Phenylphthalimides with Tumor Necrosis Factor Alpha Production-Enhancing Activity

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Phenylphthalimides (2-phenyl-1*H*-isoindole-1,3-diones) were prepared and their effects on tumor necrosis factor alpha (TNF-α) production by human leukemia cell line HL-60 stimulated with 12-*O*-tetradecanoylphorbol-13-acetate (TPA) were examined. An analysis of the structure-activity relationships of the phenylphthalimides indicated that potent enhancing activity on TPA-induced TNF-α production by HL-60 cells requires medium-sized substituent(s) at the *ortho* position(s) of the phenyl group; 2-(2,6-diisopropylphenyl)-1*H*-isoindole-1,3-dione (PP-33) increased the TNF-α production to more than 600% at the concentration of 1×10^{-5} M. Introduction of a nitro group at the phthalimide moiety of PP-33 enhanced the activity; 2-(2,6-diisopropylphenyl)-4-nitro-1*H*-isoindole-1,3-dione (4NPP-33) and its 5-nitro isomer (5NPP-33) enhanced the TNF-α production to more than 800% and 700%, respectively, at the concentration of 1×10^{-5} M. Introduction of fluorines into the phthalimide moiety of PP-33 greatly lowered the concentration of the compound necessary to elicit the TNF-α production-enhancing activity; 2-(2,6-diisopropylphenyl)-4,5,6,7-tetrafluoro-1*H*-isoindole-1,3-dione (FPP-33) showed the activity at nanomolar concentration, with the optimum concentration of 1×10^{-7} M.

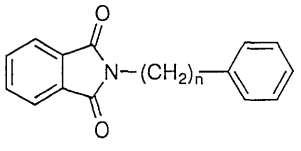
Key words tumor necrosis factor alpha; phenylphthalimide; structure–activity relationship

Tumor necrosis factor alpha (TNF-α), an important cytokine secreted mainly by activated monocyte/macrophages, was originally identified as an endotoxin-induced serum factor that causes hemorrhagic necrosis of transplanted solid tumors.[1] Because TNF-α exhibits striking cytotoxicity selectively against various tumor cells, it has attracted attention as a potential anti-tumor drug.[2] Phase I studies of recombinant TNF-α for the treatment of tumors and a successful application of host cells transduced with TNF-α gene to treat melanoma have been reported.[3–6]

Investigation of the biological effects elicited by TNF-α has revealed that it is a pleiotropic cytokine with numerous effects on mammalian cells, and its actions are initiated by binding to high-affinity receptors.[7] Though TNF-α plays a critical role in certain physiological immune systems, it causes severe damage to the host when produced in excess.[8] Therefore, TNF-α can be regarded as possessing both favorable and unfavorable effects. The favorable effects include direct tumor-killing activity,[1,9] stimulation of the host immune system,[9] and action as a growth factor of normal B-cells.[10] The unfavorable effects include induction of endotoxic shock and tissue inflammation,[11] tumor-promoting action, as well as stimulation of tumor metastasis and angiogenesis,[12,13] and stimulation of human immunodeficiency virus (HIV) replication.[14] These pleiotropic effects of TNF-α indicate that TNF-α production-enhancers in some cases and production-inhibitors in other cases would be useful as biological response modifiers (BRMs) in various circumstances.[15] Moreover, tissue and/or cell type-specific regulators of TNF-α production would be useful,[16–19] because TNF-α is rapidly cleared from the circulation.[5,20]

A possible lead compound for the above purpose is *N*(α)-phthalimidoglutarimide (thalidomide), which had been used as a hypnotic/sedative agent but was withdrawn from the market because of its teratogenicity.[16–19,21] Thalidomide is an inhibitor of TNF-α production,[14,22] and this effect has been shown to be useful for the treatment of graft-*versus*-host disease (GVHD), leprosy, Behcet's disease, lupus erythematosus, malaria, acquired immunodeficiency syndrome (AIDS), and other related diseases.[14,16,23–26] Recently, we found that the effect of thalidomide on TNF-α production is cell type-specific; *i.e.*, thalidomide inhibits TNF-α production by human peripheral macrophages stimulated with 12-*O*-tetradecanoylphorbol-13-acetate (TPA), while it enhances TNF-α production by human leukemia cell lines such as HL-60, U937 and K562.[16,27] Based on this finding, we have been engaged in structural modification of thalidomide with the aim of finding superior regulators of TNF-α production.[15,28–31] For the evaluation of the compounds obtained, TNF-α production-enhancing activity was assayed using HL-60 cells stimulated with TPA.[27–31] Our studies on structural simplification of the glutarimide moiety of thalidomide afforded alkylphthalimides which possess higher TNF-α production-enhancing activity than thalidomide; *i.e.*, adamantyl-, *tert*-butyl-, and cyclohexyl-phthalimides.[29]

Against this background, we have synthesized a series of new compounds with strong TNF-α production-enhancing activity.[15,30,31] The structure of the mother skeleton is represented in Fig. 1, where $n=0$—3. As previously reported, 2-phenyl-1*H*-isoindole-1,3-dione ($n=0$, PP-00) is inactive, the 2-benzyl analog ($n=1$, P1P-00) is weakly active, and the 2-phenethyl ($n=2$, P2P-00) and 2-phenylpropyl analogs ($n=3$, P3P-00) are active.[30] Though PP-00 is inactive, we found that intro-



n = 0 : PP - 00
n = 1 : P1P-00
n = 2 : P2P-00
n = 3 : P3P-00

Fig. 1. Mother Skeleton of Phthalimides with TNF-α Production-Enhancing Activity

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duction of a substituent(s) such as methyl and/or isopropyl groups into the phenyl moiety resulted in the appearance of a potent TNF-α production-enhancing activity.[15,31] This paper describes the TNF-α production-enhancing activity of the phenylphthalimide series ($n=0$) of compounds, laying emphasis on structure–activity relationships.

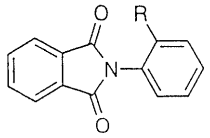
Results and Discussion

Assay System In this paper, structure–activity relationships are discussed on the basis of the TNF-α production-enhancing activity of the compounds in TPA-stimulated HL-60 cells. The HL-60 cells used produce no detectable amount of TNF-α under the usual culture conditions, but begin to produce TNF-α after treatment with TPA. The induction of TNF-α production by TPA was dose-dependent, and we chose a TPA concentration of 3 nM, because the effects of the test compounds were clearly apparent at this concentration. The amount of TNF-α produced by HL-60 cells under our standard experimental conditions (5×10^5 cells/ml, incubated in the presence of 3 nM TPA for 16 h) was 150—180 pg/ml, and the value separately determined in each set of experiments was taken as 100%. The effect of each test compound was represented as the amount (%) of TNF-α produced by HL-60 cells in the co-presence of 3 nM TPA and the test compound. The assay was performed at least in duplicate (the mean value is shown) and at least three times. The results were basically reproducible, and a typical set of data obtained at the same time is presented in each table. None of the phenylphthalimide analogs described in this paper induced TNF-α production by themselves in the concentration range investigated. Cell numbers were counted at the time when the amount of TNF-α was measured. Almost no difference in the cell numbers between incubation mixtures in the presence and absence of the test compound was observed in the concentration range investigated, unless described as "(−)" in Table 5.

Effects of *Ortho* Substituent First we investigated the effects of *ortho*-substituted phenylphthalimides on TPA-induced TNF-α production by HL-60 cells. The results are shown in Table 1. As previously reported,[29–31] PP-00 is inactive, but introduction of an alkyl group at the *ortho* position of the phenyl moiety causes the appearance of the TNF-α production-enhancing activity. In a series of *n*-alkyl-substituted compounds, the activity increased in the order of H (PP-00) ≅ Me (PP-10) < Et (PP-20) < *n*-Pr (PP-n30) < *n*-Bu (PP-n40). The increase of TNF-α production-enhancing activity in this series of compounds seems to be saturated at PP-n40, *i.e.*, compounds with a longer *n*-alkyl chain, such as *n*-C_5H_{11} (PP-n50), *n*-C_6H_{13} (PP-n60) and *n*-C_7H_{15} (PP-n70), do not show higher activity than PP-n40.

Comparison of the activity of an *n*-alkyl-substituted compound with that of the corresponding branching alkyl-substituted compound indicates that the alkyl group introduced at the *ortho*-position should be spherical; *i.e.*, the activity of PP-30 is higher than that of PP-n30, and PP-40 is more active than PP-n40. In the series of branching alkyl-substituted compounds, the activity increased in the order of Et (PP-20) < iso-Pr (PP-30) < *tert*-Bu (PP-40) ≅ adamantyl (PP-80). The activity of this series of compounds seems to be saturated at PP-40. This suggests that the maximum TNF-α production-enhancing activity shown by *ortho*-monoalkylphenylphthalimides is approximately 200%.

Table 1. Effects of *Ortho*-Substituted Phenylphthalimides on TNF-α Production by HL-60 Cells



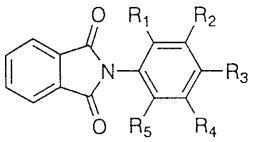
	R	TNF-α(%)[a]
None[a]	—	100
PP-00	H	95
PP-10	CH_3	102
PP-20	C_2H_5	116
PP-30	$CH(CH_3)_2$	168
PP-40	$C(CH_3)_3$	204
PP-80	Adamantyl	197
PP-V0	OCH_3	96
PP-S0	SCH_3	103
PP-n30	$(CH_2)_2CH_3$	143
PP-n40	$(CH_2)_3CH_3$	164
PP-n50	$(CH_2)_4CH_3$	159
PP-n60	$(CH_2)_5CH_3$	141
PP-n70	$(CH_2)_6CH_3$	152
PP-Pe0	$(CH_2)_2C_6H_5$	151
PP-Hm0	$(CH_2)C_6H_{11}$	190
PP-Da0	$N(CH_3)_2$	95
PP-N0	NO_2	89

a) The amount of TNF-α produced in the presence of 3 nM TPA alone (168 pg/ml) was defined as 100%. The test compounds were added at the concentration of 1×10^{-5} M.

Introduction of an electron-donating group such as MeO (PP-V0), MeS (PP-S0) and $N(Me)_2$ (PP-Da0) does not cause appearance of the activity. Introduction of an electron-withdrawing nitro group (PP-N0) seems to make the compound a TNF-α production inhibitor. Though 1×10^5 M PP-N0 reduced the amount of TNF-α produced by HL-60 cells to 89% (Table 1) without reducing the number of cells (counted at the time when the amount of TNF-α in the culture medium was measured), higher concentrations ($>5\times10^5$ M) of PP-N0 were toxic and showed cell-killing activity. Therefore, the reduction of the amount of TNF-α caused by the treatment with the low concentration of PP-N0 might be attributed to toxicity, even though this was not apparent as a reduction of the cell number.

Alkylated Phenylphthalimides The TNF-α production-enhancing activity of *ortho*-monoalkylated phenylphthalimides appeared not to exceed 200%. Therefore, we investigated the compounds with two alkyl groups (Table 2 and Fig. 2). As previously reported, *o,o'*-dimethylation (PP-11) caused appearance of the activity.[29] The *ortho* positions seems to be the best positions at which to introduce two methyl groups for potent activity; *i.e.*, PP-11 was more active than the *m,m'*-dimethylated analog, PP-0101, though the latter was moderately active. Effects of dimethylation at two *ortho* positions and at two *meta* positions were not additive, because the activity of PP-

Table 2. Effects of Alkylated Phenylphthalimides on TNF-α Production by HL-60 Cells



	R_1	R_2	R_3	R_4	R_5	TNF-α (%)[a]
None[a]	—	—	—	—	—	100
PP-00	H	H	H	H	H	102
PP-10	CH_3	H	H	H	H	104
PP-11	CH_3	H	H	H	CH_3	170
PP-0101	H	CH_3	H	CH_3	H	145
PP-11011	CH_3	CH_3	H	CH_3	CH_3	166
PP-20	C_2H_5	H	H	H	H	125
PP-21	C_2H_5	H	H	H	CH_3	192
PP-22	C_2H_5	H	H	H	C_2H_5	478
PP-30	$CH(CH_3)_2$	H	H	H	H	163
PP-31	$CH(CH_3)_2$	H	H	H	CH_3	597
PP-33	$CH(CH_3)_2$	H	H	H	$CH(CH_3)_2$	648
PP-40	$C(CH_3)_3$	H	H	H	H	207
PP-0404	H	$C(CH_3)_3$	H	$C(CH_3)_3$	H	309
PP-4004	$C(CH_3)_3$	H	H	$C(CH_3)_3$	H	128
PP-80	Adamantyl	H	H	H	H	196
PP-008	H	H	Adamantyl	H	H	292

a) The amount of TNF-α produced in the presence of 3 nM TPA alone (155 pg/ml) was defined as 100%. The test compounds were added at the concentration of 1×10^{-5} M.

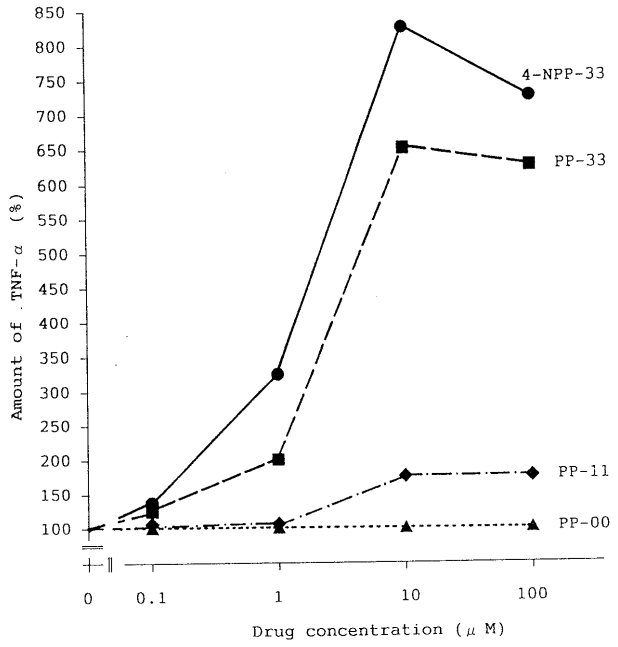


Fig. 2. Dose-Dependency Curves of PP-00, -11, -33, 4NPP-33

11011 was not higher than that of PP-11.

As was the case in the *ortho*-monoalkylated compounds (Table 1), the bulkiness of the two alkyl groups introduced seems to be critical. The activity-enhancing nature of the second alkyl group increased in the order of Me < Et < iso-Pr; *i.e.*, the TNF-α production-enhancing activity of 2-ethyl- and 2-isopropyl-6-alkylphenylphthalimides increased in the orders of [PP-20 < PP-21 < PP-22] and [PP-30 < PP-31 < PP-33], respectively. Of course, PP-31 is far more active than PP-11, and PP-21 is moderately active. PP-33 itself possesses very potent TNF-α production-enhancing activity amounting to more than 600% at 1×10^5 M. Dose-dependency curves are shown in Fig. 2.

It is curious that the *para*-adamantylphenylphthalimide (PP-008) has higher activity than the corresponding *ortho* isomer, PP-80. The former might be related not to phenylphthalimide but to another active mother skeleton, phenethylphthalimide (P2P-00, Fig. 1).[30]

Effects of Substituents on the Phthalimide Moiety Next we investigated the effects of substituents introduced at the phthalimide moiety (Table 3). To clarify the substituent effects precisely, each substituent was introduced into three typical phenylphthalimides, PP-00, PP-11 and PP-33. As shown in the table, introduction of an electron-donating group such as a hydroxy or an amino group lowered the activity. The effects elicited by introduction of these two groups are similar. In both cases, the 4-substituted analogs (4HPPs, 4APPs) show higher activity than the corresponding 5-substituted analogs (5HPPs, 5APPs). It is curious that in the case of 2,6-dimethylphenylphthalimides, amino-containing analogs (4APP-11, 5APP-11) show weaker TNF-α production-enhancing activity than the corresponding hydroxy-containing analogs (4HPP-11, 5HPP-11, respectively), while the relationship is reversed in the case of 2,6-diisopropylphenylphthalimides (4APP-33 > 4HPP-33, and 5APP-33 > 5HPP-33).

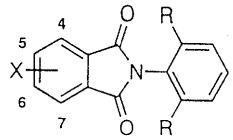
In contrast to the introduction of an electron-donating group, introduction of a nitro group dramatically increased the activity. Introduction of a nitro group into inactive PP-00 caused appearance of the activity (4NPP-00, 5NPP-00), and nitrated PP-11 (4NPP-11, 5NPP-11) and nitrated PP-33 (4NPP-33, 5NPP-33) showed very high activity. In these cases also, the TNF-α production-enhancing activity of 4-nitro analogs was higher than that of the corresponding 5-nitro analogs. The TNF-α production-enhancing effect (more than 800%) shown by 4NPP-33 (1×10^{-5} M) is the largest among the com-

pounds described in this paper. The dose-dependency curve is shown in Fig. 2.

Effects of Halogenation Effects of halogenation at the two *ortho*-positions of the phenyl moiety were investigated in 2,6-dialkylphenylphthalimides (Table 4). The TNF-α production-enhancing activity of 2,6-dihalo-phenylphthalimides decreased in the order of PP-BB > PP-CC > PP-FF, the same order as that of the size (bulkiness) of the halogen substituents.

Effects of halogenation at the phthalimide moiety were also investigated (Table 5). Interestingly, introduction of four fluorines into the phthalimide moiety (FPPs) greatly lowered the concentration of the compound which is necessary to elicit TNF-α production-enhancing activity (Fig. 3). In both FPPs and CPPs, as well as other series of compounds, the same order of the activity, that is, 2,6-diisopropyl analogs > 2,6-dimethyl analogs ≫ non-substituted analogs, is generally found. FPP-33 is the most potent compound known, if the activity is compared at 1×10^{-7} M,[15] but its activity in terms of the amount of TNF-α produced is not high. However, it might be a very specific TNF-α production enhancer, because its activity was apparent at extremely low concentrations (order of nM).[15]

Table 3. Effects of Substituents Introduced into the Phthalimide Moiety on TNF-α Production-Enhancing Activity



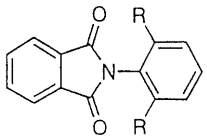
	X	R	TNF-α (%)[a]
None[a]	—	—	100
PP-00	H	H	104
PP-11	H	CH_3	168
PP-33	H	$CH(CH_3)_2$	662
4HPP-00	4-OH	H	102
4HPP-11	4-OH	CH_3	153
4HPP-33	4-OH	$CH(CH_3)_2$	289
5HPP-00	5-OH	H	104
5HPP-11	5-OH	CH_3	145
5HPP-33	5-OH	$CH(CH_3)_2$	211
4APP-00	4-NH_2	H	103
4APP-11	4-NH_2	CH_3	137
4APP-33	4-NH_2	$CH(CH_3)_2$	299
5APP-00	5-NH_2	H	108
5APP-11	5-NH_2	CH_3	131
5APP-33	5-NH_2	$CH(CH_3)_2$	278
4NPP-00	4-NO_2	H	188
4NPP-11	4-NO_2	CH_3	321
4NPP-33	4-NO_2	$CH(CH_3)_2$	831
5NPP-00	5-NO_2	H	189
5NPP-11	5-NO_2	CH_3	280
5NPP-33	5-NO_2	$CH(CH_3)_2$	728

a) The amount of TNF-α produced in the presence of 3 nM TPA alone (172 pg/ml) was defined as 100%.

Conclusion

TNF-α production-enhancing activity of phenylphthalimides and its structure–activity relationships were investigated. The structural requirement for the activity is a medium-sized hydrophobic alkyl group(s) at the *ortho* position(s) of the phenyl moiety. A typical TNF-α pro-

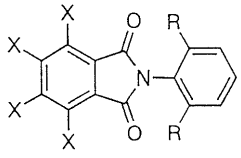
Table 4. Effects of *o,o'*-Disubstituted Phenylphthalimides on TNF-α Production by HL-60 Cells



	R	TNF-α (%)[a]
None[a]	—	100
PP-00	H	104
PP-11	CH_3	175
PP-22	C_2H_5	442
PP-33	$CH(CH_3)_2$	650
PP-FF	F	176
PP-CC	Cl	267
PP-BB	Br	342

a) The amount of TNF-α produced in the presence of 3 nM TPA alone (150 pg/ml) was defined as 100%. The test compounds were added at the concentration of 1×10^{-5} M.

Table 5. Effects of Halogenation of the Phthalimide Moiety on TNF-α Production-Enhancing Activity



	X	R	TNF-α (%)[a]				
			1×10^{-9} M	1×10^{-8} M	1×10^{-7} M	1×10^{-6} M	1×10^{-5} M
None	—	—	100	100	100	100	100
PP-33	H	$CH(CH_3)_2$	101	97	123	195	653
CPP-00	Cl	H	100	93	106	101	133
CPP-11	Cl	CH_3	98	107	108	130	(−)[b]
CPP-33	Cl	$CH(CH_3)_2$	25	99	109	151	270
FPP-00	F	H	103	110	115	(−)[b]	(−)[b]
FPP-11	F	CH_3	97	107	167	(−)[b]	(−)[b]
FPP-33	F	$CH(CH_3)_2$	114	150	347	(−)[b]	(−)[b]

a) The amount of TNF-α produced in the presence of 3 nM TPA alone (165 pg/ml) was defined as 100%. The test compounds were added at the concentrations shown in the table. *b*) Cell number was dramatically decreased, probably because of toxicity of the added compound.

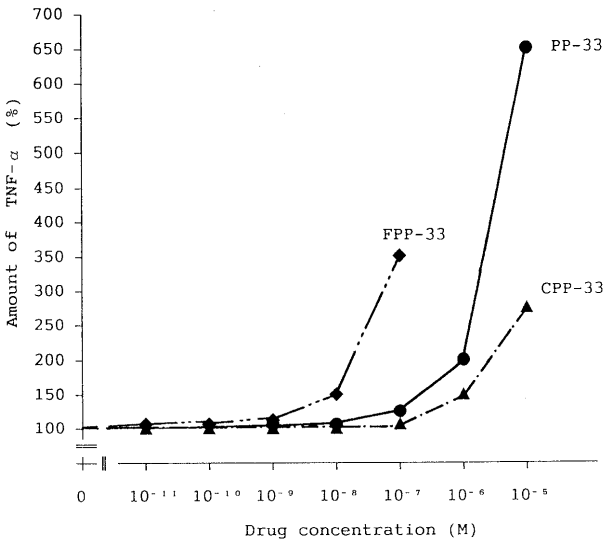


Fig. 3. Dose-Dependency Curves of PP-33, FPP-33, CPP-33

duction enhancer is PP-33. Introduction of an electron-withdrawing group, such as a nitro group, into the phthalimide moiety enhanced the activity. Substitution of the four hydrogen atoms at the phthalimide moiety of PP-33 with fluorine atoms, *i.e.*, FPP-33, greatly decreased the concentration which is necessary to elicit TNF-α production-enhancing activity. FPP-33 apparently shows the activity at concentrations of the order of 10^{-8} M. The effectiveness of this compound at such a low concentration, as well as the well-defined structure–activity relationship concerning the substituents at the two *ortho* positions of the phenyl moiety, suggests that there is a specific target molecule(s) of phthalimide-type TNF-α production enhancers. Our phthalimides, especially PP-33 and FPP-33, should be useful as tools to investigate TNF-α production-regulatory mechanisms, and they also represent lead compounds for the development of superior thalidomidal BRMs targeting TNF-α.

Experimental

TNF-α Assay The human leukemia cells HL-60 were cultured in RPMI1640 medium supplemented with 5% v/v fetal bovine serum (FBS) in a humidified atmosphere of 5% CO_2 in air at 37 °C. The exponentially growing cells in RPMI1640 medium supplemented with 10% v/v FBS (5×10^5 cells/ml) were treated with TPA (3 nM) in the presence or absence of a sample compound (at the concentration indicated in the tables and figures) for 16 h at 37 °C, using multidish-plate with 24-wells (0.5 ml of cell suspension per well was incubated). Then the number of cells was counted, morphologically checked under a microscope, and the cells were precipitated by centrifugation (1000 rpm × 10 min). The amount of TNF-α in the medium (supernatant) was measured by the use of a human TNF-α ELISA system (Amersham Co.) according to the supplier's protocol. TNF-α production by HL-60 cells was TPA-dependent, and the amount of TNF-α produced in the presence of 3 nM TPA alone (120—180 pg/ml, presented in the tables) was taken as 100%.

Chemicals Compounds were prepared by condensation of phthalic anhydride (or its derivatives) with appropriate amines in good yields.

PP-00 White needles (EtOH). mp 209—211 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.96 (2H, m), 7.80 (2H, m), 7.52 (2H, m), 7.43 (3H, m). *Anal.* Calcd for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.22; H, 4.16; N, 6.55.

PP-10 White powder (AcOEt–hexane). mp 180 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.99 (2H, m), 7.83 (2H, m), 7.40 (2H, m), 7.35 (1H, m), 7.23 (1H, d, J=5.9 Hz), 2.24 (3H, s). *Anal.* Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.03; H, 4.72; N, 5.86.

PP-20 Colorless needles (EtOH). mp 132—133 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.62—8.10 (4H, m), 6.96—7.50 (4H, m), 2.52 (2H, q, J=8.0 Hz), 1.18 (3H, t, J=8.0 Hz). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.65; H, 5.26; N, 5.54.

PP-30 Colorless needles (EtOH). mp 183 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.63—8.14 (4H, m), 6.92—7.60 (4H, m), 2.81 (1H, hep, J=6.6 Hz), 1.23 (6H, d, J=6.6 Hz). *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.07; H, 5.85; N, 5.30.

PP-40 Colorless needles (EtOH). mp 123 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.63—8.04 (4H, m), 6.83—7.63 (4H, m), 1.33 (9H, s). *Anal.* Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.50; H, 6.31; N, 5.00.

PP-80 Colorless prisms (CH_2Cl_2–hexane). mp 177 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.95—7.99 (2H, m), 7.78—7.83 (2H, m), 7.65 (1H, dd, J=7.63, 1.14 Hz), 7.45 (1H, dt, J=1.14, 7.63 Hz), 7.30 (1H, dt, J=1.14, 7.63 Hz), 6.95 (1H, dd, J=7.63, 1.14 Hz), 1.86—2.00 (9H, m), 1.59—1.64 (6H, m). *Anal.* Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.77; H, 6.45; N, 3.90.

PP-V0 White powder (EtOH). mp 158 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.92—7.97 (2H, m), 7.75—7.80 (2H, m), 7.44 (1H, dt, J=1.83, 7.93 Hz), 7.26 (1H, dd, J=7.63, 1.83 Hz), 7.08 (1H, dt, J=1.22, 7.63 Hz), 7.06 (1H, dd, J=7.93, 1.22 Hz), 3.80 (3H, s). *Anal.* Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.29; H, 4.50; N, 5.34.

PP-S0 White needles (EtOH). mp 163 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.95—8.00 (2H, m), 7.78—7.82 (2H, m), 7.47 (1H, dt, J=1.83, 7.93 Hz), 7.44 (1H, dd, J=7.93, 1.83 Hz), 7.27 (1H, dt, J=1.83, 7.93 Hz), 7.25 (1H, dd, J=7.93, 1.83 Hz), 2.42 (3H, s). *Anal.* Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20; S, 11.90. Found: C, 67.07; H, 4.23; N, 5.16; S, 11.87.

PP-n30 White needles (CH_2Cl_2–hexane). mp 94.6 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.95—7.99 (2H, m), 7.78—7.83 (2H, m), 7.42 (1H, dt, J=7.33, 1.22 Hz), 7.39 (1H, dd, J=7.79, 2.14 Hz), 7.33 (1H, dt, J=7.33, 2.14 Hz), 7.17 (1H, dd, J=7.79, 1.22 Hz), 2.47 (2H, t, J=7.79 Hz), 1.57 (2H, tq, J=7.79, 7.32 Hz), 0.86 (3H, t, J=7.32 Hz). *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.03; H, 5.56; N, 5.37.

PP-n40 White flakes (CH_2Cl_2–hexane). mp 75 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.94—7.99 (2H, m), 7.78—7.83 (2H, m), 7.42 (1H, dt, J=1.22, 7.86 Hz), 7.39 (1H, dd, J=7.25, 2.44 Hz), 7.33 (1H, dt, J=2.44, 7.25 Hz), 7.17 (1H, dd, J=1.22, 7.86 Hz), 2.49 (2H, t, J=7.78 Hz), 1.52 (2H, tt, J=7.78, 7.63 Hz), 1.23 (2H, tq, J=7.63, 7.55 Hz), 0.81 (3H, t, J=7.55 Hz). *Anal.* Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.51; H, 6.35; N, 4.99.

PP-n50 White needles (hexane). mp 78 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.95—7.99 (2H, m), 7.78—7.83 (2H, m), 7.42 (1H, dt, J=1.22, 7.94 Hz), 7.39 (1H, dd, J=7.25, 2.44 Hz), 7.33 (1H, dt, J=2.44, 7.25 Hz), 7.17 (1H, dd, J=7.94, 1.22 Hz), 2.48 (2H, t, J=7.94 Hz), 1.51—1.56 (2H, m), 1.19—1.23 (4H, m), 0.79—0.81 (3H, t, J=7.02 Hz). *Anal.* Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.70; H, 6.55; N, 4.88.

PP-n60 White needles (hexane). mp 65—66 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.95—7.98 (2H, m), 7.79—7.82 (2H, m), 7.41 (1H, dt, J=1.22, 7.63 Hz), 7.39 (1H, dd, J=7.33, 2.44 Hz), 7.33 (1H, dt, J=2.44, 7.33 Hz), 7.17 (1H, dd, J=7.63, 1.22 Hz), 2.48 (2H, t, J=7.94 Hz), 1.49—1.57 (2H, m), 1.23—1.27 (6H, m), 0.77 (1H, t, J=6.87 Hz). *Anal.* Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.95; H, 6.98; N, 4.65.

PP-n70 White needles (hexane). mp 40 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.94—7.99 (2H, m), 7.78—7.83 (2H, m), 7.41 (1H, dt, J=1.22, 7.21 Hz), 7.39 (1H, dd, J=8.02, 2.14 Hz), 7.32 (1H, dt, J=2.14, 7.21 Hz), 7.16 (1H, dd, J=8.02, 1.22 Hz), 2.48 (2H, t, J=7.94 Hz), 1.49—1.58 (2H, m), 1.10—1.27 (8H, m), 0.79 (3H, t, J=7.02 Hz). *Anal.* Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.35. Found: C, 78.77; H, 7.27; N, 4.21.

PP-Pe0 White powder (CH_2Cl_2–hexane). mp 91 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.94—7.98 (2H, m), 7.78—7.82 (2H, m), 7.40 (1H, dt, J=1.52, 7.48 Hz), 7.33—7.37 (2H, m), 7.16—7.22 (3H, m), 7.10—7.15 (1H, m), 7.04—7.08 (2H, m), 2.78—2.89 (4H, m). *Anal.* Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.85; H, 5.36; N, 4.20.

PP-Hm0 White powder (CH_2Cl_2–hexane). mp 91 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.95—7.99 (2H, m), 7.78—7.83 (2H, m), 7.40 (1H, dt, J=1.22, 7.44 Hz), 7.36 (1H, dd, J=7.78, 1.52 Hz), 7.32 (1H, dt, J=1.84, 7.44 Hz), 7.16 (1H, dd, J=7.78, 1.22 Hz), 2.39 (2H, d, J=

7.32 Hz), 1.53-1.62 (5H, m), 1.40—1.50 (1H, m), 1.00—1.16 (3H, m), 0.74—0.83 (2H, m). *Anal.* Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.69; H, 6.60; N, 4.51.

PP-Da0 White powder (CH_2Cl_2–hexane). mp 169 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.93—7.97 (2H, m), 7.76—7.80 (2H, m), 7.40 (1H, ddd, J=8.10, 7.50, 1.83 Hz), 7.21 (1H, dd, J=8.10, 1.42 Hz), 7.17 (1H, dd, J=7.50, 1.83 Hz), 7.10 (1H, dt, J=1.42, 7.50 Hz), 2.64 (6H, s). *Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.37; H, 5.29; N, 10.51.

PP-N0 Pale yellow prisms (AcOEt). mp 198—199 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.21 (1H, dd, J=7.86, 1.34 Hz), 7.96—8.00 (2H, m), 7.82—7.86 (2H, m), 7.80 (1H, dt, J=7.86, 1.34 Hz), 7.64 (1H, dt, J=7.86, 1.34 Hz), 7.54 (1H, dd, J=7.86, 1.34 Hz). *Anal.* Calcd for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.01; N, 10.44. Found: C, 62.96; H, 2.87; N, 10.16.

PP-11 Colorless needles (AcOEt–hexane). mp 204 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.97 (2H, m), 7.81 (2H, m), 7.28 (1H, t, J=7.5 Hz), 7.18 (2H, d, J=7.5 Hz), 2.19 (6H, s). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.31; N, 5.63.

PP-0101 Colorless flakes (EtOH). mp 133 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.59—8.03 (4H, m), 7.00 (3H, m), 2.36 (6H, s). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.67; H, 5.19; N, 5.72.

PP-11011 Colorless needles (EtOH). mp 198 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.62—8.09 (4H, m), 7.06 (1H, s), 2.27 (6H, s), 2.00 (6H, s). *Anal.* Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.31; H, 6.31; N, 5.10.

PP-21 White needles (EtOH). mp 130 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.62—8.10 (4H, m), 7.00—7.50 (3H, m), 2.48 (2H, q, J=7.4 Hz), 2.18 (3H, s), 1.15 (3H, t, J=7.4 Hz). *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.91; H, 5.70; N, 5.28. Found: C, 76.83; H, 5.81; N, 5.20.

PP-22 White needles (EtOH). mp 154 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.91 (4H, m), 7.32 (3H, m), 2.47 (4H, q, J=7.5 Hz), 1.16 (6H, t, J=7.5 Hz). *Anal.* Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.11; H, 6.05; N, 4.86.

PP-31 White flakes (EtOH). mp 150 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.58—8.03 (4H, m), 6.94—7.37 (3H, m), 2.76 (1H, hep, J=6.4 Hz), 2.13 (3H, s), 1.21 (4H, d, J=6.4 Hz). *Anal.* Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.20; H, 6.18; N, 5.05.

PP-33 White flakes (EtOH). mp 172 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.87 (4H, m), 7.26 (3H, m), 2.72 (2H, q, J=8.8 Hz), 1.21 (12H, d, J=8.8 Hz). *Anal.* Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.17; H, 6.74; N, 4.57.

PP-0404 White needles (EtOH). mp 208 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.93—7.97 (2H, m), 7.76—7.81 (2H, m), 7.47 (1H, t, J=1.73 Hz), 7.22 (2H, d, J=1.73 Hz), 1.35 (18H, s). *Anal.* Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.98; H, 7.47; N, 4.10.

PP-4004 Colorless powder (EtOH). mp 246—247 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.95—7.99 (2H, m), 7.78—7.82 (2H, m), 7.55 (1H, d, J=8.55 Hz), 7.44 (1H, dd, J=8.55, 2.14 Hz), 6.94 (1H, d, J=2.14 Hz), 1.30 (18H, s). *Anal.* Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.99; H, 7.49; N, 4.12.

PP-008 White needles (CH_2Cl_2–hexane). mp 221 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.94—7.96 (2H, m), 7.77—7.81 (2H, m), 7.50 (2H, d, J=8.54 Hz), 7.37 (2H, d, J=8.54 Hz), 2.10—2.13 (3H, m), 1.93—1.96 (6H, d, J=2.75 Hz), 1.74—1.83 (6H, m). *Anal.* Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.77; H, 6.45; N, 3.90.

PP-FF Colorless needles (EtOH). mp 170 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.52—8.10 (4H, m), 6.72—7.52 (3H, m). *Anal.* Calcd for $C_{14}H_7F_2NO_2$: C, 64.78; H, 2.72; F, 14.66; N, 5.40. Found: C, 64.75; H, 2.71; F, 14.84; N, 5.46.

PP-CC Colorless prisms (EtOH). mp 174 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.63—8.13 (4H, m), 7.09—7.58 (3H, m). *Anal.* Calcd for $C_{14}H_7Cl_2NO_2$: C, 57.56; H, 2.42; Cl, 24.27; N, 4.79. Found: C, 57.46; H, 2.43; Cl, 24.51; N, 4.85.

PP-BB Colorless flakes (EtOH). mp 174 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.98—8.03 (2H, m), 7.81—7.86 (2H, m), 7.70 (2H, d, J=8.24 Hz), 7.24 (1H, t, J=8.24 Hz). *Anal.* Calcd for $C_{14}H_7Br_2NO_2$: C, 44.13; H, 1.85; Br, 41.94; N, 3.68. Found: C, 44.27; H, 2.02; Br, 41.99; N, 3.80.

4HPP-00 Pale yellow powder (benzene–hexane). mp 165—167 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.81 (1H, br s), 7.66 (1H, dd, J=8.24, 7.32 Hz), 7.48—7.54 (3H, m), 7.40—7.45 (3H, m), 7.24 (1H, dd, J=8.55, 0.61 Hz). *Anal.* Calcd for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.85. Found: C, 70.58; H, 4.01; N, 5.58.

4HPP-11 Pale yellow powder (benzene–hexane). mp 146—147 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.74 (1H, br s), 7.68 (1H, t, J=7.55 Hz), 7.49 (1H, d, J=7.55 Hz), 7.24—7.30 (3H, m), 7.19 (2H, d, J=7.33 Hz), 2.18 (6H, s). *Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.93; H, 4.94; N, 5.13.

4HPP-33 White prisms (CH_2Cl_2–hexane), mp 155 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.75 (1H, br s), 7.68 (1H, dd, J=8.36, 7.33 Hz), 7.50 (1H, dd, J=8.36, 0.66 Hz), 7.46 (1H, t, J=7.86 Hz), 7.29 (2H, d, J=7.86 Hz), 7.26 (1H, dd, J=7.33, 0.66 Hz), 2.72 (2H, hept, J=6.91 Hz), 1.18 (6H, d, J=6.91 Hz), 1.17 (6H, d, J=6.91 Hz). *Anal.* Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.54; N, 4.33. Found: C, 74.36; H, 6.45; N, 4.41.

5HPP-00 Pale yellow flakes (EtOH). mp 248—250 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 12.08 (1H, br s), 7.79 (1H, d, J=8.17 Hz), 7.51 (2H, t, J=7.93 Hz), 7.42 (1H, t, J=7.93 Hz), 7.41 (2H, d, J=7.93 Hz), 7.22 (1H, d, J=2.03 Hz), 7.19 (1H, dd, J=8.17, 2.03 Hz). *Anal.* Calcd for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.85. Found: C, 70.05; H, 3.77; N, 6.02.

5HPP-11 Pale yellow needles (EtOH). mp 200—201 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.82 (1H, d, J=8.24 Hz), 7.36 (1H, d, J=2.13 Hz), 7.26 (1H, t, J=7.53 Hz), 7.17 (2H, d, J=7.53 Hz), 7.15 (1H, dd, J=8.24, 2.13 Hz), 6.62 (1H, br s), 2.17 (6H, s). *Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.74; H, 4.98; N, 5.07.

5HPP-33 White prisms (AcOEt–hexane). mp 200—201 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.83 (1H, d, J=8.24 Hz), 7.45 (1H, t, J=7.88 Hz), 7.38 (1H, d, J=2.14 Hz), 7.29 (2H, d, J=7.88 Hz), 7.14 (1H, dd, J=8.24, 2.14 Hz), 6.58 (1H, br s), 2.72 (2H, hept, J=6.93 Hz), 1.16 (12H, d, J=6.93 Hz). *Anal.* Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.54; N, 4.33. Found: C, 74.46; H, 6.47; N, 4.24.

4APP-00 Yellow needles (AcOEt–hexane). mp 180 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.35—7.52 (6H, m), 7.50 (1H, dd, J=6.41, 0.61 Hz), 6.91 (1H, d, J=8.55 Hz), 5.30 (2H, br s). *Anal.* Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.62; H, 4.39; N, 11.46.

4APP-11 Yellow needles (EtOH). mp 217—218 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.49 (1H, dd, J=8.24, 7.02 Hz), 7.25 (1H, t, J=7.56 Hz), 7.24 (1H, d, J=7.02 Hz), 7.17 (2H, d, J=7.56 Hz), 6.92 (1H, d, J=8.24 Hz), 5.28 (2H, br s), 2.17 (6H, s). *Anal.* Calcd for $C_{14}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.29; H, 5.37; N, 10.45.

4APP-33 Yellow powder (EtOH). mp 241—242 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.50 (1H, dd, J=8.32, 7.17 Hz), 7.44 (1H, t, J=7.93 Hz), 7.27 (2H, d, J=7.93 Hz), 7.26 (1H, d, J=7.17 Hz), 6.93 (1H, d, J=8.32 Hz), 2.75 (2H, hept, J=6.94 Hz), 1.17 (6H, d, J=6.94 Hz), 1.16 (6H, d, J=6.94 Hz). *Anal.* Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.69; H, 6.81; N, 8.96.

5APP-00 Pale yellow flakes (benzene–hexane). mp 207—208 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.72 (1H, d, J=7.94 Hz), 7.35—7.52 (5H, m), 7.12 (1H, d, J=2.13 Hz), 6.88 (1H, dd, J=7.94, 2.13 Hz), 4.40 (2H, br s). *Anal.* Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.59; H, 4.31; N, 11.63.

5APP-11 Pale yellow powder (benzene–hexane). mp 194 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.72 (1H, d, J=8.09 Hz), 7.24 (1H, t, J=7.53 Hz), 7.16 (2H, d, J=7.53 Hz), 7.13 (1H, d, J=2.14 Hz), 6.89 (1H, dd, J=8.09, 2.14 Hz), 4.40 (2H, br s), 2.18 (6H, s). *Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.43; H, 5.32; N, 10.27.

5APP-33 Yellow prisms (CH_2Cl_2–hexane). mp 253—254 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.72 (1H, d, J=8.19 Hz), 7.43 (1H, t, J=7.78 Hz), 7.27 (2H, d, J=7.78 Hz), 7.13 (1H, d, J=2.24 Hz), 6.91 (1H, dd, J=8.19, 2.24 Hz), 4.40 (2H, s), 2.71 (2H, hept, J=6.87 Hz), 1.16 (6H, d, J=6.87 Hz), 1.15 (6H, d, J=6.87 Hz). *Anal.* Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.61; H, 6.95; N, 8.80.

4NPP-00 Brown needles (EtOH). mp 134—136 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.25 (1H, d, J=7.78 Hz), 8.16 (1H, d, J=7.78 Hz), 7.98 (1H, t, J=7.78 Hz), 7.49—7.56 (2H, m), 7.41—7.49 (3H, m). *Anal.* Calcd for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.01; N, 10.44. Found: C, 62.54; H, 3.09; N, 10.60

4NPP-11 Brown flakes (AcOEt–hexane). mp 151 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.23 (1H, d, J=7.86 Hz), 8.19 (1H, d, J=7.86 Hz), 8.00 (1H, t, J=7.86 Hz), 7.29 (1H, t, J=7.63 Hz), 7.19 (2H, d, J=

7.63 Hz), 2.18 (6H, s). *Anal.* Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.45. Found: C, 64.94; H, 4.05; N, 9.22.

4NPP-33 Pale yellow needles (AcOEt–hexane). mp 157—158 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.23 (1H, d, J=7.86 Hz), 8.21 (1H, d, J=7.86 Hz), 8.01 (1H, t, J=7.86 Hz), 7.48 (1H, t, J=7.83 Hz), 7.30 (2H, d, J=7.83 Hz), 2.66 (2H, hept, J=6.61 Hz), 1.19 (6H, d, J=6.61 Hz), 1.18 (6H, d, J=6.61 Hz). *Anal.* Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.32; H, 5.74; N, 8.07.

5NPP-00 Pale yellow needles (EtOH). mp 192 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.78 (1H, d, J=1.93 Hz), 8.68 (1H, dd, J=8.24, 1.93 Hz), 8.17 (1H, d, J=8.24 Hz), 7.52—7.57 (2H, m), 7.43—7.48 (3H, m). *Anal.* Calcd for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.01; N, 10.44. Found: C, 62.74; H, 3.03; N, 10.22.

5NPP-11 Brown flakes (EtOH). mp 172 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.80 (1H, d, J=1.93 Hz), 8.69 (1H, dd, J=8.09, 1.93 Hz), 8.17 (1H, d, J=8.09 Hz), 7.32 (1H, t, J=7.63 Hz), 7.22 (2H, d, J=7.63 Hz), 2.16 (6H, s). *Anal.* Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.45. Found: C, 64,78; H, 4.06; N, 9.64.

5NPP-33 Pale yellow powder (EtOH–hexane). mp 161—162 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.81 (1H, d, J=2.14 Hz), 8.71 (1H, dd, J=8.14, 2.04 Hz), 8.18 (1H, d, J=8.14 Hz), 7.49 (1H, t, J=7.73 Hz), 7.32 (2H, d, J=7.73 Hz), 2.64 (2H, hept, J=6.90 Hz), 1.17 (12H, d, J=6.90 Hz). *Anal.* Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.41; H, 5.71; N, 7.93.

CPP-00 White needles ($CHCl_3$). mp 258—260 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.50—7.55 (2H, m), 7.42—7.47 (1H, m), 7.39—7.42 (2H, m). *Anal.* Calcd for $C_{14}H_5Cl_4NO_2$: C, 46.58; H, 1.40; Cl, 39.28; N, 3.88. Found: C, 46.56; H, 1.39; Cl, 39.56; N, 3.96.

CPP-11 Pale yellow needles ($CHCl_3$–EtOH). mp 228—229 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.30 (1H, t, J=7.53 Hz), 7.19 (2H, d, J=7.53 Hz), 2.15 (6H, s). *Anal.* Calcd for $C_{16}H_9Cl_4NO_2$: C, 49.39; H, 2.33; Cl, 36.45; N, 3.60. Found: C, 49.33; H, 2.20; Cl, 36.44; N, 3.65.

CPP-33 Pale yellow needles ($CHCl_3$). mp 232—234 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.48 (1H, t, J=7.83 Hz), 7.29 (2H, d, J=7.83 Hz), 2.63 (2H, hept, J=6.77 Hz), 1.17 (12H, d, J=6.77 Hz). *Anal.* Calcd for $C_{20}H_{17}Cl_4NO_2$: C, 53.96; H, 3.85; Cl, 31.86; N, 3.15. Found: C, 54.06; H, 3.84; Cl, 32.14; N, 3.14.

FPP-00 Pale yellow flakes (AcOEt–hexane). mp 202 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.52 (2H, t, J=7.32 Hz), 7.45 (2H, t, J=7.32 Hz), 7.39 (2H, d, J=7.32 Hz). *Anal.* Calcd for $C_{14}H_{15}F_4NO_2$: C, 56.96; H, 1.71; F, 25.74; N, 4.74. Found: C, 57.15; H, 1.77; F, 25.61; N, 4.75.

FPP-11 Pale yellow flakes (CH_2Cl_2–hexane). mp 173 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.30 (1H, t, J=7.48 Hz), 7.18 (2H, d, J=7.48 Hz), 2.15 (6H, s). *Anal.* Calcd for $C_{16}H_9F_4NO_2$: C, 59.45; H, 2.81; F, 23.51; N, 4.33. Found: C, 59.41; H, 3.02; F, 23.28; N, 4.42.

FPP-33 Colorless prisms (CH_2Cl_2–hexane). mp 167 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.48 (1H, t, J=7.73 Hz), 7.30 (2H, d, J=7.73 Hz), 2.63 (2H, hept, J=6.90 Hz), 1.17 (12H, d, J=6.90 Hz). *Anal.* Calcd for $C_{20}H_{17}F_4NO_2$: C, 63.32; H, 4.52; F, 20.03; N, 3.69. Found: C, 63.04; H, 4.42; F, 20.02; N, 3.77.

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