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Thiazolidinedione–Isatin Conjugates via an Uncatalyzed Diastereoselective Aldol Reaction on Water

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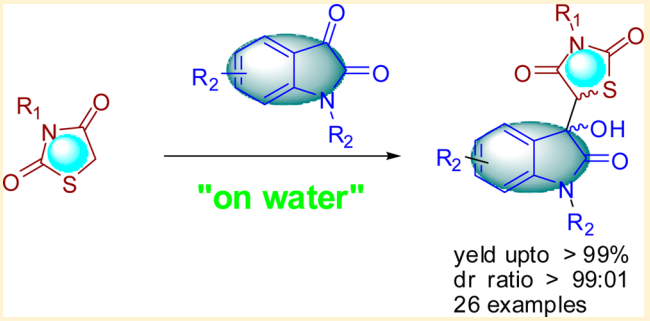
Supporting Information

ABSTRACT: An uncatalyzed aldol reaction of N-substituted thiazolidinediones with isatin derivatives has been developed "on water" to afford a new class of pharmacologically important thiazolidinedione–isatin conjugates in excellent yields and diastereoselectivities. The isatin–thiazolidine conjugate undergoes a catalyst-free stereoselective transfer aldol reaction on water. Single-crystal X-ray studies reveal that the aldol products can self-assemble to form supramolecular DNA "zipper" like structures through intermolecular hydrogen bonds and aromatic $\pi-\pi$ interactions.



The discovery and development of environmentally benign processes for stereoselective synthesis of heterocyclic compounds represent an important goal of chemical and pharmaceutical research.[1,2] Water, being the most common reaction medium for biochemical reaction, holds great promise as a green reaction medium in organic synthesis. However, poor solubility of organic compounds in water limits the use of water in organic reactions. Since the seminal work of Breslow and co-workers on rate acceleration of Diels–Alder reactions using water as a solvent,[3] significant progress has been made in the field of organic synthesis in aqueous medium.[4,5] Furthermore, the development of on water concept by Sharpless et al.[6] has inspired many aqueous organic reactions of water-insoluble reactants.[5f,g,7]

Catalytic aldol reaction has been widely studied using organic solvents and in aqueous medium.[8] However, examples of stereoselective uncatalyzed aldol reaction "in", "on", or "in the presence of" water are rare.[9] In the course of our studies directed toward development of sustainable synthetic protocols,[10] we recently reported an uncatalyzed reaction of thiazolidinedione with aromatic aldehydes.[10b] We herein present the first examples of an uncatalyzed aldol reaction of N-substituted 2,4-thiazolidinedione with isatin derivatives on water. Both isatin and thiazolidinedione[11] are heterocyclic privileged scaffolds of medicinal chemistry and potential chemotherapeutic agents. In particular, the 3-hydroxy-2-oxyindole motif is present in numerous biologically active natural molecules (Figure 1).[12−14] We presumed that this uncatalyzed C–C bond-forming reaction will be a new platform for the practical and atom-economical synthesis of thiazolidinedione–isatin conjugates,[15] which might exhibit enhanced or altered biological activities.

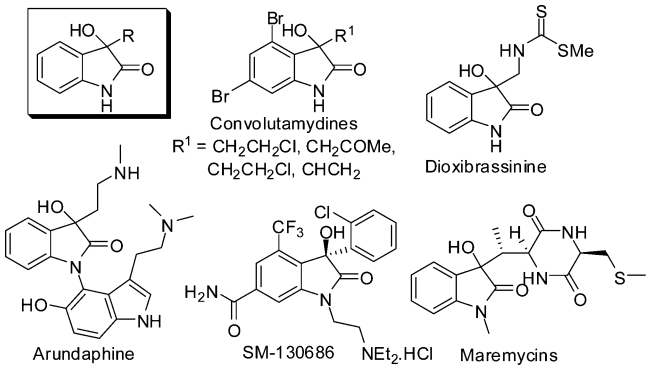


Figure 1. Bioactive natural products and small molecules containing a substituted 3-hydroxy-2-oxindole scaffold.

We initially investigated the aldolization of *N*-methyl-2,4-thiazolidinedione (**1a**) and *N*-methylisatin (**2a**) in the absence of any added catalyst using various solvents (Table 1). The reaction requires only 10 min for completion (entry 1) on water to give an excellent yield of **3aa** with moderate diastereoselectivity (dr, 88:12, *anti*/*syn*). The formation of the products **3aa** was found to be thermodynamically controlled. A superior level of diastereocontrol was realized with increasing reaction time (entries 1–3). Stirring the reaction of **1a** and **2a** on water for 2 h afforded **3aa** in 98% yield with high diastereoselectivity in favor of the *anti* isomer **3aa** (dr 98:02, entry 3). The reaction media had a dramatic effect on the yield and diastereoselectivity. It should be noted that polar aprotic

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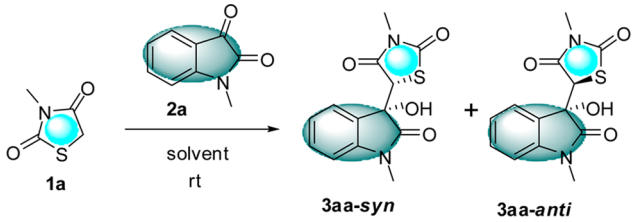
Table 1. Screening of Solvents for Aldol Reaction of *N*-Methyl Thiazolidinedione (1a) with Isatin 2a[a]



entry	solvent	time	conv (%)[b]	3aa *anti*/*syn*[b]	yield (%)
1	**water**	**10 min**	**>99**	**88:12**	**98**
2	water	30 min	>99	96:04	98
3	water	2 h	>99	98:02	98
4	DMSO	24 h	>99	90:10	96
5	**DMSO**	**10 min**	**15**	**80:20**	
6	DMF	24 h	75	88:12	70
7	**DMF**	**10 min**	**10**	**80:20**	
8	toluene	16 h	56	88:12	51
9	1,4-dioxane	20 h	20	80:20	
10	EtOAc	20 h	9		
11	acetonitrile	20 h	3		
12	EtOH	16 h	3		
13	THF	20 h	2		
14	CH_2Cl_2	20 h	NR		
15	$CHCl_3$	20 h	NR		

[a]Unless otherwise stated, all of the reactions were carried out using 1 equiv of **1a** and 1 equiv of **2a** in 0.04 M solvent. [b]The conversion was determined by ^{1}H NMR analysis of the unpurified reaction mixture.

solvents DMSO and DMF provided high conversion and selectivity (entries 4 and 6). Moderate to low conversions were observed using toluene and 1, 4-dioxane (entries 8 and 9), whereas no reaction took place in ethyl acetate, acetonitrile, ethanol, THF, dichloromethane, and chloroform (entries 10–15). The reactants **1a** and **2a** are insoluble in water and soluble in all other studied organic solvents (Table 1, entries 4–15). This study revealed that the reaction proceeded in polar aprotic solvents and water. The reaction was completed at a remarkably faster rate (10 min) on water than in DMSO (entries 1 and 5). The aldol reaction proceeded to only 15% conversion of the isatin **2a** in 10 min and took 24 h for completion in DMSO (entries 4 and 5).

Moreover, the reaction is operationally straightforward and scalable to gram scale (Figure 2). As a typical procedure, the water-insoluble solid reactants **1a** (1 equiv) and **2a** (1 equiv)

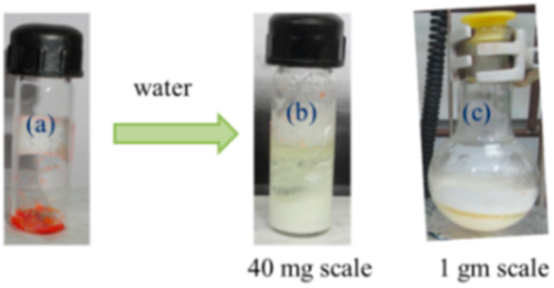


Figure 2. Reaction mixture (a) containing **1a** (0.17 mmol) and **2a** (0.17 mmol); (b) **1a** (0.17 mmol) and **2a** (0.17 mmol) after stirring for 30 min on water at rt; (c) **1a** (6.8 mmol) and **2a** (6.8 mmol) after stirring for 30 min on water at rt.

were stirred on water (0.04 M). Rapid disappearance of the reddish color of the isatin **2a** was observed to give colorless solid product **3aa** within 30 min, which was isolated by simple filtration (>99% purity). This procedure avoids the use of volatile organic solvents for extraction process.

Next, we surveyed the effect of pure water in promoting the aldolizations of N-substituted thiazolidinediones **1a–e** to a variety of isatins **2a–i** (Figure 3), and the results are presented

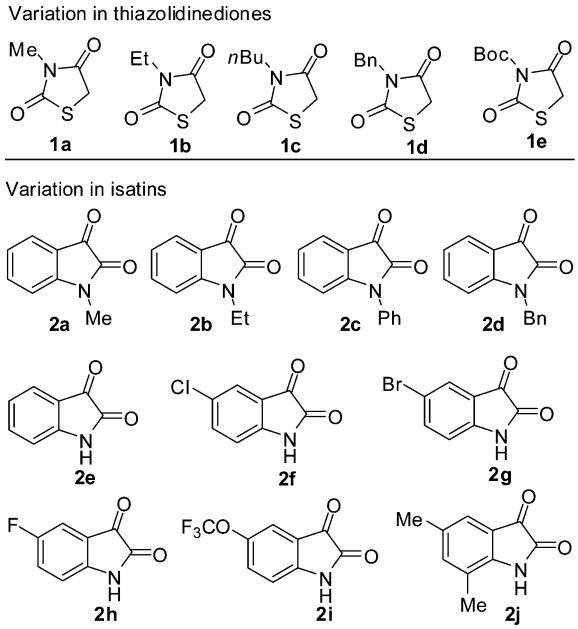


Figure 3. Thiazolidinediones and isatins used in the aldol reaction on water.

in Table 2. The protecting group on thiazolidinedione had no effect on the diastereoselectivity and the yield; however, *N*-benzylthiazolidinedione took a longer time for completion of the reaction. Reaction of isatin derivatives containing *N*-methyl, *N*-ethyl, *N*-phenyl, and *N*-benzyl substituents (**2a–d**) with N-substituted thiazolidinediones **1a–e** gave the desired hydroxy isatin derivatives **3** in excellent yields and diastereoselectivities. Among the N-substituted isatins, *N*-phenyl- and *N*-benzylisatins required a longer reaction time compared to *N*-methyl- and *N*-ethylisatin derivatives. It is noteworthy that isatin **2e** with a free NH group reacted with thiazolidinediones **1a–d** to afford the corresponding aldol products **3ae–de** with excellent yields and diastereoselectivities.

Similarly, 5-chloroisatin **2f** reacted with thiazolidinediones **1a–e** to form the corresponding aldol products **3af–ef** in high yields and selectivity. The reaction of 5-bromo **2g** and 5-fluoro **2h** isatin derivatives with thiazolidinedione **1b** afforded the aldol products **3ag** and **3ah**, respectively. However N-unprotected isatins required a longer reaction time compared to *N*-methyl- and *N*-ethyl-substituted isatin derivatives. Electron-rich trifluoromethoxy-containing isatin derivative (**2i**) resulted in aldol product **3ai** in 89% yield with 96:4 dr after 48 h. The reaction of 5,7-dimethylindoline-2,3-dione (**2j**) proceeded with the slowest rate (96 h) to afford **3aj** in 75% yield (96:4 dr). In most of the cases, the products were isolated by simple decantation or filtration. These results show that the reaction was quite general and the variation of the protecting group on the N atom on isatins and thiazolidindiones or

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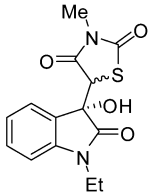
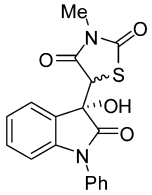
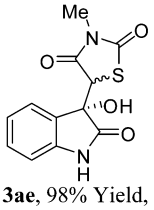
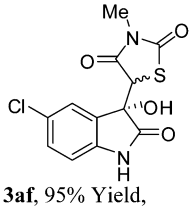
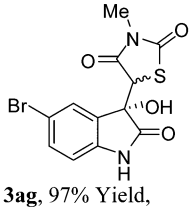
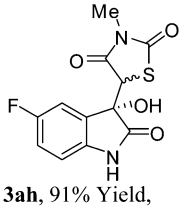
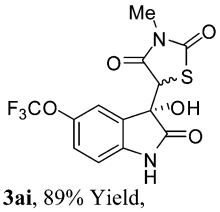
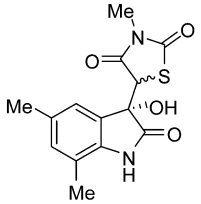
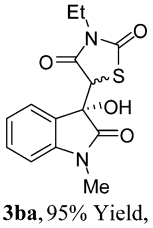
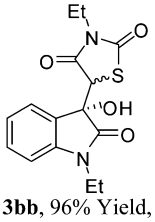
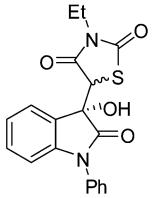
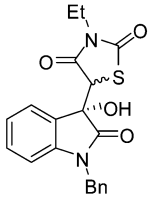
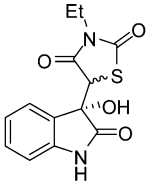
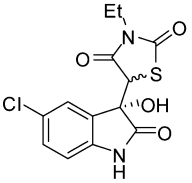
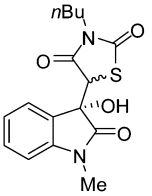
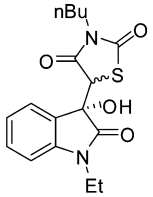
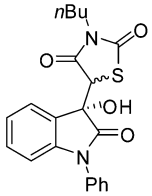
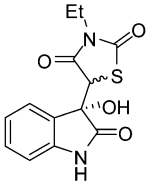
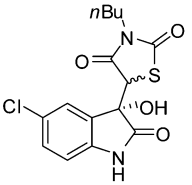
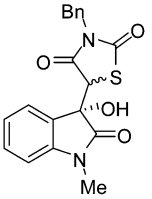
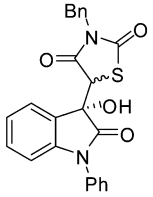
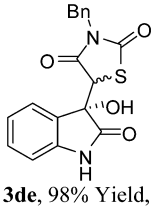
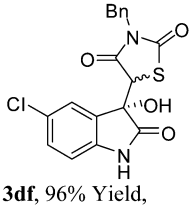
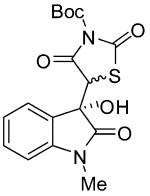
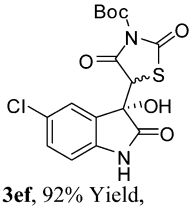
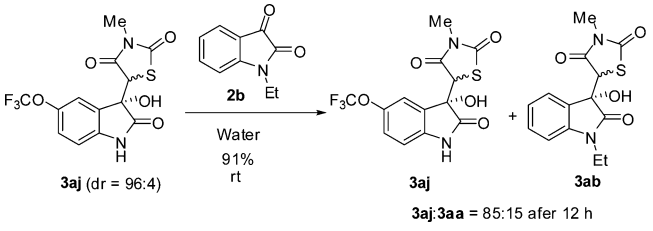
Table 2. Thiazolidinedione–Isatin Conjugates via Aldol Reactions On-Water

 **3ab**, 96% Yield, 98:2 *dr*, 12 h	 **3ac**, 98% Yield, 97:3 *dr*, 48 h	 **3ae**, 98% Yield, 98:2 *dr*, 24 h	 **3af**, 95% Yield, 98:2 *dr*, 24 h	 **3ag**, 97% Yield, 99:1 *dr*, 30 h
 **3ah**, 91% Yield, 96:4 *dr*, 48 h	 **3ai**, 89% Yield, 96:4 *dr*, 48 h	 **3aj**, 75% Yield, 96:4 *dr*, 96 h	 **3ba**, 95% Yield, 99:1 *dr*, 12 h	 **3bb**, 96% Yield, 98:2 *dr*, 12 h
 **3bc**, 97%Yield, 96:4 *dr*, 48 h	 **3bd**, 91% Yield, 94:6 *dr*, 48 h	 **3be**, 98% Yield, 98:2 *dr*, 24 h	 **3bf**, 98% Yield, 97:3 *dr*, 30 h	 **3ca**, 97% Yield, 97:3 *dr*, 24 h
 **3cb**, 97% Yield, 98:2 *dr*, 24 h	 **3cc**, 95% Yield, 97:3 *dr*, 48 h	 **3ce**, 98% Yield, 98:2 *dr*, 24 h	 **3cf**, 98% Yield, 97:3 *dr*, 24 h	 **3da**, 94% Yield, 98:2 *dr*, 24 h
 **3dc**, 92% Yield, 97:3 *dr*, 48 h	 **3de**, 98% Yield, 98:2 *dr*, 48 h	 **3df**, 96% Yield, 97:3 *dr*, 48 h	 **3ea**, 95% Yield, 96:4 *dr*, 30 h	 **3ef**, 92% Yield, 96:4 *dr*, 48 h

substituents on the aromatic ring of isatins had no effect on the yield as well as in diastereoselectivity.

In order to study the reversibility of the aldol reaction under our experimental conditions, we have modeled the transfer aldol reaction of the isatin–thiazolidinedione conjugate **3aj** with **2b** (Scheme 1). Stirring an equimolar mixture of **3aj** and isatin **2b** on water at rt afforded the transfer aldol product **3ab** and the starting aldol **3aj** in 91% yield in a ratio of 85:15, which confirms this aldol protocol is reversible. To the best of our knowledge, this represents the first example of a stereoslective uncatalyzed transfer-aldol reaction.

Scheme 1. Catalyst-Free Transfer-Aldol Reaction



Density functional theory analysis shows that the aldol products **3aa** and **3ba** show a preference for the *anti*-configuration (Figure S1, Supporting Information) as the energy of formation of *anti*-isomers was found to be lower than that of the *syn* isomers. Single-crystal X-ray analysis of **3aa** and **3ba** unambiguously confirmed that the aldol products have an *anti* configuration (Figure 4). The crystal packing shows that compounds **3aa** and **3ba** self-assemble to form an infinite 1-D hydrogen-bonded supramolecular zipper-like structure.[16]

Notably, the reaction of **1a** with **2a** did not proceed in EtOH, which may be because both reactants **1a** and **2a** are soluble in EtOH. In the case of the reaction using water, the reactants are

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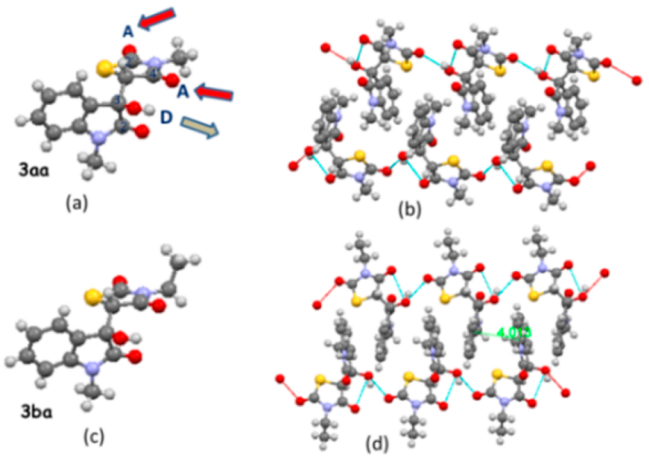

Figure 4. X-ray crystal structures of single molecule **3aa** (a) and **3ba** (c). H-bonding and $\pi-\pi$-stacking interactions in the crystal packing of **3aa** (b) and **3ba** (d).

insoluble and the reactions occur through hydrophobic effect of reactants on the surface of water. The faster reaction rate may be attributed to the strong H-bonding interactions of the hydrophilic heteroatoms of thiazolidinedione and isatin derivatives with water molecules. This H-bonding in reactions brings both the reactants close together and enhances the electrophilicity of the isatin and the nucleophilicity of the thiazolidinedione derivatives.[17]

Isatin is activated by hydrogen bonding with water in a way that C−C bond formation takes place from its *re* face with the *E*-enol of the thiazolidinedione to form the preferred *anti* product (Figure 5), which reduces the interaction between the two heteroatoms (the O-atom of isatin C3-OH and the sulfur atom of thiazolidinedione) at the transition state **A**.

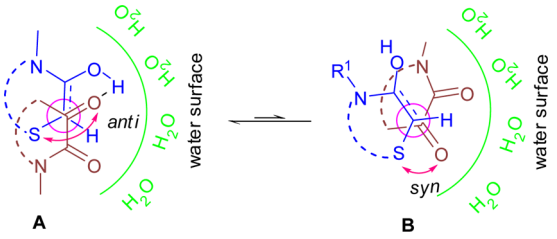

Figure 5. Proposed transition state.

In summary, a new reagent-free diastereoselective aldol reaction of thiazolidinediones with isatins on water has been developed. This protocol is direct, operationally simple (reagent free, room temperature, and sovent-free purification of products) and amenable to gram-scale synthesis of thiazolidinedione−isatin conjugates in excellent yields and diastereoselectivities. The transfer aldol reaction worked well between an isatin−thiazolidine aldol and an isatin derivative and thus represents the first catalyst-free asymmetric transfer-aldol reaction on water. These novel heterocyclic ring systems containing H-bonding motifs and hydrophobic ring system can serve as biomimetic building blocks for crystal and supramolecular engineering and participate in recognition processes in biology.

EXPERIMENTAL SECTION

General Information. All commercial reagents were used as provided unless otherwise indicated. All of the reagents and solvents were reagent grade and used without further purification. Technical-grade ethyl acetate and hexane were used for purification by flash chromatography on silica gel (100−200 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded either in $CDCl_3$ or in DMSO-d_6 solvent on a 400 or 500 MHz spectrometer at 278 K. Proton chemical shifts are reported in ppm from an internal standard of residual $CHCl_3$ (7.26 ppm) or DMSO (2.50 ppm), and carbon chemical shifts are reported using an internal standard of residual $CHCl_3$ (77.2 ppm) or DMSO (39.5 ppm). The chemical shifts are reported in ppm on scale downfield from TMS as internal standard, and signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; dt, doublet of triplet; m, multiplet. Infrared (FTIR) spectra were recorded with the KBr disk and KBr plate techniques for solid and liquid samples, ν_{max} cm^{-1}. HRMS analyses were performed with Q-TOF high resolution instruments by +ve mode electrospray ionization. Single-crystal X-ray analysis of **3aa**-*anti* and **3ba**-*anti* was recorded on a high-resolution X-ray diffractometer instrument.

General Procedure for the Preparation of 1b and 1c. EtBr or ^{n}BuCl (3.0 equiv) was added to an ice-cold solution of 2,4-thiazolidinedione (500 mg, 4.2 mmol, 1.0 equiv) and Et_3N (1.8 mL, 12.6 mmol, 3.0 equiv) in CH_2Cl_2 (25 mL) and stirred for 12 h at room temperature. The reaction mixture was quenched with water and extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was then purified by flash chromatography with ethyl acetate−hexane (5/95 to 20/80) to provide compounds **1**.

3-Ethylthiazolidine-2,4-dione (1b). Using the general procedure, EtBr (0.9 mL, 12.6 mmol, 3.0 equiv) provided **1c** (518 mg, 85%) as a colorless liquid. HRMS (ESI) calcd for $C_5H_8NO_2S$ $[M + H]^+$ 146.0270, found 146.0271; ^{1}H NMR (500 MHz, $CDCl_3$) 4.04 (q, 2H, J = 7.2 Hz), 3.96 (s, 2H), 1.20 (t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 200.9, 173.6, 39.8, 35.4, 11.9.

3-Butylthiazolidine-2,4-dione (1c). Using the general procedure, ^{n}BuCl (1.3 mL, 12.6 mmol, 3.0 equiv) provided **1c** (530 mg, 73%) as a colorless liquid: HRMS (ESI) calcd for $C_7H_{12}NO_2S$ $[M + H]^+$ 174.0583, found 174.0585; ^{1}H NMR (400 MHz, $CDCl_3$) 3.92 (s, 2H), 3.59 (t, 2H, J = 7.3 Hz), 1.57−1.52 (m, 2H), 1.32−1.27 (m, 2H), 0.90 (t, 3H, J = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 171.7, 171.4, 41.8, 33.6, 29.5, 19.8, 13.5.

General Procedure for the Aldol Reaction. A mixture of thiazolidinedione **1** (0.17 mmol, 1.0 equiv) and isatin **2** (0.17 mmol, 1.0 equiv) was stirred on water (0.04 M) at room temperature for a specified reaction time. In most cases (except **3da**, **3aj**), the solid product was filtered and dried under vacuum to afford the product **3** in high yield and purity. Compounds **3da** and **3aj** were purified by flash column chromatography using ethyl acetate−hexane (20−80).

Procedure for the Transfer-Aldol Reaction. A mixture of **3aj** (dr = 96:4, 20 mg, 0.06 mmol, 1.0 equiv) and isatin **2b** (0.96 mg, 0.06 mmol, 1.0 equiv) was stirred at room temperature on water (0.04 M) for 12 h. The reaction mixture was then purified by flash column chromatography. The conversion was calculated from ^{1}H NMR analysis of the crude reaction mixture.

5-(3-Hydroxy-1-methyl-2-oxoindolin-3-yl)-3-methylthiazolidine-2,4-dione (3aa). Using the general procedure, thiazolidinedione **1a** (22.3 mg, 0.17 mmol, 1.0 equiv) and isatin **2a** (27.4 mg, 0.17 mmol, 1.0 equiv) provided compound **3aa** (48.6 mg, 98%) as a light orange solid: mp 143−145 °C; HRMS (ESI) calcd for $C_{13}H_{13}N_2O_4S$ $[M + H]^+$ 293.0591, found 293.0589; FT-IR (KBr) 3432, 2928, 1756, 1722, 1669, 1616, 1496, 1426, 1369, 1285, 1183, 1094, 1024, 1016, 954, 878 cm^{-1}; NMR of *anti* diastereomer: ^{1}H NMR (500 MHz, CD_3SOCD_3) 7.54 (d, 1H, J = 7.9 Hz), 7.36 (t, 1H, J = 7.8 Hz), 7.07 (s, 1H), 7.02 (t, 2H, J = 7.4 Hz), 5.15 (s, 1H), 3.15 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, CD_3SOCD_3) 174.4, 171.1, 170.1, 143.9, 130.6, 126.5, 123.9, 122.4, 108.9, 74.1, 57.3, 27.1, 26.2.

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5-(1-Ethyl-3-hydroxy-2-oxoindolin-3-yl)-3-methylthiazolidine-2,4-dione (3ab). Using the general procedure, thiazolidinedione **1a** (22.3 mg, 0.17 mmol, 1.0 equiv) and isatin **2b** (29.5 mg, 0.17 mmol, 1.0 equiv) provided compound **3ab** (49.9 mg, 96%) as a colorless solid: mp 140−143 °C; HRMS (ESI) calcd for $C_{14}H_{15}N_2O_4S$ $[M + H]^+$ 307.0747, found 307.0749; FT-IR (KBr) 3264, 2990, 2877, 2372, 1748, 1617, 1469, 1458, 1422, 1347, 1283, 1256, 1196, 1116, 1071, 1023, 1009, 946, 922, 826 cm^{-1}; NMR of major diastereomer: ^1H NMR (500 MHz, CD_3SOCD_3) 7.54 (d, 1H, J = 7.4 Hz), 7.35 (t, 1H, J = 7.8 Hz), 7.05 (d, 2H, J = 7.1 Hz), 7.00 (t, 1H, J = 7.5 Hz), 5.15 (s, 1H), 3.78−3.64 (m, 2H), 2.65 (s, 3H), 1.19 (t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, CD_3SOCD_3) 174.0, 171.1, 170.0, 143.1, 130.6, 126.7, 124.1, 122.2, 108.9, 74.0, 57.3, 34.3, 27.2, 12.0.

5-(3-Hydroxy-2-oxo-1-phenylindolin-3-yl)-3-methylthiazolidine-2,4-dione (3ac). Using the general procedure, thiazolidinedione **1a** (22.3 mg, 0.17 mmol, 1.0 equiv) and isatin **2c** (37.9 mg, 0.17 mmol, 1.0 equiv) provided compound **3ac** (59.0 mg, 98%) as a colorless solid: mp 154−157 °C; HRMS (ESI) calcd for $C_{18}H_{15}N_2O_4S$ $[M + H]^+$ 355.0747, found 355.0745; FT-IR (neat) 3323, 3058, 1719, 1611, 1595, 1479, 1380, 1332, 1225, 1179, 1121, 1085, 1027, 941, 866, 818 cm^{-1}; NMR of major diastereomer: ^1H NMR (500 MHz, CD_3SOCD_3) 7.66−7.61 (m, 3H), 7.50 (t, 1H, J = 7.5 Hz), 7.46 (d, 2H, J = 8.5 Hz), 7.32 (m, 2H), 7.08 (t, 1H, J = 7.8 Hz), 6.70 (d, 2H, J = 7.9 Hz), 5.28 (s, 1H), 2.69 (s, 3H); ^{13}C NMR (125 MHz, CD_3SOCD_3) 174.1, 171.1, 170.4, 143.8, 134.0, 130.7, 129.8, 128.4, 126.6, 126.2, 124.5, 123.0, 109.3, 74.1, 57.8, 27.3.

5-(3-Hydroxy-2-oxoindolin-3-yl)-3-methylthiazolidine-2,4-dione (3ae). Using the general procedure, thiazolidinedione **1a** (22.3 mg, 0.17 mmol, 1.0 equiv) and isatin **2e** (25.0 mg, 0.17 mmol, 1.0 equiv) provided compound **3ae** (46.3 mg, 98%) as a light pink solid: mp 140−144 °C; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_4S$ $[M + H]^+$ 279.0434, found 279.0431; FT-IR (KBr) 3375, 2924, 2361, 1724, 1689, 1621, 1427, 1369, 1277, 1185, 1106, 1086, 1008, 956, 832 cm^{-1}; NMR of major diastereomer: ^1H NMR (500 MHz, CD_3SOCD_3) 10.59 (s, 1H), 7.49 (d, 1H, J = 7.5 Hz), 7.26 (t, 1H, J = 7.8 Hz), 6.99 (s, 1H), 6.93 (t, 1H, J = 7.8 Hz), 6.82 (d, 1H, J = 7.8 Hz), 5.11 (s, 1H), 2.67 (s, 1H); ^{13}C NMR (125 MHz, CD_3SOCD_3) 175.9, 171.2, 170.2, 142.7, 130.4, 127.2, 124.3, 121.7, 110.1, 74.4, 57.1, 27.2.

5-(5-Chloro-3-hydroxy-2-oxoindolin-3-yl)-3-methylthiazolidine-2,4-dione (3af). Using the general procedure, thiazolidinedione **1a** (22.3 mg, 0.17 mmol, 1.0 equiv) and isatin **2f** (30.8 mg, 0.17 mmol, 1.0 equiv) provided compound **3af** (50.5 mg, 95%) as a colorless solid: mp 173−176 °C; HRMS (ESI) calcd for $C_{12}H_{10}ClN_2O_4S$ $[M + H]^+$: 313.0044; Found, 313.0041; FT-IR (neat) 3460.2, 2914.2, 2675.8, 2345.7, 1734.1, 1702.4, 1621.5, 1508.1, 1478.3, 1369.6, 1283.4, 1250.4, 1183.4, 1132.3, 1091.0, 1070.4, 1043.8, 966.2, 931.6, 895.6 cm^{-1}; NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3) 10.77 (s, 1H), 7.45 (d, 1H, J = 2.8 Hz), 7.32 (dd, 1H, J = 2.9, 10.5 Hz), 7.16 (s, 1H), 6.85 (d, 1H, J = 10.5 Hz), 5.14 (s, 1H), 2.72 (s, 3H), ^{13}C NMR (100 MHz, CD_3SOCD_3) 175.6, 171.0, 170.1, 141.6, 130.3, 129.3, 125.5, 124.3, 111.7, 74.4, 56.7, 27.3.

5-(5-Bromo-3-hydroxy-2-oxoindolin-3-yl)-3-methylthiazolidine-2,4-dione (3ag). Using the general procedure, thiazolidinedione **1a** (22.3 mg, 0.17 mmol, 1.0 equiv) and isatin **2g** (38.4 mg, 0.17 mmol, 1.0 equiv) provided compound **3ag** (58.9 mg, 97%) as a colorless solid: mp 207 °C; HRMS (ESI) calcd for $C_{12}H_9BrN_2NaO_4S$ $[M + Na]^+$ 378.9359, found 378.9361; FT-IR (KBr) 3296, 3014, 2861, 2351, 1716, 1691, 1612, 1432, 1351, 1247, 1122, 1087, 1018, 961, 875 cm^{-1}; NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3) 10.76 (s, 1H), 7.56 (d, 1H, J = 2.0 Hz), 7.45 (dd, 1H, J = 2.0, 7.6 Hz), 7.14 (s, 1H), 6.79 (d, 1H, J = 8.4 Hz), 5.12 (s, 1H), 2.72 (s, 1H); ^{13}C NMR (100 MHz, CD_3SOCD_3) 175.4, 170.9, 170.1, 142.0, 133.1, 129.6, 127.0, 113.0, 112.1, 74.4, 56.7, 27.3.

5-(5-Fluoro-3-hydroxy-2-oxoindolin-3-yl)-3-methylthiazolidine-2,4-dione (3ah). Using the general procedure, thiazolidinedione **1a** (22.3 mg, 0.17 mmol, 1.0 equiv) and isatin **2h** (28.1 mg, 0.17 mmol, 1.0 equiv) provided compound **3ah** (45.8 mg, 91%) as a colorless solid: mp 146 °C; HRMS (ESI) calcd for $C_{12}H_{10}FN_2O_4S$ $[M + H]^+$ 297.0340, found 297.0342; FT-IR (KBr) 3345, 3142, 2856, 2373, 1762, 1645, 1516, 1421, 1375, 1245, 1196, 1143, 1096, 1017, 975, 918, 883, 835 cm^{-1}. NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3) 10.63 (s, 1H), 7.27 (dd, 1H, J = 2.4, 5.6 Hz), 7.13−7.08 (m, 2H), 6.81 (dd, 1H, J = 4.0, 4.4 Hz), 5.11 (s, 1H), 2.71 (s, 3H); ^{13}C NMR (100 MHz, CD_3SOCD_3)175.82, 170.9, 170.0, 158.7, 156.3, 138.9, 138.8, 128.8, 128.7, 116.9, 116.6, 112.1, 111.8, 111.0, 110.9, 74.6, 56.8, 27.3.

5-(3-Hydroxy-2-oxo-5-(trifluoromethoxy)indolin-3-yl)-3-methylthiazolidine-2,4-dione (3ai). Using the general procedure, thiazolidinedione **1a** (22.3 mg, 0.17 mmol, 1.0 equiv) and isatin **2i** (39.3 mg, 0.17 mmol, 1.0 equiv) provided compound **3ai** (54.8 mg, 89%) as a colorless solid: mp 200−202 °C; HRMS (ESI) calcd for $C_{13}H_{10}F_3N_2O_5S$ $[M + H]^+$ 363.0263, found 363.0265; FT-IR (KBr) 3439, 2964, 1761, 1731, 1659, 1620, 1491, 1432, 1370, 1279, 1182, 1084, 1023, 955, 879 cm^{-1}; NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3) 10.83 (s, 1H), 7.42 (s, 1H), 7.30 (d, 1H, J = 6.8 Hz), 7.24 (s, 1H), 6.92 (d, 1H, J = 6.8 Hz), 5.12 (s, 1H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, CD_3SOCD_3) 176.4, 171.4, 170.6, 143.2, 142.5, 129.2, 124.5, 118.4, 111.6, 74.9, 57.5, 27.8.

5-(3-Hydroxy-5,7-dimethyl-2-oxoindolin-3-yl)-3-methylthiazolidine-2,4-dione (3aj). Using the general procedure, thiazolidinedione **1a** (22.3 mg, 0.17 mmol, 1.0 equiv) and isatin **2j** (29.8 mg, 0.17 mmol, 1.0 equiv) provided compound **3aj** (39.0 mg, 75%) as a colorless liquid: HRMS (ESI) calcd for $C_{14}H_{14}N_2NaO_4S$ $[M + Na]^+$ 329.0572, found 329.0575; FT-IR (KBr) 3421, 2933, 1721, 1673, 1621, 1482, 1422, 1361, 1284, 1191, 1073, 1011, 955, 879 cm^{-1}; NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3) 10.51 (s, 1H), 7.11 (s, 1H), 6.88 (s, 1H), 6.85 (s, 1H), 5.08 (s, 1H), 2.69 (s, 3H), 2.16 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, CD_3SOCD_3) 176.3, 171.2, 170.2, 138.7, 132.0, 130.4, 127.2, 122.1, 119.0, 74.7, 56.9, 27.2, 20.6, 16.2.

3-Ethyl-5-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-thiazolidine-2,4-dione (3ba). Using the general procedure, thiazolidinedione **1b** (24.7 mg, 0.17 mmol, 1.0 equiv) and isatin **2a** (27.4 mg, 0.17 mmol, 1.0 equiv) provided compound **3ba** (49.4 mg, 95%) as a colorless solid: mp 169−171 °C; HRMS (ESI) calcd for $C_{14}H_{14}KN_2O_4S$ $[M + K]^+$ 345.0306, found 345.0327; FT-IR (KBr) 3414, 3059, 2880, 2371, 1673, 1605, 1496, 1440, 1300, 1266, 1214, 1161, 1093, 1022, 1008, 930, 893, 791 cm^{-1}; NMR of *anti* diastereomer: ^1H NMR (500 MHz, CD_3SOCD_3) 7.55 (d, 1H, J = 8.5 Hz), 7.36 (t, 1H, J = 8.3 Hz), 7.08 (s, 1H), 7.03−7.01 (m, 2H), 5.08 (s, 1H), 3.29−3.15 (m, 2H), 3.14 (s, 3H), 0.47 (d, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, CD_3SOCD_3) 174.4, 171.0, 169.7, 144.0, 130.6, 126.2, 123.9, 122.3, 108.8, 74.4, 57.5, 35.8, 26.2, 11.8.

3-Ethyl-5-(1-ethyl-3-hydroxy-2-oxoindolin-3-yl)thiazolidine-2,4-dione (3bb). Using the general procedure, thiazolidinedione **1b** (24.7 mg, 0.17 mmol, 1.0 equiv) and isatin **2b** (29.5 mg, 0.17 mmol, 1.0 equiv) provided compound **3bb** (52.2 mg, 96%) as a colorless solid: mp 126−128 °C; HRMS (ESI) calcd for $C_{15}H_{20}N_3O_4S$ $[M + NH_4]^+$ 338.1169, found 338.1185; FT-IR (KBr) 3256, 3063, 2937, 2740, 2373, 1746, 1703, 1687, 1610, 1508, 1489, 1438, 1390, 1349, 1289, 1193, 1140, 1123, 1088, 1062, 1013, 974, 945, 897, 788 cm^{-1}; NMR of major diastereomer: ^1H NMR (500 MHz, CD_3SOCD_3) 7.54 (d, 1H, J = 8.3 Hz), 7.35 (t, 1H, J = 7.2 Hz), 7.07 (s, 1H), 7.05 (d, 1H, J = 7.8 Hz), 6.99 (t, 1H, J = 7.2 Hz), 5.08 (s, 1H), 3.64−3.76 (m, 2H), 3.19−3.16 (m, 2H), 1.19 (t, 3H, J = 7.2 Hz), 0.47 (t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, CD_3SOCD_3)174.0, 171.0, 169.6, 143.0, 130.5, 126.4, 124.1, 122.1, 108.9, 74.2, 57.4, 35.8, 34.3, 12.0, 11.7.

3-Ethyl-5-(3-hydroxy-2-oxo-1-phenylindolin-3-yl)-thiazolidine-2,4-dione (3bc). Using the general procedure, thiazolidinedione **1b** (24.7 mg, 0.17 mmol, 1.0 equiv) and isatin **2c** (37.9 mg, 0.17 mmol, 1.0 equiv) provided compound **3bc** (60.7 mg, 97%) as a colorless solid: mp 146−149 °C; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_4S$ $[M + H]^+$ 369.0904, found 369.0907; FT-IR (neat) 3405, 2936, 2346, 1723, 1685, 1596, 1501, 1466, 1377, 1222, 1119, 1087, 1044, 1028, 992, 894 cm^{-1}; NMR of major diastereomer: ^1H NMR (500 MHz, CD_3SOCD_3) 7.66 (m, 3H), 7.52 (t, 1H, J = 8.1 Hz), 7.47 (d, 2H, J = 8.5 Hz),7.33 (s, 1H), 7.32 (t, 1H, J = 8.4 Hz), 7.09 (t, 1H, J = 7.4 Hz), 6.70 (d, 1H, J = 7.9 Hz), 5.21 (s, 1H), 3.33−3.25 (m, 2H), 0.48 (t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, CD_3SOCD_3)

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174.1, 170.9, 170.0, 143.8, 134.0, 130.7, 129.8, 128.4, 126.6, 126.0, 124.4, 122.9, 109.2, 74.4, 57.9, 35.8, 11.7.

5-(1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)-3-ethylthiazolidine-2,4-dione (3bd). Using the general procedure, thiazolidinedione **1b** (24.7 mg, 0.17 mmol, 1.0 equiv) and isatin **2d** (40.3 mg, 0.17 mmol, 1.0 equiv) provided compound **3bd** (59.1 mg, 91%) as a light brown solid: mp 129−130 °C; HRMS (ESI) calcd for $C_{20}H_{19}N_2O_4S$ $[M + H]^+$ 383.1060, found 383.1063; FT-IR (KBr) 3331, 3066, 2974, 1698, 1616, 1490, 1376, 1341, 1221, 1178, 1093, 1043, 944, 889 cm^{-1}; NMR of major diastereomer: ^1H NMR (500 MHz, CD_3SOCD_3) 7.57 (d, 1H, J = 7.5 Hz), 7.44 (d, 2H, J = 7.8 Hz), 7.34 (t, 2H, J = 7.6 Hz), 7.27 (m, 2H), 7.24 (s, 1H), 6.99 (t, 1H, J = 7.6 Hz), 6.82 (d, 1H, J = 7.9 Hz), 5.19 (s, 1H), 4.99−4.95 (m, 2H), 3.24 (tt, 2H, J = 6.8, 13.6 Hz), 0.51 (t, 2H, J = 7.1 Hz); ^{13}C NMR (125 MHz, CD_3SOCD_3) 174.7, 170.9, 169.8, 143.2, 135.9, 130.4, 128.5, 127.4, 127.3, 126.5, 124.0, 122.4, 109.5, 74.4, 57.2, 43.2, 35.8, 11.8.

3-Ethyl-5-(3-hydroxy-2-oxoindolin-3-yl)thiazolidine-2,4-dione (3be). Using the general procedure, thiazolidinedione **1b** (24.7 mg, 0.17 mmol, 1.0 equiv) and isatin **2e** (25.0 mg, 0.17 mmol, 1.0 equiv) provided compound **3be** (48.7 mg, 98%) as a light yellow solid: mp 155−157 °C; HRMS (ESI) calcd for $C_{13}H_{12}KN_2O_4S$ $[M + K]^+$ 331.0149, found 331.0151; FT-IR (KBr) 3304, 2981, 2362, 1714, 1684, 1623, 1472, 1393, 1244, 1185, 1119, 1091, 954, 892, 792 cm^{-1}; NMR of major diastereomer: ^1H NMR (500 MHz, CD_3SOCD_3) 10.57 (s, 1H), 7.48 (d, 1H, J = 7.2 Hz), 7.25 (t, 1H, J = 7.7 Hz), 6.99 (s, 1H), 6.91 (t, 1H, J = 7.6 Hz), 6.81 (d, 1H, J = 7.7 Hz), 5.03 (s, 1H), 3.23 (tq, 2H, J = 7.1, 14.0 Hz), 0.50 (t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, CD_3SOCD_3) 175.9, 171.0, 169.7, 142.6, 130.4, 126.9, 124.2, 121.5, 110.0, 74.6, 57.2, 35.8, 11.8.

5-(5-Chloro-3-hydroxy-2-oxoindolin-3-yl)-3-ethylthiazolidine-2,4-dione (3bf). Using the general procedure, thiazolidinedione **1b** (24.7 mg, 0.17 mmol, 1.0 equiv) and isatin **2f** (30.8 mg, 0.17 mmol, 1.0 equiv) provided compound **3bf** (54.3 mg, 98%) as a colorless solid: mp 170−171 °C; HRMS (ESI) calcd for $C_{13}H_{12}ClN_2O_4S$ $[M + H]^+$ 327.0201, found 327.0203; FT-IR (neat) 3286.2, 2981.8, 2938.7, 2372.6, 1717.0, 1622.1, 1507.9, 1472.0, 1444.1, 1394.3, 1376.9, 1337.4, 1221.4, 1181.4, 1132.1, 1104.5, 1042.1, 965.9, 894.2, 851.9, 792.3 cm^{-1}; NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3) 10.77 (s,1H), 7.44 (d, 1H, J = 2.7 Hz), 7.32 (dd, 1H, J = 2.8, 10.4 Hz), 7.21 (s, 1H), 6.84 (d, 1H, J = 10.3 Hz), 5.06 (s, 1H), 3.27−3.24 (m, 2H), 0.54 (t, 3H, J = 8.9 Hz); ^{13}C NMR (100 MHz, CD_3SOCD_3) 175.6, 170.8, 169.6, 141.6, 130.2, 128.9, 125.5, 124.1, 111.6, 74.6, 57.0, 35.8, 11.7.

3-Butyl-5-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-thiazolidine-2,4-dione (3ca). Using the general procedure, thiazolidinedione **1c** (29.4 mg, 0.17 mmol, 1.0 equiv) and isatin **2a** (27.4 mg, 0.17 mmol, 1.0 equiv) provided compound **3ca** (55.1 mg, 97%) as a colorless solid: mp 145−146 °C; HRMS (ESI) calcd for $C_{16}H_{18}KN_2O_4S$ $[M + K]^+$ 373.0619, found 373.0615; FT-IR (KBr) 3439, 2960, 2931, 2371, 2345, 1748, 1671, 1497, 1441, 1372, 1300, 1218, 1159, 1098, 1079, 1022, 908, 841 cm^{-1}. NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3) 7.55 (d, 1H, J = 9.0 Hz), 7.37(t, 1H, J = 9.1 Hz), 7.08 (s, 1H), 7.03−6.98 (m, 2H), 5.10 (s, 1H), 3.23−3.18 (m, 2H), 3.14 (s, 3H), 0.93−0.84 (m, 2H), 0.76−0.65 (m, 2H), 0.63−0.59 (m, 3H), ^{13}C NMR: (100 MHz, CD_3SOCD_3) 174.5, 171.2, 169.9, 144.0, 130.6, 126.2, 124.0, 122.3, 108.8, 74.3, 57.5, 40.4, 28.7, 26.2, 18.8, 13.5

3-Butyl-5-(1-ethyl-3-hydroxy-2-oxoindolin-3-yl)thiazolidine-2,4-dione (3cb). Using the general procedure, thiazolidinedione **1c** (29.4 mg, 0.17 mmol, 1.0 equiv) and isatin **2b** (29.5 mg, 0.17 mmol, 1.0 equiv) provided compound **3cb** (57.4 mg, 97%) as a colorless solid: HRMS (ESI) calcd for $C_{17}H_{21}N_2O_4S$ $[M + H]^+$ 349.1217, found 349.1219; mp 114−116 °C; FT-IR (neat) 3315, 2961, 2464, 1752, 1696, 1633, 1456, 1387, 1261, 1184, 1096, 1018, 965, 823 cm^{-1}; NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3)7.55 (d, 1H, J = 9.1 Hz), 7.35 (t, 1H, J = 9.6 Hz), 7.06−7.04 (m, 2H), 6.99 (t, 1H, J = 9.6 Hz), 5.09 (s, 1H), 3.81−3.62 (m, 2H), 3.27−3.19 (m, 2H), 1.18 (t, 3H, J = 8.9 Hz), 0.92−0.84 (m, 2H), 0.68−0.63 (m, 2H), 0.61−0.58 (m, 3H); ^{13}C NMR (100 MHz, CD_3SOCD_3) 174.0, 171.2, 169.8, 143.1, 130.5, 126.4, 124.3, 122.0, 108.8, 74.2, 57.5, 40.4, 34.3, 28.7, 18.7, 13.5, 12.0.

3-Butyl-5-(3-hydroxy-2-oxo-1-phenylindolin-3-yl)-thiazolidine-2,4-dione (3cc). Using the general procedure, thiazolidinedione **1c** (29.4 mg, 0.17 mmol, 1.0 equiv) and isatin **2c** (37.9 mg, 0.17 mmol, 1.0 equiv) provided compound **3cc** (64.0 mg, 95%) as a colorless solid: mp 139−140 °C; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_4S$ $[M + H]^+$ 397.1217, found 397.1213; FT-IR (neat) 3411, 2958, 2931, 2873, 2366, 2345, 1718, 1684, 1611, 1500, 1466, 1437, 1379, 1331, 1301, 1226, 1194, 1120, 1087, 1028, 940, 759 cm^{-1}; NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3) 7.68−7.60 (m, 3H), 7.50 (t, 1H, J = 9.16 Hz), 7.45 (d, 2H, J = 9.3 Hz), 7.33−7.29 (m, 2H), 7.07 (t, 1H, J = 9.4 Hz), 6.70 (d, 1H, J = 9.8 Hz), 5.22 (s, 1H), 3.25 (dt, 2H, J = 2.8, 8.3 Hz), 0.95−0.92 (m, 2H), 0.70−0.64 (m, 2H), 0.68−0.58 (m, 3H); ^{13}C NMR (100 MHz, CD_3SOCD_3) 174.1, 171.2, 170.2, 143.8, 134.0, 130.6, 129.8, 128.3, 126.6, 126.0, 124.6, 122.9, 109.1, 74.3, 58.0, 40.5, 28.7, 18.7, 13.5.

3-Butyl-5-(3-hydroxy-2-oxoindolin-3-yl)thiazolidine-2,4-dione (3ce). Using the general procedure, thiazolidinedione **1c** (29.4 mg, 0.17 mmol, 1.0 equiv) and isatin **2e** (25.0 mg, 0.17 mmol, 1.0 equiv) provided compound **3ce** (53.3 mg, 98%) as a colorless solid: mp 145 °C; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_4S$ $[M + H]^+$ 321.0904, found 321.0907; FT-IR (KBr) 3294, 2959, 2874, 2370, 2345, 1717, 1623, 1508, 1473, 1394, 1355, 1206, 1116, 1092, 952, 863, 781 cm^{-1}; NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3) 10.58 (s, 1H), 7.51 (d, 1H, J = 9.1 Hz), 7.25 (t, 1H, J = 8.9 Hz), 7.00 (s, 1H), 6.91 (t, 1H, J = 9.4 Hz), 6.81 (d, 1H, J = 9.6 Hz), 5.05 (s, 1H), 3.29−3.21 (m, 2H), 0.97−0.85 (m, 2H), 0.75−0.65 (m, 2H), 0.61 (t, 3H, J = 8.2 Hz); ^{13}C NMR (100 MHz, CD_3SOCD_3) 175.9, 171.3, 169.9, 142.7, 130.3, 126.9, 124.4, 121.6, 109.9, 74.5, 57.3, 40.5, 28.8, 18.8, 13.5.

3-Butyl-5-(5-chloro-3-hydroxy-2-oxoindolin-3-yl)-thiazolidine-2,4-dione (3cf). Using the general procedure, thiazolidinedione **1c** (29.4 mg, 0.17 mmol, 1.0 equiv) and isatin **2f** (30.8 mg, 0.17 mmol, 1.0 equiv) provided compound **3cf** (60.2 mg, 98%) as a colorless solid: mp 154−156 °C; HRMS (ESI) calcd for $C_{15}H_{16}ClN_2O_4S$ $[M + H]^+$ 355.0514, found 355.0517; FT-IR (neat) 3294, 2959, 2873, 2373, 1708, 1623, 1507, 1471, 1393, 1340, 1182, 967, 948, 890, 825 cm^{-1}; NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3) 10.7 (s, 1H), 7.46 (d, 1H, J = 2.8 Hz), 7.33 (dd, 1H, J = 3.0, 10.6 Hz), 7.20 (s, 1H), 6.84 (d, 1H, J = 10.3 Hz), 5.07 (s, 1H), 3.31−3.20 (m, 2H), 0.99−0.83 (s, 2H), 0.75−0.68 (m, 1H), 0.66−0.63 (m, 3H); ^{13}C NMR (100 MHz, CD_3SOCD_3) 175.7, 171.1, 169.9, 141.6, 130.3, 128.9, 125.6, 124.3, 115.6, 74.5, 57.2, 40.5, 28.9, 18.9, 13.5.

3-Benzyl-5-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-thiazolidine-2,4-dione (3da). Using the general procedure, thiazolidinedione **1d** (35.2 mg, 0.17 mmol, 1.0 equiv) and isatin **2a** (27.4 mg, 0.17 mmol, 1.0 equiv) provided compound **3da** (58.8 mg, 94%) as a colorless viscous liquid: HRMS (ESI) calcd for $C_{19}H_{16}KN_2O_4S$ $[M + K]^+$ 407.0462, found 407.0459; FT-IR (neat) 3301, 2942, 2842, 2369, 1808, 1672, 1523, 1475, 1340, 1181, 968, 832 cm^{-1}. NMR of major diastereomer: ^1H NMR (500 MHz, CD_3SOCD_3) 7.58 (d, 1H, J = 7.4 Hz), 7.46 (t, 1H, J = 7.8 Hz), 7.15 (t, 1H, J = 7.4 Hz), 7.13 (s, 1H), 7.10 (t, 2H, J = 6.7 Hz), 7.05−6.99 (m, 2H), 6.50 (d, 2H, J = 7.3 Hz), 5.26 (s, 1H), 4.45 (m, 2H), 3.15 (s, 3H); ^{13}C NMR (125 MHz, CD_3SOCD_3) 174.5, 170.9, 169.9, 144.1, 134.8, 130.7, 128.3, 127.1, 126.2, 124.3, 122.4, 108.9, 74.2, 57.9, 43.9, 26.2.

3-Benzyl-5-(3-hydroxy-2-oxo-1-phenylindolin-3-yl)-thiazolidine-2,4-dione (3dc). Using the general procedure, thiazolidinedione **1d** (35.2 mg, 0.17 mmol, 1.0 equiv) and isatin **2c** (37.9 mg, 0.17 mmol, 1.0 equiv) provided compound **3dc** (67.3 mg, 92%) as a colorless solid: mp 159 °C; HRMS (ESI) calcd for $C_{24}H_{19}N_2O_4S$ $[M + H]^+$ 431.1060, found 431.1063; FT-IR (KBr) 3326, 3065, 2928, 2369, 1715, 1695, 1611, 1501, 1457, 1342, 1162, 1086, 1028, 984, 868 cm^{-1}; NMR of major diastereomer: ^1H NMR (500 MHz, CD_3SOCD_3) 7.68 (d, 1H, J = 8.9 Hz), 7.63 (t, 2H, J = 9.6 Hz), 7.51 (t, 1H, J = 9.4 Hz), 7.45−7.43 (m, 2H), 7.40−7.38 (m, 1H), 7.14 (d, 1H, J = 9.1 Hz), 7.10−7.04 (m, 3H), 6.73 (d, 1H, J = 9.9 Hz), 6.50 (d, 2H, J = 9.1 Hz), 5.38 (s, 1H), 4.72−4.35 (m, 2H); ^{13}C NMR

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(125 MHz, CD_3SOCD_3) 174.2, 170.9, 170.3, 143.8, 134.8, 134.0, 130.9, 129.8, 128.4, 128.3, 127.1, 126.2, 125.9, 124.9, 123.1, 109.3, 74.3, 58.3, 44.0.

3-Benzyl-5-(3-hydroxy-2-oxoindolin-3-yl)thiazolidine-2,4-dione (3de). Using the general procedure, thiazolidinedione **1d** (35.2 mg, 0.17 mmol, 1.0 equiv) and isatin **2e** (25.0 mg, 0.17 mmol, 1.0 equiv) provided compound **3de** (59.0 mg, 98%) as a light yellow solid: mp 145−147 °C; HRMS (ESI) calcd for $C_{18}H_{15}N_2O_4S$ $[M + H]^+$ 355.0747, found 355.0749; FT-IR (KBr) 3304, 2936, 2362, 1714, 1684, 1623, 1472, 1393, 1377, 1244, 1185, 1091, 954, 892 cm^{-1}; NMR of major diastereomer: ^1H NMR (500 MHz, CD_3SOCD_3) 10.59 (s, 1H), 7.52 (d, 1H, J = 7.3 Hz), 7.33 (t, 1H, J = 7.7 Hz), 7.15 (t, 1H, J = 7.4 Hz), 7.09 (t, 2H, J = 7.4 Hz), 7.04 (s, 1H), 6.91 (t, 1H, J = 7.6 Hz), 6.83 (d, 1H, J = 7.7 Hz), 6.54 (d, 1H, J = 7.3 Hz), 5.20 (s, 1H), 4.45 (m, 2H); ^{13}C NMR (125 MHz, CD_3SOCD_3) 175.9, 171.0, 169.9, 142.7, 134.9, 130.5, 128.3, 127.1, 126.9, 126.2, 124.7, 121.7, 110.1, 74.5, 57.6, 43.9.

3-Benzyl-5-(5-chloro-3-hydroxy-2-oxoindolin-3-yl)-thiazolidine-2,4-dione (3df). Using the general procedure, thiazolidinedione **1d** (35.2 mg, 0.17 mmol, 1.0 equiv) and isatin **2f** (30.8 mg, 0.17 mmol, 1.0 equiv) provided compound **3df** (63.5 mg, 96%) as a colorless solid: mp 155−157 °C; HRMS (ESI) calcd for $C_{18}H_{14}ClN_2O_4S$ $[M + H]^+$ 389.0363, found 389.0365; FT-IR (neat) 3270.24, 2930.42, 1715.36, 1693.91, 1620.97, 1468.71, 1431.74, 1385.67, 1335.93, 1178.78, 1154.05, 1029.22, 1003.22, 962.29, 893.87, 846.10 cm^{-1}; NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3) 10.77 (s, 1H), 7.45 (d, 1H, J = 2.6 Hz), 7.36 (dd, 1H, J = 2.9, 10.5 Hz), 7.25 (s, 1H), 7.15 (m, 3H), 6.82 (d, 1H, J = 10.3 Hz), 6.59 (d, 1H, J = 8.7 Hz), 5.21 (s, 1H), 4.46 (d, 2H, J = 4.5 Hz); ^{13}C NMR (100 MHz, CD_3SOCD_3) 175.7, 170.8, 169.8, 141.6, 134.9, 130.5, 128.8, 124.4, 127.3, 126.1, 125.7, 124.5.

***tert*-Butyl 5-(3-Hydroxy-1-methyl-2-oxoindolin-3-yl)-2,4-dioxothiazolidine-3-carboxylate (3ea).** Using the general procedure, thiazolidinedione **1e** (36.9 mg, 0.17 mmol, 1.0 equiv) and isatin **2a** (27.4 mg, 0.17 mmol, 1.0 equiv) provided compound **3ea** (61.1 mg, 95%) as a colorless solid: mp 153−155 °C; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_6S$ $[M + H]^+$ 379.0958, found 379.09361; FT-IR (neat) 3415, 3056, 2946, 2326, 1713, 1695, 1621, 1597, 1522, 1474, 1381, 1305, 1232, 1101, 1088, 1045, 1029, 983, 912, 891 cm^{-1}; NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3) 7.55 (d, 1H, J = 8.9 Hz), 7.39 (t, 1H, J = 9.5 Hz), 7.06−7.02 (m, 3H), 4.85 (s, 1H), 3.13 (s, 1H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, CD_3SOCD_3) 174.6, 171.5, 171.0, 144.0, 130.6, 126.2, 123.9, 122.2, 108.8, 74.5, 60.6, 56.1, 27.3, 26.2.

***tert*-Butyl 5-(5-Chloro-3-hydroxy-2-oxoindolin-3-yl)-2,4-dioxothiazolidine-3-carboxylate (3ef).** Using the general procedure, thiazolidinedione **1e** (36.9 mg, 0.17 mmol, 1.0 equiv) and isatin **2f** (30.8 mg, 0.17 mmol, 1.0 equiv) provided compound **3ef** (62.4 mg, 92%) as a colorless solid: mp 177−179 °C; HRMS (ESI) calcd for $C_{16}H_{16}ClN_2O_6S$ $[M + H]^+$: 399.0412; Found, 399.0415; FT-IR (neat) 3416, 3159, 2881, 2372, 1753, 1653, 1615, 1484, 1390, 1276, 1195, 1142, 1039, 1008, 975, 895, 841 cm^{-1}; NMR of major diastereomer: ^1H NMR (400 MHz, CD_3SOCD_3) 10.73 (s, 1H), 7.46 (d, 1H, J = 2.7 Hz), 7.35 (dd, 1H, J = 2.8, 10.4 Hz), 7.14 (s, 1H), 6.85 (d, 1H, J = 10.4 Hz), 4.83 (s, 1H), 1.16 (s, 9H), ^{13}C NMR (100 MHz, CD_3SOCD_3) 175.7, 171.4, 170.9, 158.3, 141.5, 130.2, 128.9, 125.4, 124.0, 115.6, 74.7, 60.6, 55.9, 27.3.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray cystallographic data, computational methods, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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