Syntheses of Aromatic Substituted 6′-Thiothalidomides

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Abstract: A resurgence of interest in thalidomide has occurred as a consequence of its diverse immunomodulatory and anticancer actions, which has fuelled interest in synthetic analogues with higher potencies or less undesirable side effect profiles. Several novel aromatic substituted 6′-thiothalidomides were synthesized whose synthetic route and strategy were developed on the basis of an analysis of reaction mechanisms. The regioselectivity of mono-thionation of aromatic substituted thalidomides with Lawesson's reagent is described, and the chemoselectivity of hydrogenation between the nitro group and 6′-thiocarbonyl group is discussed. Full characterization of eight substituted 6′-thiothalidomides is reported.

Key words: 6′-thiothalidomides, TNF-α, thionation, regioselectivity, HMBC

Thalidomide [Figure 1; α-(*N*-phthalimido)glutarimide; **1**] has led a chequered pharmaceutical life. Withdrawn as a sedative as a consequence of its teratogenicity during the late 1950s, it was found to be effective in the management of erythema nodosum leprosum (ENL) reactions of leprosy in the 1960s, and its immunomodulatory and anticancer actions have made it a focus of pharmaceutical interest in recent decades.[1–3] The current therapeutic promise of thalidomide has motivated efforts to synthesize new, more effective analogues with reduced toxicity, and several interesting classes of compounds have subsequently been developed.[4–8] A primary mechanism that likely underlies the activity of thalidomide in ENL involves a reduction in the levels of tumor necrosis factor-α (TNF-α),[9,10] a pro-inflammatory cytokine whose initial release is critical in mediating a protective inflammatory response following an insult, but whose over-production is detrimental and associated with clinical disorders such as rheumatoid arthritis, Crohn's diseases and several neurodegenerative conditions.[11] Amongst recent thalidomide analogues, 4-amino substituted versions were found to be potent inhibitors of TNF-α release,[4,5] as assessed in cultured human peripheral blood mononuclear cells challenged to lipopolysaccharide (LPS), a major component of the outer membrane of gram-negative bacteria that is used as a pharmacological tool to induce TNF-α synthesis and release. Thiocarbonyl substituted thalidomides, similarly,

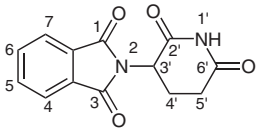

Figure 1 Structure of thalidomide

potently lower TNF-α levels without toxicity.[6] This likely occurs by reducing TNF-α synthesis rate through translational regulation, and appears to translate from cell culture studies into animals.[11] Accordingly, synthetic investigation of aromatic substituted thiothalidomides may provide pharmacologically interesting compounds of potential clinical value. Herein, we describe the synthesis, isolation and identification of aromatic substituted 6′-thiothalidomides.

The preparation of starting materials **3**–**7** is concisely shown in Scheme 1. The preparation of **3** was reported by Wyrick;[12] compounds **6** and **7** were obtained via a route described by Zhu and colleagues.[6]

The syntheses of aromatic substituted thalidomides are shown in Table 1. Whereas similar pathways for constructing the thalidomide skeleton have been reported,[4,6,13,14] it was envisioned that the use of 1,3-dicyclohexylcarbodiimide (DCC) would allow substituted phthalic acids to be directly applied to the condensation of thalidomide analogues, instead of substituted phthalic anhydrides. For example, 4-hydroxyphthalic acid **2** could be directly converted into its corresponding anhydride **3**, and then reacted with **7** in one-pot to give product **9** (36%). DCC as a dehydrating condensing agent was also used for the synthesis of some naturally occurring phthalides from Alternaria species.[15] Reactants **4** and **7** were refluxed to afford 28% of **9** in addition to 10% of **10**. This suggested that there was an equilibrium between a hydroxy and an acetoxy at the 5-position of thalidomide in acetic acid.

The syntheses of aromatic substituted 6′-thiothalidomides are shown in Table 2. The mono-thionation of aromatic substituted thalidomides principally takes place at the 6′-position using Lawesson's reagent. This is likely as a consequence of this position being the least sterically hindered of the available four amido carbonyl groups (1-, 3-, 2′- and 6′-position) of the thalidomide skeleton (Figure 2),

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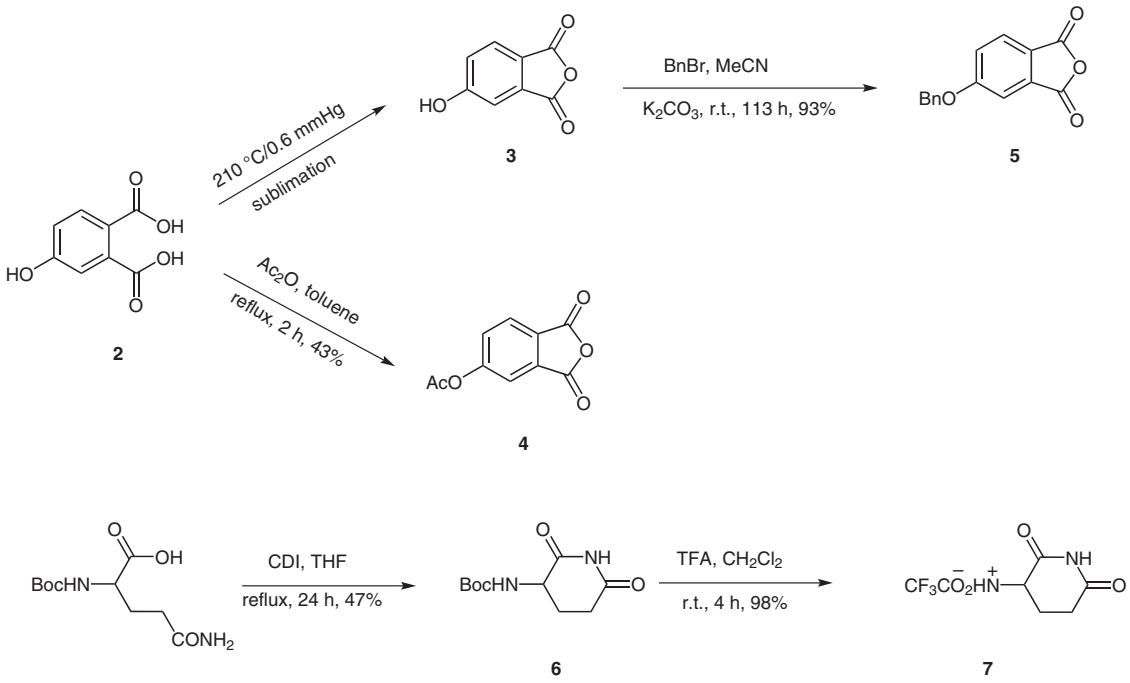
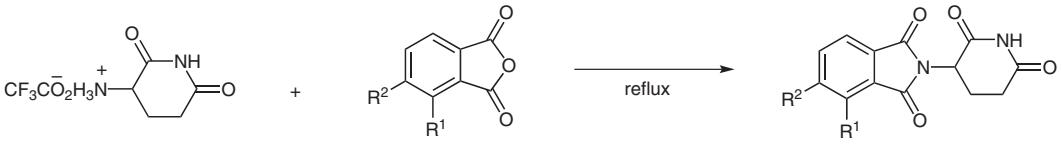


Scheme 1 Preparation of main starting materials

Table 1 Syntheses of Aromatic Substituted Thalidomides



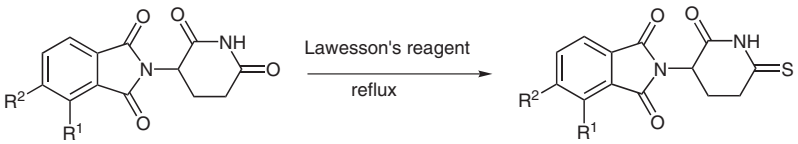
Entry	Reactant			Solvent	Product			Time (h)	Yield (%)
		R^1	R^2			R^1	R^2		
1[a]		OH	H	Et_3N/THF	**8**	OH	H	96.0	76
2[b]	**3**	H	OH	AcOH	**9**	H	OH	24.0	50
3	**4**	H	OAc	AcOH	**10**	H	OAc	52.5	10
4	**5**	H	OBn	AcOH	**11**	H	OBn	42.0	41
5		H	NO_2	AcOH	**12**[c]	H	NO_2	4.5	55
6		H	Cl	AcOH	**14**	H	Cl	4.5	75

[a] Reagents and conditions: (i) **7**, 3-hydroxyphthalic anhydride, Et_3N, THF, reflux, 24 h; (ii) DCC, DMAP (cat.), reflux, 72 h.
[b] Alternatively: (i) **2**, DCC, THF, r.t., 24 h; (ii) **7**, AcOH, reflux, 4.5 h, to give **9**, overall yield 36%.
[c] Reduction of **12** (acetone, 10% Pd/C, H_2, 40lbs, r.t., 3 h), gave 5-aminothalidomide **13** (73%).

which allows the approach and attack of Lawesson's reagent at the 6′-position.

In Figure 2, thalidomide is shown in its lowest energy conformation. As thionation of the carbonyl group with Lawesson's reagent primarily proceeds via a mechanism involving a cyclic transition state between the dithiophosphine ylide and carbonyl group, the 6′-position is the most favored. In the case of the aromatic substituted thiothalidomides detailed in Table 2, when a hydroxy or amino substituted thalidomide was thionated with Lawesson's reagent, the yield of the corresponding 6′-thiothalidomide was reduced [see entry 2 (16%) and entry 6 (8%)], since the hydroxy and amino group compete with the carbonyl group for reaction with Lawesson's reagent. The position of such a competitive group on the thalidomide skeleton is clearly important, and is exemplified by comparing en-

Table 2 Syntheses of Aromatic Substituted 6′-Thiothalidomides



Entry	Structure	Reactant		Solvent	Structure	Product		Time (h)	Yield (%)
		R^1	R^2			R^1	R^2		
1	**8**	OH	H	toluene	**15**[a]	OH	H	89.0	37
				pyridine				47.0	45
2	**9**	H	OH	toluene	**17**	H	OH	76.0	16
				pyridine				120.5	38
3	**10**	H	OAc	toluene	**18**[b]	H	OAc	91.0	46
4	**11**	H	OBn	toluene	**19**	H	OBn	103.0	13
				pyridine				47.0	20
5	**12**	H	NO_2	toluene	**20**[c]	H	NO_2	90.0	21
6	**13**	H	NH_2	toluene	**21**	H	NH_2	91.5	8
7	**14**	H	Cl	pyridine	**22**	H	Cl	47.0	56

[a] Reaction of **15** (Ac_2O, toluene, reflux, 3 h), gave **16** (44%).
[b] Reaction of **18** [$NaHCO_3$ (sat.), MeOH, r.t., 1 h], gave **17** (73%).
[c] Reaction of **20** (acetone, 10% Pd/C, H_2, 40lbs, r.t., 2 h), gave **21** (95%).

tries 1 and 2 (Table 2), where a hydroxy group lies in the 4- or 5-position, respectively, and provide 37% and 16% yields of the corresponding 6′-thiothalidomides. As a consequence of the steric effects, which are greater for the 4-hydroxy than the 5-hydroxy group of thalidomide, the latter more readily reacts with Lawesson's reagent or its dithiophosphine ylide, and hence generation of the desired 6′-thiothalidomide is reduced. Moreover, when thionation of different moieties at the same position takes place, such as between the 5-hydroxy or 5-amino with the 6′-carbonyl group, as detailed in Table 2 (entries 2 and 6), the 5-amino more effectively decreases the yield of 6′-thiothalidomide. Hence, in order to obtain hydroxy or amino substituted 6′-thiothalidomide in reasonable yields, the corresponding acetoxy or nitro substituted thiothalidomides were first synthesized. These were then hydrolyzed or reduced in 75 and 95% yield, respectively, to the desired compounds. The 95% yield for the latter conversion indicates that there is a high chemoselectivity of hydrogenation between the nitro group and the thiocarbonyl group of the aromatic substituted 6′-thiothalidomide when palladium was used as a catalyst. On the other hand, by using pyridine as the thionation solvent (Table 2; entries 1, 2, 4 and 7), the yields of the corresponding aromatic substituted 6′-thiothalidomides were higher than those obtained in toluene, due to more advantageous formation of the dithiophosphine ylide (Scheme 2).[16]

Interestingly, trimeric *p*-methoxyphenylthionophosphine oxide (**23**) was isolated from the reaction of aromatic substituted thalidomides with Lawesson's reagent. This compound has previously been characterized by IR, ^{1}H NMR, ^{31}P NMR, MS and elemental analysis.[17] Herein, we report its X-ray crystallographic structure, which appeared as an interesting twinned structure (Figure 3).[18]

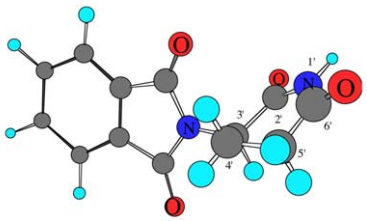
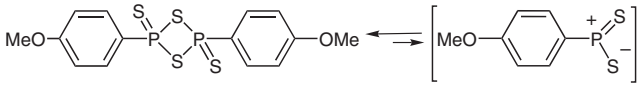


Figure 2 Structure of thalidomide generated from energy-minimization by computer modeling



Scheme 2 Lawesson's reagent and dithiophosphine ylide

The structural proofs of compounds **15**–**22** are based on 1D and 2D NMR spectra, GC-MS and elemental analyses. The 6′-thiocarbonyl group is identified as a correlative peak of 6′-C/5′-H in the (^{1}H-detected) heteronuclear multiple-bond correlation (HMBC) spectrum (Table 3). Furthermore, X-ray crystallographic analyses of **15** and **18** confirmed the structural assignments (Figure 4 and Figure 5).[19,20]

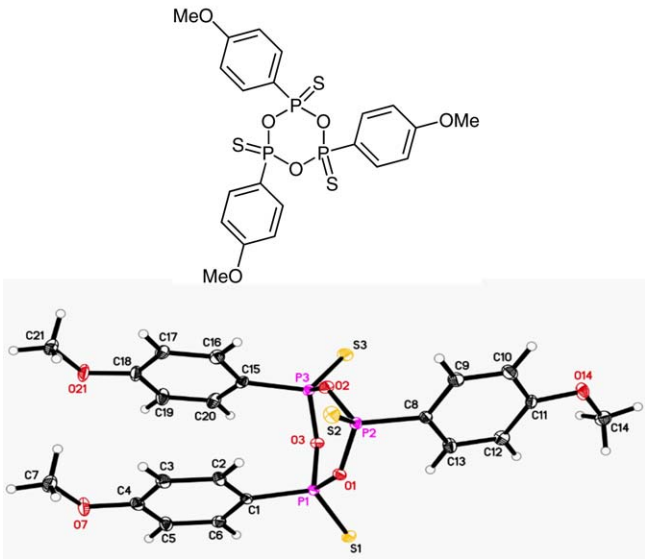


Figure 3 Compound **23** and its X-ray crystallographic structure

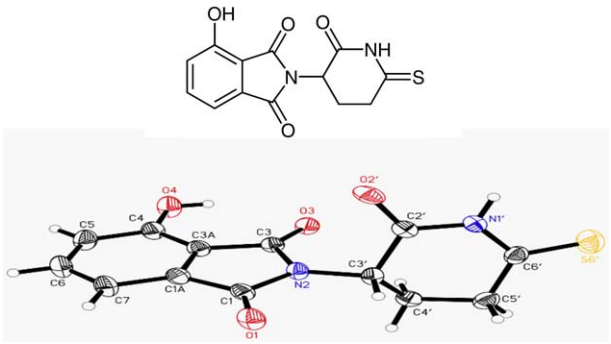


Figure 4 Compound **15** and its X-ray crystallographic structure

Taken together, these data suggest that substituent groups on the phenyl ring have no effect on the ^{13}C chemical shifts of the 6′-thiocarbonyl group (δ = 210.9 ppm in DMSO-d_6). This shift thus provides a potentially valuable means for identifying the 6′-thiocarbonyl group.

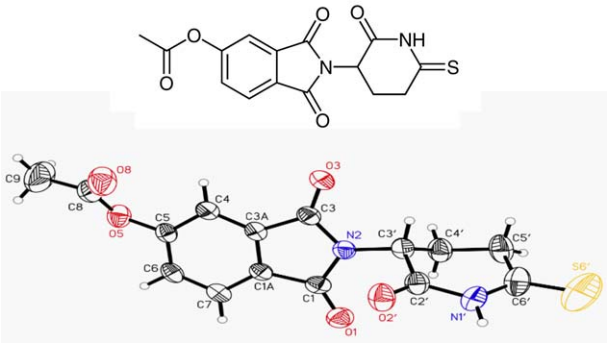


Figure 5 Compound **18** and its X-ray crystallographic structure

In summary, a synthetic route and strategy to generate aromatic substituted 6′-thiothalidomides is described. In the presence of 1,3-dicyclohexylcarbodiimide, substituted phthalic anhydride and its acid were utilized in the condensation of 3-aminoglutarimide to build a thalidomide skeleton. In the mono-thionation of aromatic substituted thalidomides with Lawesson's reagent, there is a 6′-position regioselectivity among the four available amido carbonyl groups, and selection of pyridine as solvent, rather than toluene, provided higher yields. In the event that a hydroxy or amino substituent group is present on the phenyl of the glutarimide ring of a thalidomide analogue, protection prior to thionation is necessary. In addition, our results demonstrate an excellent chemoselectivity of hydrogenation between the nitro and the 6′-thiocarbonyl group using palladium as catalyst. Finally, within the confines of the current study, it was found that substituent groups on the phenyl ring do not effect the ^{13}C NMR chemical shift of the thiocarbonyl group of an aromatic substituted 6′-thiothalidomide.

Table 3 Important Properties of Aromatic Substituted 6′-Thiothalidomides

Compound	Chemical shift (ppm)[a]		HMBC	Elemental analysis[c]		
	6′-C	5′-H	6′-C/5′-H correlation	C	H	N
15	210.9	2.43–2.60	+	53.71 (53.79)	3.55 (3.47)	9.36 (9.65)
16	206.7[b]	2.72–3.07[b]	+[b]	54.48 (54.21)	3.91 (3.64)	8.31 (8.43)
17	210.9	2.43–2.62	+	52.09 (52.17)	3.40 (3.70)	9.03 (9.36)
18	210.9	2.48–2.65	+[b]	54.88 (54.21)	3.73 (3.64)	8.38 (8.43)
19	210.9	2.44–2.56	+	63.37 (63.14)	4.54 (4.24)	6.57 (7.36)
20	210.9	2.46–2.59	+[b]	48.88 (48.90)	2.88 (2.84)	12.95 (13.16)
21	210.9	2.44–2.60	+	50.31 (50.81)	3.58 (4.26)	13.24 (13.67)
22	210.9	2.43–2.65	+	50.72 (50.57)	2.87 (2.94)	9.01 (9.07)

[a] In DMSO-d_6/TMS.
[b] In $CDCl_3$/TMS.
[c] Calculated values given in parentheses.

Melting points were determined with a Fisher–Johns apparatus and are uncorrected. ^{1}H NMR, ^{13}C NMR and 2D NMR were recorded on a Bruker AC-300 spectrometer. GC-Mass spectra were performed on a Hewlett–Packard 5973 GC-MS with chemical ionization. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. X-ray crystallographic structural studies were performed at the Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D.C.

4-Acetoxyphthalic Anhydride (4)

A solution of 4-hydroxyphthalic acid (**2**; 5.39 g, 29.6 mmol) and Ac_2O (26 mL) in toluene (100 mL) was refluxed for 2 h. The product was crystallized from the reaction solvents to give **4**.

Yield: 2.64 g (43%); white needle crystals; mp 89–91 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3CO), 7.61 (d, *J* = 8.3 Hz, 1 H, 5-CH), 7.80 (s, 1 H, 3-CH), 8.06 (d, *J* = 8.3 Hz, 1 H, 6-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.05, 119.09, 127.14, 128.13, 129.67, 133.16, 156.75, 161.86, 161.89, 168.14.

GC-MS (CI/CH_4): *m*/*z* = 207 $[M + H]^+$, 193, 179, 165, 120.

4-Benzyloxyphthalic Anhydride (5)

A mixture of 4-hydroxyphthalic anhydride (**3**; 1.37 g, 8.34 mmol), benzyl bromide (1.43 g, 8.36 mmol) and K_2CO_3 (1.23 g, 8.90 mmol) in MeCN (110 mL) was stirred at r.t. for 113 h. Thereafter, the reaction mixture was concentrated and purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 4:1) to afford **5**.

Yield: 1.96 g (93%); white crystals; mp 202–204 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.20 (s, 2 H, $PhCH_2$), 7.10–7.80 (m, 8 H, ArH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 70.71, 114.92, 116.97, 123.99, 128.82, 129.09, 129.56, 132.26, 137.45, 138.06, 161.48, 168.40, 170.18.

GC-MS (CI/CH_4): *m*/*z* = 255 $[M + H]^+$, 205, 165, 119, 91.

2-(2,6-Dioxo-3-piperidinyl)-4-hydroxy-1*H*-isoindole-1,3(2*H*)-dione (8)

To a stirred suspension of **7** (1.25 g, 5.16 mmol) in THF (100 mL) at r.t., was added a solution of 3-hydroxyphthalic anhydride (0.85 g, 5.16 mmol) in THF (50 mL) and Et_3N (1.06 g). After 10 min, the resulting solution was refluxed for 24 h under nitrogen. Thereafter, the reaction mixture was cooled to r.t. and DCC (1.06 g, 5.16 mmol) and a catalytic amount of DMAP were added. The mixture was refluxed for 72 h under nitrogen then the concentrated crude product was purified by column chromatography on silica gel (EtOAc–MeOH, 3:1) to give **8**.

Yield: 1.07 g (76%); white powder; mp 275–276 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.98–2.09 (m, 1 H, 4′-CH), 2.45–2.62 (m, 2 H, 5′-CH), 2.80–2.98 (m, 1 H, 4′-CH), 5.01–5.12 (m, 1 H, 3′-CH), 7.24 (d, *J* = 8.1 Hz, 1 H, 5-CH), 7.30 (d, *J* = 7.2 Hz, 1 H, 7-CH), 7.65 (t, *J* = 7.7 Hz, 1 H, 6-CH), 11.13 (s, 1 H, NH).

^{13}C NMR (75 MHz, CD_3OD): δ = 24.06, 32.57, 50.75, 116.33, 116.49, 124.86, 135.04, 137.86, 157.25, 168.78, 169.20, 171.90, 175.04.

GC-MS (CI/CH_4): *m*/*z* = 275 $[M + H]^+$, 247, 230, 189, 164.

2-(2,6-Dioxo-3-piperidinyl)-5-hydroxy-1*H*-isoindole-1,3(2*H*)-dione (9)

A solution of 4-hydroxyphthalic acid (**2**; 1.48 g, 8.13 mmol) and DCC (1.68 g, 8.13 mmol) in THF (88 mL) was stirred for 24 h at r.t. under nitrogen. Thereafter, a solution of **7** (1.97 g, 8.14 mmol) in AcOH (62 mL) was added dropwise to the above reaction system. The mixture was continuously stirred and refluxed for 4.5 h under nitrogen. After evaporation of the solvents, the residue was recrystallized from EtOAc to afford **9**.

Yield: 0.80 g (36%); grayish powder; mp 315 °C (dec.).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.98–2.10 (m, 1 H, 4′-CH), 2.46–2.63 (m, 2 H, 5′-CH), 2.80–2.98 (m, 1 H, 4′-CH), 5.02–5.16 (m, 1 H, 3′-CH), 7.16 (d, *J* = 7.2 Hz, 1 H, 6-CH), 7.19 (s, 1 H, 4-CH), 7.76 (d, *J* = 7.2 Hz, 1 H, 7-CH), 11.12 (s, 1 H, NH), 11.20 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.44, 31.30, 49.21, 110.32, 121.11, 121.76, 125.96, 134.43, 163.90, 167.28, 167.38, 170.33, 173.12.

GC-MS (CI/CH_4): *m*/*z* = 275 $[M + H]^+$, 259, 245, 217, 205, 163.

2-(2,6-Dioxo-3-piperidinyl)-5-acetoxy-1*H*-isoindole-1,3(2*H*)-dione (10)

A mixture of 4-acetoxyphthalic anhydride (**4**; 1.82 g, 8.83 mmol) and **7** (2.14 g, 8.84 mmol) in AcOH (67 mL) was refluxed for 52 h under nitrogen. Thereafter, the solution was concentrated and recrystallized from either EtOAc or MeOH to give **10** and **9** (0.79 g, 28%).

Yield: 0.28 g (10%); white crystals; mp 220–221 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.89–2.01 (m, 1 H, 4′-CH), 2.20 (s, 3 H, CH_3CO_2), 2.33–2.56 (m, 2 H, 5′-CH), 2.68–2.84 (m, 1 H, 4′-CH), 4.98–5.09 (m, 1 H, 3′-CH), 7.49 (d, *J* = 7.3 Hz, 1 H, 6-CH), 7.65 (s, 1 H, 4-CH), 7.88 (d, *J* = 7.3 Hz, 1 H, 7-CH), 11.30 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.25, 22.28, 31.27, 49.49, 118.02, 125.45, 128.50, 128.74, 133.37, 155.75, 166.62, 166.75, 169.19, 170.14, 173.10.

GC-MS (CI/CH_4): *m*/*z* = 317 $[M + H]^+$, 289, 274, 84.

2-(2,6-Dioxo-3-piperidinyl)-5-benzyloxy-1*H*-isoindole-1,3(2*H*)-dione (11)

A mixture of 4-benzyloxyphthalic anhydride (**5**; 704 mg, 2.77 mmol) and **7** (671 mg, 2.77 mmol) in AcOH (46 mL) was refluxed for 42 h under nitrogen. Thereafter, the solution was concentrated and purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 15:1) to give **11**.

Yield: 414 mg (41%); white crystals; mp 213–215 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01–2.10 (m, 1 H, 4′-CH), 2.61–2.87 (m, 3 H, 5′-CH, 4′-CH), 4.84–4.91 (m, 1 H, 3′-CH), 5.11 (s, 2 H, $PhCH_2$), 7.17–7.77 (m, 8 H, ArH), 8.10 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.63, 33.35, 51.26, 72.82, 111.33, 123.08, 125.72, 127.55, 129.45, 130.51, 130.79, 136.27, 137.28, 166.06, 168.90, 169.06, 170.08, 172.94.

GC-MS (CI/CH_4): *m*/*z* = 365 $[M + H]^+$, 337, 303, 275, 254, 164.

2-(2,6-Dioxo-3-piperidinyl)-5-nitro-1*H*-isoindole-1,3(2*H*)-dione (12)

To a stirred solution of **7** (0.95 g, 3.92 mmol) in AcOH (30 mL) at r.t. was added 4-nitrophthalic anhydride (0.76 g, 3.94 mmol). The reaction mixture was refluxed for 4.5 h under nitrogen and then evaporated to remove AcOH. The residue was recrystallized from EtOAc to give **12**.

Yield: 0.66 g (55%); purplish crystals; mp 230–231 °C (Lit.[21] 229–230 °C).

2-(2,6-Dioxo-3-piperidinyl)-5-amino-1*H*-isoindole-1,3(2*H*)-dione (13)

A mixture of **12** (793 mg, 2.62 mmol) and 10% Pd/C (400 mg) in acetone (50 mL) was shaken at r.t. for 3 h under H_2 (40 lbs). The mixture was filtered and concentrated to afford **13**.

Yield: 0.53 g (73%); yellow crystals; mp 320–322 °C (Lit.[21] 319–321 °C).

2-(2,6-Dioxo-3-piperidinyl)-5-chloro-1*H*-isoindole-1,3(2*H*)-dione (14)

To a stirred solution of **7** (2.10 g, 8.67 mmol) in AcOH (66 mL) at r.t., was added 4-chlorophthalic anhydride (1.58 g, 8.67 mmol). The reaction mixture was refluxed for 4.5 h under nitrogen and then evaporated to remove AcOH. The residue was recrystallized from EtOAc to give **14**.

Yield: 1.9 g (75%); pinkish powder; mp 312–313 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.01–2.12 (m, 1 H, 4′-CH), 2.50–2.68 (m, 2 H, 5′-CH), 2.81–2.99 (m, 1 H, 4′-CH), 5.11–5.22 (m, 1 H, 3′-CH), 7.90–8.05 (m, 3 H, ArH), 11.15 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.25, 31.25, 49.55, 123.97, 125.55, 130.13, 133.55, 135.05, 140.11, 166.27, 166.61, 170.02, 173.05.

GC-MS (CI/CH_4): m/z = 293 [M + H]$^+$, 265, 248, 182, 139.

2-(2-Oxo-6-thioxo-3-piperidinyl)-4-hydroxy-1*H*-isoindole-1,3(2*H*)-dione (15)

To a stirred solution of **8** (0.28 g, 1.02 mmol) in toluene (155 mL) at r.t., was added Lawesson's reagent (0.22g, 0.54 mmol). The reaction mixture was refluxed for 89 h under nitrogen. After concentration, the residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 15:1) to give **15**.

Yield: 0.11 g (37%); yellow flaky crystals; mp 252–255 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.00–2.10 (m, 1 H, 4′-CH), 2.43–2.60 (m, 2 H, 5′-CH), 3.18–3.29 (m, 1 H, 4′-CH), 5.14–5.24 (m, 1 H, 3′-CH), 7.28 (d, J = 9.0 Hz, 1 H, 5-CH), 7.35 (d, J = 7.2 Hz, 1 H, 7-CH), 7.66 (t, J = 7.9 Hz, 1 H, 6-CH), 11.14 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.02, 41.13, 48.79, 113.45, 114.70, 123.96, 133.45, 136.79, 155.86, 166.02, 167.23, 167.66, 210.92.

GC-MS (CI/CH_4): m/z = 291 [M + H]$^+$, 275, 263, 247, 164.

Anal. Calcd for $C_{13}H_{10}N_2O_4S$: C, 53.79; H, 3.47; N, 9.65. Found: C, 53.71; H, 3.55; N, 9.36.

2-(2-Oxo-6-thioxo-3-piperidinyl)-4-acetoxy-1*H*-isoindole-1,3(2*H*)-dione (16)

To a stirred suspension of **15** (67.0 mg, 0.231 mmol) in toluene (18 mL) at r.t., was added Ac_2O (1 mL). The reaction mixture was refluxed for 3 h under nitrogen. Thereafter, the solvent together with excess Ac_2O were removed. The residue was recrystallized from EtOAc to afford **16**.

Yield: 34.0 mg (44%); yellow needle crystals; mp 179–181 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.11–2.21 (m, 1 H, 4′-CH), 2.44 (s, 3 H, CH_3CO_2), 2.72–3.07 (m, 2 H, 5′-CH), 3.49–3.58 (m, 1 H, 4′-CH), 4.95–5.04 (m, 1 H, 3′-CH), 7.35–7.82 (m, 3 H, ArH), 9.40 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.05, 24.65, 40.72, 49.56, 121.87, 123.01, 129.30, 133.57, 136.63, 147.34, 165.16, 165.24, 166.63, 168.86, 206.67.

GC-MS (CI/CH_4): m/z = 333 [M + H]$^+$, 291, 275, 259, 164.

Anal. Calcd for $C_{15}H_{12}N_2O_5S$: C, 54.21; H, 3.64; N, 8.43. Found: C, 54.48; H, 3.91; N, 8.31.

2-(2-Oxo-6-thioxo-3-piperidinyl)-5-hydroxy-1*H*-isoindole-1,3(2*H*)-dione (17)

To a stirred solution of **9** (0.14 g, 0.51 mmol) in pyridine (21 mL) at r.t., was added Lawesson's reagent (0.10 g, 0.25 mmol). The reaction mixture was refluxed for 120 h under nitrogen. After concentrating, the residue was purified by column chromatography on silica gel (CH_2Cl_2–EtOH, 17:1) to give **17**.

Yield: 56 mg (38%); brown crystals; mp 316–318 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.98–2.15 (m, 1 H, 4′-CH), 2.43–2.62 (m, 2 H, 5′-CH), 3.11–3.28 (m, 1 H, 4′-CH), 5.11–5.28 (m, 1 H, 3′-CH), 7.12 (d, J = 7.2 Hz, 1 H, 6-CH), 7.17 (s, 1 H, 4-CH), 7.71 (d, J = 7.2 Hz, 1 H, 7-CH), 11.20 (s, 1 H, NH), 12.65 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.10, 41.12, 49.01, 109.48, 110.37, 121.14, 121.70, 126.03, 134.39, 163.94, 167.19, 167.63, 210.89.

GC-MS (CI/CH_4): m/z = 291 [M + H]$^+$, 275, 259, 207, 188, 176, 148.

Anal. Calcd for $C_{13}H_{10}N_2O_4S{\cdot}0.5H_2O$: C, 52.17; H, 3.70; N, 9.36. Found: C, 52.09; H, 3.40; N, 9.03.

2-(2-Oxo-6-thioxo-3-piperidinyl)-5-acetoxy-1*H*-isoindole-1,3(2*H*)-dione (18)

A mixture of **10** (400 mg, 1.26 mmol) and Lawesson's reagent (280 mg, 0.69 mmol) in toluene (250 mL) was refluxed for 91 h under nitrogen. Thereafter, the solvent was removed and the residue was recrystallized from MeOH to afford **18**.

Yield: 195 mg (46%); yellow crystals; mp 191–193 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09–2.21 (m, 1 H, 4′-CH), 2.37 (s, 3 H, CH_3CO_2), 2.71–3.09 (m, 2 H, 5′-CH), 3.49–3.60 (m, 1 H, 4′-CH), 4.98–5.10 (m, 1 H, 3′-CH), 7.48 (d, J = 7.2 Hz, 1 H, 6-CH), 7.65 (s, 1 H, 4-CH), 7.90 (d, J = 7.2 Hz, 1 H, 7-CH), 9.40 (s, 1 H, NH).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.03–2.15 (m, 1 H, 4′-CH), 2.36 (s, 3 H, CH_3CO_2), 2.48–2.65 (m, 2 H, 5′-CH), 3.18–3.28 (m, 1 H, 4′-CH), 5.22–5.33 (m, 1 H, 3′-CH), 7.64 (d, J = 7.2 Hz, 1 H, 6-CH), 7.79 (s, 1 H, 4-CH), 8.01 (d, J = 7.2 Hz, 1 H, 7-CH), 12.68 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.45, 24.70, 40.76, 49.71, 118.12, 125.67, 128.08, 129.07, 133.87, 155.98, 165.32, 166.51, 166.69, 168.84, 206.67.

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.24, 24.20, 49.30, 79.50, 118.06, 125.50, 128.53, 128.70, 133.70, 155.78, 166.49, 166.62, 167.40, 169.18, 210.89.

GC-MS (CI/CH_4): m/z = 333 [M + H]$^+$, 317, 289, 275, 205, 164.

Anal. Calcd for $C_{15}H_{12}N_2O_5S$: C, 54.21; H, 3.64; N, 8.43. Found: C, 54.88; H, 3.73; N, 8.38.

2-(2-Oxo-6-thioxo-3-piperidinyl)-5-benzyloxy-1*H*-isoindole-1,3(2*H*)-dione (19)

A mixture of **11** (220 mg, 0.60 mmol) and Lawesson's reagent (136 mg, 0.34 mmol) in toluene (440 mL) was refluxed for 103 h under nitrogen. Thereafter, the solvent was removed and the residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 9:1) to give **19**.

Yield: 30 mg (13%); gum.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.01–2.11 (m, 1 H, 4′-CH), 2.44–2.56 (m, 2 H, 5′-CH), 3.15–3.25 (m, 1 H, 4′-CH), 5.16–5.28 (m, 1 H, 3′-CH), 5.34 (s, 2 H, $PhCH_2$), 7.32–7.90 (m, 8 H, ArH), 12.65 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.06, 41.12, 49.13, 70.59, 108.89, 121.30, 123.10, 124.98, 128.16, 128.51, 128.91, 134.22, 136.39, 164.06, 166.98, 167.07, 167.56, 210.90.

GC-MS (CI/CH_4): m/z = 381 [M + H]$^+$, 255, 207, 165, 91.

Anal. Calcd for $C_{20}H_{16}N_2O_4S$: C, 63.14; H, 4.24; N, 7.36. Found: C, 63.37; H, 4.54; N, 6.57.

2-(2-Oxo-6-thioxo-3-piperidinyl)-5-nitro-1*H*-isoindole-1,3(2*H*)-dione (20)

A mixture of **12** (190 mg, 0.63 mmol) and Lawesson's reagent (139 mg, 0.34 mmol) in toluene (100 mL) was refluxed for 90 h under nitrogen. Thereafter, the solvent was removed and the residue was purified by column chromatography on silica gel (hexane–EtOAc–MeOH, 1:1:0.3) to give **20**.

Yield: 42 mg (21%); yellow crystals; mp 231–233 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15–2.26 (m, 1 H, 4′-CH), 2.81–3.08 (m, 2 H, 5′-CH), 3.50–3.59 (m, 1 H, 4′-CH), 5.02–5.10 (m, 1 H, 3′-CH), 8.09 (d, *J* = 7.8 Hz, 1 H, 7-CH), 8.65 (d, *J* = 7.8 Hz, 1 H, 6-CH), 8.70 (s, 1 H, 4-CH), 9.38 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.18, 40.31, 49.82, 119.27, 125.13, 129.72, 133.09, 136.01, 152.02, 164.48, 164.83, 165.09, 205.85.

GC-MS (CI/CH_4): *m*/*z* = 320 $[M + H]^+$, 302, 290, 274, 246, 229, 193, 163.

Anal. Calcd for $C_{13}H_9N_3O_5S$: C, 48.90; H, 2.84; N, 13.16. Found: C, 48.88; H, 2.88; N, 12.95.

2-(2-Oxo-6-thioxo-3-piperidinyl)-5-amino-1*H*-isoindole-1,3(2*H*)-dione (21)

A mixture of **20** (21.5 mg, 0.07 mmol) and 10% Pd/C (20 mg) in acetone (10 mL) was shaken at r.t. for 2 h under H_2 (40 lbs). The mixture was filtered and concentrated to afford **21**.

Yield: 19 mg (95%); yellow crystals; mp 298 °C (dec.).

Alternatively, a mixture of **13** (58 mg, 0.21 mmol) and Lawesson's reagent (47 mg, 0.12 mmol) in toluene (50 mL) was refluxed for 91 h under nitrogen. Thereafter, the solvent was removed and the residue was purified by column chromatography on silica gel (hexane–EtOAc–MeOH, 1:1:0.3) to give **21** (5 mg, 8%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.01–2.11 (m, 1 H, 4′-CH), 2.44–2.60 (m, 2 H, 5′-CH), 3.15–3.30 (m, 1 H, 4′-CH), 5.12–5.26 (m, 1 H, 3′-CH), 7.06 (d, *J* = 7.5 Hz, 1 H, 6-CH), 7.12 (s, 1 H, 4-CH), 7.65 (d, *J* = 7.5 Hz, 1 H, 7-CH), 9.06 (s, 1 H, Ar-NH_2), 9.49 (s, 1 H, Ar-NH_2), 12.61 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.16, 41.14, 48.88, 105.61, 115.65, 119.70, 125.19, 133.84, 157.72, 167.26, 167.63, 167.75, 210.91.

GC-MS (CI/CH_4): *m*/*z* = 290 $[M + H]^+$, 251, 235, 227, 207, 191, 178, 163.

Anal. Calcd for $C_{13}H_{11}N_3O_3S{\cdot}H_2O$: C, 50.81; H, 4.26; N, 13.67. Found: C, 50.31; H, 3.58; N, 13.24.

2-(2-Oxo-6-thioxo-3-piperidinyl)-5-chloro-1*H*-isoindole-1,3(2*H*)-dione (22)

To a stirred solution of **14** (1.00 g, 3.42 mmol) in pyridine (26 mL) at r.t., was added a solution of Lawesson's reagent (0.76 g, 1.88 mmol) in pyridine (7 mL) under nitrogen. The reaction mixture was refluxed for 47 h. Thereafter, the solvent was removed and the residue was recrystallized from EtOAc to give **22**.

Yield: 0.6 g (56%); yellow crystals; mp 215–217 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.01–2.15 (m, 1 H, 4′-CH), 2.43–2.65 (m, 2 H, 5′-CH), 3.14–3.30 (m, 1 H, 4′- CH), 5.23–5.37 (m, 1 H, 3′-CH), 7.95 (s, 2 H, 6-CH, 7-CH), 8.06 (s, 1 H, 4-CH), 12.89 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.91, 41.06, 49.34, 124.04, 125.59, 130.11, 133.53, 135.08, 140.15, 166.15, 166.49, 167.31, 210.87.

GC-MS (CI/CH_4): *m*/*z* = 309 $[M + H]^+$, 293, 281, 265.

^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.91, 41.06, 49.34, 124.04, 125.59, 130.11, 133.53, 135.08, 140.15, 166.15, 166.49, 167.31, 210.87.

GC-MS (CI/CH_4): *m*/*z* = 309 $[M + H]^+$, 293, 281, 265.

Anal. Calcd for $C_{13}H_9ClN_2O_3S$: C, 50.57; H, 2.94; N, 9.07. Found: C, 50.72; H, 2.87; N, 9.01.

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(18) X-ray crystal data for **23**: Empirical formula: $C_{21}H_{21}O_6P_3S_3$; Colorless; Formula weight: 558.47; Crystal system = triclinic; Space group *P*$\bar{1}$; Unit cell dimensions: *a* = 9.644 (4) Å, *b* = 12.105 (5) Å, *c* = 20.512 (9) Å; *α* = 86.147 (9)°, *β* = 85.609 (8)°, *γ* = 82.504 (9)°; *V* = 2363.2 (18) Å^3; *Z* = 4; *T* = 103 (1) K; F_{000} = 1152; *R*1 = 0.0554, *wR*2 = 0.1595. The supplementary crystallographic data for this structure (CCDC 682848) can be obtained free of charge from the Cambridge Crystallographic Data Centre via the following website: www.ccdc.cam.ac.uk/products/csd/request.

(19) X-ray crystal data for **15**: Empirical formula: $C_{13}H_{10}N_2O_4S$; Yellow; Formula weight: 290.29; Crystal system = monoclinic; Space group $P2_1/c$; Unit cell dimensions: a = 12.677 (7) Å, b = 13.698 (8) Å, c = 7.520 (4) Å; α = 90°, β = 105.474 (11)°, γ = 90°; V = 1258.6 (12) Å^3; Z = 4; T = 293 (2) K; F_{000} = 600; $R1$ = 0.0764, $wR2$ = 0.2009. The supplementary crystallographic data for this structure (CCDC 682849) can be obtained free of charge from the Cambridge Crystallographic Data Centre via the following website: www.ccdc.cam.ac.uk/products/csd/request.

(20) X-ray crystal data for **18**: Empirical formula: $C_{15}H_{12}N_2O_5S$; Yellow; Formula weight: 332.33; Crystal system = triclinic; Space group $P\bar{1}$; Unit cell dimensions: a = 6.8299 (7) Å, b = 7.9952 (9) Å, c = 14.1890 (15) Å; α = 86.247 (5)°, β = 83.849 (5)°, γ = 82.475 (5)°; V = 762.68 (14) Å^3; Z = 2; T = 293 (2) K; F_{000} = 344; $R1$ = 0.0982, $wR2$ = 0.2851. The supplementary crystallographic data for this structure (CCDC 682850) can be obtained free of charge from the Cambridge Crystallographic Data Centre via the following website: www.ccdc.cam.ac.uk/products/csd/request.

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