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Phenylhomophthalimide-type NOS inhibitors derived from thalidomide

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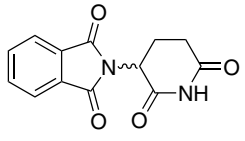
Abstract—Thalidomide shows moderate inhibitory activity toward neuronal nitric oxide synthase (nNOS) and inducible NOS (iNOS), but not toward endothelial NOS (eNOS). Structural development studies of thalidomide yielded novel phenylhomophthalimide-type NOS inhibitors with enhanced activity and different subtype selectivity.

1. Introduction

Nitric oxide (NO) is a biologically important regulator/messenger, which is produced by oxidation of L-arginine catalyzed by nitric oxide synthase (NOS).[1] NOS comprises constitutive NOS (cNOS), which requires Ca^{2+}/calmodulin for its activation, and inducible NOS (iNOS), which is independent of Ca^{2+}/calmodulin, and cNOS has been further divided into neuronal NOS (nNOS) found in the brain, and endothelial NOS (eNOS) found in the vascular endothelium. nNOS has been shown to regulate neuronal transmission and cerebral blood flow, while eNOS is implicated in vascular tone and platelet aggregation.[2,3] Excessive induction of iNOS, which is mainly expressed in activated macrophages, plays a role in the over-production of NO that is associated with inflammatory diseases.[4,5] The classical NOS inhibitors are limited to L-arginine analogs, such as N^G-nitro-L-arginine (NNA),[6] N^G-monomethyl-L-arginine (L-NMMA),[7] and N^G-nitro-L-arginine methyl ester.[8] Some of these compounds have been investigated in clinical trials. Although natural products such as flavonoids,[9] coumarins,[10] and diterpenes,[11] as well as some synthetic oxazolidine derivatives,[12] have been reported to inhibit NOS, there is little structural variation of known NOS inhibitors.

Thalidomide (**1**: Fig. 1) is a sedative/hypnotic drug, which was withdrawn from the market because of its severe teratogenicity.[13,14] In spite of this, research into thalidomide was not halted, and the drug has been established to be effective for the treatment of various diseases, including leprosy, myeloma, AIDS, and others.[15–17] The drug was approved in the United States for the treatment of leprosy in 1998, and clinical studies of its use for the treatment of various cancers, including multiple myeloma, colon cancer, prostate tumor, and breast cancer are on-going. The molecular mechanisms of the multiple pharmacological actions elicited by thalidomide are not clear, but its tumor necrosis factor (TNF)-α production-inhibitory activity has been well documented.[16–18]

We have demonstrated that the TNF-α production-regulating activity of thalidomide is bidirectional, and that thalidomide is a multi-target drug.[16,17,19] We have been engaged in structural development studies of thalidomide, and have obtained TNF-α production regulators (including bi-directional ones and pure inhibitors



1: Thalidomide

Figure 1. Structure of thalidomide (**1**).

Keywords: Thalidomide; NOS inhibitors; Structural development.
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and enhancers),[16,17,20] androgen antagonists,[16,17,20–22] peptidase inhibitors,[16,17,23–25] glucosidase inhibitors,[16,17,26,27] thymidine phosphorylase inhibitors,[28] and cyclooxygenase (COX) inhibitors.[16,17,29] We suspected that NOS is another target molecule of thalidomide, because the drug is effective against various diseases, including diabetes, in which NOS plays an important pathophysiological role. Recently, we have reported that thalidomide shows moderate inhibitory activity toward nNOS.[30] Preliminary structural development studies based on nNOS-inhibiting activity were also reported in the same paper.[30] In this paper, we report the inhibitory activity of thalidomide (**1**) toward the three subtypes of NOS, and the results of structural development studies.

2. Results and discussion

First we investigated the NOS-inhibitory activity of thalidomide (**1**) using commercially available nNOS, iNOS, and eNOS (Cayman Co., Ltd). Inhibitory activity was assayed by monitoring nitrite/nitrate production from L-arginine by NOS, using Ichimori's protocol with slight modifications.[30,31] Although the quantitative values differed from experiment to experiment, the results were basically reproducible. Typical sets of data from inhibitory activity assays of thalidomide and other compounds, as well as L-NMMA, a well-known NOS inhibitor (positive control), at the concentration of 450 μM are presented in Table 1. The concentration was determined so as to the inhibiting efficacy of thalidomide and L-NMMA being in the range of 30–60%.

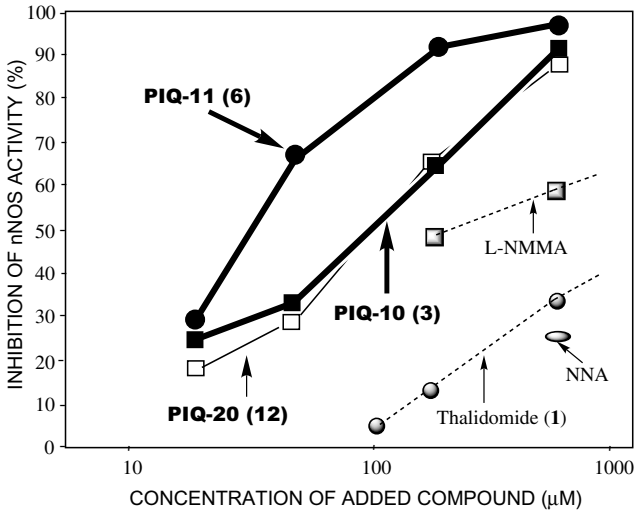
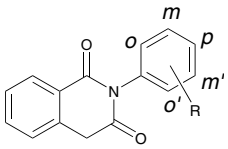


Figure 2. Inhibition of nNOS by PIQ-10 (**3**) and PIQ-11 (**6**).

Thalidomide (**1**) inhibited nNOS and iNOS with moderate potency (32–33% at 450 μM), but not eNOS (Table 1). Though the activity is less potent than that of L-NMMA at the same concentration [but slightly more potent than that of NNA (Fig. 2)], the inhibitory activity of thalidomide (**1**) toward nNOS/iNOS might explain at least some of the versatile pharmacological effects of the drug.

Next we investigated the NOS-inhibitory activity of phenylphthalimide and phenylhomophthalimide deriv-

Table 1. NOS-inhibitory activity of thalidomide (**1**) and phenylhomophthalimide derivatives (**2**–**18**)



Compounds	R	Inhibitory activity at 450 μM (%) and relative activity[a]		
		nNOS	iNOS	eNOS
L-NMMA	—	59 (1.0)[a]	81 (1.4)[a]	22 (0.4)[a]
Thalidomide (**1**)	—	33 (1.0)[a]	32 (1.0)[a]	Inactive (0)[a]
PIQ-00 (**2**)	H	60 (1.0)[a]	42 (0.7)[a]	64 (1.1)[a]
PIQ-10 (**3**)	*o*-CH_3	92 (1.0)[a]	80 (0.9)[a]	77 (0.8)[a]
PIQ-01 (**4**)	*m*-CH_3	79 (1.0)[a]	64 (0.8)[a]	31 (0.4)[a]
PIQ-001 (**5**)	*p*-CH_3	64 (1.0)[a]	49 (0.8)[a]	62 (1.0)[a]
PIQ-11 (**6**)	*o*,*o*′-$(CH_3)_2$	96 (1.0)[a]	77 (0.8)[a]	80 (0.8)[a]
PIQ-0101 (**7**)	*m*,*m*′-$(CH_3)_2$	52 (1.0)[a]	36 (0.6)[a]	55 (1.1)[a]
PIQ-11000 (**8**)	*o*,*m*-$(CH_3)_2$	76 (1.0)[a]	88 (1.2)[a]	58 (0.8)[a]
PIQ-101 (**9**)	*o*,*p*-$(CH_3)_2$	76 (1.0)[a]	88 (1.2)[a]	58 (0.8)[a]
PIQ-1001 (**10**)	*o*,*m*′-$(CH_3)_2$	82 (1.0)[a]	73 (0.8)[a]	50 (0.6)[a]
PIQ-011 (**11**)	*m*,*p*-$(CH_3)_2$	62 (1.0)[a]	10 (0.2)[a]	Inactive (0)[a]
PIQ-20 (**12**)	*o*-C_2H_5	92 (1.0)[a]	84 (0.9)[a]	57 (0.6)[a]
PIQ-02 (**13**)	*m*-C_2H_5	85 (1.0)[a]	57 (0.7)[a]	34 (0.4)[a]
PIQ-002 (**14**)	*p*-C_2H_5	69 (1.0)[a]	61 (0.9)[a]	4 (0.1)[a]
PIQ-30 (**15**)	*o*-$CH(CH_3)_2$	83 (1.0)[a]	69 (0.8)[a]	34 (0.4)[a]
PIQ-03 (**16**)	*m*-$CH(CH_3)_2$	66 (1.0)[a]	50 (0.8)[a]	Inactive (0)[a]
PIQ-003 (**17**)	*p*-$CH(CH_3)_2$	32 (1.0)[a]	26 (0.8)[a]	Inactive (0)[a]
PIQ-004 (**18**)	*p*-$C(CH_3)_3$	26 (1.0)[a]	Inactive (0)[a]	Inactive (0)[a]

[a] Values in parenthesis are the relative activity of each compound when the activity toward nNOS of that compound is defined as 1.0.

atives, which have been chosen as lead compounds based on our previous studies on enzyme inhibitors derived from thalidomide.[16–29] These compounds were prepared by routine organic synthetic methods that is, condensation of appropriate amines with phthalic or homophthalic anhydride. The structures of all the compounds were confirmed by spectroscopic (^{1}H NMR and mass) analysis, and the analytical data were consistent with expectation.[32] Phenylphthalimide derivatives investigated were inactive at the concentration range (up to 1 mM) examined (*data not shown*), but the ring-expanded analogs that is, phenylhomophthalimide derivatives (PIQs), showed NOS-inhibitory activity. Among PIQs examined, some analogs showed more potent activity than L-NMMA at 450 μM, as follows:

i: *Toward nNOS* PIQ-10 (**3**), PIQ-11 (**6**), PIQ-1001 (**10**), PIQ-20 (**12**), PIQ-02 (**13**), and PIQ-30 (**15**) showed potent inhibitory activity toward nNOS (82–96% inhibition), while L-NMMA showed 59% inhibition [dose–response curves for nNOS inhibition with PIQ-10 (**3**), PIQ-11 (**6**), and PIQ-20 (**12**) are shown in Figure 2, as well as data for thalidomide (**1**), L-NMMA and NNA]. These structure–activity relationships are consistent with those we previously reported.[30]

ii: *Toward iNOS* PIQ-11000 (**8**) and PIQ-101 (**9**) inhibited iNOS to the extent of 88%, while L-NMMA showed 81% inhibition.

iii: *Toward eNOS* PIQ-10 (**3**) and PIQ-11 (**6**) showed 77–80% inhibition of eNOS, while L-NMMA gave only 22% inhibition.

The most potent and the second most potent inhibitors among the examined compounds for each subtype of NOS are: PIQ-11 (**6**) (96%) and PIQ-10 (**3**)/PIQ-20 (**12**) (92%) for nNOS, PIQ-11000 (**8**)/PIQ-101 (**9**) (88%) and PIQ-20 (**12**) (84%) for iNOS, and PIQ-11 (**6**) (80%) and PIQ-10 (**3**) (77%) for eNOS. All of these potent inhibitors possess an *ortho*-substituent of the *N*-phenyl moiety in common, suggesting that introduction of an alkyl group at the *ortho*-position on the *N*-phenyl moiety is critical for potent activity. The activity of regio-isomers of mono-alkylated analogs decreased in the order of *ortho*-isomer > *meta*-isomer > *para*-isomer [e.g., the mono-methyl analogs: **3** > **4** > **5**, with the exception of eNOS. Mono-ethyl analogs: **12** > **13** > **14**. Mono-*iso*-propyl analogs: **15** > **16** > **17** (in the case of eNOS, **16** and **17** are inactive)]. Among the mono-*ortho*-substituted analogs, a rather small alkyl group (a methyl or an ethyl group) seems to be superior for potent activity [e.g., methyl (**3**) = ethyl (**12**) > *iso*-propyl (**15**) for nNOS, **12** > **3** > **15** for iNOS, and **3** > **12** > **15** for eNOS]. Similar tendencies were observed for *meta*- and *para*-substituted analogs.

Introduction of an alkyl group larger than an ethyl group at the *para*-position of the *N*-phenyl moiety seems to decrease the inhibitory activity of the compounds toward all of the NOS subtypes; for example, PIQ-004 (**18**: inactive toward iNOS and eNOS), PIQ-003 (**17**: inactive toward eNOS) and PIQ-002 (**14**: almost inactive toward eNOS). Concerning this activity-decreasing effect of a *para*-substituent, the sensitivity of the enzymes seems to decrease in the order of eNOS > iNOS > nNOS. Consequently, *para*-substituted analogs, PIQ-002 (**14**), PIQ-003 (**17**), and PIQ-004 (**18**) inhibit NOSs with the following decreasing order of potency: nNOS > iNOS > eNOS. A similar, but less marked, tendency was observed for *meta*-substituted analogs. The different sensitivities of the NOS subtypes to substituents resulted in the appearance of NOS-subtype selectivity. The selectivity indices (values in parenthesis in Table 1, defined as the relative inhibitory activity compared with that toward nNOS for each compound) of the majority of the PIQs fall into the range of 0.6–1.2 that is, almost nonselective. Some PIQs, especially those with *meta*- and/or *para*-substituent(s), showed selectivity indices of less than 0.4 for iNOS and/or eNOS [e.g., (i) the *meta*,*para*-dimethyl analog (PIQ-011: **11**) showed a selectivity index of 0.2 for iNOS and was inactive toward eNOS, so it is nNOS-selective, (ii) the *para*-*tert*-butyl analog (PIQ-004: **18**) is an nNOS-selective inhibitor, though it is less potent than thalidomide (**1**), (iii) the *meta*- and *para*-*iso*-propyl analogs (PIQ-03: **16** and PIQ-003: **17**) are inactive toward eNOS, and the *meta*-methyl, *meta*-ethyl, and *para*-ethyl analogs (PIQ-01: **4**, PIQ-02: **13** and PIQ-002: **14**) showed selectivity indices of 0.4, 0.4, and 0.1, respectively, for eNOS, so these five compounds are nNOS/iNOS-selective inhibitors]. The *ortho*-*iso*-propyl analog (PIQ-30: **15**) also seems to be slightly selective for nNOS/iNOS.

In conclusion, thalidomide was found to inhibit nNOS and iNOS, but not eNOS, which might in part explain the multiple pharmacological effects elicited by the drug. Some potent phenylhomophthalimide-type NOS inhibitors with higher potency than L-NMMA and with some degree of NOS-subtype selectivity were derived from thalidomide, and their structure–activity relationships were partly interpreted. Further structural development studies aiming at inhibitors with higher potency and selectivity are in progress.

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32. 2-Phenyl-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-00: **2**): mp 187–188 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.25 (d, $J = 7.7$ Hz, 1H), 7.65 (t, $J = 7.7$ Hz, 1H), 7.49 (m, 5H), 7.36 (t, $J = 7.7$ Hz, 1H), 7.21 (d, $J = 7.7$ Hz, 1H), 4.24 (s, 2H).
2-(2-Methylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-10: **3**): mp 107–108 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.26 (d, $J = 7.7$ Hz, 1H), 7.66 (t, $J = 7.7$ Hz, 1H), 7.49 (t, $J = 7.7$ Hz, 1H), 7.31–7.37 (m, 4H), 7.10 (d, $J = 7.7$ Hz, 1H), 4.24 (s, 2H), 2.14 (s, 3H).
2-(3-Methylphenyl)-1,2,3,4-tetrahydroisoquinolin-1,3-dione (PIQ-01: **4**): mp 175–178 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.22 (d, $J = 7.7$ Hz, 1H), 7.62 (t, $J = 7.7$ Hz, 1H), 7.46 (t, $J = 7.7$ Hz, 1H), 7.38 (t, $J = 7.7$ Hz, 1H), 7.33 (d, $J = 7.7$ Hz, 1H), 7.32 (s, 1H), 7.24 (d, $J = 7.7$ Hz, 2H), 4.19 (s, 2H), 2.39 (s, 3H).
2-(4-Methylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-001: **5**): mp 174–175 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.25 (d, $J = 7.7$ Hz, 1H), 7.64 (t, $J = 7.7$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 1H), 7.34 (d, $J = 7.7$ Hz, 1H), 7.31 (d, $J = 8.1$ Hz, 2H), 7.09 (d, $J = 8.1$ Hz, 2H), 4.21 (s, 2H), 2.41 (s, 3H).
2-(2,6-Dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-11: **6**): mp 129–130.4 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.27 (d, $J = 7.7$ Hz, 1H), 7.67 (t, $J = 7.7$ Hz, 1H), 7.49 (t, $J = 7.7$ Hz, 1H), 7.38 (d, $J = 7.7$ Hz, 1H), 7.25 (t, $J = 7.3$ Hz, 1H), 7.18 (d, $J = 7.3$ Hz, 2H), 4.25 (s, 2H), 2.10 (s, 6H).
2-(3,5-Dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-0101: **7**): mp 129–130 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.24 (d, $J = 7.7$ Hz, 1H), 7.63 (t, $J = 7.7$ Hz, 1H), 7.47 (t, $J = 7.7$ Hz, 1H), 7.34 (d, $J = 7.7$ Hz, 1H), 7.07 (s, 1H), 6.82 (s, 2H), 4.21 (s, 2H), 2.36 (s, 6H).
2-(2,3-Dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-11000: **8**): mp 145–146 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.25 (d, $J = 7.7$ Hz, 1H), 7.65 (t, $J = 7.7$ Hz, 1H), 7.49 (t, $J = 7.7$ Hz, 1H), 7.36 (d, $J = 7.7$ Hz, 1H), 7.20–7.24 (m, 2H), 6.95 (d, $J = 7.0$ Hz, 1H), 4.24 (s, 2H), 2.35 (s, 3H), 2.02 (s, 3H).
2-(2,4-Dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-101: **9**): mp 170.5–171 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.25 (d, $J = 7.7$ Hz, 1H), 7.65 (t, $J = 7.7$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 1H), 7.36 (d, $J = 7.7$ Hz, 1H), 7.17 (m, 1H), 7.16 (d, $J = 7.9$ Hz, 1H), 6.98 (d, $J = 7.9$ Hz, 1H), 4.23 (s, 2H), 2.37 (s, 3H), 2.09 (s, 3H).
2-(2,5-Dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-1001: **10**): mp 125–126 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.25 (d, $J = 7.7$ Hz, 1H), 7.65 (t, $J = 7.7$ Hz, 1H), 7.49 (t, $J = 7.7$ Hz, 1H), 7.36 (d, $J = 7.7$ Hz, 1H), 7.24 (d, $J = 7.7$ Hz, 1H), 7.16 (d, $J = 7.7$ Hz, 1H), 6.92 (t, $J = 7.7$ Hz, 1H), 4.23 (s, 2H), 2.35 (s, 3H), 2.08 (s, 3H).
2-(3,4-Dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-011: **11**): mp 105–107 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.25 (d, $J = 7.7$ Hz, 1H), 7.63 (t, $J = 7.7$ Hz, 1H), 7.47 (t, $J = 7.7$ Hz, 1H), 7.34 (d, $J = 7.7$ Hz, 1H), 7.27 (d, $J = 8.1$ Hz, 1H), 6.97 (s, 1H), 6.94 (d, $J = 8.1$ Hz, 1H), 4.21 (s, 2H), 2.31 (s, 3H), 2.29 (s, 3H).
2-(2-Ethylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-20: **12**): mp 123–124 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.25 (d, $J = 7.7$ Hz, 1H), 7.66 (t, $J = 7.7$ Hz, 1H), 7.49 (t, $J = 7.7$ Hz, 1H), 7.41–7.42 (m, 2H), 7.37 (d, $J = 7.7$ Hz, 1H), 7.31–7.35 (m, 2H), 4.24 (s, 2H), 2.45 (q, $J = 7.6$ Hz, 2H), 1.16 (t, $J = 7.6$ Hz, 3H).
2-(3-Ethylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-02: **13**): mp 76.5–78 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.25 (d, $J = 7.7$ Hz, 1H), 7.64 (t, $J = 7.7$ Hz, 1H), 7.42 (t, $J = 7.7$ Hz, 1H), 7.35 (d, $J = 7.7$ Hz, 1H), 7.30 (s, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.06 (t, $J = 8.0$ Hz), 7.03 (d, $J = 8.0$ Hz, 1H), 4.23 (s, 2H), 2.72 (q, $J = 8.0$ Hz, 2H), 1.17 (t, $J = 8.0$ Hz, 3H).
2-(4-Ethylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-002: **14**): mp 139–140 °C. ^{1}H NMR (500 MHz,

$CDCl_3/\delta$): 8.25 (d, $J = 7.7$ Hz, 1H), 7.64 (t, $J = 7.7$ Hz, 1H), 7.48 (d, $J = 7.7$ Hz, 1H), 7.35 (d, $J = 7.7$ Hz, 1H), 7.31 (d, $J = 8.1$ Hz, 2H), 7.12 (d, $J = 8.1$ Hz, 2H), 4.22 (s, 2H), 2.72 (q, $J = 7.6$ Hz, 2H), 1.28 (t, $J = 7.6$ Hz, 3H).

2-(2-Isopropylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-30: **15**): mp 158–160 °C. ^{1} H NMR (500 MHz, $CDCl_3/\delta$): 8.26 (d, $J = 7.7$ Hz, 1H), 7.66 (t, $J = 7.7$ Hz, 1H), 7.50 (t, $J = 7.7$ Hz, 1H), 7.42–7.48 (m, 1H), 7.37 (d, $J = 7.7$ Hz, 1H), 7.26–7.33 (m, 3H), 4.24 (s, 2H), 2.70 (m, 1H), 1.17 (d, $J = 6.9$ Hz, 6H).

2-(3-Isopropylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-03: **16**): mp 98–100 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.25 (d, $J = 7.7$ Hz, 1H), 7.64 (t, $J = 7.7$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 1H), 7.43 (d, $J = 7.7$ Hz, 1H), 7.33 (m, 2H), 7.06 (s 1H), 7.02 (d, $J = 7.7$ Hz, 1H), 4.22 (s, 2H), 2.96 (m, 1H), 1.28 (d, $J = 6.9$ Hz, 6H).

2-(4-Isopropylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (PIQ-003: **17**): mp 170–172 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.25 (d, $J = 7.7$ Hz, 1H), 7.64 (t, $J = 7.7$ Hz, 1H), 7.47 (t, $J = 7.7$ Hz, 1H), 7.36 (d, $J = 7.7$ Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 2H), 7.12 (d, $J = 8.1$ Hz, 2H), 4.23 (s, 2H), 2.97 (m, 1H), 1.29 (d, $J = 6.9$ Hz, 6H).

2-(4-*tert*-Butylphenyl)-1,2,3,4-tetrahydroisoquinolin-1,3-dione (PIQ-004: **18**): mp 170–173 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 8.25 (d, $J = 7.7$ Hz, 1H), 7.64 (t, $J = 7.7$ Hz, 1H), 7.52 (t, $J = 7.7$ Hz, 1H), 7.48 (d, $J = 7.7$ Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 2H), 7.13 (d, $J = 8.1$ Hz, 2H), 4.23 (s, 2H), 1.39 (s, 9H).