 mg, 11 mmol) and isatin (1471 mg, 10 mmol) yields 3-(4-fluorophenylimino)indolin-2-one as a yellow solid (2066 mg, 86%, δ = 7.5(1-7.6) Hz, 1H), 6.88 – 7.0 (m, 2H), 7.08 – 7.27 (m, 2H), 7.39 (m, 1H), 7.01 (t, J = 7.71 Hz, 1H), 6.47 (d, J = 7.82 Hz, 1H), 6.84 (s, 1H), 2.28 (s, 3H).

3-(4-Chlorophenylimino)indolin-2-one (1e). A reaction between 4-chloroaniline (1200 mg, 11 mmol) and isatin (1471 mg, 10 mmol) yields 3-(4-chlorophenylimino)indolin-2-one as an orange solid (2239 mg, 94%, δ = 7.5(1-7.6) Hz, 1H), 6.88 – 7.0 (m, 2H), 7.08 – 7.27 (m, 2H), 7.39 (m, 1H), 7.01 (t, J = 7.71 Hz, 1H), 6.47 (d, J = 7.82 Hz, 1H).

3-(3-Chloro-4-fluorophenylimino)indolin-2-one (1f). A reaction between 3-chloro-4-fluorobenzaldehyde (1601 mg, 10 mmol) and isatin (1471 mg, 10 mmol) yields 3-(3-chloro-4-fluorophenylimino)indolin-2-one as a bright orange solid (2500 mg, 91%, Z = 1.5/1).

3-(4-Hydroxyphenylimino)indolin-2-one (1g). A reaction between 4-aminophenol (1200 mg, 11 mmol) and isatin (1471 mg, 10 mmol) yields 3-(4-hydroxyphenylimino)indolin-2-one as a red solid (2239 mg, 94%, δ = 7.5(1-7.6) Hz, 1H), 6.88 – 7.0 (m, 2H), 7.08 – 7.27 (m, 2H), 7.39 (m, 1H), 7.01 (t, J = 7.71 Hz, 1H), 6.47 (d, J = 7.82 Hz, 1H).
indolin-2-one (252 mg, 1 mmol) yields 271 mg (67\%) of spiro-
b-lactam as a white solid.

1H NMR (400 MHz, CHLOROFORM-d) δ ppm 10.84 (s, 1H), 7.64 (d, J = 7.34 Hz, 1H), 7.36–7.41 (m, 3H), 7.17 (d, J = 8.44 Hz, 2H), 7.11 (t, J = 7.52 Hz, 1H), 6.95–7.00 (m, 3H), 6.87–6.91 (m, 2H), 5.29 (s, 1H), 3.66 (s, 3H).

13C NMR (101 MHz, DMSO-d$_6$) δ ppm 172.68, 163.50, 156.05, 141.89, 132.67, 130.79, 130.55, 129.18, 128.34, 124.62, 124.33, 122.69, 117.87, 114.76, 110.84, 66.13, 63.46, 55.27.

HRMS (ESI) calcd for C$_{23}$H$_{18}$N$_2$O$_3$ $\text{[M + H]}^+$: 405.100; found, 405.0999.

(2R*,3R*)-3-(4-Chlorophenyl)-1-(4-methoxyphenyl)spiro-
azetidine-2,3′-indoline)-2′,4-dione (trans-3b). A reaction of 2-(4-chlorophenyl)acetic acid (256 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), disopropylpropylamine (520 $\mu$L, 388 mg, 3 mmol), and 3-((4-methoxyphenyl)iminio)indolin-2-one (252 mg, 1 mmol) yields 81 mg (20\%) of spiro-b-lactam as a white solid.

1H NMR (400 MHz, DMSO-d$_6$) δ ppm 11.09 (s, 5H) 7.34 (d, J = 8.44 Hz, 12H), 7.18–7.25 (m, 18H), 6.86–7.00 (m, 30H) 6.68–6.74 (m, 12H) 5.01 (s, 6H), 3.66 (s, 18H).

13C NMR (101 MHz, DMSO-d$_6$) δ ppm 174.90, 163.31, 156.18, 142.48, 132.65, 130.90, 130.65, 129.80, 128.57, 125.35, 121.83, 121.31, 117.94, 114.77, 110.78, 65.39, 63.32, 55.28.

HRMS (ESI) calcd for C$_{23}$H$_{18}$ClN$_2$O$_3$ $\text{[M + H]}^+$: 439.0411; found, 439.0607.

(2R*,3S*)-3-(4-Bromophenyl)-1-(4-methoxyphenyl)spiro-
azetidine-2,3′-indoline)-2′,4-dione (cis-3c). A reaction of 2-(4-bromophenyl)acetic acid (323 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), disopropylpropylamine (520 $\mu$L, 388 mg, 3 mmol), and 3-((4-methoxyphenyl)iminio)indolin-2-one (252 mg, 1 mmol) yields 301 mg (67\%) of spiro-b-lactam as a white solid.

1H NMR (400 MHz, DMSO-d$_6$) δ ppm 10.84 (s, 1H), 7.64 (d, J = 7.34 Hz, 1H), 7.52 (d, J = 8.38 Hz, 2H), 7.38 (td, J = 7.72, 1.07 Hz, 1H), 7.07–7.14 (m, 3H), 6.94–7.01 (m, 3H), 6.85–6.92 (m, 2H), 5.27 (s, 1H), 3.66 (s, 3H).

13C NMR (101 MHz, DMSO-d$_6$) δ ppm 172.68, 163.50, 156.05, 141.89, 131.26, 130.97, 130.79, 130.46, 129.82, 124.62, 124.32, 122.69, 117.87, 114.76, 110.84, 66.06, 64.39, 55.27.

HRMS (ESI) calcd for C$_{23}$H$_{18}$BrN$_2$O$_3$ $\text{[M + H]}^+$: 389.0151; found, 389.1051.

(2R*,3S*)-3-(4-Bromophenyl)-1-(4-methoxyphenyl)spiro-
azetidine-2,3′-indoline)-2′,4-dione (cis-3f). A reaction of 2-(4-bromophenyl)acetic acid (323 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), disopropylpropylamine (520 $\mu$L, 388 mg, 3 mmol), and 3-(4-tolylimino)indolin-2-one (236 mg, 1 mmol) yields 132 mg (34\%) of spiro-b-lactam as a white solid.

1H NMR (400 MHz, DMSO-d$_6$) δ ppm 10.87 (s, 1H), 7.64 (d, J = 7.27 Hz, 1H), 7.36–7.42 (m, 3H), 7.07–7.20 (m, 5H), 7.01 (d, J = 7.76 Hz, 1H), 6.90 (d, J = 7.58 Hz, 1H), 6.59 (d, J = 8.50 Hz, 1H), 5.32 (s, 1H), 2.21 (s, 3H).

13C NMR (101 MHz, DMSO-d$_6$) δ ppm 172.61, 163.84, 141.83, 134.14, 133.65, 132.70, 130.79, 130.46, 130.17, 129.86, 128.36, 124.60, 124.31, 122.69, 116.12, 110.86, 65.96, 64.31, 20.42.

HRMS (ESI) calcd for C$_{23}$H$_{18}$BrN$_2$O$_3$ $\text{[M + H]}^+$: 433.0546; found, 433.0541.

(2R*,3S*)-3-(3,4-Difluorophenyl)-1-(4-methoxyphenyl)spiro-
azetidine-2,3′-indoline)-2′,4-dione (cis-3g). A reaction of 2-(3,4-difluorophenyl)acetic acid (258 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), disopropylpropylamine (520 $\mu$L, 388 mg, 3 mmol), and 3-(4-tolylimino)indolin-2-one (236 mg, 1 mmol) yields 144 mg (37\%) of spiro-b-lactam as a white solid.

1H NMR (400 MHz, DMSO-d$_6$) δ ppm 10.90 (s, 1H), 7.63 (d, J = 7.40 Hz, 1H), 7.35–7.44 (m, 2H), 7.19 (dd, J = 11.31, 7.95, 1.65 Hz, 1H), 7.07–7.13 (m, 3H), 7.00 (d, J = 7.76 Hz, 2H), 6.92 (d, J = 8.38 Hz, 2H), 5.32 (s, 1H), 2.19 (s, 3H).

13C NMR (101 MHz, DMSO-d$_6$) δ ppm 172.59, 163.58, 141.83, 134.03, 133.78, 130.87, 129.88, 125.78, 125.74, 125.70, 124.60, 124.31, 122.69, 116.12, 110.86, 65.96, 64.35, 20.43.
1H NMR (400 MHz, DMSO-d_6) δ ppm 10.91 (s, 1H), 7.68 (d, J = 7.34 Hz, 1H), 7.36–7.44 (m, 3H), 7.17 (d, J = 8.38 Hz, 2H), 7.12 (t, J = 7.58 Hz, 1H), 6.98–7.06 (m, 3H), 5.38 (s, 1H).

13C NMR (101 MHz, DMSO-d_6) δ ppm 172.27, 164.14, 141.83, 135.27, 132.80, 130.95, 130.10, 129.59, 128.38, 128.18, 124.70, 123.81, 122.78, 117.68, 110.98, 66.13, 64.62.

HRMS (ESI) calcld for C_{23}H_{18}ClN_{2}O_{2} \[ M + H^+ \]: 389.1051; found, 389.1043.

(2R*,3S*)-3-(4-Chlorophenyl)-1-(m-tolyl)spiro[azetidine-2,3′-indoline]-2′,4-dione (cis-3i). A reaction of 2-(4-chlorophenyl)acetic acid (256 mg, 1.5 mmol), 4-toluene sulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-(m-tolyl)iminoindolin-2-one (236 mg, 1 mmol) yields 86 mg (22%) of spiro-b-lactam as a white solid.

1H NMR (400 MHz, DMSO-d_6) δ ppm 10.87 (s, 1H), 7.64 (d, J = 7.27 Hz, 1H), 7.36–7.42 (m, 3H), 7.07–7.20 (m, 5H), 7.01 (d, J = 7.67 Hz, 1H), 6.90 (d, J = 7.58 Hz, 1H), 6.59 (d, J = 8.50 Hz, 1H), 5.32 (s, 1H), 2.21 (s, 3H).

13C NMR (101 MHz, DMSO-d_6) δ ppm 172.56, 164.10, 141.79, 138.98, 136.58, 132.73, 130.83, 130.38, 130.17, 129.35, 128.37, 125.13, 124.61, 124.33, 122.73, 117.06, 112.75, 110.84, 65.98, 64.27, 21.13.

HRMS (ESI) calcld for C_{23}H_{18}BrClN_{2}O_{2} \[ M + H^+ \]: 470.9906; found, 470.9896.

(2R*,3S*)-3-(4-Bromophenyl)-1-(3-chloro-4-fluorophenyl) spiro[azetidine-2,3′-indoline]-2′,4-dione (trans-3k). A reaction of 2-(4-bromophenyl)acetic acid (323 mg, 1.5 mmol), 4-toluene sulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-(3-(3-chloro-4-fluorophenyl)imino)indolin-2-one (275 mg, 1 mmol) yields 14 mg (3%) of spiro-b-lactam as a white solid.

1H NMR (400 MHz, DMSO-d_6) δ ppm 11.20 (s, 1H), 7.48 (d, J = 8.44 Hz, 2H), 7.38–7.44 (m, 2H), 2.74 (dd, J = 7.58, 1.41 Hz, 1H), 7.19 (d, J = 8.44 Hz, 2H), 6.97 (d, J = 7.76 Hz, 1H), 6.69–6.80 (m, 3H), 5.12 (s, 1H).

13C NMR (101 MHz, DMSO-d_6) δ ppm 174.30, 163.96, 142.48, 140.36, 131.52, 131.03, 130.75, 125.59, 122.03, 121.50, 120.46, 120.27, 118.46, 118.30, 116.11, 116.03, 110.96, 65.55, 63.92.

HRMS (ESI) calcld for C_{23}H_{18}BrClN_{2}O_{2} \[ M + H^+ \]: 470.9906; found, 470.9901.

(2R*,3S*)-3-(4-Chlorophenyl)-1-(4-hydroxyphenyl) spiro[azetidine-2,3′-indoline]-2′,4-dione (cis-3l). A reaction of 2-(4-chlorophenyl)acetic acid (256 mg, 1.5 mmol), 4-toluene sulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-(4-(4-hydroxyphenyl)imino)indolin-2-one (238 mg, 1 mmol) yields 94 mg (24%) of spiro-b-lactam as a white solid.

1H NMR (400 MHz, DMSO-d_6) δ ppm 10.79 (s, 1H), 9.44 (s, 1H), 7.63 (d, J = 7.29 Hz, 1H), 7.32–7.43 (m, 3H), 7.17 (d, J = 8.39 Hz, 2H), 7.10 (t, J = 7.56 Hz, 1H), 6.97 (d, J = 7.73 Hz, 1H), 6.88 (d, J = 8.82 Hz, 2H), 6.68 (d, J = 8.88 Hz, 2H), 5.24 (s, 1H).

13C NMR (101 MHz, DMSO-d_6) δ ppm 175.03, 163.17, 154.38, 141.86, 132.62, 130.69, 130.65, 130.18, 128.46, 128.30, 124.55, 124.49, 122.64, 118.24, 115.84, 110.78, 66.17, 64.33.

HRMS (ESI) calcld for C_{23}H_{18}ClN_{2}O_{3} \[ M + H^+ \]: 391.0844; found, 391.0846.

(2R*,3S*)-3-(4-Chlorophenyl)-1-(4-hydroxyphenyl) spiro[azetidine-2,3′-indoline]-2′,4-dione (trans-3l). A reaction of 2-(4-chlorophenyl)acetic acid (256 mg, 1.5 mmol), 4-toluene sulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-(4-(4-hydroxyphenyl)imino)indolin-2-one (238 mg, 1 mmol) yields 20 mg (5%) of spiro-b-lactam as a white solid.

1H NMR (400 MHz, DMSO-d_6) δ ppm 11.05 (s, 1H), 9.46 (s, 1H), 7.33 (d, J = 8.44 Hz, 2H), 7.14–7.25 (m, 3H), 6.83–6.96 (m, 3H), 6.63–6.75 (m, 4H), 4.97 (s, 1H).

13C NMR (101 MHz, DMSO-d_6) δ ppm 175.03, 163.17, 154.54, 142.46, 132.63, 131.02, 130.65, 128.56, 128.46, 125.34, 121.80, 121.48, 118.30, 115.86, 110.75, 65.44, 63.27.

HRMS (ESI) calcld for C_{23}H_{18}BrClN_{2}O_{3} \[ M + H^+ \]: 391.0844; found, 391.0844.
indolin-2-one (252 mg, 1 mmol) yields 88 mg (22%) of spiro-b-lactam as a white solid.

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 10.73 (1H, 7.61 (d, \(J = 7.34\) Hz, 1H), 7.36 (td, \(J = 7.73\), 1.08 Hz, 1H), 7.06–7.11 (m, 3H), 6.95–7.00 (m, 3H), 6.84–6.91 (m, 4H), 5.16 (s, 1H), 3.72 (s, 3H), 3.67 (s, 3H).

\(^1^C\) NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) ppm 175.23, 164.08, 158.83, 156.07, 142.43, 130.42, 130.14, 125.03, 123.57, 121.76, 121.69, 117.85, 114.73, 113.90, 110.64, 65.72, 64.04, 55.26, 55.01.

HRMS (ESI) calcd for \(\text{C}_{23}\text{H}_{18}\text{FN}_2\text{O}_3^+\) [M + H\(^+\)]: 401.1496; found, 401.1490.

\((2R,3R*)\)-1,3-bis(4-Methoxyphenyl)spiro[azetidine-2,3'-indoline]-2',4-dione (trans-3m). A reaction of 2-(4-methoxyphenyl)acetic acid (249 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 \(\mu\)L, 388 mg, 3 mmol), and 3-((4-methoxyphenyl)imino)indolin-2-one (252 mg, 1 mmol) yields 104 mg (26%) of spiro-b-lactam as a white solid.

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 11.05 (s, 1H), 7.19 (td, \(J = 7.54, 0.82\) Hz, 1H), 7.13 (d, \(J = 8.55\) Hz, 2H), 6.98 (d, \(J = 8.99\) Hz, 2H), 6.93 (d, \(J = 7.73\) Hz, 1H), 6.88 (d, \(J = 9.04\) Hz, 2H), 6.82 (d, \(J = 8.61\) Hz, 2H), 6.76 (d, \(J = 7.13\) Hz, 1H), 6.70 (t, \(J = 7.37\) Hz, 1H), 4.90 (s, 1H), 3.68 (s, 3H), 3.66 (s, 3H).

\(^1^C\) NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) ppm 175.23, 164.08, 158.83, 156.07, 142.43, 130.42, 130.14, 125.03, 123.57, 121.76, 121.69, 117.85, 114.73, 113.90, 110.64, 65.72, 64.04, 55.26, 55.01.

HRMS (ESI) calcd for \(\text{C}_{23}\text{H}_{19}\text{N}_2\text{O}_4^+\) [M + H\(^+\)]: 389.1296; found, 389.1294.

\((2R,3R*)\)-1-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)spiro[azetidine-2,3'-indoline]-2',4-dione (trans-3p). A reaction of 2-(4-methoxyphenyl)acetic acid (249 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 \(\mu\)L, 388 mg, 3 mmol), and 3-((4-hydroxyphenyl)imino)indolin-2-one (240 mg, 1 mmol) yields 198 mg (51%) of spiro-b-lactam as a white solid.

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 11.01 (s, 1H), 9.44 (s, 1H), 7.18 (td, \(J = 7.58\) Hz, 1H), 7.12 (d, \(J = 8.56\) Hz, 2H), 6.85–6.93 (m, 3H), 6.82 (d, \(J = 8.74\) Hz, 2H), 6.65–6.76 (m, 4H), 4.86 (s, 5H), 3.68 (s, 3H).

\(^1^C\) NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) ppm 175.33, 163.92, 158.80, 154.41, 142.41, 130.34, 130.12, 128.65, 125.40, 123.69, 121.84, 121.70, 118.19, 115.82, 113.88, 110.59, 65.76, 63.96, 55.01.

HRMS (ESI) calcd for \(\text{C}_{23}\text{H}_{19}\text{N}_2\text{O}_4^+\) [M + H\(^+\)]: 387.1339; found, 387.1336.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c03063.

Experimental procedure, optimization study, NMR spectra (\(^1\)H and \(^1^C\)), crystal data, and HRMS spectra of the products (PDF)

**Accession Codes**

CCDCs 2084190, 2084419, 2084848, 2084913 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; Fax: +44 1223 336033.

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Notes
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