# Solution-Phase Parallel Synthesis of 3,5,6-Substituted Indolin-2-ones

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A practical and efficient new parallel method has been developed for the synthesis of 3-substituted indolin-2-ones with a large variety of substituents at the 5- and 6-positions using 1,5-difluoro-2,4-dinitrobenzene. This 3,5,6-substituted indolin-2-one skeleton possesses three points of diversification and, thus, affords new opportunities for identification and optimization of leads in drug discovery.

## Introduction

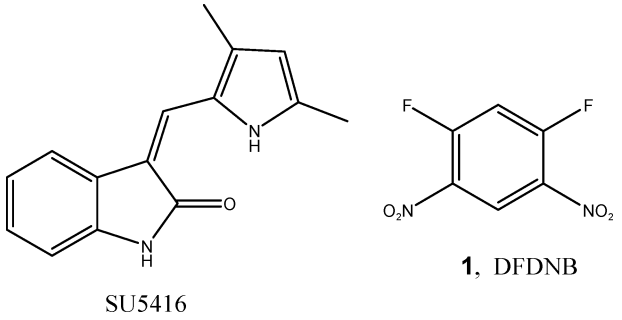
The indole pharmacophore is a fundamental constituent of a number of natural and synthetic products with multiple biological activities.[1] Indoles have been designated as privileged structures in medicinal chemistry.[2] Indolin-2-ones belong to this important class of compounds. Because of this, interest in indolin-2-ones has grown during the past few years.[3]

Indolin-2-ones have well-recognized pharmacological properties, including antirheumatic properties,[4] as well as function as receptor tyrosine kinase (RTK) inhibitors,[5] ATP competitive cyclin dependent kinase inhibitors,[6] ghrelin receptor agonists,[7] nociceptin receptor ligands,[8] 5-$HT_{1A}$ and 5-$HT_{2A}$ receptor antagonists,[9] and phosphodiesterase type II inhibitors.[10] Indolin-2-one derivatives have also been proven to inhibit the pro-inflammatory cytokine IL-2, which is related to multiple sclerosis[11] and effect the cell proliferation and cell cycle progression in the colon adenocarcinoma cell line.[12] Particularly, 3-substituted indolin-2-one derivatives are indicated as potent and selective RTK inhibitors and vascular endothelial growth factor receptor antagonists.[13] Among them, SU5416 (Figure 1) has advanced into clinical trials as an antiangiogenic agent.[14]

The varieties of 3-substituted indolin-2-ones available with substituents at the 4-, 5-, 6-, and 7-positions are limited by the previous methods of indolin-2-one synthesis.[13] Our group has developed a "scaffold-directed"[15,16] method to construct heterocyclic compound libraries using 1,5-difluoro-2,4-dinitrobenzene (DFDNB, **1**, Figure 1), such as 2-hydroxyquinoxaline,[17] benzimidazole,[18] and imidazoquinoxalinol libraries,[19] as the starting material. This DFDNB approach allowed us to efficiently synthesize 3-substituted indolin-2-ones with a large variety of substituents at the 5- and 6-positions.

## Results and Discussion

The synthetic route to 3,5,6-substituted indolin-2-ones is depicted in Scheme 1. The quantitative substitution of one of the fluorine atoms of DFDNB by secondary amines or phenols produced compound **2**. Displacement of another fluorine atom with the anion of diethyl malonate thus gave **3**.




SU5416 **1**, DFDNB

**Figure 1.** The structure of SU5416 and DFDNB.

An alternative approach to synthesize compound **3** is to first displace a fluorine atom of **1** with the anion of diethyl malonate to give **7**. However, because some disubstituted byproducts are often obtained, compound **7** should be purified for the next step, so this approach is not suitable for parallel synthesis.

Compound **4** is the essential intermediate in the synthetic route. Our group has reported the quantitative reduction of two aromatic nitro groups utilizing $HCOONH_4$ and Pd/C, $SnCl_2$, or $Na_2S_2O_4$.[17−19] However, direct treatment of **3** with such reductive reagents did not give high yields of **4**. Further investigations indicated that tin powder in hydrochloric acid[20] under reflux could convert nitroaryl malonate **3** into indolin-2-one **4** in a one-pot reaction and in high yield.

The free 6-aromatic amino group of **4** was then acylated by anhydride, sulfonyl chloride, isocyanate, or isothiocyanate to introduce the second diverse substituent.[18] Typical compounds of **5** were characterized by LC/MS , HRMS, and $^1H$ NMR (Table 1).

To introduce further diversity at the 3-position of indolin-2-ones, intermediate **5** (when R = H) was condensed with aldehydes in the presence of an organic base (Scheme 1). This reaction was carried out on a H + P parallel synthesizer, which allows simultaneous parallel heating and refluxing of the reactions. The condensation was generally finished overnight at 46 °C to give the title compound **6**.

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**Scheme 1.** Synthetic Route to 3,5,6-Substituted Indolin-2-ones

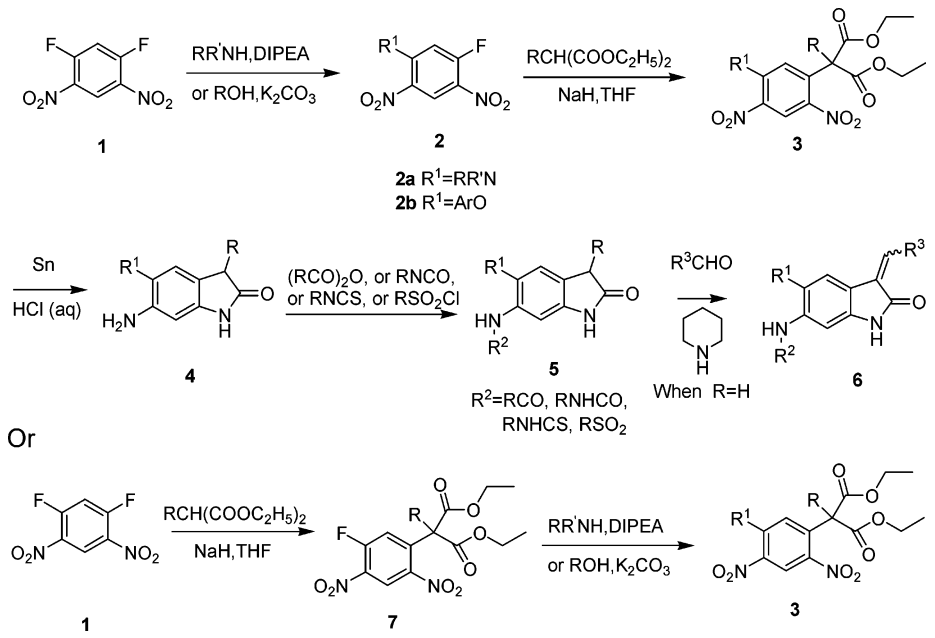
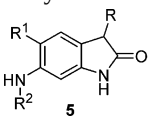
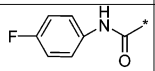
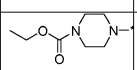
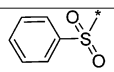
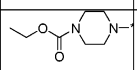
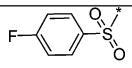
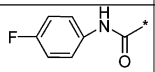
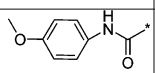
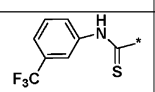
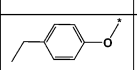
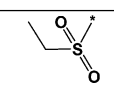


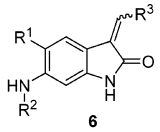

**Table 1.** Molecular Formula, Molecular Weight, HPLC Purity and HRMS of Typical Compounds **5**



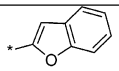
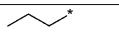
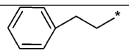
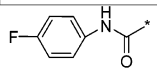
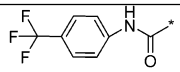
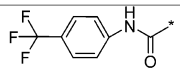
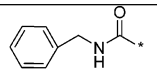

| Entry | $R^1$ | $R^2$ | R | HPLC Purity (%) | Formula | HRMS (M + $H^+$) | |
|---|---|---|---|---|---|---|---|
| | | | | | | calcd | found |
| 5a |  |  | H | 95.36 | $C_{14}H_{17}N_3O_3$ | 276.1348 | 276.1346 |
| 5b |  |  | H | 94.74 | $C_{19}H_{19}FN_4O_3$ | 371.1519 | 371.1513 |
| 5c |  |  | H | 88.95 | $C_{21}H_{24}N_4O_5S$ | 445.1546 | 445.1553 |
| 5d |  |  | H | 74.79 | $C_{21}H_{23}FN_4O_5S$ | 463.1451 | 463.1449 |
| 5e |  |  |  | 95.63 | $C_{18}H_{25}N_3O_3$ | 332.1974 | 332.1981 |
| 5f |  |  |  | 99.80 | $C_{23}H_{27}FN_4O_3$ | 427.2145 | 427.2148 |
| 5g |  |  |  | 99.95 | $C_{24}H_{30}N_4O_4$ | 439.2345 | 439.2348 |
| 5h |  |  |  | 98.00 | $C_{24}H_{27}F_3N_4O_2S$ | 493.1885 | 493.1883 |
| 5i |  |  | H | 98.88 | $C_{18}H_{20}N_2O_4S$ | 361.1222 | 361.1224 |

The configurations of the 3,5,6-substituted indolin-2-ones (**6**) may exist as either the major *Z* or major *E* isomer or a mixture, depending on the aldehydes used. The isomers were determined by NOE analysis after a proper separation. The *Z*-configured compounds should show a NOE between the proton at the C-4 position and the vinyl proton, whereas the *E*-configured compounds should show a NOE between the proton at the C-4 position and the proton(s) in the C-3 substitution of the 3,5,6-substituted indolin-2-ones (Table 2).[5a] The ratio of isomers was obtained as indicated by LC/

**Table 2.** Molecular Formula, Molecular Weight, and the Ratio of *Z* to *E* Isomers of Typical Compounds **6**



**6**

| Entry | $R^1$ | $R^2$ | $R^3$ | Formula | HRMS (M + $H^+$) | | The ratio of *Z* to *E*[#] |
|---|---|---|---|---|---|---|---|
| | | | | | calcd | found | |
| 6a |  |  |  | $C_{19}H_{19}N_3O_3S$ | 370.1225 | 370.1228 | 95.5:4.5 |
| 6b |  |  |  | $C_{19}H_{20}N_4O_3$ | 353.1614 | 353.1624 | 100:0 |
| 6c |  |  |  | $C_{23}H_{21}N_3O_4$ | 404.1610 | 404.1615 | 0:100 |
| 6d |  |  |  | $C_{18}H_{23}N_3O_3$ | 330.1818 | 330.1822 | 0.7:99.3 |
| 6e |  |  |  | $C_{20}H_{20}N_4O_3$ | 365.1614 | 365.1610 | 0:100 |
| 6f |  |  |  | $C_{23}H_{25}N_3O_3$ | 392.1974 | 392.1970 | 7.4:92.6 |
| 6g |  |  |  | $C_{24}H_{22}FN_5O_2$ | 432.1836 | 432.1836 | 98.1:1.9 |
| 6h |  |  |  | $C_{25}H_{22}F_3N_5O_2$ | 482.1804 | 482.1801 | 99.8:0.2 |
| 6i |  |  |  | $C_{25}H_{21}F_3N_4O_2S$ | 499.1416 | 499.1417 | 95.6:4.4 |
| 6j |  |  |  | $C_{25}H_{24}N_4O_2S$ | 445.1698 | 445.1689 | 92.9:7.1 |
| 6k |  |  |  | $C_{19}H_{17}F_3N_4O_2$ | 391.1382 | 391.1384 | 99.3:0.7 |
| 6l |  |  |  | $C_{19}H_{22}N_4O_2$ | 339.1821 | 339.1817 | 98.7:1.3 |
| 6m |  |  |  | $C_{19}H_{21}N_3O_2S$ | 356.1433 | 356.1307[Δ]<br>356.1311 | 56.2:43.8 |
| 6n |  |  |  | $C_{20}H_{22}N_4O_2$ | 351.1821 | 351.1819 | 0:100 |
| 6o |  |  |  | $C_{18}H_{25}N_3O_2$ | 316.2025 | 316.2028 | 13.2:86.8 |
| 6p |  |  |  | $C_{20}H_{24}N_4O_2$ | 353.1978 | 353.1977 | 3.0:97.0 |
| 6q |  |  |  | $C_{20}H_{21}F_3N_4O_2$ | 407.1695 | 407.1698 | 0:100 |
| 6r |  |  |  | $C_{24}H_{29}N_5OS$ | 436.2171 | 436.2168 | 0:100 |
| 6s |  |  |  | $C_{23}H_{29}N_3O_3$ | 396.2287 | 396.2286 | 0:100 |
| 6t |  |  |  | $C_{23}H_{29}N_3O_2S$ | 412.2059 | 412.1981[Δ]<br>412.1986 | 33.6:66.4 |
| 6u |  |  |  | $C_{26}H_{27}N_5O_5S$ | 522.1811 | 522.1807 | 99.6:0.4 |
| 6v |  |  |  | $C_{26}H_{26}FN_5O_5S$ | 540.1717 | 540.1716 | 94.2:5.8 |

[#] The major isomer was isolated and characterized by NMR. The ratio of *Z* to *E* was determined by a high-resolution LC/MS/MS analysis. [Δ] The molecular weights of *Z* and *E* isomers.

MS/MS analysis. Compounds containing an alkyl or aryl substituent at the C-3 position of the 3,5,6-substituted indolin-2-ones existed as the major *E* isomer forms (Table 2, entries **6d**, **6f**, and **6o**). Compound analogues containing a pyrrole substituent at the C-3 position existed as the major *Z* isomer forms (Table 2, entries **6b**, **6g**, **6h**, **6k**, **6l**, **6u**, and **6v**). Replacement of the proton on the N-1′ position of the pyrrole ring (Table 2, entries **6p** and **6q**) or changing the pyrrole ring to a pyridine ring (Table 2, entries **6e**, **6n**, and **6r**) afforded the *E* isomer. 3-[(Substituted furanyl)methylidenyl]-indolin-2-ones appeared to favor the *E* isomer forms (Table 2, entries **6c** and **6s**). Indolin-2-ones having a 3-substituted thienyl ring existed as either *Z* or *E* isomers (Table 2, entries **6a**, **6i**, **6j**, **6m**, and **6t**). The ratio of *Z* to *E* for each compound is shown in Table 2.

In summary, a practical and efficient new parallel method has been developed for the synthesis of 3-substituted indolin-2-ones with a large variety of substituents at the 5- and 6-positions using 1,5-difluoro-2,4-dinitrobenzene. This 3,5,6-substituted indolin-2-one skeleton possesses three points of diversification and, thus, affords new opportunities for identification and optimization of leads in drug discovery.

## Experimental Section

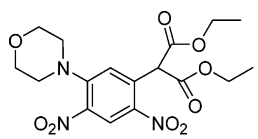
All chemical reagents were purchased from Acros Organics (Geel, Belgium) and used without further purification. Tetrahydrofuran (THF) was dried by molecular sieve and redistilled from sodium before use. Acetone was treated with anhydrous $K_2CO_3$. HPLC analysis or purification was performed on a Gilson HPLC system equipped with a Gilson UV/vis-152 detector, a Gilson 322 pump, and a Gilson 215 liquid hander. The employed column was a Kromasil C18 column (4.6 $\mu$m, 4.6 mm × 50 mm) from Dikma for analysis or a Kromasil C18 column (5.0 $\mu$m, 10 mm × 250 mm) for purification. The eluent was a mixture of acetonitrile and water containing 0.05% HCOOH with a linear gradient from 5:95 (v:v) acetonitrile−$H_2O$ to 95:5 (v:v) acetonitrile−$H_2O$ within 5 min at a 1 mL/min or 3 mL/min flow rate for analysis or purification, respectively. The UV detection was carried out at UV wavelength of 254 nm. Automatic HPLC/MS analysis was performed on a ThermoFinnigan LCQ-Advantage mass spectrometer equipped with an Agilent pump, an Agilent detector, an Agilent liquid handler, and a fluent splitter. The elution gradient, flow rate, and detection wavelength were the same as above. Five percent of the eluent was split into the MS system. Mass spectra were recorded in either positive or negative ion mode using electrospray ionization (ESI). High-resolution LC/MS was carried out by Agilent LC/MSD TOF using a column of Agilent Zorbax SB-C18 (rapid resolution, 2.1 × 30 mm, 3.5 $\mu$m) at a flow of 0.40 mL/min. The solvent was MeOH/water, 75:25 (v:v), containing 5 mmol/L ammonium formate. The ion source was electrospray ionization (ESI). All NMR experiments were carried out on a Varian Mercury 300- or 400-MHz NMR spectrometer using $CDCl_3$ or DMSO-$d_6$ as the solvent. Parallel synthesis was carried out on an H + P Labortechnik GmbH parallel synthesizer.

**General Procedure for the Synthesis of Intermediate 2. Method 1.** To a magnetically stirred solution of 1.0 equiv (typically 5.0 mmol) of 1,5-difluoro-2,4-dinitrobenzene and 1.0 equiv of *N*-diisopropylethylamine (DIPEA) in 50 mL of THF was added dropwise a solution of 1.0 equiv of secondary amine in 50 mL of THF. The reaction mixture was continuously stirred for an additional 1 h at room temperature. After the solvent was evaporated, water was added to precipitate **2**. The desired intermediate **2** then was collected by filtration and washed thoroughly with water. Intermediate **2** was not purified and used directly for the next reaction. For a typical compound, 4-(5-fluoro-2,4-dinitrophenyl)-morpholine, 1.30 g of yellow powder, was obtained in 95.9% yield, with an HPLC purity >99%.

**Method 2.** To a magnetically stirred solution of 1.0 equiv (typically 5.0 mmol) of 1,5-difluoro-2,4-dinitrobenzene in 20 mL of acetone, 1.0 equiv of phenol and 2.0 equiv of anhydrous $K_2CO_3$ were added. The reaction mixture was shaken mechanically at room temperature for more than 5 h until the total disappearance of **1** monitored by HPLC analysis. Undissolved excess $K_2CO_3$ was filtered. The solvent was evaporated. The residue was used directly for the next reaction. Typical compound, 1-(4-ethylphenoxy)-5-fluoro-2,4-dinitrobenzene, was analyzed by HPLC at UV 254 nm wavelength that indicated 92% in purity.

**General Procedure for the Synthesis of Intermediate 3.** To the mixture of 15 mmol of sodium hydride in 30 mL of THF was added dropwise a solution of 15 mmol of diethyl malonate in 20 mL of THF. The reaction mixture was continuously stirred for an additional 1 h at room temperature. Compound **2** (10 mmol) then was added, and the mixture was strongly stirred for 30 min at room temperature. After the solvent was evaporated, water then was added. The solution was carefully neutralized to pH 2−3 with 2.0 mol/L HCl and then extracted twice with ethyl acetate (100 mL × 2). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum to give crude **3**, which was directly used for the next reaction. The representative compound **3a** as red solid was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether and characterized by $^1$H NMR.

**2-(5-Morpholin-4-yl-2,4-dinitrophenyl)-malonic Acid Diethyl Ester (3a).** $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.305 (t, 6H, $J$ = 7.2 Hz), 3.246 (t, 4H, $J$ = 4.8 Hz), 3.850 (t, 4H, $J$ = 4.8 Hz), 4.246−4.312 (m, 4H), 5.500 (s, 1H), 7.140 (s, 1H), 8.690 (s, 1H). MS (*m/z*): calcd, 411.1; found, 412. 0 $[M + H]^+$.

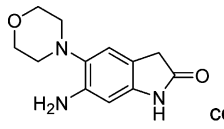


compound 3a

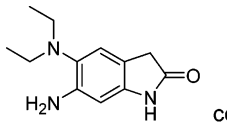
**General Procedure for the Synthesis of Intermediate 4.** To the solution of 30 mmol of **3** in 50 mL of ethanol was added 15 equiv of 12 mol/L hydrochloric acid. Then tin powder (5 equiv) was partially and slowly added under strong stirring. After the completion of the addition of the tin powder, the reaction mixture was refluxed for an additional 5 h. The solvent was then evaporated. The solution was

stirred vigorously and neutralized cautiously with 40% NaOH until the mixture had a pH of ~7. The mixture was filtered. The water layer was extracted with 100 mL of ethyl acetate twice. The tin salts were washed thoroughly with ethyl acetate twice. After combination of the extracted and washed ethyl acetates, the organic solvent was washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was purified on silica gel to yield **4** being eluted by the ethyl acetate/petroleum ether system and characterized by $^1$H NMR.

**6-Amino-5-morpholin-4-yl-1,3-dihydroindol-2-one (4a).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.695 (t, 4H, $J$ = 4.4 Hz), 3.261 (s, 2H), 3.710 (t, 4H, $J$ = 4.4 Hz), 4.868 (s, 2H), 6.241 (s,1H), 6.814 (s,1H), 10.018 (s,1H). HRMS calcd for $C_{12}H_{16}N_3O_2$ 234.1243, found 234.1249.

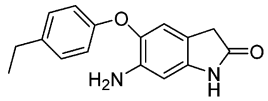

compound 4a

**6-Amino-5-diethylamino-1,3-dihydroindol-2-one (4b).** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.864 (t, 6H, $J$ = 7.2 Hz), 2.780 (q, 4H, $J$ = 7.2 Hz), 3.250 (s, 2H), 4.844 (brs, 2H), 6.202 (s,1H), 6.821 (s,1H), 10.024 (s, 1H). HRMS calcd for $C_{12}H_{18}N_3O$ 220.1450, found 220.1249.

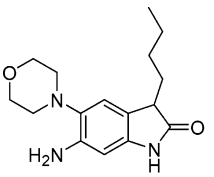

compound 4b

Compound

**6-Amino-5-(4-ethylphenoxy)-1,3-dihydroindol-2-one (4c).** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.129 (t, 3H, $J$ = 7.5 Hz), 2.535 (q, 2H, $J$ = 7.5 Hz), 3.263 (s, 2H), 4.867 (brs, 2H), 6.329 (s,1H), 6.657 (s,1H), 6.738−6.787 (m, 2H), 7.078−7.117 (m, 2H), 10.141 (s, 1H). HRMS calcd for $C_{16}H_{17}N_2O_2$ 269.1290, found 269.1298.


compound 4c

**6-Amino-3-butyl-5-morpholin-4-yl-1,3-dihydroindol-2-one (4d).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 0.823 (t, 3H, $J$ = 7.0 Hz), 1.164−1.270 (m, 4H), 1.630−1.788 (m, 2H), 2.652−2.743 (m, 4H), 3.191 (t, 1H, $J$ = 6.0 Hz), 3.675−3.714 (m, 4H), 4.862 (s, 2H), 6.223 (s,1H), 6.809 (s,1H), 9.952 (s,1H). HRMS calcd for $C_{16}H_{24}N_3O_2$ 290.1868, found 290.1872.

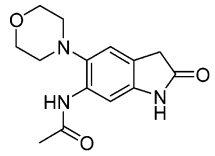

compound 4d

**General Procedure for the Synthesis of Intermediate 5. Method 1.** To a solution of 0.10 mmol of **4** in 1.5 mL of THF, 0.12 mmol of different acylating reagent (anhydride, isocyanate, or isothiocyanate) was added. The reaction mixture was stirred mechanically on an H + P Labortechnik GmbH parallel synthesizer at 46 °C for at least 12 h. The solvent then was evaporated in vacuum.

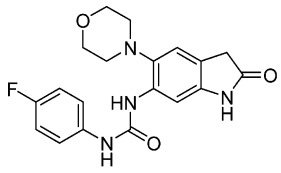
**Method 2.** To a solution of 0.10 mmol of **4** in 1.5 mL of dry DCM, 0.1 mmol of pyridine and 0.12 mmol of sulfonyl chloride were added. After the reaction mixture was stirred at 60 °C for more than 5h, the solvent was evaporated in vacuum.

The representative compounds **5a**−**5i** were further purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether.

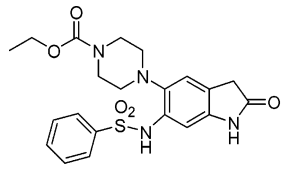
**Compound 5a: *N*-(5-Morpholin-4-yl-2-oxo-2,3-dihydro-1*H*-indol-6-yl)-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.126 (s, 3H), 2.721 (t, 4H, $J$ = 4.5 Hz), 3.404 (s, 2H), 3.773 (t, 4H, $J$ = 4.5 Hz), 7.132 (s, 1H), 7.693 (s, 1H), 8.925 (s, 1H), 10.260 (s, 1H).


compound 5a

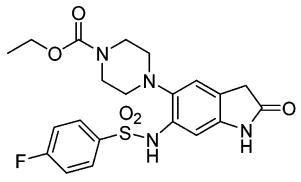
**Compound 5b: 1-(4-Fluorophenyl)-3-(5-morpholin-4-yl-2-oxo-2,3-dihydro-1*H*-indol-6-yl)-urea.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.728 (t, 4H, $J$ = 4.2 Hz), 3.390 (s, 2H), 3.820 (t, 4H, $J$ = 4.2 Hz), 7.130 (m, 2H), 7.135 (s, 1H), 7.490 (m, 2H), 7.740 (s, 1H), 8.271 (s, 1H), 9.572 (s, 1H), 10.281 (s, 1H).


compound 5b

**Compound 5c: 4-(6-Benzenesulfonylamino-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-piperazine-1-carboxylic Acid Ethyl Ester.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.168 (t, 3H, $J$ = 7.2 Hz), 2.183−2.201 (m, 4H), 3.343−3.358 (m, 6H), 4.023 (q, 2H, $J$ = 7.2 Hz), 6.997 (s, 1H), 7.072 (s, 1H), 7.509−7.740 (m, 5H), 8.931 (s, 1H), 10.320 (s, 1H).

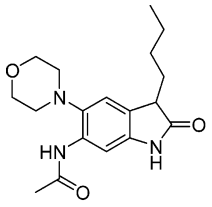

compound 5c

**Compound 5d: 4-[6-(4-Fluorobenzenesulfonylamino)-2-oxo-2,3-dihydro-1*H*-indol-5-yl]-piperazine-1-carboxylic Acid Ethyl Ester.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.173 (t, 3H, $J$ = 6.9 Hz), 2.262 (br, 4H), 3.365 (br, 6H), 4.030 (q, 2H, $J$ = 6.9 Hz), 6.965 (s, 1H), 7.094 (s, 1H), 7.375−7.434 (m, 2H), 7.769−7.816 (m, 2H), 9.029 (s, 1H), 10.314 (s, 1H).



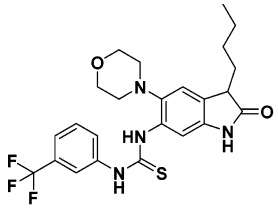
compound 5d

**Compound 5e: *N*-(3-Butyl-5-morpholin-4-yl-2-oxo-2,3-dihydro-1*H*-indol-6-yl)-acetamide.** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 0.818 (t, 3H, $J$ = 7.0 Hz), 1.156−1.269 (m, 4H), 1.715−1.842 (m, 2H), 2.116 (s, 3H), 2.726 (t, 4H, $J$ = 4.4 Hz), 3.340 (t, 1H, $J$ = 5.8 Hz), 3.766 (t, 4H, $J$ = 4.4 Hz), 7.138 (s, 1H), 7.678 (s, 1H), 8.906 (s, 1H), 10.199 (s, 1H).



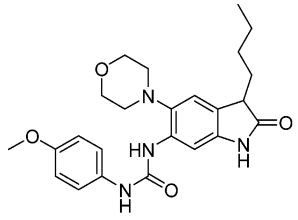
compound 5e

**Compound 5f: 1-(3-Butyl-5-morpholin-4-yl-2-oxo-2,3-dihydro-1*H*-indol-6-yl)-3-(4-fluorophenyl)-urea.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.841 (t, 3H, $J$ = 6.75 Hz), 1.152−1.253 (m, 4H), 1.734−1.881 (m, 2H), 2.745 (br, 4H), 3.357 (br, 1H), 3.825 (br, 4H), 7.108−7.167 (m, 2H), 7.137 (s, 1H), 7.470−7.516 (m, 2H), 7.773 (s, 1H), 8.271 (s, 1H), 9.579 (s, 1H), 10.236 (s, 1H).



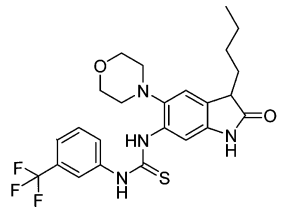
compound 5f

**Compound 5g: 1-(3-Butyl-5-morpholin-4-yl-2-oxo-2,3-dihydro-1*H*-indol-6-yl)-3-(4-methoxyphenyl)-urea.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.839 (t, 3H, $J$ = 6.75 Hz), 1.151−1.250 (m, 4H), 1.706−1.875 (m, 2H), 2.728 (br, 4H), 3.349 (br, 1H), 3.726 (s, 3H), 3.795 (br, 4H), 6.876−6.906 (m, 2H), 7.132 (s, 1H), 7.365−7.394 (m, 2H), 7.756 (s, 1H), 8.219 (s, 1H), 9.323 (s, 1H), 10.220 (s, 1H).



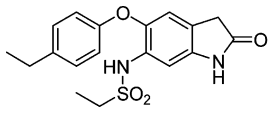
compound 5g

**Compound 5h: 1-(3-Butyl-5-morpholin-4-yl-2-oxo-2,3-dihydro-1*H*-indol-6-yl)-3-(3-trifluoromethylphenyl)-thiourea.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.847 (t, 3H, $J$ = 6.9 Hz), 1.243−1.376 (m, 4H), 1.738−1.899 (m, 2H), 2.729−2.758 (m, 4H), 3.382 (t, 1H, $J$ = 5.7 Hz), 3.626−3.653 (m, 4H), 7.131 (s, 1H), 7.507−7.827 (m, 4H), 8.024 (s, 1H), 9.374 (s, 1H), 10.280 (s, 1H), 10.411 (s, 1H).



compound 5h

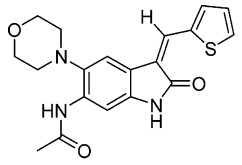
**Compound 5i: *N*-(5-(4-ethylphenoxy)-2-oxoindolin-6-yl)ethanesulfonamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.130 (t, 3H, $J$ = 7.2 Hz), 1.149 (t, 3H, $J$ = 7.5 Hz), 2.559 (q, 2H, $J$ = 7.5 Hz), 2.998 (q, 2H, $J$ = 7.2 Hz), 3.395 (s, 2H), 6.788 (s, 1H), 6.848−6.877 (m, 2H), 6.931 (s, 1H), 7.159−7.188 (m, 2H), 9.252 (s, 1H), 10.323 (s, 1H).



compound 5i

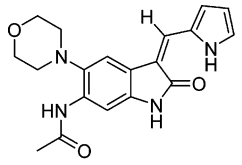
**General Procedure for the Synthesis of compound 6.** To a solution of 0.10 mmol of **5** (when R = H) in 2.0 mL of ethanol, 1.2 equiv of aldehyde and 0.2 equiv of piperidine were added. The reaction mixture was stirred mechanically on an H + P Labortechnik GmbH parallel synthesizer at 46 °C overnight. The solvent then was evaporated in vacuum, and the residue was purified on silica gel to afford products **6** in over 80% yield. The *Z* or *E* isomer was separated by an HPLC system under detection of UV 254 nm wavelength. The configuration of *Z* or *E* was determined by NOE experiment. The ratio of *Z* and *E* was analyzed by HPLC/MS analysis.

**Compound 6a: (*Z*)-*N*-(5-Morpholin-4-yl-2-oxo-3-thiophen-2-ylmethylene-2,3-dihydro-1*H*-indol-6-yl)-acetamide.** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.148 (s, 3H), 2.801 (t, 4H, $J$ = 4.4 Hz), 3.803 (t, 4H, $J$ = 4.4 Hz), 7.220 (dd, 1H, $J$ = 3.6, 5.2 Hz), 7.677 (s, 1H), 7.761 (s, 1H), 7.831 (d, 1H, $J$ = 5.2 Hz), 7.891 (d, 1H, $J$ = 3.6 Hz), 8.038 (s, 1H), 9.009 (s, 1H), 10.460 (s, 1H).



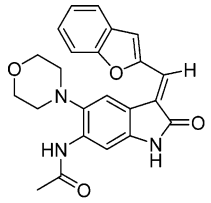
compound 6a

**Compound 6b: (*Z*)-*N*-[5-Morpholin-4-yl-2-oxo-3-(1*H*-pyrrol-2-ylmethylene)-2,3-dihydro-1*H*-indol-6-yl]-acetamide.** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.140 (s, 3H), 2.797 (t, 4H, $J$ = 4.4 Hz), 3.799 (t, 4H, $J$ = 4.4 Hz), 6.325−6.334 (m, 1H), 6.748−6.757 (m, 1H), 7.306−7.309 (m, 1H), 7.611 (s, 1H), 7.701 (s, 1H), 7.776 (s, 1H), 8.976 (s, 1H), 10.751 (s, 1H), 13.238 (s, 1H).



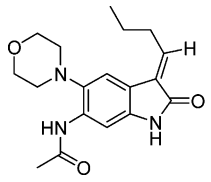
compound 6b

**Compound 6c: (*E*)-*N*-(3-Benzofuran-2-ylmethylene-5-morpholin-4-yl-2-oxo-2,3-dihydro-1*H*-indol-6-yl)-acetamide.** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.188 (s, 3H), 2.889 (t, 4H, $J$ = 4.4 Hz), 3.874 (t, 4H, $J$ = 4.4 Hz), 7.352 (s, 1H), 7.376 (d, 1H, $J$ = 7.6 Hz), 7.535 (t, 1H, $J$ = 7.6 Hz), 7.602 (s, 1H), 7.661 (d, 1H, $J$ = 8.4 Hz), 7.779 (d, 1H, $J$ = 7.6 Hz), 7.848 (s, 1H), 8.435 (s, 1H), 9.074 (s, 1H), 10.532 (s, 1H).



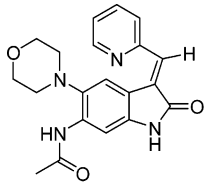
compound 6c

**Compound 6d: (*E*)-*N*-(3-Butylidene-5-morpholin-4-yl-2-oxo-2,3-dihydro-1*H*-indol-6-yl)-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.979 (t, 3H, $J$ = 7.5 Hz), 1.560−1.633 (m, 2H), 2.145 (s, 3H), 2.564−2.638 (m, 2H), 2.774 (br, 4H), 3.787 (br, 4H), 6.650 (t, 1H, $J$ = 7.8 Hz), 7.376 (s, 1H), 7.778 (s, 1H), 9.019 (s, 1H), 10.322 (s, 1H).



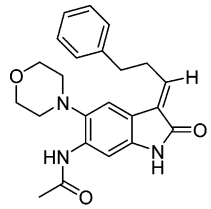
compound 6d

**Compound 6e: (*E*)-*N*-(5-Morpholin-4-yl-2-oxo-3-pyridin-2-ylmethylene-2,3-dihydro-1*H*-indol-6-yl)-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.171 (s, 3H), 2.774−2.804 (m, 4H), 3.804−3.834 (m, 4H), 7.427 (s, 1H), 7.436−7.447 (m, 1H), 7.819 (s, 1H), 7.853−7.847 (m, 1H), 7.911−7.968 (m, 1H), 8.887−8.900 (m, 1H), 9.059 (s, 1H), 9.115 (s, 1H), 10.498 (s, 1H).



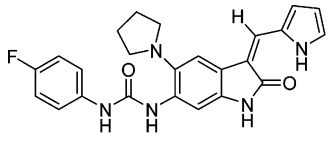
compound 6e

**Compound 6f: (*E*)-*N*-[5-Morpholin-4-yl-2-oxo-3-(3-phenylpropylidene)-2,3-dihydro-1*H*-indol-6-yl]-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.152 (s, 3H), 2.908−2.977 (m, 4H), 2.769 (t, 4H, $J$ = 3.9 Hz), 3.798 (t, 4H, $J$ = 4.2 Hz), 6.660 (t, 1H, $J$ = 6.75 Hz), 7.164−7.351 (m, 5H), 7.467 (s,1H), 7.766 (s, 1H), 9.016 (s,1H), 10.319 (s,1H).



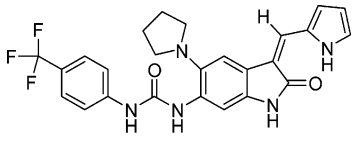
compound 6f

**Compound 6g**: **(*Z*)-1-(4-Fluorophenyl)-3-[2-oxo-5-pyrrolidin-1-yl-3-(1*H*-pyrrol-2-ylmethylene)-2,3-dihydro-1*H*-indol-6-yl]-urea.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.958 (br, 4H), 2.990 (br, 4H), 6.304−6.315 (m, 1H), 6.71−6.72 (m, 1H), 7.088−7.147 (m, 2H), 7.281 (br, 1H), 7.495−7.506 (m, 2H), 7.568 (s, 1H), 7.622 (s, 1H), 7.767 (s, 1H), 8.324 (s,1H), 9.548 (s, 1H), 10.722 (s,1H), 13.235 (s,1H).



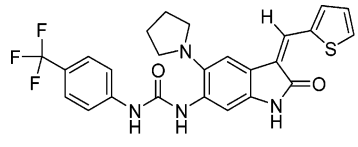
compound 6g

**Compound 6h: (*Z*)-1-[2-Oxo-5-pyrrolidin-1-yl-3-(1*H*-pyrrol-2-ylmethylene)-2,3-dihydro-1*H*-indol-6-yl]-3-(4-trifluoromethylphenyl)-urea.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.968 (br, 4H), 3.004 (br, 4H), 6.300−6.328 (m, 1H), 6.719−6.731 (m, 1H), 7.289 (br, 1H), 7.588−7.722 (m, 6H), 7.773 (s, 1H), 8.467 (s, 1H), 9.929 (s, 1H), 10.744 (s, 1H), 13.239 (s, 1H).



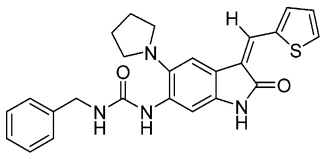
compound 6h

**Compound 6i: (*Z*)-1-(2-Oxo-5-pyrrolidin-1-yl-3-thiophen-2-ylmethylene-2,3-dihydro-1*H*-indol-6-yl)-3-(4-trifluoromethylphenyl)-urea.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.982 (br, 4H), 3.005 (br, 4H), 7.289 (br, 1H), 7.632−7.733 (m, 6H), 7.853 (s, 1H), 7. 945−7.961 (m, 1H), 8.080 (s, 1H), 8.579 (s, 1H), 10.030 (s, 1H), 10.481 (s, 1H).



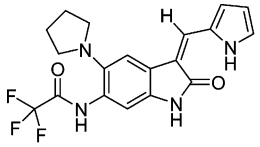
compound 6i

**Compound 6j: (*Z*)-1-Benzyl-3-(2-oxo-5-pyrrolidin-1-yl-3-thiophen-2-ylmethylene-2,3-dihydro-1*H*-indol-6-yl)-urea.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.923 (br, 4H), 2.936 (br, 4H), 4.306 (d, 2H, $J$ = 5.4 Hz), 7.257−7.348 (m, 6H), 7.576 (s, 1H), 7. 696−7.771 (m, 2H), 7.866 (s, 1H), 7.922 (d, 1H, $J$ = 5.1 Hz), 8.025 (s, 1H), 8.238 (s, 1H), 10.412 (s, 1H).



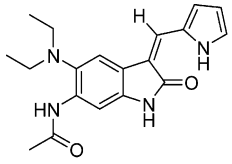
compound 6j

**Compound 6k: (*Z*)-2,2,2-Trifluoro-*N*-[2-oxo-5-pyrrolidin-1-yl-3-(1*H*-pyrrol-2-ylmethylene)-2,3-dihydro-1*H*-indol-6-yl]-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.862−1.904 (m, 4H), 3.073−3.115 (m, 4H), 6.334−6.362 (m, 1H), 6.792−6.815 (m, 1H), 7.014 (s, 1H), 7.333−7.354 (m, 1H), 7.467 (s, 1H), 7.804 (s, 1H), 10.614 (s, 1H), 10.741 (s, 1H), 13.315 (s, 1H).



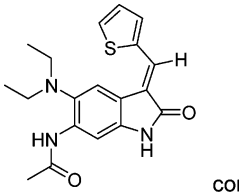
compound 6k

**Compound 6l: (*Z*)-*N*-[5-Diethylamino-2-oxo-3-(1*H*-pyrrol-2-ylmethylene)-2,3-dihydro-1*H*-indol-6-yl]-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.885 (t, 6H, $J$ = 7.05 Hz), 2.125 (s, 3H), 2.915 (q, 4H, $J$ = 7.05 Hz), 6.321 (q, 1H, $J$ = 2.1, 3.6 Hz), 6.741 (t, 1H, $J$ = 1.5 Hz), 7.300 (br, 1H), 7.623 (s, 1H), 7.664 (s, 1H), 7.911 (s, 1H), 9.157 (s, 1H), 10.782 (s, 1H), 13.228 (s, 1H).



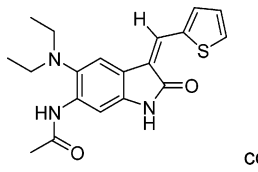
compound 6l

**Compound 6m-1: (*E*)-*N*-(5-Diethylamino-2-oxo-3-thiophen-2-ylmethylene-2,3-dihydro-1*H*-indol-6-yl)-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.892 (t, 6H, $J$ = 7.2 Hz), 2.132 (s, 3H), 2.919 (q, 4H, $J$ = 7.2 Hz), 7.187−7.217 (m, 1H), 7.677 (s, 1H), 7.812−7.829 (m, 1H), 7.883−7.900 (m, 2H), 8.000 (s, 1H), 9.190 (s, 1H), 10.485 (s, 1H).



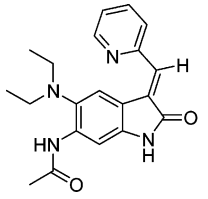
compound 6m-1

**Compound 6m-2: (*Z*)-*N*-(5-Diethylamino-2-oxo-3-thiophen-2-ylmethylene-2,3-dihydro-1*H*-indol-6-yl)-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.922 (t, 6H, $J$ = 7.2 Hz), 2.158 (s, 3H), 2.923 (q, 4H, $J$ = 7.2 Hz), 7.278−7.307 (m, 1H), 7.673 (s, 1H), 7.738−7.750 (m, 1H), 7.955 (s, 1H), 7.974 (br, 1H), 8.081 (s, 1H), 9.210 (s, 1H), 10.525 (s, 1H).



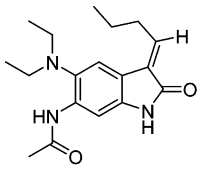
compound 6m-2

**Compound 6n: (*E*)-*N*-(5-Diethylamino-2-oxo-3-pyridin-2-ylmethylene-2,3-dihydro-1*H*-indol-6-yl)-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.913 (t, 6H, $J$ = 7.05 Hz), 2.156 (s, 3H), 2.910 (q, 4H, $J$ = 7.05 Hz), 7.413 (s, 1H), 7.432−7.454 (m, 1H), 7.824 (d, 1H, $J$ = 8.1 Hz), 7.912 (s, 1H), 7.901−7.958 (m, 1H), 8.828 (d, 1H, $J$ = 4.2 Hz), 9.109 (s, 1H), 9.239 (s, 1H), 10.510 (s, 1H).



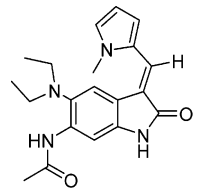
compound 6n

**Compound 6o: (*E*)-*N*-(3-Butylidene-5-diethylamino-2-oxo-2,3-dihydro-1*H*−indol-6-yl)-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.878 (t, 6H, $J$ = 6.9 Hz), 0.959 (t, 3H, $J$ = 7.35 Hz), 1.548−1.620 (m, 2H), 2.130 (s, 3H), 2.524−2.598 (m, 2H), 2.888 (q, 4H, $J$ = 6.9 Hz), 6.644 (t, 1H, $J$ = 7.6 Hz), 7.359 (s, 1H), 7.893 (s, 1H), 9.183 (s, 1H), 10.343 (s, 1H).



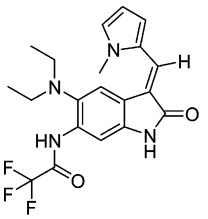
compound 6o

**Compound 6p: (*E*)-*N*-[5-Diethylamino-3-(1-methyl-1*H*-pyrrol-2-ylmethylene)-2-oxo-2,3-dihydro-1*H*-indol-6-yl]-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.889 (t, 6H, $J$ = 6.9 Hz), 2.139 (s, 3H), 2.840 (q, 4H, $J$ = 6.9 Hz), 3.748 (s, 3H), 6.295−6.316 (m, 1H), 6.862−6.870 (m, 1H), 7.140 (br, 1H), 7.310 (s, 1H), 7.820 (s, 1H), 7.916 (s, 1H), 9.164 (s, 1H), 10.400 (s, 1H).



compound 6p

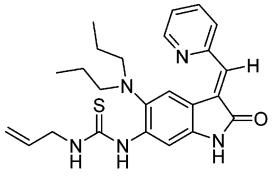
**Compound 6q: (*E*)-*N*-[5-Diethylamino-3-(1-methyl-1*H*-pyrrol-2-ylmethylene)-2- oxo-2,3-dihydro-1*H*-indol-6-yl]-2,2,2-trifluoroacetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.893 (t, 6H, $J$ = 7.05 Hz), 2.877 (q, 4H, $J$ = 7.05 Hz), 3.771 (s, 3H), 6.326−6.347 (m, 1H), 6.931−6.941 (m, 1H), 7.186−7.192 (m, 1H), 7.428 (s, 1H), 7.727 (s, 1H), 7.932 (s, 1H), 10.300 (s, 1H), 10.572 (s, 1H).



compound 6q

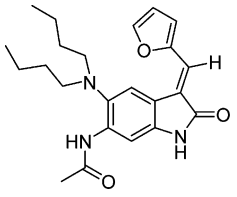
**Compound 6r: (*E*)-1-Allyl-3-(5-dipropylamino-2-oxo-3-pyridin-2-ylmethylene-2,3-dihydro-1*H*-indol-6-yl)-thio-urea.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.791 (t, 6H, $J$ = 7.5 Hz), 1.317−1.392 (m, 4H), 2.804 (t, 4H, $J$ = 7.8 Hz), 4.151 (br, 2H), 5.122−5.248 (m, 2H), 5.839−5.948 (m, 1H), 7.401 (s, 1H), 7.416−7.461 (m, 1H), 7.811−7.837 (m, 1H),

7.901−7.958 (m, 1H), 8.241 (s, 1H), 8.817−8.830 (m, 1H), 8.994 (br, 1H), 9.085 (s, 1H), 9.343 (s, 1H), 10.509 (s, 1H).



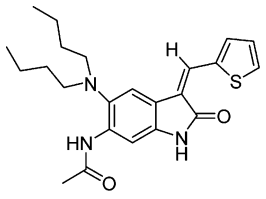
compound 6r

**Compound 6s: (*E*)-*N*-(5-Dibutylamino-3-furan-2-yl-methylene-2-oxo-2,3-dihydro-1*H*-indol-6-yl)-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.825 (t, 6H, $J$ = 7.05 Hz), 1.237−1.333 (m, 8H), 2.133 (s, 3H), 2.852 (t, 4H, $J$ = 6.75 Hz), 6.771−6.788 (m, 1H), 7.173 (s, 1H), 7.184−7.191 (m, 1H), 7.905 (s, 1H), 8.138−8.143 (m, 1H), 8.262 (s, 1H), 9.162 (s, 1H), 10.466 (s, 1H).



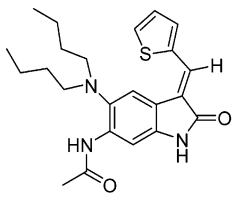
compound 6s

**Compound 6t-1: (*Z*)-*N*-(5-(Dibutylamino)-2-oxo-3-(thiophen-2-ylmethylene)indolin-6-yl)-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.828 (t, 6H, $J$ = 6.6 Hz), 1.256−1.279 (m, 8H), 2.116 (s, 3H), 2.821−2.843 (m, 4H), 7.188−7.218 (m, 1H), 7.714 (s, 1H), 7.814−7.832 (m, 1H), 7.878−7.892 (m, 2H), 8.004 (s, 1H), 9.154 (s, 1H), 10.490 (s, 1H).



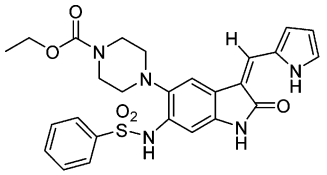
compound 6t-1

**Compound 6t-2: (*E*)-*N*-(5-(Dibutylamino)-2-oxo-3-(thiophen-2-ylmethylene)indolin-6-yl)-acetamide.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.820 (t, 6H, $J$ = 6.6 Hz), 1.250−1.289 (m, 8H), 2.138 (s, 3H), 2.842 (t, 4H, $J$ = 6.9 Hz), 7.273−7.302 (m, 1H), 7.673 (s, 1H), 7.737−7.749 (m, 1H), 7.940 (s, 1H), 7.965−7.981 (m, 1H), 8.104 (s, 1H), 9.144 (s, 1H), 10.532 (s, 1H).



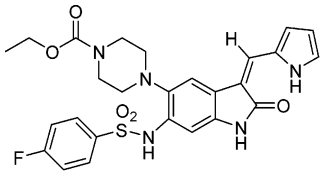
compound 6t-2

**Compound 6u: (*Z*)-4-[6-Benzenesulfonylamino-2-oxo-3-(1*H*-pyrrol-2-ylmethylene)-2,3-dihydro-1*H*-indol-5-yl]-piperazine-1-carboxylic Acid Ethyl Ester.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.185 (t, 3H, $J$ = 7.05 Hz), 2.264 (br, 4H), 3.401 (br, 4H), 4.045 (q, 2H, $J$ = 7.05 Hz), 6.312−6.340 (m, 1H), 6.700−6.713 (m, 1H), 7.057 (s, 1H), 7.321 (br, 1H), 7.509−7.749 (m, 7H), 8.993 (s, 1H), 10.832 (s, 1H), 13.188 (s, 1H).



compound 6u

**Compound 6v: (*Z*)-Ethyl-4-(3-((1*H*-pyrrol-2-yl)-methylene)-6-(4-fluorophenylsulfonamido)-2-oxoindolin-5-yl)piperazine-1-carboxylate.** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.188 (t, 3H, $J$ = 7.2 Hz), 2.328 (br, 4H), 3.424 (br, 4H), 4.049 (q, 2H, $J$ = 7.2 Hz), 6.314−6.342 (m, 1H), 6.712−6.724 (m, 1H), 7.025 (s, 1H), 7.325 (br, 1H), 7.370−7.429 (m, 2H), 7.618 (s, 1H), 7.687 (s, 1H), 7.780−7.827 (m, 2H), 9.079 (s, 1H), 10.827 (s, 1H), 13.180 (s, 1H).



compound 6v

## References and Notes


(1) Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415−2437.

(2) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930.

(3) (a) Teichert, A.; Jantos, K.; Harms, K.; Studer, A. *Org. Lett.* **2004**, *6*, 3477−3480. (b) Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Garaliene, V.; Farruggia, G.; Masotti, L. *Bioorg. Med. Chem.* **2004**, *12*, 1121−1128. (c) Olgen, S.; Akaho, E.; Nebioglu, D. *Il Farmaco* **2005**, *60*, 497−506.

(4) Robinson, R. P.; Reiter, L. A.; Barth, W. E.; Campeta, A. M.; Cooper, K.; Cronin, B. J.; Destito, R.; Donahue, K. M.; Falkner, F. C.; Fiese, E. F.; Johnson, D. L.; Kuperman, A. V.; Liston, T. E.; Malloy, D.; Martin, J. J.; Mitchell, D. Y.; Rusek, F. W.; Shamblin, S. L.; Wright, C. F. *J. Med. Chem.* **1996**, *39*, 10−18.

(5) (a) Sun, L.; Tran, N.; Tang, T.; App, H.; Hirth, P.; McMahon, G.; Tang, C. *J. Med. Chem.* **1998**, *41*, 2588−2603. (b) Guan, H. P.; Laird, A. D.; Blake, R. A.; Tang, C.; Liang, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 187−190. (c) Messaoudi, S.; Sancelme, M.; Polard-Housset, V.; Aboab, B.; Moreau, P.; Prudhomme, M. *Eur. J. Med. Chem.* **2004**, *39*, 453−458.

(6) (a) Bramson, H. N.; Corona, J.; Davis, S. T.; Dickerson, S. H.; Edelstein, M.; Frye, S. V.; Gampe, R. T., Jr.; Harris, P. A.; Hassell, A.; Holmes, W. D.; Hunter, R. N.; Lackey, K. E.; Lovejoy, B.; Luzzio, M. J.; Montana, V.; Rocque, W. J.; Rusnak, D.; Shewchuk, L.; Veal, J. M.; Walker, D. H.; Kuyper, L. F. *J. Med. Chem.* **2001**, *44*, 4339−4358. (b) Dermatakis, A.; Luk, K.-C.; DePinto, W. *Bioorg. Med. Chem.* **2003**, *11*, 1873−1881. (c) Woodard, C. L.; Li, Z.; Kathcart, A. K.; Terrell, J.; Gerena, L.; Lopez-Sanchez, M.; Kyle, D. E.; Bhattacharjee, A. K.; Nichols, D. A.; Ellis, W.; Prigge, S. T.; Geyer, J. A.; Waters, N. C. *J. Med. Chem.* **2003**, *46*, 3877−3882.

(7) (a) Tokunaga, T.; Hume, W. E.; Umezome, T.; Okazaki, K.; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi, H.; Nagata, R. *J. Med. Chem.* **2001**, *44*, 4641−4649. (b) Tokunaga, T.; Hume, W. E.; Nagamine, J.; Kawamura, T.; Taiji, M.; Nagata, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1789−1792.

(8) Zaveri, N. T.; Jiang, F.; Olsen, C. M.; Deschamps, J. R.; Parrish, D.; Polgar, W.; Toll, L. *J. Med. Chem.* **2004**, *47*, 2973−2976.
(9) Mokrosz, M. J.; Charakchieva-Minol, S.; Kozioł, A.; Kłodzińska, A.; Chojnacka-Wójcik, E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1229−1231.
(10) Chambers, R. J.; Abrams, K.; Garceau, N. Y.; Kamath, A. V.; Manley, C. M.; Lilley, S. C.; Otte, D. A.; Scott, D. O.; Sheils, A. L.; Tess, D. A.; Vellekoop, A. S.; Zhang, Y.; Lam, K. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 307−310.
(11) Bouérat, L.; Fensholdt, J.; Liang, X. F.; Havez, S.; Nielsen, S. F.; Hansen, J. R.; Bolvig, S.; Andersson, C. *J. Med. Chem.* **2005**, *48*, 5412−5414.
(12) Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Garaliene, V.; Welsh, W.; Arora, S.; Farruggia, G.; Masotti, L. *J. Med. Chem.* **2005**, *48*, 5604−5607.
(13) (a) Sun, L.; Tran, N.; Liang, C.; Tang, F.; Rice, A.; Schreck, R.; Waltz, K.; Shawver, L. K.; McMahon, G.; Tang, C. *J. Med. Chem.* **1999**, *42*, 5120−5130. (b) Sun, L.; Tran, N.; Liang, C.; Hubbard, S.; Tang, F.; Lipson, K.; Schreck, R.; Zhou, Y.; McMahon, G.; Tang, C. *J. Med. Chem.* **2000**, *43*, 2655−2663. (c) Sun, L.; Liang, C.; Shirazian, S.; Zhou, Y.; Miller, T.; Cui, J.; Fukuda, J. Y.; Chu, J.-Y.; Nematalla, A.; Wang, X.; Chen, H.; Sistla, A.; Luu, T. C.; Tang, F.; Wei, J.; Tang, C. *J. Med. Chem.* **2003**, *46*, 1116−1119.
(14) (a) Ye, C.; Sweeny, D.; Sukbuntherng, J.; Zhang, Q.; Tan, W.; Wong, S.; Madan, A.; Ogilvie, B.; Parkinson, A.; Antonian, L. *Toxicol. in Vitro* **2006**, *20*, 154−162. (b) Dowlati, A.; Robertson, K.; Radivoyevitch, T.; Waas, J.; Ziats, N. P.; Hartman, P.; Abdul-Karim, F. W.; Wasman, J. K.; Jesberger, J.; Lewin, J.; McCrae, K.; Ivy, P.; Remick, S. C. *Clin. Cancer Res.* **2005**, *11*, 7938−7944. (c) O'Donnell, A.; Padhani, A.; Hayes, C.; Kakkar, A. J.; Leach, M.; Trigo, J. M.; Scurr, M.; Raynaud, F.; Phillips, S.; Aherne, W.; Hardcastle, A.; Workman, P.; Hannah, A.; Judson, I. *Br. J. Cancer* **2005**, *93*, 876−883. (d) Hoff, P. M.; Wolff, R. A.; Bogaard, K.; Waldrum, S.; Abbruzzese, J. L. *Jpn. J. Clin. Oncol.* **2006**, *36*, 100−103. (e) Lockhart, A. C.; Cropp, G. F.; Berlin, J. D.; Donnelly, E.; Schumaker, R. D.; Schaaf, L. J.; Hande, K. R.; Fleischer, A. C.; Hannah, A. L.; Rothenberg, M. L. *Am. J. Clin. Oncol.* **2006**, *29*, 109−115.
(15) Liu, G.; Fan, Y. M.; Carlson, J. R.; Zhao, Z. G.; Lam, K. S. *J. Comb. Chem.* **2000**, *2*, 467−474.
(16) Wu, X. H.; Liu, G.; Zhang, J.; Wang, Z. G.; Xu, S.; Zhang, S. D.; Zhang, L.; Wang, L. *Mol. Diversity* **2004**, *8*, 165−174.
(17) Zhang, L.; Liu, G.; Zhang, S. D.; Yang, H. Z.; Li, L.; Wu, X. H.; Yu, J. L.; Kou, B. B.; Xu, S.; Li, J.; Sun, G. C.; Ji, Y. F.; Cheng, G. F. *J. Comb. Chem.* **2004**, *6*, 431−436.
(18) Li, L.; Liu, G.; Wang, Z. G.; Yuan, Y. Y.; Zhang, C. X.; Tian, H. Y.; Wu, X. H.; Zhang, J. *J. Comb. Chem.* **2004**, *6*, 811−821.
(19) Zhang, J.; Zhang, L.; Zhang, S. D.; Wang,Y. H.; Liu, G. *J. Comb. Chem.* **2005**, *7*, 657−664.
(20) (a) Walsh, D. A.; Moran, H. W.; Shamblee, D. A.; Uwaydah, I. M.; Welstead, W. J., Jr.; Sancilio, L. F.; Dannenburg, W. N. *J. Med. Chem.* **1984**, *27*, 1379−1388. (b) Kraynack, E. A.; Dalgard, J. E.; Gaeta, F. C. A. *Tetrahedron Lett.* **1998**, *39*, 7679−7682.

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