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Original article

3-Bromo-*4*-(1*H*-3-indolyl)-2,5-dihydro-1*H*-2,5-pyrroledione derivatives as new lead compounds for antibacterially active substances

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Abstract

A number of new compounds containing 3-bromo-2,5-dihydro-1*H*-2,5-pyrroledione and indole substructures were found to have antibacterial activity against resistant strains of *Staphylococcus aureus*, *Mycobacterium smegmatis* and some other Gram positive bacteria. The investigated compounds exhibit minimal inhibition concentrations (*MIC*'s) lower than those of ciprofloxacin, vancomycin and doxycycline resp. A different spectrum of activity, suggests a mechanism of action different to vancomycin and doxycycline. This might be important in circumventing existing resistance mechanisms. Here we report about the synthesis and on the antibacterial activity in a structure activity relationship study.

Keywords: SAR-study; Antibacterial; Indole derivatives; Resistant *Staphylococcus aureus*; *Mycobacterium smegmatis*

1. Introduction

The emergence of bacterial resistance to the available antibiotics of various structural classes has become a problem in the medical world. While use of antibiotics allowed physicians to successfully treat numerous diseases over the last decades, almost all bacteria treated with antibiotics have developed at least some degree of resistance against these drugs [1]. In many countries, an increasing number of clinical isolates of multiresistant *Staphylococcus aureus* strains has been observed [2] and the pathogenetic potential in nosocomial and community acquired infections is well known [3]. Substituted 2,5-dihydro-1*H*-2,5-pyrrolediones and their reduced derivatives **1a**–**g** have interesting biological activities. For example, arcyriarubin A **(1a)** (Fig. 1) and related compounds, in which one indole substituent can be replaced by various heterocycles, show high antimicrobial [4] and antiviral [5–8] activity and are potent protein kinase C (PKC)-inhibitors [9]. Recently we reported on the antimicrobial activity of pyrrole-substituted 2,5-dihydro-1*H*-2,5-pyrrolediones (e.g. **1h**, **1i**), developed by our group [10].

As announced, we carried out further investigations that led to indole-substituted 2,5-dihydro-1*H*-2,5-pyrrolediones exhibiting even higher antimicrobial activities. These compounds are derivatives of 3-bromo-4-(1*H*-3-indolyl)-2,5-dihydro-1*H*-2,5-pyrroledione with variable substituents in indole 2-position (R^1) (Fig. 2).

In the present work we demonstrate the results of a structure-activity investigation of this new class of compounds.

2. Chemistry

2.1. Synthesis of the compounds

The preparation of compounds comprises two main steps. The first part leads to a 2-substituted indole, using 2-methylaniline and carboxylic acid derivatives as starting materials. In the second part we linked a 3,4-dibromo-2,5-dihydro-1*H*-2,5-pyrro-

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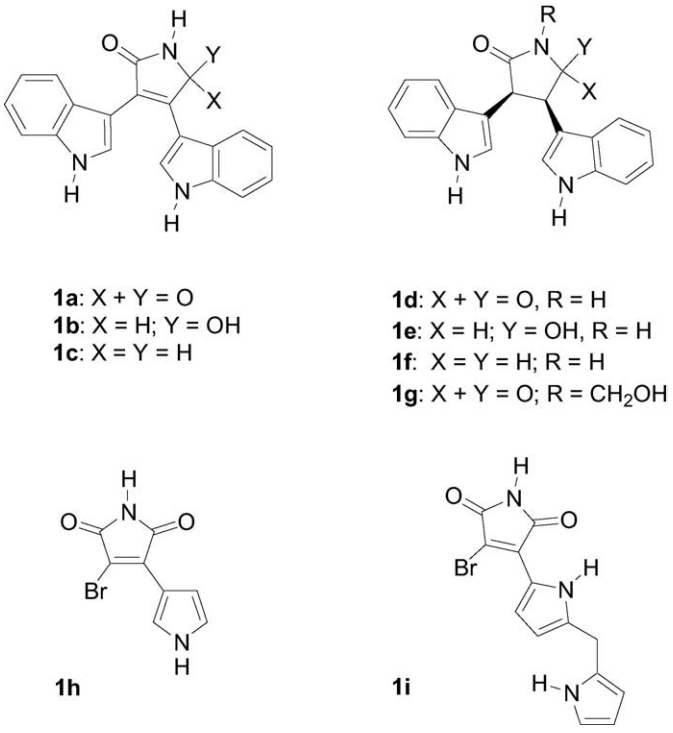


Fig. 1. Chemical structure of arcyriarubin A **(1a)** and related biological active compounds.

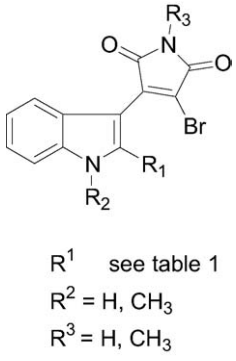
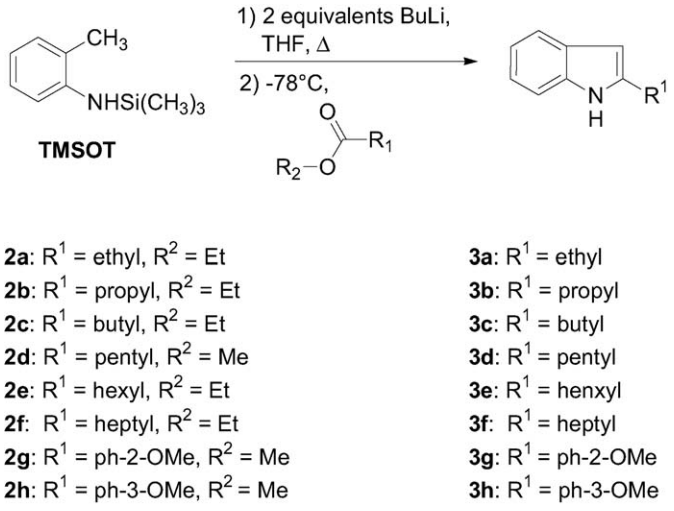


Fig. 2. General structure of 3-bromo-4-(1*H*-3-indolyl)-2,5-dihydro-1*H*-2,5-pyrrolediones investigated.

ledione derivative to the indole-3-position to give the title compounds.

One series of compounds consists of simple 2-alkylindoles. We prepared the indoles **3a**–**h** in analogy to the protocols of Smith et al. (Scheme 1) [11,12]. Thus, *N*-trimethylsilyl-2-toluidine (TMSOT) was lithiated with two equivalents of *n*-BuLi leading to metallation at the NH–Si– and the methyl group. This product acts as a strong nucleophile. We reacted the Li_2TMSOT suspension, after cooling to –78 °C, with carboxylic acid esters to give the desired 2-substituted indoles. Analogously 2-phenylindoles were available using substituted benzoic acid esters.

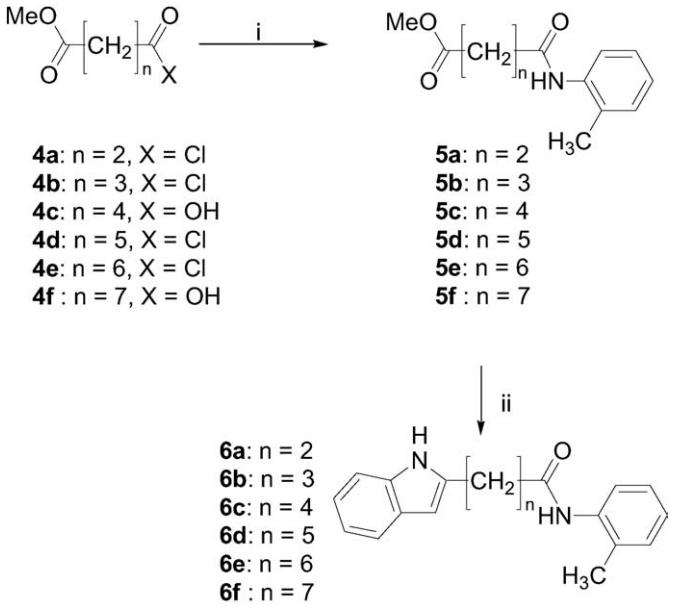
We got another series of compounds by linking a 2-methylanilide substructure to the indole-2-position by an alkyl spacer. We had to modify Smith's [11,12] method to prepare the spacer linked indole-2-methylanilides **6a**–**f**. We prepared the ester 2-



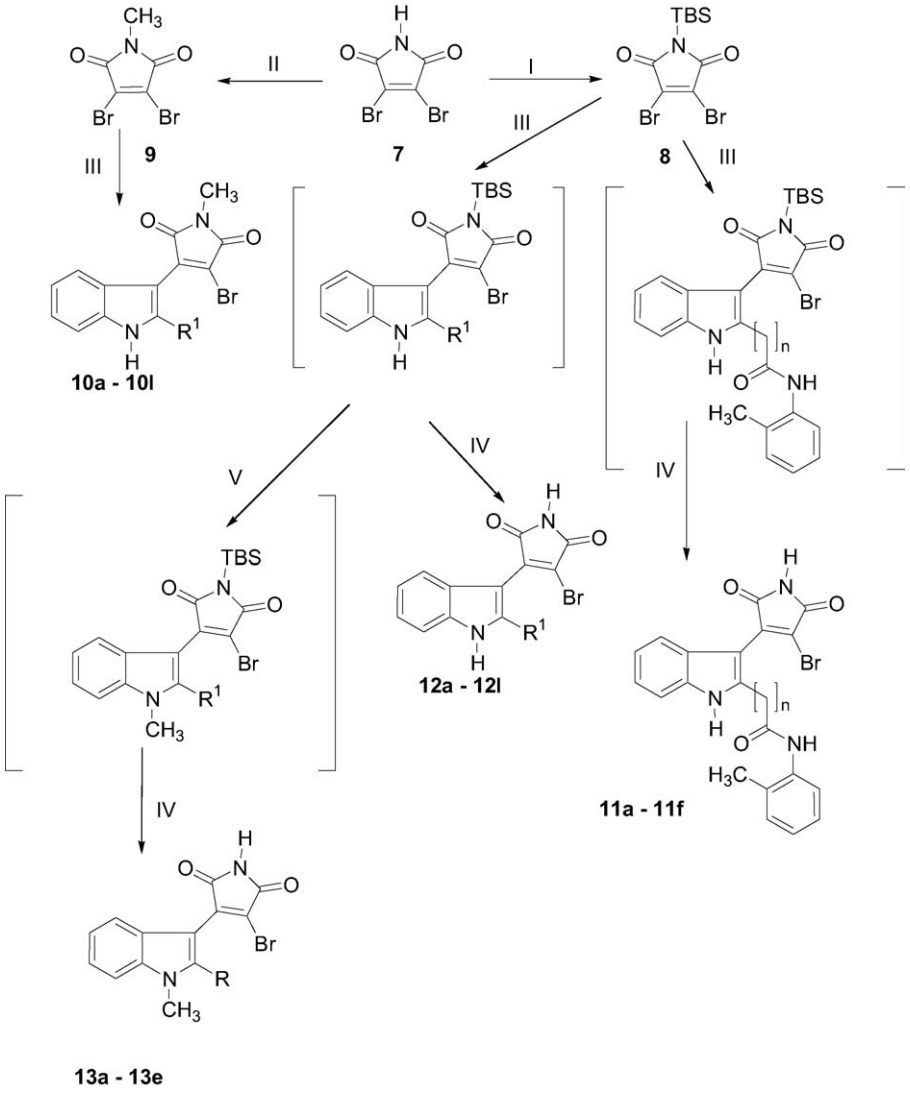
Scheme 1. Formation of the 2-alkyl- and 2-methoxyphenyl indoles according to Smith [11,12].

methylanilides from the dicarboxylic acid monoesters or monoester halides **4a**–**f** and 2-methylaniline. These ester 2-methylanilides **5** had to be *N*-metallated with *n*-BuLi before being reacted with Li_2TMSOT. Otherwise, the amide H protonates the Li_2TMSOT, regenerating its methyl group and so is preventing the indole formation. Therefore, we added one equivalent of *n*-BuLi at –78 °C before we added the Li_2TMSOT suspension. Using this procedure, we got the desired indoles **6a**–**f** in yields of about 10–20%.

Several authors described the introduction of 3,4-dibromo-2,5-dihydro-1*H*-2,5-pyrroledione **7** at the indole-3-position (Scheme 3) in the lit. According to Brenner [13], the indole was metallated by Grignard's reagent to form a nucleophile at C-3 position. This nucleophile can undergo a S_N reaction with **7**



Scheme 2. Conditions: (i) X = Cl: 2-methylaniline, NEt_3, Δ, **12h**; for X = OH: 2-methylaniline, dicyclohexylcarbodiimide, *p*-TosOH, pyridine, **12h**; (ii) *n*-BuLi, Li_2TMSOT,–78 °C > RT.



Scheme 3. Conditions: (I) TBSCl, NaH, THF; (II) DMS, acetone, K_2CO_3; (III) indole derivative (for R^1 and *n* see Table 1), LiHMDS, THF, –20 °C; (IV) NBu_4F, THF; (V) DMS, BuLi, THF.

substituting one bromide to form the final product. In our hands, however, this method led to low yields and products that were difficult to purify. We got better results using a modified method, described by Murase et al. [14]: First we protected the N of **7** by a *tert*-butyl-dimethylsilyl group (TBS) and got the product **8** [14]. The indole reactant was metallated with lithium hexamethyldisilazane LiHMDS [15] (Scheme 3). The reaction of the lithiated indole and **8** led to silyl-protected products, which we could only isolate as raw materials containing remaining indoles. After removal of the silyl protecting group by tetrabutylammonium fluoride [14], we could easily isolate the final products.

In order to study the effects of the N-hydrogen bond on its biological effect, we masked the imide NH as well as the indole NH by methylation. We accomplished the formal methylation of the imide NH by reacting the substituted indoles with 1-methyl-3,4-dibromo-2,5-dihydro-1*H*-2,5-pyrroledione (**9**) [16]. For the methylation of the indole NH, the silyl-protected raw materials were reacted with dimethylsulfate (DMS) prior to removing the silyl protecting group. The main formation pathways are shown in Scheme 3. A survey of the final products is presented in table 1.

To show the importance of the bromine substituent, we hydrogenated the double bond of the 2,5-dihydro-1*H*-2,5-pyrroledione core of **12a**. The reaction was accompanied by loss of the bromine substituent to give the indole substituted pyrrolidinedione **14**. This we further processed to **15**, regenerating the former double bond by an oxidative dehydrogenation with DDQ in the presence of a catalytic amount of 4-toluenesulfonic acid (Scheme 4).

3. Pharmacology

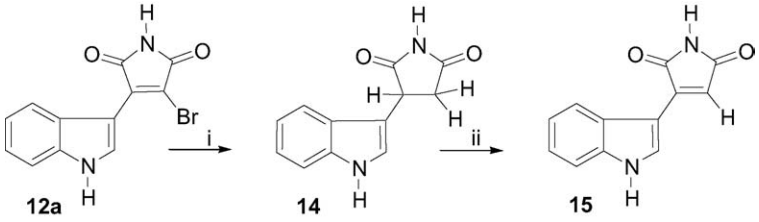
3.1. General antimicrobial properties

The compounds **12a** and **12l** are two typical substances of the synthesized series. Their antibacterial activities against some Gram positive and Gram negative bacteria are shown in

Table 1
Substituents for the compounds, described in Scheme 3

Compound $R^2 = H$ $R^3 = CH_3$	R^1	Compound $R^2 = H$ $R^3 = H$	N[a]	Compound $R^2 = H$ $R^3 = H$	R^1	Compound $R^2 = CH_3$ $R^3 = H$	R^1
10a	H	**11a**	2	**12a**	H	**13a**	Methyl
10b	Methyl	**11b**	3	**12b**	Methyl	**13b**	Butyl
10c	Ethyl	**11c**	4	**12c**	Ethyl	**13c**	Hexyl
10d	Propyl	**11d**	5	**12d**	Propyl	**13d**	Phenyl
10e	Butyl	**11e**	6	**12e**	Butyl	**13e**	Ph-4-OMe
10f	Pentyl	**11f**	7	**12f**	Pentyl		
10g	Hexyl			**12g**	Hexyl		
10h	Heptyl			**12h**	Heptyl		
10i	Phenyl			**12i**	Phenyl		
10j	ph-2-OMe			**12j**	Ph-2-OMe		
10k	ph-3-OMe			**12k**	Ph-3-OMe		
10l	ph-4-OMe			**12l**	Ph-4-OMe		

[a] For R^1 and N see scheme 3.



Scheme 4. Conditions: (i) Pd/C, H_2 CH_3OH; (ii) 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), 4-toluenesulfonic acid, benzene, RT.

Table 2 in comparison to the activities of therapeutically used antibiotics in terms of minimal inhibitory concentrations (*MIC*) (determination see Section 6).

Among the Gram positive bacteria the epidemic strain *S. aureus* 134/93 strain is resistant to ciprofloxacin (**Cip**) and methicillin (**Meth**). *S. aureus* SG 511 is a laboratory strain, sensitive to all compounds used. *Enterococcus faecalis* 1528 and *Mycobacterium smegmatis* SG 987 are resistant to **Meth**. *E. faecalis* 1528 additionally to vancomycin (**Vanc**). The Gram negative bacteria *Escherichia coli* SG 458 and *Pseudomonas aeruginosa* SG are resistant to **Meth**, **Vanc, 12a**, and **12l**, *P. aeruginosa* SG 137 additionally to doxycycline (**Dox**).

Against the multiresistant *S. aureus* 134/93 **12a** is in the activity range of **Dox** and **Vanc**. **12l** and some other compounds of the synthesized series (see Tables 3 and 4) were more active against *S. aureus* 134/93 than **Dox** and **Vanc**. The synthesized compounds show lower activities against other Gram positive bacteria and unlike **Dox** they are inactive against Gram negative bacteria. **12a** has the simplest structure within the group of synthesized and tested compounds, showing characteristic ac-

Table 2
Antimicrobial activity of **12a** and some of its derivatives against various Gram positive and Gram negative bacteria. MIC values for Ciprofloxacin (Cip), Methicillin (Meth), Docycycline (Dox) and Vancomycine (Vanc) are given for comparison

	MIC (μg ml^{-1})					
Compound	*S. aureus* 134/93	*S. aureus* SG.511	*E. faecalis* 1528	*M. smegmatis* SG 987	*E. coli* SG 458	*P. aeruginosa* SG 137
12a[a]	3.12	1.56	12.5	12.5	> 50	50
12l[a]	0.13	< 0.05	12.5	13.1	> 50	50
Cip[a]	25	< 0.05	0.4	0.2	< 0.05	0.1
Meth[a]	> 100	0.8	50	> 100	50	> 100
Dox[a]	6.25	< 0.05	12.5	< 0.05	0.4	> 100
Vanc[a]	1.56	0.4	> 100	25	100	> 100
	MIC [10^{-6} M]					
12a[b]	10.6	5.3	42.6	42.6	> 170	170
12l[b]	0.33	< 0.12	31.3	30.0	> 125	125
Cip[b]	82.6	< 0.16	1.3	0.66	< 0.16	0.33
Meth[b]	> 265	2.12	133	> 265	133	265
Dox[b]	13.7	< 0.11	27.5	< 0.11	0.88	> 220
Vanc[b]	1.1	0.28	70	17.5	70	> 70

Table 3
Activity of compounds **12b**–**12h** against *S. aureus* 134/93

Compound	R^1	*MIC* μg^{-1} ml^{-1}	*MIC* per 10^{-6} M	p*MIC*	Δ	log(*P*)
12b	Methyl	0.39	1.28	5.8	0.1	2.26
12c	Ethyl	1.09	3.41	5.5	–0.3	2.41
12d	Propyl	0.32	0.96	6.0	0.1	2.58
12e	Butyl	0.235	0.68	6.2	0.1	2.84
12f	Pentyl	0.14	0.38	6.3	0.0	3.08
12g	Hexyl	0.095	0.253	6.6	0.1	3.35
12h	Heptyl	0.075	0.193	6.7	–0.1	3.65

Table 4
Antibacterial activities of compounds **10a–l**, **11a–f**, **12a**, **12i–l** and **13a–e** against *S. aureus* 134/93

Compound	R^1	*MIC* μg^{-1} ml^{-1}	*MIC* per 10^{-6} M	p*MIC*	Δ	log(*P*)
10a	H	0.76	2.49	5.6	–0.6	2.94
10b	Methyl	12.5	39.16	4.4	–1.6	2.73
10c	Ethyl	6.25	18.76	4.7	–1.4	2.87
10d	Propyl	3.125	9.00	5.1	–1.2	3.06
10e	Butyl	0.4	1.11	6.0	–0.5	3.35
10f	Pentyl	0.8[b]	2.13	5.7	–1.1	3.63
10g	Hexyl	0.8[b]	2.05	5.7	–1.2	3.84
10h	Heptyl	1.6[b]	3.97	5.4	–1.8	4.19
10i	Phenyl	0.39	1.02	6.0	–0.3	3.03
10j	ph-2-OMe	0.4	0.93	6.0	–0.1	2.86
10k	ph-3-OMe	0.4	0.93	6.0	–0.2	2.99
10l	ph-4-OMe	0.156	0.38	6.4	0.1	3.03
13a	Methyl	12.5	39.16	4.4	–1.6	2.69
13b	Butyl	0.1	0.28	6.6	0.1	3.28
13c	Hexyl	0.312	0.80	6.1	–0.8	3.84
13d	Phenyl	0.20	0.51	6.3	0.0	3.11
13e	ph-4-OMe	0.156	0.38	6.4	0.1	3.15
11a	$N = 2$[a]	0.49	1.08	6.0	0.1	2.58
11b	$N = 3$[a]	0.15	0.32	6.5	0.6	2.60
11c	$N = 4$[a]	0.13	0.28	6.6	0.6	2.65
11d	$N = 5$[a]	0.23	0.47	6.3	0.3	2.74
11e	$N = 6$[a]	0.56	1.10	6.0	–0.2	2.91
11f	$N = 7$[a]	0.2	0.38	6.4	0.1	3.07
12a	H	3.12	10.7	5.0	–0.7	2.34
12i	Phenyl	0.35	0.95	6.0	0.1	2.58
12j	ph-2-OMe	0.4	0.96	6.0	0.3	2.34
12k	ph-3-OMe	0.1	0.24	6.6	0.7	2.54
12l	ph-4-OMe	0.13[c]	0.33	6.5	0.6	2.59

[a] For R^1 and *N* see scheme 3.
[b] The compounds haven't been completely soluble in the testing procedure.

tivities against the different strains of microorganisms. Therefore, we selected **12a** as a lead for a structure activity study.

3.2. Structure activity relationship for S. aureus 134/93

The compounds **14** and **15** and all indoles, which we prepared according to Scheme 2, are inactive against *S. aureus* 134/93. Therefore, we regard **12a** to be the simplest active principle, the bromine substituent in pyrrole-3-position seems to be necessary for the activity. Table 3 shows the *MIC*'s for the homologous series of the 2-alkylated derivatives of **12a** (**12b**–**12h**). The activity of the compounds increases with the length of the alkyl substituent. If we define

$$\mathrm{pMIC} = -\log(\mathrm{MIC}/\mathrm{moll}^{-1}) \quad (1)$$

we find a linear correlation between p*MIC* and log(*P*). *P* is the partition coefficient of the compound in the *n*-octanol/water system and describes the hydrophobic properties of a compound. Linear regression led to the function

$$\mathrm{pMIC} = 0.79\ \log(P) + 3.87 \quad (2)$$

with a correlation coefficient of 94%. The experimental error, estimated from the dilution steps used in the antimicrobial tests (see Section 6), is

$$\Delta\mathrm{pMIC} = \pm.3 \quad (3)$$

The results of multiple *MIC*-determinations with the same compounds were all within that limit. Δ describes the deviation of an observed p*MIC* (p*MIC*(obs)) to the value, expected from the log(*P*)-function (2) (p*MIC*(cal)), that is

$$\Delta = \mathrm{pMIC(obs)} - \mathrm{pMIC(cal)} \quad (4)$$

The *MIC*'s of the other compounds are listed in Table 4.

Compounds **10b**–**10h** are a homologous series of 2-alkyl-derivatives, which are all methylated at the imide-N-position ($R^3 = CH_3$). With the only exception that **10a** shows a greater activity than **12a**, this methylation usually reduces the activity of the materials. The activity of **10b**–**10h** is on average 10 times smaller than expected from eq. (2). The effect of imide-N-methylation is much smaller in the case of the phenyl substituted derivatives **10i**–**10l**. If we compare the *MIC*'s of the compounds **10i**–**10l** with the *MIC*'s of the corresponding non methylated compounds **12i**–**12l**, we observe a reduction in activity only in the case of **10k**. The methylated compounds, however, are more hydrophobic than the non methylated ones. If we take the different log(*P*) values into account and compare the Δ values instead of the *MIC's*, the compounds **10i**, **10j** and **10l** show a reduction in activity slightly above the limit of experimental error.

The compounds **13a**–**13e** are methylated at the indole N-position ($R^2 = CH_3$). The effect of this derivatization is not uniform. With **13b** and **13d** the methylation shows no effect. The alkyl derivatives **13a** and **13c** show low activity, and the 4-methoxyphenyl-derivative **13e** shows a reduction in activity only in Δ (relative to Δ of **12l**) but not in *MIC*. From these results we can only draw the conclusion that the indole-N-methylation usually does not improve the activity.

Compound **11d** was a side product of a target compound in another study and we tested it as a mater of routine. Because we have found **11d** to be an active material, we synthesized the homologous series **11a**–**11f** in which we varied the length of the alkyl spacer (expressed by *n*, see scheme 3). The *MIC's* do not strongly depend on the spacer length. If we use the Δ's for analysis, however, we found the compounds **11b** and **11c** more active than expected from eq. (2) while all other compounds of this series have p*MIC*'s fitting to the log(*P*) function. Obviously, we observe a maximum in Δ, if the alkyl spacer consists of three or four methylene units. We find a similar dependence in the series of the 2-methoxyphenyl derivatives. The distance of the methoxy group from the indole-2-position increases in the sequence **12j** < **12k** < **12l**. The compounds **12k** and **12l** are more active than **12i,** but **12j** is not. In this series, the activity depends also on the distance of a polar substituent to the indol-2-position. This dependence is still, but only partly recognizable in the series of the imide-N-methylated methoxyphenyl derivatives **10j**–**10l**. **10l** is more active than **10i**, but **10j** and **10k** are not. Finally, the effect of the methoxy group is extinguished in the indole-N-methylated derivative **13e**. **13e** shows the same *MIC* as **13d** and the methoxy group does not improve the activity in this case.

3.3. Structure activity relationship for M. smegmatis SG 987

The compounds **12a** and **12l** show only moderate activities against the Gram positive bacteria *E. faecalis* 1528 and *M. smegmatis* SG 987 (see Table 2). In the case of *M. smegmatis* SG 987, however, we have found also a linear correlation between p*MIC* of the compounds **12b**–**12h** and log (*P*) as we have observed with *S. aureus* 134/93. Linear regression led to the function

$$\mathrm{pMIC} = 1.63\ \log(P) + 0.57 \quad (5)$$

with a correlation coefficient of 95%. The activity increases of about 100 times if we vary the alkyl group to make the materials more hydrophobic (see Table 5).

Consequently, we have included *M. smegmatis* SG 987 in our study, and we give the results of the other compounds in Table 6.

Methylation of the imid-N-position led on average to a 10-fold reduction in activity. This effect is considerably strong with the indole-2-alkylated derivatives **10a**–**10h**. With the phenyl substituted compounds **10i**–**10l** we find a reduction in activity only in Δ but not in *MIC*. Methylation of the indole-N-position (**13a**–**13e**) led in all cases to a reduction in activity if we use Δ for analysis. The compounds **13a** and **13e**, however, show the same *MIC's* as their non methylated derivatives **12b** and **12l**, respectively. In the homologous series **11a**–**11f** the 2-methylanilide substructure also increases the activity against *M. smegmatis* SG 987 relative to the expected values of eq. (5) in some cases. We found this effect with **11e** ($N = 6$) and **11f** ($N = 7$). Compound **11b** ($N = 3$) shows also a slightly larger activity than the compounds **11a**, **11c** and **11d**. Among the compounds **12j**–**12l**, compound **12k** shows a larger activity than **12i**. Among the compounds **10j**–**10l,** compound **10k** shows a larger activity than **10i**.

4. Discussion

The results, shown in Table 2, demonstrate that the derivatives of **12a** are antibacterial principles, showing selective activity against different bacterial strains. The fact that they have a spectrum of activity against the investigated bacteria different to **Dox** and **Vanc** indicates a different mechanism of action. This might be important in circumventing existing resistance mechanisms. The activities of the compounds **12b**–**12h** depend on their hydrophobicities. Correlation between log(*P*) and biological activity has been frequently observed [17]. One possible

Table 5
Activity of compounds **12b**–**12h** against *M. smegmatis* SG 987

Compound	R^1	*MIC* μg^{-1} ml^{-1}	*MIC* per 10^{-6} M	P*MIC*	Δ	log(*P*)
12b	Methyl	25.0	82	4.1	–0.1	2.26
12c	Ethyl	7.95	25	4.6	0.1	2.41
12d	Propyl	8.3	25	4.6	–0.2	2.58
12e	Butyl	2.17	6.25	5.2	0.0	2.84
12f	Pentyl	0.56	1.55	5.8	0.2	3.08
12g	Hexyl	0.14	0.37	6.4	0.4	3.35
12h	Heptyl	0.30	0.77	6.1	–0.4	3.65

Table 6
Antibacterial activities of compounds **10a–l**, **11a–f**, **12a**, **12i–l** and **13a–e** against *M. smegmatis* SG 987

Compound	R^1	*MIC* μg^{-1} ml^{-1}	*MIC* per 10^{-6} M	p*MIC*	Δ	log(*P*)
10a	H	6.25	20.5	4.7	–0.6	2.89
10b	Methyl	50	157	3.8	–1.2	2.73
10c	Ethyl	50	150	3.8	–1.4	2.87
10d	Propyl	25	72	4.1	–1.4	3.06
10e	Butyl	25	69	4.2	–1.8	3.35
10f	Pentyl	12[b]	33	4.5	–2.0	3.63
10g	Hexyl	3.12[b]	8.0	5.1	–1.7	3.84
10h	Heptyl	No activity[b]	–	–	–	4.19
10i	Phenyl	12.5	32.8	4.5	–1.0	3.03
10j	ph-2-OMe	6.25	15.0	4.8	–0.4	2.86
10k	ph-3-OMe	3.125	7.5	5.1	–0.3	2.99
10l	ph-4-OMe	12.5	30.4	4.5	–1.0	3.03
13a	Methyl	12.5	39	4.4	–0.5	2.69
13b	Butyl	6.25	17	4.8	–1.1	3.28
13c	Hexyl	No activity	–	–	–	3.84
13d	Phenyl	No activity	–	–	–	3.11
13e	ph-4-OMe	12.5	30.3	4.5	–1.2	3.15
11a	$N = 2$[a]	25.0	55.3	4.3	–0.5	2.58
11b	$N = 3$[a]	8.0	17.1	4.8	–0.1	2.60
11c	$N = 4$[a]	25	52.0	4.3	–0.6	2.65
11d	$N = 5$[a]	12.5	25.3	4.6	–0.4	2.74
11e	$N = 6$[a]	0.25	0.49	6.3	1.0	2.91
11f	$N = 7$[a]	0.41	0.78	6.1	0.5	3.07
12a	H[c]	12.5	43	4.4	0.0	2.34
12i	Phenyl	18.4	50	4.3	–0.5	2.58
12j	ph-2-OMe	12.5	33	4.5	0.1	2.34
12k	ph-3-OMe	3.125	7.5	5.1	0.4	2.54
12l	ph-4-OMe	13.1	30.0	4.5	–0.3	2.59

[a] For R^1 and *N* see Scheme 3.
[b] The compounds haven't been completely soluble in the testing procedure.

explanation is that the active materials have to permeate the hydrophobic double layer of a cell membrane to reach their target inside the cell [18]. In the case of *M. smegmatis* SG 987, the slope of the log(*P*) function (eq. (5)) is two times larger than in the case of *S. aureus* 134/93 (eq.(2)). This indicates that hydrophobic materials can invade the cells of *M. smegmatis* SG 987 easier than those of *S. aureus* 134/93. This result is easy to understand, because pathogenic mycobacteria are wrapped by a high amount of mycolic acid esters [19], making their cell surface more hydrophobic than those of most other bacteria. Therefore, the experimental observations are in good agreement with the hypothesis that the permeation properties of the active materials are reflected by the observed log(*P*) functions indicating a predominant lipid pathway [20]. In this case, however, the hydrophobicity of the active materials should influence the activity of all investigated compounds and the effect should not be limited to the compounds **12a**–**12h**. If we want to take into account the effect of the different hydrophobicities of our compounds, we can use the Δ's for analysis instead of the p*MIC*'s. Although the most important conclusions of our study do not strongly depend on it, there are some indications that the use of the Δ's is justified. The p*MIC*'s of **10a**–**10h** also depend on log (*P*) but the limited solubility of some of this compounds in the testing procedure affects the quantitative correlation in this series. Finally, compounds **11a**, **11d**–**11f**, **12i** and **12j** have activities against *S. aureus* 134/93 fitting to eq. (2) although they are not 2-alkylated derivatives of **12a**.

If a derivatization causes a deviation of $\Delta > +/-0.3$ from the log(*P*) function (or from Δ of a fitting reference, if more than one derivatization is made) in several derivatives, it is very unlikely that only different permeation properties cause this effect. We have to suspect a special effect on physiological processes inside the bacterial cell.

We have observed two of such derivatization effects in our study, which we consider to be important. One of them is the reduction of activity in the case of imide-N-methylation. It is observed with *S. aureus* 134/93 and *M. smegmatis* SG 987 to approximately the same extent. Therefore, the imide NH is important for the activity against both microorganisms. Another derivatization effect is the increase of activity by polar substituents linked by a spacer to the indole-2-position. The compounds **11b**, **11c**, **12k** and **12l** show higher activities against *S. aureus* 134/93 than expected from eq. (2). All these compounds have hydrogen-bond-acceptors (CO in the case of **11b, 11c** and OCH_3 in the case of **12k**, **12l**) linked in a distance of three (**11b**, **12k**) or four (**11c**, **12l**) C–C bond lengths to the indole-2-position. Possibly the carbonyl and methoxy-groups produce the observed effect by a similar interaction inside the bacteria cell. In the case of *M. smegmatis* SG 987, the compounds **11e** and **11f** have shown higher p*MIC*'s than expected from eq. (5). Their 2-methylanilide substructures are situated at larger distances from the indole-2-position than in the case of *S. aureus* 134/93. On the other hand, **11b** shows a slightly larger activity than **11a** and **11c,** and **10k** as well as **12k** show

larger activities against *M. smegmatis* SG 987 than the simple phenyl derivatives **10i** and **12i**, respectively. All this compounds have their hydrogen bond acceptors in nearly the same distance from the indole-2-position and most of them show an improved activity also against *S. aureus* 134/93. Also in the case of *M. smegmatis* SG 987, we could improve the activity by linking hydrogen bond acceptors by spacers to the indol-2-position. In this respect, both microorganisms have shown again similar results in the structure activity relationship, presented here.

5. Conclusion

The new compounds described were found to have antibacterial activity against resistant strains of *S. aureus*, *M. smegmatis* and some other Gram positive bacteria whereas they are inactive against Gram negative bacteria.

Some of our new compounds show minimal inhibition concentrations (*MIC*'s) against resistant strains lower than those of ciprofloxacin, vancomycin and doxycycline resp., which are widely used in antiinfective therapy. Furthermore, they show a different spectrum of activity against the investigated bacteria suggesting a mechanism of action different to vancomycin and doxycycline. This might be important in circumventing existing resistance mechanisms.

In most cases, the activity of our compounds against *S. aureus* and *M. smegamtis* improves by increasing hydrophobic properties as well as by hydrogen bond acceptors, depending on their distance from the indole-2-position. Methylation of the imide-NH reduces the activity. The extent depends on the nature of the substituent in indole-2-position, which we consider to be important.

6. Experimental

6.1. Biological testing procedure

The in vitro antibacterial activities were assessed by determination of minimal inhibitory concentrations (*MIC*'s) using a standard micro broth dilution method in Mueller Hinton medium (DIFCO) according to the NCCLS-guidelines [21]. The test and reference compounds were stepwise diluted in the culture medium in a range from 100 to 0.05 μg ml^{-1}. In every dilution step the concentration was reduced to half of the amount before. The Gram positive (*S. aureus* SG 511, *M. smegmatis* SG 987) and Gram negative (*E. coli* SG 458, *P. aeruginosa* SG 137) test organisms were obtained from the stock of the Hans Knöll Institute or were clinical isolates (*S. aureus* 134/93, *E. faecalis* 1528), kindly provided by W. Witte (Robert Koch-Institute, Werningerode Branch, Germany). Inocula of test organisms were adjusted to approximately 10^5 CFU ml^{-1} (CFU = colony forming units). After strains were incubated for 18–20 h (*M. smegmatis* SG 987 for 48 h) at 37 °C, the *MIC*'s were read as the lowest concentration of compound allowing no visible growth.

6.2. Chemistry

Melting points were recorded on a Büchi 512 heating stage and are not corrected. Proton Nuclear magnetic resonance spectra were recorded on a Bruker AC 250 (250 MHz) spectrometer. DMSO-d_6 was used as solvent if not stated otherwise. FT-IR-spectroscopy was performed on a Nicolet 410 FT-IR-spectrometer. Microanalyses were performed by Analytisches Lab. Univ. Regensburg and were within ± 0.4% of the theoretical values. Thin layer chromatography (TLC) was carried out on Al-sheets coated with 60 F_{245} silica. Column chromatography (CC) was carried out using Merck 60 (70–230 mesh ASTM) silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures.

log(*P*)-values were determined using HPLC retention data [17]. All compounds were dissolved in methanol and subjected to HPLC:

column: LiChrospher 100 RP-18 (5 μm) 250 × 4 mm, Merck Art. 50983; eluent: methanol/water/acetic acid (80 + 20 + 0.1), adjusted with ammonia to pH 5.5; flow: 1.00 ml min^{-1}; detection: 254 nm; temperature: 25 °C. From the retention data, the capacity factor k' is calculated according to eq. (6):

$$k' = \log\left((t_R/t_o) - 1\right) \quad (6)$$

with t_R = retention time of the compound, and t_o = retention time of methanol. From k' we have determined log(*P*) using a linear function which was calibrated with the following reference substances: 4-nitrophenole (log(*P*) = 1.91 [22]), 4-chlorophenole (log(*P*) = 2.39 [22]), benzophenone (log(*P*) = 3.18 [23]), naphthalene (log(*P*) = 3.44 [24]) and anthracene (log(*P*) = 4.49 [24]). We have carried out two series of determinations, using two different specimen of columns and separately mixed eluents. Every log(*P*) value, given in tables, is an average value of two estimations. The deviation was on average ± 0.03 and in no time larger than ± 0.1 log(*P*) units.

6.2.1. Formation of ester-amides from carboxylic acid chlorides and 2-methylaniline (**5a**; **5b**; **5e**)

We dissolved 2-methylaniline (0.066 mol) and triethylamine (0.066 mol) in dry CH_2Cl_2 (200 ml). The solution was cooled with ice, and the acid chloride (0.066 mol) was carefully added dropwise. Then the solution was heated to reflux for 12 h, cooled, the precipitated triethylammonium chloride was filtered off, and the residue was purified by CC (CH_2Cl_2/ethyl acetate 6:1). The products were obtained as colorless powders.

*6.2.1.1. Methyl 4-(2-methylphenyl)amino-4-oxobutanoate (**5a**) [25].* Yield: 13.8 g (62 mmol; 94% from methyl 4-chloro-4-oxo-butanoate); m.p. 72 °C (Lit. 78 °C [25]); IR (KBr) ν: 3355, 2929–2857, 1705, 1659, 1588, 1493, 1458; 747 cm^{-1}.

*6.2.1.2. Methyl 5-(2-methylphenyl)amino-5-oxopentanoate (**5b**).* Yield: 13.52 g (57 mmol; 86% from methyl 5-chloro-5-oxo-pentanoate); m.p. 60 °C; ^{1}H-NMR δ 1.84 (m, 2 H), 2.18 (s; 3 H, CH_3), 2.37 (t; J = 7.4 Hz, 2 H), 2.38 (t, J = 7.4 Hz, 2 H),

3.60 (s; 3 H, OCH_3), 7.06 (m; 1 H, 4-H), 7.15 (m; 1 H, 5-H), 7.19 (d; J_o = 7.1 Hz, 1 H, 3-H), 7.35 (d; J_o = 7.5 Hz, 1 H, 6-H), 9.26 (s; 1 H, NH); IR (KBr) ν: 3450, 3245–2960, 1736, 1651, 1613, 1584, 1541, 750 cm^{-1}. Anal. ($C_{13}H_{17}NO_3$) C, H, N.

6.2.1.3. Methyl 8-(2-methylphenyl)amino-8-oxooctanoate ***(5e)***. Yield: 5.93 g (21 mmol; 64% from 33 mmol methyl 8-chloro-8-oxo-octanoate); m.p. 68 °C; R_f 0.21 (CH_2Cl_2/ethyl acetate 9:1); ^{1}H-NMR δ 1.30 (m; 4 H), 1.56 (m; 4 H), 2.18 (s; 3 H, CH_3), 2.30 (t; J = 7.5 Hz, 4 H), 3.58 (s; 3 H, OCH_3), 7.06 (m; 1 H, 4-H), 7.14 (m; 1 H, 5-H), 7.19 (d; J_o = 7.9 Hz, 1 H, 3-H), 7.34 (d; J_o = 7.1 Hz, 1 H, 6-H), 9.21 (s; 1 H, NH); IR (KBr) ν: 3295, 3023–2853, 1734, 1659, 1611, 1588, 1524; 758 cm^{-1}. Anal. ($C_{16}H_{23}NO_3$) C, H, N.

*6.2.2. Formation of ester amides from dicarboxylic acid monomethyl esters and 2-methylaniline (****5c****; 5f)*

Dicarboxylic acid monomethyl ester (0.03 mol), 2-methylaniline (0.03 mol), *N,N′*-dicyclohexylcarbodiimide (0.03 mol) and *p*-toluenesulphonic acid monohydrate (0.003 mol) were dissolved in pyridine (50 ml) and stirred for 12 h. Precipitated *N,N*-dicyclohexylurea was filtered off, the solvent was removed in vacuo, and the remaining oil was dissolved in CH_2Cl_2 and purified by CC (CH_2Cl_2/ethyl acetate 6:1). The products were obtained as colorless powders.

6.2.2.1. Methyl 6-(2-methylphenyl)amino-6-oxohexanoate ***(5c)***. Yield: 6.1 g (24 mmol; 80% from methyl 6-methoxy-6-oxo-hexanic acid; m.p. 61 °C; R_f 0.38 (CH_2Cl_2/ethyl acetate 6:1); ^{1}H-NMR δ 1.60 (m; 4 H), 2.18 (s; 3 H, CH_3), 2.35 (m; 4 H), 3.59 (s; 3 H, OCH_3), 7.07 (m; 1 H, 4-H), 7.14 (m; 1 H, 5-H), 7.19 (d; J_o = 7.9 Hz, 1 H, 3-H), 7.35 (d; J_o = 7.5 Hz, 6-H), 9.24 (s; 1 H, NH); IR (KBr) ν: 3287, 3027–2851, 1736, 1651, 1588, 1533, 760 cm^{-1}. Anal. ($C_{14}H_{19}NO_3$) C, H, N.

6.2.2.2. Methyl 9-(2-methylphenyl)amino-9-oxononanoate ***(5f)***. Yield: 12.8 g (44 mmol; 73% from 60 mmol 8-methoxy-9-oxononanoic acid; m.p. 45 °C; R_f 0.6 (CH_2Cl_2/ethyl acetate 9:1); ^{1}H-NMR δ 1.30 (m; 6 H), 1.55 (m; 4 H), 2.18 (s; 3 H, CH_3), 2.30 (m; 4 H), 3.58 (s; 3 H, OCH_3), 7.07 (m; 1 H, 4-H), 7.13 (m; 1 H, 5-H), 7.19 (d; J_o = 7.5 Hz, 1 H, 3-H), 7.34 (d; J_o = 7.5 Hz, 1 H, 6-H), 9.21 (NH); IR (KBr) ν: 3288, 2935–2854, 1738, 1652, 1588, 1532, 754 cm^{-1}. Anal. ($C_{17}H_{25}NO_3$) C, H, N.

6.2.3. Preparation of methyl 7-(2-methylphenyl)amino-7-oxoheptanoate ***(5d)***

Triethylamine (0.26 mol) and 2-methylaniline (0.13 mol) were dissolved in 100 ml of methanol. Pimeoylchloride (0.13 mol) was carefully added and the mixture was refluxed overnight, than the solvent was removed in vacuo. Water (100 ml) was added to the residue, than the products were extracted with ethyl acetate, dried with Na_2SO_4 and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (50 ml). Most of the bis toluyl side product precipitated and was filtered off. The solution was purified by CC on SiO_2; CH_2Cl_2.

Yield: 7.0 g (27 mmol; 20%); m.p. 60 °C; R_f 0.23 (CH_2Cl_2/ethylacetate 9:1); ^{1}H-NMR: δ 1.31 (m; 2 H), 1.57 (m; 4 H), 2.17 (s; 1 H, CH_3), 2.30 (t; J = 7.3 Hz, 4 H), 3.57 (s; 3 H, OCH_3), 7.04 (m; 1 H, 4-H), 7.13 (m; 1 H, 5-H), 7.17 (d; J_o = 7.5 Hz, 1 H, 3-H), 7.33 (d; J_o = 7.35 Hz, 1 H, 6-H), 9.21 (s; 1 H, NH); IR (KBr) ν: 3295, 2929–2361, 1732, 1651, 1588, 1530, 1258, 1175; 756 cm^{-1}. Anal. ($C_{15}H_{20}NO$). C, H, N.

6.2.4. Formation of the 2-alkyl- and 2-methoxyphenyl indoles according to Smith [11,12] ***(3a–3h)***

Trimethylsilyl-o-toluidine (TMSOT, 0.0145 mol) [11] was dissolved in dry hexane (60 ml). Under N_2 n-BuLi (0.029 mol, 1.6 M solution in hexane) was added dropwise at RT. Then the solution was heated to reflux for 4 h. During the reaction a red precipitate occurred, and the solution turned orange. The metallated TMSOT might burn when it is exposed to air.

The obtained suspension was cooled to –78 °C, and then a solution of 0.014 mol of ester in 30 ml THF was added slowly, so that the temperature did not rise above –70 °C. After stirring overnight, while slowly warming up to RT, the solution was refluxed for 2 h, poured on ice (200 g) and stirred until most of the ice was molten. The mixture was extracted with ethyl acetate (4 × 100 ml), the extract was dried over Na_2SO_4 and concentrated in vacuo. The indole spot on TLC acquires a yellow color after several h. The raw material was purified by CC (CH_2Cl_2). We separated the alkylindoles as oils and processed them without further purification. References are given for the characterization of the products.

6.2.4.1. 2-Ethyl-1H-indole ***(3a)*** *[26]*. Yield: 0.64 g (4.4 mmol; 30% from **2a**); R_f 0.83 (CH_2Cl_2).

6.2.4.2. 2-Propyl-1H-indole ***(3b)*** *[27]*. Yield: 0.62 g (3.9 mmol; 27% from **2b**); R*f* 0.81 (CH_2Cl_2).

6.2.4.3. 2-Buthyl-1H-indole ***(3c)*** *[28]*. Yield: 0.43 g (2.5 mmol; 18% from **2c**); R_f 0.88 (CH_2Cl_2).

6.2.4.4. 2-Pentyl-1H-indole ***(3d)*** *[29]*. Yield: 0.28 g (1.5 mmol; 10% from **2d**); R_f 0.90 CH_2Cl_2).

6.2.4.5. 2-Hexyl-1H-indole ***(3e)*** *[29]*. Yield: 0.65 g (3.2 mmol; 22% from **2e**); R_f 0.95 (CH_2Cl_2).

6.2.4.6. 2-Heptyl-1H-indole ***(3f)*** *[30]*. Yield: 0.78 g (3.6 mmol; 25% from **2f**); R_f 0.88 (CH_2Cl_2).

6.2.4.7. 2-(2-Methoxyphenyl)-1H-indole ***(3g)***. Yield: 0.77 g (3.45 mmol; 24% from methyl-2-methoxybenzoate); R_f 0.7 (CH_2Cl_2); m.p. 83 °C; ^{1}H-NMR δ 3.37 (s; 3 H, OCH_3), 6.94 (d; J = 2 Hz, 1 H, ind 3-H), 6.97–7.15 (m; 4 H, ind 5-H, ph 4-H, ph 5-H, ph 6-H), 7.30 (m; 1 H, ind 6-H), 7.44 (d; J_o = 8.3 Hz, 1 H, ind 7-H), 7.52 (d; J_o = 7.5 Hz, 1 H, ind 4-H), 7.80 (m; 1 H, ph 3-H), 11.18 (s; 1 H, NH); IR (KBr) ν:

3446, 3041−2842, 1476, 1464, 1451, 1435, 1360, 1342, 1310, 1236 cm^{-1}. Anal. ($C_{15}H_{13}NO$) C, H, N.

*6.2.4.8. 2-(3-Methoxyphenyl)-1H-indole (**3h**)*. Yield: 0.60 g (2.7 mmol; 18% from methyl-3-methoxybenzoate); R_f 0.83 (CH_2Cl_2); m.p. 136 °C; ^{1}H-NMR δ 3.83 (s; 3 H, OCH_3), 6.85–6.90 (m; 1 H, ind 5-H), 7.09 (m; 1 H, ind 6-H), 7.35–7.45 (m; 4 H, ph 2-H, ph 4-H, ph 5-H, ind 7-H), 7.52 (d; J_o = 7.5 Hz, 1 H, ind 4-H), 12.51 (s; 1 H, NH); IR (KBr) ν: 3396, 1601, 1482, 1464, 1454, 1435, 1350, 1304, 1263, 1235, 1219, 1177, 1165, 1036, 852, 785, 758, 677 cm^{-1}. Anal. ($C_{17}H_{13}NO$) Calc. 80.69 C, H 5.87, N 6.27. Found C 80.08, H 5.59, N 6.09.

*6.2.5. Formation of the indole-amides from the dicarboxylic acid methyl ester amides (**6a**–**6f**)*

In one flask, TMSOT (0.014 mol) was lithiated according to the procedure described above for **3a**–**h**. In a second flask, a solution of dicarboxylic acid mono esteramide (0.014 mol) in dry THF (50 ml) was cooled under N_2 to –80 °C, then *n*-butyllithium (0.014 mol, 1.6 M solution in hexane) was added slowly, so that the temperature in the solution did not rise above –70 °C. Then the Li_2TMSOT suspension was added in the same way. The mixture was stirred overnight while slowly warming up to RT. Then it was poured onto ice (200 g) and stirred until most of the ice was molten. The mixture was extracted with ethyl acetate (4 × 100 ml), the extract was dried over Na_2SO_4 and concentrated in vacuo yielding a dark oil. The raw material was purified by CC (CH_2Cl_2/ethyl acetate mixtures, which are cited below following the R_f values of the compounds). The products precipitate as colorless crystals after removing most of the solvent under reduced pressure and adding pentane to promote precipitation.

*6.2.5.1. 3-(1H-2-Indolyl)-N-(o-methylphenyl)propionylamide (**6a**)*. Yield: 0.36 g (1.29 mmol; 9% from **5a** [24]); m.p. 173 °C; R_f 0.47 (CH_2Cl_2/ethyl acetate 6:1); ^{1}H-NMR δ 2.15 (s; 3 H, CH_3); 2.78 (t; J = 7.5 Hz, 2 H), 3.05 (t; J = 7.5 Hz, 2 H), 6.19 (s; 1 H, ind 3-H), 6.91 (m; 1 H, ind 5-H), 6.99 (m; 1 H, ind 6-H), 7.05 (m; 1 H, tol 4-H), 7.14 (m; 1 H, tol 5-H), 7.19 (d; J_o = 7.1 Hz, 1 H, tol 3-H), 7.28 (d; J_o = 7.9 Hz, 1 H, ind 7-H), 7.38 (d; J_o = 7.0 Hz, 1 H, tol 6-H), 7.41 (d; J_o = 7.5 Hz, 1 H, ind 4-H), 9.34 (s; 1 H, NH), 10.92 (s; 1 H, NH); IR (KBr) ν: 3355, 3291, 2950–2700, 1663, 1501, 754, 741 cm^{-1}. Anal. ($C_{18}H_{18}N_2O$) C, H, N.

*6.2.5.2. 4-(1H-2-Indolyl)-N-(o-methylphenyl)butanoylamide (**6b**)*. Yield: 1.13 g (3.86 mmol; 27% from **5b**); m.p. 107 °C; R_f 0.51 (CH_2Cl_2/ethyl acetate 6:1); ^{1}H-NMR δ 2.04 (m; 2 H), 2.18 (s; 3 H, CH_3), 2.40 (t; J_o = 7.5 Hz, 2 H), 2.78 (t; J_o = 7.5 Hz, 2 H), 6.16 (s; 1 H, ind 3-H), 6.92 (m; 1 H, ind 5-H), 6.99 (m; 1 H, ind 6-H), 7.07 (m; 1 H, tol 4-H), 7.13 (m; 1 H, tol 5-H), 7.19 (d; J_o = 7.5 Hz, 1 H, tol 3-H), 7.27 (d; J_o = 8.3 Hz, 1 H, ind 7-H), 7.36 (d; J_o = 7.5 Hz, 1 H, tol 6-H), 7.41 (d; J_o = 7.5 Hz, 1 H, ind 4-H), 9.26 (s; 1 H, NH), 10.93 (s; 1 H, NH); IR ν: 3395, 3295, 3054–2800, 1653, 1588, 1530; 752 cm^{-1}. Anal. ($C_{19}H_{20}N_2O$) C, H, N.

*6.2.5.3. 5-(1H-2-Indolyl)-N-(o-methylphenyl)pentanoylamide (**6c**)*. Yield: 0.79 g (2.58 mmol; 18% from **5c**); m.p. 153 °C; R_f 0.33 (CH_2Cl_2/ethyl acetate 8:1); ^{1}H-NMR δ 1.71 (m; 4 H), 2.17 (s; 3 H, CH_3), 2.38 (t; J_o = 6.7 Hz, 2 H), 2.75 (t; J = 6.7 Hz, 2 H) 6.13 (s; 1 H, ind 3-H), 6.91 (m; 1 H, ind 5-H), 6.98 (m; 1 H, ind 6-H), 7.06 (m; 1 H, tol 4-H), 7.14 (m; 1 H, tol 5-H), 7.19 (d; J_o = 7.5 Hz, 1 H, tol 3-H), 7.27 (d; 7.9 Hz, 1 H, ind 7-H), 7.36 (d; J_o = 7.7 Hz, 1 H, tol 6-H), 7.39 (d; J_o = 7.0 Hz, 1 H, ind 4-H), 9.24 (s; 1 H, NH), 10.89 (s; 1 H, NH); IR(KBr) ν: 3363, 3276, 3052–2861, 1663, 1501; 752 cm^{-1}. Anal. ($C_{20}H_{22}N_2O$) C, H, N.

*6.2.5.4. 7-(1H-2-Indolyl)-N-(o-methylphenyl)hexanoylamide (**6d**)*. Yield: 1.1 g (3.43 mmol; 24% from 5d); m.p. 93 °C; R_f 0.41 (CH_2Cl_2/ethyl acetate 9:1); ^{1}H-NMR δ 1.39 (m; 2 H), 1.68 (m; 4 H), 1.68 (m; 4 H), 2.15 (s; 3 H, CH_3), 2.32 (t; J = 7.3 Hz, 2 H), 2.71 (t; J = 7.3 Hz, 2 H), 6.11 (s; 1 H, ind. 3-H), 6.89 (m; 1 H, ind 5-H), 6.97 (m; 1 H, ind 6-H), 7.05 (m; 1 H, tol 4-H), 7.12 (m; 1 H, tol 5-H), 7.17 (d; J = 7.9 Hz, 1 H, tol 3-H), 7.24 (d; J = 7.9 Hz, 1 H, ind 7-H), 7.32 (d; J = 7.5 Hz, 1 H, tol 6-H), 7.37 (d; J = 7.5 Hz, 1 H, ind 4-H), 9.20 (s; 1 H, NH), 10.86 (s; 1 H, NH); IR (KBr) ν: 3405, 3307, 2934, 2863, 1653, 1588, 1528, 783, 748 cm^{-1}. Anal. ($C_{21}H_{24}N_2O$) C, H, N.

*6.2.5.5. 7-(1H-2-Indolyl)-N-(o-methylphenyl)heptanoylamide (**6e**)*. Yield: 0.45 g (1.35 mmol; 12% from **5e**); m.p. 123–125 °C; R_f 0.22 (CH_2Cl_2/ethyl acetate 9:1); ^{1}H-NMR δ 1.38 (m; 4 H), 1.61 (m; 2 H), 1.70 (m; 2 H), 2.17 (s; 3 H, CH_3), 2.35 (t, J = 7.0 Hz, 2 H), 2.71 (t, J = 7.5 Hz, 2 H), 6.11 (s, 1 H, ind 3-H), 6.90 (m; 1 H, ind 5-H), 6.97 (m; 1 H, ind 6-H), 7.05 (m; 1 H, tol 4-H), 7.14 (m; 1 H, tol 5-H), 7.19 (d, J_o = 7.5 Hz, 1 H, tol 3-H), 7.26 (d, J_o = 8.3 Hz, 1 H, ind 7-H), 7.35 (d, J_o = 8.7 Hz, 1 H, tol 6-H), 7.38 (d, J_o = 8.3 Hz, 1 H, ind 4-H) 9.20 (s; 1 H, NH), 10.87 (s, 1H, NH); IR (KBr) ν: 3425, 3253, 2927–2861, 1649, 1607, 1584, 1541, 764, 748 cm^{-1}. Anal. ($C_{22}H_{26}N_2O$) C, H, N.

*6.2.5.6. 8-(1H-2-Indolyl)-N-(o-methylphenyl)octanoylamide (**6f**)*. Yield: 0.85 g (2.44 mmol; 17% from **5f**); m.p. 95 °C; R_f 0.7 (CH_2Cl_2/ethyl acetate 9:1); ^{1}H-NMR δ 1.35 (m; 6 H), 1.66 (m; 4 H), 2.17 (s; 3 H, CH_3), 2.32 (t; J = 7.3 Hz, 2 H), 2.70 (t; J = 7.5 Hz, 2 H), 6.11 (s; 1 H, ind 3-H), 6.90 (m; 1 H, ind 5-H), 6.97 (m; 1 H, ind 6-H), 7.06 (m; 1 H, tol 4-H), 7.13 (m; 1 H, tol 5-H), 7.18 (d; J_o = 7.5 Hz, 1 H, tol 3-H), 7.25 (d; J_o = 7.9 Hz, 1 H, ind 7-H), 7.34 (d; J_o = 9.1 Hz, 1 H, tol 6-H), 7.38 (d; J_o = 8.7 Hz, 1 H, ind 4-H), 9.21 (s; 1 H, NH), 10.86 (s; 1 H, NH); IR (KBr) ν: 3394, 3052–2853, 1651, 1586, 1530, 1485; 748 cm^{-1}. Anal. ($C_{23}H_{28}N_2O$) C, H, N.

6.2.6. Condensation of 8 or 9 with indole derivatives—general procedure A

The indole derivative (2 mmol) was dissolved in dry THF (10 ml) and cooled under N_2 to –20 °C. Then 4 ml of LiHMDS

(1 M in THF) were slowly added. After stirring the solution for 45 min, 2 mmol of TBS-dibromomaleinimide (**8**) or N-methyl-dibromomaleinimide (**9**) in 10 ml of THF were added within 3 h. The solution was stirred for 15 min, poured into sat. aq. NH_4Cl (100 ml), extracted with ethyl acetate (4 × 50 ml), dried over Na_2SO_4, concentrated in vacuo and purified by CC (CH_2Cl_2/ethyl acetate; mixtures cited below following every R_f value).

*6.2.6.1. 1-Methyl-3-bromo-4-(1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (**10a**) [13]*. Yield: 0.46 g (1.5 mmol; 75% from indole and **9**); m.p. 145 °C (dec.) (Lit. 145 °C [13]); R_f 0.22 (CH_2Cl_2); ^{1}H-NMR δ 3.01 (s; 3 H, CH_3), 7.18–7.72 (m; 5 H, aromat.), 12.33 (s; 1 H, NH); IR (KBr) ν: 3270, 3115–2985, 1760, 1710, 1595, 1495, 1460, 1430 cm^{-1}.

*6.2.6.2. 1-Methyl-3-bromo-4-(2-methyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrrole-dione (**10b**)*. Yield: 0.38 g (1.19 mmol; 59% from 2-methyl indole and **9**); m.p. 160 °C (dec.); R_f 0.33; ^{1}H-NMR δ 2.40 (s; 3 H, CH_3), 3.00 (s; 3 H, NCH_3), 7.01 (m; 1 H, 5-H), 7.10 (m; 1 H, 6-H), 7.35 (d; J_o = 7.1 Hz, 1 H, 7-H), 7.37 (d; J_o = 7.1 Hz, 1 H, 4-H), 11.75 (s; 1 H, NH); IR (KBr) ν: 3361, 2925, 1771, 1705, 1624, 1613, 1422, 1379, 752, 735 cm^{-1}. Anal. ($C_{14}H_{11}BrN_2O_2$) C, H, N.

*6.2.6.3. 1-Methyl-3-bromo-4-(2-ethyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrrole-dione (**10c**)*. Yield: 0.23 g (0.69 mmol; 34% from **3a** and **9**); m.p. 140 °C (dec.); R_f 0.53 (CH_2Cl_2); ^{1}H-NMR δ 1.28 (t; J = 7.5 Hz, 3 H, CH_3), 2.73 (q; J_o = 7.5 Hz, 2 H, CH_2), 3.00 (s; 3 H, CH_3), 7.02 (m; 1 H, 5-H), 7.11 (m; 1 H, 6-H), 7.34 (d; J_o = 7.5 Hz, 1 H, 7-H), 7.37 (d; J_o = 7.15 Hz, 1 H, 4-H), 11.71 (s; 1 H, NH); IR (KBr) ν: 3378, 2979, 1771, 1705, 1626, 1433, 1385, 1140, 1001, 748, 735 cm^{-1}. Anal. ($C_{15}H_{13}BrN_2O_2$) C, H, N.

*6.2.6.4. 1-Methyl-3-bromo-4-(2-propyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrrole-dione (**10d**)*. Yield: 0.33 g (0.95 mmol; 47% from **3b** and **9**), m.p. 155 °C; R_f 0.65 (CH_2Cl_2); ^{1}H-NMR δ 0.86 (t; J = 7.25 Hz, 3 H, CH_3), 1.73 (m; 2 H, CH_2), 2.70 (t; J = 7.3 Hz, 2 H, CH_2), 3.00 (s; 3 H, CH_3), 7.02 (m; 1 H, 5-H), 7.10 (m; 1 H, 6-H), 7.33 (d; J_o = 7.5 Hz, 1 H, 7-H), 7.36 (d; J_o = 7.5 Hz, 1 H, 4-H), 11.68 (s; 1 H, NH); IR (KBr) ν: 3378, 2965, 1771, 1707, 1624, 1431, 1383, 749 cm^{-1}. Anal. ($C_{16}H_{15}BrN_2O_2$) C, H, N.

*6.2.6.5. 1-Methyl-3-bromo-4-(2-butyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrrole-dione (**10e**)*. Yield: 0.48 g (1.3 mmol; 66% from **3c** and **9**), m.p. 115 °C; R_f 0.6 (CH_2Cl_2); ^{1}H-NMR δ 10.16 (t; J = 7.3 Hz, 3 H, CH_3), 1.27 (m; 2 H, CH_2), 1.66 (m; 2 H, CH_2), 2.73 (t; J = 7.3 Hz, 2 H, CH_2), 3.00 (s; 3 H, CH_3), 7.01 (m; 1 H, 5-H), 7.10 (m; 1 H, 6-H), 7.33 (d; J_o = 7.5 Hz, 1 H, 4-H), 7.36 (d; J = 7.9 Hz, 1 H, 4-H), 11.68 (s; 1 H, NH); IR (KBr) ν: 3373, 2964, 1773, 1709, 1624, 1460, 1439, 1385, 1192, 1138, 995, 735 cm^{-1}. Anal. ($C_{17}H_{17}BrN_2O_2$) C, H, N.

*6.2.6.6. 1-Methyl-3-bromo-4-(2-pentyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrrole-dione (**10f**)*. Yield: 0.41 g (1.09 mmol; 55% from **3d** and **9**); m.p. 80 °C; R_f 0.72 (CH_2Cl_2); ^{1}H-NMR δ 0.83 (t; J = 6.6 Hz, 3 H, CH_3), 1.23 (m; 4 H, CH_2), 1.67 (m; 2 H, CH_2), 2.72 (t; J = 7.8 Hz, 2 H, CH_2), 3.00 (s; 3 H, NCH_3), 7.01 (m; 1 H, 5-H), 7.10 (m; 1 H, 6-H), 7.33 (d; J_o = 8.3 Hz, 1 H, 7-H), 7.36 (d; J_o = 7.5 Hz, 1 H, 4-H), 11.69 (s; 1 H, NH); IR (KBr) ν: 3361, 2954, 2930, 1173, 1707, 1626, 1613, 1460, 1439, 1338, 737 cm^{-1}. Anal. ($C_{18}H_{19}BrN_2O_2$) C, H, N.

*6.2.6.7. 1-Methyl-3-bromo-4-(2-hexyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrrole-dione (**10g**)*. Yield: 0.32 g (0.82 mmol; 56% from **3e** and **9**); m.p. 100 °C; R_f 0.74 (CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 0.87 (t; J = 6.6 Hz, 3 H, CH_3), 1.30 (m; 6 H, CH_2), 1.70 (m; 2 H, CH_2), 2.82 (t; J = 7.4 Hz, 2 H, CH_2), 3.18 (s; 3 H, NCH_3), 7.16 (m, 1 H, 5-H), 7.21 (m; 1 H, 6-H), 7.36 (m; 1 H, 7-H), 7.43 (m; 1 H, 4-H), 8.38 (s; 1 H, NH); IR (KBr) ν: 3351, 1773, 1707, 1460, 1437, 1385, 989, 739 cm^{-1}. Anal. ($C_{19}H_{21}BrN_2O_2$) C, H, N.

*6.2.6.8. 1-Methyl-3-bromo-4-(2-heptyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrrole-dione (**10h**)*. Yield: 0.28 g (0.69 mmol; 46% from **3f** and **9**); m.p. 75 °C; R_f 0.77 (CH_2Cl_2); ^{1}H-NMR δ 0.82 (t; J = 6.4 Hz, 3 H, CH_3), 1.21 (m; 6 H, CH_2), 1.66 (m; 2 H, CH_2), 2.72 (t; J = 7.3 Hz, 2 H, CH_2), 3.00 (s; 3 H, NCH_3), 7.01 (m, 1 H, 5-H), 7.10 (m; 1 H, 6-H), 7.33 (d; J_o = 7.9 Hz, 1 H, 7-H), 7.36 (d; J_o = 7.9 Hz, 1 H, 4-H), 11.68 (s; 1 H, NH); IR (KBr) ν: 3361, 2929, 1773, 1705, 1613, 1460, 1439, 1383, 987, 808, 737 cm^{-1}. Anal. ($C_{20}H_{13}BrN_2O_2$) C, H, N.

*6.2.6.9. 1-Methyl-3-bromo-4-(2-phenyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrrole-dione (**10i**)*. Yield: 0.65 g (1.7 mmol; 56% from 2-phenylindole and **9**); m.p. 225 °C; R_f 0.59 (CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 3.11 (s; 3 H, CH_3), 7.22 (m; 1 H, ind 5-H), 7.29 (m; 1H, ind 6-H), 7.41 (m; 1 H, ph 4-H), 7.42–7.50 (m; 4 H, ind 4-H, ind 7-H, ph 3-H, ph 5-H), 7.58 (d; J_o = 7.15 Hz, 2 H, ph 2-H, ph 6-H), 8.68 (s; 1 H, NH); IR (KBr) ν: 3444, 2925, 1771, 1705, 1624, 1451; 752, 737, 696 cm^{-1}. Anal. ($C_{19}H_{13}BrN_2O_2$) C, H, N.

*6.2.6.10. 1-Methyl-3-bromo-4-(2-(2-methoxyphenyl)-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (**10j**)*. Yield: 0.56 g (1.36 mmol; 68% from **3g** and **9**); m. p. 185 °C; R_f 0.36 (CH_2Cl_2); ^{1}H-NMR δ 2.95 (s; 3 H, NCH_3), 3.68 (s, 3 H, NCH_3), 7.00–7.11 (m; 3 H, ind 5-H, ph 4-H, ph 5-H), 7.18 (m; 1 H, ind 6-H), 7.34–7.41 (m; 2 H, ph 3-H, ph 6-H), 7.46 (d; J_o = 6.7 Hz, 1 H, ind 7-H), 7.48 (d; J_o = 6.3 Hz, 1 H, ind 4-H), 11. 91 (s; 1 H, NH); IR (KBr) ν: 3351, 3062–2834, 1775, 1709, 1620, 1466, 1439, 1379, 1298, 1250, 1180, 1155, 1101, 980, 850, 741, 733 cm^{-1}. Anal. ($C_{20}H_{15}BrN_2O_3$) C, H, N.

*6.2.6.11. 1-Methyl-3-bromo-4-(2-(3-methoxyphenyl)-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (**10k**)*. Yield: 0.515 g

(1.25 mmol; 63% from **3h** and **9**); m.p. 162 °C; R_f 0.33 (CH_2Cl_2); ^{1}H-NMR δ 2.97 (s; 3 H, NCH_3), 3.80 (s; 3 H, OCH_3), 6.95 (m; 1 H, ph 6-H), 7.07–7.17 (m: 3 H, ind 5-H, ph 2-H, ph 4-H); 7.22 (m; 1 H, ind 6-H), 7.34 (m; 1 H, ph 5-H), 7.47 (d; J_o = 7.9 Hz, 1 H, ind 7-H), 7.49 (d; J_o = 7.9 Hz, 1 H, ind 4-H), 12.14 (s; 1 H, NH); IR (KBr) ν: 3378, 2954, 1775, 1711, 1626, 1611, 1491, 1437, 1379, 1229, 1204, 987, 789, 737 cm^{-1}. Anal. ($C_{20}H_{15}BrN_2O_3$) C, H, N.

6.2.6.12. 1-Methyl-3-bromo-4-(2-(4-methoxyphenyl)-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione ***(10l)***. Yield: 0.63 g (1.5 mmol; 51% from 2-(4-methoxyphenyl)-1*H*-indole [31] and **9**); m.p. 227 °C; R_f 0.64 (CH_2Cl_2); ^{1}H-NMR δ 2.98 (s; 3 H, NCH_3), 3.80 (s; 3 H, OCH_3), 7.02 (d; J_o = 8.7 Hz, 2 H, ph 3-H, ph 5-H), 7.08 (m; 1 H, ind H-5), 7.19 (m; 1 H, ind 6-H), 7.44 (d; J_o = 3.6 Hz, 1 H, ind H-7), 7.47 (d; J_o = 4.0 Hz, 1 H, ind H-4), 7.53 (d, J_o = 8.7 Hz, 2 H, ph 2-H, ph 6-H), 12.04 (s, 1H, ind NH); IR (KBr) ν: 3397, 1767, 1707, 1622, 1495, 1441, 914, 746 cm^{-1}. Anal. ($C_{20}H_{15}BrN_2O_3$) C, H, N.

6.2.7. Removal of the silyl-protecting group [14]—general procedure B

The raw silyl-protected indole-maleinimide (1 mmol), obtained from the procedure described in general Procedure A, was dissolved in THF (100 ml) under N_2, tetrabutylammonium fluoride trihydrate (1.2 mmol) was added, and the mixture was stirred for 2 h, poured on to ice, mixed with saturated NH_4Cl solution (200 ml) and extracted with ethyl acetate (2 × 100 ml). The extract was dried over Na_2SO_4, the solvent was removed in vacuo and the remaining oil was purified by CC (CH_2Cl_2/ethyl acetate, mixtures are cited below, following the R_f value of the compounds). The solution was concentrated in vacuo in order to obtain a nearly saturated solution of the product in ethyl acetate. A small amount of CH_2Cl_2 was added, and the product precipitated in small red crystals.

6.2.7.1. 3-(3-(4-Bromo-2,5-dihydro-1H-2,5-pyrroledione-3-yl)-1H-2-indolyl)-N-(2-methylphenyl)propionylamide ***(11a)***. Yield: 0.09 g (0.2 mmol; 10% from 2 mmol **6a** and **8**); m.p. 195 °C (dec.); R_f 0.17 (CH_2Cl_2/ethyl acetate 9:1); ^{1}H-NMR δ 2.12 (s; 3 H, CH_3), 2.78 (t; J = 7.5 Hz, 2 H), 3.09 (m; 2 H), 7.04 (m; 1 H, ind 5-H), 7.05 (m; 1 H, tol 4-H), 7.07 (m; 1 H, ind 6-H), 7.13 (m; 1 H, tol 5-H), 7.17 (d; J_o = 7.1 Hz, 1 H, tol 3-H), 7.34 (d; J_o = 6.3 Hz, 1 H, tol 6-H), 7.36 (d; J_o = 7.2 Hz, 1 H, ind 7-H), 7.39 (d; J_o = 7.5 Hz, ind 4-H), 9.27 (s; 1 H, NH), 11.37 (s; 1 H, NH), 11.74 (s; 1 H, NH); IR (KBr) ν: 3338, 3228, 3060–2650, 1771, 1755, 1719, 1707, 1672, 1640, 1539, 740 cm^{-1}. Anal. ($C_{22}H_{18}BrN_3O_3$) Calc. C 58.42, H 4.01, N 9.29. Found C 58.96, H 4.40, N 8.75.

6.2.7.2. 4-(3-(4-Bromo-2,5-dihydro-1H-2,5-pyrroledione-3-yl)-1H-2-indolyl)-N-(2-methylphenyl)butanoylamide ***(11b)***. Yield: 0.15 g (0.32 mmol; 16% from 2 mmol **6b** and **8**); m.p. 135 °C (dec.); R_f 0.13 (CH_2Cl_2/ethyl acetate 6:1); ^{1}H-NMR δ 2.03 (m; 2 H), 2.15 (s; 3 H, CH_3), 2.33 (t; J = 7.2 Hz, 2 H), 2.83 (m; 2 H), 7.03 (m; 1 H, ind 5-H), 7.07 (m; 1 H, tol 4-H), 7.09 (m; 1 H, ind 6-H), 7.13 (m; 1 H, tol 5-H), 7.18 (d; J_o = 7.5 Hz, 1 H, tol 3-H), 7.32 (d; J_o = 8.7 Hz, 1 H, tol 6-H), 7.35 (d; J_o = 8.7 Hz, 1 H, ind 7-H), 7.39 (d; J_o = 7.5 Hz, 1 H, ind 4-H), 9.25 (s; 1 H, NH), 11.38 (s; 1 H, NH), 11.76 (s; 1 H, NH); IR (KBr) ν: 3345, 3235, 3060–2500, 1771, 1757, 1725, 1642, 1530, 743 cm^{-1}. Anal. ($C_{23}H_{20}BrN_3O_3$) Calc. C, H, N.

6.2.7.3. 5-(3-(4-Bromo-2,5-dihydro-1H-2,5-pyrroledione-3-yl)-1H-2-indolyl)-N-(2-methylphenyl)pentanoylamide ***(11c)***. Yield: 0.16 g (0.33 mmol; 16% from 2 mmol **6c** and **8**); m.p. 185 °C (dec.); R_f 0.12 (CH_2Cl_2/ethyl acetate 9:1). ^{1}H-NMR δ 1.61 (m; 2 H), 1.74 (m; 2 H), 2.15 (s; 3 H, CH_3), 2.33 (t; J = 7.1 Hz, 2 H), 2.77 (t; J_o = 6.7 Hz, 2 H), 7.03 (m; 1 H, ind 5-H), 7.05 (m; 1 H, tol 4-H), 7.12 (m; 1 H, ind 6-H), 7.13 (m; 1 H, tol 5-H), 7.18 (d; J_o = 7.1 Hz, 1 H, tol 3-H), 7.34 (d; J_o = 8.3 Hz, 2 H, tol 6-H, ind 7-H), 7.37 (d; J_o = 7.9 Hz, 1 H, ind 4-H), 9.21 (s; 1 H, NH), 11.37 (s; 1 H, NH), 11.712 (s; 1 H, NH); IR (KBr) ν: 3390, 3300; 3054–2857, 1734, 1701, 1665, 1524, 748 cm^{-1}. Anal. ($C_{24}H_{22}BrN_3O_3$) C, H, N.

6.2.7.4. 6-(3-(4-Bromo-2,5-dihydro-1H-2,5-pyrroledione-3-yl)-1H-2-indolyl)-N-(2-methylphenyl)hexanoylamide ***(11d)***. Yield: 0.08 g (0.16 mmol; 16% from 1 mmol **6d** and **8**); m.p. 186–188 °C (dec.); R_f 0.11 (CH_2Cl_2/ethyl acetate 9:1); ^{1}H-NMR δ 1.31 (m; 2H), 1.60 (m; 2 H), 1.72 (m; 2 H), 2.14 (s; 3 H, CH_3), 2.29 (t; J = 7.1 Hz, 2 H), 2.74 (t; J = 7.0 Hz, 2 H), 7.02 (m; 1 H, ind 5-H), 7.05 (m; 1 H, tol 4-H), 7.11 (m, 1 H, ind 6-H), 7.12 (m; 1 H, tol 5-H), 7.20 (d; J_o = 7.5 Hz, 1 H, tol 3-H), 7.33 (d, J_o = 8.3 Hz, 2 H, tol 6-H, ind 7-H), 7.36 (d, J_o = 7.9 Hz, 1 H, ind 4-H), 9.18 (s; 1 H, NH), 11.36 (s; 1 H, NH), 11.68 (s, 1 H, NH); IR (KBr) ν: 3370, 2932–2363, 1773, 1725, 1653, 1624, 1522, 1458; 740 cm^{-1}. Anal. ($C_{25}H_{24}BrN_3O_3$) C, H, N.

6.2.7.5. 7-(3-(4-Bromo-2,5-dihydro-1H-2,5-pyrroledione-3-yl)-1H-2-indolyl)-N-(2-methylphenyl)heptanoylamide ***(11e)***. Yield: 0.077 g (0.15 mmol; 10% from 1.5 mmol **6e** and **8**); m.p. 178 °C; R_f 0.06 (CH_2Cl_2/ethyl acetate 9:1); ^{1}H-NMR δ 1.31 (m; 4 H), 1.58 (t; J = 6.0 Hz, 2 H), 1.70 (t; J = 6.3 Hz, 2 H), 2.19 (s; 3 H, CH_3), 2.96 (t; J = 7.5 Hz, 2 H), 2.74 (t; J = 7.5 Hz, 2 H), 7.03 (m; 1 H, ind 5-H), 7.07 (m; 1 H, tol 4-H), 7.11 (m; 1 H, ind 6-H), 7.15 (m; 1 H, tol 5-H), 7.18 (d; J_o = 7.1 Hz, 1 H, tol 3-H), 7.34 (m; 2H, ind 7-H, tol 6-H), 7.37 (d; J_o = 7.5 Hz, 1 H, ind 4-H), 9.19 (s; 1 H, NH), 11.37 (s; 1 H, NH), 11.68 (s; 1 H NH); IR (KBr) ν: 3340, 3210, 2963–2855, 1771, 1717, 1653, 1624, 1530; 741 cm^{-1}. Anal. ($C_{26}H_{26}BrN_3O_3$) Calc. C 61.42, H 5.15, N 8.26. Found C 60.85, H 5.11, N 8.12.

6.2.7.6. 8-(3-(4-Bromo2,5-dihydro-1H-2,5-pyrroledione-3-yl)-1H-2-indolyl)-N-(2-methylphenyl)octanoylamide ***(11f)***. Yield: 0.21 g (0.4 mmol; 20% from 2 mmol **6f** and **8**); m.p. 145–150 °C (THF/pentane); R_f 0.17 (CH_2Cl_2/ethyl acetate 9:1); ^{1}H-NMR δ 1.19 (m; 6 H), 1.56 (m; 2 H), 1.68 (m; 2 H), 2.16 (s; 3 H, CH_3), 2.29 (t; J = 7.0 Hz, 2 H), 2.74 (t;

J = 7.5 Hz, 2 H), 7.02 (m; 1 H, ind 5-H), 7.05 (m; 1 H, tol 4-H), 7.08 (m; 1 H, ind 6-H), 7.14 (m; 1 H, tol 5-H), 7.18 (d; J_o = 7.5 Hz, 1 H, tol 3-H), 7.34 (m; 2 H, tol 7-H, ind 7-H), 7.37 (d; J_o = 7.5 Hz, 1 H, ind 4-H), 9.19 (s; 1 H, NH), 11.38 (s; 1 H, NH), 11.68 (s; 1 H, NH); IR (KBr) ν: 3345, 3216, 2927–2855, 1771, 1719, 1647, 743 cm^{-1}. Anal. ($C_{27}H_{28}BrN_3O_3$) C, H, N.

6.2.7.7. 3-Bromo-4-(1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (12a) [32]. Yield: 0.1 g (0.34 mmol; 17% from 2 mmol indole and **8**); m.p. 195 °C (Lit. 196 °C [32]); ^{1}H-NMR δ 7.12–7.26 (m; 2 H, 5-H, 6-H), 7.51 (d; J_o = 7.7 Hz, 1 H), 7.90 (d; J_o = 7.7 Hz, 1 H), 8.04 (d; J_m = 3 Hz, 1 H, 2-H), 11.35 (s; 1 H, NH), 12.10 (s; 1 H, NH); IR (KBr) ν: = 3340, 3270, 3140–3035, 1760, 1700, 1620, 1610, 1490, 1460 cm^{-1}.

*6.2.7.8. 3-Bromo-4-(2-methyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (**12b**).* Yield: 0.23 g (0.74 mmol; 37% from 2 mmol 2-methylindole and **8**); m.p. 185 °C (dec.); R_f 0.36 (CH_2Cl_2); ^{1}H-NMR δ 2.41 (s; 3 H, CH_3), 7.02 (m; 1 H, 5-H), 7.10 (m; 1 H, 6-H), 7.35 (d, J_o = 7.6 Hz, 1 H, 7-H), 7.36 (d; J_o = 7.5 Hz, 1 H, 4-H), 11.32 (s; 1 H, NH), 11.72 (s; 1 H, NH). IR (KBr) ν: 3349, 3220, 3062–2695, 1771, 1753, 1626, 1613, 1541; 739 cm^{-1}. Anal. ($C_{13}H_9BrN_2O_2$) C, H, N.

*6.2.7.9. 3-Bromo-4-(2-ethyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (**12c**).* Yield: 0.365 g (1.14 mmol; 57% from 2 mmol **3a** and **8**); m.p. 160 °C (dec.); R_f 0.6 (CH_2Cl_2/ethyl acetate 9:1); ^{1}H-NMR δ 1.28 (t; J_o = 7.5 Hz, 3 H, CH_3), 2.74 (m; 2 H), 7.03 (m; 1 H, 5-H), 7.11 (m; 1 H, 6-H), 7.34 (d; J_o = 8.2 Hz, 1 H, 7-H) 7.37 (d; J_o = 7.7 Hz, 1 H, 4-H) 10.69 (s; 1 H, NH), 11.70 (s; 1 H, NH). IR (KBr) ν: 3347, 3214, 3058–2689, 1771, 1753 1715, 1624, 1607 1493, 740 cm^{-1}. Anal. ($C_{14}H_{11}BrN_2O_2$) C, H, N.

*6.2.7.10. 3-Bromo-4-(2-propyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (**12d**).* Yield: 0.42 g (1.26 mmol; 63% from 2 mmol **3d** and **8**); m.p. 150 °C; R_f 0.7 (CH_2Cl_2/ethyl acetate 1:9); ^{1}H-NMR δ 0.87 (t; J_o = 7.5 Hz, 3 H, CH_3), 1.70 (m; 2 H), 2.71 (t; J = 7.7 Hz, 2 H), 7.03 (m; 1 H, 5-H), 7.11 (m; 1 H, 6-H), 7.34 (d; J_o = 7.9 Hz, 1 H, 7-H), 7.37 (d; J_o = 7.9 Hz, 1H, 4-H), 11.37 (s; 1 H, NH), 11.672 (s; 1 H, NH). IR (KBr) ν: 3378, 3222, 3066–2871, 1775, 1757, 1719, 1624, 1609 1489, 741 cm^{-1}. Anal. ($C_{15}H_{13}BrN_2O_2$) C, H, N.

*6.2.7.11. 3-Bromo-4-(2-butyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (**12e**).* Yield: 0.272 g (0.78 mmol; 39% from 2 mmol **3c** and **8**); m.p. 155 °C; R_f 0.18 (CH_2Cl_2); ^{1}H-NMR δ 0.85 (t; J = 7.1 Hz, 3 H, CH_3), 1.26 (m; 2 H), 1.65 (m; 2 H), 2.72 (t; J = 7.5 Hz, 2 H), 7.01 (m; 1 H, 5-H), 7.10 (m; 1 H, 6-H), 7.32 (d; J_o = 8.7 Hz, 1 H, 7-H), 7.36 (d; J_o = 7.5 Hz, 4-H), 11.35 (s; 1 H, NH), 11.66 (s; 1 H, NH); IR (KBr) ν: 3416, 3224, 2947–2854, 1773, 1766, 1716, 1616, 1538, 1488; 741 cm^{-1}. Anal. ($C_{16}H_{15}BrN_2O_2$) C, H, N.

*6.2.7.12. 3-Bromo-4-(2-pentyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (**12f**).* Yield: 0.281 g (0.78 mmol; 38% from 2 mmol **3d** and **8**); m.p. 150 °C (dec.); R_f 0.3 (CH_2Cl_2); ^{1}H-NMR δ 0.83 (t; J = 6.7 Hz, 3 H, CH_3), 1.30 (m; 4 H), 1.70 (m; 2 H), 2.73 (t; J = 7.0 Hz, 2 H), 7.02 (m; 1 H, 5-H), 7.11 (m; 1 H, 6-H), 7.34 (d; J = 8.8 Hz, 1 H, 7-H), 7.37 (d; J = 7.5 Hz, 1 H, 4-H), 11.36 (s; 1 H, NH), 11.67 (s; 1 H, NH). IR (KBr) ν: 3345, 3222, 2957–2869, 1771, 1753, 1717, 1624, 1607, 1493, 743 cm^{-1}. Anal. ($C_{17}H_{17}BrN_2O_2$) C, H, N.

*6.2.7.13. 3-Bromo-4-(2-hexyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (**12g**).* Yield: 0.325 g (0.87 mmol; 43% from 2 mmol **3e** and **8**); m.p. 135 °C (dec.); R_f 0.22 (CH_2Cl_2); ^{1}H-NMR δ: 0.82 (t; J = 6.3 Hz, 3 H, CH_3); 1.23 (m; 6 H), 1.67 (m; 2 H), 2.73 (t; J = 7.1 Hz, 2 H), 7.03 (m; 1 H, 5-H), 7.11 (m; 1 H, 6-H), 7.33 (d; J_o = 8.3 Hz, 1 H, 7-H), 7.36 (d; J_o = 7.9 Hz, 1 H, 4-H), 11.37 (s; 1 H, NH), 11.67 (s; 1 H, NH). IR (KBr) ν: 3342, 3226, 2929, 1771, 1721, 1707, 1607, 1535, 743 cm^{-1}. Anal. ($C_{18}H_{19}BrN_2O_2$) C, H, N.

*6.2.7.14. 3-Bromo-4-(2-heptyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (**12h**).* Yield: 0.314 g (0.8 mmol; 40% from 2 mmol **3f** and **8**); m.p. 153 °C (dec.); R_f 0.36 (CH_2Cl_2); ^{1}H-NMR δ 0.83 (t; J = 6.7 Hz, 3 H, CH_3), 1.22 (m; 8 H); 1.66 (m; 2 H), 2.73 (t; J = 7.5 Hz, 2 H), 7.03 (m; 1 H, 5-H), 7.11 (m; 1 H, 6-H), 7.33 (d; J = 8.3 Hz, 1 H, 7-H), 7.37 (d; J = 8.0 Hz, 1 H, 4-H), 11.37 (s; 1 H, NH), 11.67 (s; 1 H, NH); IR (KBr) ν: 3341, 3216, 3062–2689, 1771, 1755, 1719, 1624, 1493, 742 cm^{-1}. Anal. ($C_{19}H_{19}BrN_2O_2$) C, H, N.

*6.2.7.15. 3-Bromo-4-(2-phenyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (**12i**).* Yield: 0.247 g (0.67 mmol; 33% from 2 mmol 2-phenylindole); m.p. 270 °C; R_f 0.11 (CH_2Cl_2); ^{1}H-NMR δ 7.11 (m; 1 H, ind 5-H), 7.22 (m; 1 H, ind 6-H), 7.38 (m; 1 H, ph 4-H), 7.46 (d; J_o = 6.5 Hz, 1 H, ind 7-H), 7.47 (m; 2 H, ph 3-H, ph 5-H), 7.49 (d; J_o = 8.3 Hz, 1 H, ind 4-H), 7.57 (m; 2 H, ph 2-H, ph 6-H), 11.12 (s; 1 H, NH), 12.14 (s; 1 H, NH); IR (KBr) ν: 3363, 3183, 1769, 1709, 1620, 1580, 1481, 770, 750, cm^{-1}. Anal. ($C_{18}H_{11}BrN_2O_2$) C, H, N.

*6.2.7.16. 3-Bromo-4-(2-(2-methoxyphenyl)-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (**12j**).* Yield: 0.17 g (0.45 mmol; 22% from 2 mmol **3g**); m.p. 205 °C; R_f 0.18 (CH_2Cl_2); ^{1}H-NMR δ 3.69 (s; 3 H, OCH_3), 7.01–7.11 (m; 3 H, ind 5-H, ph 4-H, ph 5-H), 7.18 (m; 1 H, ind 6-H), 7.34–7.41 (m; 2 H, ph 3-H, ph 6-H), 7.46 (d; J_o = 7.9 Hz, 1 H, ind 7-H), 7.47 (d; J_o = 7.9 Hz, 1 H, ind 4-H), 11.22 (s; 1 H, NH), 11.89 (s; 1 H, NH); IR (KBr) ν: 3353, 2834–2280, 1775, 1717, 1616, 1601, 1489, 1466, 1452, 1441, 1327, 1298, 1277, 1248, 1204, 1028, 739 cm^{-1}. Anal. ($C_{19}H_{13}BrN_2O_3$) C, H, N.

*6.2.7.17. 3-Bromo-4-(2-(3-methoxyphenyl)-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione (**12k**).* Yield: 0.082 g (0.21 mmol; 10% from 2 mmol **3h**); m.p. 225 °C; R_f 0.1 (CH_2Cl_2); ^{1}H-NMR δ 3.79 (s; 3H, OCH_3), 6.95 (m; 1 H, ph

6-H), 7.07–7.13 (m; 3 H, ind 5-H, ph 4-H, ph 2-H), 7.21 (m; 1 H, ind 6-H), 7.36 (m; 1 H ph 5-H) 7.46 (d; J_o = 6.7 Hz, 1 H, ind 7-H), 7.48 (d; J_o = 7.1 Hz, 1 H, ind 4-H), 11.37 (s; 1 H, NH), 12.13 (s; 1 H, NH); IR (KBr) ν: 3064, 1773, 1707, 1613, 1578, 1533, 1485, 1445, 1335, 1288, 1261, 1223, 1205, 1180, 1146, 1119, 1031, 910, 885, 783, 752, 694 cm^{-1}. Anal. ($C_{19}H_{13}BrN_2O_3$) C, H, N.

6.2.7.18. 3-Bromo-4-(2-(4-methoxyphenyl)-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione ***(12l)***. Yield: 0.320 g (0.8 mmol; 40% from 2 mmol 2-(4-Methoxyphenyl)-1*H*-indole [31]); m.p. 262 °C; R_f 0.15 (CH_2Cl_2); ^{1}H-NMR δ 3.80 (s; 3 H, OCH_3), 7.04 (d; J_o = 9.1 Hz, 2 H, ph 3-H, ph 5-H), 7.09 (m; 1 H, ind 5-H), 7.19 (m; 1 H, ind 6-H), 7.43 (d; J_o = 7.1 Hz, 1 H, ind 7-H), 7.46 (d; J_o = 9.1 Hz, 1 H, ind 4-H), 7.50 (d; J_o = 8.7 Hz, 2 H, ph 2-H, ph 6-H), 11.26 (s; 1 H, NH), 12.03 (s; 1 H, NH). IR (KBr) ν: 3376, 1771, 1721, 1609, 1580, 1495, 837, 746 cm^{-1}. Anal. ($C_{19}H_{13}BrN_2O_3$) C, H, N.

6.2.8. Methylation of the silyl-protected indolyl-maleinimide derivatives

A solution of the silyl-protected products (1 mmol) from indole derivative and **8**, produced by the procedure described in general procedure A, in THF (10 ml) was cooled to –78 °C under N_2. Then n-BuLi (1.1 mmol 1.6 M solution in hexane) was added slowly, and the mixture was stirred for 1 h. Then DMS (0.6 mmol) was added, and the solution was stirred overnight while slowly warming to RT. Then it was poured into a saturated solution of NH_4Cl (100 ml), extracted with ethyl acetate, dried over Na_2SO_4, concentrated in vacuo and purified by CC (CH_2Cl_2). The products were collected as crude oils and were directly used for the procedure described in general procedure B to remove the silyl protection group.

6.2.8.1. 3-Bromo-4-(1,2-dimethyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione ***(13a)***. Yield: 0.25 g (0.78 mmol; 39% from 2 mmol silyl-protected **12b**); m.p. 195 °C; R_f 0.29 (CH_2Cl_2); ^{1}H-NMR δ 2.39 (s; 3 H, NCH_3), 3.75 (s, 3 H, OCH_3), 7.06 (m; 1 H, 5-H), 7.17 (m; 1 H, 6-H), 7.37 (d; J_o = 7.52 Hz, 7-H), 7.49 (d; J_o = 7.9 Hz, 1 H, 4-H), 11.35 (s; 1 H, NH); IR (KBr) ν: 3212, 3062, 2927, 1767, 1713, 1611, 1597, 1412, 1323, 999, 746, 486 cm^{-1}. Anal. ($C_{14}H_{11}BrN_2O_2$) C, H, N.

6.2.8.2. 3-Bromo-4-(1-methyl-2-butyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrrole-dione ***(13b)***. Yield: 0.216 g (0.61 mmol; 31% from 2 mmol silyl-protected **12e**); m.p. 165 °C; R_f 0.34 (CH_2Cl_2); ^{1}H-NMR δ 0.83 (t; J = 7.1 Hz, 3 H, CH_3), 1.27 (m; 2 H, CH_2), 1.54 (m; 2 H, CH_2), 2.79 (t; J = 7.5 Hz, 2 H, CH_2); 3.77 (s; 3 H, NCH_3), 7.07 (m; 1 H, 5-H), 7.18 (m; 1 H, 6-H), 7.32 (d; J_o = 7.5 Hz, 1 H, 7-H), 7.49 (d; J_o = /.49, 1 H, 4-H), 11.40 (s; 1 H, NH); IR (KBr) ν: 3233, 2959, 2871, 1759, 1713, 1622, 1472, 1329, 1016, 740 cm^{-1}. Anal. ($C_{17}H_{17}BrN_2O_2$) C, H, N.

6.2.8.3. 3-Bromo-4-(1-methyl-2-hexyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrrole-dione ***(13c)***. Yield: 0.27 g (0.69 mmol; 35% from 2 mmol silyl-protected **12g**); m.p. 120 °C; R_f 0.26 (CH_2Cl_2); ^{1}H-NMR δ 0.80 (t; J = 6.4 Hz, 3 H, CH_3), 1.19 (m; 6 H), 1.55 (m; 2 H), 2.80 (t; J = 7.4 Hz, 2 H), 3.77 (s; 3 H, NCH_3), 7.04 (m; 1 H, 5-H), 7.18 (m; 1 H, 6-H), 7.32 (d; J_o = 7.15 Hz, 1 H, 7-H), 7.49 (d; J_o = 7.9 Hz, 1 H, 4-H), 11.41 (s; 1 H, NH). IR (KBr) ν: 3204, 2961–2859, 1775, 1763 1725, 1622, 1472; 740 cm^{-1}. Anal. ($C_{19}H_{21}BrN_2O_2$) C, H, N.

6.2.8.4. 3-Bromo-4-(1-methyl-2-phenyl-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrrole-dione ***(13d)***. Yield: 0.027 g (0.07 mmol; 3.5% from 2 mmol silyl-protected **12i**); m.p. 245 °C; R_f = 0.41 (CH_2Cl_2); ^{1}H-NMR δ: 3.77 (s; 3 H, CH_3), 7.26 (m; 1 H, 5-H), 7.35 (m; 1 H, 6-H), 7.38–7.51 (m; 6 H, arom.), 7.59 (m; 2 H, ph 2-H, ph 6-H); IR (KBr) ν: 3193, 1771, 1715, 1616, 1472, 743 cm^{-1}. Anal. ($C_{19}H_{13}BrN_2O_2$) C, H, N.

6.2.8.5. 3-Bromo-4-(1-methyl-2-(4-methoxyphenyl)-1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione ***(13e)***. Yield: 0.400 g (9.7 mmol; 10% from 10 mmol of silyl-protected **12l**); m.p. 225 °C; R_f: 0.15 (CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ: 3.75 (s; 1 H, NCH_3); 3.87 (s; 1 H, OCH_3); 6.99 (d; J_o = 6.7 Hz; 2 H, ph 3-H); 7.22–7.44 (m; 5 H, arom.); 7.57 (d; J_o = 7.9 Hz; 1 H, ind 5-H); IR (KBr) ν: 3222, 2934–2836, 1775, 1717, 1611, 1535, 1483, 843, 752 cm^{-1}. Anal. ($C_{20}H_{15}BrN_2O_3$) C, H, N.

6.2.9. Preparation of 3-(1H-3-indolyl)-2,5-pyrrolidinedione ***(14)*** *[33]*

0.7 mmol **12a** were stirred together with 0.2 g Pd/C (5%) in 5 ml of methanol under low H_2 pressure. Then the catalyst was removed by filtration through Celite. The filtrate was evaporated under reduced pressure, and the residue was crystallized from methanol.

Yield: 0.11 g (0.51 mmol; 75%); m.p. 195 °C (Lit. 196 °C [33]); ^{1}H-NMR δ 2.76 (m; 1 H), 3.18 (m; 1 H), 4.33 (m; 1 H), 6.96–7.43 (m; 5 H, aromat.), 11.02 (s; 1 H, NH), 11.30 (s; 1 H, NH). IR (KBr) ν: 3405, 3040–2990, 1490, 1460 cm^{-1}.

6.2.10. Preparation of 3-(1H-3-indolyl)-2,5-dihydro-1H-2,5-pyrroledione ***(15)***

The pyrrolidinedione **14 (**0.5 g, 2.33 mmol) was dissolved in benzene (200 ml), and DDQ (0.58 g, 2.57 mmol) and *p*-toluenesulfonic acid (0.05 g, 0.26 mmol) were added. After stirring for 30 min at RT. the solvent was removed; the residue was dissolved in ethyl acetate (200 ml) and washed with saturated $NaHSO_3$ solution (100 ml) and brine (100 ml). The organic phase was separated and dried over Na_2SO_4, the solvent was removed in vacuo and the residue was purified by CC (CH_2Cl_2/ethyl acetate 7:3).

Yield: 0.23 g (1.08 mmol; 47%); m.p. 201 °C; ^{1}H-NMR δ 6.79 (s; 1 H), 7.17–7.98 (m; 4 H, arom.), 8.36 (d; J = 3.0 Hz, 1 H, 2-H), 10.75 (s; 1 H, NH); IR (KBr) ν: 3395, 3080–3010, 1755, 1690, 1605, 1500, 1460 cm^{-1}. Anal. ($C_{12}H_8N_2O_2$) C, H, N.

Appendix A. Additional information: compound number combustion elemental analysis

Analysis

3g	Calc.	C 80.69	H 5.87	N 6.27	Found	C 80.48	H 5.54	N 6.19
3h	Calc.	C 80.69	H 5.87	N 6.27	Found	C 80.08	H 5.59	N 6.09
5b	Calc.	C 66.38	H 7.23	N 5.96	Found	C 66.43	H 7.32	N 5.91
5c	Calc.	C 67.47	H 7.63	N 5.62	Found	C 67.57	H 7.78	N 5.88
5d	Calc.	C 68.44	H 7.98	N 5.32	Found	C 68.35	H 8.06	N 5.41
5e	Calc.	C 69.31	H 8.30	N 5.05	Found	C 69.22	H 8.46	N 5.00
5f	Calc.	C 70.10	H 8.59	N 4.81	Found	C 70.04	H 8.72	N 4.88
6a	Calc.	C 77.69	H 6.47	N 10.07	Found	C 77.60	H 6.62	N 9.99
6b	Calc.	C 78.05	H 6.89	N 9.58	Found	C 77.70	H 7.05	N 9.24
6c	Calc.	C 78.43	H 7.18	N 9.15	Found	C 78.18	H 7.25	N 9.10
6d	Calc.	C 78.75	H 7.50	N.8.75	Found	C 78.63	H 7.65	N 8.71
6e	Calc.	C 79.01	H 7.84	N 8.38	Found	C 78.65	H 7.87	N 8.14
6f	Calc.	C 79.31	H 8.05	N 8.05	Found	C 78.95	H 8.22	N 7.79
10b	Calc.	C 52.69	H 3.47	N 8.78	Found	C 52.67	H 3.56	N 8.67
10c	Calc.	C 54.07	H 3.93	N 8.41	Found	C 54.14	H 4.09	N 8.21
10d	Calc.	C 55.35	H 4.35	N 8.07	Found	C 55.31	H 4.22	N 7.95
10e	Calc.	C 56.52	H 4.74	N 7.75	Found	C 56.38	H 4.69	N 7.70
10f	Calc.	C 57.61	H 5.10	N 7.47	Found	C 57.74	H 5.14	N 7.08
10g	Calc.	C 58.62	H 5.44	N 7.20	Found	C 58.69	H 5.44	N 7.20
10h	Calc.	C 59.56	H 5.75	N 6.95	Found	C 59.32	H 5.72	N 6.89
10i	Calc.	C 59.86	H 3.44	N 7.35	Found	C 60.01	H 3.70	N 7.21
10j	Calc.	C 58.41	H 3.67	N 6.81	Found	C 58.42	H 4.04	N 6.59
10k	Calc.	C 58.41	H 3.67	N 6.81	Found	C 58.44	H 3.85	N 6.62
10l	Calc.	C 58.41	H 3.67	N 6.81	Found	C 58.26	H 3.75	N 6.64
12b	Calc.	C 51.14	H 2.92	N 9.18	Found	C 50.93	H 3.18	N 8.89
12c	Calc.	C 52.66	H 3.45	N 8.78	Found	C 52.65	H 3.57	N 8.60
12d	Calc.	C 54.05	H 3.90	N 8.41	Found	C 53.96	H 4.00	N 8.12
12e	Calc.	C 55.33	H 4.32	N 8.07	Found	C 55.04	H 4.49	N 7.92
12f	Calc.	C 56.51	H 4.71	N 7.76	Found	C 56.26	H 4.77	N 7.51
12g	Calc.	C 57.61	H 5.10	N 7.47	Found	C 57.59	H 5.22	N 7.20
12h	Calc.	C 58.61	H 5.39	N 7.20	Found	C 58.60	H 5.40	N 7.20
12i	Calc.	C 58.88	H 3.02	N 7.63	Found	C 58.68	H 3.43	N 7.29
12j	Calc.	C 57.45	H 3.20	N 7.05	Found	C 57.55	H 3.59	N 6.87
12k	Calc.	C 57.45	H 3.30	N 7.05	Found	C 57.20	H 3.49	N 6.74
12l	Calc.	C 57.45	H 3.30	N 7.05	Found	C 57.55	H 3.59	N 6.87
12 m	Calc.	C 50.17	H 3.31	N 8.36	Found	C 50.61	H d.77	N 7.98
11a	Calc.	C 58.42	H 4.01	N 9.29	Found	C 58.96	H 4.40	N 8.75
11b	Calc.	C 59.24	H 4.32	N 9.01	Found	C 59.01	H 4.46	N 8.87
11c	Calc.	C 60.01	H 4.62	N 8.75	Found	C 60.01	H 4.84	N 8.16
11d	Calc.	C 60.74	H 4.89	N 8.50	Found	C 60.65	H 5.03	N 8.25
11e	Calc.	C 61.42	H 5.15	N 8.26	Found	C 60.85	H 5.11	N 8.12
11f	Calc.	C 62.07	H 5.40	N 8.04	Found	C 61.73	H 5.48	N 7.75
13a	Calc.	C 52.69	H 3.47	N 8.78	Found	C 52.87	H 3.86	N 8.48
13b	Calc.	C 56.52	H 4.74	N 7.75	Found	C 56.60	H 4.85	N 7.56
13c	Calc.	C 58.62	H 5.44	N 7.20	Found	C 58.88	H 5.39	N 7.30
13d	Calc.	C 59.86	H 3.44	N 7.35	Found	C 59.60	H 3.80	N 7.21
13e	Calc.	C 58.41	H 3.68	N 6.81	Found	C 58.80	H 3.82	N 6.72
15	Calc.	C 67.92	H 3.80	N 13.20	Found	C 68.33	H 4.12	N 12.00

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