# Oxindole-Based Inhibitors of Cyclin-Dependent Kinase 2 (CDK2): Design, Synthesis, Enzymatic Activities, and X-ray Crystallographic Analysis

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Two closely related classes of oxindole-based compounds, 1*H*-indole-2,3-dione 3-phenylhydrazones and 3-(anilinomethylene)-1,3-dihydro-2*H*-indol-2-ones, were shown to potently inhibit cyclin-dependent kinase 2 (CDK2). The initial lead compound was prepared as a homologue of the 3-benzylidene-1,3-dihydro-2*H*-indol-2-one class of kinase inhibitor. Crystallographic analysis of the lead compound bound to CDK2 provided the basis for analogue design. A semiautomated method of ligand docking was used to select compounds for synthesis, and a number of compounds with low nanomolar inhibitory activity versus CDK2 were identified. Enzyme binding determinants for several analogues were evaluated by X-ray crystallography. Compounds in this series inhibited CDK2 with a potency ∼10-fold greater than that for CDK1. Members of this class of inhibitor cause an arrest of the cell cycle and have shown potential utility in the prevention of chemotherapy-induced alopecia.

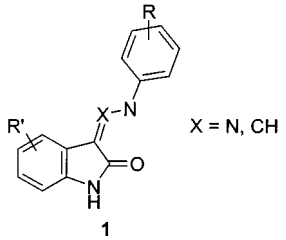
## Introduction

The cyclin-dependent kinases (CDKs) are key regulators of the cell cycle,[1] the complex process by which cells divide.[2] The cell division cycle is commonly viewed as an orderly progression through four distinct phases: (1) G1 (gap 1), the phase in which the cell prepares for DNA synthesis, (2) S (synthesis), the stage in which DNA is replicated, (3) G2 (gap 2), the phase in which the cell prepares for mitosis, and (4) M (mitosis), the stage that leads to chromosome segregation and daughter cell formation. CDKs provide much of the control that is required for the cell to move through these phases in a coordinated manner.

As their name implies, the activity of CDKs is dependent upon a regulatory subunit called a cyclin. Members of the cyclin family bind to and activate their CDK partners.[3] For example, cyclins A and B activate CDK1, cyclins A and E regulate the activity of CDK2, and the D-type cyclins are associated with CDK4. While the concentration of the CDKs remains relatively constant throughout the cell cycle, cyclin expression and degradation occur in a periodic fashion.[4] The rise and fall of cyclin concentrations are timed to provide specific CDK activities as they are needed for progression through the various stages of the cell cycle. Thus, cyclin D is expressed in G1, leading to the phosphorylation of the retinoblastoma protein by CDK4; CDK2 is activated by cyclin E in late G1 and by cyclin A during DNA synthesis; and cyclin B controls the activity of CDK1 during mitosis. Other mechanisms for CDK regulation, such as phosphorylation-dephosphorylation and endogenous protein inhibitors, also play important roles in cell cycle control.[5,6]

The recognition of the importance of CDKs to the process of cell division has stimulated an interest in them as potential targets for proliferative diseases such as cancer, psoriasis, and restenosis,[7−9] and for the prevention of chemotherapy-associated side effects such as alopecia.[10,11] A number of small-molecule inhibitors of CDKs have been identified[12−17] and are described in recent reviews.[18−21] Flavopiridol is the first CDK inhibitor to progress into clinical trials and is being evaluated as an anticancer agent.[22,23] In addition, peptide inhibitors of CDK2 were recently shown to preferentially induce transformed cells to undergo programmed cell death (apoptosis) relative to untransformed cells.[24]

Here we describe the discovery of a new class of CDK inhibitor, represented by structure **1**, that stops cell




**1**

cycle progression by inhibiting CDK2 activity in cells and has shown potential utility in the prevention of chemotherapy-induced alopecia.[11] The initial lead identification, structure-based analogue design, compound synthesis, kinase inhibition data, and X-ray crystal-

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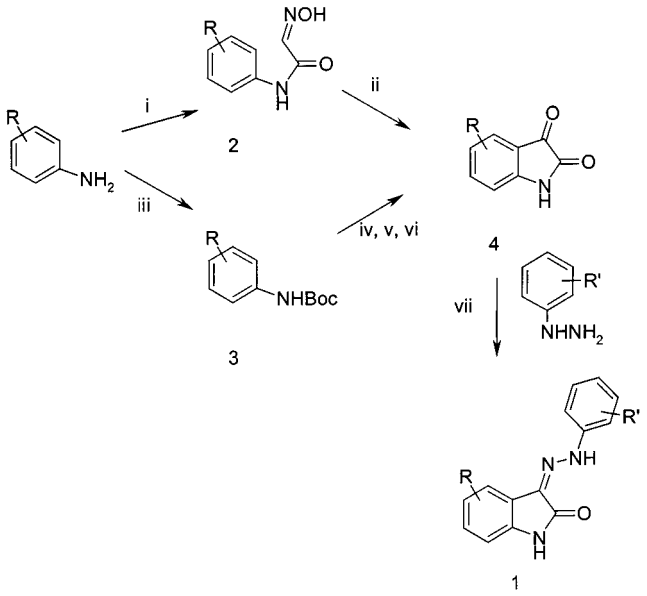
**Scheme 1**[a]



[a] Conditions: (i) chloral hydrate, $NH_2OH$ HCl, $Na_2SO_4$, EtOH/$HCl_{(aq)}$; (ii) $H_2SO_{4(conc)}$ or $BF_3OEt_2$; (iii) $(tBuOCO)_2O$, THF; (iv) 2.5 equiv t-BuLi, THF; (v) $EtO_2CCO_2Et$, THF; (vi) $HCl_{(aq)}$; (vii) 1 equiv HCl, EtOH.

lographic structures of CDK2/inhibitor complexes are reported. Compounds with low nanomolar $IC_{50}$ values for CDK2 were identified, and CDK2 binding determinants were evaluated through crystallographic analyses.

## Chemistry

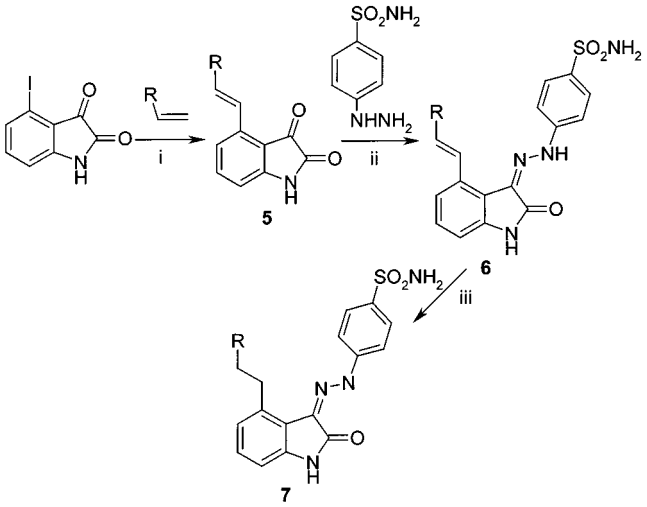
**Isatins and Isatin Hydrazones.** Substituted isatins **4** typically were prepared via the classical Sandmeyer reaction[25] involving conversion of the substituted aniline with hydroxylamine and chloral hydrate to the intermediate isonitrosoacetanilide **2**, followed by cyclization in either concentrated sulfuric acid or boron trifluoride etherate as shown in Scheme 1. Alternatively, for some meta-substituted anilines (R = iPr, Ph, OEt) where this methodolgy failed, the isatin synthesis of Hewawasam and Meanwell[26] was followed. In that procedure, the aniline was protected as the *tert*-butylcarbonate (**3**). Ortho-lithiation of intermediate **3** and treatment with diethyl oxalate gave the α-ketoester, which upon exposure to aqueous acid underwent cyclization to the isatin. Subsequent condensation of the substituted isatin **4** with an arylhydrazine in ethanol, either using the hydrazine salt or one equivalence of hydrochloric acid, yielded the isatin hydrazone **1**.

A number of 4-alkylisatin hydrazones **7** were prepared as shown in Scheme 2. Heck coupling of 4-iodoisatin with alkenes produced 4-alkenylisatins **5**, which were converted to the corresponding hydrazones **6**. Subsequent reduction furnished the 4-alkylisatin hydrazones **7**.

A series of 5-carboxamides **10** were prepared from the pentafluorophenyl ester **9**, which was derived from the corresponding carboxylic acid **8** by treatment with pentafluorophenyl trifuoroacteamide (Scheme 3).

**Oxindoles.** Oxindoles **12** were obtained, as delineated in Scheme 4, either directly from the corresponding isatin **4** by Wolf Kishner reduction[27] or alternatively from the substituted aniline via the Gassman synthesis.[28] This latter procedure involved sequential treatment of the aniline with *tert*-butyl hypochlorite, ethyl (methylthio)acetate, triethylamine, and hydrochloric acid to give the 3-methylthiooxindole **11,** which was desulfurized with zinc or Raney nickel to give the corresponding oxindole **12**. A modification of the Gassman procedure[29] involving initial mixing of ethyl (methylthio)acetate and sulfuryl chloride, followed by addition of the aniline with one equivalent of Proton Sponge and finally triethylamine treatment, was employed to prepare compounds that were not accessible via the original Gassman procedure, e.g., the oxindole ester (R = 5-$CO_2$Me). Conversion of the oxindole to the dimethylaminomethinyloxindole or ethoxymethinyloxindole **13** (X = H) was achieved with dimethylformamide-*N*,*N*-di-*tert*-butyl acetal or diethoxymethyl acetate, respectively, and subsequent condensation with an aniline yielded the enamine **14** (X = H). The corresponding methyl-substituted enamines **14** (X = Me) were obtained using dimethylacetamide-*N*,*N*-dimethyl acetal following the same procedure.

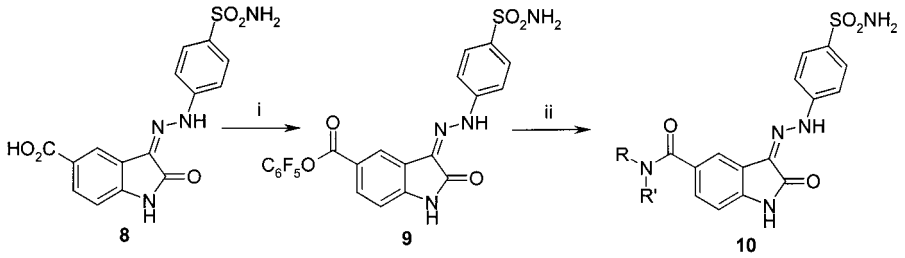
**Scheme 2**[a]



[a] Conditions: (i) $Pd(OAc)_2$, $Et_3N$, $P(o\text{-}Tol)_3$, $CH_3CN$; (ii) EtOH, cat $HCl_{(aq)}$; (iii) $H_2$ Pd/C, MeOH/THF.

**Stereochemistry.** As viewed by their $^1H$ NMR spectra, the isatin hydrazones and corresponding enamines exist predominately as the *Z* (cis) conformation in solution, presumably due to the intramolecular hydrogen bonding between the NH of the hydrazone/enamine linkage and the carbonyl group of the indolinone. Confirmation of this stereochemistry was achieved for the enamine by observation of a nuclear Overhauser effect between the 4-position proton of the oxindole ring system and the vinyl hydrogen of the enamine linkage for the 5-carboxylic ester (R = 5-$CO_2{}^i$Bu, compound **55**, Table 1). In some analogues where a heteroatom (O or N) containing functionality was substituted at the 4-position of the oxindole, allowing formation of an alternative hydrogen bond with the linker NH in the E (trans) conformation, $^1H$ NMR spectra of equilibrated samples corresponded to mixtures of *Z* and *E* isomers. For example, the 4-phenoxy derivative **32** was observed as a 5:2 *Z*:*E* mixture after 10 days of equilibration, and the 4-carboxamido analogue **40** was found as a 1:7 *Z*:*E* mixture. Occasionally, compounds in the series precipitated from the reaction solution as a mixture of *Z* and

**Scheme 3**[a]

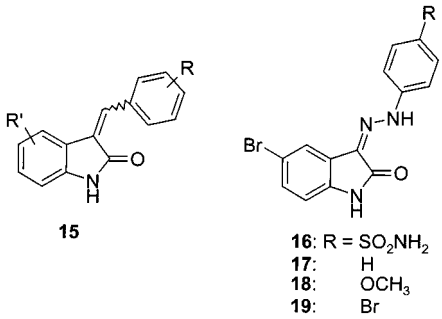



[a] Conditions: (i) $CF_3CO_2C_6F_5$; (ii) RR′NH, pyridine, $CH_3CN$.

*E* isomers, as indicated by NMR. However, in the absence of a hydrogen bond acceptor at position-4, equilibration led to disappearance of signals for the *E* isomer.

## Results and Discussion

**Lead Discovery.** As part of an ongoing effort to identify selective inhibitors of protein kinases, analogues of the 3-(benzylidene)indolin-2-ones **15** were examined. The indolin-2-ones **15** are known inhibitors of receptor tyrosine kinases, such as epidermal growth factor receptor and Her-2,[30] and a closely related compound shows selective inhibition of vascular endothelial growth factor receptor 2 kinase.[31] Compounds **16**−**19**, available in one synthetic step from commercial materials, were prepared as homologues of compounds **15** and assayed for inhibition of various kinases. Compounds **17**−**19** were inactive ($IC_{50}$ >10 $\mu$M) against all kinases tested, but compound **16** selectively inhibited CDK2 ($IC_{50}$ = 60 nM) and served as the lead compound for the work described here.

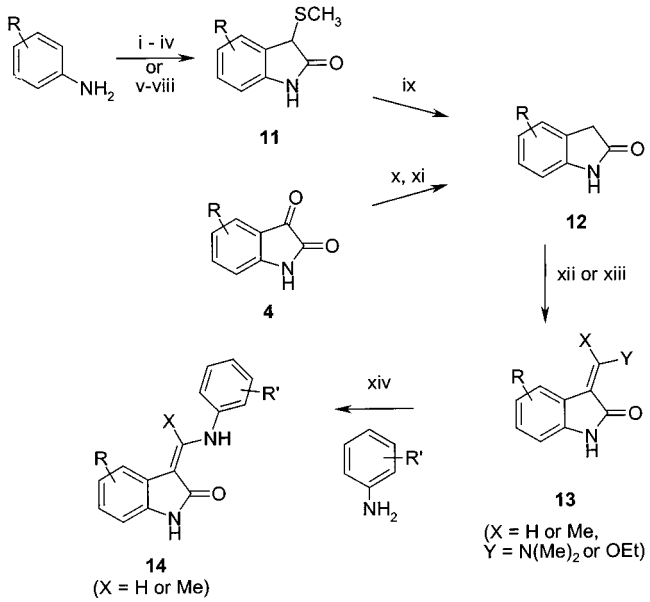



**15**

**16**: R = $SO_2NH_2$
**17**: H
**18**: $OCH_3$
**19**: Br

**Analogue Design**. A structure-based selection process was used to explore analogues in this series of compounds. CDK2[32] and its complexes with ATP,[32−34] cyclin A,[35,36] the protein inhibitor p27,[37] and small molecule inhibitors[12,20,38] have been studied by X-ray crystallography.[5] To evaluate and select potential analogues for synthesis, we utilized the crystal structure of compound **16** bound to the inactive form of CDK2 (Figure 1). This monomeric form of the kinase offers crystallographic advantages over the activated cyclin A complex, including higher resolution, a smaller structure, and one molecule in the asymmetric unit versus two for the cyclin A complex. However, the activation of CDK2 by complexing with cyclin A induces conformational changes in the protein that affect the ATP binding site to some degree. The most significant effect involves a rotation of the C-helix, which alters the active-site geometry in the region of the triad of catalytic active-site residues Lys-33, Glu-51, and Asp-145. As discussed below, the amino group of Lys-33 was considered to be a potential interaction site for inhibitors. Thus, structures of inhibitor complexes with inactive CDK2 should be viewed with some caution, especially regarding inhibitor−protein interactions involving the Lys-33 region of the enzyme.

**Scheme 4**[a]

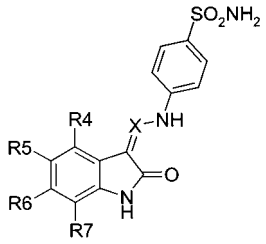



[a] Conditions: (i) t-BuOCl, THF; (ii) $MeSCO_2Et$; (iii) $Et_3N$; (iv) $HCl_{(aq)}$; (v) $MeSCO_2Et$; (vi) $SO_2Cl_2$; (vii) Proton Sponge; (viii) $Et_3N$; (ix) Zn, HOAc or RaNi; (x) $NH_2NH_2$, EtOH; (xi) NaOEt, EtOH; (xii) $Me_2NCH(Ot\text{-}Bu)_2$, DMF or $MeCO_2CH(OEt)_2$, AcOH; (xiii) $Me_2NC(Me)(Ot\text{-}Bu)_2$; (xiv) 1 equiv HCl, EtOH.

Inhibitor **16** was found to occupy the ATP binding site of CDK2 as shown in Figure 1. The oxindole ring system of compound **16** interacted with CDK2 in a manner analogous to that observed for compounds in inhibitor class **15** bound to fibroblast growth factor receptor kinase.[39] Two hydrogen bonds were formed between the lactam moiety of compound **16** and CDK2. Specifically, the amide NH was H-bonded to the backbone carbonyl of Glu-81 and the amide carbonyl oxygen was H-bonded with the backbone NH of Leu-83. Those interactions were analogous to hydrogen bonds between ATP and CDK2.

Inspection of the CDK2/compound **16** structure furnished a number of guidelines for analogue design. The 7-position of the oxindole ring system was positioned close to the side chain of Phe-80 and appeared to be too sterically crowded to permit substitution. The 6-position projected toward a small cavity at the back of the binding cleft and into the region affected by cyclin A association. This cavity is smaller in size, relative to

**Table 1.** CDK1 and CDK2 Inhibitory Activities of Compounds **16**−**81**




| cmpd no. | R4 | R5 | R6 | R7 | X | kinase $IC_{50}$ (nM) CDK1 | CDK2 |
|---|---|---|---|---|---|---|---|
| | | Lead | | | | | |
| **16** | H | Br | H | H | N | 780 | 60 |
| | | Linker | | | | | |
| **17** | H | H | H | H | N | 1300 | 120 |
| **18** | H | H | H | H | CH | 3000 | 690 |
| **19** | H | H | H | H | $CCH_3$ | 2300 | 360 |
| **20** | H | Cl | H | H | N | 300 | 43 |
| **21** | H | Cl | H | H | $CCH_3$ | 220 | 22 |
| **22** | H | 5-oxazolyl | H | H | N | 10 | 2.3 |
| **23** | H | 5-oxazolyl | H | H | CH | 17. | 2.5 |
| **24** | H | 5-oxazolyl | H | H | $CCH_3$ | 7.1 | 2.0 |
| | | 4-Substituents | | | | | |
| **25** | I | H | H | H | N | 110 | 4.6 |
| **26** | $-CH_2CH_3$ | H | H | H | N | 46 | 7.9 |
| **27** | $-CH(CH_3)_2$ | H | H | H | N | 37 | 2.5 |
| **28** | $-CH_2CH(CH_3)_2$ | H | H | H | N | 19 | 1.2 |
| **29** | $-CH{=}C(CH_3)_2$ | H | H | H | N | 15 | 1.5 |
| **30** | $-OCH_2CH_3$ | H | H | H | N | 550 | 93 |
| **31** | $-OCH(CH_3)_2$ | H | H | H | N | 41 | 3.4 |
| **32** | -OPh | H | H | H | N | 290 | 13 |
| **33** | $-(CH_2)_2$-(4-pyridyl) | H | H | H | N | 290 | 21 |
| **34** | $-CH{=}CH$-(4-phenol) | H | H | H | N | 170 | 9.3 |
| **35** | $-(CH_2)_2$-(4-phenol) | H | H | H | N | 150 | 12 |
| **36** | 3-pyrazolyl | H | H | H | N | 250 | 19 |
| **37** | $-CO_2CH_2CH_3$ | H | H | H | CH | 130 | 8.9 |
| **38** | $-CH_2OH$ | H | H | H | CH | 1700 | 54 |
| **39** | $-NO_2$ | H | H | H | N | >1000 | 2400 |
| **40** | $-CONH_2$ | H | H | H | N | >1000 | >1000 |
| | | 5-Substituents | | | | | |
| **41** | H | F | H | H | N | 290 | 34 |
| **42** | H | I | H | H | N | 95 | 11 |
| **43** | H | $-CH_3$ | H | H | N | 330 | 46 |
| **44** | H | -OH | H | H | N | 77 | 10 |
| **45** | H | $-OCH_3$ | H | H | N | 210 | 12 |
| **46** | H | $-NO_2$ | H | H | N | 710 | 15 |
| **47** | H | $-NH_2$ | H | H | N | 1400 | 74 |
| **48** | H | $-N(CH_3)_2$ | H | H | CH | 2800 | 310 |
| **49** | H | $-SO_2CH_3$ | H | H | N | 350 | 16 |
| **50** | H | $-SO_2NH_2$ | H | H | N | 170 | 43 |
| **51** | H | $-SO_3H$ | H | H | N | 130 | 15 |
| **52** | H | $-CO_2H$ | H | H | CH | 150 | 28 |
| **53** | H | $-CO_2CH_3$ | H | H | CH | 12 | 2.1 |
| **54** | H | $-CO_2CH_2CH(CH_3)_2$ | H | H | CH | 19 | 3.0 |
| **55** | H | $-COCH_2CH(CH_3)_2$ | H | H | CH | 16 | 1.9 |
| **56** | H | $-CONH_2$ | H | H | N | 2.8 | 4.5 |
| **57** | H | $-CON(CH_3)_2$ | H | H | N | 130 | 17 |
| **58** | H | $-CONH(CH_2)_2$-(1*H*-imidazol-4-yl) | H | H | N | 69 | 12 |
| **59** | H | $-CONH(CH_2)_3$-(1*H*-imidazol-1-yl) | H | H | N | 230 | 25 |
| **60** | H | $-CONHCH_2$-(4-pyridyl) | H | H | N | 74 | 8.9 |
| **61** | H | $-CONHCH_2$-(3-pyridyl) | H | H | N | 51 | 2.1 |
| **62** | H | $-CONHCH_2C(CH_3)_2CH_2OH$ | H | H | N | 60 | 6.8 |
| **63** | H | $-CONHCH_2$-(2,6-dimethoxyphenyl) | H | H | N | 9.3 | 1.7 |
| | | 6-Substituents | | | | | |
| **64** | H | H | Br | H | N | 520 | 43 |
| **65** | H | H | $-CH_2CH_3$ | H | N | 660 | 21 |
| **66** | H | H | $-CH(CH_3)_2$ | H | N | 790 | 75 |
| **67** | H | H | $-C(CH_3)_3$ | H | N | >10 000 | >10 000 |
| **68** | H | H | $-CH_2OH$ | H | CH | 740 | 61 |
| **69** | H | H | -OPh | H | N | >10 000 | >10 000 |

**Table 1** (Continued)

| cmpd no. | R4 | R5 | R6 | R7 | X | kinase $IC_{50}$ (nM) CDK1 | CDK2 |
|---|---|---|---|---|---|---|---|
| | | | 7-Substituents | | | | |
| **70** | H | H | H | $-CH_3$ | CH | >10 000 | >10 000 |
| **71** | H | $-CH_3$ | H | $-CH_3$ | CH | >10 000 | >10 000 |
| **72** | H | Cl | H | $-CH_3$ | CH | >10 000 | >10 000 |
| | | | 4,5-Substituents | | | | |
| **73** | Cl | $-CH_3$ | H | H | N | 250 | 13 |
| **74** | Cl | $-OCH_3$ | H | H | N | 1700 | 54 |
| **75** | $-CH_3$ | $-NO_2$ | H | H | N | 87 | 4.6 |
| **76** | -CH=N-NH- | | H | H | N | 120 | 13 |
| **77** | -C(Cl)=N-NH- | | H | H | N | 83 | 2.2 |
| **78** | -N=N-NH- | | H | H | N | 150 | 9.5 |
| **79** | -S-CH=N- | | H | H | N | 43 | 7.1 |
| **80** | -S-CH=N- | | H | H | CH | 29 | 2.8 |
| **81** | -CH=CH-CH=N- | | H | H | N | 12 | 1.6 |
| **82** | -CH=CH-CH=N- | | H | H | CH | 15 | 1.5 |

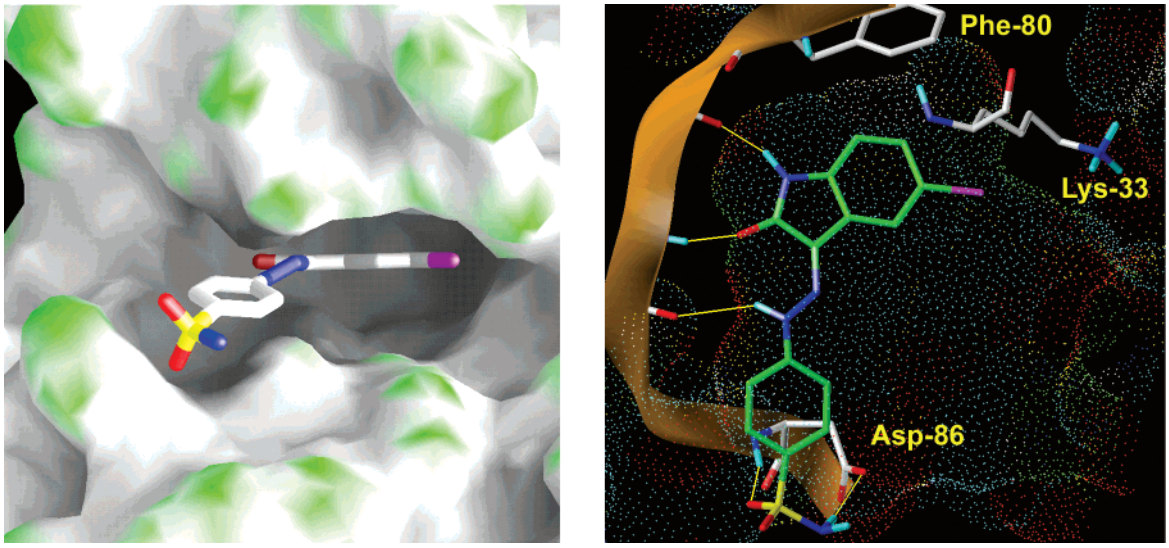



**Figure 1.** Crystal structure of compound **16** bound to CDK2. (A) Surface representation of CDK2 illustrating the binding site cavity. The oxindole portion of compound 16 was bound deep inside the pocket, and the sulfonamide functionality was positioned at the opening to the cleft. Inhibitor atoms are colored as follows: C, white; N, blue; O, red; S, yellow; Br, purple. (B) The binding cavity is illustrated with a dot surface. Hydrogen bonds between compound **16** and protein are shown as yellow lines. Atom coloring is as in A except the inhibitor carbon atoms are green and hydrogen atoms are light blue.

many other protein kinases, due to the bulkiness of the Phe-80 side chain. That part of the cleft appeared to be compatible with small substituents. The juxtaposition of the 5-position and Lys-33 suggested hydrogen-bond acceptors at that location on the oxindole might enhance inhibitor affinity. Lipophilic substituents at position-4 appeared to be appropriate for the relatively hydrophobic environment of that region of the protein (Val-18 and Leu-134). In addition to these observations regarding potential oxindole substitution, the structure also suggested that the sulfonamide group positioned at the cleft opening might provide a site for substitution that could be used to alter compound properties such as solubility and pharmacokinetics, without negatively affecting enzyme affinity and possibly increasing affinity and selectivity.

Molecular modeling was used to evaluate and select potential substituents at the 4−7 positions of the oxindole template. A semiautomated computational procedure was developed to generate and dock virtual analogues in this class of inhibitor to CDK2. The synthetic routes to the oxindole ring system that we employed generally utilized anilines as starting materials (see Chemistry section). A set of 410 anilines, considered compatible with synthesis conditions, was selected from commercially available anilines using a molecular weight cutoff of 250. Each of the selected aniline structures was then electronically converted to the corresponding analogue of compound **16**, and the hypothetical analogue was docked into the ATP binding site of the CDK2/cyclin A structure. The details of this docking procedure are provided in the experimental section. Synthetic targets were selected using a combination of molecular mechanics energy scores and careful visual inspection of each docked structure. The initial set of prepared compounds resulting from this protocol, e.g., compounds **22**, **27**, **31**, **49**, **50**, **56**, **79**, and **81** (Table 1), were potent inhibitors of CDK2 and provided the basis for subsequent synthetic efforts. The use of modeling for designing substituents on the pendant hydrazone or enamine portion of the inhibitors was not pursued extensively because of the complexities associated with evaluating the effects of solvent at the protein−solvent interface.

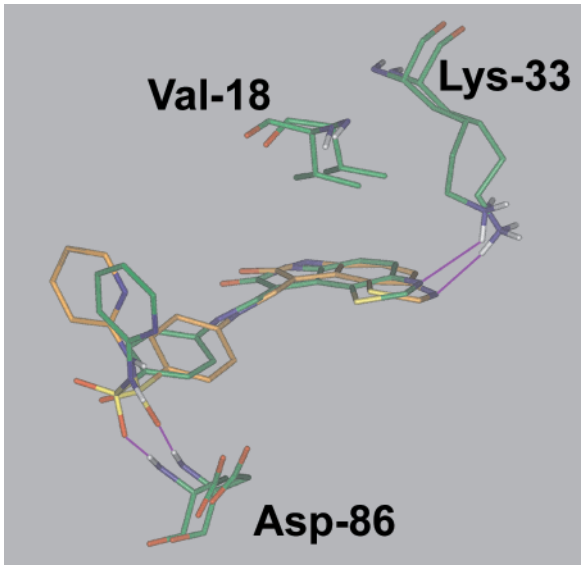



**Figure 2.** A comparison of the two complexes in the asymmetric unit of the crystal structure of compound **91** bound to CDK2/cyclin (A) Hydrogen bonds between inhibitor and protein are shown as purple lines. Atom coloring: H, white; protein C, green; inhibitor (complex 1) C, orange; inhibitor (complex 2) C, green; N, blue; O, red; S, yellow.

Results from compounds prepared in this study are discussed below and organized by regions of the core inhibitor template.

**Hydrazone/Enamine Linker.** The hydrazone linkage between the inhibitor's indolinone ring and phenyl group imposed a number of synthetic restrictions on the accessibility of potential inhibitors, limiting the diversity of phenyl substituents that could be explored. Replacement of the hydrazone connection with an enamine would provide significantly expanded access to substituents on both the indolinone and phenyl rings through well-established synthetic routes. This synthetic flexibility permitted the preparation of a diverse set of inhibitors that were used to develop an understanding of CDK2 inhibition and selectivity. Preparation and evaluation of hydrazone-enamine pairs of compounds demonstrated that the enamine substitution for hydrazone was essentially inconsequential to enzyme binding (compare compounds **17** and **18**, **22** and **23**, **79** and **80**, and **81** and **82**, Table 1). Molecular modeling evaluation was concordant with that observation.

Also consistent with structural and modeling considerations was the observation that the carbon atom of the enamine linkage could be substituted with groups larger than hydrogen, such as methyl, without negatively affecting inhibition of CDK2 (compare CDK2 $IC_{50}$ values for compounds **18** versus **19**, **20** versus **21**, and **23** versus **24)**. In recent patent literature, a group from Boerhringer Ingelheim describe related CDK inhibitors containing an aryl-substituted enamine linkage.[40]

**4-Substituents.** As pointed out above, binding of inhibitor **16** to CDK2 placed the 4-position in a hydrophobic region of the enzyme active site. Thus, hydrophobic substituents were expected to enhance affinity for CDK2, while hydrophilic groups would be detrimental. These expectations were realized as evidenced by the inhibitory activities of compounds **25**−**40** (Table 1). Compounds with lipophilic substituents such as ethyl, isopropyl, isobutyl, and isobutenyl (compounds **26**−**29**) were potent inhibitors of CDK2 with $IC_{50}$ values in the range of 1−8 nM.

The 4-position projected toward the opening of the binding site, and large hydrophobic substituents were accommodated, as illustrated by compounds **33**−**35**. In contrast, hydrophilic groups at the 4-position generally were detrimental to binding. For example, the 4-nitro and 4-amido derivatives **39** and **40** showed relatively weak inhibition of CDK2.

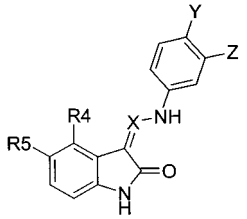
**5-Substituents.** Many of the compounds containing substituents at the 5-position were designed to interact with CDK2 via hydrogen bonding to the side chain of Lys-33 and/or the backbone NH of Asp-145. Carboxylic esters were particularly active inhibitors (Table 1), an observation consistent with those substituents being capable of forming a hydrogen bond with Lys-33 and positioning a hydrophobic group in the lipophilic region near position 4. The 5-ozazolyl-substituted derivatives **22**−**24** also fit that paradigm and were potent inhibitors of the enzyme. In addition, the amide group was found to be a favorable 5-substituent and provided a convenient handle for introducing water-solubilizing substituents (compounds **56**−**62**). Modeling suggested a particularly favorable steric fit for the dimethoxyphenyl group of amide **63**, consistent with its effective inhibition of CDK2. Charged substituents such as sulfonic and carboxylic acids provided no advantage over similar neutral substituents. For example, the carboxylic acid **52** was 10-fold weaker than the corresponding methyl ester **53** as an inhibitor of CDK2. Fluorine, iodine, and methyl substituents at the 5-position were also compatible with kinase binding. However, the dimethylamino-containing compound **48** was a relatively poor inhibitor.

**6-Substituents.** The inhibition activities of 6-substituted analogues (Table 1) were in accord with the relatively small CDK2 pocket adjacent to that position in the enzyme structure. Smaller substituents such as ethyl (**65**), isopropyl (**66**), and hydroxymethyl (**68**) moderately contribute to affinity as compared to the corresponding 6-hydrogen derivatives **17** and **18**. In contrast, no measurable inhibition was observed for compounds containing larger substituents such as *tert*-butyl (**67**) and phenoxy (**69**).

**7-Substituents.** In the crystal structure of compound **16** in complex with CDK2 (Figure 1), the 7-position of the inhibitor was oriented toward the side chain methylene group of Phe-80 with a C-7 to C$\beta$ distance of 3.3 Å. Therefore, substituents at position-7 would be expected to encounter unfavorable steric interactions with the enzyme. The lack of activity found for 7-methyl derivatives (see Table 1) was consistent with that expectation. For example, comparison of the CDK2 $IC_{50}$ values of the 5,7-dimethyl derivative **71** and the 5-methyl analogue **43** (see Table 1) indicated that 7-methyl substitution produced a >200-fold decrease in affinity.

**4,5-Disubstituents.** Disubstitution at the 4- and 5-positions can provide highly potent inhibitors of CDK2. As shown in Table 1, compounds with 4,5-fused heterocycles that contain a hydrogen bond acceptor at the 5-position and hydrophobic character at the 4-position, such as compounds **80** and **81**, display high affinity for CDK2. The structure of compound **91** bound to the CDK2/cyclin A complex illustrates the potential for hydrogen bonds to the side chain of Lys-33 and the

**Table 2.** CDK1 and CDK2 Inhibitory Activities for Compounds **83**−**109**




| | | | | | | kinase $IC_{50}$ (nM) | |
|---|---|---|---|---|---|---|---|
| cmpd no. | R4 | R5 | Y | Z | X | CDK1 | CDK2 |
| **83** | | -S−CH═N- | $-SO_2NHCH_3$ | H | CH | 64 | 5.6 |
| **84** | | -S−CH═N- | $-SO_2N(CH_3)_2$ | H | CH | 50 | 4.6 |
| **85** | | -S−CH═N- | $-SO_2NH(CH_2)_2OH$ | H | CH | 41 | 4.7 |
| **86** | | -S−CH═N- | $-SO_2NH(CH_2)_2$-imidazol-5-yl | H | CH | 38 | 3.6 |
| **87** | | -S−CH═N- | $-SO_2NH(CH_2)_2O(CH_2)_2OH$ | H | CH | 12 | 0.54 |
| **88** | | -S−CH═N- | $-SO_2NH[(CH_2)_2O]_4CH_3$ | H | CH | 72 | 4.5 |
| **89** | | -S−CH═N- | $-SO_2N(CH_3)[(CH_2)_2O]_4CH_3$ | H | CH | 45 | 1.0 |
| **90** | | -S−CH═N- | $-SO_2NH$-phenyl | H | CH | 41 | 4.3 |
| **91** | | -S−CH═N- | $-SO_2NH$-pyrid-2-yl | H | CH | 100 | 9.7 |
| **92** | | -S−CH═N- | $-SO_2N(CH_3)$-pyrid-2-yl | H | CH | 64 | 5.6 |
| **93** | | -S−CH═N- | $-SO_2NH$-2,6-dimethylphenyl | H | CH | 14 000 | 281 |
| **94** | | -S−CH═N- | $-SO_2NHCH_2$-phenyl | H | CH | 52 | 5.6 |
| **95** | | -S−CH═N- | $-SO_2NH$-isoquinol-2-yl | H | CH | 42 | 9.5 |
| **96** | | -S−CH═N- | $-SO_2NHC(NH_2)$═NH | H | CH | 45 | 3.3 |
| **97** | | -S−CH═N- | $-SO_2NHCOCH_3$ | H | CH | 910 | 75 |
| **98** | H | H | $-SO_2NHCH_3$ | H | CH | 2900 | 560 |
| **99** | H | H | $-SO_2NH(CH_2)_2N(CH_3)_2$ | H | CH | 5500 | 1000 |
| **100** | H | H | $-SO_2NH$-thiazol-2-yl | H | CH | 3800 | 1000 |
| **101** | H | H | $-SO_2NHC(NH_2)$═NH | H | CH | 2500 | 660 |
| **102** | | -S−CH═N- | $-SO_2CH_3$ | H | CH | 39 | 5.7 |
| **103** | | -S−CH═N- | $-CH_2SO_2NH_2$ | H | CH | 100 | 7.5 |
| **104** | | -S−CH═N- | $-CH_2SO_2NHCH_3$ | H | CH | 170 | 26 |
| **105** | | -S−CH═N- | $-CH_2SO_2NHCH_3$ | H | N | 56 | 5.7 |
| **106** | | -S−CH═N- | $-CH_2SO_2NH(CH_2)_2OH$ | H | CH | 200 | 13 |
| **107** | | -S−CH═N- | $-CH_2SO_2CH_3$ | H | CH | 1200 | 50 |
| **108** | | -S−CH═N- | $-CH_2SO_2CH_2$- | | CH | 31 | 14 |
| **109** | H | oxazol-5-yl | $-CH_2SO_2CH_2$- | | CH | 19 | 8.9 |

backbone NH of Asp-145, although the inhibitor was found to bind somewhat differently in the two complexes within the asymmetric unit. The two complexes are compared in Figure 2. In complex 1, the thiazole nitrogen atom of compound **91** was 3.1 Å from the amino nitrogen of Lys-33 and 3.5 Å from the backbone nitrogen of Asp-145. The corresponding distances in complex 2 were 3.3 and 3.8 Å, respectively. Complex 1 appeared to be the more relevant of the two complexes on the basis of other CDK2/cyclin A/inhibitor crystal structures that often showed no electron density for the inhibitor in complex 2.

**N-Substituted Sulfonamides.** As shown in Figure 1, the sulfonamide moiety of compound **16** interacts with Asp-86 at the opening to the binding cleft of CDK2. The sulfonamide moiety forms hydrogen bonds with the backbone NH and the side chain carboxylate functionality of Asp-86. The position of the sulfonamide at the solvent interface suggested that sulfonamide substituents might have little interaction with the enzyme and would project into solution. This orientation at the mouth of the binding cleft suggested that sulfonamide substituents might be used to modify properties such as solubility and pharmacokinetic parameters without detrimentally affecting enzyme affinity.

The inhibition data shown in Table 2 illustrates the relative insensitivity of CDK2 to substituents on the sulfonamide group. One exception was the 2,6-dimethylphenyl analogue **93**, which was significantly weaker as an inhibitor of CDK2 than the other substituted sulfonamides. The poor activity of this compound presumably was related to the expected steric constraints imposed by the ortho-methyl groups of the phenyl moiety.

Our initial assumption was that both hydrogen bonds between the sulfonamide and protein were important to affinity. However, the inhibitory activities of disubstituted sulfonamide derivatives and crystal structures of several monosubstituted sulfonamide analogues bound to CDK2 indicated that the hydrogen bond between sulfonamide and backbone NH played the more important role in binding. As shown in Table 2, similar inhibition activities were observed for $-SO_2N(CH_3)R$ and $-SO_2N(H)R$ pairs of compounds: **83** versus **84**, **88** versus **89**, and **91** versus **92**. These data suggest that the sulfonamide NH−carboxylate (Asp-86) hydrogen bond observed in the crystal structure of the CDK2 complex with compound **16** was not significantly contributing to the protein/ligand affinity. This conclusion was supported by additional crystallographic data. For example, the *N*-methylsulfonamide derivative **83**, which is equipotent to the corresponding unsubstituted sulfonamide **80**, was found to bind to CDK2 with a sulfonamide oxygen H-bonded to the backbone NH of Asp-86 but with its *N*-methyl group, not its NH, oriented toward the carboxylate of Asp-86 (see Figure 3). The amino(imino)methyl substituted sulfonamide analogue **101** was found to bind to CDK2 with its sulfonamide NH positioned away from Asp-86 (see Figure 3). The heterocyclic-substituted sulfonamide derivatives **92** and

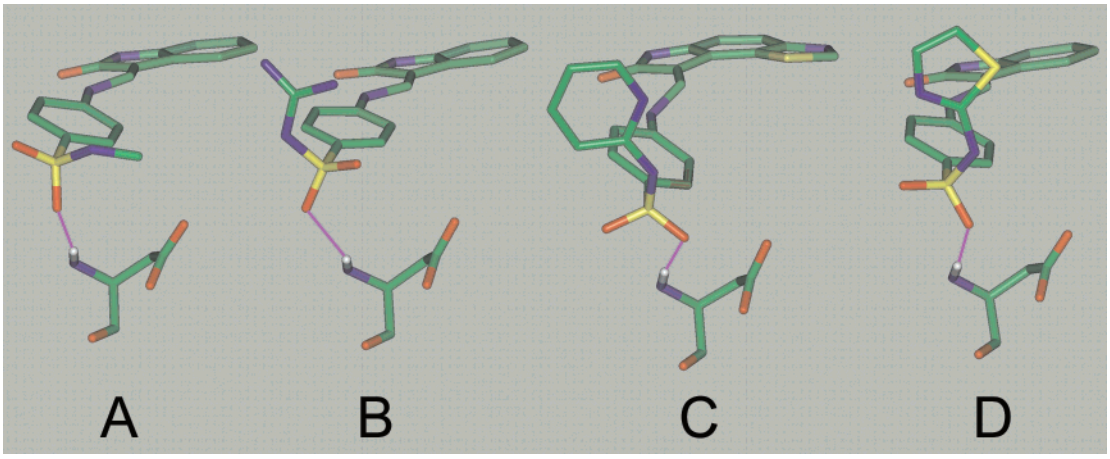



**Figure 3.** Crystal structures of CDK2 bound to compounds (A) **98**, (B) **101**, (C), **91**, and (D) **100**, illustrating the interaction between inhibitor and Asp-86. Hydrogen bonds are indicated as purple lines. Atom coloring: H, white; C, green; N, blue; O, red; S, yellow.

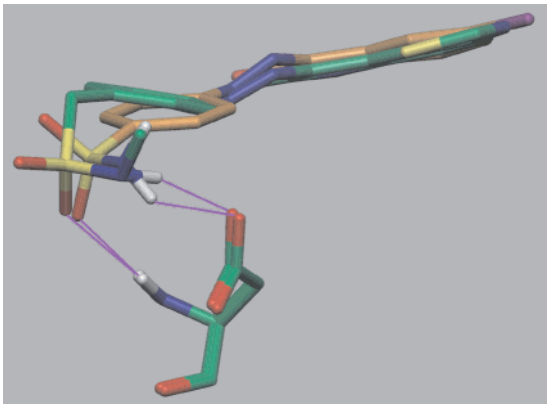


**Figure 4.** Crystal structure comparison of compounds **105** and **16** bound to CDK2. Coloring as in Figure 3, except carbon atoms of compound **16** are orange.

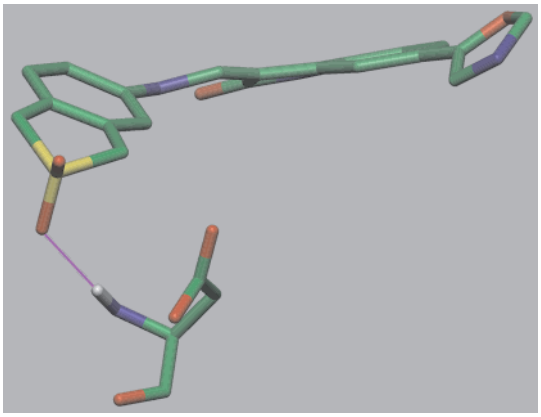


**Figure 5.** Crystal structure of compound **109** bound to CDK2. Coloring as in Figure 3.

**100** both bound to the kinase with the sulfonamide NH oriented toward the carboxylate of Asp-86 but at an N-to-O distance of 5 and 4 Å, respectively. In each of the above structures, the sulfonamide oxygen was H-bonded to the backbone NH of Asp-86, suggesting an importance to that interaction. As will be discussed below, the latter H-bond was a consistent feature in two other related sulfone-containing compounds.

**Sulfonamide Replacements.** In concert with the conclusion that the sulfonamide NH was not important to binding, the methyl sulfone analogue **102** was found to strongly inhibit CDK2, as shown in Table 2. Interestingly, compounds in which the sulfonamide was linked to the phenyl ring by a methylene group were also significantly active, as exemplified by compounds **103** and **105**. An X-ray crystal structure of compound **105** bound to CDK2 showed that the inhibitor was able to adopt a conformation that provided interactions between the sulfonamide and Asp-86 similar to those observed for compound **16**, as illustrated in Figure 4.

A crystal structure of the fused cyclic sulfone **109** bound to CDK2 showed a hydrogen bond from the sulfone to the backbone NH of Asp-86 (see Figure 5), similar to that observed in the other CDK2 complexes described above.

**Kinase Selectivity.** The compounds in the series described here were generally about 10-fold more potent as inhibitors of CDK2 than of CDK1. The correlation coefficient relating $pIC_{50}$ values for CDK2 versus CDK1 was 0.90. This observation is in accord with the relatively high overall sequence similarity (69% identity) between the two kinases and the essentially identical composition of the ATP binding sites (residues 79, 84, and 85 differ but their side chains project away from the ATP site). The compounds displayed a range of activity against a panel of other protein kinases but were generally selective for CDK2. A typical example is compound **91**, which showed the following inhibition activities [kinase, $IC_{50}$ (nM)]: CDK4, 130; c-fms, 950; erbB-2, >10000; erk-2, 21000; gsk-3, 56; lck, 980; mek, 25000; p38, 32000; src, 440; raf, 7600; tie-2, 3500; VEGFR-2, 22.

**Cellular Activities.** The most potent and CDK2-selective compounds were evaluated in two cellular assays: an anti-proliferation assay and a mechanistic assay that measures progression from G1- to S-phase (example data shown in Table 3). The compounds inhibited proliferation of tumor cells, with $IC_{50}$ values consistent with CDK2 inhibitors that are competitive with respect to ATP. The anti-proliferative activity of the compounds was up to 8-fold selective for the tumor cells relative to the HFF normal cell line. The compounds were also active in blocking progression of cells into S-phase, consistent with the role of CDK2 activity in the regulation of G1/S phase progression. The anti-proliferative activity of compound **91** has been shown

**Table 3.** Cell-Based Data for a Selected Set of Compounds ($IC_{50}$, $\mu$M)

| cmpd no. | G1/S | HFF | HT29 | MDAMB468 | RKO | SW620 |
|---|---|---|---|---|---|---|
| **27** | 1.8 | 5.9 | 14. | 4.4 | 1.4 | 4.8 |
| **54** | 2.3 | 3.6 | 2.0 | 2.0 | 0.89 | 1.4 |
| **63** | 1.1 | 1.0 | 0.66 | 0.17 | 1.3 | 0.79 |
| **81** | 0.29 | 1.9 | 3.1 | 0.81 | 0.39 | 0.87 |
| **83** | 0.65 | 3.2 | 3.0 | 1.8 | 0.59 | 2.1 |
| **88** | 5.4 | 5.0 | 4.4 | 2.4 | 1.5 | 2.9 |
| **90** | 3.3 | 4.3 | 2.2 | 1.4 | 0.91 | 1.1 |
| **91** | 2.6 | 13. | 5.1 | 6.8 | 1.7 | 10. |
| **94** | 7.8 | 2.5 | 1.8 | 2.2 | 0.65 | 2.3 |
| **102** | 8.3 | 5.9 | 2.7 | 4.5 | 0.95 | 2.8 |
| **108** | 1.5 | 7.9 | 6.2 | 6.0 | 1.1 | 4.7 |

to arrest cells and protect normal cells from chemotherapy-induced toxicity.[11] These data were consistent with an anti-proliferative mechanism expected for inhibition of CDK2 and suggested that this series of inhibitors has therapeutic potential for treating proliferative disorders, including chemotherapy-induced alopecia.

## Conclusions

The compounds described here represent a novel class of CDK2 inhibitor. Crystallographic analysis showed that the initial lead compound was bound in the ATP site of the kinase, and structure-assisted methods provided an effective means of developing a large set of compounds with low nanomolar CDK2 $IC_{50}$ values. Binding interactions were studied through analogue synthesis and X-ray crystallographic analysis of several CDK2/inhibitor complexes. A hydrogen bond between inhibitors and the backbone NH of Asp-86 near the opening of the ATP binding cleft of CDK2 was of particular interest and appeared to play a significant role in affinity. Members of this series of inhibitors cause an arrest of the cell cycle and exhibit a selective killing effect on several tumor cell lines.[41] In addition, these compounds may have utility in the prevention of chemotherapy-induced hair loss.[11]

## Experimental Section

**General Methods.** $^1$H NMR spectra were obtained on VARIAN Unity Plus NMR spectrophotometers at 300 or 400 MHz. Mass spectra were obtained on Micromass Platform II mass spectrometers from Micromass Ltd., Altrincham, UK, using either atmospheric chemical ionization (APCI) or electrospray ionization (ESI). Analytical thin-layer chromatography (TLC) was used to verify the purity of some intermediates that could not be isolated or that were too unstable for full characterization and to follow the progress of reactions. Merck Silica gel 60 (230−400 mesh) was employed for the flash chromatographic purification of some compounds.

**Procedure A**. A typical procedure for the synthesis of isatin[25] is exemplified by the preparation of 6*H*-[1,3]thiazolo-[5,4-*e*]indole-7,8-dione. To a 1-L flask was added a magnetic stir bar, 85 g of sodium sulfate, and 100 mL of water. The mixture was magnetically stirred until all the solids were dissolved. To the resultant aqueous solution was added a solution of 6-aminobenzothiazole (4.96 g, 33.0 mmol) in 50 mL of 1 N aqueous hydrochloric acid and 10 mL of ethanol. The mixture was stirred, and chloral hydrate (6.0 g, 36 mmol) was added. To the resultant solution was added a solution of hydroxylamine hydrochloride (7.50 g, 108 mmol) in 30 mL of water. The final mixture was heated with stirring to a gentle boil until all solids dissappeared, and heating was continued for an additional 15 min. The flask was removed from the heat, and the solution was poured onto 500 g of ice. The mixture was stirred as the product precipitated from solution. The precipitate was collected by suction filtration, washed thoroughly with water, filtered, and air-dried to provide 6.9 g (94%) of *N*-benzothiazol-6-yl-2-hydroxyimino-acetamide, $^1$H NMR (DMSO-$d_6$): $\delta$ 12.2 (s, 1H), 10.4 (s, 1H), 9.2 (s, 1H), 8.5 (s, 1H), 7.9 (d, 1H), 7.7 (m, 1H), 7.7 (s, 1H); APCI *m*/*z* 220 $(M-H)^-$. To a 1-L three-neck round-bottom flask was placed a magnetic stir bar and 100 mL of concentrated sulfuric acid. The flask was fitted with a thermometer to monitor the temperature of the reaction. The sulfuric acid was heated to 100 °C, and 10.0 g (45.2 mmol) of *N*-benzothiazol-6-yl-2-hydroxyimino-acetamide was added slowly. The solution was heated for ∼1 h, and the reaction mixture was poured into 750 g of ice and water. The residual reaction mixture in the reaction vessel was washed out with an additional 20 mL of cold water. The aqueous slurry was stirred for about 1 h and filtered. The solid was washed thoroughly with water, filtered, and air-dried to yield 4.3 g (46%) of 6*H*-[1,3]thiazolo[5,4-*e*]indole-7,8-dione: $^1$H NMR (DMSO-$d_6$): $\delta$ 11.1 (s, 1H), 9.2 (s, 1H), 8.2 (d, 1H), 7.0 (d, 1H); APCI *m*/*z* 203 $(M-H)^-$.

**Procedure B.** A second method for 1H-indol-2,3-dione (isatin) synthesis[42] is exemplified by the preparation of 6-phenoxy-1H-indole-2,3-dione. To a stirred solution of 1.0 g (6.0 mmol) of chloral hydrate in 25 mL of water was added 7.0 g (22 mmol) of sodium sulfate decahydrate, followed by a solution of 1.18 g (17.0 mmol) of hydroxylamine hydrochloride in 10 mL of water. A solution of 1.0 g (5.4 mmol) of 3-phenoxyaniline in 10 mL of 1.0 N HCl was then added with stirring. The resulting suspension was warmed, and 40 mL of 95% EtOH was added to dissolve the suspension. The solution was refluxed for 0.75 h and then cooled to ambient temperature. The resulting solid was collected by vacuum filtration and air-dried to afford 0.95 g (67%) of 2-hydroxyimino-*N*-(3-phenoxyphenyl)acetamide as a solid: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.42 (d, $J$ = 8.4 Hz, 1H), 7.06 (d, $J$ = 7.9 Hz, 2H), 7.18 (t, $J$ = 7.3 Hz, 1H), 7.25−7.50 (m, 5H), 7.64 (s, 1H), 10.29 (s, 1H), 12.21 (s, 1H); APCI: *m*/*z* 255 $(M-H)^-$. A suspension of 0.15 g (0.58 mmol) of 2-hydroxyimino-*N*-(3-phenoxyphenyl)acetamide in 0.4 mL of $BF_3$ etherate was heated to 85 °C for 0.75 h. The mixture was cooled to room temperature, and 10 g of crushed ice was added. The resulting solid was collected by vacuum filtration and subjected to flash chromatography on silica gel (hexane/EtOAc 1.5:1) to afford 6-phenoxy-1H-indole-2,3-dione as a solid (0.018 g, 13%): $^1$H NMR (DMSO-$d_6$): $\delta$ 6.44 (d, $J$ = 2.0 Hz, 1H), 6.56 (dd, $J$ = 2.0, 8.4 Hz, 1H), 7.08 (d, $J$ = 8.2 Hz, 1H), 7.22−7.29 (m, 1H), 7.38−7.46 (m, 2H), 7.52 (d, $J$ = 8.4 Hz, 1H), 9.05 (s, 1H); APCI: *m*/*z* 255 $(M+Na)^+$.

**Procedure C.** A third method for 1H-indol-2,3-dione (isatin) synthesis:[26] preparation of 4-isopropoxy-1H-indol-2,3-dione and conversion to 4-[*N*′-(4-isopropoxy-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazino]-benzenesulfonamide (**31**). A solution of 3.78 g (25.0 mmol) of 3-isopropoxy aniline and 5.46 g (25.0 mmol) of di-*tert*-butyl dicarbonate in 25 mL of THF was heated to reflux for 2 h. The solution was cooled to ambient temperature, and solvent was removed in vacuo. The residue was dissolved in 100 mL of EtOAc, and the solution was washed with three 50-mL portions of 0.5 M citric acid and 50 mL of brine. The solution was dried over $MgSO_4$, and removal of solvent in vacuo afforded *N*-(*tert*-butyloxy-carbonyl)-3-isopropoxyaniline as a white solid (5.75 g, 92%): mp 79−81 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 1.21 (d, $J$ = 6.0 Hz, 6H), 1.43 (s, 9H), 4.46 (septet, $J$ = 6 Hz, 1H), 6.47 (dd, $J$ = 2.1, 8.1 Hz, 1H), 6.94 (d, $J$ = 8.1 Hz, 1H), 7.0−7.1 (m, 2H), 9.23 (s, 1H); APCI: *m*/*z* 274 $(M+Na)^+$. To a solution of 2.5 g (10 mmol) of *N*-(*tert*-butyloxycarbonyl)-3-isopropoxyaniline in 15 mL of dry THF at −78 °C was added 15 mL (25 mmol) of 1.7 M *tert*-butyllithium in hexanes. The mixture was stirred at −20 °C for 2 h. A solution of 1.84 g (12.5 mmol) of diethyl oxalate in 10 mL of dry THF was added slowly over 5 min, and the mixture was stirred at −20 °C for 2 h. The reaction mixture was then poured into 100 mL of 1.0 N HCl and extracted with two 100-mL portions of EtOAc. Solvent was removed in vacuo, and the residue was dissolved in 100 mL of a 1:1 mixture of EtOH and 6 N HCl and heated to reflux for 1 h. The mixture

was cooled to ambient temperature and was extracted with four 100-mL portions of EtOAc. The combined extracts were evaporated to dryness to provide crude 4-isopropoxy-1H-indol-2,3-dione, which was dissolved in 10 mL of EtOH containing 0.50 g (2.2 mmol) of 4-hydrazinobenzenesulfonamide hydrochloride. The solution was heated to 80 °C for 1 h and cooled to ambient temperature. The resulting solid was collected by vacuum filtration and purified by flash chromatography on silica gel (EtOAc/hexane 3:2) to afford the title compound as a yellow solid (0.052 g, 1.4%): mp >250 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 3.35 (d, $J$ = 6 Hz, 6H), 4.74 (septet, $J$ = 6 Hz, 1H), 6.48 (d, $J$ = 7.7 Hz, 1H), 6.69 (d, $J$ = 8 Hz, 1H), 7.14−7.2 (m, 3H), 7.47 (d, $J$ = 8.7 Hz, 2H), 7.75 (d, $J$ = 8.7 Hz, 2H), 11.01 (s, 1H), 12.79 (s, 1H); APCI: $m/z$ 373 $(M-H)^-$. Anal. ($C_{17}H_{18}N_4O_4S$) C, H, N, S.

**Procedure D.** A general method for 1,3-dihydro-indol-2-one (oxindole) synthesis:[29] preparation of 2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid methyl ester and conversion to 2-oxo-3-(4-sulfamoyl-phenylamino-methylene)-2,3-dihydro-1H-indole-5-carboxylic acid methyl ester (**53**). A solution of 2.66 g (20.0 mmol) of ethyl (methylthio)acetate dissolved in 200 mL of dichloromethane was cooled with stirring to −70 °C and 2.7 g (20 mmol) of sulfuryl chloride was added. The reaction was stirred for 30 min at −70 °C, and a solution of 3.0 g (20 mmol) of methyl 4-aminobenzoate and 4.3 g (20 mmol) of Proton Sponge in 250 mL of dichloromethane was added dropwise over 1 h. The resulting pink slurry was treated with 2.3 g (23 mmol) of TEA in one portion, and the solution was allowed to warm to room temperature. The solution was washed with three 250-mL portions of water, dried over $MgSO_4$, and concentrated to give an oil, which was subjected to chromatography on silica gel eluting with hexane:EtOAc (1:1) to yield 2.0 g (42% yield) of 3-methylthio-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid methyl ester: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.97 (s, 3H), 3.35 (s, 3H), 4.67 (s, 1H), 6.97 (d, $J$ = 8.2 Hz, 1H), 7.84 (s, 1H), 7.91 (d, $J$ = 8.2 Hz, 1H), 10.97 (s, 1H). A solution of 2.0 g (8.4 mmol) of 3-methylthio-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid methyl ester in 20 mL of acetic acid was treated with 10 g of zinc powder. The reaction mixture was stirred for 2 h at room temperature, filtered through Celite, and concentrated to dryness. The residue was chromatographed on silica gel eluting with hexane:EtOAc (1:1) to yield 1.6 g (99% yield) of 2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid methyl ester as a pink solid: $^1$H NMR (DMSO-$d_6$): $\delta$ 3.52 (s, 2H), 3.77 (s, 3H), 6.87 (d, $J$ = 8.2 Hz, 1H), 7.74 (s, $J$ = 1H), 7.80 (d, $J$ = 8.2 Hz, 1H), 10.72 (br s, 1H). Conversion to the 3-dimethylamino-methylene-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid methyl ester (mixture of *E* and *Z* isomers) was carried out via procedure F in 49% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 3.29 *Z* (s, 6H), 3.31 *E* (s, 6H), 3.76 *Z* (s, 3H), 3.76 *E* (s, 3H), 6.74 *Z* (d, $J$ = 8.1 Hz, 1H), 6.81 *E* (d, $J$ = 8.2 Hz, 1H), 7.47−7.50 *Z* (m, 1H), 7.50−7.52 *E* (m, 1H), 7.57 *E* (dd, $J$ = 1.3, 8.2 Hz, 1H), 7.74 *Z* (s, 1H), 7.89 *Z* (s, 1H), 7.94 *E* (s, 1H), 10.33 *Z* (bs, 1H), 10.43 *E* (bs, 1H). The title compound was prepared in 41% yield from 3-[(dimethylamino)methylene]oxindole-5-carboxylic acid methyl ester and 4-aminobenzenesulfonamide according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 3.81 (s, 3H), 6.92 (d, $J$ = 8.2 Hz, 1H), 7.26 (s, 2H), 7.60 (d, $J$ = 8.4 Hz, 2H), 7.69 (d, $J$ = 8.2 Hz, 1H), 7.75 (d, $J$ = 8.4 Hz, 2H), 8.29 (s, 1H), 8.86 (d, $J$ = 12.4 Hz, 1H), 10.80 (d, $J$ = 12.4 Hz, 1H), 10.94 (s, 1H); APCI $m/z$ 372 $(M-1)^-$. Anal. ($C_{17}H_{15}N_3O_5S$) C, H, N, S.

**Procedure E.** A general method for condensing isatins and phenylhydrazines: preparation of 3-{[4-(aminosulfonyl)phenyl]-hydrazono}-2-oxo-2,3-dihydro-1H-indole-5-sulfonamide (**50**)**.** A solution of 2,3-dioxo-5-indolinesulfonamide (0.29 g, 1.3 mmol) and 4-hydrazinobenzenesulfonamide hydrochloride (0.32 g, 1.4 mmol) in 26 mL of ethanol was stirred at reflux for 2 h. Solid was collected from the hot suspension by filtration and was air-dried to give 0.43 g (83%) of the title compound, mp >250 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 7.04 (d, $J$ = 8.4 Hz, 1H), 7.25 (s, 2H), 7.26 (s, 2H), 7.60 (d, $J$ = 8.9 Hz, 2H), 7.70 (dd, $J$ = 8.2, 1.9 Hz, 1H), 7.78 (d, $J$ = 8.7 Hz, 2H), 7.98 (d, $J$ = 1.6 Hz, 1H), 11.43 (s, 1H), 12.75 (s, 1H); APCI $m/z$ 395 $(M)^-$. Anal. ($C_{14}H_{13}N_5O_5S_2 \cdot {}^1/_2H_2O$) C, H, N, S.

**Procedure F.** A method for 3-[(dimethylamino)methylene]-1,3-dihydro-2*H*-indol-2-one formation: preparation of 8-[(dimethylamino)methylene]-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-e]indol-7-one. To a suspension of 1.0 g (5.3 mmol) of 6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one in 7.5 mL of DMF was added 1.38 g (6.80 mmol) of *N*,*N*-dimethylformamide-di-*tert*-butyl acetal. The mixture was stirred at ambient temperature for 1 h and diluted with 7.5 mL of $Et_2O$. The resulting precipitate was isolated by filtration to afford the title compound as a tan solid (1.0 g, 77%): $^1$H NMR (DMSO-$d_6$): $\delta$ 3.33 (bs, 3H), 3.59 (bs, 3H), 6.97 (d, $J$ = 8.4, 1H), 7.33 (s, 1H), 7.62 (d, $J$ = 8.4, 1H), 9.13 (s,1H), 10.29 (s, 1H); APCI- MS: $m/z$ 246 $(M+H)^+$.

**Procedure G.** A general method for enamine formation: preparation of 4-{[(7-oxo-6,7-dihydro-8*H*-[1,3]thiazolo[5,4-*e*]-indol-8-ylidene)methyl]amino}-*N*-(2-pyridinyl)benzenesulfonamide (**91**). To a 25-mL round-bottom flask was added a stir bar, 246 mg (1.00 mmol) of 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one, 249 mg (1.00 mmol) of sulfapyridine, and 10 mL of ethanol. The flask was fitted with a water-cooled reflux condenser, and the mixture was heated to reflux using an oil bath with stirring for 18 h. The reaction was allowed to cool and was filtered. The precipitate was washed with excess ethanol and dried under vacuum to yield 321 mg (71%) of the title compound: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.87 (br t, 1H), 7.12 (d, $J$ = 8.4 Hz, 1H), 7.16 (br d, $J$ = 8.2 Hz, 1H), 7.54 (d, $J$ = 8.7 Hz, 2H), 7.72 (dt, $J$ = 1, 7.3 Hz, 1H), 7.82 (d, $J$ = 8.4 Hz, 1H), 7.87 (d, $J$ = 8.7 Hz, 2H), 8.04 (br d, 1H), 8.06 (d, $J$ = 12.0 Hz, 1H), 9.27 (s, 1H), 10.91 (s, 1H), 11.14 (d, $J$ = 12.0 Hz, 1H); APCI+ MS $m/z$ 450 $(M+H)^+$. Anal. ($C_{21}H_{15}N_5O_3S_2$) C, H, N, S. Note: One equivalent of strong acid, e.g., HCl or methanesulfonic acid, is generally required in this reaction. The acid can be supplied as the aniline salt or as a separate component. Similar conditions can be used for condensing anilines with 3-dimethylaminomethylene-, 3-*tert*-butoxymethylene-, and 3-hydroxymethylene-substituted 2,3-dihydro-1H-indol-2-ones.

**Procedure H.** A method for 5-N-substituted amide formation: preparation of 2-oxo-3[(4-sulfamoyl-phenyl)-hydrazono]-2,3-dihydro-1H-indole-5-carboxylic acid dimethylamide (**57**). 2-Oxo-3-[(4-sulfamoyl-phenyl)-hydrazono]-2,3-dihydro-1H-indole-5-carboxylic acid was prepared from 1H-indole-2,3-dione-5-carboxylic acid and 4-sulfonamidophenyl-hydrazine hydrochloride according to procedure E. To a suspension of 2.75 g (7.63 mmol) of the 2-oxo-3[(4-sulfamoyl-phenyl)-hydrazono]-2,3-dihydro-1H-indole-5-carboxylic acid in 20 mL of DMF was added 1.38 mL (8.03 mmol) pentafluorophenyltrifluoroacetate (PFPTFA), 0.69 mL (8.53 mmol) pyridine, and the suspension was stirred under $N_2$ for 20 min. TLC (silica gel, 20% MeOH/$CH_2Cl_2$) indicated residual starting material remained, and the reaction was treated with 10 mL DMF and additional PFPTFA and pyridine (equal portions to above). The reaction was stirred overnight and then poured into 400 mL of ether. The solution was washed with two 500-mL portions of water, and 300 mL of EtOAc was added to dissolve precipitate. The solution was washed with 500 mL of water, dried over $Na_2SO_4$, filtered through silica gel and concentrated to remove ether. The resulting solid was collected by filtration, washed with 50 mL of 1:1 ethyl acetate:hexanes, and dried overnight in a vacuum oven at 70 °C to give the title compound as a bright yellow solid (2.30 g, 57%): mp >230 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 12.77 (s, 1H), 11.68 (s, 1H), 8.32 (d, $J$ = 1.9 Hz, 1H), 8.11 (dd, $J$ = 1.9 Hz, $J$ = 8.2 Hz, 1H), 7.79 (d, $J$ = 8.9 Hz, 2H), 7.67 (d, $J$ = 8.9 Hz, 2H), 7.28 (s, 2H), 7.16 (d, $J$ = 8.4 Hz, 1H); APCI: $m/z$ 525 $(M-H)^-$. Anal. ($C_{21}H_{11}N_4O_5SF_5$) C, H, N. To 100 mg (0.190 mmol) 2-oxo-3[(4-sulfamoyl-phenyl)-hydrazono]-2,3-dihydro-1H-indole-5-carboxylic acid pentafluorophenyl ester in 5 mL of acetonitrile was added 50 $\mu$L (5.6 M in ethanol, 0.28 mmol) of a solution of dimethylamine and 20 $\mu$L (0.25 mmol) of pyridine, and the reaction was stirred overnight. The solution was concentrated, and the resulting solid was triturated under EtOAc to give the title compound as a yellow solid (39 mg, 53%): mp >230 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 12.71 (s, 1H), 11.22 (s, 1H), 7.75 (d, $J$ = 8.8 Hz, 2H), 7.60 (s, 1H),

7.58 (d, $J$ = 8.8 Hz, 2H), 7.31 (dd, $J$ = 1.7, 8.1 Hz, 1H), 7.23 (s, 2H), 6.93 (d, $J$ = 8.0 Hz, 1H), 2.95 (s, 6H); APCI: $m/z$ 386 (M-H). Anal. ($C_{17}H_{17}N_5O_5S\cdot{}^1/_2H_2O$) C, H, N.

**Procedure I.** A general method for introducing 4-substituents via palladium-catalyzed coupling: preparation of 4-(*N′*-{4-[2-(4-hydroxyphenyl)-vinyl]-2-oxo-1,2-dihydro-indol-3-ylidene}-hydrazino)benzenesulfonamide (**34**). A mixture of 1.0 g (3.6 mmol) of 4-iodo-1H-indole-2,3-dione,[43] 0.42 g (4.2 mmol) of TEA, 0.06 g (0.27 mmol) of palladium(II) acetate, 0.16 g (0.54 mmol) of tri-*o*-tolylphosphine, and 5.0 g (4.2 mmol) of a 10% solution of 4-vinylphenol in propylene glycol was suspended in 15 mL of dry acetonitrile in a Pyrex sealed tube and heated to 100 °C for 4 h. The mixture was cooled to room temperature, quenched with 50 mL of 10% hydrochloric acid, and extracted with two 100-mL portions of EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated to give a brown solid, which was subjected to chromatography on silica gel, eluting with hexane:EtOAc (3:1), to yield 0.125 g (13%) of *trans*-4-[2-(4-hydroxyphenyl)-vinyl]-1H-indole-2,3-dione as a red solid: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.6−7.6 (m, 8H), 7.77 (d, $J$ = 16.4 Hz, 1H), 9.85 (bs, 1H), 11.00 (bs, 1H); APCI $m/z$ 264 (M-1)$^-$. Condensation of *trans*-4-[2-(4-hydroxyphenyl)-vinyl]-1H-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E gave the title compound in 27% yield as an orange solid: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.78 (d, $J$ = 7.8 Hz, 1H), 6.88 (d, $J$ = 8.7 Hz, 2H), 7.26 (t, $J$ = 7.8 Hz, 1H),), 7.29 (s, 2H), 7.36 (d, $J$ = 16.5 Hz, 1H), 7.47 (d, $J$ = 7.8 Hz, 1H), 7.53 (d, $J$ = 8.7 Hz, 2H), 7.57 (d, $J$ = 8.7 Hz, 2H),), 7.81 (d, $J$ = 8.7 Hz, 2H), 8.03 (d, $J$ = 16.5 Hz, 1H), 9.78 (s, 1H), 11.17 (s, 1H), 13.02 (s, 1H); APCI $m/z$ 433 (M-1)$^-$. Anal. ($C_{22}H_{18}N_4O_4S\cdot{}^1/_2H_2O$) C, H, N, S.

**8-(Methylsulfanyl)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]-indol-7-one (11).** Under a nitrogen atmosphere, a solution of 116 mL (121 g, 0.900 mol) of ethyl methylthioacetate and 1.33 L of dichloromethane was cooled to −74 °C with a dry ice/acetone bath. Sulfuryl chloride (70.0 mL, 118 g, 0.870 mol) was added over a 5 min period with temperature maintained between −70 and −74 °C, and the clear, colorless solution was stirred at −70 to −74 °C for 25 min. A solution of 157 mL (117 g, 0.900 mol) of *N*-ethyl-diisopropylamine, 131 g (0.870 mol) of 6-aminobenzothiazole, and 1 L of dichloromethane was added over a period of 100 min with temperature maintained between −69 and −74 °C. An additional 0.9 L of dichloromethane was added to dissolve a cream-colored precipitate, and the solution was stirred for 30 min. Triethylamine was added over a 2-min period, causing a temperature rise to −48 °C. After 15 min the cooling bath was removed, and the brown-orange solution was warmed to −30 °C over a 45-min period with a heat gun. The solution was concentrated under vacuum at 20 °C, and the resulting dark orange oil was treated with 1.4 L of 0.5 N HCl and 1.3 L of *tert*-butylmethyl ether. The mixture was stirred for 2.5 h at room temperature. The golden precipitate was isolated by filtration and dried in a vacuum at room temperature to furnish 92 g (44%) of the title compound, $^1$H NMR (DMSO-$d_6$): $\delta$ 1.78 (s, 3H), 4.87 (s, 1H), 7.07 (d, $J$ = 8.5 Hz, 1H), 7.97 (d, $J$ = 8.5 Hz, 1H), 9.19 (s, 1H), 10.79 (br s, 1H). Anal. ($C_{10}H_8N_2OS_2\cdot 0.1\ H_2O\cdot C_5H_{12}O$) C, H, N, S.

**6,8-Dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one (12).** A mixture of 2.7 g (11 mmol) of 8-(methylsulfanyl)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one, 3.0 g of activated Zn, 41 mL of acetic acid, and 41 mL of THF was heated at 60−65 °C for 3.5 h. The gray-green mixture was filtered through a sintered glass funnel containing a 0.5 in. pad of Celite, and the pad was washed with 40 mL of hot 1:1 THF:acetic acid. Water (200 mL) was added to the filtrate, and the pale yellow mixture was stirred for 10 min. The resulting solid was isolated by filtration, washed with 25 mL of water, and dried under vacuum at 70 °C to furnish 1.05 g (49%) of the title compound as a pale yellow solid, $^1$H NMR (DMSO-$d_6$): $\delta$ 3.75 (s, 2H), 7.04 (d, 8.5 Hz, 1H), 7.90 (d, $J$ = 8.5 Hz, 1H), 9.17 (s, 1H), 10.59 (s, 1H). Anal. ($C_9H_6N_2OS$) C, H, N, S.

**8-(Ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one (13).** A mixture of 116.7 g (0.61 mol) of oxindole, 787 mL (701 g, 4.73 mol) of triethylorthoformate, and 2.4 L of acetic acid was heated at reflux for 1.5 h. The dark brown solution was cooled to 50 °C over a period of 1 h, and the solution was concentrated to an oil under vacuum at 45 °C. The oil was taken up in 3.9 L of ethanol and concentrated to half volume. The resulting solid was collected by filtration, washed with two 600-mL portions of ethanol, and dried under vacuum at 60 °C to furnish 97 g (64%) of the title compound as an orange solid, $^1$H NMR (DMSO-$d_6$): $\delta$ 1.42 (t, $J$ = 7.1 Hz, 3H), 4.42 (q, $J$ = 7.1 Hz, 2H), 7.02 (d, $J$ = 8.6 Hz, 1H), 7.68 (s, 1H), 7.82 (d, $J$ = 8.6 Hz, 1H), 9.07 (s, 1H), 10.50 (s, 1H). Anal. ($C_{12}H_{10}N_2O_2S\cdot 0.4\ C_2H_4O_2$) C, H, N, S. Concentration of filtrate provided an additional 27 g of desired product for an overall yield of 82%.

**4-[2-(5-Bromo-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-hydrazino]benzenesulfonamide (16).** 4-Hydrazinobenzenesulfonamide hydrochloride (0.60 g, 2.6 mmol) was dissolved in EtOH (80 mL). 5-Bromoisatin (0.50 g, 2.2 mmol) was added, and the reaction temperature was increased to reflux for 2 h. The reaction mixture was cooled to room temperature, and solids were collected by filtration. The solids were washed twice with EtOH (15 mL each) and once with diethyl ether (20 mL) and were dried under vacuum for 16 h to afford an orange solid (0.87 g 100%): $^1$H NMR (DMSO-$d_6$): $\delta$ 12.74 (s, 1H); 11.20 (s, 1H); 7.78 (d, $J$ = 8.7 Hz, 2H); 7.74 (d, $J$ = 1.8 Hz, 1H); 7.63 (d, $J$ = 8.7 Hz, 2H); 7.42 (dd, $J$ = 8.4, 1.8 Hz, 1H); 7.27 (bs, 2H); 6.87 (d, $J$ = 8.4 Hz, 1H); ES-MS: 394 (M-H)$^-$. Anal. ($C_{14}H_{11}N_4O_3SBr$) C, H, N, S.

**4-[2-(2-Oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazino]-benzenesulfonamide (17).** The title compound was prepared from isatin and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.88 (d, $J$ = 7.8 Hz, 1H), 7.02 (t, $J$ = 7.5 Hz, 1H), 7.20 (s, 2H), 7.23 (t, $J$ = 7.8 Hz, 1H), 7.51 (d, $J$ = 8.7 Hz, 2H), 7.53 (d, $J$ = 7.5 Hz, 1H), 7.74 (d, 8.7 Hz, 2H), 11.04 (s, 1H), 12.74 (s, 1H); APCI $m/z$ 315 (M-H)$^-$.

**4-{[(2-Oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-amino}benzenesulfonamide (18)**. The title compound was prepared from 3-(ethoxymethylene)-1,3-dihydro-2*H*-indol-2-one and sulfanilamide according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.80 (m, 1H), 6.90 (m, 1H), 6.99 (m, 1H), 7.21 (s, 2H), 7.49 (d, $J$ = 8.7 Hz, 2H), 7.55 (d, $J$ = 7.5 Hz, 1H), 7.73 (d, $J$ = 8.7 Hz, 2H), 8.58 (d, $J$ = 12.3 Hz, 1H), 10.52 (s, 1H), 10.78 (d, $J$ = 12.3 Hz, 1H); APCI $m/z$ 314 (M-H)$^-$. Anal. ($C_{15}H_{13}N_3O_3S$) C, H, N, S.

**4-{[1-(2-Oxo-1,2-dihydro-3*H*-indol-3-ylidene)ethyl]-amino}benzenesulfonamide (19).** 3-(1-Dimethylaminoethylidene)-1,3-dihydroindol-2-one was prepared from 1,3-dihydroindol-2-one and *N*,*N*-dimethylacetamide dimethyl acetal according to procedure F. Condensation of 3-(1-dimethylaminoethylidene)-1,3-dihydroindol-2-one and sulfanilamide according to procedure G provided the title compound: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.61 (s, 3H), 6.94 (d, $J$ = 7.5 Hz, 1H), 6.99 (t, $J$ = 7.5 Hz, 1H), 7.07 (t, $J$ = 7.5 Hz, 1H), 7.41 (s, 2H), 7.42 (d, $J$ = 7.5 Hz, 1H), 7.48 (d, $J$ = 8.6 Hz, 2H), 7.87 (d, $J$ = 8.6 Hz, 2H), 10.70 (s, 1H), 12.34 (s, 1H); ES-MS $m/z$ 328 (M-H)$^-$. Anal. ($C_{16}H_{14}N_3O_3S\cdot{}^1/_2H_2O$) C, H, N, S.

**4-[2-(5-Chloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-hydrazino]benzenesulfonamide (20)**. Condensation of 5-chloroisatin and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E afforded the title compound: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.90 (d, $J$ = 8.2 Hz, 1H), 7.24 (m, 3H), 7.60 (m, 3H), 7.76 (d, $J$ = 8.7 Hz, 2H), 11.17 (s, 1H), 12.73 (s, 1H); APCI $m/z$ 350 (M)$^-$. Anal. ($C_{14}H_{11}N_4O_3SCl$) C, H, N, S, Cl.

**4-{[1-(5-Chloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-ethyl]amino}benzenesulfonamide (21).** 3-(1-Dimethylaminoethylidene)-5-chloro-1,3-dihydroindol-2-one was prepared from 5-chloro-1,3-dihydroindol-2-one and *N*,*N*-dimethylacetamide dimethyl acetal according to procedure F. Condensation of 3-(1-dimethylaminoethylidene)-5-chloro-1,3-dihydroindol-2-one and sulfanilamide according to procedure G provided the title compound: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.53 (s, 3H), 6.87 (d, $J$ = 8.2 Hz, 1H), 7.03 (dd, $J$ = 1.5, 8.2 Hz, 1H), 7.35 (d, $J$ =

1.5 Hz, 1H), 7.37 (s, 2H), 7.44 (d, $J$ = 8.6 Hz, 2H), 7.83 (d, $J$ = 8.6 Hz, 2H), 10.78 (s, 1H), 12.35 (s, 1H); ES-MS $m/z$ 362 $(M-H)^-$. Anal. ($C_{16}H_{14}N_3O_3ClS \cdot {}^1/_2H_2O$) C, H, N, S.

**4-[1-(5-Oxazol-5-yl-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazino]benzenesulfonamide (5:1 *E*:*Z* isomer mixture) (22).** The title mixture of isomers was prepared from 5-(oxazol-5-yl)-1H-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: mp >250 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ (5:1 ratio of *Z*:*E* isomers), *E* 6.97 (d, $J$ = 8.2 Hz, 1H), *Z* 7.00 (d, $J$ = 8.2 Hz, 1H), *E* 7.23 (s, 2H), *Z* 7.25 (s, 2H), *Z* 7.61 (d, $J$ = 9.1 Hz, 2H), *E* 7.61 (d, $J$ = 9.1 Hz, 2H), *Z* 7.62 (dd, $J$ = 8.2, 1.7 Hz, 1H), *Z* 7.65 (s, 1H), *E* 7.65 (s, 1H), *E* 7.65 (dd, $J$ = 8.2, 1.5 Hz, 1H), *Z* 7.78 (d, $J$ = 8.9 Hz, 2H), *E* 7.81 (d, $J$ = 8.9 Hz, 2H), *Z* 7.90 (d, $J$ = 1.7 Hz, 1H), *Z* 8.40 (s, 1H), *E* 8.43 (s, 1H), *E* 8.47 (d, $J$ = 1.3 Hz, 1H), *E* 10.83 (s, 1H), *E* 10.98 (s, 1H), *Z* 11.25 (s, 1H), *Z* 12.78 (s, 1H); ESI $m/z$ 382 $(M-H)^-$. Anal. ($C_{17}H_{13}N_5O_4S \cdot 1.2\ H_2O \cdot 0.4\ C_2H_6O$) C, H, N.

**4-({[5-(1,3-Oxazol-5-yl)-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene]methyl}amino)benzenesulfonamide (23).** The title compound was prepared in 68% yield from ethoxymethylene-5-oxazol-5-yl-1,3-dihydro-indol-2-one and 4-aminobenzenesulfonamide hydrochloride according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 10.79 (d,1H), 10.73 (s, 1H), 8.76 (d, 1H), 8.38 (s, 1H), 8.0 (s, 1H), 7.77 (d, 2H), 7.56 (d, 2H), 7.43 (s, 1H), 7.40 (d, 1H), 7.26 (s, 2H), 6.91 (d, 1H); APCI: $m/z$ 381 $(M-H)^-$.

**4-[1-(5-Oxazol-5-yl-2-oxo-1,2-dihydro-indol-3-ylidene)-ethylamino]benzenesulfonamide (24).** 3-(1-Dimethylaminoethylidene)-5-(oxazol-5-yl)-1,3-dihydroindol-2-one was prepared from 5-(oxazol-5-yl)-1,3-dihydroindol-2-one and *N*,*N*-dimethylacetamide dimethyl acetal according to procedure F. Condensation of 3-(1-dimethylaminoethylidene)-5-(oxazol-5-yl)-1,3-dihydroindol-2-one and sulfanilamide according to procedure G provided the title compound: mp >250 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 2.51 (s, 0.8H, DMSO), 2.61 (s, 3H), 6.97 (d, $J$ = 8.2 Hz, 1H), 7.37 (s, 2H), 7.40 (dd, $J$ = 8.0, 1.5 Hz, 1H), 7.45 (d, $J$ = 8.8 Hz, 2H), 7.56 (s, 1H), 7.66 (d, $J$ = 1.2 Hz, 1H), 7.83 (d, $J$ = 8.5 Hz, 2H), 8.34 (s, 1H), 10.85 (s, 1H), 12.33 (s, 1H); APCI $m/z$ 395 $(M-H)^-$. Anal. ($C_{19}H_{16}N_4O_4S \cdot 0.1\ C_2H_6OS \cdot 0.6\ H_2O$) C, H, N, S.

**4-[*N*′-(4-Iodo-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazino]benzenesulfonamide (25).** The title compound was prepared from 4-iodo-1H-indole-2,3-dione[43] and 4-sulfonamidophenyl-hydrazine hydrochloride according to procedure E in 87% overall yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.93 (d, $J$ = 7.6 Hz, 1H), 6.99 (t, $J$ = 7.6 Hz, 1H), 7.25 (s, 2H), 7.50 (d, $J$ = 7.6 Hz, 1H), 7.66 (d, $J$ = 8.7 Hz, 2H), 7.77 (d, $J$ = 8.7 Hz, 2H), 11.17 (s, 1H), 12.94 (s, 1H); APCI $m/z$ 441 $(M-H)^-$. Anal. ($C_{14}H_{11}IN_4O_3S$) C, H, N, S.

**4-[2-(4-Ethyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazino]benzenesulfonamide (26)**. The title compound was prepared from 4-ethyl-1H-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.24 (t, $J$ = 7.4 Hz, 3H), 2.94 (q, $J$ = 7.4 Hz, 2H), 6.73 (d, $J$ = 7.7 Hz, 1H), 6.88 (d, $J$ = 7.7 Hz, 1H), 7.17 (t, $J$ = 7.7 Hz, 1H), 7.22 (s, 2H), 7.46 (d, $J$ = 8.7 Hz, 2H), 7.76 (d, $J$ = 8.7 Hz, 2H), 11.07 (s, 1H), 12.94 (s, 1H); APCI $m/z$ 343 $(M-H)^-$. Anal. ($C_{16}H_{16}N_4O_3S \cdot {}^2/_3H_2O$) C, H, N, S.

**4-[*N*′-(4-Isopropyl-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazino]benzenesulfonamide (27)**. The title compound was prepared from 4-isopropyl-1H-indole-2,3-dione[44] and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E in 73% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.30 (d, $J$ = 6.7 Hz, 6H), 3.82 (septet, $J$ = 6.7 Hz, 1H), 6.76 (d, $J$ = 7.8 Hz, 1H), 7.01 (d, $J$ = 7.8 Hz, 1H), 7.23 (t, $J$ = 7.8 Hz, 1H), 7.24 (s, 2H), 7.48 (d, $J$ = 8.7 Hz, 2H), 7.79 (d, $J$ = 8.7 Hz, 2H), 11.10 (s, 1H), 13.05 (s, 1H); APCI $m/z$ 357 $(M-1)^-$. Anal. ($C_{17}H_{18}N_4O_3S$) C, H, N, S.

**4-[*N*′-(4-Isobutyl-2-oxo-1,2-dihydro-indol-3-ylidene)hydrazino]benzenesulfonamide (28).** A mixture of 0.20 g (1.0 mmol) of 4-(2-methyl-propenyl)-1H-indole-2,3-dione and 0.05 g of 10% palladium on charcoal in 25 mL of EtOAc was subjected to hydrogenation on a Parr apparatus at 46 psi for 1 h. The mixture was filtered through Celite, and the filtrate was concentrated to dryness. The solid was purified by chromatography on silica gel, eluting with hexane:EtOAc (4:1), to furnish 0.027 g (13%) of 4-isobutyl-1H-indole-2,3-dione: $^1$H NMR (DMSO-$d_6$): $\delta$ 0.89 (d, $J$ = 6.7 Hz, 6H), 1.86 (nonet, $J$ = 6.7 Hz, 1H), 2.72 (d, $J$ = 6.7 Hz, 1H), 6.74 (d, $J$ = 7.8 Hz, 1H), 6.86 (d, $J$ = 7.8 Hz, 1H), 7.48 (t, $J$ = 7.8 Hz, 1H), 11.03 (s, 1H). Condensation of 4-isobutyl-1H-indole-2,3-dione and 4-sulfonamido- phenylhydrazine hydrochloride according to procedure E gave the title compound in 65% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 0.96 (d, $J$ = 6.4 Hz, 6H), 2.05 (m, 1H), 2.87 (d, $J$ = 7.0 Hz, 2H), 6.79 (d, $J$ = 7.6 Hz, 1H), 6.85 (d, $J$ = 7.6 Hz, 1H), 7.20 (t, $J$ = 7.6 Hz, 1H), 7.26 (s, 2H), 7.51 (d, $J$ = 8.5 Hz, 2H), 7.81 (d, $J$ = 8.5 Hz, 2H), 11.13 (s, 1H), 13.03 (s, 1H); APCI $m/z$ 371 $(M-H)^-$. Anal. ($C_{18}H_{20}N_4O_3S \cdot {}^1/_2H_2O$) C, H, N, S.

**4-{*N*′-[4-(2-Methyl-propenyl)-2-oxo-1,2-dihydro-indol-3-ylidene]hydrazino}benzenesulfonamide (29).** By methods described in procedure I, 4-(2-methyl-propenyl)-1H-indole-2,3-dione was prepared from 4-iodo-1H-indole-2,3-dione and isobutylene in 34% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.82 (s, 3H), 1.90 (s, 3H), 6.79 (d, $J$ = 7.9 Hz, 1H), 6.94 (d, $J$ = 7.9 Hz, 1H), 7.47 (t, $J$ = 7.9 Hz, 1H), 10.97 (s, 1H); APCI $m/z$ 200 $(M-1)^-$. Condensation of 4-(2-methyl-propenyl)-1H-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E gave the title compound as a yellow solid (51% yield): $^1$H NMR (DMSO-$d_6$): $\delta$ 1.84 (s, 3H), 2.04 (s, 3H), 6.78 (s, 1H), 6.79 (d, $J$ = 7.8 Hz, 1H), 6.96 (d, $J$ = 7.8 Hz, 1H), 7.24 (t, $J$ = 7.8 Hz, 1H), 7.24 (s, 2H), 7.48 (d, $J$ = 8.8 Hz, 2H), 7.80 (d, $J$ = 8.8 Hz, 2H), 11.11 (s, 1H), 12.91 (s, 1H); APCI $m/z$ 369 $(M-1)^-$. Anal. ($C_{18}H_{18}N_4O_3S$) C, H, N, S.

**4-[2-(4-Ethoxy-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-hydrazino]benzenesulfonamide (30)**. Condensation of 4-ethoxy-1*H*-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride using procedure E provided the title compound: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.44 (t, $J$ = 7.0, 3H), 4.13 (q, $J$ = 7.0 Hz, 2H), 6.50 (d, $J$ = 7.5 Hz, 1H), 6.68 (d, $J$ = 8.4 Hz, 1H), 7.15−7.21 (m, 3H), 7.46 (d, $J$ = 8.8 Hz, 2H), 7.74 (d, $J$ = 8.8, 2H), 11.03 (s, 1H), 12.78 (s, 1H); APCI: $m/z$ 359 $(M-H)^-$. Anal. ($C_{16}H_{16}N_4O_4S$) C, H, N, S.

**4-[*N*′-(2-Oxo-4-phenoxy-1,2-dihydro-indol-3-ylidene)-hydrazino]benzenesulfonamide (4:10 mixture of *E* and *Z* isomers) (32)**. The title compound was prepared from 3-phenoxyaniline and 4-sulfonamidophenyl-hydrazine hydrochloride according to procedure C: mp >250 °C;$^1$H NMR (DMSO-$d_6$, equilibrated for 10 days at room temperature): $\delta$ 6.42 *E* (d, $J$ = 8.4 Hz, 1H), 6.70 *E* (d, $J$ = 7.7 Hz, 1H), 6.76 *Z* (d, $J$ = 8.2 Hz, 1H), 6.82 *Z* (d, $J$ = 7.8 Hz, 1H), 6.99 *Z* (d, $J$ = 8.1 Hz, 2H), 7.06 *Z* (d, $J$ = 8.8 Hz, 2H), 7.1−7.6 *E* (m, 10H), 7.1−7.6 *Z* (m, 6H), 7.62 *Z* (d, $J$ = 8.8 Hz, 2H), 7.74 *E* (d, $J$ = 8.7 Hz, 2H), 10.88 *E* (s, 1H), 11.18 *E* (s, 1H), 11.27 *Z* (s, 1H), 12.77 *Z* (s, 1H); APCI: $m/z$ 407 $(M-H)^-$. Anal. ($C_{20}H_{16}N_4O_4S$) C, H, N, S.

**4-{*N*′-[2-Oxo-4-(2-pyridin-4-yl-ethyl)-1,2-dihydro-indol-3-ylidene]hydrazino}benzenesulfonamide (33).** A mixture of 3.0 g (20 mmol) of 3-nitroiodobenzene, 3.5 mL (25 mmol) of TEA, 0.045 g (0.20 mmol) of palladium(II) acetate, and 2.77 g (25.0 mmol) of 4-vinylpyridine was suspended in 4 mL of dry acetonitrile in a Pyrex sealed tube and heated to 100 °C for 48 h. The mixture was cooled to room temperature and was quenched with 200 mL of 10% hydrochloric acid. The resulting yellow solid was isolated by filtration and partitioned between 250 mL of EtOAc and 250 mL of 1 N aqueous sodium hydroxide. The organic phase was dried over $MgSO_4$ and concentrated to give 3.0 g (66%) of 4-[2-(3-nitrophenyl)ethenyl]-pyridine as a yellow solid: $^1$H NMR (DMSO-$d_6$): $\delta$ 3.0−4.6 (br s, 1H), 7.71−7.78 (m, 2H), 8.07 (d, $J$ = 15.8 Hz, 1H), 8.13−8.16 (m, 3H), 8.24 (d, $J$ = 8.0 Hz, 1H), 8.56 (s, 1H), 8.84 (d, $J$ = 5.7 Hz, 2H); ESI $m/z$ 227 $(M+1)^+$. A portion (1.3 g, 7.1 mmol) of this solid was dissolved in 100 mL of EtOAc, and 0.5 g of 10% palladium on charcoal was added. The mixture was hydrogenated on a Parr apparatus at 40 psi for 1.5 h. Another 0.5 g batch of 10% palladium on charcoal was added, and the mixture was subjected to further hydrogenation for 1 h. The palladium catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated to give 1.13 g (100%) of 3-(4-pyridinyl)ethylaniline: $^1$H NMR (DMSO-$d_6$): $\delta$

2.69 (m, 2H), 2.80 (m, 2H), 4.9 (bs, 2H), 6.33 (d, $J$ = 7.7 Hz, 2H), 6.38 (s, 1H), 6.86 (t, $J$ = 7.7 Hz, 1H), 7.20 (d, $J$ = 5.8 Hz, 2H), 8.41 (d, $J$ = 5.8 Hz, 2H). Conversion of 3-[2-(4-pyridinyl)-ethyl]-aniline to 4-(2-pyridin-4-yl-ethyl)-1H-indole-2,3-dione was accomplished according to procedure A in 24% overall yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.80 (m, 2H), 3.10 (m, 2H), 6.70 (d, $J$ = 8.0 Hz, 1H), 6.81 (d, $J$ = 8.0 Hz, 1H), 7.24 (m, 2H), 7.40 (t, $J$ = 8.0 Hz, 1H), 8.42 (bs, 2H), 11.00 (s, 1H). Conversion of 4-(2-pyridin-4-yl-ethyl)-1H-indole-2,3-dione to the title compound was accomplished according to procedure E in 40% overall yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.98 (t, $J$ = 7.9 Hz, 2H), 3.30 (m, 2H, underneath water peak), 6.78 (d, $J$ = 7.7 Hz, 1H), 6.88 (d, $J$ = 7.6 Hz, 1H), 7.17 (t, $J$ = 7.6 Hz, 1H), 7.25 (s, 2H), 7.29 (d, $J$ = 6.0 Hz, 2H), 7.37 (d, $J$ = 8.8 Hz, 2H), 7.66 (d, $J$ = 8.8 Hz, 2H), 8.47 (d, $J$ = 6.0 Hz, 2H), 11.13 (s, 1H), 12.98 (s, 1H); APCI $m/z$ 420 (M-1)$^-$. Anal. ($C_{21}H_{19}N_5O_3S\cdot 0.15$ HCl) C, H, N, S.

**4-(*N*′-{4-[2-(4-Hydroxyphenyl)-ethyl]-2-oxo-1,2-dihydro-indol-3-ylidene}hydrazino)benzenesulfonamide (35)**. A mixture of 0.028 g (0.64 mmol) of 4-(*N*′-{4-[2-(4-hydroxyphenyl)-vinyl]-2-oxo-1,2-dihydro-indol-3-ylidene}-hydrazino)-benzenesulfonamide and 0.015 g of 10% palladium on charcoal in 60 mL of MeOH:THF (4:1) was subjected to hydrogenation on a Parr apparatus at 50 psi for 1 h. The mixture was filtered through Celite, and the filtrate was concentrated to give 0.026 g (93%) of the title compound as a yellow solid: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.82 (t, $J$ = 8.0 Hz, 2H), 3.23 (t, $J$ = 8.0 Hz, 2H), 6.69 (d, $J$ = 8.4 Hz, 2H), 6.78 (d, $J$ = 7.7 Hz, 1H), 6.89 (d, $J$ = 7.7 Hz, 1H), 7.07 (d, $J$ = 8.4 Hz, 2H), 7.18 (t, $J$ = 7.7 Hz, 1H), 7.26 (s, 2H), 7.45 (d, $J$ = 8.8 Hz, 2H), 7.71 (d, $J$ = 8.8 Hz, 2H), 9.20 (bs, 1H), 11.12 (s, 1H), 13.02 (s, 1H); APCI $m/z$ 435 (M-1)$^-$. Anal. ($C_{22}H_{20}N_4O_4S\cdot H_2O$) C, H, N, S.

**4-{*N*′-[2-Oxo-4-(1H-pyrazol-3-yl)-1,2-dihydro-indol-3-ylidene]hydrazino}benzenesulfonamide (36).** 4-(1H-Pyrazol-3-yl)-1H-indole-2,3-dione was prepared from 3-(1H-pyrazol-3-yl)aniline according to procedure A. The title compound was prepared from 4-(1H-pyrazol-3-yl)-1H-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.72 (s, 1H), 7.22 (s, 2H), 7.39 (s, 1H), 7.48−7.60 (m, 4H), 7.76 (d, $J$ = 8.7 Hz, 2H), 7.77 (s, 1H), 11.11 (s, 1H), 12.93 (s, 1H); ESI: $m/z$ 381 (M-H)$^-$.

**2-Oxo-3-(4-sulfamoyl-phenylamino)-methylene]-2,3-dihydro-1H-indole-4-carboxylic acid ethyl ester (37).** The title compound was prepared from 2-oxo-2,3-dihydro-1H-indole-4-carboxylic acid ethyl ester[45,46] and sulfanilamide according to procedure G in 14% overall yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.33 (t, $J$ = 7.1 Hz, 3H), 4.37 (q, $J$ = 7.1 Hz, 2H), 7.10 (d, $J$ = 7.6 Hz, 1H), 7.15 (t, $J$ = 7.6 Hz, 1H), 7.30 (s, 2H), 7.41 (d, $J$ = 8.6 Hz, 2H), 7.57 (d, $J$ = 7.6 Hz, 1H), 7.82 (d, $J$ = 8.6 Hz, 2H), 9.50 (d, $J$ = 12.6 Hz, 1H), 10.96 (s, 1H), 11.75 (d, $J$ = 12.6 Hz, 1H); APCI $m/z$ 386 (M-1)$^-$.

**4-({[4-(Hydroxymethyl)-2-oxo-1,2-dihydro-3H-indol-3-ylidene]methyl}amino)benzenesulfonamide (38)**. Procedures analogous to those used in the preparation of the corresponding 6-hydroxymethyl isomer provided the title compound: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.37 (d, $J$ = 5.0 Hz, 3H), 4.68 (s, 2H), 5.31 (br s, 1H), 6.78 (d, $J$ = 7.5 Hz, 1H), 6.92 (d, $J$ = 7.5 Hz, 1H), 7.00 (t, $J$ = 7.5 Hz, 1H), 7.34 (q, $J$ = 5.0 Hz, 1H), 7.44 (d, $J$ = 8.6 Hz, 2H), 7.71 (d, $J$ = 8.6 Hz, 2H), 8.32 (d, $J$ = 12.2 Hz, 1H), 10.65 (s, 1H), 11.26 (d, $J$ = 12.2 Hz, 1H); ES $m/z$ 358 (M-1)$^-$. Anal. ($C_{17}H_{17}N_3O_4S$) C, H, N, S.

**4-[*N*′-(4-Nitro-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazino]benzenesulfonamide (39).** The title compound was prepared from 4-nitro-1H-indole-2,3-dione[47] and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E in 33% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 7.23 (d, $J$ = 7.7 Hz, 1H), 7.31 (s, 2H), 7.47 (t, $J$ = 7.9 Hz, 1H), 7.56 (d, $J$ = 7.9 Hz, 2H), 7.59 (d, $J$ = 7.2 Hz, 1H), 7.83 (d, $J$ = 7.7 Hz, 2H), 11.59 (s, 1H), 13.20 (s, 1H); APCI $m/z$ 361 (M)$^-$. Anal. ($C_{14}H_{11}N_5O_5S$) C, H, N, S.

**3-{[4-(Aminosulfonyl)phenyl]hydrazono}-2-oxo-4-indolinecarboxamide (20:3 *E:Z* isomer ratio) (40)**. 1H-Indole-2,3-dione-4-carboxamide was prepared from aniline-3-carboxamide according to procedure A in 3% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 7.17 (d, $J$ = 8.1 Hz, 1H), 7.32 (d, $J$ = 8.1 Hz, 1H), 7.56 (t, $J$ = 8.1 Hz, 1H), 8.02 (bs, 2H), 11.86 (bs, 1H); APCI+MS $m/z$ 191 (M+1)$^+$. Condensation of 1H-indole-2,3-dione-4-carboxamide with 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E gave the title compound in 31% yield: $^1$H NMR (DMSO-$d_6$, equilibrated for 10 days at room temperature): *E* isomer, $\delta$ 7.11 (d, $J$ = 8.3 Hz, 1H), 7.18 (s, 2H), 7.27 (d, $J$ = 8.8 Hz, 2H), 7.32 (d, $J$ = 7.0 Hz, 1H), 7.51 (d, $J$ = 7.4 Hz, 1H), 7.75 (d, $J$ = 8.8 Hz, 2H), 8.0 (bs, 2H), 10.40 (s, 1H), 10.80 (s, 1H); *Z* isomer, $\delta$ 11.10 (s, 1H), 13.11 (s, 1H); APCI $m/z$ 359 (M)$^-$. Anal. ($C_{15}H_{13}N_5O_4S\cdot 0.12$ $H_2O$) C, H, N, S.

**4-[2-(5-Fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-hydrazino]benzenesulfonamide (41)**. The title compound was prepared from 5-fluoro-1*H*-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride using procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.87 (dd, $J$ = 4.3, 8.4 Hz, 1H), 7.05 (dt, $J$ = 2.6, 9.1 Hz, 1H), 7.21 (s, 2H), 7.38 (dd, $J$ = 2.6, 8.4 Hz, 1H), 7.56 (d, $J$ = 8.8 Hz, 2H), 7.74 (d, $J$ = 8.8 Hz, 2H), 11.05 (s, 1H), 12.75 (s, 1H); APCI $m/z$ 333 (M-H)$^-$. Anal. ($C_{14}H_{11}N_4O_3FS$) C, H, N, S.

**4-[2-(5-Iodo-2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazino]benzenesulfonamide (42)**. Condensation of 5-iodo-1*H*-indole-2,3-dione and 4-hydrazino-benzenesulfonamide hydrochloride according to procedure E provided the title compound: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.74 (d, $J$ = 8.2 Hz, 1H), 7.24 (s, 2H), 7.56 (dd, $J_1$ = 1.7, $J_2$ = 8.2 Hz, 1H), 7.60 (d, $J$ = 8.8 Hz, 2H), 7.75 (d, $J$ = 8.8 Hz, 2H), 7.86 (d, $J$ = 1.7, 1H), 11.15 (s, 1H), 12.70 (s, 1H); APCI: $m/z$ 441 (M-H)$^-$. Anal. ($C_{14}H_{11}N_4O_3SI$) C, H, N, S, I.

**4-[*N*′-(5-Methyl-2-oxo-1,2-dihydro-indol-3-ylidene)hydrazino]benzenesulfonamide (43).** The title compound was prepared from 5-methyl-1H-indole-2,3-dione[47] and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E in 86% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.3 (s, 3H), 6.76 (d, $J$ = 7.9 Hz, 1H), 7.11 (d, $J$ = 7.9 Hz, 1H), 7.20 (s, 2H), 7.57 (d, $J$ = 8.8 Hz, 2H), 7.77 (d, $J$ = 8.8 Hz, 2H), 8.02 (s, 1H), 10.51 (s, 1H), 10.62 (s, 1H); APCI $m/z$ 329 (M-1)$^-$. Anal. ($C_{15}H_{14}N_4O_3S$) C, H, N, S.

**4-[*N*′-(5-Hydroxy-2-oxo-1,2-dihydro-indol-3-ylidene)hydrazino]benzenesulfonamide (44).** The title compound was prepared from 5-hydroxy-1H-indole-2,3-dione[48] and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E in 30% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.79 (dd, $J$ = 2.2, 8.3 Hz, 1H), 6.72 (d, $J$ = 8.3 Hz, 1H), 6.98 (d, $J$ = 2.2 Hz, 1H), 7.25 (s, 2H), 7.53 (d, $J$ = 8.7 Hz, 2H), 7.78 (d, $J$ = 8.7 Hz, 2H), 9.20 (s, 1H), 10.80 (s, 1H), 12.82 (s, 1H); APCI $m/z$ 331 (M-H)$^-$.

**4-[*N*′-(5-Methoxy-2-oxo-1,2-dihydro-indol-3-ylidene)hydrazino]benzenesulfonamide (45).** The title compound was prepared from 5-methoxy-1H-indole-2,3-dione[47] and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: mp >250 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 3.80 (s, 3H), 6.87 (s, 2H), 7.20 (s, 1H), 7.28 (s, 2H), 7.60 (d, $J$ = 8.8 Hz, 2H), 7.81 (d, $J$ = 8.8 Hz, 2H), 10.93 (s, 1H), 12.85 (s, 1H); APCI $m/z$ 344.9 (M-H)$^-$.

**4-[*N*′-(5-Nitro-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazino]benzenesulfonamide (46)**. The title compound was prepared from 5-nitro-1H-indole-2,3-dione[47] and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E in 94% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 7.14 (d, $J$ = 8.6 Hz, 1H), 7.33 (s, 2H), 7.75 (d, $J$ = 8.8 Hz, 2H), 7.84 (d, $J$ = 8.8 Hz, 2H), 8.23 (dd, $J$ = 2.2, 8.6 Hz, 1H), 8.42 (d, $J$ = 2.2 Hz, 1H), 11.76 (s, 1H), 12.78 (s, 1H). Anal. ($C_{14}H_{11}N_5O_5S$) C, H, N.

**4-[*N*′-(5-Amino-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazino]benzenesulfonamide hydrochloride (47)**. The title compound was prepared from 5-amino-1H-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.95 (d, $J$ = 8 Hz, 1H), 7.2 (d, $J$ = 8 Hz, 1H), 7.26 (s, 2H), 7.46 (s, 1H), 7.5 (d, $J$ = 8 Hz, 2H), 7.8 (d, $J$ = 8 Hz, 2H), 9.7 (br s, 3H), 11.2 (s, 1H), 12.8 (s, 1H); APCI $m/z$ 330.2 (M-H)$^-$.

**4-({[5-(Dimethylamino)-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene]methyl}amino)benzenesulfonamide (48).** The title

compound was prepared from 5-(dimethylamino)-3-(ethoxymethylene)-1,3-dihydro-2*H*-indol-2-one and sulfanilimide using procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 10.78 (d, $J$ = 12.2 Hz,-1H), 10.20 (s, 1H), 8.57 (d, $J$ = 12.1 Hz, 1H), 7.75 (d, $J$ = 8.6 Hz, 2H), 7.48 (d, $J$ = 8.8 Hz, 2H), 7.23 (s, 2H), 7.18 (s, 1H), 6.66 (d, $J$ = 8.4 Hz, 1H), 6.48 (d, $J$ = 8.5 Hz, 1H), 2.82 (s, 6H). APCI $m/z$ 357 (M-1). Anal. ($C_{17}H_{18}N_4O_3S\cdot1.4H_2O$) C, H, N.

**4-[*N*′-(5-Methylsulfonyl-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazino]benzenesulfonamide (49).** 5-Methylsulfonyl-1H-indole-2,3-dione was prepared from 4-methylsulfonylaniline according to procedure A: $^1$H NMR (DMSO-$d_6$): $\delta$ 3.21 (s, 3H), 7.07 (d, $J$ = 8.3 Hz, 1H), 7.92 (d, $J$ = 1.7 Hz, 1H), 8.05 (dd, $J$ = 8.2, 2.0 Hz, 1H), 11.46 (s,1H); APCI $m/z$ 225 $(M)^-$. The title compound was prepared from 5-methylsulfonyl-1H-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: mp >250 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 3.20 (s, 3H), 7.11 (d, $J$ = 8.3 Hz, 1H), 7.26 (s, 2H), 7.65 (d, $J$ = 8.9 Hz, 2H), 7.78 (d, $J$ = 8.7 Hz, 2H), 7.79 (dd, $J$ = 8.2, 1.9 Hz, 1H), 8.06 (d, $J$ = 1.6 Hz, 1H), 11.54 (s, 1H), 12.75 (s, 1H); APCI $m/z$ 394 $(M)^-$. Anal. ($C_{15}H_{14}N_4O_5S_2\cdot$ 0.9 $H_2O$) C, H, N, S.

**2-Oxo-3-[(4-sulfamoyl-phenyl)-hydrazono]-2,3-dihydro-1H-indole-5-sulfonic acid sodium salt (51)**. The title compound was prepared from 1H-indole-2,3-dione-5-sulfonic acid and 4-hydrazinobenzenesulfonamide according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.83 (d, $J$ = 8.0 Hz, 1H), 7.22 (s, 2H), 7.50 (dd, $J$ = 1.7, 8.0 Hz, 1H), 7.56 (d, $J$ = 8.7 Hz, 2H), 7.76 (d, $J$ = 8.7 Hz, 2H), 7.77 (d, $J$ = 1.7 Hz, 1H), 11.12 (s, 1H), 12.70 (s, 1H); APCI: $m/z$ 395 $(M\text{-}H)^-$. Anal. ($C_{14}H_{11}N_4O_6S_2Na\cdot0.9\ H_2O\cdot0.2\ C_2H_6O$) C, H, N S.

**3-{[4-(Aminosulfonyl)anilino]methylene}-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid (52).** The title compound was prepared from 3-[(dimethylamino)methylene]-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid and sulfanilamide according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.91 (d, $J$ = 8.1 Hz, 1H), 7.26 (s, 2H), 7.60 (d, $J$ = 8.8 Hz, 2H), 7.68 (d, $J$ = 8.1 Hz, 1H), 7.77 (d, $J$ = 8.8 Hz, 2H), 8.29 (s, 1H), 8.85 (d, $J$ = 12.3 Hz, 1H), 10.79 (d, $J$ = 12.3 Hz, 1H), 10.90 (s, 1H), 12.4 (br s, 1H).

**Isobutyl 3-{[4-(aminosulfonyl)anilino]methylene}-2-oxo-2,3-dihydro-1H-indole-5-carboxylate (54).** 3-Methylthio-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid isobutyl ester was prepared in 59% yield from isobutyl 4-aminobenzoate using the procedures of Gassman and van Bergen:[28] $^1$H NMR (DMSO-$d_6$): $\delta$ 0.93 (d, $J$ = 6.6 Hz, 6H), 1.93 (s, 3H), 1.98 (septet, $J$ = 6.6 Hz, 1H), 4.02 (m, 2H), 4.62 (s, 1H), 6.92 (d, $J$ = 8.2 Hz, 1H), 7.79 (s, 1H), 7.86 (d, $J$ = 8.2 Hz, 1H), 10.91 (s, 1H); ESI $m/z$ 302 $(M+Na)^+$. Zinc reduction of 3-methylthio-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid isobutyl ester according to the method of Gassman and van Bergen[28] provided 2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid isobutyl ester in 99% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 0.93 (d, $J$ = 6.6 Hz, 6H), 1.97 (septet, $J$ = 6.6 Hz, 1H), 3.53 (s, 2H), 3.99 (d, $J$ = 6.6 Hz, 2H), 6.88 (d, $J$ = 8.2 Hz, 1H), 7.75 (s, 1H), 7.82 (d, $J$ = 8.2 Hz, 1H), 10.72 (s, 1H); ESI $m/z$ 256 $(M+Na)^+$. Conversion of 2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid isobutyl ester to 3-[(dimethylamino)methylene]-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid isobutyl ester (mixture of *E* and *Z* isomers) was accomplished in 75% yield according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 0.94 *Z* (d, $J$ = 8.8 Hz, 6H), 0.94 *E* (d, $J$ = 8.8 Hz, 6H), 1.94−2.01 *Z* and *E* (m, 2H), 3.30 *Z* (s, 6H), 3.32 *E* (s, 6H), 3.97−3.99 *Z* and *E* (m, 4H), 6.75 *Z* (d, $J$ = 8.2 Hz, 1H), 6.83 *E* (d, $J$ = 8.2 Hz, 1H), 7.47 *E* (s, 1H), 7.53 *Z* (d, $J$ = 0.8.2 Hz, 1H), 7.59 *E* (d, $J$ = 8.2 Hz, 1H), 7.73 *Z* (s, 1H), 7.88 *Z* (s, 1H), 7.98 *E* (s, 1H), 10.34 *Z* (bs, 1H), 10.44 *E* (bs, 1H); ESI $m/z$ 289 $(M+H)^+$. The title compound was prepared in 66% yield from 3-[(dimethylamino)methylene]-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid isobutyl ester and 4-aminobenzenesulfonamide hydrochloride according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 0.96 (d, $J$ = 6.6 Hz, 6H), 2.01 (septet, $J$ = 6.6 Hz, 1H), 4.04 (d, $J$ = 6.6 Hz, 2H), 6.93 (d, $J$ = 8.2 Hz, 1H), 7.26 (s, 2H), 7.60 (d, $J$ = 8.7 Hz, 2H), 7.71 (dd, $J$ = 1.6, 8.2 Hz, 1H), 7.76 (d, $J$ = 8.7 Hz, 2H), 8.27 (s, 1H), 8.86 (d, $J$ = 12.5 Hz, 1H), 10.83 (d, $J$ = 12.5 Hz, 1H), 10.95 (s, 1H). NOESY correlation was observed between the C-4 proton at 8.27 ppm and the enamino vinylic proton at 8.86 ppm, consistent with the *Z* configuration of the enamino double bond; APCI $m/z$ 414.

**4-({[5-(3-Methylbutanoyl)-2-oxo-1,2-dihydro-3H-indol-3-ylidene]methyl}amino)benzenesulfonamide (55).** 3-[(Dimethylamino)methylene]-5-(3-methylbutanoyl)-1,3-dihydro-2*H*-indol-2-one was prepared according to procedure F and condensed with sulfanilamide as in procedure G to provide the title compound: $^1$H NMR (DMSO-$d_6$): 10.93 (s, 1H), 10.79 (d, $J$ = 12.5 Hz, 1H), 8.83 (d, $J$ = 12.5 Hz, 1H), 8.28 (s, 1H), 7.77 (d, $J$ = 8.8 Hz, 2H), 7.71 (dd, $J$ = 8.1, 1.3 Hz, 1H), 7.59 (d, $J$ = 8.8 Hz, 2H), 7.26 (s, 2H), 6.91 (d, $J$ = 8.1 Hz, 1H), 2.84 (d, $J$ = 6.8 Hz, 2H), 2.16 (m, 1H), 0.92 (d, $J$ = 6.8 Hz, 6H). APCI $m/z$ 398 $(M\text{-}H)^-$. Anal. ($C_{20}H_{21}N_3O_4S$) C, H, N.

**3-{[4-(Aminosulfonyl)phenyl]hydrazono}-2-oxo-2,3-dihydro-1H-indole-5-carboxamide (56)**. The title compound was prepared from 2,3-dioxo-5-indolinecarboxamide and 4-hydrazinobenzenesulfonamide according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.90 (d, $J$ = 8.2 Hz, 1H), 7.22 (s, 2H), 7.36 (s, 1H), 7.57 (d, $J$ = 8.7 Hz, 2H), 7.79 (d, $J$ = 8.7, 2H), 7.84 (d, $J$ = 7.4 Hz, 2H), 8.57 (s, 1H), 10.88 (s, 2H); APCI: $m/z$ 358 $(M\text{-}H)^-$. Anal. ($C_{15}H_{13}N_5O_4S$) C, H, N, S.

**3-{[4-(Aminosulfonyl)phenyl]hydrazono}-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-2-oxo-2,3-dihydro-1*H*-indole-5-carboxamide (58).** The title compound was prepared from 2-oxo-3[(4-sulfamoyl-phenyl)-hydrazono]-2,3-dihydro-1H-indole-5-carboxylic acid pentafluorophenyl ester and 2-(1*H*-imidazol-4-yl)ethylamine according to procedure H: mp >230 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 2.75 (t, $J$ = 7.4 Hz, 2H), 3.48 (m, 2H), 6.81 (s, 1H), 6.97 (d, $J$ = 7.2 Hz, 1H), 7.25 (s, 2H), 7.54 (s, 1H), 7.60 (d, $J$ = 8.6 Hz, 2H), 7.79 (m, 3H), 8.08 (s, 1H), 8.57 (br t, $J$ = 6 Hz, 1H), 11.31 (s, 1H), 11.88 (br s, 1H), 12.76 (s, 1H). Anal. ($C_{20}H_{18}N_7O_4S$) C, H, N.

**3-{[4-(Aminosulfonyl)phenyl]hydrazono}-*N*-[3-(1*H*-imidazol-1-yl)propyl]-2-oxo-2,3-dihydro-1*H*-indole-5-carboxamide (59).** The title compound was prepared from 2-oxo-3[(4-sulfamoyl-phenyl)-hydrazono]-2,3-dihydro-1H-indole-5-carboxylic acid pentafluorophenyl ester and 3-(1*H*-imidazol-1-yl)propylamine according to procedure H: mp >230 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 1.96 (p, $J$ = 6.7 Hz, 2H), 3.24 (m, 2H), 4.01 (t, $J$ = 6.8 Hz, 2H), 6.88 (s, 1H), 6.97 (d, $J$ = 8.1 Hz, 1H), 7.21 (s, 1H), 7.25 (s, 2H), 7.60 (d, $J$ = 8.7 Hz, 2H), 7.66 (s, 1H), 7.79 (d, $J$ = 8.7 Hz, 2H), 7.81 (d, $J$ = 8.1 Hz, 1H), 8.08 (s, 1H), 8.51 (t, $J$ = 5.5 Hz, 1H), 11.32 (s, 1H), 12.77 (s, 1H). Anal. ($C_{21}H_{21}N_7O_4S\cdot{}^1/_2H_2O$) C, H, N.

**3-{[4-(Aminosulfonyl)phenyl]hydrazono}-2-oxo-*N*-(4-pyridinylmethyl)-2,3-dihydro-1H-indole-5-carboxamide) (60).** The title compound was prepared from 2-oxo-3[(4-sulfamoyl-phenyl)-hydrazono]-2,3-dihydro-1H-indole-5-carboxylic acid pentafluorophenyl ester and (4-pyridyl)-methylamine according to procedure H: mp 211−215 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 4.46 (d, $J$ = 5.9 Hz, 2H), 6.97 (d, $J$ = 8.2 Hz, 1H), 7.21 (s, 2H), 7.27 (d, $J$ = 5.6 Hz, 2H), 7.56 (d, $J$ = 8.7 Hz, 2H), 7.75 (d, $J$ = 8.7 Hz, 2H), 7.83 (dd, $J$ = 1.3, 8.2 Hz, 1H), 8.13 (s, 1H), 8.46 (d, $J$ = 5.6 Hz, 2H), 9.09 (t, $J$ = 5.9 Hz, 1H), 11.31 (s, 1H), 12.73 (s, 1H). Anal. ($C_{21}H_{18}N_6O_4S\cdot H_2O$) C, H, N.

**3-{[4-(Aminosulfonyl)phenyl]hydrazono}-2-oxo-N-(3-pyridinylmethyl)-2,3-dihydro-1H-indole-5-carboxamide (61).** The title compound was prepared from 2-oxo-3[(4-sulfamoyl-phenyl)-hydrazono]-2,3-dihydro-1H-indole-5-carboxylic acid pentafluorophenyl ester and (3-pyridyl)methylamine according to procedure H: mp 211−215 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 4.46 (d, $J$ = 5.7 Hz, 2H), 6.95 (d, $J$ = 8.2 Hz, 1H), 7.21 (s, 2H), 7.31 (dd, $J$ = 4.5, 7.8 Hz, 1H), 7.56 (d, $J$ = 8.7 Hz, 2H), 7.68 (d, $J$ = 7.8 Hz, 1H), 7.75 (d, $J$ = 8.7 Hz, 2H), 7.81 (dd, $J$ = 1.5, 8.2 Hz, 1H), 8.10 (d, $J$ = 1.5 Hz, 1H), 8.41 (d, $J$ = 4.5 Hz, 1H), 8.51 (s, 1H), 9.06 (t, $J$ = 5.7 Hz, 1H), 11.30 (s, 1H), 12.73 (s, 1H). Anal. ($C_{21}H_{18}N_6O_4S\cdot H_2O$) C, H, N.

**3-{[4-(Aaminosulfonyl)phenyl]hydrazono}-*N*-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-5-indolinecarboxamide (62).** The title compound was prepared from 2-oxo-3[(4-sulfamoyl-phenyl)-hydrazono]-2,3-dihydro-1H-indole-5-carboxylic acid pentafluorophenyl ester and 3-hydroxy-2,2-dimeth-

ylpropylamine according to procedure H: mp >230 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 0.79 (s, 6H), 3.07 (d, $J$ = 6.2 Hz, 2H), 3.10 (d, $J$ = 6.2 Hz, 2H), 4.59 (t, $J$ = 6.2, 1H), 6.94 (d, $J$ = 8.2 Hz, 1H), 7.21 (s, 2H), 7.56 (d, $J$ = 8.8 Hz, 2H), 7.76 (d, $J$ = 8.8 Hz, 2H), 7.79 (d, $J$ = 1.3 Hz, 1H), 8.05 (d, $J$ = 1.3 Hz, 1H), 8.39 (t, $J$ = 6.2 Hz, 1H), 11.29 (s, 1H), 12.75 (s, 1H). Anal. ($C_{20}H_{23}N_5O_5S$) C, H, N.

**3-{[4-(Aminosulfonyl)phenyl]hydrazono}-*N*-(2,6-dimethoxybenzyl)-2-oxo-5-indolinecarboxamide (63)**. The title compound was prepared from 2-oxo-3[(4-sulfamoyl-phenyl)-hydrazono]-2,3-dihydro-1H-indole-5-carboxylic acid pentafluorophenyl ester and 2,6-dimethoxybenzylamine according to procedure H: mp > 250 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 3.76 (s, 6H), 4.43 (d, $J$ = 4.2 Hz, 2H), 6.65 (d, $J$ = 8.4 Hz, 2H), 6.91 (d, $J$ = 8.2 Hz, 1H), 7.23 (s, 2H), 7.25 (d, $J$ = 8.2 Hz, 1H), 7.56 (d, $J$ = 8.6 Hz, 2H), 7.79 (m, 3H), 8.07 (s, 1H), 8.13 (br s, 1H), 11.27 (s, 1H), 12.76 (s, 1H); APCI $m/z$ 532 $(M+Na)^+$; Anal. ($C_{24}H_{23}N_5O_6S\cdot{}^1/_2H_2O$)
C, H, N, S.

**4-[*N*′-(6-Bromo-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazino]benzenesulfonamide (64).** The title compound was prepared from 6-bromo-1H-indole-2,3-dione[49] and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: mp >250 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 7.05 (s, 1H), 7.23 (d, $J$ = 8.1 Hz, 1H), 7.50 (d, $J$ = 8.1 Hz, 1H), 7.56 (d, $J$ = 8.7 Hz, 2H), 7.75 (d, $J$ = 8.7 Hz, 2H), 11.2 (s, 1H), 12.7 (s, 1H); APCI $m/z$ 395 $(M-H)^-$.

**4-[*N*′-(6-Ethyl-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazino]benzenesulfonamide (65).** The title compound was prepared from 6-ethyl-1H-indole-2,3-dione[44] and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E in 79% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.16 (t, $J$ = 7.5 Hz, 3H), 2.60 (q, $J$ = 7.5 Hz, 2H), 6.74 (s, 1H), 6.89 (d, $J$ = 7.5 Hz, 1H), 7.22 (s, 2H), 7.46 (d, $J$ = 7.5 Hz, 1H), 7.50 (d, $J$ = 8.7 Hz, 1H), 7.75 (d, $J$ = 8.7 Hz, 2H), 11.02 (s, 1H), 12.70 (s, 1H); APCI $m/z$ 343 $(M-H)^-$. Anal. ($C_{16}H_{16}N_4O_3S\cdot 0.32\ H_2O$) C, H, N, S.

**4-[2-(6-Isopropyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-hydrazino]benzenesulfonamide (66)**. The title compound was prepared from 6-isopropyl-1*H*-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.17 (d, $J$ = 6.9 Hz, 6H), 2.88 (septet, $J$ = 6.9 Hz, 1H), 6.75 (s, 1H), 6.92 (d, $J$ = 7.8 Hz, 1H), 7.21 (s, 2H), 7.46 (d, $J$ = 7.8 Hz, 1H), 7.50 (d, $J$ = 8.7 Hz, 2H), 7.74 (d, $J$ = 8.7 Hz, 2H), 11.01 (s, 1H), 12.71 (s, 1H); APCI $m/z$ 357 $(M-H)^-$.

**4-[2-(6-*tert*-Butyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-hydrazino]benzenesulfonamide (67).** The title compound was prepared from 6-*tert*-butyl-1*H*-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure F: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.26 (s, 9H), 6.88 (d, $J$ = 1.4 Hz, 1H), 7.09 (dd, $J$ = 1.4, 8.0 Hz, 1H), 7.21 (s, 2H), 7.47 (d, $J$ = 8.0 Hz, 1H), 7.50 (d, $J$ = 8.7 Hz, 2H), 7.75 (d, $J$ = 8.7 Hz, 2H), 10.97 (s, 1H), 12.72 (s, 1H); AP-MS $m/z$ 371 $(M-H)^-$. Anal.($C_{18}H_{20}N_4O_3S$) C, H, N, S.

**4-[(6-Hydroxymethyl-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-amino]benzenesulfonamide (68).** A solution of 0.42 g (2.0 mmol) of 6-hydroxymethyl-3-methysulfanyl-1,3-dihydro-indol-2-one in DMF (10 mL) was treated with 0.32 g (2.1 mmol) of *tert*-butyldimethylsilyl chloride and 0.15 g (2.2 mmol) of imidazole and stirred for 16 h. The solution was diluted with 50 mL of hexane and 50 mL of EtOAc, washed with brine, dried over $MgSO_4$ and concentrated to give 0.28 g (43%) of 3-methylsulfanyl-6-(*tert*-butyldimethylsilyloxy)methyl-1,3-dihydro-indol-2-one as a clear oil which crystallized upon storage at room temperature: $^1$H NMR (DMSO-$d_6$): $\delta$ 0.01 (s, 6H), 0.97 (s, 9H), 2.00 (s, 3H), 4.52 (s, 1H), 4.72 (s, 2H), 6.85 (s, 1H), 6.96 (d, $J$ = 7.7 Hz, 1H), 7.25 (d, $J$ = 7.7 Hz, 1H), 10.54 (s, 1H). A solution of 0.28 g (0.86 mmol) of 3-methylsulfanyl-4-(*tert*-butyldimethylsilyloxy)methyl-1,3-dihydro-indol-2-one in THF (10 mL) was stirred with saturated ammonium chloride solution (10 mL), and activated zinc dust (2 g) was added. The mixture was stirred 16 h at room temperature. The organic phase was separated, dried over $MgSO_4$, and concentrated to give 0.32 g of impure 4-(*tert*-butyldimethylsilyloxy)methyl-1,3-dihydro-indol-2-one as a gummy white solid: $^1$H NMR (DMSO-$d_6$): $\delta$ 0.04 (s, 6H), 0.87 (s, 9H), 3.39 (s, 2H), 4.62 (s, 2H), 6.75 (s, 1H), 6.81 (d, $J$ = 7.5 Hz, 1H), 7.10 (d, $J$ = 7.5 Hz, 1H), 10.30 (bs, 1H). A solution of 0.32 g (1.2 mmol) of 4-(*tert*-butyldimethylsilyloxy)methyl-1,3-dihydro-indol-2-one in DMF dimethylacetal (3 mL) was heated to 100 °C for 0.75 h. The excess DMF dimethylacetal was removed under high vacuum, and the resulting dark oil was chromatographed on silica gel, eluting with EtOAc/MeOH (98:2), to give 0.16 g (41%) of 3-dimethylaminomethylene-6-(*tert*-butyldimethylsilyloxy)methyl-1,3-dihydro-indol-2-one (11:9 mixture of *E* and *Z* isomers) as a yellow solid: $^1$H NMR (DMSO-$d_6$, peak areas normalized using the combined peak areas for $\delta$ 9.88 and 9.66 as 1H): $\delta$ 0.21 (s, 2.70H), 0.34 (s, 3.3H), 0.85 (s, 4.05H), 0.86 (s, 4.95H), 3.25 (s, 2.70H), 3.30 (s, 3.30H), 4.58 (s, 0.9H), 4.59 (s, 1.1H), 6.64−6.71 (m, 2H), 7.16 (d, $J$ = 7.7 Hz, 0.45H), 7.29 (d, $J$ = 8.3 Hz, 0.55H), 7.33 (s, 0.55H), 7.47 (s, 0.45H), 9.88 (s,0.55H) 9.96 (s, 0.45H); APCI $m/z$ 331 $(M+1)^+$. A solution of 0.334 g (1.00 mmol) of 3-(dimethylamino)-methylene-6-(*tert*-butyldimethylsilyloxy)methyl-1,3-dihydro-indol-2-one in 2-methylpropanol (3 mL) was treated with 0.174 g (1.00 mmol) of sulfanilamide and 0.25 g (4.0 mmol) of acetic acid. The solution was refluxed for 3 h and cooled to room temperature. The resulting yellow precipitate was isolated by filtration, washed with ethanol, and dried to yield 0.134 g (29%) of 6-([*tert*-butyldimethyl-silyloxy]methyl-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-amino]-benzenesulfonamide (*Z* isomer): $^1$H NMR (DMSO-$d_6$): $\delta$ 0.05 (s, 6H), 0.87 (s, 9H), 4.65 (s, 2H), 6.81 (s, 1H), 6.85 (d, $J$ = 8.0 Hz, 1H), 7.23 (s, 2H), 7.49−7.51 (m, 3H), 7.75 (d, $J$ = 8.4 Hz, 2H), 8.56 (d, $J$ = 12.3 Hz, 1H), 10.52 (s, 1H), 10.76 (d, $J$ = 12.3 Hz, 1H); APCI $m/z$ 458 $(M-H)^-$. To a solution of 0.125 g (2.80 mmol) of 6-([*tert*-butyldimethylsilyloxy]methyl-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-amino]-benzenesulfonamide in THF (5 mL) was added 0.27 mL of a 1 M solution of *tert*-butylammonium fluoride in THF, and the mixture was stirred at room temperature for 1 h. The resulting yellow precipitate was isolated by filtration, washed with THF, and dried. Chromatographic purification of the solid on silica gel, eluting with a hexane to EtOAc gradient, gave 0.053 g (55%) of the title compound: $^1$H NMR (DMSO-$d_6$): $\delta$ 4.43 (d, $J$ = 5.8 Hz, 2H), 5.08 (t, $J$ = 5.8 Hz, 1H), 6.82 (s, 1H), 6.85 (d, $J$ = 8.2 Hz, 1H), 7.23 (s, 2H), 7.50 (d, $J$ = 7.5 Hz, 2H), 7.74 (d, $J$ = 8.7 Hz, 3H), 8.56 (d, $J$ = 12.2 Hz, 1H), 10.54 (s, 1H), 10.75 (d, $J$ = 12.1 Hz, 1H); APCI $m/z$ 345 $(M-H)^-$. Anal. ($C_{16}H_{15}N_3O_4S\cdot{}^1/_2H_2O$) C, H, N, S.

**4-[*N*′-(2-Oxo-6-phenoxy-1,2-dihydro-indol-3-ylidene)-hydrazino]benzenesulfonamide (69).** The title compound was prepared from 6-phenoxy- and 4-hydrazinobenzenesulfonamide according to procedure E in 87% yield: mp >250 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 6.42 (d, $J$ = 2.2 Hz, 1H), 6.73 (dd, $J_1$ = 2.2 Hz, $J_2$ = 8.5 Hz, 1H), 7.17 (d, $J$ = 8 Hz, 2H), 7.25 (s, 1H), 7.28 (d, $J$ = 7.4 Hz, 2H), 7.49 (t, $J$ = 7.9 Hz, 2H), 7.73 (d, $J$ = 8.8 Hz, 2H), 7.82 (d, $J$ = 8.8 Hz, 2H), 8.25 (d, $J$ = 8.5 Hz, 2H), 10.61 (s, 1H), 10.65 (s, 1H); APCI: $m/z$ 431 $(M+Na)^+$. Anal. ($C_{20}H_{16}N_4O_4S\cdot{}^1/_4H_2O$) C, H, N, S.

**4-[2-(7-Methyl-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-hydrazino]benzenesulfonamide (70)**. The title compound was prepared from 7-methyl-1H-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.21 (s, 3H), 6.98 (t, $J$ = 7.5 Hz, 1H), 7.10 (d, $J$ = 7.5 Hz, 1H), 7.24 (s, 2H), 7.41 (d, $J$ = 7.5 Hz, 1H), 7.56 (d, $J$ = 8.8 Hz, 2H), 7.78 (d, $J$ = 8.8 Hz, 2H), 11.14 (s, 1H), 12.81 (s, 1H); APCI: $m/z$ 329 $(M-H)^-$. Anal. ($C_{15}H_{14}N_4O_3S$) C, H, N, S.

**4-[2-(5,7-Dimethyl-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-hydrazino]benzenesulfonamide (71).** The title compound was prepared from 5,7-dimethyl-1H-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.19 (s, 3H), 2.27 (s, 3H), 6.92 (s, 1H), 7.24 (s, 3H), 7.55 (d, $J$ = 8.8 Hz, 2H), 7.77 (d, $J$ = 8.8 Hz, 2H), 11.03 (s, 1H), 12.79 (s, 1H); APCI: $m/z$ 343 $(M-H)^-$. Anal. ($C_{16}H_{16}N_4O_3S$) C, H, N, S.

**4-[2-(5-Chloro-7-methyl-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazino]benzenesulfonamide (72).** The title

compound was prepared from 5-chloro-7-methyl-1H-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.23 (s, 3H), 7.17 (d, $J$ = 1.8 Hz, 1H), 7.26 (s, 2H), 7.45 (d, $J$ = 1.8 Hz, 1H), 7.62 (d, $J$ = 8.7 Hz, 2H), 7.78 (d, $J$ = 8.7 Hz, 2H), 11.26 (s, 1H), 12.78 (s, 1H); APCI: $m/z$ 364 $M^-$. Anal. ($C_{15}H_{13}N_4O_3SCl$) C, H, N, Cl, S.

**4-[2-(4-Chloro-5-methyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazino]benzenesulfonamide (73)**. The title compound was prepared from 4-chloro-5-methyl-1H-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.32 (s, 3H), 6.80 (d, $J$ = 8 Hz, 1H), 7.22 (d, $J$ = 8 Hz, 1H), 7.25 (s, 2H), 7.56 (d, $J$ = 8.6 Hz, 2H), 7.79 (d, $J$ = 8.6 Hz, 2H), 11.20 (s, 1H), 13.00 (s, 1H); APCI: $m/z$ 363 (m-H)$^-$. Anal. ($C_{15}H_{13}N_4O_3SCl$) C, H, N, S, Cl.

**4-[2-(4-Chloro-5-methoxy-2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazino]benzenesulfonamide (74)**. The title compound was prepared from 4-chloro-5-methoxy-1H-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 3.86 (s, 3H), 6.87 (d, $J$ = 8.5 Hz, 1H), 7.07 (d, $J$ = 8.5 Hz, 1H), 7.30 (s, 2H), 7.60 (d, $J$ = 8.6 Hz, 2H), 7.83 (d, $J$ = 8.6 Hz, 2H), 11.15 (s, 1H), 13.09 (s, 1H); APCI: $m/z$ 379 (M-H)$^-$. Anal. ($C_{15}H_{13}N_4O_4SCl$) C, H, N, S, Cl.

**4-[2-(4-Methyl-5-nitro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazino]benzenesulfonamide (75)**. The title compound was prepared from 4-methyl-5-nitro-1H-indole-2,3-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.79 (s, 3H), 6.90 (d, $J$ = 8.6 Hz, 1H), 7.24 (s, 2H), 7.52 (d, $J$ = 8.7 Hz, 2H), 7.62 (d, $J$ = 8.7 Hz, 2H), 7.77 (d, $J$ = 8.6 Hz, 1H), 7.90 (d, $J$ = 8.6 Hz, 1H), 11.60 (s, 1H), 13.03 (s, 1H); ES-MS $m/z$ 374 (M-H)$^-$. Anal. ($C_{15}H_{13}N_5O_5S\cdot{}^1/_2H_2O$) C, H, N, S.

**4-[*N*′-(7-Oxo-6,7-dihydro-3H-pyrrolo[3,2-e]indazol-8-ylidene)-hydrazino]benzenesulfonamide (76).** The title compound was prepared from 3,6-dihydro-pyrrolo[3,2-e]indazole-7,8-dione[50] and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E in 8% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 7.02 (d, $J$ = 8.7 Hz, 1H), 7.28 $Z$ (s, 2H), 7.51 (d, $J$ = 8.6 Hz, 2H), 7.68 (d, $J$ = 8.8 Hz, 1H), 7.82 (d, $J$ = 8.7 Hz, 2H), 8.34 (s, 1H), 10.98 (s, 1H), 12.90 (s, 1H), 13.20 (s, 1H); APCI $m/z$ 356 (M)$^-$. Anal. ($C_{15}H_{12}N_6O_3S\cdot 1.46\ H_2O\cdot 0.2\ C_4H_8O_2$) C, H, N, S.

**4-[*N*′-(1-Chloro-7-oxo-6,7-dihydro-3H-pyrrolo[3,2-e]indazol-8-ylidene)-hydrazino]benzenesulfonamide (77).** 1-Chloro-3,6-dihydro-pyrrolo[3,2-e]indazole-7,8-dione was prepared from 5-amino-3-chloroindazole according to procedure A in 38% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 7.08 (d, $J$ = 7.9 Hz, 1H), 7.92 (d, $J$ = 7.9 Hz, 1H), 10.95 (s, 1H), 13.70 (s, 1H). Condensation of 1-chloro-3,6-dihydro-pyrrolo[3,2-e]indazole-7,8-dione and 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E gave the title compound in 45% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 7.11 (d, $J$ = 8.8 Hz, 1H), 7.26 (s, 2H), 7.51 (d, $J$ = 8.8 Hz, 1H), 7.64 (d, $J$ = 8.8 Hz, 2H), 7.82 (d, $J$ = 8.8 Hz, 2H), 11.17 (s, 1H), 13.25 (s, 1H), 13.41 (s, 1H): APCI $m/z$ 389/391 (M-H)$^-$. Anal. ($C_{15}H_{11}ClN_6O_3S$) C, H, N, S.

**4-[2-(7-Oxo-6,7-dihydro[1,2,3]triazolo[4,5-e]indol-8(3H)-ylidene)hydrazino]benzenesulfonamide (mixture of *E* and *Z* isomers) (78)**. 1,6-Dihydro[1,2,3]triazolo[4,5-*e*]indole-7,8-dione was prepared according to procedure A in 56% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.93 (d, $J$ = 8.6 Hz, 1H), 8.32 (d, $J$ = 8.6 Hz, 1H), 11.14 (s, 1H); APCI $m/z$ 189 $(M+1)^+$. Condensation of 1,6-dihydro[1,2,3]triazolo[4,5-*e*]indole-7,8-dione with 4-hydrazinobenzenesulfonamide hydrochloride according to procedure E gave the title compound in 15% yield: $^1$H NMR (DMSO-$d_6$): $\delta$ 7.06 $Z$ (d, $J$ = 8.4 Hz, 1H), 7.24 $E$ (d, $J$ = 8.4 Hz, 1H), 7.30 $Z$ (s, 2H), 7.30 $E$ (s, 2H), 7.55 $E$ (d, $J$ = 8.5 Hz, 2H), 7.82 $Z$ (d, $J$ = 8.5 Hz, 2H), 7.82 $E$ (d, $J$ = 8.5 Hz, 1H), 7.90 $E$ (d, $J$ = 8.7 Hz, 2H), 7.90 $Z$ (d, $J$ = 8.8 Hz, 2H), 7.98 $Z$ (d, $J$ = 8.4 Hz, 1H), 10.86 $E$ (s, 1H), 11.35 $Z$ (s, 1H), 12.87 $Z$ (s, 1H), 12.95 $E$ (s, 1H), 16.00 $Z$ (s, 1H), 16.25 $E$ (s, 1H); APCI $m/z$ 356 (M-H)$^-$. Anal. ($C_{14}H_{11}N_7O_3S\cdot H_2O$) C, H, N, S.

**4-[2-(7-Oxo-6,7-dihydro-8H-[1,3]thiazolo[5,4-e]indol-8-ylidene)hydrazino]benzenesulfonamide (79)**. The title compound was prepared from 6*H*-[1,3]thiazolo[5,4-*e*]indole-7,8-dione and 4-hydrazinobenzene sulfonamide hydrochloride according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 7.11 (d, $J$ = 8.6 Hz,1H), 7.26 (s, 2H), 7.59 (d, $J$ = 8.7 Hz, 2H), 7.81 (d, $J$ = 8.7 Hz, 2H), 7.97 (d, $J$ = 8.4 Hz, 1H), 9.29 (s, 1H), 11.24 (s, 1H), 12.67 (s, 1H); APCI $m/z$ 372 (M-H)$^-$. Anal. ($C_{15}H_{11}N_5O_3S_2$) C, H, N, S.

**4-{[(7-oxo-6,7-dihydro-8*H*-[1,3]thiazolo[5,4-*e*]indol-8-ylidene)methyl]amino}benzenesulfonamide (80)**. The title compound was prepared from 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one and sulfanilimide in 94% yield (contaminated with 8% 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one) according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 7.12 (d, $J$ = 8.3 Hz, 1H), 7.31 (s, 2H), 7.58 (d, $J$ = 9.0 Hz, 2H), 7.82 (m, 3H), 8.07 (d, $J$ = 8.3 Hz, 1H), 9.26 (s, 1H), 10.92 (s, 1H), 11.16 (d, $J$ = 12.1 Hz, 1H). Anal. ($C_{16}H_{12}N_4O_3S\cdot 0.08\ C_{12}H_{10}N_2O_2S\cdot{}^1/_3C_2H_6O$) C, H, N, S.

**4-[*N*′-2-Oxo-2,3-dihydropyrrolo[3,2-f]quinolin-1-ylidene)-hydrazino]benzenesulfonamide (81).** The title compound was prepared in 24% yield from 3-H-pyrrolo[3,2-*f*]quinoline-1,2-dione and 4-hydrazinobenzene sulfonamide hydrochloride according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 7.27 (s, 2H), 7.53 (d, $J$ = 8.8 Hz, 1H), 7.67 (d, $J$ = 8.8 Hz, 2H), 7.76 (dd, $J$ = 4.7, 8.4 Hz, 1H), 7.80 (d, $J$ = 8.8 Hz, 2H), 8.00 (d, $J$ = 8.9 Hz, 1H), 8.89 (d, $J$ = 3.7, 1H), 9.16 (d, $J$ = 8.2 Hz, 1H), 11.46 (s, 1H), 13.10 (s, 1H). APCI $m/z$ 368 $(M+H)^+$. Anal. ($C_{17}H_{13}N_5O_3S\cdot{}^3/_4\ HCl\cdot{}^2/_3H_2O$) C, H, N, S.

**4-{[(2-Oxo-2,3-dihydro-1H-pyrrolo[3,2-*f*]quinolin-1-ylidene)methyl]amino}benzenesulfonamide (82).** The title compound was prepared from 1-[(dimethylamino)methylene]-1,3-dihydro-2*H*-pyrrolo[3,2-*f*]quinolin-2-one and sulfanilamide according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 7.32 (s, 2H), 7.47 (d, $J$ = 8.8 Hz, 1H), 7.55 (dd, $J$ = 8.8, 4.2 Hz, 1H), 7.70 (d, $J$ = 8.7 Hz, 2H), 7.79 (d, $J$ = 8.8 Hz, 1H), 7.82 (d, $J$ = 8.7 Hz, 2H), 8.78 (d, $J$ = 3.4 Hz, 1H), 8.90 (m, 2H), 11.09 (s, 1H), 11.91 (d, $J$ = 11.8 Hz, 1H); APCI $m/z$ 365 (M-H)$^-$. Anal. ($C_{18}H_{14}N_4O_3S\cdot 0.4\ H_2O$) C, H, N.

***N*-Methyl-4-{[(7-oxo-6,7-dihydro-8H-[1,3]thiazolo[5,4-e]-indol-8-ylidene)methyl]amino}benzenesulfonamide (83)**. The title compound was prepared from 4-amino-*N*-methylbenzenesulfonamide and 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.36 (d, $J$ = 5.1 Hz, 3H), 7.08 (d, $J$ = 8.4 Hz, 1H), 7.34 (q, $J$ = 5.1 Hz, 1H), 7.58 (d, $J$ = 8.7 Hz, 2H), 7.72 (d, $J$ = 8.7 Hz, 2H), 7.79 (d, $J$ = 8.4 Hz, 1H), 8.05 (d, $J$ = 12.1 Hz, 1H), 9.23 (s, 1H), 10.89 (s, 1H), 11.14 (d, $J$ = 12.1 Hz, 1H); APCI $m/z$ 385 (M-H)$^-$. Anal. ($C_{17}H_{14}N_4O_3S_2\cdot{}^1/_2H_2O$) C, H, N, S.

***N*,*N*-Dimethyl-4-{[(7-oxo-6,7-dihydro-8H-[1,3]thiazolo-[5,4-e]indol-8-ylidene)methyl]amino}benzenesulfonamide (84).** The title compound was prepared from 4-amino-*N*,*N*-dimethylbenzenesulfonamide and 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.56 (s, 6H), 7.08 (d, $J$ = 8.4 Hz, 1H), 7.61 (d, $J$ = 8.7 Hz, 2H), 7.70 (d, $J$ = 8.7 Hz, 2H), 7.79 (d, $J$ = 8.4 Hz, 1H), 8.05 (d, $J$ = 12.1 Hz, 1H), 9.23 (s, 1H), 10.89 (s, 1H), 11.16 (d, $J$ = 12.1 Hz, 1H); APCI $m/z$ 399 (M-H)$^-$. Anal. ($C_{18}H_{16}N_4O_3S_2\cdot{}^1/_2H_2O$) C, H, N, S.

***N*-(2-Hydroxyethyl)-4-{[(7-oxo-6,7-dihydro-8H-[1,3]thiazolo[5,4-e]indol-8-ylidene)methyl]amino}benzenesulfonamide (85).** The title compound was prepared in 51% yield from *N*-(2-hydroxyethyl)-4-aminobenzenesulfonamide and 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.74 (q, $J$ = 6.0 Hz, 2H), 3.32 (q, $J$ = 6.0 Hz, 2H), 4.64 (t, $J$ = 6.0 Hz, 1H), 7.08 (d, $J$ = 8.5 Hz, 1H), 7.50 (t, $J$ = 6.0 Hz, 1H), 7.56 (d, $J$ = 8.7, 2H), 7.74 (d, $J$ = 8.7 Hz, 2H), 7.79 (d, $J$ = 8.5 Hz, 1H), 8.05 (d, $J$ = 12.0 Hz, 1H), 9.23 (s, 1H), 10.88 (s, 1H), 11.14 (d, $J$ = 12.0 Hz, 1H); APCI $m/z$ 415 (M-H)$^-$. Anal. ($C_{18}H_{16}N_4O_4S_2\cdot 2\ H_2O$) C, H, N, S.

***N*-[2-(1H−Imidazol-5-yl)ethyl]-4-{[(7-oxo-6,7-dihydro-8H-[1,3]thiazolo[5,4-e]indol-8-ylidene)methyl]amino}-**

**benzenesulfonamide hydrochloride (86)**. The title compound was prepared from 4-amino-*N*-[2-(1H-imidazol-5-yl)ethyl]benzene sulfonamide and 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.77 (t, $J$ = 6.6 Hz, 2H), 3.05 (q, $J$ = 6.6 Hz, 2H), 7.13 (d, $J$ = 8.4 Hz, 1H), 7.40 (s, 1H), 7.59 (d, $J$ = 8.8 Hz, 2H), 7.73−7.85 (m, 3H), 8.07 (d, $J$ = 12.0 Hz, 1H), 8.96 (s, 1H), 9.27 (s, 1H), 10.95 (s, 1H), 11.18 (d, $J$ = 12.0 Hz, 1H), 14.20 (bs, 2H); ESI: $m/z$ 467 $(M+H)^+$. Anal. ($C_{21}H_{18}N_6O_3S_2$·HCl·2 $H_2O$) C, H, N, S, Cl.

***N*-[2-(2-Hydroxyethoxy)ethyl]-4-{[(7-oxo-6,7-dihydro-8H-[1,3]thiazolo[5,4-e]indol-8-ylidene)methyl]amino}-benzenesulfonamide (87).** The title compound was prepared from 4-amino-*N*-(2-(2-hydroxyethoxy)ethyl)-benzenesulfonamide and 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo-[5,4-*e*]indol-7-one according to procedure G: $^1$H NMR (DMSO-$d_6$): (2.88 (q, $J$ = 6.0 Hz, 2H), 3.31 (t, $J$ = 5.0 Hz, 2H), 3.36 (t, $J$ = 5.8 Hz, 2H), 3.42 (t, $J$ = 5.1 Hz, 2 Hz), 4.5 (br s, 1H), 7.10 (d, $J$ = 8.4 Hz, 1H), 7.59 (d, $J$ = 8.8 Hz, 2H), 7.60 (t, $J$ = 6.0 Hz, 1H), 7.77 (d, $J$ = 8.7 Hz, 2H), 7.81 (d, $J$ = 8.6 Hz, 1H), 8.07 (d, $J$ = 12.2 Hz, 1H), 9.25 (s, 1H), 10.91 (s, 1H), 11.16 (d, $J$ = 12.2 Hz, 1H); APCI $m/z$ 459 $(M-H)^-$. Anal. ($C_{20}H_{20}N_4O_5S_2$·$H_2O$) C, H, N.

**4-{[(7-Oxo-6,7-dihydro-8H-[1,3]thiazolo[5,4-e]indol-8-ylidene)methyl]amino}-*N*-(3,6,9,12-tetraoxatridec-1-yl)-benzenesulfonamide (Z-isomer) (88).** A solution of 2.3 g (6.3 mmol) of toluene-4-sulfonic acid 2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester and ∼4 mL (∼60 mmol) of ammonium hydroxide in 10 mL of ethanol was stirred overnight at ∼60 °C. The solvent was removed on a rotary evaporator, and the residue was sequentially redissolved in ethanol and concentrated several times. The residue was then dissolved in ethanol, treated with ∼1.5 mL of TEA, and concentrated on a rotary evaporator. This residue was dissolved in 10 mL of THF, and 1.4 g (6.0 mmol) of 4-*N*-acetylsulfanilyl chloride and 1 mL (7 mmol) of TEA were added. The reaction mixture was stirred 1.5 h at room temperature and then 30 min at reflux. The solution was concentrated onto silica gel and chromatographed with an EtOAc to 5% MeOH/EtOAc gradient to give 4-*N*-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethyl)-sulfonamidophenyl]acetamide as an oil (1.92 g, 79%): $^1$H NMR (DMSO-$d_6$): $\delta$ 2.05 (s, 3H), 2.83 (q, $J$ = 5.9 Hz, 2H), 3.19 (s, 3H), 3.30−3.48 (m, 14H), 7.52 (t, $J$ = 5.8 Hz, 1H), 7.68 (d, $J$ = 8.8 Hz, 2H), 7.72 (d, $J$ = 8.8 Hz, 2H), 10.27 (s, 1H); APCI $m/z$ 403 $(M-H)^-$. A solution of 1.9 g (4.7 mmol) of *N*-[4-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethylsulfamoyl)-phenyl]-acetamide and 0.45 g (4.7 mmol) of methanesulfonic acid in 15 mL of ethanol was stirred at ∼70 °C for 24 h. Excess TEA was added, and the solvent was removed on a rotary evaporator. The residue was applied to a short column of silica gel and eluted with EtOAc to give 4-(*N*-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]ethoxy}ethyl)-sulfonamidoaniline as an oil (1.2 g, 70%): $^1$H NMR (DMSO-$d_6$): $\delta$ 2.76 (q, $J$ = 6.0 Hz, 2H), 3.20 (s, 3H), 3.32 (t, $J$ = 6.2 Hz, 2H), 3.37−3.48 (m, 12H), 5.88 (s, 2H), 6.56 (d, $J$ = 8.7 Hz, 2H), 7.11 (t, $J$ = 6.0 Hz, 1H), 7.37 (d, $J$ = 8.7 Hz, 2H); APCI $m/z$ 361 $(M-H)^-$. The title compound was prepared from 4-(*N*-(2-{2-[2-(2-methoxyethoxy)-ethoxy]-ethoxy}ethyl)sulfonamidoaniline and (8*Z*)-8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one according to procedure G: mp 158−159 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 2.87 (dt, $J$ = 5.6, 5.6 Hz, 2H), 3.17 (s, 3H), 3.33−3.38 (m, 4H), 3.38−3.47 (m, 10H), 7.10 (d, $J$ = 8.3 Hz, 1H), 7.58 (d, $J$ = 8.7 Hz, 2H), 7.63 (t, $J$ = 5.7 Hz, 1H), 7.77 (d, $J$ = 8.7 Hz, 2H), 7.81 (d, $J$ = 8.5 Hz, 1H), 8.06 (br d, $J$ = 8.9 Hz, 1H), 9.25 (s, 1H), 10.91 (s, 1H), 11.16 (br d, $J$ = 10.8 Hz, 1H); APCI $m/z$ 561 $(M-H)^-$. Anal. ($C_{25}H_{30}N_4O_7S_2$·$^1/_3H_2O$) C, H, N.

**4-{[(7-Oxo-6,7-dihydro-8H-[1,3]thiazolo[5,4-e]indol-8-ylidene)methyl]amino}-*N*-phenylbenzenesulfonamide (90).** The title compound was prepared from 4-amino-*N*-phenylbenzenesulfonamide and 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.97 (t, $J$ = 7.5 Hz, 1H), 7.07 (m, 3H), 7.18 (t, $J$ = 7.5 Hz, 2H), 7.50 (d, $J$ = 8.7 Hz, 2H), 7.69 (d, $J$ = 8.7 Hz, 2H), 7.78 (d, $J$ = 8.6 Hz, 1H), 8.00 (d, $J$ = 12.0 Hz, 1H), 9.22 (s, 1H), 10.18 (s, 1H), 10.87 (s, 1H), 11.09 (d, $J$ = 12.0 Hz, 1H); ES-MS $m/z$ 447 $(M-H)^-$. Anal. ($C_{22}H_{16}N_4O_3S_2$) C, H, N, S.

***N*-Methyl-4-{[(7-oxo-6,7-dihydro-8H-[1,3]thiazolo[5,4-e]-indol-8-ylidene)methyl]amino}-*N*-(2-pyridinyl)benzene-sulfonamide (92).** The title compound was prepared from 4-amino-*N*-(2-pyridinyl)benzenesulfonamide and 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 3.18 (s, 3H), 7.08 (d, $J$ = 8.5 Hz, 1H), 7.21 (dd, $J$ = 5.0, 7.3 Hz, 1 H), 7.52 (m, 4H), 7.79 (d, $J$ = 8.5 Hz, 1H), 7.82 (m, 1H), 8.02 (d, $J$ = 12.0 Hz, 1H), 8.28 (d, $J$ = 3.2 Hz, 1H), 9.23 (s, 1H), 10.89 (s, 1H), 11.13 (d, $J$ = 12.0 Hz, 1H); APCI $m/z$ 462 $(M-H)^-$. Anal. ($C_{22}H_{17}N_5O_3S_2$·0.7 HCl) C, H, N, S.

***N*-(2,6-Dimethylphenyl)-4-{[(7-oxo-6,7-dihydro-8H-[1,3]-thiazolo[5,4-e]indol-8-ylidene)methyl]amino}benzenesul-fonamide (93).** The title compound was prepared from 4-amino-*N*-(2,6-dimethylphenyl)benzenesulfonamide and 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.94 (s, 6H), 6.97 (m, 3H), 7.08 (d, $J$ = 8.4 Hz, 1H), 7.54 (d, $J$ = 8.9 Hz, 2H), 7.79 (d, $J$ = 8.9 Hz, 2H), 8.06 (d, $J$ = 12.1 Hz, 1H), 9.23 (s, 1H), 10.90 (s, 1H), 11.18 (d, $J$ = 12.1 Hz, 1H). Anal. ($C_{24}H_{20}N_4O_3S_2$) C, H, N, S.

***N*-Benzyl-4-{[(7-oxo-6,7-dihydro-8*H*-[1,3]thiazolo[5,4-*e*]-indol-8-ylidene)methyl]amino}benzenesulfonamide (94).** The title compound was prepared from 4-amino-*N*-benzylbenzenesulfonamide and 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 3.98 (d, $J$ = 6.2 Hz, 2H), 7.13 (d, $J$ = 8.4 Hz, 1H), 7.25 (m, 5H), 7.59 (d, $J$ = 8.7 Hz, 2H), 7.80 (d, $J$ = 8.7 Hz, 2H), 7.84 (d, $J$ = 8.4 Hz, 1H), 8.09 (m, 2H), 9.28 (s, 1H), 10.94 (s, 1H), 11.18 (d, $J$ = 12.1 Hz, 1H); APCI $m/z$ 461 $(M-H)^-$. Anal. ($C_{23}H_{18}N_4O_3S_2$·$^3/_2H_2O$) C, H, N, S.

**8-{[4-({[Amino(imino)methyl]amino}sulfonyl)anilino]-methylene}-7-oxo-7,8-dihydro-6H-[1,3]thiazolo[5,4-e]in-dole (96).** The title compound was prepared in 26% yield from 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one and 4-amino-*N*-(amino-imino-methyl)-benzenesulfonamide according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.64 (br s, 4H), 7.08 (d, $J$ = 8.4 Hz, 1H), 7.47 (d, $J$ = 8.6 Hz, 2H), 7.71 (d, $J$ = 8.6 Hz, 2H), 7.78 (d, $J$ = 8.4 Hz, 1H), 8.03 (d, $J$ = 12.2, 1H), 9.22 (s, 1H), 10.86 (s, 1H), 11.10 (d, $J$ = 12.2 Hz, 1H); APCI+MS $m/z$ 415 $(M+H)^+$. Anal. ($C_{17}H_{14}N_6O_3S_2$·$2H_2O$) C, H, N, S.

***N*-Acetyl-4-{[(7-oxo-6,7-dihydro-8H-[1,3]thiazolo[5,4-e]-indol-8-ylidene)methyl]amino}benzenesulfonamide (97).** The title compound was prepared in 26% yield from 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one and *N*-acetyl-4-aminobenzenesulfonamide according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 1.87 (s, 3H), 7.08 (d, $J$ = 8.4 Hz, 1H), 7.57 (d, $J$ = 8.8 Hz, 2H), 7.80 (d, $J$ = 8.4 Hz, 1H), 7.85 (d, $J$ = 8.8 Hz, 2H), 8.04 (d, $J$ = 12.0, 1H), 9.24 (s, 1H), 10.90 (s, 1H), 11.16 (d, $J$ = 12.0, 1H), 11.98 (s, 1H); ESI $m/z$ 413 $(M-H)^-$. Anal. ($C_{18}H_{14}N_4O_4S_2$) C, H, N, S.

***N*-Methyl-4-{[(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-methyl]amino}benzenesulfonamide (98).** The title compound was prepared from 3-(ethoxymethylene)-1,3-dihydro-2*H*-indol-2-one and 4-amino-*N*-methylbenzenesulfonamide according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.40 (d, $J$ = 5.2 Hz, 3H), 6.85 (d, $J$ = 7.6 Hz, 1H), 6.94 (t, $J$ = 7.6 Hz, 1H), 7.04 (t, $J$ = 7.6 Hz, 1H), 7.33 (q, $J$ = 5.2 Hz, 1H), 7.57 (d, $J$ = 8.7 Hz, 2H), 7.60 (d, $J$ = 7.6 Hz, 1H), 7.72 (d, $J$ = 8.7 Hz, 2H), 8.63 (d, $J$ = 12.4 Hz, 1H), 10.57 (s, 1H), 10.84 (d, $J$ = 12.4 Hz, 1H); APCI $m/z$ 328 $(M-H)^-$. Anal. ($C_{16}H_{15}N_3O_3S$) C, H, N, S.

**4-{[(2-Oxo-1,2-dihydro-3*H*-indol-3-ylidene)methyl]-amino}-*N*-(1,3-thiazol-2-yl)benzenesulfonamide (100).** The title compound was prepared from 4-amino-*N*-(1,3-thiazol-2-yl)benzenesulfonamide and 3-(ethoxymethylene)-1,3-dihydro-2*H*-indol-2-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.82 (d, $J$ = 4.6 Hz, 1H), 6.84 (d, $J$ = 7.8 Hz, 1H), 6.93 (d, $J$ = 7.8 Hz, 1H), 7.03 (t, $J$ = 7.4 Hz, 1H), 7.25 (d, $J$ = 4.6 Hz, 1H), 7.49 (d, $J$ = 8.8 Hz, 2H), 7.59 (d, $J$ = 7.4 Hz, 1H),

7.75 (d, $J$ = 8.8 Hz, 2H), 8.60 (d, $J$ = 12.3 Hz, 1H), 10.56 (s, 1H), 10.81 (d, $J$ = 12.3 Hz, 1H), 12.68 (s, 1H); ES-MS $m/z$ 397 $(M-H)^-$. Anal. ($C_{18}H_{14}N_4O_3S_2$) C, H, N, S.

**3-{[4-({[Amino(imino)methyl]amino}sulfonyl)anilino]methylene}-2-oxo-2,3-dihydro-1*H*-indole (101).** The title compound was prepared from 1-amino-4-({[amino(imino)methyl]amino}sulfonyl)benzene and 3-(ethoxymethylene)-1,3-dihydro-2*H*-indol-2-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 6.7 (br s, 4H), 6.84 (d, $J$ = 7.6 Hz, 1H), 6.93 (t, $J$ = 7.6 Hz, 1H), 7.03 (t, $J$ = 7.6 Hz, 1H), 7.47 (d, $J$ = 8.7 Hz, 2H), 7.59 (d, $J$ = 7.6 Hz, 1H), 7.71 (d, $J$ = 8.7 Hz, 2H), 8.61 (d, $J$ = 12.2 Hz, 1H), 10.55 (s, 1H), 10.80 (d, $J$ = 12.2 Hz, 1H); APCI $m/z$ 356 $(M-H)^-$. Anal. ($C_{16}H_{15}N_5O_3S\cdot H_2O$) C, H, N, S.

**8-{[4-(Methylsulfonyl)anilino]methylene}-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one (102).** The title compound was prepared from 4-(methylsulfonyl)aniline and 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 3.21 (s, 3H), 7.13 (d, $J$ = 8.4 Hz, 1H), 7.66 (d, $J$ = 8.7 Hz, 2H), 7.84 (d, $J$ = 8.4 Hz, 1H), 7.91 (d, $J$ = 8.7 Hz, 2H), 8.10 (d, $J$ = 12.0 Hz, 1H), 9.28 (s, 1H), 10.95 (s, 1H), 11.21 (d, $J$ = 12.0 Hz, 1H); APCI $m/z$ 370 $(M-H)^-$. Anal. ($C_{17}H_{13}N_3O_3S_2$) C, H, N, S.

**(4-{[(7-Oxo-6,7-dihydro-8H-[1,3]thiazolo[5,4-e]indol-8-ylidene)methyl]amino}phenyl)methanesulfonamide (103).** The title compound was prepared in 25% yield from 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one and 4-aminophenylmethane sulfonamide according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 11.1 (d,1H), 10.9 (s, 1H), 9.3 (s, 1H), 8.1 (d, 1H), 7.8 (d, 1H), 7.5 (q, 4H), 7.2 (d, 1H), 6.9 (s, 2H), 4.2 (s, 2H); APCI $m/z$ 387 $(M+H)^+$.

***N*-Methyl-(4-{[(7-oxo-6,7-dihydro-8*H*-[1,3]thiazolo[5,4-*e*]indol-8-ylidene)methyl]amino}phenyl)methanesulfonamide (104)**. The title compound was prepared from 4-[(methylsulfonyl)methyl]aniline and 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.58 (d, $J$ = 4.8 Hz, 3H), 4.32 (s, 2H), 6.90 (q, $J$ = 4.8 Hz, 1H), 7.12 (d, $J$ = 8.4 Hz, 1H), 7.40 (d, $J$ = 8.4 Hz, 2H), 7.45 (d, $J$ = 8.4 Hz, 2H), 7.80 (d, $J$ = 8.4 Hz, 1H), 8.05 (d, $J$ = 12.3 Hz, 1H), 9.26 (s, 1H), 10.86 (s, 1H), 11.05 (d, $J$ = 12.3 Hz, 1H); APCI $m/z$ 399 $(M-H)^-$. Anal. ($C_{18}H_{16}N_4O_3S_2\cdot H_2O$) C, H, N, S.

***N*-Methyl-{4-[2-(7-oxo-6,7-dihydro-8H-[1,3]thiazolo[5,4-e]indol-8-ylidene)hydrazino]phenyl}methanesulfonamide (105)**. The title compound was prepared from 4-hydrazinobenzyl methyl sulfone and 6*H*-[1,3]thiazolo[5,4-*e*]indole-7,8-dione according to procedure E: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.54 (d, $J$ = 4.8 Hz, 3H), 4.29 (s, 2H), 6.87 (q, $J$ = 4.8 Hz, 1H), 7.12 (d, $J$ = 8.5 Hz, 1H), 7.38 (d, $J$ = 8.5 Hz, 2H), 7.49 (d, $J$ = 8.5 Hz, 2H), 7.95 (d, $J$ = 8.5 Hz, 1H), 9.27 (s, 1H), 11.20 (s, 1H), 12.63 (s, 1H); APCI: $m/z$ 400 $(M-H)^-$. Anal. ($C_{17}H_{15}N_5O_3S_2\cdot {}^1/_2H_2O$) C, H, N, S.

***N*-(2-Hydroxyethyl)(4-{[(7-oxo-6,7-dihydro-8H-[1,3]-thiazolo[5,4-e]indol-8-ylidene)methyl]amino}phenyl)-methanesulfonamide (106)**. The title compound was prepared from (4-aminophenyl)-*N*-(2-hydroxyethyl)methanesulfonamide and 8-(hydroxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo-[5,4-*e*]indol-7-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.95 (q, $J$ = 6.0 Hz, 2H), 3.40 (q, $J$ = 6.0 Hz, 2H), 4.32 (s, 2H), 4.72 (t, $J$ = 6.0 Hz, 1H), 7.02 (t, $J$ = 6.0 Hz, 1H), 7.11 (d, $J$ = 8.4 Hz, 1H), 7.40 (d, $J$ = 8.8 Hz, 2H), 7.44 (d, $J$ = 8.8 Hz, 2H), 7.46 (d, $J$ = 8.8 Hz, 2H), 7.79 (d, $J$ = 8.5, 1H), 8.05 (d, $J$ = 12.3, 1H), 9.25 (s, 1H), 10.86 (s, 1H), 11.05 (d, $J$ = 12.3 Hz, 1H), 12.78 (s, 1H); APCI: $m/z$ 431 $(M+H)^+$. Anal. ($C_{19}H_{18}N_4O_4S_2\cdot H_2O$) C, H, N S.

**8-({4-[(Methylsulfonyl)methyl]anilino}methylene)-6,8-dihydro-7H-[1,3]thiazolo[5,4-e]indol-7-one (107).** The title compound was prepared in 66% yield from 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one and 4-methylsulfonylmethylaniline according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 2.90 (s, 3H), 4.47 (s, 2H), 7.12 (d, $J$ = 8.4 Hz, 1H), 7.44 (d, $J$ = 8.8 Hz, 2H), 7.47 (d, $J$ = 8.8 Hz, 2H), 7.80 (d, $J$ = 8.4 Hz, 1H), 8.07 (d, $J$ = 12.3 Hz, 1H), 9.26 (s, 1H), 10.87 (s, 1H), 11.07 (d, $J$ = 12.3 Hz, 1H); APCI $m/z$ 384 $(M-H)^-$. Anal. ($C_{18}H_{15}N_3O_3S_2\cdot {}^1/_3\ H_2O$) C, H, N, S.

**8-{[(2,2-Dioxido-1,3-dihydro-2-benzothien-5-yl)amino]methylene}-6,8-dihydro-7H-[1,3]thiazolo[5,4-e]indol-7-one (108).** The title compound was prepared in 37% yield from 8-(ethoxymethylene)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one and 2,2-dioxo-1,3-dihydrobenzo[*c*]thiophene-5-ylamine according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 11.11 (d,-1H), 10.89 (s, 1H), 9.27 (s, 1H), 8.06 (d, 1H), 7.82 (d, 1H), 7.47 (m, 2H), 7.13 (d, 1H), 6.98 (d, 1H), 6.5 (m, 2H); APCI $m/z$ 384 $(M+H)^+$. Anal. ($C_{18}H_{13}N_3O_3S_2\cdot H_2O$) C, H, N, S: C, 53.85; H, 3.77; N, 10.47; S, 15.97. Found: C, 53.84; H, 3.84; N, 10.36; S, 15.95.

**3-{[(2,2-Dioxido-1,3-dihydro-2-benzothien-5-yl)amino]methylene}-5-(1,3-oxazol-5-yl)-1,3-dihydro-2*H*-indol-2-one (109)**. The title compound was prepared from 2,2-dioxido-1,3-dihydro-2-benzothien-5-ylamine and 3-(ethoxymethylene)-5-(1,3-oxazol-5-yl)-1,3-dihydro-2*H*-indol-2-one according to procedure G: $^1$H NMR (DMSO-$d_6$): $\delta$ 4.45 (s, 2H), 4.50 (s, 2H), 6.93 (d, $J$ = 8.4 Hz, 1H), 7.37−7.51 (m, 5H), 7.99 (s, 1H), 8.39 (s, 1H), 8.73 (d, $J$ = 12.3 Hz, 1H), 10.70 (s, 1H), 10.75 (d, $J$ = 12.3 Hz, 1H); APCI $m/z$ 392 $(M-H)^-$. Anal. ($C_{20}H_{15}N_3O_4S\cdot H_2O$) C, H, N, S.

**Molecular Modeling**. Favorable substitutions on the core oxindole template (positions 4−7) were identified via a ligand-protein docking protocol. Initially, commercially available anilines were identified and converted to their corresponding SMILES[51] strings. These anilines were prefiltered for chemically reactive groups and molecular weight criteria to yield an initial starting set of 410 anilines. In-house virtual chemistry algorithms were then used to convert the anilines to the corresponding 4-[2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazino]benzene-sulfonamides. In the case of asymmetric anilines containing a meta-substituent, two possible oxindole products could result from the chemistry (yielding 4- or 6-substituted oxindoles), and both products were investigated via the docking algorithms.

The SMILES strings were then converted to the X-PLOR[52] psf/pdb molecule format via in-house algorithms. Initially, the atomic coordinates for each molecule were assigned dummy values. The molecule psf/pdb's served as input for an X-PLOR high-temperature dynamics script for conformational searching. Each molecule was heated at 2000 °C for 0.5 ps, followed by a 0.2 ps simulation at 100 °C, followed by 200 steps of minimization. This process was repeated 100 times for each molecule to yield 100 starting conformations. Conformations with energy greater than 7.5 kcal/mol above the lowest energy structure identified were rejected. Remaining conformations were rms superimposed, and, in cases where two structures had a heavy atom rms deviation of less than 0.25 Å, the higher energy structure was rejected. The lowest energy conformation for each molecule was used as input for a Gaussian[53] quantum mechanics calculation to obtain partial atomic charges. Molecules were optimized using the semiempirical PM3 basis set followed by a Hartree−Fock 3-21G* single point calculation.[54,55] In the latter step, charges were obtained using the CHELPG methodology.[56]

Molecule topologies and conformations were then converted into a format suitable for use in docking calculations employing the Macromodel software package.[57] The initial protein conformation was taken from the CDK2-cyclin A-flavopiridol complex solved in-house. Additionally, the X-ray structure of CDK2 in complex with compound **16** was used to generate an initial positioning for the oxindole template. Initial docking was accomplished by rms fitting to the coordinates for the oxindole moiety of compound **16**. These coordinates were also used as positional restraints for the conformations of the derivative molecules. Energy minimization calculations were then performed using the GB/SA solvation model[58] with 12 Å cutoffs for nonbonded interactions. Residues within an 8 Å sphere of the ATP binding site were allowed to adjust to the presence of the ligand while other atoms within the protein were restrained.

Following minimization, the molecules were scored and sorted according to "binding" energy. This energy included ligand internal energy differences (relative to the lowest energy

**Table 4.** Crystallographic Data

| compd no. | **16** | **98** | **105** | **100** | **101** | **109** | **91** |
|---|---|---|---|---|---|---|---|
| space group | $P2_12_12_1$ | $P2_12_12_1$ | $P2_12_12_1$ | $P2_12_12_1$ | $P2_12_12_1$ | $P2_12_12_1$ | $P6_222$ |
| cell: a | 54.14 | 72.39 | 72.76 | 72.53 | 72.45 | 72.68 | 184.95 |
| b | 72.71 | 73.96 | 73.78 | 74.04 | 73.90 | 73.72 | 184.95 |
| c | 72.93 | 54.06 | 54.00 | 54.08 | 54.10 | 54.17 | 212.83 |
| resolution (Å) | 500−2.2 | 500−2.2 | 500−2.0 | 500−2.0 | 500−2.0 | 500−2.0 | 500−2.8 |
| no. of obs | 157 652 | 51 192 | 104 211 | 44 454 | 60 211 | 98 375 | 50 936 |
| no. of unique reflns | 13 325 | 13 376 | 19 360 | 17 232 | 19 110 | 19 650 | 541 713 |
| completeness (%) | 87.9 | 87.6 | 95.6 | 85.0 | 93.8 | 96.9 | 95.5 |
| Rmerge (%) | 7.1 | 4.3 | 4.2 | 6.0 | 5.2 | 5.2 | 7.0 |
| Rfactor (%) | 20.0 | 18.4 | 19.1 | 18.7 | 20.3 | 19.1 | 21.8 |
| Rfree (%) | 23.9 | 22.4 | 23.5 | 22.8 | 23.8 | 22.2 | 26.3 |
| ave B | 37.1 | 32.7 | 31.5 | 36.0 | 32.5 | 36.7 | 55.3 |
| Rms bonds (Å) | 0.009 | 0.009 | 0.009 | 0.009 | 0.011 | 0.009 | 0.010 |
| Rms angles (°) | 1.4 | 1.4 | 1.3 | 1.3 | 2.0 | 1.4 | 1.4 |

conformation), protein−ligand interaction energies, and solvation energy differences. Internal energy differences within the protein were excluded. The coordinates for the lowest energy bound conformation of each molecule were then saved to file. Each final docked molecule structure was visually inspected. This inspection, in conjunction with a consideration of the binding energy scores, was used to select molecules for synthesis.

**Crystallography**. The procedures for protein expression, purification, crystallization, and crystal structure determination of the CDK2 complexes reported here have been described previously.[11,38,59] All structures were derived from CDK2 or CDK2/cyclin A crystals that were soaked in solutions containing inhibitor. Crystallographic data is shown in Table 4.

**Enzymology.** Human CDK2/cyclin A was expressed in insect cells and purified as previously described for the production of CDK2,[59] except for the following changes. Human CDK2 and human cyclin A were coexpressed in Baculovirus-infected T.ni cells. An HS (Poros) column was equilibrated in 25 mM HEPES (pH 7.5), 25 mM NaCl, 2 mM EDTA, and human CDK2/cyclin A was eluted from this column with 0.3 M NaCl. Final purification was accomplished using a Pharmacia S-200 Superdex column in place of the S-75 column used for the CDK2 preparation. CDK2/cyclin A was stored at −80 °C prior to use.

Human CDK1 was expressed and purified using the procedures noted above for the production of CDK2 except for the following changes. Human CDK1/cyclin A was expressed in baculovirus-infected *Sf9* cells. The complex was step-eluted from the HS column (Poros) with 0.4 M NaCl. Enzyme-containing fractions were aliquoted and stored at −80 °C.

Enzyme assays were performed in 96-well plates. Briefly, compounds were diluted in 100% DMSO and transferred in 25−100% DMSO. Serial 2- or 3-fold dilutions were made. Assays contained 100 mM HEPES (pH 7.5), 10 mM $MgCl_2$, 0.1% BSA, 5% DMSO (with and without inhibitor), 1.4 $\mu$M [$\gamma$-$^{32}$P]ATP (0.07 $\mu$Ci/well), 1.5 $\mu$M of the peptide Biotin-aminohexyl-Ala−Arg−Arg−Pro−Met−Ser−Pro−Lys−Lys−Lys−Ala-$CONH_2$ and enzyme. Reactions were allowed to proceed for 20−30 min (CDK2) or 30−60 min (CDK1). The DMSO solutions were added to the assay plate first, and the reactions were initiated by the addition of enzyme. Enzyme concentrations in the assays were 5−10 nM for both CDK1/cyclin A and CDK2/cyclin A as determined by protein titration. The enzyme catalyzed reactions were terminated by the addition of four assay volumes of 100 mM EDTA in PBS (pH 7.0) containing 0.5 mg of Neutravidin-coated SPA beads (Amersham Pharmacia). The plates were allowed to sit undisturbed for 8−24 h prior to quantitation using a scintillation counter.

Values for $pIC_{50}$ were obtained using nonlinear regression analysis according to the equation $y = \text{bkgnd} + ((B_0 - \text{bkgnd})/(1 + [\text{inhibitor}]/10^{-pIC_{50}}))$ where $B_0$ is the enzyme activity in the absence of inhibitor and $y$ is the measured activity. The average standard deviation of $pIC_{50}$ values for this assay was 0.36.

**Cell Anti-Proliferation Assay**. Inhibition of cell growth was measured by a standard MTT assay using a panel of tumor cell lines (RKO, HT29, SW620, MDAMB468) and cells isolated from human foreskin fibroblasts (HFF). Briefly, cells were seeded (2500 to 5000 cells/well) in 96-well plates and allowed to attach for ∼24 h. Cells were incubated with compound for 72 h in DMEM media containing 10% fetal bovine serum. The cellular metabolic activity, an indicator of cell viability, was assessed using MTT.[60] Cells were treated with a range of compound concentrations in duplicate to generate dose−response curves. The compound concentration required to inhibit 50% of cell growth ($IC_{50}$) was determined using a nonlinear regression analysis.

**G1/S Phase Progression Assay**. Inhibition of progression of cells from G1 into S-phase was measured using a BrdU incorporation assay. HFF cells were grown to confluency for synchronization. Cells were then plated in 96-well plates for ∼18 h, compound was added for 2 h, then cells were co-treated with BrdU for 4 h. BrdU incorporated into cellular DNA was detected and quantitated using an antibody sandwich BrdU ELISA. Dose response curves were generated by varying the compound concentration (in triplicate). The compound concentration required to inhibit 50% of BrdU incorporation ($IC_{50}$) was determined using a nonlinear regression analysis.

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