Articles

Bis(1*H*-2-indolyl)methanones as a Novel Class of Inhibitors of the Platelet-Derived Growth Factor Receptor Kinase

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The novel lead bis(1*H*-2-indolyl)methanone inhibits autophosphorylation of platelet-derived growth factor (PDGF) receptor tyrosine kinase in intact cells. Various substituents in the 5- or 6-position of one indole ring increase or preserve potency, whereas most modifications of the ring structures and of the methanone group as well as substitution at both indoles result in weak or no activity. An ATP binding site model, derived by homology from the FGFR-1 tyrosine kinase crystal structure suggesting hydrogen bonds of one indole NH and the methanone oxygen with the backbone carbonyl and amide, respectively, of Cys684, explains why only one indole moiety is open for substitution and locates groups in the 5- or 6-position outside the pocket. The hitherto most active derivatives, **39**, **53** and **67**, inhibit both isoforms of the PDGF receptor kinase in intact cells, with IC_{50} of 0.1−0.3 μM, and purified PDGFβ-receptor in vitro, with IC_{50} of 0.09, 0.1, or 0.02 μM, respectively. PDGF-stimulated DNA synthesis is inhibited by these derivatives with IC_{50} values of 1−3 μM. Kinetic analysis of **53** showed an ATP-competitive mode of inhibition. The compounds are inactive or weakly active toward a number of other tyrosine kinases, including the FGF receptor 1, EGF receptor, and c-Src kinase, as well as toward serine-threonine kinases, including different PKC isoforms and GRK2, and appear therefore selective for PDGF receptor inhibition.

Introduction

Aberrant expression and activity of platelet-derived growth factors (PDGFs) and their cognate receptors of the class III receptor tyrosine kinase family (for reviews, see refs 1−3) have been found in various disease states, including different cancers, atherosclerosis, and fibrosis.[4−7] Examples include the autocrine activation of resident PDGF receptors by aberrantly expressed PDGF in human glioma cells[8−10] and constitutively active fusion proteins of PDGFβ-receptor in human chronic myelomonocytic leukemia.[11,12] In other forms of human cancer, tumor-derived PDGF may be involved in stroma cell stimulation and thereby indirectly force tumor growth.[13] Also, PDGF seems to be involved in the regulation of the interstitial tissue pressure,[14] which may be relevant in the context of conventional chemotherapeutic treatment of tumors. Therefore, the investigation of different strategies to block PDGF receptor signaling activity has attracted much interest. Low molecular weight direct inhibitors of the PDGF receptor tyrosine kinase activity with diverse structures have been described, including quinolines,[15,16] quinoxalines,[17−19] pyridopyrimidines,[20,21] phenylaminopyrimidines,[22] phenylbenzimidazoles,[23] indolin-2-ones,[24−26] leflunomide,[27] and pyrrolo(3,4)-beta-carbolinediones.[28] Many of these compounds suppress disease-relevant PDGFR signaling in various experimental models. When screening a chemical library for effects on PDGFR autophosphorylation in a cellular assay system, we observed a strong inhibition by bis(1*H*-2-indolyl)methanone. This paper presents the synthesis and structure−activity relationships for bis(1*H*-2-indolyl)methanone derivatives. Many of the compounds are rather potent. Inhibition of the PDGFR kinase is direct, targeted at the ATP-site, and selective when compared to a panel of tyrosine and serine-threonine kinases.

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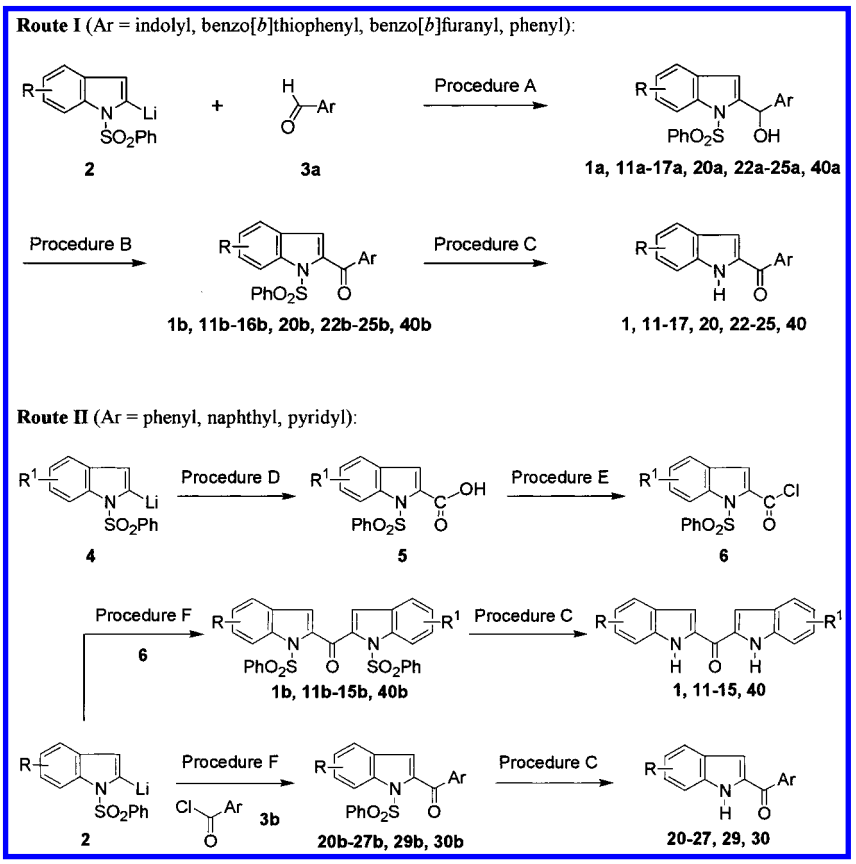
Scheme 1[a]



[a] (A) THF, −78 °C; (B) PDC/PTFA, CH_2Cl_2, rt, 2 h to 21 d; (C) either 1. NaOH/H_2O/EtOH, reflux, 2 to 12 h, or TBAF/THF, 50 °C, 0.5 to 4 h; (D) THF, −78 °C, CO_2, CH_2Cl_2, 6 M HCl, reflux, 1 h; (E) $SOCl_2$, reflux, 2 h; F: THF, −78 °C to rt, 12 h.

Results and Discussion

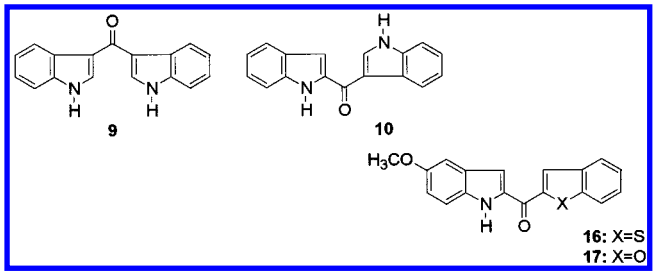
Synthesis of Bis(1H-2-indolyl)methanone Derivatives and Related Compounds. Bis(1*H*-2-indolyl)methanone (**1**) and the corresponding derivatives **11**−**15** and **40** were synthesized as described[29] by coupling of the respective aldehyde **3a**, oxidation of the resulting carbinols **1a**, **11a**−**15a**, and **40a** and deprotection of the *N*-phenylsulfonated ketones **1b**, **11b**−**15b**, and **40b** (Scheme 1, route I). The same reaction sequence was used for the preparation of the 2-benzoylindoles **20** and **22**−**25**. Additionally, all these ketones as well as other 2-aroylindole derivatives (**21**, **26**, **27**, **29**, and **30**) can be prepared by condensation of N-protected 2-lithiated indole **2** with suitable acid chlorides **6** or **3b** (Scheme 1, route II). The necessary methoxyindoles for the preparation of compounds **11**−**15** were obtained by an easy and efficient synthesis, elaborated by Leimgruber and Batcho.[34]

Following the general reaction sequence described in Scheme 1, route I, we also prepared 1*H*-2-indolyl(1*H*-3-indolyl)methanone (**10**)[32,33] (Chart 1) via the N-protected carbinol **10a** using 1-phenylsulfonyl-1*H*-indole-3-carbaldehyde instead of the 2-carbaldehyde of type **3a**. Employing the 2-aldehydes of benzo[*b*]furan[35] and benzo[*b*]thiophene[36] afforded the O,S-related benzo[*b*]furan and benzo[*b*]thiophene analogues **16** and **17** (Chart 1). Bisbenzo[*b*]thiophen-2-ylmethanone (**18**) was also synthesized in analogy to Scheme 1, route I, by condensing 2-lithiated benzo[*b*]furan with the respective 2-aldehyde.

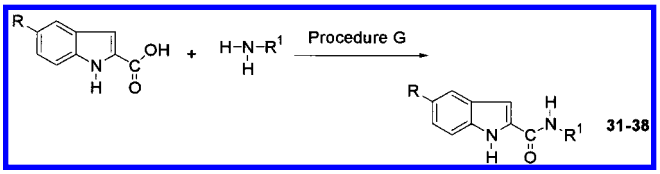
Also, various indolylcarboxamide derivatives were synthesized. Condensation of indole-2-carboxylic acid with different amines resulted in moderate yields by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI·HCl) in dry CH_2Cl_2[37] (Scheme 2).

Because of the high activity of the 5-methoxyindole compound **11** (see below), we synthesized the corresponding 5-hydroxy derivative **39** and, in turn, functionalized the 5-hydroxy group. Following literature procedures, we failed to obtain compound **39** by using benzylthiol/$AlCl_3$[38] or trimethylchlorosilane/NaI[39] for cleaving the ether **11** (Scheme 3). Therefore, we followed the methodology described in Scheme 1 and prepared

Chart 1

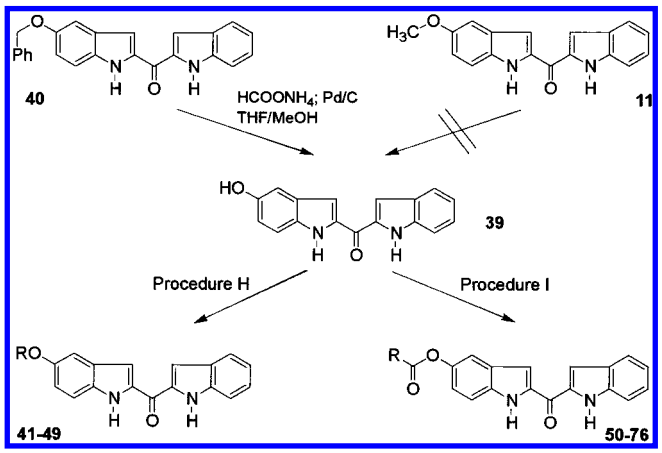


Scheme 2[a]



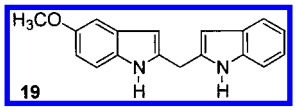
[a] (G) EDCI·HCl, CH_2Cl_2, rt.

Scheme 3[a]

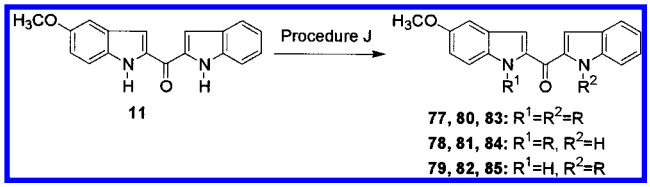


[a] (H) R-halide/K_2CO_3, acetone; (I) RCO_2Cl/pyridine, ethyl acetate.

Chart 2



Scheme 4[a]



[a] If 1 equiv of each alkyl halide (R-Hal) is employed, the disubstituted (R^1=R^2=R) and two monosubstituted derivatives (R^1=H, R^2=R or R^1=R and R^2=H) are obtained in a ratio of 2:1:1. The substitution pattern of the N-alkylated species could be identified by 2-dimensional NOESY−^{1}H NMR analysis and according to the fragmentation pattern in mass spectrometry.

the ketone **40** starting from 5-benzyloxyindole and indole-2-carbaldehyde (route I) or indole-2-carboxylic acid (route II). In the next step, **39** could easily be obtained by removing the benzyl group with ammonium formate and Pd/C as described[40] (Scheme 3). As compound **39** showed similar activity as **11**, further analogues were prepared according to Scheme 3. Since it was impossible to remove the benzyl group from the *N*-phenylsulfonyl protected derivative of **40**, the protecting groups had to be removed before further derivatization.

Bis(1*H*-3-indolyl)methanone (**9**)[30,31] (Chart 1) and 1,2-bis(1*H*-2-indolyl)-1,2-ethandione (**7**)[50] were obtained by following described procedures.[30]

The bis(1*H*-2-indolyl)methane **19** (Chart 2), in which the indole moieties are bridged via a methylene group instead of a carbonyl group, was synthesized by treating the bisindole **11** with hydrazine hydrate in diethylene glycol. For preparation of the N-alkylated and benzylated species **77**−**85**, compound **11** was reacted with the respective alkyl- and benzyl halides (Scheme 4).

SAR for Inhibition of PDGFR Autophosphorylation in a Cellular Assay. Bis(1*H*-2-indolyl)methanone (**1**) caused a strong inhibition of PDGF receptor activity (IC_{50} 1 μM), which was similar to the effect of the used reference compound, quinoxaline AG1295. The precursor compounds as well as 1,2-bis(1*H*-2-indolyl)-1,2-ethanedione (**7**)[50] were inactive. The same is true for bis(1*H*-3-indolyl)methanone (**9**) and 1*H*-2-indolyl(1*H*-3-indolyl)methanone (**10**) as well as for 1*H*-2-indolyl(5-methoxy-1*H*-2-indolyl)methane (**19**). Taken together, these results suggest that a carbonyl group bridging the two indolyl residues in the 2,2′-position is characteristic of the new pharmacophore.

Methoxy-substitution in the 5- or 6-position increases the efficacy of inhibition compared to the parent compound **1**, whereas substitution in 7-position leads to inactivity (Table 1). The 5,5′-dimethoxy-substituted derivative **14** is only weakly active. Also, methyl substitution in position 5 reduces activity compared to compound **1**. The favorable effect of methoxy substituents agrees with previous results for quinolines,[16] where a 4-methoxyphenyl group in the 2-position as well as 6,7-dimethoxy substitution has led to the most potent PDGFRβ inhibitors.

Substitution of the 1′-nitrogen by sulfur or oxygen in compound **16** and **17**, respectively, leads to moderately or strongly reduced activity in comparison with compound **11**. If both nitrogens are exchanged by sulfur, a completely inactive compound results (**18**) (Table 1).

Phenyl (**20**−**23**, **25**−**28**), naphthyl (**29**), and pyridyl (**30**) replacement of one indolyl ring leads to inactivity (IC_{50} > 30 μM, data not shown). Only the 4-methoxyphenyl compound **24** has some residual potency (IC_{50} = 3−10 μM).

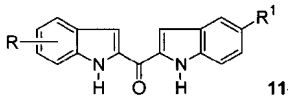
With the exception of the weakly active compound **33** (IC_{50} = 10−30 μM), all the carboxamides **31**, **32**, and **34**−**38** were inactive (IC_{50} > 30 μM).

Derived from the 5-OH compound **39**, a series of diverse ether and ester structures (compounds **40**−**76**, Table 1) indicates that a certain variability of substituents is tolerated in the 5-position of the lead structure **1**. Nevertheless, empirical structure−activity relationships based on some inactive derivatives and on an IC_{50} range of about 2 orders of magnitude are evident. On average, esters seem to be more active than ethers. The 5-dimethylaminomethyl ester **53** is the most potent derivative so far. Unbranched, short alkyl chains are favorable (**41**, **50**, **52**, **54**) with decreasing activity from methyl to *n*-propyl. Among larger substituents, unbranched aralkyl (**55**, **58**, **61**, **69**) and aryl groups (**57**, **60**, **66**, **68**, **72**) are superior to long, ω-iodinated alkyl chains (**44**, **47**) and cycloalkyl rings (**46**, **70**, **71**). Potency is slightly lowered in substituted phenyl derivatives (IC_{50} of **60** < **61** < **69** < **56** < **51** < **64**). Only bulky phenoxyphenyl or benzoylphenyl substituents lead to inactivity (**74**-**76**), which also results from nonpolar, α-branched substituents (**48**, **73**). A polar α-branch, however, is favorable (**59**). This striking positive effect of polarity is even more obvious if nitrogen or oxygen atoms are introduced in alkyl or cycloalkyl groups (compare **42** and **49** with **46**, **43** and **45** with **44** and **47**, **53** with **52**, and **67** with **52**).

Modeling of Inhibitor Interaction with the PDGFRβ Kinase Domain. It is rather difficult to explain the structure−activity relationships described so far without structural information about the PDGFRβ tyrosine kinase domain. Kinetic analysis (see below) suggests that the bis(1*H*-2-indolyl)methanones, as many other tyrosine kinase inhibitors, interact with the ATP binding site. Recently, we have derived a

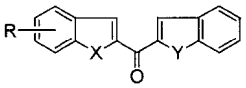
Table 1. Inhibition of PDGF Receptor Tyrosine Kinase by Bis(1*H*-2-indolyl)methanones and Related Compounds

compd.	[a]IC_{50} (μM)
AG1295	0.5-1



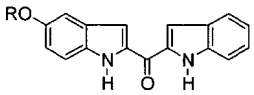
11-15

compd.	R	R^1	[a]IC_{50} (μM)
11	5-OCH_3	H	0.3
12	6-OCH_3	H	0.3
13	7-OCH_3	H	>30
14	5-OCH_3	OCH_3	10 - 30
15	5-CH_3	H	7.5



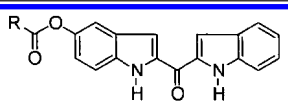
16-18

compd.	R	X	Y	[a]IC_{50} (μM)
16	5-OCH_3	N-H	S	1.0
17	5-OCH_3	N-H	O	4.0
18	H	S	S	>30

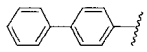
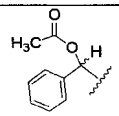


39-49

compd.	R	[a]IC_{50} (μM)
39	H	0.2
40	benzyl	10 - 30
41	ethyl	2.3
42	2-(N-morpholino)-ethyl	2.5
43	$(CH_2)_3$-NMe_2	3.2
44	n-C_4H_8-I	5 - 20
45	2-(dimethylamino)ethyl	0.8
46	cyclohexylmethyl	>30
47	5-iodopentyl	> 20
48	1-phenylethyl	>30
49	2-(N-piperidino)ethyl	0.8



50-76

50	methyl	0.3
51	4-methoxyphenyl	3.2
52	n-propyl	1.1
53	dimethylaminomethyl	0.1
54	ethyl	0.9
55	(2-thiophenyl)methyl	0.8
56	2-acetoxyphenyl	2.2
57		1.7
58	2-phenylethyl	1.2
59		0.9
60	phenyl	0.8
61	(3-methoxyphenyl)methyl	1.0
62	2-chlorophenyl	4.6
63	4-nitrophenyl	0.9
64	3,4,5-trimethoxyphenyl	4.1
65	-CH=CH-Ph	3.4
66	2-furanyl	0.6
67	$-CH_2-O-CH_3$	0.2
68	2-quinolyl	0.4
69	4-ethoxyphenyl	1.3
70	cyclopropyl	9.1
71	cyclobutyl	5.7
72	3-pyridyl	1.0
73	diphenylmethyl	>30
74	2-phenoxyphenyl	>30
75	3-phenoxyphenyl	>30
76	2-benzoylphenyl	>30

[a] IC_{50} were determined by measuring inhibition of PDGF receptor autophosphorylation in intact Swiss 3T3 cells as described[18] and outlined in detail under Experimental.

putative structure of the PDGFRβ tyrosine kinase by homology modeling (program COMPOSER,[41] implemented in SYBYL-6.6, Tripos Inc.), starting from different FGFR-1 tyrosine kinase crystal structures.[42−44] This model was used to dock inhibitors of the bis(1*H*-2-indolyl)methanone class and of different other structural families[45] (to be published in detail elsewhere). Initially, two alternative docking modes of the bis(1*H*-2-indolyl)methanones, both based on a bidentate hydrogen-bond donor−acceptor system and on the projection of one indole ring inside and the other one outside the catalytic cleft, came into question according to corresponding binding patterns of inhibitors cocrystallized with FGFR-1 tyrosine kinase (see Figure 1).

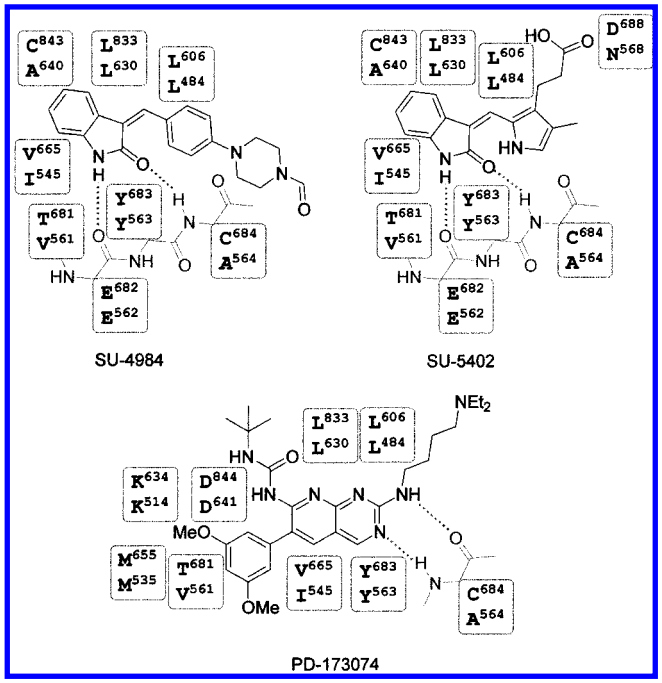


Figure 1. Structures of the FGFR-1 kinase inhibitors SU-4984, SU-5402,[43] and PD-173074,[44] with schematic representation of their binding modes and of important corresponding PDGFRβ (above) and FGFR-1 kinase residues (below).

The first one, derived from the complexes with SU-4984 and SU-5402,[43] contains hydrogen bonds of the inner indole NH with the oxygen of the Glu682 (FGFR-1: Glu562) backbone and of the methanone oxygen with the NH function of Cys684 (FGFR-1: Ala564). The latter bond is also present in the second mode resembling the crystal structure with PD-173074[44] (see Figure 2a), but now the outer indole nitrogen serves as hydrogen donor for the backbone oxygen of Cys684. Assuming the first mode would imply closely superimposed indolinone and indolylmethanone moieties of SU-5402 and **67**, respectively. However, the low activity of the 5,5′-dimethoxy derivative **14** compared to that of the 5-methoxy compound **11** (Table 2) indicates limited space around the inner indolyl system, contrary to the higher degrees of freedom for 5- and 6-substitution at the corresponding moiety of potent indolinone PDGFRβ inhibitors.[24−26] Thus, the inner indole ring of the bis(1*H*-2-indolyl)-methanones should penetrate more deeply into the binding cleft than that of SU-5402, and therefore, the second binding mode corresponding to that of PD-173074 must be suggested (see Figure 2). The unsubstituted moieties of compounds **16** and **17** are also more probably inside the pocket due to their 5-methoxyindole substituents, but they do not provide hydrogen donor atoms for Glu682. Nevertheless, the modeled distance of about 3.5 Å between the heteroatoms of the inner heterocycle and the backbone oxygen of Glu682 might indicate an electrostatic attraction in the case of bisindoles (see Figure 2b) and repulsion in the case of the less active compounds **16** and **17**.

All docking calculations were performed with SYBYL6.6 (Tripos Inc.) on a SGI Indigo^2 workstation. After initial optimization of the complexes with the Kollman all-atom force field, final energy minimizations of the ligands and the binding site region were performed with the Tripos force field. In Figure 2b,

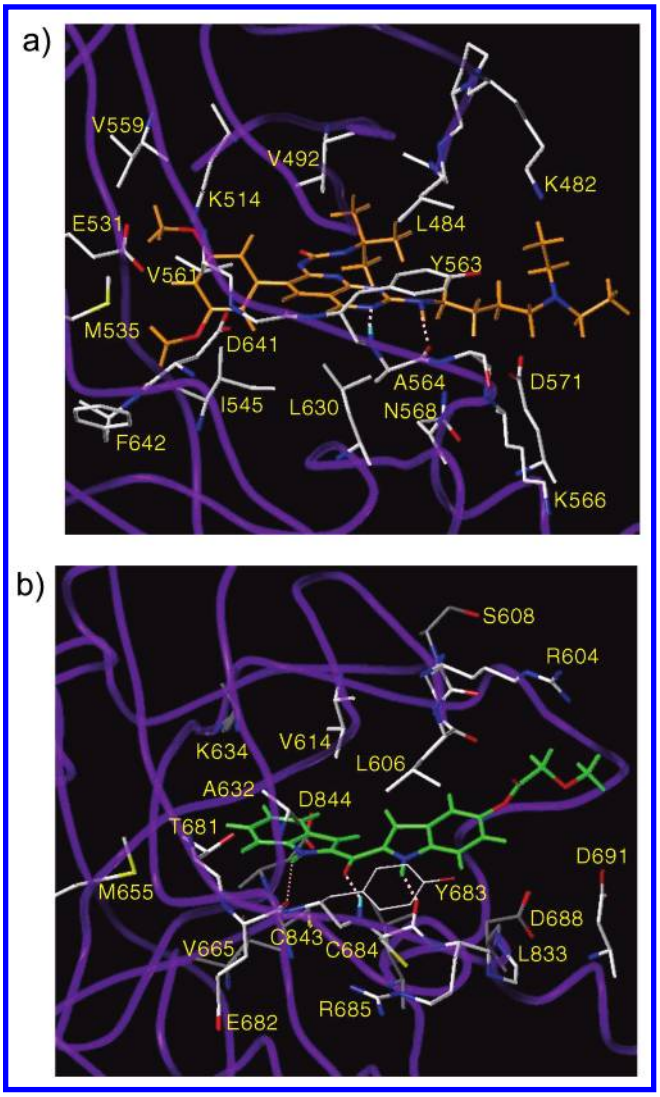


Figure 2. Suggested binding mode of bis(1*H*-2-indolyl)-methanones to PDGFRβ kinase in comparison with the crystal structure of FGFR-1 kinase complexed with PD-173074.[44] Hydrogen bonds are represented as pink dashed lines. Important residues are drawn and labeled. (a) PD-173074 (C- and H-atoms orange) bound to FGFR-1 kinase. (b) Compound **67** (C- and H-atoms green) docked into the PDGFRβ kinase model; the third interaction between the inner indole-NH and the Glu-682 oxygen (thin dashed line) is weak and hypothetical.

compound **67** is docked in a propeller-like energy-minimum conformation with an angle of about 22° between both indole planes. However, detailed conclusions about the active conformation of the inner indole ring and about the fine structure of surrounding residues in the pocket are not possible, despite the highly homologous catalytic domains of FGFR-1 and PDGFRβ kinases. The main reason for this uncertainty is the different conformation of the nucleotide binding loop between strands β1 and β2 in FGFR-1 kinase crystal structures. In complex with ATP,[42] with PD-173074,[44] and with SU-4984,[43] this region is poorly ordered, but with SU-5402,[43] it is ordered so that the highly conserved Phe489 caps the hydrophobic pocket in which the oxindole binds. Thus, it cannot be ruled out that a specific arrangement of the corresponding loop in the PDGFRβ kinase narrows the binding site in comparison to the model in Figure 2b. Nevertheless, the inactivity

Table 2. Inhibition of Different Protein Kinases and of Growth Factor Dependent Cell Proliferation by Selected Bis(1*H*-2-indolyl)methanones

	IC_{50} (μM)			
	50	**39**	**53**	**67**
Phosphorylation assays				
PDGFR (Swiss 3T3 cells)[a]	0.3	0.2	0.1	0.2
PDGFβ-R (in vitro, purified receptor)[b]	0.07	0.09	0.1	0.02
PDGFβ-R (in vitro, Sf9-derived GST-fusion protein)[c]	4.9	0.6	1.3	4.2
PDGFβ-R (PAE cells)[d]	0.1	0.2	0.1	0.1
PDGFα-R (PAE cells)[d]	0.2	1.0	0.1	0.3
FGFR-1 (PAE cells)[d]	>10	>10	>10	>10
EGFR (A431 cells)[d]	>30	>30	>30	>30
Src (src-NIH3T3 cells)[d]	>30	>30	>30	>30
GRK2 (in vitro)[e]	>100	nt	>100	>100
PKCι (in vitro)[f]	17.0	>100	15.1	20.4
PKCϵ AE (in vitro)[f]	>100	>30	30	>100
DNA synthesis in Swiss 3T3 cells,[g] stimulated with				
PDGFBB	1.7	1.3	2.5	2.6
EGF	9.5	5.1	4.6	10−30
bFGF	ca. 10	10−30	10−30	10−30
FCS	8.8	5.5	2.1	10−30
Other:				
proliferation sis-NIH3T3 (inducible PDGF-B expression)[g]	nt	3.2	3.5	nt

[a] Inhibition of autophosphorylation of endogenous PDGF receptors in Swiss 3T3 cells was determined as described.[18] [b] Kinase was purified from membranes of PDGFβ receptor overexpressing cells, and assays were performed as described.[18,19,53] [c] A constitutively active GST-fusion protein of the cytoplasmic domain of PDGFβ receptor was expressed in Sf9 cells, and kinase assays with the isolated fusion protein were performed as in Hofmann et al.[55] [d] Autophosphorylation of the respective kinases in intact cells was determined by immunoblotting.[53] [e] GRK2 was overexpressed in 293 cells and activity determination was done as in Kassack et al.[54] [f] His-tagged PKC-isoforms were overexpressed in COS7 cells. The assays are outlined in the Experimental Section. [g] See Experimental Section for details on these assays. nt, not tested.

of the bisindolylmethanones as FGFR-1 kinase inhibitors (see Table 2) also supports the suggested binding mode: The more bulky FGFR-1 kinase residue Val561 replacing Thr681 in the PDGFRβ kinase is far inside the pocket and should interfere with the phenyl moiety of the inner indole system.

Figure 2b shows that the 5-substituent of the ester derivative **67** is projected outside the catalytic cleft, explaining to a certain extent the high degrees of freedom for rather different groups in this position without substantial loss of PDGFRβ inhibition (see Table 2). However, it becomes obvious that the 5-substituents are surrounded by short chains of the β1 strand, Arg604 to Ser608 (corresponding to Lys482 to Glu486 in the FGFR-1 kinase), and of the hinge region, Arg685 to Asp688 (FGFR-1: Ser565 to Asn568). Among these residues, the side chain of Leu606 as part of the hydrophobic pocket perpendicularly interacts with the outer indole ring. The backbone and side chains, respectively, of the other residues form something like polar "banks", which may explain the correlation of activity with polarity in the 5-position. According to the low variability of the activity data and to the relatively high distances, however, specific dipole−dipole interactions and polarization effects should not dominate. An effect first described by Franks,[46] concluding that the substituent with its solvent shell somehow "freezes" to the solvated surface of polar amino acids, is more likely. Water around various polar groups should then greatly attenuate large differences in geometry, dipole moments, and hydrogen-bonding abilities**.** Low variability of FGFR-1 and PDGFRβ kinase inhibition was also observed on very diversely 2-substituted pyrido[2,3-*d*]-pyrimidines.[47] Deriving binding models for these compounds, Trumpp-Kallmeyer et al.[21] also concluded that large, flexible groups in 2-position extend out of the binding pocket and are exposed to solvent. On the other hand, the model in Figure 2 illustrates that bulky branches in the α-position of the ester substituents and phenoxy-substituted phenyl groups lead to inactivity, since they would interfere with the β1 strand and/or the hinge region. According to the cellular assay, additional effects due to membrane transport and distribution cannot be ruled out, but they are not dominant, since the activity−hydrophobicity correlation is rather inverse. As shown by in vitro phosphorylation assays (see below), hydrolysis of the esters into compound **39** can also be neglected.

The proposed binding mode is further supported by compounds **77**−**85**, some N-mono- and dialkylated and -benzylated derivatives of the active compound **11** (Scheme 4).

The hydrogen-donor function of the indole NH is preserved in the monosubstituted compounds, but according to the model, any bulk at the inner indole nitrogen would interfere with the residues Thr681 and Glu682. Consequently, all derivatives of this type are inactive (data not shown).

Selectivity of Kinase Inhibition and Effects on Cell Proliferation. Selected potent compounds were further characterized. The inhibition of PDGFβ-receptor kinase purified from a cell line with high level overexpression was tested in an in vitro autophosphorylation assay. The IC_{50} values are equal to or lower than those in the intact cell test (Table 2), probably mainly due to higher ATP levels in the Swiss 3T3 fibroblasts. Structure−activity relationships are slightly different, since the methoxymethyl derivative **67** is in vitro about five times more active than compounds **39** and **53**. The autophosphorylation of a GST-fusion protein of the PDGFβ-receptor cytoplasmic domain expressed in Sf9 cells is also inhibited, but with 1−2 orders of magnitude higher IC_{50} values compared to those in the purified receptor test (Table 2, ATP concentration 10 μM in both assays). The lower susceptibility of the Sf9 cell-derived PDGFRβ kinase−GST fusion protein may be the consequence of its constitutive activity. Abl tyrosine kinase has recently been reported to bind the ATP-site directed inhibitor STI571 preferentially in the inactive kinase conformation.[48] The reversed structure−activity relationships—the unsubstituted 5-OH derivative **39** is now most active and compounds **50** and **67** are least active—suggest that the fringe of the binding site in the PDGFRβ kinase−GST fusion protein is changed, possibly due to an active-like, specific conformation of the β1-β2 loop and/or the hinge region. Taken together, the inhibition results obtained with purified and with recombinant kinase demonstrate that compounds of the bis(1*H*-2-indolyl)methanone family are direct inhibitors of the PDGFβ-receptor tyrosine kinase. The selectivity of the compounds was first investigated by testing the inhibition of other kinases in cellular phosphorylation assays (Table 2). Both subtypes of the PDGF receptor,

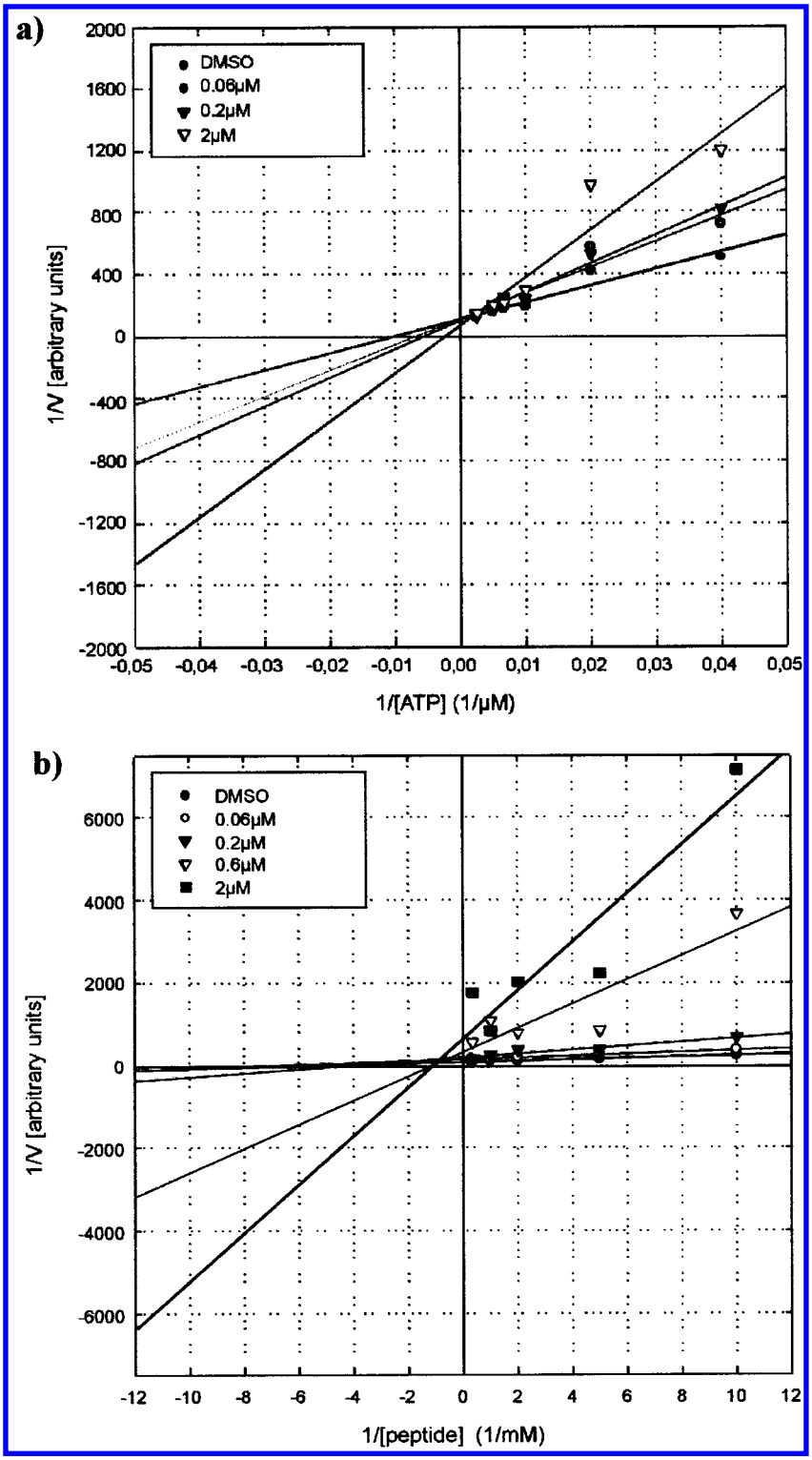


Figure 3. Kinetic evaluation of PDGFβ-receptor kinase inhibition by a bis(1*H*-2-indolyl)methanone. Purified PDGFβ-receptor kinase was assayed in vitro in the presence of different concentrations of compound **53** with the synthetic peptide KY571 as a substrate. Assays were performed with a fixed concentration of KY571 and variable concentration of ATP (a) or fixed ATP concentration and variable KY571 concentration (b). The data are shown in a Lineweaver−Burk representation.

PDGFRα and PDGFRβ, are similarly well inhibited. No effects up to 30 μM are observed on EGF receptor kinase, FGF receptor 1-kinase, and Src-kinase (Table 2). G-protein coupled receptor kinase 2 (GRK2), a serine-threonine kinase, is not affected by any of the compounds up to 100 μM (Table 2). Also an in vitro assay of PKC isoforms ι and ϵ measuring exogenous peptide substrate phosphorylation revealed only weak or no inhibition by the tested derivatives (Table 2). For compound **53**, the following IC_{50} values were determined with a panel of different kinase GST-fusion proteins in vitro: ErbB2, 51.0 μM; IGF1 receptor, 24.0 μM; CDK2/cyclin E, 28.0 μM; JAK2, 29.0 μM; PKB/Akt, 34.0 μM; PKCα, 89.0 μM; PKCϵ, 90 μM; and PKCζ, >100 μM. Compared to the PDGFβ-receptor kinase with 18.5 to 77-fold lower IC_{50} values in the same type of assay, these

kinases are thus markedly less sensitive or even insensitive to inhibition by the bis(1*H*-2-indolyl)methanone derivative **53**.

All tested compounds inhibit the PDGF-stimulated DNA synthesis in Swiss 3T3 fibroblasts with an IC_{50} of about 1 order of magnitude above that for inhibition of cellular PDGF receptor phosphorylation (Table 2). Interestingly, the stimulation with other mitogens results in different selectivities for individual compounds. Compound **67** has little effect on DNA synthesis stimulated by bFGF or fetal calf serum, whereas the other compounds inhibit mitogenesis induced by other agents. Thus, for these bis(1*H*-2-indolyl)methanone derivatives, further targets may exist in mitogenic pathways initiated by different mitogens. Inhibition of PDGF-dependent cell proliferation is also observed in NIH3T3 cells, engineered to inducibly express PDGF-B (Table 2). All compounds have additionally been tested in proliferation assays using the cancer cell lines L1210, MCF7, SKOV3, and HeLa. Most compounds are inactive in these assays (data not shown), excluding some general mechanism of cytostatic/cytotoxic action. As an exception among the potent kinase inhibitors, compound **11** exhibits toxic effects on fibroblasts upon incubation for 24 h or longer (data not shown), which have also been observed in other cellular assays with this compound upon long-term incubation.

Kinetic Evaluation of PDGF Receptor Kinase Inhibition by Compound 53. The inhibition mechanism of **53** was investigated as described,[19] using purified human PDGFβ-receptor and a synthetic peptide substrate derived from the sequence around the autophosphorylation site Tyr751 ("KY751"). Inhibition by different concentrations of **53** was measured by both varying KY751 concentration at ATP saturation and ATP concentration at nearly saturation with KY751. Results are depicted in Figure 3 in a Lineweaver−Burk representation of the data. The type of inhibition is competitive with respect to ATP (Figure 3a) and close to noncompetitive with respect to the peptide substrate (Figure 3b). Similar to previous observations with other tyrosine kinase inhibitors, these findings indicate the ATP-binding region as the main site of interaction of the bis(1*H*-2-indolyl)methanone inhibitors with the PDGF receptor.

Conclusions

We have identified a novel family of ATP-competitive PDGF receptor tyrosine kinase inhibitors, bis(1*H*-2-indolyl)methanones. The most active compounds are the 5-hydroxyl derivative **39** and its esters **53** and **67**. One unsubstituted moiety (indole, benzofuran, benzothiophen) is always necessary for sufficient activity. Rather different substituents in the 5- or 6-position of the other moiety (essentially indole) are possible without substantial loss of PDGFRβ inhibition. Docking studies using a molecular model of the PDGFRβ kinase domain suggest a binding mode of the compounds where the outer indole NH and the methanone oxygen are hydrogen bound with the backbone carbonyl and amide, respectively, of Cys684 and where groups in the 5- or 6-position are projected outside the catalytic cleft. The hitherto most active bis(1*H*-2-indolyl)methanone derivatives are significantly more potent than leflunomide,[27] the previously described pyrrolo(3,4)-betacarbolinediones[28] and the widely used quinoxaline derivative AG1295,[17−19] which was applied as standard throughout this study. By comparison with published data, the present bis(1*H*-2-indolyl)methanone derivatives exhibit similar potency in cellular assays as 2-phenylaminopyrimidines, for example, CGP53716[22] and CGP57148/STI751,[49] and phenylbenzimidazoles.[23] They are less active, but apparently more selective, PDGFRβ kinase inhibitors than several indoline-2-ones.[24−26] PDGF-mediated cell proliferation can be significantly blocked by different bis(1*H*-2-indolyl)methanones. Thus, these compounds are interesting candidates for application in disease states with pathological PDGF-receptor signaling as certain cancers and artherosclerosis/restenosis.

Experimental Section

Elemental analyses was done by the Analytical Lab at University Regensburg. Melting points were determined on a Büchi 512 or a Reichert hot-stage microscope. FT IR spectra were collectecd with a Nicolet 510. ^{1}H NMR spectra were determined with a Bruker 250 (250 MHz). MS data were collected with a Varian MAT 311A (EI, 70 eV). All reactions were carried out under nitrogen, dried over self-indicating silica gel, concentrated H_2SO_4, and KOH.

5-Methoxy-1-phenylsulfonyl-1*H*-*indole*. During 20 min, NaH (1.29 g, 43.0 mmol) (80% in paraffin) was added to a stirred solution of 5-methoxyindole (6.18 g, 42.0 mmol) in 60 mL of anhydrous DMF at 0 °C. After stirring at room temperature for 1 h, benzenesulfonyl chloride (4.9 mL, 43.0 mmol) was added slowly. The reaction mixture was stirred for an additional hour and then poured into 500 mL of 5% aq $NaHCO_3$ and extracted with ether (3 × 250 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a beige solid. Recrystallization from ethanol afforded 9.88 g (82%) of the title compound as colorless crystals. Mp: 97−98 °C. IR (KBr): ν = 3068, 2842, 1611 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.73 (s, 3 H), 6.77−6.78 (m, 1H), 6.92−6.97 (m, 1H), 7.11−7.12 (m, 1H), 7.54−7.61 (m, 2H), 7.64−7.71 (m, 1H), 7.75−7.77 (m, 1H), 7.81−7.84 (m, 1H), 7.91−7.95 (m, 2H). EI-MS (70 eV) *m*/*z* (%): 287 (48) [M$^{+\bullet}$], 146 (100), 141 (6), 131 (8), 103 (18), 77 (46). Anal. ($C_{15}H_{13}NO_3S$): C, H, N.

5-Benzyloxy-1-phenylsulfonyl-1*H*-indole was prepared in a manner similar to 5-methoxy-1-phenylsulfonyl-1*H*-indole, using 5-benzyloxyindole. Yield: 6.13 g (75%) of colorless crystals. Mp: 79−81 °C. IR (KBr): ν = 3064, 3035, 2905, 2873, 1601, 1582, 1537 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 5.09 (s, 2H), 6.76 (d, J = 3.5 Hz, 1H), 7.02 (dd, J = 8.9 Hz, 3.5 Hz, 1 H), 7.20 (d, J = 3.5 Hz, 1 H), 7.27−7.97 (m, 12 H). EI-MS (70 eV) *m*/*z* (%): 363 (58) [M$^{+\bullet}$], 272 (30), 223 (9), 141 (21), 91 (100). Anal. ($C_{21}H_{17}NO_3S$): C, H, N.

1,2 Bis(1*H*-2-indolyl)-1,2-ethandione (7).[50]

Bis(1*H*-3-indolyl)methanone (9).[30]

Procedure A (Scheme 1, Route I): Synthesis of the Substituted (1-Phenylsulfonyl-1*H*-2-indolyl)methanols 1a, 10a−17a, 20a, 22a−25a, and 40a and of the Analogue Bisbenzo[b]thiophen-2-ylmethane (18a). *n*-Butyllithium (9.9 mL, 15.9 mmol) was added dropwise to a solution of anhydrous diisopropylamine (2.23 mL, 15.9 mmol) in dry THF (15 mL) at −78 °C. After stirring for 10 min, the mixture was allowed to warm to 0 °C, then it was stirred for 30 min. A solution of the appropriate 1-phenylsulfonylindole (14.0 mmol) in dry THF (22 mL) was added within 10 min, and the reaction mixture was kept stirring at 0 °C for an additional 30 min, before the respective (1-phenylsulfonyl-1*H*-2-indolyl)lithium **3** so obtained was cooled to −78 °C again.

2-Formyl-1-phenylsulfonyl-1*H*-indole[29] **2** (4.39 g, 15.4 mmol) (or, depending on the desired product, any other suitable aldehyde) in dry THF (15 mL) was added slowly. After warming to room temperature overnight, the mixture was poured into 1% aq HCl (100 mL), and the organic layer was

separated. The water layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were washed successively with bicarbonate and brine. After drying (Na_2SO_4), the solvent was evaporated under reduced pressure to leave a foamy solid, which was subjected to column chromatography (SiO_2; ethyl acetate/hexane 4/1) or recrystallized from ethanol, yielding the product as light yellowish crystals.

Bis(1-phenylsulfonyl-1*H*-2-indolyl)methanol (1a).[29]

(1-Phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1H-3-indolyl)methanol (10a). Yield: 4.41 g (55%). Mp: 88−90 °C. IR (KBr): ν = 3533, 3064, 1605 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 6.35 (d, J = 6 Hz, 1H), 6.62 (s, 1H), 6.64 (s, 1H), 7.15−7.74 (m, H), 7.86−8.04 (m, H). PI-FDMS (CH_2Cl_2) *m*/*z* (%): 542 (100) [$M^{+\bullet}$]. Anal. ($C_{29}H_{22}N_2O_5S_2$·0.25ethyl acetate): C, H, N.

(5-Methoxy-1-phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1H-2-indolyl)methanol (11a). Yield: 6.49 g (81%). Mp: 150−152 °C. IR (KBr): ν = 3450, 1449, 1368 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.73 (s, 3H), 6.57 (s, 2H), 6.70−6.72 (m, 1H), 6.91−6.95 (m, 1H), 7.07−7.08 (m, 1H), 7.20−7.36 (m, 3H), 7.48−7.56 (m, 5H), 7.61−7.68 (m, 2H), 7.87−8.04 (m, 6H). EI-MS (70 eV) *m*/*z* (%): 572 (3) [$M^{+\bullet}$], 290 (12), 250 (14), 142 (37), 125 (32), 77 (100). Anal. ($C_{30}H_{24}N_2O_6S_2$): C, H, N.

(6-Methoxy-1-phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1H-2-indolyl)methanol (12a). Yield: 6.73 g (84%). Mp: 180 °C. IR (KBr): ν = 3429, 3066, 2966 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.82 (s, 3H), 6.50 (s, 1H), 6.62−6.67 (m, 2H), 6.86−6.90 (m, 1H), 7.20−7.43 (m, 4H), 7.49−7.67 (m, 8H), 7.97−8.04 (m, 5H). MS (70 eV) *m*/*z* (%): 572 (4) [$M^{+\bullet}$], 290 (9), 142 (37), 125 (19), 94 (16), 77 (100). Anal. ($C_{30}H_{24}N_2O_6S_2$): C, H, N.

(7-Methoxy-1-phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1H-2-indolyl)methanol (13a). Yield: 4.41 g (55%). Mp: 148−150 °C. IR (KBr): ν = 3543, 3064, 2962 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.53 (s, 3H), 4.19−4.21 (m, 1H), 6.36 (s, 1H), 6.67−6.70 (m, 1H), 6.94−6.98 (m, H), 7.07−7.13 (m, 1H), 7.21−7.57 (m, 10H), 7.72−7.75 (m, 2H), 8.06−8.14 (m, 3H). EI-MS (70 eV) *m*/*z* (%): 572 (3) [$M^{+\bullet}$], 492 (3), 430 (4), 351 (5), 290 (6), 250 (9), 142 (64), 77 (100). Anal. ($C_{30}H_{24}N_2O_6S_2$): C, H, N.

Bis(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)methanol (14a). Yield: 6.41 g (76%). Mp: 104−105 °C. IR (KBr): ν = 3435, 3092, 2962 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.73 (s, 6H), 6.53 (s, 2H), 6.68−6.71 (m, 1H), 6.91−6.95 (m, 2H), 7.07−7.08 (m, 2H), 7.16−7.18 (m, 1H), 7.49−7.55 (m, 4H), 7.61−7.67 (m, 2H), 7.87−7.91 (m, 2H), 7.95−7.98 (m, 4H). EI-MS (70 eV) *m*/*z* (%): 602 (1) [$M^{+\bullet}$], 462 (1), 320 (6), 250 (12), 142 (28), 109 (33), 77 (100). Anal. ($C_{31}H_{26}N_2O_7S_2$): C, H, N.

(5-Methyl-1-phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1H-2-indolyl)methanol (15a). Yield: 5.61 g (72%), mp 140−141 °C. IR (KBr): ν = 3523, 3066, 2921 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 2.33 (s, 3H), 6.57 (d, J = 4.35 Hz, 1H), 6.71 (d, J = 5.68 Hz, 1H), 7.12−7.37 (m, 5H), 7.47−7.68 (m, 7H), 7.83−8.07 (m, 6H). PI-FDMS (dichloromethane) *m*/*z* (%):556 (100) [$M^{+\bullet}$], 557 (32), 558 (12). Anal. ($C_{30}H_{24}N_2O_5S_2$·0.25ethyl acetate): C, H, N.

(Benzo[b]thiophen-2-yl)(5-methoxy-1-phenylsulfonyl-1H-2-indolyl)methanol (16a). Yield: 4.47 g (71%). Mp: 71−73 °C. IR (KBr): ν = 3433, 3062, 2937 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.73 (s, 3H), 6.73−6.77 (m, 2H), 6.85 (s, 1H), 6.89−6.94 (m, 1H), 7.10−7.11 (m, 1H), 7.30−7.36 (m, 3H), 7.43−7.49 (m, 2H), 7.58−7.64 (m, 1H), 7.76−7.81 (m, 3H), 7.87−7.91 (m, 2H). EI-MS (70 eV) *m*/*z* (%): 449 (46) [$M^{+\bullet}$], 307 (100), 291 (37), 174 (86), 161 (61), 77 (61). Anal. ($C_{24}H_{19}NO_4S_2$): C, H, N.

(Benzo[b]furan-2-yl)(5-methoxy-1-phenylsulfonyl-1H-2-indolyl)methanol (17a). Yield: 5.22 g (86%). Mp: 118−119 °C. IR (KBr): ν = 3452, 2836, 1216 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.78 (s, 3H), 6.71−6.74 (m, 2H), 6.95−6.99 (m, 2H), 7.05−7.14 (m, 2H), 7.20−7.31 (m, 3H), 7.36−7.40 (m, 1H), 7.44−7.54 (m, 2H), 7.59−7.68 (m, 2H), 7.88−7.92 (m, 2H). EI-MS (70 eV) *m*/*z* (%): 433 (43) [$M^{+\bullet}$], 291 (100), 276 (34), 174 (55), 77 (63). Anal. ($C_{24}H_{19}NO_5S$): C, H, N.

Bisbenzo[b]thiophen-2-yl-methanol (18a). Yield: 3.69 g (89%) of needles. Mp: 130−131 °C. IR (KBr): ν = 3475, 1630 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 6.43−6.44 (m, 1H), 6.93−6.95 (m, 1H), 7.27−7.35 (m, 4H), 7.37−7.38 (m, 2H), 7.76−7.83 (m, 2H), 7.85−7.96 (m, 2H). EI-MS (70 eV) *m*/*z* (%): 296 (69) [$M^{+\bullet}$], 234 (18), 161 (100), 135 (72), 89 (23). Anal. ($C_{17}H_{10}OS_2$): C, H, N.

(5-Methoxy-1-phenylsulfonyl-1*H*-2-indolyl)phenylmethanol (20a). Yield: 4.74 g (86%). Mp: 51−52 °C. IR (KBr): ν = 3064, 2834, 1615 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.72 (s, 3H), 6.15−6.18 (m, 1H), 6.37−6.39 (m, 1H), 6.60 (s, 1H), 6.86−6.91 (m, 1H), 7.06−7.07 (m, 1H), 7.28−7.39 (m, 5H), 7.47−7.53 (m, 2H), 7.60−7.67 (m, 1H), 7.73−7.77 (m, 2H), 7.84−7.87 (m, 1H). EI-MS (70 eV) *m*/*z* (%): 393 (63) [$M^{+\bullet}$], 251 (100), 224 (21), 105 (61), 77 (44). Anal. ($C_{22}H_{19}NO_4S$): C, H, N.

2-Methoxyphenyl-(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)methanol (22a). Yield: 2.43 g (41%) of light red crystals. Mp: 75−76 °C. IR (KBr): ν = 3068, 2961, 1603 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.70 (s, 3H), 3.75 (s, 3H), 6.10−6.12 (m, 1H, exchangeable), 6.68−6.77 (m, 2H), 6.86−6.91 (m, 2H), 6.94−7.05 (m, 3H), 7.45−7.49 (m, 1H), 7.54−7.70 (m, 3H), 7.86−7.95 (m, 3H). EI-MS (70 eV) *m*/*z* (%): 423 (27) [$M^{+\bullet}$], 281 (35), 135 (100), 77 (34). Anal. ($C_{23}H_{21}NO_5S$): C, H, N.

3-Methoxyphenyl-(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)methanol (23a). Yield: 4.03 g (68%). Mp: 121−122 °C. IR (KBr): ν = 3095, 2958, 1605 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.72 (s, 6H), 6.16−6.18 (m, 1H, exchangeable), 6.34−6.36 (m, 1H), 6.56 (s, 1H), 6.84−6.95 (m, 4H), 7.06−7.07 (m, 1H), 7.23−7.29 (m, 1H), 7.47−7.53 (m, 2H), 7.61−7.67 (m, 1H), 7.79−7.79 (m, 2H), 7.85−7.88 (m, 1H). EI-MS (70 eV) *m*/*z* (%): 423 (72) [$M^{+\bullet}$], 266 (100), 250 (23), 135 (45), 77 (27). Anal. ($C_{23}H_{21}NO_5S$): C, H, N.

4-Methoxyphenyl-(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)methanol (24a). Yield: 4.57 g (77%) of light red crystals. Mp: 78−79 °C. IR (KBr): ν = 3442, 3068, 2935 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.72 (s, 3H), 3.74 (s, 3H), 6.03−6.05 (m, 1H, exchangeable), 6.31−6.33 (m, 1H), 6.63 (s, 1H), 6.85−6.90 (m, 3H), 7.06−7.07 (m, 1H), 7.23−7.29 (m, 2H), 7.45−7.51 (m, 2H), 7.60−7.73 (m, 3H), 7.83−7.87 (m, 1H). EI-MS (70 eV) *m*/*z* (%): 423 (27) [$M^{+\bullet}$], 281 (100), 265 (18), 250 (17), 173 (18), 135 (31), 77 (25). Anal. ($C_{23}H_{21}NO_5S$): C, H, N.

2,4-Dimethoxyphenyl-(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)methanol (25a). Yield: 3.88 g (61%), mp 119−120 °C. IR (KBr): ν = 3002, 2941, 1591 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.69 (s, 3H), 3.73 (s, 3H), 3.78 (s, 3H), 5.75−5.77 (m, 1H, exchangeable), 6.15 (s, 1H), 6.51−6.60 (m, 3H), 6.85−6.89 (m, 1H), 7.00−7.01 (m, 1H), 7.26−7.29 (m, 1H), 7.51−7.68 (m, 3H), 7.84−7.90 (m, 3H). EI-MS (70 eV) *m*/*z* (%): 453 (23) [$M^{+\bullet}$], 311 (60), 284 (25), 173 (67), 165 (100), 77 (39). Anal. ($C_{24}H_{23}NO_6S$): C, H, N.

(5-Benzyloxy-1-phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1*H*-2-indolyl)methanol (40a). Yield: 7.18 g (79%). Mp: 94−97 °C. IR (KBr): ν = 3532, 1611 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.07 (s, 2H), 6.54 (s, 1H), 6.58 (s, 1 H), 6.70 (d, J = 2.7 Hz, 1 H), 7.00 (dd, J = 1 Hz, 3.6 Hz, 1 H), 7.15−8.01 (m, 22 H). PI-FDMS (CH_2Cl_2); *m*/*z* (%): 648 (100) [$M^{+\bullet}$]. Anal. ($C_{36}H_{28}N_2O_6S_2$): C, H, N.

Procedure B (Scheme 1, Route 1): Preparation of the (1-Phenylsulfonyl-1*H*-2-indolyl)methanones 1b, 10b−16b, 20b, 22b−25b, 40b and of the Analogue Bisbenzo[b]thiophen-2-ylmethanone (18). PDC (pyridinium dichromate) (11.66 g, 31.0 mmol) and PTFA (pyridinium trifluoroacetate) (2.48 g, 155 mmol) were added to a solution of the respective (1-phenylsulfonyl-1*H*-2-indolyl)methanol derivative (6.2 mmol) (**1a**, **10a**−**16a**, **20a**, **22a**−**25a** or **40a**, procedure A) in 40 mL of dry CH_2Cl_2 and for the preparation of **18** to a solution of **18a** in 40 mL of dry CH_2Cl_2. When the oxidation was completed (2 h to 3 weeks, TLC control) solid chromium waste was removed by filtration through SiO_2. Evaporation of the solvent left a foamy material, which was purified by column chromatography on silica gel with CH_2Cl_2/ethyl acetate as eluent, leading to light yellow cristals.

Bis(1-phenylsulfonyl-1*H*-2-indolyl)methanone (1b).[29]

(1-Phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1*H*-3-indolyl)methanone (10b). Yield: 0.58 g (58%). Mp: 181−182 °C. IR (KBr): ν = 3060, 1650, 1607, 1584, 1537, 1480, 1449

cm^{-1}. ^{1}H NMR (DMSO-d_6): δ =.7.37−7.81 (m, 12H); 8.02−8.30 (m, 7H), 8.57 (s, 1H). PI-FDMS (CH_2Cl_2); *m/z* (%): 540 (100) [M$^{+\bullet}$]. Anal. ($C_{29}H_{20}N_2O_5S_2$): C, H, N.

5-Methoxy-1-phenylsulfonyl-1*H*-2-indolyl(1-phenylsulfonyl-1H-2-indolyl)methanone (11b). Yield: 2.23 g (63%). Mp: 204−205 °C. IR (KBr): ν = 3064, 2838, 1652 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.80 (s, 3H), 7.19−7.26 (m, 2H), 7.37−7.43 (m, 1H), 7.51−7.80 (m, 10H), 8.01−8.20 (m, 6H). EI-MS (70 eV) *m/z* (%): 570 (39) [M$^{+\bullet}$], 429 (40), 365 (15), 288 (100), 245 (37), 77 (83). Anal. ($C_{30}H_{22}N_2O_6S_2$): C, H, N.

6-Methoxy-1-phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1*H*-2-indolyl)methanone (12b). Yield: 1.49 g (42%) of light red crystals. Mp: 184−186 °C. IR (KBr): ν = 3078, 2838, 1613 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.93 (s, 3H), 7.04−7.08 (m, 1H), 7.40−7.43 (m, 1H), 7.52−7.83 (m, 12H), 8.05−8.09 (m, 4H), 8.14−8.18 (m, 1H). EI-MS (70 eV) *m/z* (%): 570 (42) [M$^{+\bullet}$], 430 (39), 290 (35), 288 (94), 273 (37), 245 (22), 77 (100). Anal. ($C_{30}H_{22}N_2O_6S_2$): C, H, N.

(7-Methoxy-1-phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1*H*-2-indolyl)methanone (13b). Yield: 1.98 g (56%). Mp: 129−130 °C. IR (KBr): ν = 3068, 2972, 1663 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.72 (s, 3H), 6.87−6.90 (m, 1H), 7.18−7.33 (m, 4H), 7.35−7.36 (m, 1H), 7.45−7.66 (m, 8H), 8.14−8.18 (m, 1H), 8.28−8.32 (m, 2H), 8.51−8.55 (m, 2H). EI-MS (70 eV) *m/z* (%): 570 (19) [M$^{+\bullet}$], 430 (37), 289 (100), 144 (20), 77 (58). Anal. ($C_{30}H_{22}N_2O_6S_2$): C, H, N.

Bis(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)methanone (14b). Yield: 2.05 g (55%). Mp: 190−191 °C. IR (KBr): ν = 3008, 2941, 1657 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.80 (s, 6H), 7.18−7.26 (m, 4H), 7.44 (s, 2H), 7.68−7.75 (m, 6H), 8.02−8.08 (m, 6H). EI-MS (70 eV) *m/z* (%): 600 (20) [M$^{+\bullet}$], 536 (6), 460 (55), 395 (13), 319 (100), 147 (36), 77 (77). Anal. ($C_{31}H_{24}N_2O_7S_2$): C, H, N.

(5-Methyl-1-phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1*H*-2-indolyl)methanone (15b). Yield: 1.79 g (52%). Mp: 189−191 °C. IR (KBr): ν = 3064, 1663, 1605 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.40 (s, 3H), 7.33−7.48 (m, 2H), 7.51−7.75 (m, 11H), 8.02−8.21 (m, 6H). PI-FDMS (dichloromethane) *m/z* (%): 554 (100) [M$^{+\bullet}$], 555 (31), 556 (13). Anal. ($C_{30}H_{22}N_2O_5S_2$• 0.25 ethyl acetate): C, H, N.

(Benzo[*b*]thiophen-2-yl)(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)methanone (16b). Yield: 1.83 g (66%) of beige crystals. Mp: 82−83 °C. IR (KBr): ν = 3066, 2937, 1640 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.79 (s, 3H), 7.12−7.17 (m, 1H), 7.22−7.23 (m, 1H), 7.46−7.47 (m, 1H), 7.51−7.55 (m, 1H), 7.57−7.65 (m, 3H), 7.70−7.75 (m, 1H), 7.93−7.99 (m, 3H), 8.09−8.16 (m, 2H), 8.25 (s, 1H). EI-MS (70 eV) *m/z* (%): 447 (63) [M$^{+\bullet}$], 306 (100), 291 (14), 263 (33), 235 (39), 173 (39), 77 (31). Anal. ($C_{24}H_{17}NO_4S_2$): C, H, N.

Bisbenzo[*b*]thiophen-2-ylmethanone (18). Yield: 1.39 g (76%). Mp: 161 °C. IR (KBr): ν = 3054, 1617 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.51−7.64 (m, 4H), 8.12−8.16 (m, 4H), 8.62 (s, 2H). EI-MS (70 eV) *m/z* (%): 294 (100) [M$^{+\bullet}$], 266 (9), 161 (52), 133 (21), 89 (21). Anal. ($C_{17}H_{10}OS_2$): C, H.

(5-Methoxy-1-phenylsulfonyl-1*H*-2-indolyl)phenylmethanone (20b). Yield: 1.48 g (61%) of colorless needles. Mp: 148 °C. IR (KBr): ν = 3064, 2964, 1663 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.77 (s, 3H), 7.09−7.14 (m, 1H), 7.19−7.21 (m, 3H), 7.57−7.65 (m, 4H), 7.68−7.77 (m, 2H), 7.88−7.92 (m, 4H). EI-MS (70 eV) *m/z* (%): 391 (82) [M$^{+\bullet}$], 250 (100), 207 (20), 179 (25), 105 (32), 77 (51). Anal. ($C_{22}H_{17}NO_4S$): C, H, N.

2-Methoxyphenyl(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)-1-methanone (22b). Yield:

1.54 g (59%) of colorless needles. Mp: 179 °C. IR (KBr): ν = 3067, 2985, 1648 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.67 (s, 3H), 3.75 (s, 3H), 7.01 (s, 1H), 7.06−7.21 (m, 4H), 7.55−7.74 (m, 5H), 7.90−7.96 (m, 3H). EI-MS (70 eV) *m/z* (%): 421 (100) [M$^{+\bullet}$], 280 (58), 265 (49), 249 (90), 160 (78), 135 (56), 77 (86). Anal. ($C_{23}H_{19}NO_5S$): C, H, N.

3-Methoxyphenyl-(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)methanone (23b). Yield:

1.75 g (67%) of colorless needles. Mp: 181 °C. IR (KBr): ν = 3083, 2958, 1663 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.77 (s, 3H), 3.84 (s, 3H), 7.10−7.14 (m, 1H), 7.19−7.22 (m, 2H), 7.29−7.34 (m, 1H), 7.40−7.64 (m, 5H), 7.69−7.76 (m, 1H), 7.89−7.96 (m, 3H). EI-MS (70 eV) *m/z* (%): 421 (72) [M$^{+\bullet}$], 280 (100), 265 (20), 249 (31), 135 (20), 77 (49). Anal. ($C_{23}H_{19}NO_5S$): C, H, N.

4-Methoxyphenyl-(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)methanone (24b). Yield: 1.68 g (64%) of beige crystals. Mp: 129−130 °C. IR (KBr): ν = 3066, 2937, 1611 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.77 (s, 3H), 3.80 (s, 3H), 6.16 (s, 1H), 6.88−6.93 (m, 1H), 7.01−7.04 (m, 2H), 7.12−7.40 (m, 7H), 7.55−7.61 (m, 1H), 7.82−7.86 (m, 1H). EI-MS (70 eV) *m/z* (%): 421 (72) [M$^{+\bullet}$], 357 (22), 280 (100), 252 (32), 173 (42), 135 (56), 77 (57). Anal. ($C_{23}H_{19}NO_5S$): C, H, N.

2,4-Dimethoxyphenyl-(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)methanone (25b). Yield: 1.48 g (53%) of colorless crystals. Mp: 62−64 °C. IR (KBr): ν = 3046, 2943, 1653 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.64 (s, 3H), 3.75 (s, 3H), 3.88 (s, 3H), 6.64−6.69 (m, 2H), 6.92 (s, 1H), 7.02−7.07 (m, 1H), 7.13−7.14 (m, 1H), 7.57−7.74 (m, 4H), 7.85−7.95 (m, 3H). EI-MS (70 eV) *m/z* (%): 451 (100) [M$^{+\bullet}$], 311 (74), 295 (40), 279 (76), 264 (34), 173 (97), 165 (72), 160 (62), 77 (72). Anal. ($C_{24}H_{21}NO_6S$): C, H, N.

(5-Benzyloxy-1-phenylsulfonyl-1*H*-2-indolyl)(1-phenylsulfonyl-1*H*-2-indolyl)methanone (40b). Yield: 4.50 g (45%). Mp: 111−113 °C. IR (KBr): ν = 3067, 2956, 1655, 1607 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 5.15 (s, 2H), 7.22−8.19 (m, 24 H). PI-FDMS (CH_2Cl_2); *m/z* (%): 646 (100) [M$^{+\bullet}$]. Anal. ($C_{36}H_{26}N_2O_6S_2$): C, H, N.

Preparation also According to Procedure F (Scheme 1, Route II).

Procedure C (Scheme 1, Route I): Removal of the Phenylsulfonyl Protection Group To Form the (1*H*-2-Indolyl)methanones 1, 10−17, 20−27, 29, 30, and 40. Method 1. Some of the N-protected methanone derivatives prepared by procedure B (**21b**, **26b**) (1.8 mmol) were heated in ethanol (40 mL) and 10% aq NaOH (20 mL) under reflux for 12 h. After cooling, the solution was poured into brine (100 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to leave the crude product, which was subjected to column chromatography (SiO_2; CH_2Cl_2). The treatment of **17a** with NaOH in refluxing ethanol as described above resulted in the formation of **17**. Thus, Method 1 was used for the preparation of compounds **17**, **21**, and **26**.

Method 2. A mixture of the respective N-protected methanone derivative prepared by procedure B (1.8 mmol) and TBAF (tetrabutylammonium fluoride trihydrate) (0.79 g, 2.5 mmol) in THF/MeOH 1:1 (20 mL) was gently refluxed. When TLC indicated that the reaction was completed (30 min to 4 h), part of the solvent was removed to allow precipitation of the yellow product. Compounds **1**, **10**−**16**, **20**, **22**−**25**, **27**, **29**, **30**, and **40** were prepared according to method 2.

Bis(1*H*-2-indolyl)methanone (1).[29]

1*H*-2-indolyl(1H-3-indolyl)methanone (10).[32,33]

(5-Methoxy-1*H*-2-indolyl)(1H-2-indolyl)methanone (11) was prepared according to method 2. Yield: 0.48 g (91%). Mp: 219−222 °C. IR (KBr): ν = 3398, 2839, 1615 cm^{-1}.^{1}H NMR (DMSO-d_6): δ = 3.80 (s, 3H), 6.96−7.00 (m, 1H), 7.09−7.15 (m, 1H), 7.19−7.20 (m, 1H), 7.28−7.34 (m, 1H), 7.40−7.43 (m, 1H), 7.50−7.57 (m, 3H), 7.75−7.78 (m, 1H), 11.85 (s, 1H), 11.96 (s, 1H). EI-MS (70 eV) *m/z* (%): 290 (95) [M$^{+\bullet}$], 173 (100), 158 (26), 147 (42), 117 (20). Anal. ($C_{18}H_{14}N_2O_2$): C, H, N.

(6-Methoxy-1*H*-2-indolyl)(1H-2-indolyl)methanone (12) was prepared according to method 2. Yield: 0.43 g (82%). Mp: 266−267 °C. IR (KBr): ν = 3398, 1615, 1545 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.82 (s, 3H), 6.76−6.80 (m, 1H), 6.92−6.93 (m, 1H), 7.08−7.14 (m, 1H), 7.26−7.32 (m, 1H), 7.49−7.57 (m, 3H), 7.62−7.65 (m, 1H), 7.73−7.76 (m, 1H), 11.81 (s, 1H), 11.91 (s, 1H). EI-MS (70 eV) *m/z* (%): 290 (100) [M$^{+\bullet}$], 173 (40), 147 (38), 117 (22), 89 (14). Anal. ($C_{18}H_{14}N_2O_2$): C, H, N.

(7-Methoxy-1*H*-2-indolyl)(1H-2-indolyl)methanone (13) was prepared according to method 2. Yield: 0.48 (g 91%). Mp: 277 °C. IR (KBr): ν = 3384, 3072, 1592 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.94 (s, 3H), 6.83−6.86 (m, 1H), 7.02−7.15 (m, 2H),

7.28−7.34 (m, 2H), 7.49−7.53 (m, 3H), 7.74−7.77 (m, 1H), 11.79 (s, 1H), 11.94 (s, 1H). EI-MS (70 eV) *m/z* (%): 290 (100) [$M^{+\bullet}$], 173 (48), 144 (49), 130 (16), 117 (24), 89 (23). Anal. ($C_{18}H_{14}N_2O_2$): C, H, N.

Bis(5-methoxy-1*H*-2-indolyl)methanone (14) was prepared according to method 2. Yield: 0.47 g (81%). Mp: 202−204 °C. IR (KBr): ν = 3305, 2923, 1630 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.80 (s, 6H), 6.95−7.00 (m, 2H), 7.19−7.20 (m, 2H), 7.39−7.47 (m, 4H), 11.83 (s, 2H). EI-MS (70 eV) *m/z* (%): 320 (84) [$M^{+\bullet}$], 173 (62), 147 (100), 132 (27), 104 (6). Anal. ($C_{19}H_{16}N_2O_3$): C, H, N.

(1*H*-2-*Indolyl*)(5-methyl-1*H*-2-indolyl)methanone (15) was prepared according to method 2. Yield: 0.28 g (57%). Mp: 184−186 °C. IR (KBr): ν = 3450, 3297, 1618 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 2.39 (s, 3H), 7.06−7.20 (m, 2H), 7.26−7.62 (m, 6H), 7.71−7.82 (m, 1H), 11.83 (s, 1H), 11.97 (s, 1H). EI-MS (70 eV) *m/z* (%): 274 (100) [$M^{+\bullet}$], 158 (48), 144 (29), 131 (71), 117 (38). Anal. ($C_{18}H_{14}N_2O$): C, H, N.

(Benzo[*b*]thiophen-2-yl)(5-methoxy-1*H*-2-indolyl)-1-methanone (16) was prepared according to method 2. Yield: 0.51 g (92%). Mp: 200 °C. IR (KBr): ν = 3298, 3052, 1592 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.80 (s, 3H), 6.99−7.04 (m, 1H), 7.19−7.20 (m, 1H), 7.41−7.44 (m, 1H), 7.48−7.61 (m, 3H), 8.10−8.14 (m, 2H), 8.54 (s, 1H), 11.93 (s, 1H). EI-MS (70 eV) *m/z* (%): 307 (100) [$M^{+\bullet}$], 173 (82), 158 (51), 130 (33). Anal. ($C_{18}H_{13}NO_2S$): C, H, N.

(Benzo[*b*]furan-2-yl)(5-methoxy-1*H*-2-indolyl)methanone (17) was prepared according to method 1, the title compound was synthesized by treating **17a** with NaOH in refluxing ethanol, resulting in oxidation and loss of the phenylsulfonyl protection group: Yield: 0.09 g (18%). Mp: 231−233 °C. IR (KBr): ν = 2836, 1098 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.80 (s, 3H), 7.03−7.04 (m, 1H), 7.22−7.23 (m, 1H), 7.38−7.44 (m, 2H), 7.56−7.63 (m, 1H), 7.74−7.75 (m, 1H), 7.81−7.90 (m, 2H), 8.00−8.01 (m, 1H), 11.96 (s, 1H). EI-MS (70 eV) *m/z* (%): 291 (100) [$M^{+\bullet}$], 276 (9), 173 (41), 158 (37), 130 (31). Anal. ($C_{18}H_{13}NO_3$): C, H, N.

(5-Methoxy-1*H*-2-indolyl)phenylmethanone (20) was prepared according to method 2. Yield: 0.41 g (90%) of needles. Mp: 162 °C. IR (KBr): ν = 3311, 3008, 1625 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.77 (s, 3H), 6.96−7.03 (m, 2H), 7.15−7.16 (m, 1H), 7.39−7.43 (m, 1H), 7.56−7.62 (m, 2H), 7.65−7.72 (m, 1H), 7.90−7.95 (m, 2H), 11.86 (br. s, 1H). EI-MS (70 eV) *m/z* (%): 251 (100) [$M^{+\bullet}$], 236 (28), 158 (10), 130 (10), 105 (13), 77 (19). Anal. ($C_{16}H_{13}NO_2$): C, H, N.

(1*H*-2-Indolyl)phenylmethanone (21) was prepared according to method 1. Yield: 0.45 g (73%). Mp: 145−147 °C. IR (KBr): ν = 3314, 3081, 1669 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 7.08−7.16 (m, 2H), 7.29−7.37 (m, 1H), 7.48−7.75 (m, 5H), 7.91−7.97 (m, 2H), 11.90 (s, 1H). EI-MS (70 eV) *m/z* (%): 221 (100) [$M^{+\bullet}$], 204 (13), 144 (36), 89 (28), 77 (30). Anal. ($C_{15}H_{11}NO$): C, H, N.

2-Methoxyphenyl-(5-methoxy-1*H*-2-indolyl)methanone (22) was prepared according to method 2. Yield: 0.44 g (87%). Mp: 127 °C. IR (KBr): ν = 3303, 3070, 1620 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.73 (s, 3H), 3.75 (s, 3H), 6.67 (s, 1H), 6.93−6.98 (m, 1H), 7.04−7.10 (m, 2H), 7.17−7.21 (m, 1H), 7.35−7.41 (m, 2H), 7.50−7.57 (m, 1H), 11.77 (s, 1H). EI-MS (70 eV) *m/z* (%): 281 (100) [$M^{+\bullet}$], 263 (14), 250 (11), 220 (14), 173 (27), 161 (29), 135 (18), 77 (19). Anal. ($C_{17}H_{15}NO_3$): C, H, N.

3-Methoxyphenyl-(5-methoxy-1*H*-2-indolyl)methanone (23) was prepared according to method 2. Yield: 0.43 g (85%). Mp: 147−148 °C. IR (KBr): ν = 3294, 3066, 1688 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.77 (s, 3H), 3.86 (s, 3H), 6.96−7.01 (m, 1H), 7.05−7.06 (m, 1H), 7.16−7.17 (m, 1H), 7.22−7.27 (m, 1H), 7.38−7.42 (m, 2H), 7.47−7.51 (m, 2H), 11.85 (s, 1H). EI-MS (70 eV) *m/z* (%): 281 (100) [$M^{+\bullet}$], 266 (23), 250 (8), 158 (19), 130 (14). Anal. ($C_{17}H_{15}NO_3$): C, H, N.

4-Methoxyphenyl-(5-methoxy-1*H*-2-indolyl)methanone (24) was prepared according to method 2. Yield: 0.44 g (86%). Mp: 165 °C. IR (KBr): ν = 3276, 3062, 1625 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.77 (s, 3H), 3.88 (s, 3H), 6.94−6.99 (m, 1H), 7.02−7.03 (m, 1H), 7.09−7.16 (m, 3H), 7.39−7.41 (m, 1H), 7.92−7.98 (m, 2H), 11.78 (s, 1H). EI-MS (70 eV) *m/z* (%): 281 (100) [$M^{+\bullet}$], 173 (54), 158 (42), 135 (23), 77 (13). Anal. ($C_{17}H_{15}NO_3$): C, H, N.

2,4-Dimethoxyphenyl-(5-methoxy-1*H*-2-indolyl)methanone (25) was prepared according to method 2. Yield: 0.45 g (81%). Mp: 160−161 °C. IR (KBr): ν = 3286, 2960, 1623 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.74 (s, 3H), 3.75 (s, 3H), 3.86 (s, 3H), 6.61−6.66 (m, 1H), 6.71 (s, 2H), 6.92−6.96 (m, 1H), 7.08−7.09 (m, 1H), 7.34−7.42 (m, 2H), 11.69 (br. s, 1H). EI-MS (70 eV) *m/z* (%): 311 (86) [$M^{+\bullet}$], 280 (6), 173 (100), 165 (18). Anal. ($C_{18}H_{17}NO_4$): C, H, N.

3,4-Dichlorophenyl-(5-methoxy-1*H*-2-indolyl)methanone (26) was prepared according to method 1. Yield: 0.53 g (64%). Mp: 190−192 °C. IR (KBr): ν = 3316, 1620 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.80 (s, 3H), 6.93−7.18 (m, 4H), 7.80−7.92 (m, 2H), 8.03−8.12 (m, 1H), 11.95 (s, 1H). EI-MS (70 eV) *m/z* (%): 319 (100) [$M^{+\bullet}$], 304 (31), 241 (10), 173 (16), 130 (15). Anal. ($C_{16}H_{11}Cl_2NO_2$·0.4 dichloromethane): C, H, N.

(5-Methoxy-1*H*-2-indolyl)-2-nitrophenylmethanone (27) was prepared according to method 2. Yield: 0.21 g (40%). Mp: 185−187 °C. IR (KBr): ν = 3299, 3072, 1609 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.73 (s, 3H), 6.69 (s, 1H), 7.01 (dd, J = 2.4, 9.0 Hz, 1H), 7.07−7.08 (m, 1H), 7.40 (d, J = 9.0 Hz, 1H), 7.79−7.95 (m, 3H), 8.23−8.27 (m, 1H), 12.04 (br. s, 1H). EI-MS (70 eV) *m/z* (%): 296 (65) [$M^{+\bullet}$], 162 (100), 134 (22), 119 (19), 104 (37), 76 (17). Anal. ($C_{16}H_{12}N_2O_4$): C, H, N.

1-Naphthyl-(5-methoxy-1*H*-2-indolyl)methanone (29) was prepared according to method 2. Yield: 0.58 g (59%). Mp: 174−175 °C. IR (KBr): ν = 3301, 3050, 1611 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.72 (s, 3H), 6.76 (s, 1H), 6.98−7.12 (m, 2H), 7.40−7.47 (m, 1H), 7.53−7.70 (m, 3H), 7.82−7.89 (m, 1H), 8.03−8.20 (m, 3H), 12.02 (s, 1H). EI-MS (70 eV) *m/z* (%): 301 (100) [$M^{+\bullet}$], 300 (47), 286 (12), 284 (13), 158 (11), 127 (26). Anal. ($C_{20}H_{15}NO_2$): C, H, N.

(5-Methoxy-1*H*-2-indolyl)(2-pyridyl)methanone (30) was prepared according to method 2. Yield: 0.30 g (65%). Mp: 201 °C. IR (KBr): ν = 3328, 3067, 1649 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.73 (s, 3H), 7.98−8.04 (m, 1H), 8.12−8.22 (m, 2H), 8.31−8.39 (m, 2H), 8.53−8.60 (m, 1H), 8.69−8.71 (m, 1H), 8.83−8.85 (m, 1H), 11.84 (s, 1H). EI-MS (70 eV) *m/z* (%): 252 (100) [$M^{+\bullet}$], 237 (18), 173 (88), 158 (49), 77 (13). Anal. ($C_{15}H_{12}N_2O_2$): C, H, N.

(5-Benzyloxy-1*H*-2-indolyl)(1*H*-2-indolyl)methanone (40) was prepared according to method 2. Yield: 1.51 g (53%). Mp: 199−201 °C. IR (KBr): ν = 3458, 3313, 1618, 1582 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.14 (s, 2H), 7.04−7.77 (m, 14 H), 11.86 (s, 1H), 11.95 (s, 1H). EI-MS (70 eV) *m/z* (%): 366 (100) [$M^{+\bullet}$], 275 (83), 158 (47), 144 (9), 130 (18), 91 (75). Anal. ($C_{24}H_{18}N_2O_2$): C, H, N.

Preparation of 2-Aminophenyl(5-methoxy-1*H*-2-indolyl)methanone (28). The title compound was obtained by reduction of **27** (1.48 g, 5.00 mmol) in 10 mL of dry methanol.[51] Yield: 1.10 g (83%) of needles. Mp: 144−145 °C. IR (KBr): ν = 3486, 3311, 1615 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.76 (s, 3H), 6.60−6.67 (m, 3H), 6.83−6.96 (m, 3H), 7.15 (m, 1H), 7.26−7.41 (m, 2H), 7.82−7.86 (m, 1H), 11.69 (br. s, 1H). EI-MS (70 eV) *m/z* (%): 266 (100) [$M^{+\bullet}$], 238 (49), 223 (26), 195 (14), 120 (17), 92 (21), 84 (32). Anal. ($C_{16}H_{14}N_2O_2$): C, H, N.

Procedure D (Scheme 1, Route II): Preparation of 1-Phenylsulfonyl-1*H*-2-indolecarboxylic Acids (5). The appropriate 1-phenylsulfonylindole was lithiated at −78 °C for 1 h, as described above in procedure A. An excess of solid and dry carbon dioxide was added. The mixture was warmed to room temperature overnight and the solvent removed under reduced pressure. To the white solid obtained, were added CH_2Cl_2 (about 3.0 mL per mmol) and hydrochloric acid (6 N, 1.0 mL/mmol), and the mixture was refluxed for 1 h. The organic layer was washed with hydrochloric acid (2 N; 1.0 mL/mmol) and dried (Na_2SO_4). Removing the solvent under reduced pressure left an oily residue that was crystallized from diethyl ether. Thus, (1-phenylsulfonyl-1*H*-2-indolyl)carboxylic acid[52] and 5-benzyloxy-1-phenylsulfonyl-1*H*-indole-2-carboxylic acid were prepared:

1-Phenylsulfonyl-1*H*-2-indolecarboxylic Acid.[52]

5-Benzyloxy-1-phenylsulfonyl-1*H*-*i*ndole-2-carboxylic Acid. Starting from 5-benzyloxy-1-phenylsulfonyl-1*H*-indole (50.0 g, 137.6 mmol), the title compound was obtained as colorless crystals (43.7 g, 77%). Mp: 175−178 °C. IR (KBr): ν = 1700 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 5.11 (s, 2H), 7.13−7.74 (m, 11 H), 7.90−7.97 (m, 3H), 13.56 (br. s, 1H). EI-MS (70 eV) *m*/*z* (%): 407 (2) [M$^{+\bullet}$], 363 (19), 272 (16), 222 (6), 141 (20), 91 (100). Anal. ($C_{22}H_{17}NO_5S$): C, H, N.

Procedure E (Scheme 1, Route II): Preparation of 1-Phenylsulfonyl-1*H*-2-indolecarboxylic Acid Chlorides (6). The appropriate 1-phenylsulfonyl-1*H*-2-indolecarboxylic acid (5.0 mmol) (cf., procedure D, Scheme 1, route II) was dissolved in thionyl chloride (10.0 mL) and refluxed for 1 h. Excess thionyl chloride was removed under reduced pressure, and the acid chloride was dried in vacuo. An analytical sample could be obtained by column chromatography (SiO_2/CH_2Cl_2) and crystallization from CH_2Cl_2/hexane. Thus, 1-phenylsulfonyl-1*H*-2-indolecarboxylic acid chloride and 5-benzyloxy-1-phenylsulfonyl-1*H*-2-indolecarboxylic acid chloride were prepared.

1-Phenylsulfonyl-1*H*-2-indolecarboxylic acid chloride: Yield: quantitative, of colorless crystals. Mp: 122−123 °C. IR (KBr): ν = 1760 cm^{-1}. Anal. ($C_{15}H_{10}ClNO_3S$): C, H, N.

5-Benzyloxy-1-phenylsulfonyl-1*H*-2-indolecarboxylic Acid Chloride. Yield: quantitative, of light yellowish crystals. Mp: 130−131 °C. IR (KBr): ν = 1750 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 5.11 (s, 2H), 7.10−7.66 (m, 11H), 7.98−8.17 (m, 3H). Anal. ($C_{22}H_{16}ClNO_4S$): C, H, N.

Procedure F (Scheme 1, Route II): Preparation of (1-Phenylsulfonyl-1*H*-2-indolyl)methanones (1b, 10b−16b, 20b, 22b−25b, 40b) and Other (1-Phenylsulfonyl-1H-2-indolyl)aroyl Derivatives (21b, 26b, 27b, 29b, and 30b) by Reaction of (1-Phenylsulfonyl-1H-indolyl)-2-lithium 3 with Carboxylic Acid Chlorides. At −78 °C a solution of the respective (1-phenylsulfonyl-1*H*-indolyl)-2-lithium (**3**) (5.0 mmol) (cf. Procedure A) was added slowly to the appropriate 1-phenylsulfonyl-1*H*-indole-2-carboxylic acid chloride **6** (5.5 mmol) (cf. procedure E) or the appropriate benzoic acid chloride (5.5 mmol) in dry THF (15.0 mL). The mixture was allowed to warm to room temperature overnight, hydrolyzed with aqueous $NaHCO_3$ (300 mL; 2%), and extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried (Na_2SO_4). Column chromatography (SiO_2/CH_2Cl_2) and crystallization from diethyl ether/light petrol (4:1) afforded the product as colorless to faintly yellowish crystals. Thus, the title compounds **21b**, **26b**, **27b**, **29b**, and **30b** were prepared. (For the preparation of compounds **1b**, **10b**−**16b**, **20b**, **22b**−**25b**, and **40b**, we followed procedures A and B, Scheme 1, route I, as described above.)

(1-Phenylsulfonyl-1*H*-2-indolyl)phenylmethanone (21b): From **3** and benzoic acid chloride. 1.17 g (65%). Mp: 142−143 °C. IR (KBr): ν = 3071, 1661, 1599 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.29−7.41 (m, 2H), 7.49−7.80 (m, 8H), 7.91−8.09 (m, 5H). EI-MS (70 eV) *m*/*z* (%): 361 (68) [M$^{+\bullet}$], 297 (37), 220 (100), 192 (30), 165 (34), 105(39), 77 (95). Anal. ($C_{21}H_{15}NO_3S$): C, H, N.

3,4-Dichlorophenyl-(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)methanone (26b) was prepared from **3** and 3,4-dichloro-benzoic acid chloride. 1.66 g (72%). Mp: 141−144 °C. IR (KBr): ν = 3091, 2929, 1663 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.78 (s, 3H), 7.10−7.21 (m, 2H), 7.33 (s, 1H), 7.56−7.75 (m, 3H), 7.80−7.98 (m, 5H), 8.04 (d, J = 1.8 Hz, 1H). EI-MS (70 eV) *m*/*z* (%): 459 (58) [M$^{+\bullet}$], 395 (9), 318 (27), 283 (100), 268 (27), 173 (26). Anal. ($C_{22}H_{15}Cl_2NO_4S$): C, H, N.

(5-Methoxy-1-phenylsulfonyl-1-H-2-indolyl)-2-nitrophenylmethanone (27b) was prepared from **3** and 2-nitrobenzoic acid chloride. Yield: 1.27 g (47%) of beige crystals. Mp: 190−191 °C. IR (KBr): ν = 3070, 1673, 1650 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.77 (s, 3H), 7.19−7.24 (m, 3H), 7.64−7.80 (m, 4H), 7.86−7.94 (m, 2H), 8.05−8.13 (m, 3H), 8.16−8.23 (m, 1H). EI-MS (70 eV) *m*/*z* (%): 436 (24) [M$^{+\bullet}$], 134 (100), 104 (57), 77 (41). Anal. ($C_{22}H_{16}N_2O_6S$): C, H, N.

(5-Methoxy-1-phenylsulfonyl-1*H*-2-indolyl)(1-naphthyl)methanone (29b) was prepared from **3** and naphthalene-1-carbonic acid chloride. Yield: 1.06 g (48%) mp 225−228 °C. IR (KBr): ν = 3071, 3008, 1652 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.75 (s, 3H), 7.11−7.23 (m, 3H), 7.56−7.79 (m, 7H), 7.92−7.99 (m, 3H), 8.07−8.12 (m, 1H), 8.20−8.27 (m, 1H), 8.60−8.67 (m, 1H). EI-MS (70 eV) *m*/*z* (%): 441 (24) [M$^{+\bullet}$], 300 (100), 285 (11), 257 (19), 228 (12). Anal. ($C_{26}H_{19}NO_4S$): C, H, N.

5-Methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2-pyridinyl)-methanone (30b) was prepared from **3** and 2-pyridinecarbonic acid chloride. Yield: 0.98 g (75%) of colorless crystals. Mp: 207 °C. IR (KBr): ν = 3002, 1671, 1615, cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.75 (s, 3H), 7.04−7.09 (m, 1H), 7.16−7.17 (m, 1H), 7.27 (s, 1H), 7.53−7.59 (m, 2H), 7.63−7.72 (m, 2H), 7.79−7.85 (m, 3H), 8.05−8.16 (m, 2H), 8.70−8.73 (m, 1H). EI-MS (70 eV) *m*/*z* (%): 492 (9) [M$^{+\bullet}$], 251 (100), 208 (11), 179 (9), 77 (15). Anal. ($C_{21}H_{16}N_2O_4S$): C, H, N.

Preparation of 1*H*-2-Indolyl(5-methoxy-1H-2-indolyl)-methane (19). Compound **11** (0.35 g, 1.21 mmol), 0.30 g of KOH, and 0.15 mL of hydrazine hydrate were dissolved in 12 mL of diethylene glycol and heated to 195 °C within 2 h. After cooling to room temperature, 10 mL of water was added and the mixture was extracted with dichloromethane (2 × 10 mL). The combined extracts were dried over Na_2SO_4, and the solvent was removed in vacuo. Column chromatography (SiO_2/CH_2Cl_2) and crystallization from methanol afforded 0.28 g (84%) of the product as colorless crystals. Mp: 112 °C. IR (KBr): ν = 3400, 1620, 1595 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.71 (s, 3H), 4.18 (s, 2H), 6.14 (d, J = 1.2 Hz, 1H), 6.20 (d, J = 1.2 Hz, 1H), 6.65 (dd, J1 = 2.5 Hz., J^2 = 9.3 Hz, 1H), 6.89−7.40 (m, 3H), 7.17 (d, J = 9.3 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H), 10.81 (s, 1H), 11.0 (s, 1H). MS (70 eV) *m*/*z* (%): 276 (100) [M$^{+\bullet}$], 232 (15), 160 (35), 130 (35), 117 (32). Anal. ($C_{18}H_{16}N_2O$): C, H, N.

Procedure G (Scheme 2): Preparation of the Amide Derivatives 31−38. The appropriate amine (6.2 mmol) was added to a solution of the indole-2-carboxylic acid (6.2 mmol) and EDCI·HCl (1.78 g, 9.3 mmol) in 7 mL of dry CH_2Cl_2. This mixture was stirred for 30 min and poured into 2 N HCl (50 mL). The two-phase system was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with $NaHCO_3$ solution and water. After drying (Na_2SO_2), the solvent was reduced to allow precipitation of the product, which was washed with ice-cold CH_2Cl_2:

N-Phenyl-1H-2-indolecarboxamide (31). Yield: 1.22 g (83%) of colorless crystals. Mp: 192−193 °C. IR (KBr): ν = 3425, 3344, 1646 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.04−7.14 (m, 2H), 7.19−7.26 (m, 1H), 7.34−7.49 (m, 4H), 7.66−7.70 (m, 1H), 7.80−7.83 (m, 2H), 10.20 (s, 1H), 11.74 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 236 (70) [M$^{+\bullet}$], 144 (100), 116 (14), 93 (36), 89 (43). Anal. ($C_{15}H_{12}N_2O$): C, H, N.

N-Phenyl-5-methoxy-1H-2-indolecarboxamide (32). Yield: 1.44 g (87%) of green crystals. Mp: 197 °C. IR (KBr): ν = 3384, 3289, 1656 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.78 (s, 3H), 6.86−6.90 (m, 1H), 7.07−7.14 (m, 2H), 7.33−7.40 (m, 4H), 7.79−7.82 (m, 2H), 10.14 (br. s, 1H), 11.58 (br. s, 1H). EI-MS (70 eV) *m*/*z* (%): 266 (66) [M$^{+\bullet}$], 173 (100), 146 (14), 119 (27). Anal. ($C_{16}H_{14}N_2O_2$): C, H, N.

N-3-Trifluoromethylphenyl-1H-2-indolecarboxamide (33). Yield: 1.47 g (78%) of light yellow crystals. Mp: 160 °C (dec). IR (KBr): ν = 3375, 3325, 1681 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.06−7.12 (m, 1H), 7.21−7.28 (m, 1H), 7.44−7.50 (m, 3H), 7.59−7.72 (m, 2H), 8.10−8.13 (m, 1H), 8.25 (br. s, 1H), 10.50 (br. s, 1H), 11.79 (br. s, 1H). EI-MS (70 eV) *m*/*z* (%): 304 (39) [M$^{+\bullet}$], 144 (100), 116 (15), 89 (42). Anal. ($C_{16}H_{11}N_2OF_3$): C, H, N.

N-3-Trifluoromethylphenyl-5-methoxy-1H-2-indolecarboxamide (34). Yield: 1.53 g (74%) of light green crystals. Mp: 203 °C. IR (KBr): ν = 3369, 3305, 1702 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.79 (s, 3H), 6.88−6.92 (m, 1H), 7.15−7.16 (m, 1H), 7.35−7.39 (m, 2H), 7.43−7.47 (m, 1H), 7.59−7.65 (m, 1H), 8.09−8.13 (m, 1H), 8.24 (br. s, 1H), 10.45 (br. s, 1H), 11.64 (br. s, 1H). EI-MS (70 eV) *m*/*z* (%): 334 (71) [M$^{+\bullet}$], 315 (5), 173 (100), 146 (16), 119 (25). Anal. ($C_{17}H_{13}N_2O_2F_3$): C, H, N.

N-4-Trifluoromethylphenyl-5-methoxy-1H-2-indolecarboxamide (35). Yield: 1.60 g (77%) of light green crystals. Mp: 262−264 °C. IR (KBr): ν = 3379, 3365, 1702 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.78 (s, 3H), 6.87−6.92 (m, 1H), 7.15−7.16 (m, 1H), 7.35−7.38 (m, 2H), 7.72−7.76 (m, 2H), 8.02−8.06 (m, 2H), 10.47 (br. s, 1H), 11.66 (br. s, 1H). EI-MS (70 eV) *m*/*z* (%): 334 (77) [M$^{+\bullet}$], 315 (5), 173 (100), 146 (17), 119 (27). Anal. ($C_{17}H_{13}N_2O_2F_3$): C, H, N.

N-2-Naphthyl-5-methoxy-1H-2-indolecarboxamide (36). Yield: 1.69 g (86%) of yellow crystals. Mp: 210−211 °C. IR (KBr): ν = 3380, 3258, 1646 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.79 (s, 3H), 6.87−6.91 (m, 1H), 7.15−7.16 (m, 1H), 7.36−7.39 (m, 1H), 7.43−7.44 (m, 1H), 7.54−7.66 (m, 4H), 7.87−7.90 (m, 1H), 7.96−8.04 (m, 2H), 10.38 (br. s, 1H), 11.61 (br. s, 1H). EI-MS (70 eV) *m*/*z* (%): 316 (44) [M$^{+\bullet}$], 174 (30), 143 (100), 119 (19). Anal. ($C_{20}H_{16}N_2O_2$): C, H, N.

N-4-(1,5-Dimethyl-2-phenyl-2,3-dihydro-1H-3-pyrazolyl)-1H-2-indolecarboxamide (37). Yield: 1.59 g (74%) of light yellow crystals. Mp: 283 °C. IR (KBr): ν = 3419, 3309, 1696, 1648 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.20 (s, 3H), 3.11 (s, 3H), 7.02−7.09 (m, 1H), 7.17−7.24 (m, 1H), 7.31−7.56 (m, 7H), 7.64−7.66 (m, 1H), 9.58 (s, 1H), 11.65 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 346 (2) [M$^{+\bullet}$], 286 (100), 143 (52), 115 (64), 88 (14). Anal. ($C_{20}H_{18}N_4O_2$): C, H, N.

N-4-(1,5-Dimethyl-2-phenyl-2,3-dihydro-1H-3-pyrazolyl)-5-methoxy-1H-2-i ndolecarboxamide (38). Yield: 1.52 g (69%) of colorless crystals. Mp: 259−260 °C. IR (KBr): ν = 3423, 3267, 1648 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.20 (s, 3H), 3.11 (s, 3H), 3.77 (s, 3H), 8.84−6.88 (m, 1H), 7.11−7.12 (m, 1H), 7.26 (m, 1H), 7.30−7.41 (m, 4H), 7.50−7.53 (m, 2H), 9.52 (s, 1H), 11.50 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 376 (47) [M$^{+\bullet}$], 203 (35), 174 (33), 119 (31), 84 (35), 56 (100). Anal. ($C_{21}H_{20}N_4O_3$): C, H, N.

Preparation of (5-Hydroxy-1*H*-2-indolyl)(1H-2-indolyl)-methanone (39) (Scheme 3). A mixture of **40** (4.00 g, 10.92 mmol), ammonium formate (12.00 g, 188.80 mmol), and Pd/C (2.0 g) in methanol/THF (1/1 v/v) (200 mL) was stirred at 40 °C for 4 h. After removal of the catalyst, the solvent was evaporated to leave an oily material. Ethyl acetate (200 mL) and water (100 mL) were added. The organic layer was washed with water and dried (Na_2SO_4), and the solvent was evaporated. Treatment of the residue with a little diethyl ether results in crystallization of **39**, which was washed with ether: Yield: 1.95 g (65%) of yellow crystals. Mp: 249−251 °C. IR (KBr): ν = 3457, 3320, 1707, 1618 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 6.84−7.76 (m, 9H), 8.93 (s, 1H), 11.68 (s, 1H), 11.92 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 276 (100) [M$^{+\bullet}$], 159 (63), 144 (26), 133 (27), 117 (31), 105 (10). Anal. ($C_{17}H_{12}N_2O_2$·0.2ethyl acetate): C, H, N.

Procedure H: Preparation of the Alkyl Derivatives 41−49 (Scheme 3). The respective alkyl halide (5.50 mmol) was added together with K_2CO_3 (0.70 g, 5.00 mmol) to a solution of **39** (0.28 g, 1.00 mmol) in acetone (40 mL). The mixture was heated at reflux for 70 h. After removal of the acetone, the mixture was poured into ice−water (100 mL) and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo. The crude product was crystallized from ethyl acetate/dichloromethane to yield the compounds as yellow crystals.

(5-Ethoxy-1*H*-2-indolyl)(1H-2-indolyl)methanone (41). Yield: 0.13 g (44%). Mp: 168−169 °C. IR (KBr): ν = 3451, 3291, 1655, 1618 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.36 (t, *J* = 2.8 Hz, 3H), 1.36 (q, *J* = 2.8 Hz, 2H), 6.94−7.78 (m, 9H), 11.82 (s, 1H), 11.95 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 304 (100) [M$^{+\bullet}$], 275 (19), 187 (49), 158 (38), 144 (15), 130 (28). Anal. ($C_{19}H_{16}N_2O_2$): C, H, N.

1*H*-2-Indolyl-[5-(2-(morpholin-1-yl)ethoxy)-1H-2-indolyl]-methanone (42). Yield: 0.16 g (40%). Mp: 98−101 °C. IR (KBr): ν = 3289, 3062, 1599 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.45−2.58 (m, 4H), 2.72 (t, *J* = 5.8 Hz, 2H), 3.56−3.63 (m, 4H), 4.12 (t, *J* = 5.8 Hz, 2H), 6.95−7.01 (m, 1H), 7.08−7.22 (m, 2H), 7.27−7.58 (m, 5H), 7.73−7.78 (m, 1H), 11.83 (s, 1H), 11.98 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 389 (9) [M$^{+\bullet}$], 114 (14), 100 (100). Anal. ($C_{23}H_{23}N_3O_3$·0.33ethyl acetate): C, H, N.

1*H*-2-Indolyl-[5-(3-dimethylaminopropyloxy)-1H-2-indolyl]methanone (43). Yield: 0.18 g (50%). Mp: 163−166 °C. IR (KBr): ν = 3278, 2952, 1736 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.00 (q, *J* = 2.7 Hz, 2H), 2.36 (s, 6H), 2.65 (t, *J* = 2.7 Hz, 2H), 4.03 (t, *J* = 2.7 Hz, 2H), 6.96−7.77 (m, 9H), 11.84 (s, 1H), 11.96 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 361 (8) [M$^{+\bullet}$], 86 (22), 58 (100). Anal. ($C_{22}H_{23}N_3O_2$·2.25dichloromethane): C, H, N.

5-(4-Iodobutoxy-1*H*-2-indolyl)(1H-2-indolyl)methanone (44). Yield: 0.22 g (47%). Mp: 110−113 °C. IR (KBr): ν = 3455, 3291, 1661, 1618 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.78−2.03 (m, 4H), 3.38 (t, *J* = 2.7 Hz, 2H), 4.02 (t, *J* = 2.5 Hz, 2H), 6.95−8.99 (m, 9H), 11.84 (s, 1H), 11.95 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 458 (20) [M$^{+\bullet}$], 330 (26), 276 (18), 183 (100), 55 (97). Anal. ($C_{21}H_{19}IN_2O_2$): C, H, N.

1*H*-2-Indolyl-[5-(2-dimethylaminoethoxy)-1H-2-indolyl]-methanone (45). Yield: 0.13 g (38%). Mp: 143−145 °C. IR (KBr): ν = 3235, 2950, 1605, 1593 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.37 (s, 6H), 2.84 (t, *J* = 2.2 Hz, 2H), 4.13 (t, *J* = 2.3 Hz, 2H), 6.97−7.77 (m, 9H), 11.86 (s, 1H), 11.96 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 347 (9) [M$^{+\bullet}$], 72 (14), 58 (100). Anal. ($C_{21}H_{21}N_3O_2$·2.0dichloromethane): C, H, N.

(5-Cyclohexylmethoxy-1*H*-2-indolyl)(1H-2-indolyl)methanone (46). Yield: 0.19 g (52%). Mp: 185 °C (dec). IR (KBr): ν = 3457, 3293, 1676, 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.00−1.35 (m, 5H), 1.66−1.99 (m, 6H), 3.80 (d, *J* = 2.5 Hz, 2H), 6.95−7.78 (m, 9H), 11.82 (s, 1H), 11.95 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 372 (79) [M$^{+\bullet}$], 276 (100), 159 (68), 117 (42). Anal. ($C_{24}H_{24}N_2O_2$): C, H, N.

5-(5-Iodopenthoxy-1*H*-2-indolyl)-1H-2-indolylmethanone (47). Yield: 0.19 g (41%). Mp: 127−130 °C. IR (KBr): ν = 3422, 3287, 1721, 1618 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.52−1.67 (m, 2H), 1.72−1.99 (m, 4H), 3.39 (t, *J* = 2.6 Hz, 2H), 4.04 (t, *J* = 2.6 Hz, 2H), 6.95−7.78 (m, 9H), 11.83 (s, 1H), 11.95 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 472 (100) [M$^{+\bullet}$], 344 (30), 276 (47), 197 (44), 159 (93). Anal. ($C_{22}H_{21}IN_2O_2$): C, H, N.

1*H*-*2*-Indolyl-[5-(1-phenylethoxy)-1H-2-indolyl]methanone (48). Yield: 0.20 g (52%). Mp: 151−153 °C. IR (KBr): ν = 3457, 3299, 1713, 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.57 (d, *J* = 2.6 Hz, 3H), 5.48 (q, *J* = 2.6 Hz, 1H), 6.89−7.75 (m, 14H), 11.79 (s, 1H), 11.91 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 380 (19) [M$^{+\bullet}$], 276 (100), 159 (38), 144 (17), 117 (22), 105 (88). Anal. ($C_{25}H_{20}N_2O_2$): C, H, N.

1*H*-2-Indolyl-[5-(2-piperidin-1-ylethoxy)-1H-2-indolyl]-methanone (49). Yield: 0.14 g (36%). Mp: 104−106 °C. IR (KBr): ν = 3286, 1742, 1591 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.32−1.57 (m, 6H), 2.40−2.48 (m, 4H), 2.70 (t, *J* = 5.9 Hz, 2H), 4.06 (t, *J* = 5.9 Hz, 2H), 6.95−7.01 (m, 1H), 7.08−7.58 (m, 7H), 7.73−7.79 (m, 1H). EI-MS (70 eV) *m*/*z* (%): 387 (5) [M$^{+\bullet}$], 276 (4), 98 (100). Anal. ($C_{24}H_{25}N_3O_2$·0.66ethyl acetate): C, H, N.

Procedure I: Preparation of the Ester Derivatives 50−76 (Scheme 3). The appropriate acid chloride (3.0 mmol) was added to a solution of **39** (0.28 g, 1.0 mmol) in ethyl acetate (10 mL)/pyridine (2 mL) and stirred for 20 h. After pouring the mixture into ice−water (100 mL) and extraction with ethyl acetate, the organic layer was dried (Na_2SO_4). Removing the solvent in vacuo left the crude product, which was crystallized from ethyl acetate/dichloromethane, yielding the respective compound as yellow crystals.

[2-(1*H*-2-indolylcarbonyl)-1H-5-indolyl]ethanoate (50). Yield: 0.19 g (60%). Mp: 223−224 °C. IR (KBr): ν = 3424, 3330, 1750 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.30 (s, 3H), 7.05−7.78 (m, 9H), 11.99 (s, 1H), 12.07 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 318 (58) [M$^{+\bullet}$], 276 (100), 159 (60), 144 (24), 133 (24), 117 (34). Anal. ($C_{19}H_{14}N_2O_3$·0.25ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-4-methoxybenzoate (51). Yield: 0.24 g (58%). Mp: 262−264 °C. IR (KBr): ν = 3411, 3334, 1717, 1603 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.90 (s, 3H), 7.10−8.15 (m, 13H), 12.00 (s, 1H), 12.11 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 410 (11) [M$^{+\bullet}$], 135 (100). Anal. ($C_{25}H_{18}N_2O_4$·0.5ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]butanoate (52). Yield: 0.22 g (64%). Mp: 201−204 °C. IR (KBr): ν = 3422, 3334, 1746, 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.00 (t, *J* = 2.9 Hz, 3H), 1.67 (sext., *J* = 2.9 Hz, 2H), 2.58 (t, *J* = 2.9 Hz,

2H), 7.04−7.84 (m, 9H), 12.00 (s, 1H), 12.07 (s, 1H). EI-MS (70 eV) *m/z* (%): 346 (25) [$M^{+\bullet}$], 276 (100), 159 (44), 144 (20), 117 (28). Anal. ($C_{21}H_{18}N_2O_3$·0.15ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]dimethylaminoethanoate (53). Yield: 0.15 g (41%). Mp: 215−217 °C. IR (KBr): ν = 3374, 1761, 1620, cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.36 (s, 6H), 3.49 (s, 2H), 7.06−7.78 (m, 9H), 12.00 (s, 1H), 12.09 (s, 1H). EI-MS (70 eV) *m/z* (%): 361 (1) [$M^{+\bullet}$], 333 (4), 276 (5), 58 (100). Anal. ($C_{21}H_{19}N_3O_3$·0.25ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]propanoate (54): 0.21 g (62%). Mp: 236−238 °C. IR (KBr): ν = 3426, 3330, 1748, 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.16 (t, J = 3.0 Hz, 3H), 2.62 (q, J = 3.0 Hz, 2H), 7.04−7.78 (m, 9H), 11.99 (s, 1H), 12.07 (s, 1H). EI-MS (70 eV) *m/z* (%): 332 (35) [$M^{+\bullet}$], 276 (100), 159 (51), 144 (20), 117 (26). Anal. ($C_{20}H_{16}N_2O_3$· 0.25dichloromethane): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-2-thiophenylethanoate (55). Yield: 0.19 g (48%). Mp: 224−226 °C. IR (KBr): ν = 3432, 3320, 1757, 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 4.26 (s, 2H), 7.02−7.78 (m, 12H), 12.00 (s, 1H), 12.10 (s, 1H). EI-MS (70 eV) *m/z* (%): 400 (22) [$M^{+\bullet}$], 276 (100), 159 (50), 97 (91). Anal. ($C_{23}H_{16}N_2O_3S$·0.25ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-O-acetylsalicylate (56). Yield: 0.24 g (55%). Mp: 133−135 °C. IR (KBr): ν = 3303, 1744, 1735 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.27 (s, 3H), 7.10−7.19 (m, 2H), 7.29−7.36 (m, 2H), 7.49−7.66 (m, 6H), 7.75−7.82 (m, 2H), 8.19−8.21 (m, 1H), 12.05 (d, J = 0.5 Hz, 1H), 12.14 (d, J = 0.5 Hz, 1H). EI-MS (70 eV) *m/z* (%): 438 (5) [$M^{+\bullet}$], 396 (15), 318 (19), 276 (100). Anal. ($C_{26}H_{18}N_2O_5$·1.0ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-4-phenylbenzoate (57). Yield: 0.27 g (59%). Mp: 286 °C (dec). IR (KBr): ν = 3413, 3336, 1717 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.05−7.15 (m, 1H), 7.24−7.39 (m, 2H), 7.42−7.82 (m, 11H), 7.93, 8.25 (AA′BB′, 4H), 12.02 (s, 1H), 12.14 (s, 1H). EI-MS (70 eV) *m/z* (%): 456 (21) [$M^{+\bullet}$], 276 (11), 181 (100), 152(19). Anal. ($C_{30}H_{20}N_2O_3$·0.5ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-2-phenylpropanoate (58). Yield: 0.27 g (66%). Mp: 211−213 °C. IR (KBr): ν = 3426, 3326, 1748, 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.98 (m, 4H), 6.96−7.00 (m, 1H), 7.10−7.14 (m, 1H), 7.23−7.40 (m, 7H), 7.48−7.53 (m, 2H), 7.60 (bs, 2H), 7.74−7.78 (m, 1H), 12.00 (s, 1H), 12.07 (s, 1H). EI-MS (70 eV) *m/z* (%): 408 (15) [$M^{+\bullet}$], 276 (100), 159 (39), 144 (17), 117 (21). Anal. ($C_{26}H_{20}N_2O_3$·0.25ethyl acetate): C, H, N.

D,L-**[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-α-acetoxy-α-phenylethanoate (59).** Yield: 0.22 g (49%). Mp: 194−196 °C. IR (KBr): ν = 3401, 3313, 1759, 1740 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.21 (s, 3H), 6.24 (s, 1H), 6.90−6.92 (m, 1H), 7.11−7.13 (m, 1H), 7.28−7.67 (m, 11H), 7.74−7.76 (m, 1H), 11.99 (s, 1H), 12.12 (s, 1H). EI-MS (70 eV) *m/z* (%): 452 (13) [$M^{+\bullet}$], 276 (100), 159 (35), 144 (15), 117 (21). Anal. ($C_{27}H_{20}N_2O_5$· 0.25ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]benzoate (60). Yield: 0.23 g (61%). Mp: 257−260 °C. IR (KBr): ν = 3425, 3316, 1726, 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.10−7.32 (m, 3H), 7.51−7.68 (m, 7H), 7.74−7.80 (m, 2H), 8.16−8.19 (m, 2H), 12.01 (s, 1H), 12.14 (s, 1H). EI-MS (70 eV) *m/z* (%): 380 (20) [$M^{+\bullet}$], 276 (3), 158 (5), 105 (100), 77 (25). Anal. ($C_{24}H_{16}N_2O_3$· 0.25ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-3-methoxyphenylethanoate (61). Yield: 0.28 g (67%). Mp: 212−215 °C. IR (KBr): ν = 3424, 3328, 3054, 2836, 1752 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.78 (s, 3H), 3.96 (s, 2H), 6.86−7.15 (m, 5H), 7.27−7.35 (m, 2H), 7.46−7.60 (m, 5H), 7.75−7.77 (m, 1H), 12.00 (s, 1H), 12.09 (s, 1H). EI-MS (70 eV) *m/z* (%): 424 (10) [$M^{+\bullet}$], 276 (100), 159 (56), 144 (24), 117 (28). Anal. ($C_{26}H_{20}N_2O_4$): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-2-chlorobenzoate (62). Yield: 0.24 g (57%). Mp: 252−254 °C. IR (KBr): ν = 3456, 3322, 1740, 1618 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.10−7.16 (m, 1H), 7.24−7.35 (m, 2H), 7.50−7.79 (m, 9H), 8.10−8.13 (m, 1H), 12.02 (s, 1H), 12.16 (s, 1H). EI-MS (70 eV) *m/z* (%): 414 (17) [$M^{+\bullet}$], 276 (4), 158 (9), 141 (33), 139 (100), 111 (13). Anal. ($C_{24}H_{15}ClN_2O_3$·0.25ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-4-nitrobenzoate (63). Yield: 0.18 g (43%). Mp: 274−276 °C. IR (KBr): ν = 3429, 3338, 1737, 1618 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.10−7.15 (m, 1H), 7.26−7.35 (m, 2H), 7.50−7.78 (m, 6H), 8.38−8.46 (m, 4H), 12.01 (s, 1H), 12.16 (s, 1H). EI-MS (70 eV) *m/z* (%): 425 (32) [$M^{+\bullet}$], 276 (100), 159 (68), 150 (52), 133 (31), 117 (46). Anal. ($C_{24}H_{15}N_3O_5$·0.25ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-3,4,5-trimethoxybenzoate (64). Yield: 0.24 g (51%). Mp: 216−219 °C. IR (KBr): ν = 3467, 3292, 1732 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.79 (s, 3H), 3.90 (s, 6H), 7.10−7.35 (m, 3H), 7.45−7.64 (m, 6H), 7.76−7.78 (m, 1H), 12.01 (s, 1H), 12.13 (s, 1H). EI-MS (70 eV) *m/z* (%): 470 (9) [$M^{+\bullet}$], 276 (21), 195 (100), 159 (14), 133 (6), 117 (10). Anal. ($C_{27}H_{22}N_2O_6$·0.33ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]cinnamate (65). Yield: 0.15 g (36%). Mp: 226−228 °C. IR (KBr): ν = 3409, 3328, 1769, 1715 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 6.81−6.97 (m, 1H), 7.09−7.18 (m, 2H), 7.24−7.35 (m, 1H), 7.43−7.63 (m, 8H), 7.75−7.96 (m, 4H), 12.00 (s, 1H), 12.11 (s, 1H). EI-MS (70 eV) *m/z* (%): 406 (17) [$M^{+\bullet}$], 276 (22), 159 (15), 131 (100), 103 (26). Anal. ($C_{26}H_{18}N_2O_3$): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-2-furancarboxylate (66). Yield: 0.21 g (58%). Mp: 245−246 °C. IR (KBr): ν = 3446, 3314, 1740 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 6.81−6.83 (m, 1H), 7.09−7.35 (m, 3H), 7.50−7.63 (m, 6H), 7.76−7.78 (m, 1H), 8.11−8.12 (m, 1H), 12.01 (s, 1H), 12.14 (s, 1H). EI-MS (70 eV) *m/z* (%): 370 (28) [$M^{+\bullet}$], 276 (6), 158 (11), 117 (9), 95 (100). Anal. ($C_{22}H_{14}N_2O_4$·0.25ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]methoxyethanoate (67). Yield: 0.23 g (67%). Mp: 202−203 °C. IR (KBr): ν = 3428, 3328, 1771 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.40 (s, 3H), 4.35 (s, 2H), 7.08−7.16 (m, 2H), 7.28−7.36 (m, 1H), 4.49−7.63 (m, 5H), 7.74−7.80 (m, 1H), 12.00 (s, 1H), 12.10 (s. 1H). EI-MS (70 eV) *m/z* (%): 348 (15) [$M^{+\bullet}$], 320 (10), 275 (10), 158 (22), 130 (24), 45 (100). Anal. ($C_{20}H_{16}N_2O_4$): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-2-quinolinecarboxylate (68). Yield: 0.14 g (33%). Mp: 286−288 °C. IR (KBr): ν = 3469, 3301, 1744 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.09−7.18 (m, 1H), 7.28−7.37 (m, 2H), 7.49−7.85 (m, 7H), 7.89−7.98 (m, 1H), 8.13−8.37 (m, 3H), 8.67−8.68 (m, 1H), 12.02 (s, 1H), 12.16 (s, 1H). EI-MS (70 eV) *m/z* (%): 431 (8) [$M^{+\bullet}$], 387 (15), 276 (100), 159 (94), 144 (41), 128 (58). Anal. ($C_{27}H_{17}N_3O_3$·0.5dichloromethane): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-4-ethoxybenzoate (69). Yield: 0.18 g (42%). Mp: 254−256 °C. IR (KBr): ν = 3444, 3313, 1721 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.38 (t, J = 6.7 Hz, 3H), 4.16 (q, J = 6.7 Hz, 2H), 7.10−7.19 (m, 2H), 7.12, 7.81 (AB, J = 8.7 Hz, 4H), 7.21−7.35 (m, 1H), 7.50−7.63 (m, 5H), 7.75−7.78 (m, 1H), 12.00 (s, 1H), 12.11 (s, 1H). EI-MS (70 eV) *m/z* (%): 424 (13) [$M^{+\bullet}$], 149 (100). Anal. ($C_{26}H_{20}N_2O_4$): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]cyclopropylcarboxylate (70). Yield: 0.22 g (63%). Mp: 268−270 °C. IR (KBr): ν = 3422, 3345, 1735 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.00−1.10 (m, 4H), 1.87−1.99 (m, 1H), 7.05−7.16 (m, 2H), 7.28−7.33 (m, 1H), 7.46−7.63 (m, 5H), 7.74−7.79 (m, 1H), 12.00 (s, 1H), 12.10 (s, 1H). EI-MS (70 eV) *m/z* (%): 344 (58) [$M^{+\bullet}$], 276 (100), 159 (31), 144 (14), 69 (86), 41 (49). Anal. ($C_{21}H_{16}N_2O_3$·0.25dichloromethane): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]cyclobutanecarboxylate (71). Yield: 0.24 g (67%). Mp: 238−240 °C. IR (KBr): ν = 3423, 3336, 1740 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.83−2.12 (m, 2H), 2.22−2.43 (m, 4H), 3.39−3.53 (m, 1H), 7.03−7.16 (m, 2H), 7.28−7.35 (m, 1H), 7.45−7.63 (m, 5H), 7.74−7.80 (m, 1H), 11.95 (s, 1H), 12.05 (s, 1H). EI-MS (70 eV) *m/z* (%): 358 (27) [$M^{+\bullet}$], 276 (100), 159 (25), 117 (20), 55 (58). Anal. ($C_{22}H_{18}N_2O_3$): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-3-pyridinecarboxylate (72). Yield: 0.18 g (48%). Mp: 248−250 °C. IR (KBr): ν = 3065, 1730, 1595 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.09−7.17 (m, 1H), 7.26−7.41 (m, 2H), 7.49−7.71 (m, 6H),

7.73−7.79 (m, 1H), 8.45−8.60 (m, 1H), 8.86−8.95 (m, 1H), 9.27−9.33 (m, 1H), 12.00 (s, 1H), 12.15 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 381 (45) [$M^{+\bullet}$], 276 (17), 159 (12), 117 (15), 106 (100), 78 (34). Anal. ($C_{23}H_{15}N_3O_3$·0.25ethyl acetate): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]diphenylethanoate (73). Yield: 0.28 g (60%). Mp: 289−290 °C. IR (KBr): ν = 3463, 3332, 1742 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.57 (s, 1H), 6.98−7.18 (m, 2H), 7.27−7.62 (m, 16H), 7.73−7.78 (m, 1H), 12.00 (s, 1H), 12.10 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 470 (5) [$M^{+\bullet}$], 276 (75), 194 (59), 167 (98), 165 (100). Anal. ($C_{31}H_{22}N_2O_3$·0.25ethyl acetate): C, H, N..

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-2-phenoxybenzoate (74). Yield: 0.18 g (39%). Mp: 252−260 °C. IR (KBr) ν = 3436, 3324, 1711 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 6.96−7.04 (m, 3H), 7.08−7.20 (m, 3H), 7.27−7.54 (m, 7H), 7.57−7.63 (m, 2H), 7.68−7.80 (m, 2H), 8.07−8.13 (m, 1H), 11.98 (s, 1H), 12.08 (s, 1H); EI-MS (70 eV) *m*/*z* (%): 472 [M^+] (39). Anal. ($C_{30}H_{20}N_2O_4$): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-3-phenoxybenzoate (75). Yield: 0.19 g (40%). Mp: 242−245 °C. IR (KBr) ν = 3439, 3331, 1708 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 7.08−7.35 (m, 6H), 7.39−7.66 (m, 10H), 7.68−7.78 (m, 1H), 7.92−7.96 (m, 1H), 11.99 (s, 1H), 12.11 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 472 [M^+] (28), 197 (100). Anal. ($C_{30}H_{20}N_2O_4$): C, H, N.

[2-(1*H*-2-Indolylcarbonyl)-1H-5-indolyl]-2-benzoylbenzoate (76). Yield: 0.15 g (31%). Mp: 250−258 °C. IR (KBr) ν = 3436, 3322, 1725 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 6.78−6.81 (m, 1H), 7.08−7.15 (m, 1H), 7.23−7.24 (m, 1H), 7.28−7.34 (m, 2H), 7.42−7.91 (m, 13H), 8.21−8.25 (m, 1H), 11.97 (s, 1H), 12.07 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 484 [M^+] (22), 209 (100). Anal. ($C_{31}H_{20}N_2O_4$): C, H, N.

Procedure J: Preparation of N-Substituted Derivatives 77−85 (Scheme 4). At 0 °C sodium hydride (60% suspension in paraffin) (0.16 g, 4.0 mmol) was added to **11** (0.40 g, 1.4 mmol) in 10 mL of anhydrous THF. After 30 min, the respective alkyl iodide was added to benzyl bromide (1.4 mmol), and the reaction mixture was stirred for 10 h. At room temperature, water was carefully added and the mixture was poured into sat. $NaHCO_3$ solution (50 mL). The organic layer was separated, the aqueous layer was extracted with ether (3 × 15 mL), and the combined organic layers were dried (Na_2SO_4). Removal of the solvent resulted in yellow crystals, which were subjected to flash chromatography (SiO_2; CH_2Cl_2). The two different N-monoalkylated and the N-dialkylated compounds could be isolated as yellow crystals in a 1:1:2 ratio [**77** (0.18 g, 43%), **78** (0.09 g, 20%) and **79** (0.09 g, 20%)].

(1-Methyl-1*H*-2-indolyl)(1-methyl-5-methoxy-1*H*-2-indolyl)methanone (77). Yield: 0.18 g (43%). Mp: 148−149 °C. IR (KBr): ν = 1611 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.79 (s, 3H), 4.01 (s, 3H), 4.03 (s, 3H), 7.04−7.09 (m, 1H), 7.14−7.24 (m, 4H), 7.37−7.44 (m, 1H), 7.54−7.58 (m, 1H), 7.62−7.65 (m, 1H), 7.73−7.76 (m, 1H). EI-MS (70 eV) *m*/*z* (%): 318 (100) [$M^{+\bullet}$], 174 (33), 144 (39), 130 (15), 89 (18). Anal. ($C_{20}H_{18}N_2O_2$): C, H, N.

(1*H*-2-Indolyl)(1-methyl-5-methoxy-1*H*-2-indolyl)methanone (78). Yield: 0.09 g (20%). Mp: 190 °C. IR (KBr): ν = 3326, 1602 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.80 (s, 3H), 4.00 (s, 3H), 7.03−7.15 (m, 2H), 7.22−7.23 (m, 1H), 7.29−7.34 (m, 3H), 7.50−7.57 (m, 2H), 7.73−7.76 (m, 1H), 11.96 (br. s, 1H). EI-MS (70 eV) *m*/*z* (%): 340 (100) [$M^{+\bullet}$], 161 (27), 146 (15), 130 (22), 89 (14). Anal. ($C_{19}H_{16}N_2O_2$): C, H, N.

(1-Methyl-1*H*-2-indolyl)(5-methoxy-1*H*-2-indolyl)methanone (79). Yield: 0.09 g (20%). Mp: 176−177 °C. IR (KBr): ν = 3317, 1609 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.78 (s, 3H), 4.02 (s, 3H), 6.96−7.01 (m, 1H), 7.15−7.21 (m, 2H), 7.25−7.26 (m, 1H), 7.37−7.43 (m, 3H), 7.61−7.65 (m, 1H), 7.76−7.79 (m, 1H), 11.85 (br. s, 1H). EI-MS (70 eV) *m*/*z* (%): 304 (100) [$M^{+\bullet}$], 173 (43), 160 (15), 131 (47), 89 (17). Anal. ($C_{19}H_{16}N_2O_2$): C, H, N.

(1-Ethyl-1*H*-2-indolyl)(1-ethyl-5-methoxy-1H-2-indolyl)-methanone (80). Yield: 0.20 g (43%). Mp: 99−100 °C. IR (KBr): ν = 1611 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.35 (m, 6H), 3.79 (s, 3H), 4.56 (m, 4H), 7.03−7.08 (m, 1H), 7.14−7.21 (m, 4H), 7.36−7.43 (m, 1H), 7.56−7.60 (m, 1H), 7.65−7.68 (m, 1H), 7.73−7.76 (m, 1H). EI-MS (70 eV) *m*/*z* (%): 346 (100) [$M^{+\bullet}$], 202 (29), 144 (28). Anal. ($C_{22}H_{22}N_2O_2$): C, H, N.

(1*H*-2-Indolyl)(1-ethyl-5-methoxy-1H-2-indolyl)methanone (81). Yield: 0.08 g (17%). Mp: 142−143 °C. IR (KBr): ν = 3355, 1594 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.33 (t, J = 7.0 Hz, 3H), 3.80 (s, 3H), 4.54 (q, J = 7.0 Hz, 2H), 7.02−7.15 (m, 2H), 7.23−7.24 (m, 1H), 7.28−7.35 (m, 3H), 7.49−7.59 (m, 2H), 7.73−7.76 (m, 1H), 11.96 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 318 (100) [$M^{+\bullet}$], 303 (29), 174 (19), 158 (20), 130 (36). Anal. ($C_{20}H_{18}N_2O_2$): C, H, N.

(1-Ethyl-1*H*-2-indolyl)(5-methoxy-1H-2-indolyl)methanone (82). Yield: 0.09 g (20%). Mp: 101−102 °C. IR (KBr): ν = 3355, 1602 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.35 (t, J = 7 Hz, 3H), 3.78 (s, 3H), 4.57 (q, J = 7 Hz, 2H), 6.96−7.01 (m, 1H), 7.15−7.21 (m, 2H), 7.24−7.25 (m, 1H), 7.36−7.43 (m, 3H), 7.63−7.67 (m, 1H), 7.76−7.79 (m, 1H), 11.85 (br. s, 1H). EI-MS (70 eV) *m*/*z* (%): 318 (100) [$M^{+\bullet}$], 303 (25), 173 (28), 160 (13), 158 (11), 145 (33), 130 (38). Anal. ($C_{20}H_{18}N_2O_2$): C, H, N.

(1-Benzyl-1*H*-2-indolyl)(1-benzyl-5-methoxy-1H-2-indolyl)methanone (83). Yield: 0.24 g (36%). Mp: 132 °C. IR (KBr): ν = 1621 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.78 (s, 3H), 5.81 (s, 2H), 5.84 (s, 2H), 6.99−7.06 (m, 5H), 7.14−7.38 (m, 11H), 7.50−7.54 (m, 1H), 7.60−7.63 (m, 1H), 7.76−7.79 (m, 1H). EI-MS (70 eV) *m*/*z* (%): 470 (81) [$M^{+\bullet}$], 379 (55), 236 (65), 206 (70), 91 (100). Anal. ($C_{32}H_{26}N_2O_2$): C, H, N.

(1*H*-2-Indolyl)(1-benzyl-5-methoxy-1H-2-indolyl)methanone (84). Yield: 0.12 g (23%). Mp: 171 °C. IR (KBr): ν = 3334, 1596 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.80 (s, 3H), 5.84 (s, 2H), 6.99−7.34 (m, 10H), 7.46−7.54 (m, 3H), 7.73−7.76 (m, 1H), 11.96 (br. s, 1H). EI-MS (70 eV) *m*/*z* (%): 380 (100) [$M^{+\bullet}$], 303 (21), 206 (21), 190 (71). Anal. ($C_{25}H_{20}N_2O_2$): C, H, N.

(1-Benzyl-1*H*-2-indolyl)(5-methoxy-1H-2-indolyl)-1-methanone (85). Yield: 0.11 g (21%). Mp: 170 °C. IR (KBr): ν = 3355, 3031, 2831 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.79 (s, 3H), 5.87 (s, 2H), 6.96−7.00 (m, 1H), 7.06−7.09 (m, 2H), 7.14−7.27 (m, 6H), 7.32−7.40 (m, 2H), 7.51 (s, 1H), 7.60−7.64 (m, 1H), 7.79−7.82 (m, 1H), 11.85 (s, 1H). EI-MS (70 eV) *m*/*z* (%): 380 (100) [$M^{+\bullet}$], 303 (15), 236 (20), 190 (65). Anal. ($C_{25}H_{20}N_2O_2$): C, H, N.

Biochemical and Biological Assays.

Kinase Assays. Swiss 3T3 fibroblasts (ATCC CCL 92) were cultivated in DMEM/10% FCS (Life Technologies). The effect on PDGF-stimulated tyrosine phosphorylation was measured by subjecting quiescent cultures in 24-well plates (NUNC) to a medium change into serum-free DMEM (0.4 mL per well) and treating them with the test compounds in DMSO (final DMSO concentration 1%) or solvent for 2 h. The cells were subsequently stimulated with 100 ng/mL human recombinant PDGF-BB (TEBU/Peprotech) or with the corresponding solvent for 10 min at room temperature, washed twice with PBS, and extracted with lysis buffer containing Hepes, pH 7.5, 1% Triton X-100, phosphatase, and protease inhibitors as described.[18] A 10 μg sample of protein of identically treated cell extracts was subjected to SDS−PAGE with 7.5% gels and immunoblotting with anti-phosphotyrosine antibodies. Quantification of IC_{50} values was based on the intensity of the signal for autophosphorylated PDGF receptor. Titration was done using four to eight inhibitor concentrations within a range of 2 orders of magnitude, which was selected on the basis of preliminary experiments. IC_{50} values were obtained by curve-fitting of the results using the program Sigma Plot 2.0 (Jandel Corp.). With three independent experiments, SEM were in the range of ±50%. Quinoxaline AG1295 served as a reference compound for these determinations.[18] Porcine aortic endothelial (PAE) cells expressing human PDGFα- or β-receptors and human FGF receptor-1 were kindly provided by Dr. L. Claesson-Welsh (Uppsala). Testing inhibition of the respective receptor kinases in these cells was done as described.[53] To measure effects on EGF receptor phosphorylation, A431 cells (ATCC CRL 1555) were starved overnight in serum-free medium, treated for 2 h with the compounds, thereafter stimulated with 100 ng/mL EGF (TEBU/Peprotech) for 10 min, and subjected to extraction and immunoblotting as described above. In vitro kinase reactions with purified PDGFβ-receptor were performed as

described[18,19,53]. Src-dependent tyrosine phosphorylation in src-transformed NIH3T3 fibroblasts was determined as described.[53]

GRK2 activity was measured in vitro by employing lysates of GRK2-overexpressing 293 cells as the source of kinase and rhodopsin purified from bovine rod outer segments as described.[54]

For PKC assays, COS-7 cells were transiently transfected with expression plasmids for the different RGS-HIS6-tagged PKC isoforms. Cells were scraped off from the dishes in PBS and centrifuged for 5 min at 1000*g*. The pellet was resuspended in 500 μL of lysis buffer containing 150 mM NaCl, 50 mM HEPES pH 7.5, 1% Nonidet P-40, 50 μg/mL leupeptin, 50 μg/mL aprotinine, and 1 mM phenylmethylsulfonyl fluoride (PMSF) and incubated for 10 min on ice. Cell lysates were centrifuged at 10000*g* for 10 min, and the supernatant was transferred to a fresh tube. Equilibrated Ni^{2+}-NTA agarose (100 μL) (Qiagen) was added, and the tubes were rotated for 1 h to allow binding of Ni^{2+}-agarose to the RGS-His6-tagged PKCs. The beads with bound PKCs were then washed four times with lysis buffer supplemented with 50 mM imidazole, and the purified PKCs were eluted with 500 mM imidazole in 20 mM tris(hydroxymethyl)aminomethane (Tris)-HCl, pH 7.5. About 100 ng of purified PKC were added to 100 μL of assay buffer containing 20 mM Tris-HCl, pH 7.5, 20 mM $MgCl_2$, 50 μM substrate peptide PKCα-19−31/Ser25 (ALEXIS), 40 μM ATP, and 1 μCi [γ-^{33}P]-ATP (NEN). In addition, for measurement of PKC-ϵ, 10 μM sonified phosphatidylserine and 10 μM 12-*O*-tetradecanoylphorbol-13-acetate (TPA) were added. The reaction was incubated for 10 min at 30 °C and stopped on ice. A portion of the reaction mix (50 μL) was transferred to phosphocellulose disk sheets (GIBCO BRL). The phosphocellulose sheets were washed three times with 1% phosphoric acid and twice with distilled water and transferred to scintillation vials containing 4 mL of liquid scintillation fluid, and the radioactivity was measured in a liquid scintillation counter.

In vitro assays with Sf9-derived kinase GST-fusion proteins were performed as described in Hofman et al.[55]

Kinetic experiments with purified human PDGFβ-receptor were performed as described.[19] The concentration of ATP was varied from 25 to 400 μM, and with the concentration of KY751 substrate peptide fixed at 3 mM, the concentration of the peptide KY751 was varied from 0.1 to 3 mM with the ATP concentration fixed at 400 μM.

Cell Growth Parameters. DNA synthesis in Swiss 3T3 fibroblasts stimulated by different agents was determined in 24-well plates by incorporation of methyl-[^{3}H]thymidine, as described.[18] Alternatively, Swiss 3T3 cells were grown in 96-well plates to confluency. The medium was changed for serum-free DMEM and inhibitors (final DMSO concentration 1%) and growth factors were added as desired. DNA synthesis was measured by incorporation of BrdU with an ELISA kit (Roche) exactly according to the instructions of the manufacturer. NIH3T3 cell lines expressing the gene for human PDGF-B chain in an inducible manner were generated as described earlier for other oncogenes[56] and were kept in DMEM, supplemented with 10% donor calf serum (DCS), previously tested for absence of tetracycline. In DMEM with 2% DCS the growth of these cells requires induction of PDGF-B expression. Inhibitors were tested under these conditions, and the effect on proliferation was evaluated after 48 h by an XTT proliferation assay using a cell proliferation kit (Roche, Mannheim) according to the instructions of the manufacturer.

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