Organocatalytic Stereoselective Synthesis of Fluorinated 3,3′-Linked Bisoxindoles

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Abstract

A highly diastereoselective organocatalytic method that produces 3-fluoro-3′-hydroxy-3,3′-bisoxindoles and the corresponding 3-fluoro-3′-amino derivatives having two adjacent chirality centers from fluorooxindoles and isatins in high yields is described. The reaction occurs in protic solvents at room temperature, it can be upscaled without compromising yield and stereoselectivity, and chromatographic product purification is not required.

Graphical abstract
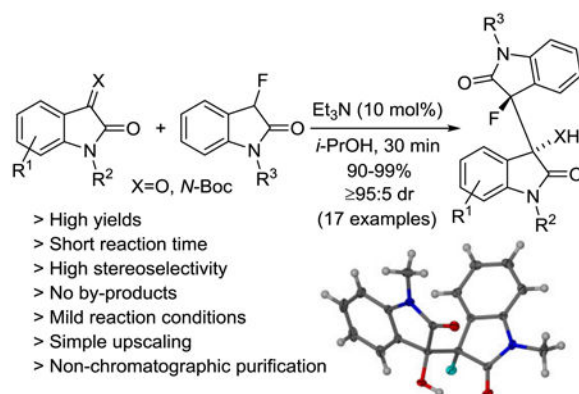
The unique physicochemical properties and widespread use of fluorinated organic compounds in the health sciences continues to attract considerable attention. Numerous studies have shown that incorporation of fluorine can improve the therapeutic index of biologically active compounds.[1] The introduction of synthetic methods that produce fluorinated derivatives of natural compounds and future drug candidates therefore remains of considerable interest. The construction of carbon-carbon bonds with reactive organofluorine intermediates, however, is often limited by undesirable side reactions and decomposition pathways. Various synthetic strategies that address these issues, for example by mild in situ production of fluoroenolates, have emerged in recent years.[2] The 3,3-disubstituted oxindole scaffold is a privileged structural motif and a challenging synthetic target,[3] especially if

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multiple stereocenters are present.[4] The medicinal utility and potential of 3-fluorooxindoles, including the potassium ion channel modulator Maxipost (Figure 1),[5] has inspired the development of several methods that accomplish direct fluorination of 3-alkyl and 3-aryloxindoles.[6] More recently, synthetic alternatives that accomplish C-C bond formation with 3-fluorooxindoles have emerged.[7]

A remaining drawback of fluorooxindole transformations is that the use of inert reaction conditions and elaborate work-up procedures generating substantial amounts of chemical waste are required in most cases. Because environmental and sustainability aspects together with operational safety, time efficiency and overall cost considerations play an increasingly important role in industrial and academic laboratories we decided to develop a practical method that addresses these issues using 3-fluorooxindoles as starting material. The reaction with isatins was of particular interest to us as it produces a challenging dimeric oxindole scaffold exhibiting a 3,3′-linkage with two adjacent chirality centers.

We began our search for an environmentally benign, economically attractive method by screening the reaction of N-phenyl-3-fluorooxindole, **1**, and isatin, **2**, in water and alcoholic solvents in the presence of catalytic amounts of inexpensive triethylamine at room temperature (Table 1). We found that the reaction proceeds smoothly in the presence of 20 mol% of base in water and is almost complete after stirring for 2 hours at room temperature (entry 1). The formation of the bisoxindole **3** was almost quantitative and occurred with high stereoselectivity. We did not detect formation of by-products and determined the diastereomeric ratio, dr, of **3** as 24:1. As expected, catalytic amounts of the base are required for this reaction and **3** was not formed in the absence of Et$_3$N (entry 2). Screening of other protic solvents revealed that the conversion, reaction time and diastereoselectivity can be further improved (entries 3-6). In addition to optimization of the reaction conditions, we examined the possibility of non-chromatographic product isolation to minimize the overall solvent consumption and labor. Using 10 mol% of triethylamine in isopropyl alcohol we observed that **3** is produced quantitatively from **1** and **2** with 49:1 dr in just 30 minutes (entry 6). Under these conditions, the bisoxindole precipitated quantitatively which greatly facilitates product isolation and renders chromatographic work-up unnecessary.

Having optimized reaction conditions and a work-up procedure that are both practical and environmentally benign, we continued to determine the reaction scope of the organocatalytic bisoxindole formation. 3-Fluoro-3′-hydroxy-1-phenyl-3,3′-bisoxindole, **3**, was isolated in 96% yield and 99:1 dr (Scheme 1). The reaction between fluorooxindole **1** and isatins carrying a halide or a methyl group at position 5 in the fused benzene ring gave the corresponding bisoxindoles **4-7** in 90-96% yield and with at least 95:5 dr. The reaction tolerates substituents at all positions in the isatin electrophile. The chlorinated bisoxindoles **8**-**10** were produced with very similar results compared to **4**. When we employed other brominated and fluorinated isatins in this reaction we obtained **11**-**13** in 91-92% yields and very high dr's. The isatin compound can also be substituted at the nitrogen. 3-Fluoro-3′-hydroxy-1,1′-diphenyl-3,3′-bisoxindole, **14**, and the N-methyl analogue **15** were isolated in almost quantitative amounts and in excellent diastereomeric ratio. The reaction with N-methylisatin and N-methyl-3-fluorooxindole was also conducted in the presence of 20 mol% of triethylamine using either THF or dichloromethane as solvent. In both cases, the reaction

occurs under homogeneous conditions and without precipitation of the product **15** which was obtained in quantitative yield and with >99:1 dr. This suggests that the high diastereoselectivity is achieved in solution and not a result of preferential crystallization of one diastereomer from a mixture of rapidly interconverting isomers of **15** (asymmetric transformation of the second kind). Finally the introduction of a strong electron-withdrawing nitro group and an electron-donating methoxy into the isatin ring showed little effects on the chemical and stereochemical outcome. We obtained **16** and **17** in 92-94% yield and very high dr. The triethylamine catalyzed reaction thus affords a variety of 3,3′-bridged bisoxindoles exhibiting two adjacent quaternary chiral centers in almost quantitative yields and with remarkable diastereoselectivity. Our organocatalytic method is operationally simple and leads to multifunctional bisoxindole alkaloid scaffolds. The protocol has several attractive features in addition to the high yields and dr values that are noteworthy. The C-C bond formation is accomplished within 30 minutes using mild reaction conditions, i.e. at room temperature and under air, and we did not observe by-product formation. All products **3**-**17** were isolated by precipitation and purified by careful washing with isopropyl alcohol-petroleum ether mixtures. The work-up does not require any chromatography which typically is time-consuming and increases both cost and waste production.[8]

To reveal the stereochemical outcome of this reaction we resorted to X-ray crystallography. We were able to grow a single crystal of racemic 3-fluoro-3′-hydroxy-1,1′-dimethyl-3,3′-bisoxindole, **15**, by slow evaporation of a solution containing small amounts of ethyl acetate in hexanes.[9] Crystallographic analysis confirmed that the reaction favors formation of the homochiral diastereomer (Figure 2).

To the best of our knowledge, the synthesis of 3-fluoro-3′-hydroxy-3,3′-bisoxindoles has not been reported to date and **3**-**17** are new compounds. Few examples of palladium catalyzed carbon-carbon bond formation with fluorooxindole 1 in dichloromethane and toluene, respectively, are known.[7d,10] These methods accomplish asymmetric allylic alkylations and arylations with high yields and stereoselectivities but long reaction times and chromatographic work-up are required. Han and Soloshonok introduced a noncatalytic diastereoselective Mannich reaction via detrifluoroacetylative generation of intermediate 3-fluorooxindole enolates which achieves carbon-carbon bond formation with yields and dr's very similar to our method.[7c,11] This reaction is fast and proceeds in etheral solvents or acetonitrile but large excess of base and LiBr additives are required in addition to chromatographic product purification. A very similar copper catalyzed asymmetric aldol-type reaction that utilizes the same detrifluoroacetylation concept was recently reported.[12] An inherent drawback of the detrifluoroacetylative enolate generation, however, is the production of stoichiometric amounts of trifluoroacetic acid waste. In comparison to these methods our protocol establishes a significant green chemistry advance as waste resulting from by-products or additives, chromatographic work-up and the use of transition metals are avoided. Thakur and Meshram reported an interesting diastereoselective formation of 3-hydroxy-3,3′-bisoxindoles through catalyst-free on-water synthesis.[13] We found, however, that this protocol cannot be generally used for the synthesis of the fluorinated bisoxindoles **3**-**17**. While we successfully reproduced their results with oxindole and isatin, the reaction

between *N*-phenyl-3-fluorooxindole and either isatin or *N*-phenylisatin using the on-water protocol gave **3** and **14**, respectively, in only 3-5% yield after 24 hours.

We decided to run the reaction between **1** and **2** at the gram scale to determine if the overall efficiency and the environmentally attractive features of our method can be maintained without compromising yield and diastereoselectivity (see Experimental Section). We found that even at the increased reaction scale the product formation is complete within 30 minutes and **3** was isolated in 95% yield and with 99:1 dr. More than one gram of the bisoxindole **3** was thus obtained with an E-factor of 22 and without the use of expensive catalysts and additives or hazardous solvents.[14]

Our method is not limited to isatin electrophiles. When we applied the fluorooxindoles **1** and **20** in the reaction with *N*-Boc imine **18** we were pleased to find that the correspnding amines **19** and **21** were produced in 90-92% yield and with very high dr using the same method (Scheme 2). The reactivity of 3-fluorooxindoles in protic solvents and the utility of our environmentally benign C-C bond formation procedure also extends to Michael additions.[15] Employing **1** and 1,1-bis(phenylsulfonyl)ethane, **22**, in essentially the same protocol used above we were able to prepare **23** in 99% yield.[7a,16] This reaction occurs in isopropyl alcohol in the presence of 10 mol% of triethylamine and is complete within 30 minutes. Again, chromatographic product purification was not necessary.

In summary, we have introduced an organocatalytic method that produces 3-fluoro-3′-hydroxy-3,3′-bisoxindoles or the corresponding 3-fluoro-3′-amines carrying two vicinal chirality centers in high yields and stereoselectivities. The reaction occurs in non-hazardous isopropyl alcohol or other protic solvents at room temperature within 30 minutes in the presence 10 mol% of triethylamine as catalyst and the bisoxindole formation can be upscaled without compromising yields and diastereoselectivity. Furthermore, the formation of by-products was not observed and chromatographic product purification is not necessary.

Experimental Section

Commercially available isatins, reagents and solvents were used as purchased without further purification. 3-Fluorooxindole was synthesized by following literature procedures.[7d] NMR spectra were obtained at 400 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 100 MHz (^{13}C NMR) in deuterated dimethylsulfoxide, acetone or deuterated chloroform. Proton chemical shifts are reported in ppm relative to the solvent peak or TMS.

General Procedure

A mixture of 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and an isatin (0.20 mmol) were added to 1.0 mL of isopropyl or methyl alcohol. Triethylamine (2.8 μL, 0.020 mmol) was added and the solution was stirred for 30 minutes. The resulting solid was isolated after addition of 1.0 mL of petroleum ether and decanting off the liquid. The crude product was purified by washing the solid three times with 1.0 mL of petroleum ether-isopropyl alcohol (1:1).

3-Fluoro-3′-hydroxy-1-phenyl-[3,3′-biindoline]-2,2′-dione

Compound **3** was obtained as a white crystalline solid in 96% yield (72 mg, 0.19 mmol) and >99:1 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and isatin (30 mg, 0.20 mmol) after sonication in isopropyl alcohol for 30 minutes as described above. Decomp. 204 °C. ^{1}H NMR (399 MHz, DMSO-d_6): δ = 10.44 (s, 1H), 7.51 – 7.33 (m, 4H), 7.28 (dd, J = 7.6, 7.6 Hz, 1H), 7.15 (dd, J = 7.5, 7.5 Hz, 1H), 6.98 (s, 1H), 6.95 – 6.90 (m, 2H), 6.84 – 6.77 (m, 2H), 6.62 (d, J = 8.0 Hz, 1H), 6.37 (d, J = 6.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.8 (d, $J_{C\text{-}F}$ = 2.4 Hz), 168.5 (d, $J_{C\text{-}F}$ = 21.6 Hz), 144.4 (d, $J_{C\text{-}F}$ = 5.1 Hz), 142.9, 132.9, 132.0 (d, $J_{C\text{-}F}$ = 2.6 Hz), 130.7, 129.7, 128.6, 126.9, 126.4, 125.7 (d, $J_{C\text{-}F}$ = 4.1 Hz), 124.8, 123.2 (d, $J_{C\text{-}F}$ = 2.5 Hz), 121.6 (d, $J_{C\text{-}F}$ = 18.8 Hz), 121.3, 109.8, 109.2, 94.0 (d, $J_{C\text{-}F}$ = 205.3 Hz), 77.0 (d, $J_{C\text{-}F}$ = 23.8 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -177.2. Anal. Calcd. for $C_{22}H_{15}FN_2O_3$: C, 70.58; H, 4.04; N, 7.48. Found: C, 70.39; H, 4.20; N, 7.40.

Large Scale Synthesis of 3

A mixture of 3-fluoro-1-phenylindolin-2-one (911 mg, 4.0 mmol) and isatin (602 mg, 4.0 mmol) were added to 4.0 mL of isopropyl alcohol. Triethylamine (56.5 μL, 0.40 mmol) was added and the solution was stirred for 30 minutes. The resulting product **3** was obtained as a white solid in 95% yield (1.43 g, 3.8 mmol) and >99:1 dr after adding 6.0 mL of isopropyl alcohol, filtration and washing the solid with a total of 20 mL of petroleum ether-isopropyl alcohol (1:1).

5′-Chloro-3-fluoro-3′-hydroxy-1-phenyl-[3,3′-biindoline]-2,2′-dione

Compound **4** was obtained as a white solid in 94% yield (77 mg, 0.19 mmol) and 96:4 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 5-chloroisatin (37 mg, 0.20 mmol) after stirring in isopropyl alcohol for 30 minutes as described above. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.62 (s, 1H), 7.54 - 7.38 (m, 5H), 7.35 (dd, J = 8.3, 2.1 Hz, 1H), 7.25 – 7.16 (m, 2H), 7.01 – 6.93 (m, 2H), 6.82 (d, J = 8.3 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.26 (bs, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.4 (d, $J_{C\text{-}F}$ = 2.2 Hz), 168.2 (d, $J_{C\text{-}F}$ = 21.6 Hz), 144.4 (d, $J_{C\text{-}F}$ = 5.1 Hz), 141.8, 132.9, 132.3 (d, $J_{C\text{-}F}$ = 2.6 Hz), 130.5, 129.8, 128.7, 127.6 (d, $J_{C\text{-}F}$ = 4.1 Hz), 127.0, 126.3, 125.3, 124.8, 123.4 (d, $J_{C\text{-}F}$ = 2.4 Hz), 121.2 (d, $J_{C\text{-}F}$ = 19.0 Hz), 111.4, 109.2, 93.9 (d, $J_{C\text{-}F}$ = 206.4 Hz), 77.1 (d, $J_{C\text{-}F}$ = 24.2 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -177.9. Anal. Calcd. for $C_{22}H_{14}ClFN_2O_3$: C, 64.64; H, 3.45; N, 6.85. Found: C, 64.46; H, 3.50; N, 6.71.

5′-Bromo-3-fluoro-3′-hydroxy-1-phenyl-[3,3′-biindoline]-2,2′-dione

Compound **5** was obtained as a white solid in 91% yield (83 mg, 0.18 mmol) and 95:5 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 5-bromoisatin (48 mg, 0.20 mmol) after stirring in isopropyl alcohol for 30 minutes as described above. ^{1}H NMR (400 MHz, acetone-d_6): δ = 9.40 (s, 1H), 7.48 – 7.41 (m, 3H), 7.40 – 7.26 (m, 2H), 7.24 – 7.16 (m, 2H), 7.10 (s, 1H), 6.95 (dd, J = 7.3, 7.3 Hz, 1H), 6.82 – 6.73 (m, 2H), 6.63 (d, J = 7.7 Hz, 1H), 5.85 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.3 (d, $J_{C\text{-}F}$ = 2.0 Hz), 168.2 (d, $J_{C\text{-}F}$ = 21.6 Hz), 144.4 (d, $J_{C\text{-}F}$ = 5.0 Hz), 142.1, 133.3, 132.8, 132.3, 129.8, 128.7, 128.0 (d, $J_{C\text{-}F}$ = 4.4 Hz), 127.6, 127.0, 126.3, 123.4, 121.2 (d, $J_{C\text{-}F}$ = 19.1 Hz), 112.8, 111.9, 109.2,

94.0 (d, J_{C-F} = 206.9 Hz), 77.0 (d, J_{C-F} = 24.1 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -177.4. Anal. Calcd. for $C_{22}H_{14}BrFN_2O_3$: C, 58.30; H, 3.11; N, 6.18. Found: C, 58.30; H, 3.19; N, 6.08.

3,5′-Difluoro-3′-hydroxy-1-phenyl-[3,3′-biindoline]-2,2′-dione

Compound **6** was obtained as a white solid in 96% yield (75 mg, 0.19 mmol) and 96:4 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 5-fluoroisatin (34 mg, 0.20 mmol) after stirring in isopropyl alcohol for 30 minutes as described above. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.50 (s, 1H), 7.54 – 7.47 (m, 2H), 7.46 – 7.40 (m, 2H), 7.34 (m, 1H), 7.21 – 7.12 (m, 3H), 7.04 – 6.96 (m, 2H), 6.81 (dd, J = 8.6, 4.2 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.14 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.7 (d, J_{C-F} = 2.4 Hz), 168.2 (d, J_{C-F} = 21.6 Hz), 157.4 (d, J_{C-F} = 237.8 Hz), 144.4 (d, J_{C-F} = 5.2 Hz), 139.1 (d, J_{C-F} = 1.9 Hz), 132.9, 132.3 (d, J_{C-F} = 2.5 Hz), 129.8, 128.7, 127.2 (dd, J_{C-F} = 7.8, 4.0 Hz), 126.9, 126.3, 123.3 (d, J_{C-F} = 2.4 Hz), 121.2 (d, J_{C-F} = 19.0 Hz), 117.1 (d, J_{C-F} = 23.1 Hz), 112.4 (d, J_{C-F} = 25.0 Hz), 110.8 (d, J_{C-F} = 7.8 Hz), 109.3, 93.8 (d, J_{C-F} = 205.7 Hz), 77.4 (d, J_{C-F} = 24.1 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -122.5 (m), -177.51. Anal. Calcd. for $C_{22}H_{14}F_2N_2O_3$: C, 67.35; H, 3.60; N, 7.14. Found: C, 67.05; H, 3.56; N, 7.03.

3-Fluoro-3′-hydroxy-5′-methyl-1-phenyl-[3,3′-biindoline]-2,2′-dione

Compound **7** was obtained as a white solid in 90% yield (70 mg, 0.18 mmol) and 97:3 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 5-methylisatin (33 mg, 0.20 mmol) after sonication in isopropyl alcohol for 30 minutes as described above. ^{1}H NMR (399 MHz, DMSO-d_6): δ = 10.31 (s, 1H), 7.54 – 7.37 (m, 4H), 7.27 (m, 1H), 7.17 – 7.07 (m, 2H), 6.99 – 6.93 (m, 2H), 6.87 (s, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 6.23 (bs, 1H), 2.06 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.2 (d, J_{C-F} = 2.8 Hz), 168.9 (d, J_{C-F} = 21.7 Hz), 144.9 (d, J_{C-F} = 5.1 Hz), 140.8, 133.5, 132.4 (d, J_{C-F} = 2.7 Hz), 131.1, 130.6, 130.2, 129.0, 127.3, 126.9, 126.2 (d, J_{C-F} = 3.8 Hz), 126.1, 123.5 (d, J_{C-F} = 2.4 Hz), 122.1, 121.9, 109.7 (d, J_{C-F} = 48.5 Hz), 94.4 (d, J_{C-F} = 205.1 Hz), 77.8 (d, J_{C-F} = 23.8 Hz), 21.0. ^{19}F NMR (376 MHz, DMSO-d_6): δ = -177.6. Anal. Calcd. for $C_{23}H_{17}FN_2O_3$: C, 71.13; H, 4.41; N, 7.21. Found: C, 70.76; H, 4.51; N, 7.13.

7′-Chloro-3-fluoro-3′-hydroxy-1-phenyl-[3,3′-biindoline]-2,2′-dione

Compound **8** was obtained as a white solid in 91% yield (74 mg, 0.18 mmol) and >99.1 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 7-chloroisatin (37 mg, 0.20 mmol) after stirring in isopropyl alcohol for 30 minutes as described above. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.94 (s, 1H), 7.54 – 7.40 (m, 4H), 7.40 – 7.32 (m, 2H), 7.23 – 7.14 (m, 2H), 7.01 – 6.95 (m, 2H), 6.87 (dd, J = 7.9, 7.9 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.36 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.7 (d, J_{C-F} = 2.3 Hz), 168.2 (d, J_{C-F} = 21.6 Hz), 144.4 (d, J_{C-F} = 5.1 Hz), 140.6, 132.9, 132.3 (d, J_{C-F} = 2.7 Hz), 130.6, 129.8, 128.7, 127.6 (d, J_{C-F} = 4.1 Hz), 126.9, 126.4, 123.4, 123.3 (d, J_{C-F} = 2.5 Hz), 122.7, 121.3 (d, J_{C-F} = 18.8 Hz), 114.0, 109.3, 93.8 (d, J_{C-F} = 205.7 Hz), 77.5 (d, J_{C-F} = 24.1 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -177.0. Anal. Calcd. for $C_{22}H_{14}ClFN_2O_3$: C, 64.64; H, 3.45; N, 6.85. Found: C, 64.40; H, 3.47; N, 6.78.

4′-Chloro-3-fluoro-3′-hydroxy-1-phenyl-[3,3′-biindoline]-2,2′-dione

Compound **9** was obtained as a white solid in 94% yield (77 mg, 0.19 mmol) and 99:1 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 4-chloroisatin (37 mg, 0.20 mmol) after stirring in isopropyl alcohol for 30 minutes as described above. ^{1}H NMR (399 MHz, DMSO-d_6): δ = 10.64 (s, 1H), 7.58 – 7.52 (m, 2H), 7.47 (m, 1H), 7.38 – 7.30 (m, 2H), 7.25 – 7.20 (m, 2H), 7.02 (d, J = 8.1 Hz, 1H), 6.97 (dd, 7.6, 7.6 Hz, 1H), 6.83 (m, 1H), 6.79 (s, 1H), 6.72 (d, J = 7.7 Hz, 1H), 6.66 (d, J = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.6 (d, J_{C-F} = 6.0 Hz), 168.6 (d, J_{C-F} = 22.1 Hz), 144.8, 144.4 (d, J_{C-F} = 5.2 Hz), 138.9, 133.2, 132.2 (d, J_{C-F} = 2.8 Hz), 132.1, 131.6, 129.7, 128.5, 126.5, 126.3, 123.6, 122.9 (dd, J_{C-F} = 6.3, 2.1 Hz), 121.9 (d, J_{C-F} = 18.7 Hz), 109.4, 108.7, 93.5 (d, J_{C-F} = 206.1 Hz), 80.0 (d, J_{C-F} = 24.9 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -169.5. Anal. Calcd. for $C_{22}H_{14}ClFN_2O_3$: C, 64.64; H, 3.45; N, 6.85. Found: C, 64.38; H, 3.48; N, 6.75.

6′-Chloro-3-fluoro-3′-hydroxy-1-phenyl-[3,3′-biindoline]-2,2′-dione

Compound **10** was obtained as a white solid in 96% yield (79 mg, 0.19 mmol) and 98:2 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 6-chloroisatin (37 mg, 0.20 mmol) after stirring in isopropyl alcohol for 30 minutes as described above. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.64 (s, 1H), 7.53 – 7.38 (m, 5H), 7.21 – 7.14 (m, 2H), 7.02 – 6.95 (m, 2H), 6.89 (d, J = 8.0, 1H), 6.83 (s, 1H), 6.66 (d, J = 7.9 Hz, 1H), 6.35 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.7 (d, J_{C-F} = 2.2 Hz), 168.3 (d, J_{C-F} = 21.6 Hz), 144.4, 144.3 (d, J_{C-F} = 5.1 Hz), 135.1, 132.9, 132.3 (d, J_{C-F} = 2.6 Hz), 129.8, 128.7, 127.0, 126.3, 124.6 (d, J_{C-F} = 4.3 Hz), 123.4 (d, J_{C-F} = 2.5 Hz), 121.4, 121.2, 121.2, 109.9, 109.3, 93.9 (d, J_{C-F} = 205.8 Hz), 76.7 (d, J_{C-F} = 24.1 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -177.1. Anal. Calcd. for $C_{22}H_{14}ClFN_2O_3$: C, 64.64; H, 3.45; N, 6.85. Found: C, 64.49; H, 3.63; N, 6.69.

3,6′-Difluoro-3′-hydroxy-1-phenyl-[3,3′-biindoline]-2,2′-dione

Compound **11** was obtained as a white solid in 92% yield (72 mg, 0.18 mmol) and 98:2 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 6-fluoroisatin (34 mg, 0.20 mmol) after stirring in isopropyl alcohol for 30 minutes as described above. ^{1}H NMR (399 MHz, DMSO-d_6): δ = 10.63 (bs, 1H), 7.54 – 7.37 (m, 5H), 7.18 (dd, J = 7.5, 7.5 Hz, 1H), 7.08 (s, 1H), 7.03 – 6.96 (m, 2H), 6.69 – 6.59 (m, 3H), 6.36 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.0 (d, J_{C-F} = 2.2 Hz), 168.4 (d, J_{C-F} = 21.7 Hz), 163.6 (d, J_{C-F} = 245.3 Hz), 144.8 (d, J_{C-F} = 12.7 Hz), 144.3 (d, J_{C-F} = 5.1 Hz), 132.9, 132.2 (d, J_{C-F} = 2.7 Hz), 129.8, 128.6, 127.0, 126.5 (m), 126.3, 123.3 (d, J_{C-F} = 2.4 Hz), 121.7 (dd, J_{C-F} = 4.4, 2.8 Hz), 121.4 (d, J_{C-F} = 18.9 Hz), 109.3, 107.6 (d, J_{C-F} = 22.5 Hz), 98.0 (d, J_{C-F} = 27.0 Hz), 93.9 (d, J_{C-F} = 205.5 Hz), 76.5 (d, J_{C-F} = 24.1 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -109.8 (m), -176.7. Anal. Calcd. for $C_{22}H_{14}F_2N_2O_3$: C, 67.35; H, 3.60; N, 7.14. Found: C, 66.96; H, 3.76; N, 7.08.

6′-Bromo-3-fluoro-3′-hydroxy-1-phenyl-[3,3′-biindoline]-2,2′-dione

Compound **12** was obtained as a white solid in 91% yield (83 mg, 0.18 mmol) and 97:3 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 6-bromoisatin (46 mg, 0.20 mmol) after stirring in isopropyl alcohol for 30 minutes as described above. ^{1}H NMR (399

MHz, DMSO-d_6): δ = 10.62 (s, 1H), 7.54 – 7.36 (m, 5H), 7.22 – 7.12 (m, 2H), 7.06 – 6.93 (m, 4H), 6.65 (d, J = 7.9 Hz, 1H), 6.29 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.5 (d, J_{C-F} = 2.3 Hz), 168.3 (d, J_{C-F} = 21.4 Hz), 144.5, 144.3 (d, J_{C-F} = 5.2 Hz), 132.9, 132.2 (d, J_{C-F} = 2.7 Hz), 129.7, 128.7, 126.9, 126.5, 126.3, 125.0 (d, J_{C-F} = 4.2 Hz), 124.1, 123.5, 123.3 (d, J_{C-F} = 2.5 Hz), 121.3 (d, J_{C-F} = 18.9 Hz), 112.6, 109.3, 93.8 (d, J_{C-F} = 206.0 Hz), 76.8 (d, J_{C-F} = 24.2 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -177.2. Anal. Calcd. for $C_{22}H_{14}BrFN_2O_3$: C, 58.30; H, 3.11; N, 6.18. Found: C, 58.04; H, 3.29; N, 6.07.

3,5′,6′-Trifluoro-3′-hydroxy-1-phenyl-[3,3′-biindoline]-2,2′-dione

Compound **13** was obtained as a white solid in 91% yield (75 mg, 0.18 mmol) and 98:2 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 5,6-difluoroisatin (38 mg, 0.20 mmol) after stirring in isopropyl alcohol for 30 minutes as described above. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.66 (bs, 1H), 7.55 – 7.51 (m, 2H), 7.47 – 7.43 (m, 2H), 7.33 (m, 1H), 7.28 – 7.14 (m, 3H), 7.09 – 7.04 (m, 2H), 6.89 (dd, J = 10.3, 6.8 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 6.36 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.7 (d, J_{C-F} = 2.6 Hz), 168.1 (d, J_{C-F} = 21.8 Hz), 150.9 (dd, J_{C-F} = 247.8, 13.9 Hz), 144.9 (dd, J_{C-F} = 240.0, 13.5 Hz), 144.3 (d, J_{C-F} = 5.3 Hz), 139.8 (d, J_{C-F} = 10.2 Hz), 132.9, 132.3, 129.8, 128.7, 126.8, 126.2, 123.4, 121.7, 121.0 (d, J_{C-F} = 18.9 Hz), 114.3 (d, J_{C-F} = 20.2 Hz), 109.3, 99.9 (d, J_{C-F} = 22.4 Hz), 93.6 (d, J_{C-F} = 205.6 Hz), 77.0 (d, J_{C-F} = 24.5 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -135.0 (m), -148.5 (m), -177.0. Anal. Calcd. for $C_{22}H_{13}F_3N_2O_3$: C, 64.39; H, 3.19; N, 6.83. Found: C, 64.30; H, 3.24; N, 6.81.

3-Fluoro-3′-hydroxy-1,1′-diphenyl-[3,3′-biindoline]-2,2′-dione

Compound **14** was obtained as a white solid in 97% yield (87 mg, 0.19 mmol) and 98:2 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 1-phenylisatin (46 mg, 0.20 mmol) after sonication in methyl alcohol for 30 minutes as described above. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.58 – 7.37 (m, 9H), 7.36 – 7.19 (m, 4H), 7.01 – 6.83 (m, 3H), 6.66 (dd, J = 12.6, 8.0 Hz, 2H), 6.42 (bs, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 171.7 (d, J_{C-F} = 1.4 Hz), 168.5 (d, J_{C-F} = 21.6 Hz), 144.4 (d, J_{C-F} = 5.2 Hz), 144.0, 133.7, 132.8, 132.3 (d, J_{C-F} = 2.5 Hz), 130.9, 129.8, 129.7, 128.7, 128.3, 127.2, 126.6, 126.4, 124.9, 124.7 (d, J_{C-F} = 4.4 Hz), 123.4 (d, J_{C-F} = 2.4 Hz), 122.6, 121.3 (d, J_{C-F} = 18.9 Hz), 109.3, 109.0, 94.5 (d, J_{C-F} = 207.4 Hz), 76.7 (d, J_{C-F} = 23.7 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -176.8. Anal. Calcd. for $C_{28}H_{19}FN_2O_3$: C, 74.66; H, 4.25; N, 6.22. Found: C, 74.55; H, 4.27; N, 6.21.

3-Fluoro-3′-hydroxy-1,1′-dimethyl-[3,3′-biindoline]-2,2′-dione

Compound **15** was obtained as a white crystalline solid in 99% yield (65 mg, 0.20 mmol) and >99:1 dr from 3-fluoro-1-methylindolin-2-one (33 mg, 0.20 mmol) and 1-methylisatin (33 mg, 0.20 mmol) after sonication in methanol for 30 minutes by as described above. Decomp. 196 °C. ^{1}H NMR (399 MHz, CDCl$_3$): δ = 7.72 (d, J = 7.1 Hz, 1H), 7.46 (dd, J = 7.8, 7.8 Hz, 1H), 7.31 (dd, J = 7.8, 7.8 Hz, 1H), 7.22 (dd, J = 7.6, 7.6 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.79 – 6.73 (m, 2H), 6.10 (d, J = 7.5 Hz, 1H), 5.68 (s, 1H), 3.26 (s, 3H), 2.85 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 173.4 (d, J_{C-F} = 8.3 Hz), 171.4 (d, J_{C-F} = 21.2 Hz), 144.9 (d, J_{C-F} = 4.8 Hz), 144.6, 132.3 (d, J_{C-F} = 3.0 Hz), 131.3, 127.0 (d, J_{C-F} = 3.0 Hz),

125.2, 124.3, 123.7, 123.2 (d, J_{C-F} = 2.6 Hz), 121.5 (d, J_{C-F} = 18.2 Hz), 109.3, 108.4, 90.4 (d, J_{C-F} = 200.8 Hz), 79.2 (d, J_{C-F} = 24.6 Hz), 26.4, 26.1. ^{19}F NMR (376 MHz, CDCl$_3$): δ = -174.4. Anal. Calcd. for C$_{18}$H$_{15}$FN$_2$O$_3$: C, 66.25; H, 4.63; N, 8.58. Found: C, 66.39; H, 4.68; N, 8.71.

3-Fluoro-3′-hydroxy-5′-nitro-1-phenyl-[3,3′-biindoline]-2,2′-dione

Compound **16** was obtained as a white solid in 92% yield (77 mg, 0.18 mmol) and 97:3 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 5-nitroisatin (36 mg, 0.20 mmol) after stirring in isopropyl alcohol for 30 minutes as described above. ^{1}H NMR (399 MHz, DMSO-d$_6$): δ = 11.22 (bs, 1H), 8.25 (dd, J = 8.7, 2.3 Hz, 1H), 7.56 – 7.41 (m, 6H), 7.25 (dd, J = 7.6, 7.6 Hz, 1H), 7.11 (s, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.97 – 6.87 (m, 2H), 6.67 (d, J = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 174.0 (d, J_{C-F} = 1.7 Hz), 168.0 (d, J_{C-F} = 21.5 Hz), 149.2, 144.2 (d, J_{C-F} = 5.1 Hz), 141.7, 132.7, 132.5 (d, J_{C-F} = 2.7 Hz), 129.8, 128.7, 127.8, 127.2, 126.4, 126.1, 123.6 (d, J_{C-F} = 2.2 Hz), 120.8 (d, J_{C-F} = 19.0 Hz), 120.4, 110.2, 109.5, 93.8 (d, J_{C-F} = 207.0 Hz), 76.5 (d, J_{C-F} = 24.5 Hz). ^{19}F NMR (376 MHz, DMSO-d$_6$): δ = -177.5. Anal. Calcd. for C$_{22}$H$_{14}$FN$_3$O$_5$: C, 63.01; H, 3.37; N, 10.02. Found: C, 63.10; H, 3.57; N, 9.90.

3-Fluoro-3′-hydroxy-6′-methoxy-1-phenyl-[3,3′-biindoline]-2,2′-dione

Compound **17** was obtained as a white solid in 94% yield (76 mg, 0.19 mmol) and 99:1 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 6-methoxyisatin (36 mg, 0.20 mmol) after stirring in isopropyl alcohol for 30 minutes as described above. ^{1}H NMR (399 MHz, DMSO-d6): δ = 10.35 (s, 1H), 7.49 – 7.30 (m, 5H), 7.11 (dd, J = 7.2, 6.7 Hz, 1H), 6.96 – 6.90 (m, 2H), 6.80 (s, 1H), 6.58 (d, J = 7.9 Hz, 1H), 6.33 – 6.27 (m, 2H), 6.25 – 6.16 (m, 1H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 174.2 (d, J_{C-F} = 2.2 Hz), 168.6 (d, J_{C-F} = 21.7 Hz), 161.4, 144.4 (d, J_{C-F} = 6.9 Hz), 133.0, 132.0 (d, J_{C-F} = 2.7 Hz), 129.7, 128.6, 126.9, 126.4, 125.8, 123.2 (d, J_{C-F} = 2.4 Hz), 121.8, 121.7, 117.4 (d, J_{C-F} = 4.4 Hz), 109.2, 106.3, 96.4, 94.0 (d, J_{C-F} = 205.4 Hz), 76.7 (d, J_{C-F} = 23.9 Hz), 55.4. ^{19}F NMR (376 MHz, DMSO-d$_6$): δ = -176.4. Anal. Calcd. for C$_{23}$H$_{17}$FN$_2$O$_4$: C, 68.31; H, 4.24; N, 6.93. Found: C, 68.26; H, 4.29; N, 6.91.

tert-Butyl (1′-benzyl-3-fluoro-2,2′-dioxo-1-phenyl-[3,3′-biindolin]-3′-yl)carbamate

Compound **19** was obtained as a white crystalline solid in 92% yield (104 mg, 0.18 mmol) and >99:1 dr from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and tert-butyl (1-benzyl-2-oxoindolin-3-ylidene)carbamate (67 mg, 0.20 mmol) after stirring in isopropyl alcohol for 24 hours as described above. Decomp. 178 °C. ^{1}H NMR (399 MHz, CDCl$_3$): δ = 7.70 (d, J = 7.5 Hz, 1H), 7.59 – 7.40 (m, 6H), 7.32 (dd, J = 7.8, 7.8 Hz, 1H), 7.24 – 7.02 (m, 5H), 6.74 – 6.56 (m, 5H), 5.83 (d, J = 7.5 Hz, 1H), 4.89 (d, J = 15.7 Hz, 1H), 4.45 – 4.28 (m, 1H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.4 (d, J_{C-F} = 8.0 Hz), 170.0 (d, J_{C-F} = 21.8 Hz), 154.09, 145.1 (d, J_{C-F} = 5.1 Hz), 144.0, 135.2, 133.1, 132.1 (d, J_{C-F} = 2.4 Hz), 130.1, 129.8, 128.8, 128.6, 127.2, 126.9, 126.8, 126.0, 125.4 (d, J_{C-F} = 2.8 Hz), 123.2 (d, J_{C-F} = 2.4 Hz), 123.1, 120.5 (d, J_{C-F} = 18.0 Hz), 110.0, 109.1, 90.5 (d, J_{C-F} = 204.3 Hz), 80.3, 66.6 (d, J_{C-F} = 22.9 Hz), 44.3, 28.1. ^{19}F NMR (376 MHz, CDCl$_3$): δ = -170.5. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{34}$H$_{30}$FN$_3$O$_4$Na 586.2118; Found 586.2111.

tert-Butyl (1,1′-dibenzyl-3-fluoro-2,2′-dioxo-[3,3′-biindolin]-3′-yl)carbamate

Compound **21** was obtained as a white solid in 91% yield (105 mg, 0.18 mmol) and 96:4 dr from 1-benzyl-3-fluoroindolin-2-one (48 mg, 0.20 mmol) and tert-butyl (1-benzyl-2-oxoindolin-3-ylidene)carbamate (67 mg, 0.20 mmol) after stirring in isopropyl alcohol for 24 hours as described above. ^{1}H NMR (399 MHz, CDCl$_3$): δ = 7.67 (d, J = 7.4 Hz, 1H), 7.54 (s, 1H), 7.44 – 7.37 (m, 2H), 7.33 – 7.24 (m, 4H), 7.18 (dd, J = 7.5, 7.5 Hz, 1H), 7.15 – 7.06 (m, 2H), 6.99 (dd, J = 7.5, 7.5 Hz, 2H), 6.68 – 6.59 (m, 3H), 6.57 – 6.45 (m, 2H), 5.69 (d, J = 7.5 Hz, 1H), 5.13 (d, J = 15.9 Hz, 1H), 4.93 (d, J = 15.7 Hz, 1H), 4.79 (d, J = 15.8 Hz, 1H), 4.47 – 4.25 (m, 1H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.2 (d, J_{C-F} = 7.5 Hz), 170.7 (d, J_{C-F} = 23.1 Hz), 154.1, 144.1 (d, J_{C-F} = 5.0 Hz), 143.9, 135.2, 134.5, 132.1 (d, J_{C-F} = 3.1 Hz), 130.0, 128.9, 128.6, 127.8, 127.4, 127.1, 126.9, 125.9, 125.5 (d, J_{C-F} = 3.0 Hz), 123.1, 122.9 (d, J_{C-F} = 2.7 Hz), 120.9 (d, J_{C-F} = 17.8 Hz), 110.2, 109.1, 91.4 (d, J_{C-F} = 201.9 Hz), 80.3, 66.2 (d, J_{C-F} = 23.1 Hz), 44.5, 44.3, 28.2. ^{19}F NMR (376 MHz, CDCl$_3$): δ = -167.1. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{35}$H$_{32}$FN$_3$O$_4$Na 600.2275; Found 600.2267.

3-(2,2-Bis(phenylsulfonyl)ethyl)-3-fluoro-1-phenylindolin-2-one

Compound **23** was obtained as a white crystalline solid in 99% yield (106 mg, 0.20 mmol) from 3-fluoro-1-phenylindolin-2-one (45 mg, 0.20 mmol) and 1,1-bis(phenylsulfonyl)ethene (65 mg, 0.20 mmol) after stirring in isopropyl alcohol for 30 minutes as described above. Mp. 127-128 °C. ^{1}H NMR (399 MHz, DMSO-d$_6$): δ = 7.99 – 7.87 (m, 4H), 7.84 – 7.76 (m, 2H), 7.72 -7.56 (m, 7H), 7.54 – 7.41 (m, 4H), 7.23 (dd, J = 7.5, 7.5 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 5.69 (dd, J = 4.4, 4.4 Hz, 1H), 3.42 (ddd, J = 17.9, 14.1, 4.3 Hz, 1H), 3.02 (ddd, J = 32.4, 17.3, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 170.4 (d, J_{C-F} = 23.0 Hz), 143.1 (d, J_{C-F} = 5.2 Hz), 137.8, 136.9, 135.1, 134.9, 132.9, 132.2 (d, J_{C-F} = 2.9 Hz), 129.8, 129.5, 129.4, 129.4, 129.0, 128.7, 126.4, 125.3, 124.1, 123.9 (d, J_{C-F} = 2.1 Hz), 110.1, 89.3 (d, J_{C-F} = 188.9 Hz), 76.1, 30.3 (d, J_{C-F} = 30.6 Hz). ^{19}F NMR (376 MHz, DMSO-d$_6$): δ = -155.2 (dd, J = 32.4, 13.9 Hz). HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{28}$H$_{22}$FNO$_5$S$_2$Na 558.0821; Found 558.0816.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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8. 8 In some cases, sonication of the reaction mixture facilitates product precipitation and isolation (see Experimental Section).

9. 9 CCDC 1557938 contains the supplementary crystallographic data for bisoxindole **15**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (44) 1223-336-033; or deposit@ccdc.cam.ac.uk)

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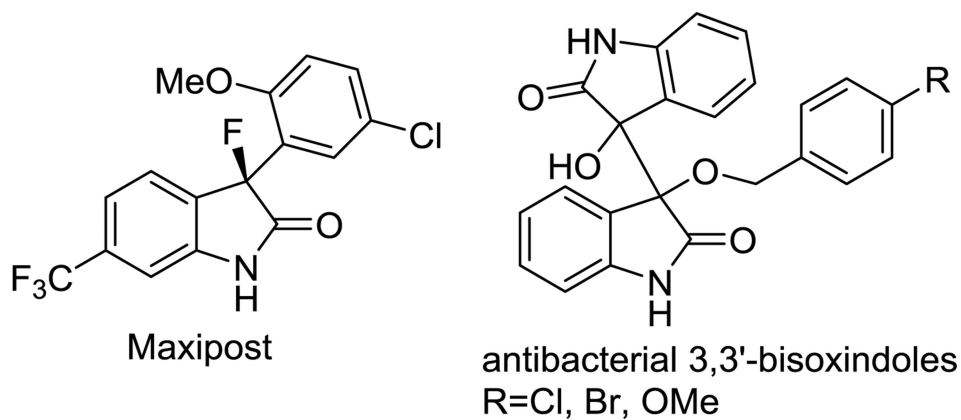
Figure 1.
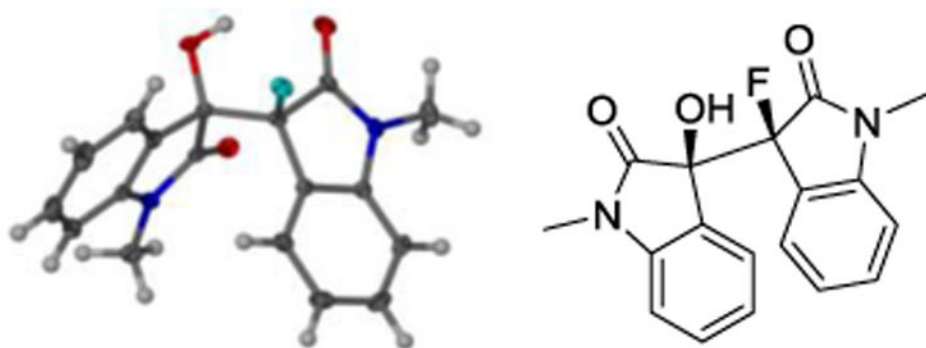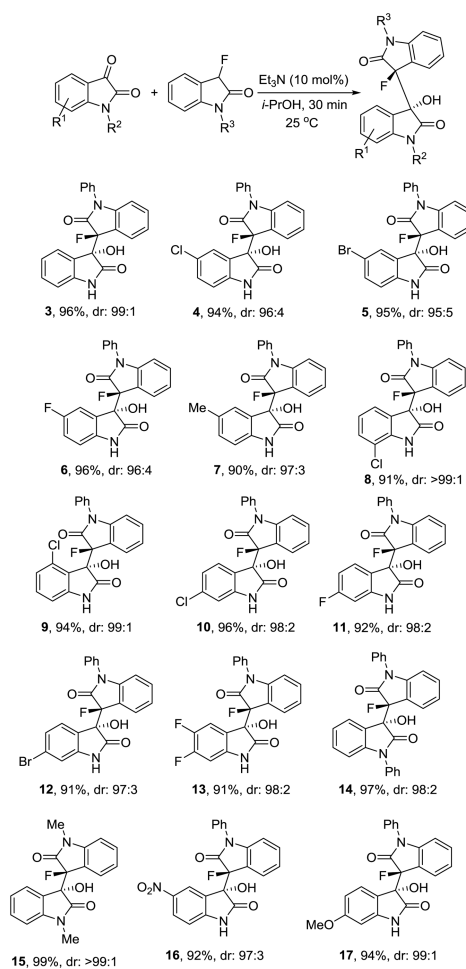Structures of Maxipost and biologically active 3,3′-bisoxindoles.

Figure 2.
X-ray structure of 3,3′-bisoxindole **15** (only one enantiomer is shown).

Scheme 1.
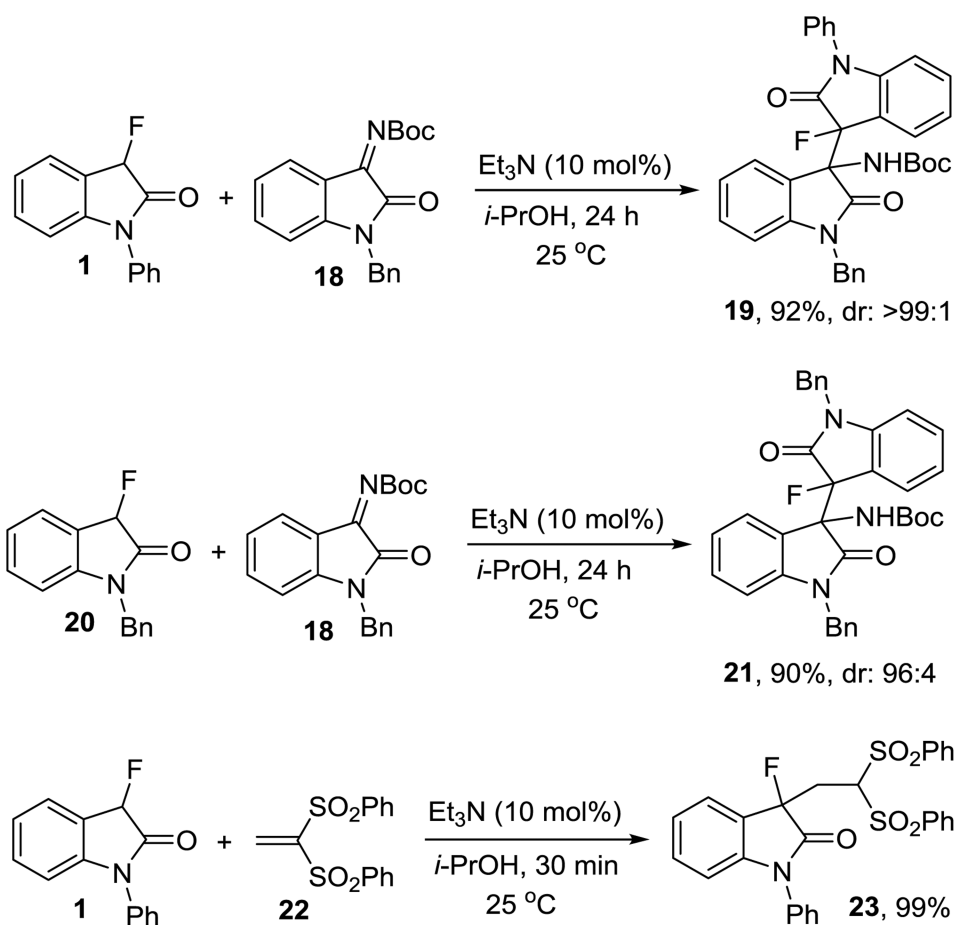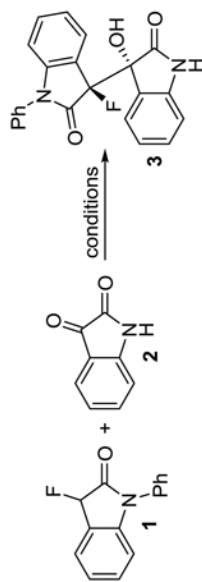Synthesis of 3,3′-bridged bisoxindoles **3**-**17** (only one enantiomer is shown).

Scheme 2.
Additions to *N*-Boc imine **18** and the Michael acceptor **22**.

Table 1

Optimization of the organocatalytic C–C bond formation with *N*-phenyl-3-fluorooxindole, **1**, and isatin, **2**.

Entry	Solvent	Base (mol%)	Time (min)	Conversion^a (%)	Diastereomeric ratio^a
1	H_2O	Et_3N (20)	120	93	24:1
2	H_2O	none	120	0	n/a
3	MeOH	Et_3N (20)	60	99	49:1
4	MeOH/H_2O (1:1)	Et_3N (20)	60	95	24:1
5	EtOH	Et_3N (20)	60	96	24:1
6	*i*-PrOH	Et_3N (20)	30	99	49:1
7	*i*-PrOH	Et_3N (10)	30	99	49:1

General reaction conditions: Et_3N (10–20 mol%) was added to a mixture of oxindole **1** (45.4 mg, 0.2 mmol) and isatin **2** (30.0 mg, 0.2 mmol) in 1.0 mL of the solvent at room temperature.

^{a}Based on ^{19}F and ^1H NMR analysis.