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Increasing the antioxidant capability via the synergistic effect of coupling diphenylamine with sterically hindered phenol

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Abstract: A series of novel diphenylamine-phenol antioxidants were synthesised that combined the two antioxidant types into a single molecule. These antioxidants were then functionalised with alkyl chains to aid their solubility in hydrocarbon media. As part of a structure-activity study, diphenylamine derivatives were also generated bearing carboxylic acid functionalities in either the *ortho*, *meta* or *para* position with respect to the secondary amine. Methyl or ethyl spacers were also incorporated between the carboxylic acid and the aromatic ring. The antioxidant ability of the diphenylamine-phenols was evaluated using Differential Scanning Calorimetry (DSC) and compared to commercially available antioxidants Irganox L135 and Irganox L57 both as individual components and when blended together. The diphenylamine-phenol antioxidant with an ethyl spacer between the diphenylamine and carboxylic acid in the *meta* position with respect to the secondary amine functionality showed an impressive oxidation induction time of *ca.* 24 minutes in direct comparison with the blend of Irganox L135 and Irganox L57 (*ca*. 16 minutes).

Keywords: Synergism, Dual functional antioxidants, Diphenylamines, Phenols, Oxidative Stability Studies

1. Introduction

Oxidative degradation of hydrocarbon materials such as oils, fuels, biofuels, and polymers is a common problem in several industrial processes. [1-4] In particular, when an automotive lubricant or a lubricant for any mechanical system is being used, this oxidizes more easily, depending on its type (paraffinic, naphthenic, or aromatic), to form harmful species which can shorten its service life and ultimately damage the physical integrity of the machinery. [5-6] Among several possibilities to reduce or prevent the speed of lubricant oxidation, antioxidants are the key additives incorporated by chemical industries in their lubricant formulations to protect oils from oxidative degradation and prolong service life. [7-11] Phenols and diphenylamines constitute the bulk of radical trapping antioxidants that are incorporated into lubricant formulations because of their high inherent reactivities toward peroxyl radicals and the persistence of the resultant radicals toward both O_2 and non-radical species. [12-14] Phenols, especially sterically hindered phenols, are environmentally friendly and have low toxicity which make them prevalent in automotive lubricating oils but are restricted from high temperature applications because of their poor thermal stability and liability to failure owing to photochromatic effect under severe conditions. [15-18] In contrast, diphenylamines have better performance at elevated temperatures but the antioxidant performance still needs to be improved. [19-21] Complying with these limitations, there is an increasing demand to meet strict emission legislation whilst enhancing fuel economy thus forcing the petrochemical industry to develop highly effective antioxidants for used in fuels. [22] Therefore, in order to meet these demands upon the properties of lubricating oils, improving via the synergistic means the performance of commercial antioxidants using sulfur-, phosphorus- and heavy metal-free compounds is desirable. [23] The term ‘synergism’ in this case refers to the cooperative action of two or more additive species in such a way that the total antioxidant effect is greater than the sum of the individual effects taken independently. [24] It is well-known, particularly in some lubricant formulations that, sterically hindered phenols and

diphenylamines, when added to the oil simultaneously can remarkably enhance the antioxidant efficiency due to their intermolecular synergistic effect. [25-28] These exciting results prompted us to design a series of antioxidants that combines the sterically hindered phenol and diphenylamine moieties into a single structure to form a bifunctional antioxidant. The benefits of this approach are that increasing molecular weight of the antioxidant could also improve the thermal stability at elevated temperatures and could reduce the amount of additives used in formulations. [29] Although considerable efforts have been devoted to investigating and improving the individual antioxidant capabilities of hindered phenols and diphenylamines through structural variations [30-33], only a few examples have been reported that detail the inclusion of both functional groups within the same compound. [34-35] Recently Liu *et al.* [36] designed a new type of antioxidant which combined the two antioxidant types into a one molecule via Schiff base **(Figure 1)**. These Schiff base antioxidants bridged phenolic diphenylamine antioxidants (**SPD1** and **SPD2**) exhibited better thermal stability and antioxidant efficiency than the commonly used commercial antioxidants. Inspired by this study, we report the design and synthesis of a series of novel mixed diphenylamine-phenol antioxidants that combine the two traditional antioxidants into one molecule in addition to alkyl chains to gain better solubility. To further investigate the structure-activity relationship, diphenylamine derivatives that possess carboxylic acid functionalities in either *ortho*, *meta* or *para* position with respect to the secondary amine and methyl or ethyl spacers were incorporated between the carboxylic acid and the aromatic ring. Their antioxidant ability was examined using pressurised differential scanning calorimetry (PDSC) and the antioxidant performance compared to the current industry antioxidants Irganox L135 and Irganox L57 (**Figure 2**) both as individual components and as a synergistic blend together.

2. Results and discussion

2.1. Synthesis

The palladium catalysed Buchwald-Hartwig amination [37-39] was used to synthesise the ester derivative **3** (see SI **Scheme S1**). [40-41] After base catalysed ester hydrolysis, the acid derivative of diphenylamine **4** and 3-(3,5 di *tert*-butyl 4 hydroxyphenyl)propionic acid **7** were attached to the first generation hydroxyl linker **6**. [29] Two different synthetic procedures were targeted, both utilising *N,N'* dicyclohexylcarbodiimide (DCC) mediated coupling. The first approach, shown in **Scheme 1**, involved a statistical reaction whereby **4**, the hindered phenol **7** and **6** were reacted in a ratio of 1:1:1. The statistical reaction yielded successfully the desired compound **8** in *ca.* 30%, however, the competing by-products **9** and **10**, shown in **Figure 3**, were isolated in a yield of *ca.* 30% each, respectively. To improve production of **8**, an alternative synthetic methodology was utilised where a mono-phenolic hydroxyl linker **5** was synthesised from the reaction of **7** with a single hydroxyl functionality of **6**. Subsequently, the reaction of **5** with diphenylamine **4** via DCC mediated coupling (**Scheme 2**) afforded the desired mixed amine-phenol **8** with an improved yield of *ca.* 70%. To investigate the structure-activity relationships of the novel mixed amine-phenol, *para*-substituted derivatives of mixed amino-phenol **11** and *bis*(diphenylamine) **13** (see **Series 1**, **Table 1**) were prepared by reacting 2-(4-(phenylamino)phenyl)acetic acid **12** with **5** and **6** following the above synthetic methodology (see SI **Scheme S2**). To further refine the structure of the mixed amine-phenols, an additional alkyl chain was introduced in **Series 2** by employing 4-butylaniline **16** as the starting material. The most effective position to link the diphenylamine to the hydroxyl linker was also investigated and *ortho*, *meta* and *para* carboxylic acid substituted diphenylamines were synthesised via the Buchwald-Hartwig amination [37-39] methodology previously described. The esters **14** (*ortho*), **17** (*meta*) and **19** (*para*) were generated, followed by base hydrolysis to afford the carboxylic acids **21**-**23** in good yields (>80%) as shown in **Scheme 3**. [42-45] Successful coupling of 4-butylaniline **16** to methyl 3-bromobenzoate **18** and methyl

4-bromobenzoate **20** was achieved to yield the *meta* and *para* diphenylamines **17** and **19**, respectively (isolated yields *ca.* 50%). However, the synthesis of **14**, using methyl 2-bromobenzoate **15**, proved to be more challenging and a low yield of only *ca.* 25% was achieved. In an attempt to improve the yield, K_2CO_3 was used as a base for the Buchwald-Hartwig amination reaction and a significant improvement in the isolated yield (53%) was observed. With the (*ortho*, *meta* and *para*)-substituted diphenylamines derivatives **21**-**23** and mono-phenolic hydroxyl linker **5** in hand, mixed amine-phenols **24**-**26** were prepared successfully employing the same methodology described to generate **Series 1**. In addition, the *bis*(diphenylamines) **27**-**29** were also generated from the reaction of **21**-**23** with first generation diol linker **6** (see **Series 2**, **Table 2**). To conclude the series, the inclusion of a methyl or ethyl spacer between the carboxylic acid and aromatic ring was also investigated. The esters **30** (*meta* $-CH_2CH_2-$), **32** (*para* $-CH_2-$) and **34** (*para* $-CH_2CH_2-$) were generated first by coupling of **16** to **31**, **33** and **35** respectively, followed by ester hydrolysis to yield the carboxylic acids **36**-**38** in a yield of *ca.* 80% as shown in **Scheme 4**. The monophenol hydroxyl linker **5** was then functionalised with the carboxylic acid diphenylamine derivatives (**36**-**38**) to prepare a series of mixed amine-phenols (**39**-**41**) as shown in (see **Series 3**, **Table 3**). In addition, the *bis*(diphenylamines) (**42**-**44**) were also generated by the reaction of carboxylic acid diphenylamine derivatives with the first generation diol linker **6.**

2.2. Oxidative stability studies

To assess the antioxidant potential, **8, 9, 11** and **13** were blended into a synthetic lubricant base oil - Durasyn 164 (a polyalphaolefin, hydrogenated hydrocarbon base oil composed of dec-1-ene trimers typically used in lubricating oils). At this stage it was found that the miscibility of the *bis*(diphenylamines) **9** and **13** in the lubricant base oil was poor and hence oxidative stability analysis was not feasible. In comparison, the mixed amine-phenols exhibited better solubility even though an extended heating period was required to ensure full

dissolution. Current commercial antioxidants Irganox L135 and Irganox L57 were used as a comparison and samples were prepared by blending of 0.5% w/w of each antioxidant in 50 mL of the lubricant base oil. The blends were analysed using (PDSC) to monitor the heat effects associated with phase transitions and chemical reactions as a function of temperature. Oxidation induction time (OIT) and oxidation onset temperature (OOT) were utilised to study the effect of antioxidants on the stability of the oil sample. OIT analysis revealed that the presence of **8** and **11** in the base oil had resulted in increase in the stability of the sample as shown in **Figure 4**. The induction time was increased from <1 minute for the unblended base oil to *ca.* 10-13 minutes for the blended samples. In addition, **8** and **11** showed superior performance to both commercial antioxidants, Irganox L135 and Irganox L57. However, the synergistic effect of having both functionalities on the same compound did not outweigh the effect of blending both together as evident in the L135/L57 blend (*ca*. 16 minutes). The methylene spacer in the mixed amine-phenol **11** appeared to have a positive effect on the antioxidant capabilities, revealing an induction time of *ca.* 3 minutes longer than **8**. OOT analysis was also performed and the results for each oil blend are shown in **Figure 5** where again, a significant increase in temperature (*ca.* 251 °C) was observed for both **8** and **11** when incorporated into the blend compared to the base oil in isolation (*ca.* 223 °C). The above results revealed that these compounds did have antioxidant capabilities but physical properties such as solubility was an issue. OIT analysis of **24-26** bearing an additional alkyl chain for enhanced solubility were then carried out that revealed a difference in the antioxidant capabilities of each compound (**Figure 6**) demonstrating that there was clearly a favoured substitution position on the ring for enhanced antioxidant properties. The mixed amine-phenol **24** (*ca.* 7 minutes) exhibited the quickest OIT in comparison to **25** and **26** and this poor performance can be attributed to the *ortho* substitution which allowed intramolecular hydrogen bonding between the aromatic amine proton and the carbonyl oxygen from the

ester moiety. In comparison, the mixed-amine phenol **25**, which was substituted in the *meta* position, revealed the best oxidation induction time of 13 minutes. Interestingly, this result still was not greater than a simple 1:1 blend (0.25% w/w of each of Irganox L135 and Irganox L57) of Irganox L135 and Irganox L57 (*ca.* 16 minutes), however, some improvement was observed from **Series 1**. A direct comparison was made between the oxidation induction times from **Series 1** and **2** to determine the structural characteristics that were contributing to an increase in induction time (**Figure 7**). Comparison of the *meta* substituted mixed amine-phenols **8** and **25** (from **Series 1** and **2**, respectively) revealed that an increase in oxidation time was observed upon addition of an alkyl chain. It was proposed that this increase was associated with an improved solubility in the lubricant base oil and hence better diffusion within the medium was achieved. Additionally, comparison of the *para* substituted mixed amine-phenols **11** and **26** revealed that incorporation of a methylene spacer between the aromatic ring and the ester moiety had an even greater effect on the OIT than just the addition of a solubilising group. This was believed to be a result of a change in the electronics of the system and instead of the strongly electron-withdrawing ester moiety, the methyl spacer provided some electron-donating capacity to the aromatic ring. Oxidation onset temperature was also analysed and revealed the same trend of increasing oxidative stability from **24** *(ortho)* to **26** *(para)* to **25** *(meta)* (**Figure 8**). The *ortho* substituted mixed amine-phenol **24** revealed an oxidation onset temperature of *ca.* 243 °C that was significantly less than that observed for the Irganox L57 (*ca.* 249 °C). The *para* and *meta* substituted mixed amine-phenols (**26** and **25**, respectively), however, revealed the ability to perform in the higher temperature region associated with diphenylamines. Oxidative stability analysis of the *bis*(diphenylamines) proved more challenging as the solubility in the lubricant base oil remained an issue even with the additional butyl chain. OIT analysis (**Figure 9**) revealed very poor results for the series of *bis*(diphenylamines) whereby only **28** was able to stabilise the

base oil for more than 3 minutes. OOT analysis also revealed the same trend where **28** provided the best stabilisation out of the series, however, it was noted that none of the new species were able to perform better than Irganox L57. The poor dispersion within the lubricant oil significantly hindered the radical scavenging ability of this series of *bis*(diphenylamines) and it was proposed that an additional branched alkyl unit would need to be incorporated to disrupt the ordered structures and hence improve solubility. These results did, however, give confirmation that there was a synergistic effect occurring in the mixed amine-phenols where both induction time and onset temperature were significantly increased through incorporation of a phenolic moiety. To conclude the series, (*meta* -CH_2CH_2-), (*para* -CH_2-) and (para -CH_2CH_2-) substituted mixed amine-phenols with a butyl chain were synthesised and their antioxidant capabilities were investigated. OIT analysis of **39**-**41** revealed a dramatic increase in the stabilisation capabilities of all three compounds where the induction time for each exceeded that of the Irganox L135/57 1:1 blend as shown in **Figure 10**. The highest induction time of *ca.* 24 minutes was revealed for the mixed amine-phenol **39** possessing an ethyl spacer between the aromatic ring and the ester moiety. Interestingly, Liu *et al.* have also reported [36] similar OIT results for their Schiff base bridged phenolic diphenylamine antioxidants with a maximum value of *ca.* 25 minutes. An increase of *ca*. 4 minutes was observed from **40** (*ca.* 23 minutes) to **41** (*ca.* 19 minutes) where an additional methylene unit was introduced. This result indicated that stabilisation of the secondary amine, through electron donation, was a significant factor in increasing the antioxidant capabilities of these compounds. It was also proposed that the ethyl spacers provided the ideal contact distance between the diphenylamine and the phenol, therefore potentially increasing the ability of amine regeneration. A direct comparison of the *meta* substituted compounds (**8**, **25** and **39**) from the three series revealed the increase in induction time associated with each of the structural developments (**Figure 11**). This highlighted the significance of enhanced solubility

through the inclusion of an alkyl chain which increased the induction time by *ca.* 3 minutes (**25**). In addition, inclusion of electron donating substituents as opposed to electron withdrawing substituents increased the oxidation induction time by a further *ca.* 10 minutes (**39**). OOT analysis also revealed excellent stability properties from the mixed amine-phenols where **39**, **40** and **41** all performed (*ca.* 254 °C) in the same temperature region as the L135/57 blend (**Figure 12**). The *bis*(diphenylamines) **42**-**44** also revealed similar solubility issues as seen in **Series 2**, however, the OIT did not exceed that of the aromatic amine Irganox L57 hence reinforcing further the excellent synergistic effects of combining both diphenylamines and sterically hindered phenols within the same compound.

3. Conclusions

In summary, three series of mixed amine-phenols and *bis*(diphenylamines) were synthesised successfully, blended into the lubricant base oil and analysed for their oxidative stability properties, highlighting interesting structure-activity relationships. The mixed amine-phenols were all soluble in the lubricant base oil at 0.5% w/w which was further improved through the introduction of a butyl chain on the aniline ring. Even with the additional alkyl chain, all of the *bis*(diphenylamines) derivatives revealed poor solubility and hence oxidation induction times and oxidation onset temperatures were all lower than the current diphenylamine antioxidant Irganox L57. **Series 2** of the mixed amine-phenols revealed that *meta* and *para* substitution provided the best oxidative stability properties. These properties were further enhanced in **Series 3** through the inclusion of methyl or ethyl spacers between the diphenylamine and the ester moiety from the attachment to the mono-phenol linker. It was observed that meta substitution with an ethyl spacer provided the longest oxidation induction time of *ca.* 23 minutes, which was *ca.* 8 minutes longer than the current 1:1 synergistic blend of Irganox L135 and Irganox L57.

4. Experimental

4.1. General procedure for purification, characterisation, thermal and oxidative analysis

Reagents and solvents were purchased from Sigma Aldrich and used without further purification except for 3-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-propionic acid **7** which was purchased from Alfa Aesar. All solvents were dried and freshly distilled prior to use. Tetrahydrofuran (THF) was distilled under a nitrogen atmosphere from sodium and benzophenone. Dichloromethane was distilled under a nitrogen atmosphere from calcium hydride. Thin layer chromatography (TLC) was performed on aluminium sheets coated with Merck silica gel 60 F_{24}. Spots were visualised under ultra-violet light (254 nm) with potassium permanganate as the visualising agent. Column chromatography was performed using Merck silica gel 60 (40-63 µm particle size) and a mobile phase as specified. Melting points were recorded using a Stuart MP10 melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded using either $CDCl_3$ or DMSO-d_6 as solvent on either a Bruker Nanobay 400 or Bruker DPX 400 operating at 400 MHz for ^{1}H NMR or at 100 MHz for ^{13}C NMR. Infrared (IR) spectroscopic analysis was carried out using a Perkin Elmer 100 FT-IR instrument with a diamond ATR sampling attachment with samples either as solids or oils. Mass spectrometry analysis was carried out on a Thermo-Fisher Scientific Orbitrap XL LC-MS. Samples were prepared as methanol solutions (1 mg/mL) and were ionised using electrospray ionisation (ESI) and the parent mass ions were quoted. Thermogravimetric analysis (TGA) was performed using a TA instrument TGA 2950. TGA was carried out under a nitrogen atmosphere from ambient temperature to 500 °C at a rate of 10 °C/min using a sample of approximately 10 mg. Pressurised differential scanning calorimetry (PDSC) was carried out at the BP Technology Centre, Pangbourne. Oxidation induction time (OIT) was performed using a TA instrument Q10 (0010-0141) or Q20 (0020P-0137). The industry standard CEC L 085-99 method was followed whereby 2 mg of sample was added to an aluminium crucible.

The cell was pressurised to 6.9 bar with cylinder air and the temperature was raised to 50 °C and held isothermally for 5 minutes. The temperature was then ramped at 20 °C/min to 210 °C and held isothermally until the oxidation of the sample was induced. The time of onset of the exotherm minus the time taken to reach 210 °C was reported. PDSC oxidation onset temperature (OOT) was performed using a TA instrument 2910. An in-house method was used whereby 0.5 mg of sample was added to an aluminium crucible. The cell was pressurised to 34.5 bar with cylinder air with a flow of 60 mL/min. The temperature was raised to 50 °C and was allowed to stabilise before heating at 50 °C/min to 350 °C. The temperature at which the oxidation exotherm occurred was reported. All tests were carried out in duplicate and error bars in the figures represent the standard deviations.

4.2. Synthesis

*4.2.1. Preparation of methyl 3-(phenylamino)benzoate **(3)*** [40]

In a 25 mL round-bottomed flask, toluene (10 mL) was degassed with argon for 20 minutes. Under a flow of argon, $Pd(OAc)_2$ (0.05 g, 0.23 mmol), BINAP (0.23 g, 0.37 mmol) and Cs_2CO_3 (2.12 mmol, 6.51 mmol) were added and left to stir for a further 20 minutes. To the mixture, methyl (3-bromobenzoate) **1** (1.01 g, 4.65 mmol) and aniline **2** (0.51 mL, 5.58 mmol) were added. The reaction was stirred at 120 °C and monitored by thin layer chromatography (TLC) for 24 hours. Upon completion, the reaction was cooled to room temperature and filtered through Celite®, with hexane as the eluent, followed by concentration under reduced pressure. The residue was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (90:10) (R_f = 0.23) to afford 0.87 g (82%) of **3** as a pale yellow solid; M.p. 110-112 °C (literature M.p. 110-111 °C) [40]; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 3.90 (s, 3H,-COO*CH*$_3$), 5.81 (s, 1H, -NH), 6.98 (*app*. t, 1H, app *J*=8 Hz, *CH*$_{para}$C$_4$H$_4$-NH), 7.09 (*app*. d, 2H, CH$_{para}$*C*$_2$*H*$_{2meta}$C$_2$H$_{2ortho}$-NH), 7.23 (m, 1H, HN-CH-C(COOCH$_3$)-CHCH*CH*-), 7.29

(m, 3H, C_2H_{2ortho}-HN-CH-C(COOCH$_3$)-CH*CH*CH-), 7.57 (*app.* d, 1H, HN-CH-C(COOCH$_3$)-*CH*), 7.72 (m, 1H, HN-*CH*-C(COOCH$_3$)); ^{13}C NMR (100 MHz/CDCl$_3$)/ppm, δ = 52.2, 118.2, 118.4, 121.5, 121.77, 121.80, 129.4, 129.3, 131.4, 142.4, 143.6, 167.1; Found $[M+H]^+$ ($C_{14}H_{14}NO_2$) m/z = 228.1019 (Calc. 228.1025); IR (ATR) *v*/cm^{-1}: 3358, 3030, 1694, 1578, 1294, 744.

4.2.2. Preparation of 3-(phenylamino)benzoic acid ***(4)*** [41]

To a solution of **3** (0.50 g, 2.20 mmol) in ethanol (10 mL), aqueous potassium hydroxide (0.25 g, 4.40 mmol) was added at room temperature. The mixture was then allowed to stir at 100 °C for a minimum of 1 hour and was monitored closely by TLC until consumption of **3** was observed. Upon completion, the reaction was allowed to cool and the ethanol was removed *in vacuo*. The remaining solution was cooled to 0 °C and acidified to pH 2 with 2M HCl. The resulting precipitate was collected *via* vacuum filtration and washed with water (15 ml). The precipitate was then dissolved in chloroform (20 mL) and washed with brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to yield 0.38 g (81 %) of **4** as a white solid; M.p. 140-142 °C (literature M.p. 140-141 °C) [41]; ^{1}H NMR (400 MHz/CDCl$_3$)/ppm, δ = 6.99 (*app*. t, 1H, app *J* = 8 Hz, $CH_{para}C_4H_4$-NH), 7.10 (*app*. d, 2H, $CH_{para}C_2H_{2meta}C_2H_{2ortho}$-NH), 7.30 (m, 4H, C_2H_{2ortho}-HN-CH-C(COOH)-CH*CHCH*-), 7.64 (*app.* d, 1H, HN-CH-C(COOH)-*CH*), 7.77 (m, 1H, HN-*CH*-C(COOCH$_3$)); ^{13}C NMR (100 MHz/CDCl$_3$)/ppm, δ = 118.5, 118.6, 122.0, 122.2, 129.5, 129.6, 130.5, 142.2, 143.8, 172.2; Found $[M+H]^+$ ($C_{13}H_{12}NO_2$) m/z = 214.0863 (Calc. 214.0868); IR (ATR) *v*/cm^{-1}: 3398, 2992-2540 (br), 1682, 1584, 1464, 1294, 748.

4.2.3. Preparation of the mono-phenolic linker ***(5)***

The first generation hydroxyl linker **6** (5.01 g, 22.3 mmol), *N,N'*-dicyclohexylcarbodiimide (DCC) (0.92 g, 4.46 mmol) and DPTS (60%) were dissolved in dry dichloromethane (50 mL)

and cooled to 0 °C. To this, a solution of 3-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-propionic acid **7** (1.24 g, 4.46 mmol) in dry dichloromethane (20 mL) was added dropwise to the solution. The reaction was left to stir at room temperature and was monitored closely by TLC (90:10 hexane/ethyl acetate) until any small formation of the diphenol was observed (Rf = 0.38). The reaction mixture was filtered to remove the white *N, N'*-dicyclohexylurea (DCU) precipitate and the filtrate was concentrated *in vacuo*. The crude product was immediately subjected to flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.24) to afford 2.15 g (95%) of **5** as a colourless oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.89 (t, 6H, -CH_2*CH_3*), 1.15 (s, 3H, -CH_3), 1.28-1.37 (m, 8H, COO-CH_2-CH(*CH_2*CH_3)-*$CH_2CH_2CH_2$*CH_3), 1.43 (s, 18H, CH_3 *tert*-butyl), 1.59 (m, 1H, COO-CH_2-*CH*(CH_2CH_3)-C_4H_9), 2.53 (s(br), 1H, -OH), 2.62 (t, 2H, Ar-CH_2*CH_2*-COO-), 2.86 (t, 2H, Ar-*CH_2*CH_2-COO-), 3.57 (m, 2H, HO-*CH_2*-C,), 4.05 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.20 (d, 1H, COO-*CH*-C *equatorial*), 4.33 (d, 1H, COO-*CH*-C *axial*), 5.09 (s, 1H, Ar-*OH*), 6.98 (s, 2H, Ar-*CH*); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 11.0, 14.1, 17.6, 23.0, 23.8, 28.9, 30.4, 30.9, 34.3, 36.3, 38.7, 48.3, 64.9, 65.7, 67.3, 124.7, 130.7, 136.0, 152.3, 173.4, 174.6; Found $[M+Na]^+$ ($C_{30}H_{50}O_6Na$) m/z = 529.3500 (Calc. 529.3505); IR (ATR) *v*/cm^{-1}: 3528, 2960, 1726, 1140, 1042.

*4.2.4. Preparation of the mixed amine-phenol **(8)***

The mono-phenolic linker **5** (0.34 g, 0.67 mmol), 3-(phenylamino)benzoic acid **4** (0.16 g, 0.74 mmol) and DPTS (60%) were dissolved in dry dichloromethane (10 mL) and stirred at room temperature for 30 minutes. To the solution, DCC (0.15 g, 0.74 mmol) dissolved in dry dichloromethane (10 mL) was added over 15 minutes. The reaction was left overnight at room temperature under a nitrogen atmosphere. The reaction mixture was filtered to remove the white DCU precipitate and the filtrate was concentrated. The residue was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.32) to afford 0.31 g (46%) of **8** as a viscous yellow oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.84 (t,

6H, -CH_2*CH_3*), 1.23-1.36 (m, 12H, alkyl -CH_2 , -CH_3), 1.42 (s, 18H, CH_3 *tert*-butyl), 1.56 (m, 1H, -CH), 2.60 (t, 2H, Ar-CH_2*CH_2*-COO), 2.85 (t, 2H, Ar-*CH_2*CH_2-COO), 4.04 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.34 (s, 2H, Ar-COO-*CH_2*-C), 4.44 (s, 2H, Ar-COO-*CH_2*-C), 5.08 (s, 1H, -OH), 5.87 (s, 1H, -NH), 6.97 (m, 3H, Ar*CH_{para}*C_4H_4-NH and Ph-*CH*), 7.09 (*app*. d, 2H, ArCH_{para}*C_2H_{2meta}*C_2H_{2ortho}-NH), 7.30 (m, 4H, Ar*C_2H_{2ortho}*-HN-ArCH-C(COOH)-CH*CHCH*-), 7.50 (*app.* d, 1H, HN-ArCH-C(COOH)-*CH*), 7.67 (m, 1H, HN-Ar*CH*-C($COOCH_3$); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ =11.0, 14.1, 18.0, 22.9, 23.7, 28.9, 30.3, 30.9, 34.3, 36.2, 38.7, 46.6, 65.6, 66.1, 67.5, 118.0, 118.5, 121.5, 121.7, 121.9, 124.7, 129.4, 129.5, 130.8, 136.0, 142.2, 143.7, 152.2, 166.0, 172.7, 172.9; Found $[M+Na]^+$ ($C_{43}H_{59}NO_7Na$) m/z = 724.4184 (Calc. 724.4189); IR (ATR) *v*/cm^{-1}: 3641, 3385, 2960, 1731, 1517, 1132, 749.

4.2.5. Preparation of the bis(diphenylamine) ***(9)***

The first generation hydroxyl linker **6** (0.28 g, 1.12 mmol), 3-(phenylamino)benzoic acid **4** (0.50 g, 2.34 mmol) and DPTS (60%) were dissolved in dry dichloromethane (20 mL). To the solution, DCC (0.48 g, 2.34 mmol) dissolved in dry dichloromethane (10 mL) was added over 15 minutes. The reaction was left overnight at room temperature under a nitrogen atmosphere. The reaction mixture was filtered to remove the white DCU precipitate and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.4) to afford 0.47 g (66%) of **9** as a viscous orange oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.81(m, 6H, -CH_2*CH_3*), 1.20-1.33 (m, 8H, alkyl -CH_2), 1.41 (s, 3H, -CH_3), 1.54 (m, 1H, -CH), 4.06 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.55 (s, 4H, Ar-COO-*CH_2*-C), 5.79 (s(br), 2H, -NH), 6.97 (*app*. t, 2H, *app*. *J* = 8 Hz, *CH_{para}*C_4H_4-NH), 7.08 (*app*. d, 4H, *app*. *J* = 8 Hz, CH_{para}*C_2H_{2meta}*C_2H_{2ortho}-NH), 7.29 (m, 8H, *C_2H_{2ortho}*-HN-CH-C($COOCH_3$)-CH*CHCH*-), 7.51 (*app*. d, 2H, *app. J* = 4 Hz, HN-CH-C($COOCH_3$)-*CH*), 7.65 (app. s, 2H, HN-*CH*-C($COOCH_3$)); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 10.9, 14.0, 18.1, 22.9, 23.7, 28.9, 30.3, 38.7, 46.8, 66.3, 67.5, 118.1, 118.5, 121.4, 121.7,

121.9, 129.5, 130.8, 142.2, 146.7, 166.0, 172.9; Found $[M+H]^+$ ($C_{39}H_{45}N_2O_6$) m/z = 637.3272 (Calc. 637.3278); IR (ATR) *v*/cm^{-1}:3380, 2960, 1714, 1590, 1494, 1204, 1104, 746.

4.2.6. Preparation of mixed amine-phenol ***(11)***

The mono-phenolic linker **5** (0.74 g, 1.46 mmol), 2-(4-(phenylamino)phenyl)acetic acid **12** (0.50 g, 2.20 mmol), DPTS (60%) and DCC (0.45 g, 2.20 mmol) were allowed to react according to the general mixed amine-phenol procedure. The crude product was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.31) to afford 0.75 g (72%) of **11** as a viscous pale yellow oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.87 (m, 6H, -CH_2*CH_3*), 1.16 (s, 3H, -CH_3), 1.31-1.36 (m, 8H, alkyl -CH_2), 1.42 (s, 18H, CH_3 *tert*-butyl), 1.54 (m, 1H, -CH), 2.57 (t, 2H, *J* = 8 Hz, Ar-CH_2*CH_2*-COO), 2.83 (t, 2H, *J* = 8 Hz, Ar-*CH_2*CH_2-COO), 3.54 (s, 2H, Ar-*CH_2*-COO), 4.01 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.22 (m, 4H, CH_2-COO-*CH_2*-C), 5.07 (s, 1H, Ar*OH*), 5.68 (s, 1H, -NH), 6.92 (*app.* t, 1H, *app*. *J* = 8 Hz, *CH_{para}*C_4H_4-NH), 6.97 (s, 2H, Ph-CH), 7.03 (m, 4H, Ar*CH_{ortho}*-NH-Ar*CH_{ortho}*), 7.14 (*app*. d, 2H, *J* = 12 Hz, NH-ArCH*CH*-C(CH_2COO-)), 7.25 (*app*. t, 4H, *J* = 8 Hz, ArCH_{para}*CH_{meta}*CH_{ortho}-NH); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 10.9, 14.0, 17.8, 22.9, 23.7, 28.9, 30.3, 30.8, 34.3, 36.2, 38.7, 40.5, 46.4, 65.4, 65.8, 67.4, 117.8, 121.0, 124.7, 126.0, 129.3, 130.2, 130.8, 136.0, 142.2, 143.0, 152.2, 171.3, 172.6, 172.8; Found $[M+H]^+$ ($C_{44}H_{62}NO_7$) m/z = 716.4524 (Calc. 716.4526); IR (ATR) *v*/cm^{-1}: 3641, 3385, 2960, 1731, 1517, 1132, 749.

4.2.7. Preparation of bis(diphenylamine) ***(13)***

The first generation hydroxyl linker **6** (0.43 g, 1.91 mmol), 2-(4-(phenylamino)phenyl)acetic acid **12** (1.01 g, 4.40 mmol), DPTS (60%) and DCC (0.91 g, 4.40 mmol) were allowed to react according to the general bis(diphenylamine) procedure. The crude product was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20)

(R_f = 0.43) to afford 0.98 g (77%) of **13** as a viscous dark red oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.86 (m, 6H, -CH_2*CH_3*), 1.16 (s, 3H, -CH_3), 1.25-1.35 (m, 8H, alkyl -CH_2), 1.54 (m, 1H, -CH), 3.52 (s, 4H, Ar-*CH_2*-COO), 3.98 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.17 (d, 2H, *J* = 8 Hz, Ar-COO-*CH_2*-C), 4.24 (d, 2H, *J* = 12 Hz, Ar-COO-*CH_2*-C), 5.67 (s, 2H, -NH), 6.92 (*app.* t, 2H*, app*. *J* = 8 Hz, *$CH_{para}C_4H_4$*-NH), 6.99 (*app*. d, 4H, *app*. *J* = 8 Hz, NH-*CH*CH-(CH_2COO-)), 7.04 (*app*. d, 4H, *app. J* = 8 Hz, Ar$CH_{para}CH_{meta}$*CH_{ortho}*-NH), 7.10 (*app.* d, 4H, *app*. *J* = 8 Hz, NH-CH*CH*-(CH_2COO-)), 7.25 (*app.* t, 4H, *app*. *J* = 8 Hz, ArCH_{para}*CH_{meta}*CH_{ortho}-NH); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 10.9, 14.1, 17.9, 22.9, 23.7, 28.8, 30.3, 38.6, 40.4, 46.3, 65.6, 67.4, 117.9, 121.0, 126.0, 129.3, 130.2, 142.2, 143.0, 171.3, 172.8; Found $[M+H]^+$ ($C_{41}H_{49}N_2O_6$) m/z = 665.3585 (Calc. 665.3591); IR (ATR) *v*/cm^{-1}: 3385, 2960, 1727, 1596, 1516, 1132, 746.

*4.2.8. Preparation of methyl 2-((4-butylphenyl)amino)benzoate **(14)***

Methyl (2-bromobenzoate) **15** (1.00 g, 4.65 mmol) and 4-butylaniline **16** (0.88 mL, 5.58 mmol) were added to $Pd(OAc)_2$ (0.02 g, 0.09 mmol), BINAP (0.12 g, 0.18 mmol) and K_2CO_3 (0.90 g, 6.51 mmol) and were allowed to react according to the general Buchwald-Hartwig amination procedure. The crude residue was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.38) to afford 0.70 g (53%) of **14** as a white solid; M.p. 135-137 °C; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.95 (t, 3H, *J* = 8 Hz, -*CH_3*$CH_2CH_2CH_2$Ar), 1.39 (*sex*., 2H, *J* = 8 Hz, -CH_3*CH_2*CH_2CH_2Ar), 1.61 (*quin*., 2H, *J* = 8 Hz, -CH_3CH_2*CH_2*CH_2Ar), 2.61 (t, 2H, *J* = 8 Hz, -$CH_3CH_2CH_2$*CH_2*Ar), 3.91 (s, 3H,-COO*CH_3*), 6.70 (*app*. t, 1H, app *J* = 8 Hz, H_3COOC-CH*CH*CHCHC-NH), 7.17 (*app*. s, 4H, C_4H_9-Ar*CH*), 7.20 (*app*. d, 1H, H_3COOC-CHCHCH*CH*C-NH), 7.29 (*app*. t, 1H, H_3COOC-CHCH*CH*CHC-NH), 7.96 (*app.* d, 1H, H_3COOC-*CH*CHCHCHC-NH), 9.40 (s, 1H,-NH); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 14.0, 22.4, 33.8, 35.1, 51.7, 111.4, 113.8, 116.6, 122.6, 123.1, 126.2,

129.3, 131.6, 134.1, 138.2, 138.6, 148.6, 169.0; Found $[M+H]^+$ ($C_{18}H_{22}NO_2$) m/z = 284.1645 (Calc. 284.1651); IR (ATR) *v*/cm^{-1}: 3321, 2928, 1684, 1514, 1230, 1082, 746.

4.2.9. Preparation of methyl 3-((4-butylphenyl)amino)benzoate ***(17)*** [42]

Methyl (3-bromobenzoate) **18** (0.50 g, 2.33 mmol) and 4-butylaniline **16** (0.44 mL, 2.79 mmol) were added to $Pd(OAc)_2$ (0.02 g, 0.08 mmol), BINAP (0.10 g, 0.16 mmol) and Cs_2CO_3 (1.06 g, 3.26 mmol) and were allowed to react according to the general Buchwald-Hartwig amination procedure. The crude residue was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.36) to afford 0.35 g (55%) of **17** as a pale yellow solid; M.p. 101-103 °C (literature M.p. 101-103 °C) [42]; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.93 (t, 3H, *J* = 8 Hz, -*CH*$_3$$CH_2CH_2CH_2$Ar), 1.36 (*sex*., 2H, *J* = 8 Hz, -CH_3*CH*$_2$$CH_2CH_2$Ar), 1.59 (*quin.*, 2H, *J* = 8 Hz, -CH_3CH_2*CH*$_2$$CH_2$Ar), 2.57 (t, 2H, *J* = 8 Hz, -$CH_3CH_2CH_2$*CH*$_2$Ar), 3.89 (s, 3H,-COO*CH*$_3$), 5.72 (s, 1H, -NH), 7.03 (*app*. d, 2H, *app. J* = 8 Hz, HN-Ar*CHCH*), 7.11 (*app*. d, 2H, *app. J* = 8 Hz, C_4H_9-Ar*CHCH*), 7.19 (*app*. d, 1H, *app. J* = 8 Hz, HN-CH-C($COOCH_3$)-CHCH*CH*-NH), 7.28 (*app*. t, 1H, *J* = 8 Hz, HN-CH-C($COOCH_3$)-CH*CH*CH-NH), 7.52 (*app.* d, 1H, *J* = 8 Hz, HN-CH-C($COOCH_3$)-*CH*CHCH-NH), 7.66 (*app.* s, 1H, HN-*CH*-C($COOCH_3$)); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 14.0, 22.4, 33.8, 35.0, 52.1, 117.4, 119.3, 120.7, 121.1, 129.3, 129.4, 131.3, 136.9, 139.7, 144.3, 167.2; Found $[M+H]^+$ ($C_{18}H_{22}NO_2$) m/z = 284.1646 (Calc. 284.1651); IR (ATR) *v*/cm^{-1}: 3364, 2927, 1700, 1288, 1217, 750.

4.2.10. Preparation of methyl 4-((4-butylphenyl)amino)benzoate ***(19)***

Methyl (4-iodobenzoate) **20** (1.00 g, 3.82 mmol) and 4-butylaniline **16** (0.72 mL, 4.58 mmol) were added to $Pd(OAc)_2$ (0.02 g, 0.08 mmol), BINAP (0.10 g, 0.16 mmol) and Cs_2CO_3 (1.74 g, 5.35 mmol) and were allowed to react according to the general Buchwald-Hartwig amination procedure. The crude residue was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.36) to afford 0.54 g (50 %) of **19** as a

waxy brown solid; M.p. 51-53 °C; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.94 (t, 3H, *J* = 8 Hz, -*CH*$_3$CH$_2$CH$_2$CH$_2$Ar), 1.38 (*sex*., 2H, *J* = 8 Hz, -CH$_3$*CH*$_2$CH$_2$CH$_2$Ar), 1.61 (*quin*., 2H, *J* = 8 Hz, -CH$_3$CH$_2$*CH*$_2$CH$_2$Ar), 2.59 (t, 2H, *J* = 8 Hz, -CH$_3$CH$_2$CH$_2$*CH*$_2$Ar), 3.87 (s, 3H,-COO*CH*$_3$), 5.94 (s, 1H, -NH), 6.93 (*app*. d, 2H, *app. J* =12 Hz, HN-Ar*CHCH*-CHCH-C(COOCH$_3$)), 7.09 (*app*. d, 2H, *app. J* = 8 Hz, HN-Ar*CHCH*), 7.15 (*app*. d, 1H, *app. J* = 8 Hz, C$_4$H$_9$-Ar*CHCH*), 7.89 (*app*. d, 2H, *J* = 8 Hz, Ar*CHCH*-C(COOCH$_3$)); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 14.0, 22.4, 33.7, 35.1, 51.7, 114.0, 120.6, 121.2, 129.4, 131.5, 138.2, 138.3, 148.7, 167.0; Found $[M+H]^+$ ($C_{18}H_{22}NO_2$) m/z = 284.1645 (Calc. 284.1651); IR (ATR) *v*/cm^{-1}:3340, 2922. 1689, 1591, 1435, 1285, 754.

*4.2.11. Preparation of 2-((4-butylphenyl)amino)benzoic acid **(21)*** [43]

Aqueous potassium hydroxide (36 mL, 7.27 mmol) was added to **14** (1.03 g, 3.63 mmol) in ethanol (20 mL) at room temperature and allowed to react according to the general ester hydrolysis procedure to yield 0.90 g (92 %) of **21** as a pale yellow solid; M.p. 147-148 °C (literature M.p. 147-150 °C) [43]; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.95 (t, 3H, *J*= 8 Hz, -*CH*$_3$CH$_2$CH$_2$CH$_2$Ar), 1.39 (*sex.*, 2H, *J* = 8 Hz, -CH$_3$*CH*$_2$CH$_2$CH$_2$Ar), 1.61 (*quin*., 2H, *J* = 8 Hz, -CH$_3$CH$_2$*CH*$_2$CH$_2$Ar), 2.61 (t, 2H, *J* = 8 Hz, -CH$_3$CH$_2$CH$_2$*CH*$_2$Ar), 6.72 (*app*. t, 1H, app *J* = 8 Hz, HOOC-CH*CH*CHCHC-NH), 7.15 (*app*. d, 1H, HOOC-CHCHCH*CH*C-NH), 7.18 (*app*. s, 4H, C$_4$H$_9$-Ar*CH*), 7.33 (*app*. t, 1H, HOOC-CHCH*CH*CHC-NH), 8.01(*app*. d, 1H, HOOC-*CH*CHCHCHC-NH), 9.25 (s, 1H,-NH); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 14.0, 22.4, 33.7, 35.1, 109.9, 113.9, 116.7, 123.1, 123.7, 126.3, 129.4, 132.5, 135.2, 137.8, 139.1, 149.5, 173.2; Found $[M+H]^+$ ($C_{17}H_{22}NO_2$) m/z = 270.1490 (Calc. 270.1494); IR (ATR) *v*/cm^{-1}:3333, 3000-2480 (br), 2922, 1650, 1574, 1514, 1441, 1256, 746.

*4.2.12. Preparation of 3-((4-butylphenyl)amino)benzoic acid **(22)*** [44]

Aqueous potassium hydroxide (14 mL, 2.76 mmol) was added to **17** (0.39 g, 1.38 mmol) in ethanol (7 mL) at room temperature and allowed to react according to the general ester hydrolysis procedure to yield 0.30 g (81 %) of **22** as a pale yellow solid; M.p. 146-148 °C (literature M.p. 146-149 °C) [44]; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.94 (t, 3H, *J* = 8 Hz, -*CH*$_3$$CH_2CH_2CH_2$Ar), 1.38 (*sex.*, 2H, *J* = 8 Hz, -CH_3*CH*$_2$$CH_2CH_2$Ar), 1.60 (*quin*., 2H, *J* = 8 Hz, -CH_3CH_2*CH*$_2$$CH_2$Ar), 2.58 (t, 2H, *J* = 8 Hz, -$CH_3CH_2CH_2$*CH*$_2$Ar), 7.04 (*app*. d, 2H, *app. J* = 8 Hz, HN-Ar*CHCH*), 7.13 (*app*. d, 2H, *app. J* = 8 Hz, C_4H_9-Ar*CHCH*), 7.23 (*app*. d, 1H, *app. J* = 8 Hz, HN-CH-C(COOH)-CHCH*CH*-NH), 7.32 (*app*. t, 1H, *J* = 8 Hz, HN-CH-C(COOH)-CH*CH*CH-NH), 7.60 (*app.* d, 1H, *J* = 8 Hz, HN-CH-C(COOH)-*CH*CHCH-NH), 7.72 (*app.* s, 1H, HN-*CH*-C(COOH)-CHCHCH-NH); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 14.0, 22.4, 33.8, 35.0, 117.6, 119.5, 121.4, 121.7, 129.4, 129.5, 130.4, 137.1, 139.5, 144.5, 172.0; Found $[M+H]^+$ ($C_{17}H_{22}NO_2$) m/z = 270.1489 (Calc. 270.1494); IR (ATR) *v*/cm^{-1}: 3386, 3000-2500 (br), 2928, 1687, 1520, 1288, 746.

4.2.13. Preparation of 4-((4-butylphenyl)amino)benzoic acid ***(23)*** [45]

Aqueous potassium hydroxide (18 mL, 3.53 mmol) was added to **19** (0.50 g, 1.76 mmol) in ethanol (9 mL) at room temperature and allowed to react according to the general ester hydrolysis procedure to yield 0.41 g (86%) of **23** as a white solid; M.p. 138-140 °C (literature M.p. 138-140 °C) [45]; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.94 (t, 3H, *J* = 8 Hz, -*CH*$_3$$CH_2CH_2CH_2$Ar), 1.39 (*sex.*, 2H, *J* = 8 Hz, -CH_3*CH*$_2$$CH_2CH_2$Ar), 1.61 (*quin*., 2H, *J* = 8 Hz, -CH_3CH_2*CH*$_2$$CH_2$Ar), 2.60 (t, 2H, *J* = 8 Hz, -$CH_3CH_2CH_2$*CH*$_2$Ar), 6.00 (s, 1H, -NH), 6.94 (*app*. d, 2H, *app. J* = 12 Hz, HN-Ar*CHCH*-CHCH-C(COOH));), 7.11 (*app*. d, 2H, *app. J* = 8 Hz, HN-Ar*CHCH*), 7.17 (*app*. d, 1H, *app. J* = 8 Hz, C_4H_9-Ar*CHCH*), 7.96 (*app*. d, 2H, *J* = 8 Hz, Ar*CHCH*-C(COOH)); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 14.0, 22.4, 33.7, 35.1, 113.9, 119.4, 121.6, 129.4, 132.3, 137.9, 138.6, 149.5, 171.5; Found $[M+H]^+$ ($C_{17}H_{22}NO_2$) m/z =

270.1489 (Calc. 270.1494); IR (ATR) *v*/cm^{-1}: 3406, 3070-2545 (br), 2921, 1663, 1598, 1513, 1288, 1175, 755.

*4.2.14. Preparation of mixed amine-phenol **(24)***

The mono-phenolic linker **5** (0.21 g, 0.40 mmol), 2-((4-butylphenyl)amino)benzoic acid **21** (0.40 g, 1.49 mmol), DPTS (60%) and DCC (0.31 g, 1.49 mmol) were allowed to react according to the general mixed amine-phenol procedure. The crude product was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (90:10) (R_f =0.25) to afford 0.25 g (82%) of **24** as a yellow oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.85 (m, 6H, -CH_2*CH_3*), 0.94 (t, 3H, *J* = 8 Hz, -*CH_3*$CH_2CH_2CH_2$Ar), 1.25-1.38 (m, 13H, -*CH_2*CH_3, -*CH_3* and CH_3*CH_2*CH_2CH_2Ar), 1.42 (s, 18H, CH_3 *tert*-butyl), 1.60 (m, 3H, -CH_3CH_2*CH_2*CH_2Ar and -*CH*(CH_2CH_3)), 2.61 (m, 4H, Ph-CH_2*CH_2*-COO- and -C_3H_7*CH_2*Ar), 2.85 (t, 2H, *J* = 8 Hz, Ph-*CH_2*CH_2-COO-), 4.08 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.37 (s, 2H, COO-*CH_2*-C), 4.42 (s, 2H, COO-*CH_2*-C), 5.07 (s, 1H, -OH), 6.67 (*app*. t, 1H, -OOC-CH*CH*CHCHC-NH), 6.97 (s, 2H, Ph-*CH*), 7.15 (m, 5H, C_4H_9-Ar*CH* and -OOC-CHCH*CH*CHC-NH), 7.29 (app. d, 1H, *J* = 8 Hz, -OOC-CHCHCH*CH*C-NH), 7.85 (*app*. d, 1H, *J* = 8 Hz, -OOC-*CH*CHCHCHC-NH), 9.31 (s, 1H, -NH); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 10.9, 14.0, 18.0,22.4, 22.9, 23.7, 28.9, 30.3, 30.9, 33.7, 34.3, 35.1, 36.2, 38.7, 46.6, 65.8, 67.5, 110.7, 113.8, 116.7, 123.3, 124.7, 129.3, 130.8, 131.4, 135.9, 137.9, 138.8, 148.8, 152.2, 167.8, 172.7, 173.0; Found $[M+Na]^+$ ($C_{47}H_{67}NO_7Na$) m/z = 780.4810 (Calc. 780.4815); IR (ATR) *v*/cm^{-1}: 3636, 3324, 2960, 1731, 1516, 1225, 1134, 748.

*4.2.15. Preparation of mixed amine-phenol **(25)***

The mono-phenolic linker **5** (0.61 g, 1.20 mmol), 3-((4-butylphenyl)amino)benzoic acid **22** (0.48 g, 1.80 mmol), DPTS (60%) and DCC (0.37 g, 1.80 mmol) were allowed to react according to the general mixed amine-phenol procedure. The crude product was purified by

flash column chromatography on silica eluting with hexane/ethyl acetate (90:10) (R_f =0.23) to afford 0.75 g (82%) of **25** as a dark yellow oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.84 (m, 6H, -CH_2*CH_3*), 0.93 (t, 3H, *J* = 8 Hz, -*CH_3*$CH_2CH_2CH_2$Ar), 1.23-1.39 (m, 13H, -*CH_2*CH_3, -*CH_3* and CH_3*CH_2*CH_2CH_2Ar), 1.42 (s, 18H, CH_3 *tert*-butyl), 1.57 (m, 3H, -CH_3CH_2*CH_2*CH_2Ar and -*CH*(CH_2CH_3)), 2.59 (m, 4H, Ph-CH_2*CH_2*-COO- and -C_3H_7*CH_2*Ar), 2.84 (t, 2H, *J* = 8 Hz, Ph-*CH_2*CH_2-COO-), 4.05 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.34 (s, 2H, COO-*CH_2*-C), 4.43 (s, 2H, COO-*CH_2*-C), 5.07 (s, 1H, -OH), 5.75 (s, 1H, -NH), 6.97 (s, 2H, Ph-*CH*), 7.02 (*app*. d, 1H, *app*. *J* = 8 Hz, Ar*CH*-C(C_4H_9)), 7.11 (*app*. d, 2H, *app*. *J* = 8 Hz, Ar*CH*-CNH), 7.21(*app*. d, 2H, *app*. *J* = 8 Hz, HN-CH-C(COO-)-CHCH*CH*-), 7.28 (m, 1H, HN-CH-C(COO-)-CH*CH*CH-), 7.46 (*app*. d, 1H, *J* = 8 Hz, HN-CH-C(COO-)-*CH*CHCH-), 7.60 (m, 1H, HN-*CH*-C(COO-)); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 11.0, 14.0, 17.9, 22.4, 22.9, 23.7, 28.9, 30.3, 30.9, 33.8, 34.3, 35.0, 36.2, 38.7, 46.6, 65.7, 66.1, 67.4, 117.3, 119.4, 120.7, 121.0, 124.7, 129.4, 130.8, 130.9, 136.0, 144.4, 152.2, 166.1, 172.7, 172.9; Found $[M+H]^+$ ($C_{47}H_{68}NO_7$) m/z = 758.4961 (Calc. 758.4996); IR (ATR) *v*/cm^{-1}:3633, 3381, 2955, 1725, 1213, 749.

*4.2.16. Preparation of mixed amine-phenol **(26)***

The mono-phenolic linker **5** (0.50 g, 0.99 mmol), 4-((4-butylphenyl)amino)benzoic acid **23** (0.40 g, 1.49 mmol), DPTS (60%) and DCC (0.31 g, 1.49 mmol) were allowed to react according to the general mixed amine-phenol procedure. The crude product was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f =0.33) to afford 0.65 g (86%) of **26** as an orange oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.84 (m, 6H, -CH_2*CH_3*), 0.94 (t, 3H, *J* = 8 Hz, -*CH_3*$CH_2CH_2CH_2$Ar), 1.24-1.21 (m, 11H, -*CH_2*CH_3, -*CH_3*), 1.36 (m, 2H, CH_3*CH_2*CH_2CH_2Ar), 1.42 (s, 18H, CH_3 *tert*-butyl), 1.58 (m, 3H, -CH_3CH_2*CH_2*CH_2Ar and -*CH*(CH_2CH_3)), 2.60 (m, 4H, Ph-CH_2*CH_2*-COO- and -C_3H_7*CH_2*Ar), 2.84 (t, 2H, J=8 Hz, Ph-*CH_2*CH_2-COO-), 4.06 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.34 (s, 2H, COO-*CH_2*-C), 4.40 (s, 2H, COO-*CH_2*-C), 5.07 (s, 1H, -OH), 5.97 (s, 1H, -NH), 6.91 (*app*.

d, 2H, *app*. *J* = 8 Hz, NH-ArC-*CH*), 6.97 (s, 2H, Ph-*CH*), 7.06 (*app*. d, 2H, *app. J* = 8 Hz, Ar*CH*-C(C_4H_9)), 7.15 (*app*. d, 2H, *app*. *J* = 8 Hz, Ar*CH*-CNH), 7.84 (*app*. d, 2H, *app*. *J* = 8 Hz, Ar*CH*-C(COO-)); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 11.0, 14.0, 14.1, 17.9, 22.3, 22.9, 23.7, 28.9, 30.3, 30.9, 33.7, 34.3, 35.0, 36.2, 38.7, 46.7, 65.6, 65.7, 67.4, 114.0, 119.9, 121.3, 124.7, 129.4, 130.9, 131.6, 135.9, 138.1, 138.4, 149.0, 152.2, 165.9, 172.8, 173.1; Found $[M+Na]^+$ ($C_{47}H_{67}NO_7Na$) m/z = 780.4810 (Calc. 780.4815); IR (ATR) *v*/cm^{-1}: 3636, 3361, 2960, 1715, 1598, 1517, 1170, 754.

4.2.17. Preparation of bis(diphenylamine) ***(27)***

The first generation hydroxyl linker **6** (0.20 g, 0.91 mmol), 2-((4-butylphenyl)amino)benzoic acid **21** (0.56 g, 2.09 mmol), DPTS (60%) and DCC (0.43 g, 2.09 mmol) were allowed to react according to the general bis(diphenylamine) procedure. The crude product was purified by flash column chromatography on silica eluting with chloroform/hexane (70:30) (R_f =0.56) to afford 0.56 g (82%) of **27** as a yellow oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ =0.83 (m, 6H, -CH_2*CH_3*), 0.92 (t, 6H, *J* = 8 Hz, -*CH_3*$CH_2CH_2CH_2$Ar), 1.21-1.40 (m, 12H, -*CH_2*CH_3 and CH_3*CH_2*CH_2CH_2Ar), 1.46 (s, 3H, -CH_3), 1.60 (m, 5H, -CH_3CH_2*CH_2*CH_2Ar and -*CH*(CH_2CH_3)), 2.59 (t, 4H, *J* = 8 Hz, -$CH_3CH_2CH_2$*CH_2*Ar), 4.10 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.56 (s, 4H, COO-*CH_2*-C), 6.66 (*app*. t, 2H, *app*. *J* = 8 Hz, -OOC-CH*CH*CHCHC-NH), 7.15 (m, 10H, C_4H_9-Ar*CH* and -OOC-CHCHCH*CH*C-NH), 7.30 (m, 2H, -OOC-CHCH*CH*CHC-NH), 7.88 (*app*. d, 2H, *app*. *J* = 8 Hz, -OOC-*CH*CHCHCHC-NH), 9.32 (s, 2H, -NH); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 10.9, 14.0, 22.4, 22.9, 23.7, 28.9, 30.3, 33.7, 35.1, 46.9, 66.0, 67.6, 110.7, 113.8, 116.6, 123.3, 126.2, 129.3, 131.4, 134.4, 138.0, 138.7, 148.8, 167.8, 173.1; Found $[M+Na]^+$ ($C_{47}H_{60}N_2O_6Na$) m/z = 771.4344 (Calc. 771.4349); IR (ATR) *v*/cm^{-1}:3320, 2960, 1683, 1514, 1216, 1074, 745.

4.2.18. Preparation of bis(diphenylamine) ***(28)***

The first generation hydroxyl linker **6** (0.17 g, 0.74 mmol), 3-((4-butylphenyl)amino)benzoic acid **22** (0.46 g, 1.70 mmol), DPTS (60%) and DCC (0.35 g, 1.70 mmol) were allowed to react according to the general bis(diphenylamine) procedure. The crude product was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.50) to afford 0.42 g (75%) of **28** as a pale yellow oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.80 (m, 6H, -CH_2*CH_3*), 0.93 (t, 6H, *J* = 8 Hz, -*CH_3*$CH_2CH_2CH_2$Ar), 1.19-1.37 (m, 12H, -*CH_2*CH_3 and CH_3*CH_2*CH_2CH_2Ar), 1.40 (s, 3H, -*CH_3*), 1.58 (m, 5H, -CH_3CH_2*CH_2*CH_2Ar and -*CH*(CH_2CH_3)), 2.56 (t, 4H, *J* = 8 Hz, -C_3H_7*CH_2*Ar), 4.05 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.55 (s, 4H, COO-*CH_2*-C), 5.74 (s, 2H, -NH), 7.00 (*app*. d, 4H, *app*. *J* = 8 Hz, Ar*CH*-C(C_4H_9)), 7.10 (*app*. d, 4H, *app*. *J* = 8 Hz, Ar*CH*-CNH), 7.18 (m, 2H, HN-CH-C(COO-)-CHCH*CH*-), 7.25 (m, 2H, HN-CH-C(COO-)-CH*CH*CH-), 7.46 (*app*. d, 2H, *app*. *J* = 8 Hz, HN-CH-C(COO-)-*CH*CHCH-), 7.60 (m, 2H, HN-*CH*-C(COO-)); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 11.0, 14.0, 18.1, 22.3, 22.9, 23.7, 28.9, 30.3, 33.8, 35.0, 38.7, 46.8, 66.3, 67.5, 117.3, 118.9, 119.4, 120.6, 121.0, 126.3, 129.3, 130.8, 136.9, 139.6, 144.4, 166.1, 172.9; Found $[M+Na]^+$ ($C_{47}H_{60}N_2O_6Na$) m/z = 771.4343 (Calc. 771.4349); IR (ATR) *v*/cm^{-1}:3376, 2960, 1721, 1515, 1208, 1103, 747.

4.2.19. Preparation of bis(diphenylamine) ***(29)***

The first generation hydroxyl linker **6** (0.15 g, 0.65 mmol), 4-((4-butylphenyl)amino)benzoic acid **23** (0.40 g, 1.49 mmol), DPTS (60%) and DCC (0.31 g, 1.49 mmol) were allowed to react according to the general bis(diphenylamine) procedure. The crude product was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.53) to afford 0.44 g (90%) of **29** as a pale orange oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.82 (m, 6H, -CH_2*CH_3*), 0.94 (t, 6H, *J* = 8 Hz, -*CH_3*$CH_2CH_2CH_2$Ar), 1.20-1.38 (m, 15H, -*CH_2*CH_3, -CH_3, and CH_3*CH_2*CH_2CH_2Ar), 1.61 (m, 5H, -CH_3CH_2*CH_2*CH_2Ar and -*CH*(CH_2CH_3)), 2.59 (t, 4H, *J* = 8 Hz, -$CH_3CH_2CH_2$*CH_2*Ar), 4.08 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.52 (s, 4H, COO-*CH_2*-C), 5.96 (s, 2H, -NH), 6.90 (*app*. d, 4H, *app*. *J* =

8 Hz, Ar*CH*-CNH), 7.08 (*app*. d, 4H, *app*. *J* = 8 Hz, Ar*CH*-C(C_4H_9)), 7.15 (*app*. d, 4H, *app. J* = 8 Hz, Ar*CH*-CNH), 7.85 (*app.* d, 4H, *app*. *J* = 8 Hz Ar*CH*-C(COO-)); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 10.9, 14.0, 18.1, 22.3, 22.9, 23.7, 28.9, 30.3, 33.7, 35.0, 38.7, 47.0, 65.9, 67.4, 114.0, 120.0, 121.2, 129.4, 131.6, 138.1, 138.1, 148.9, 165.9, 173.2; Found $[M+Na]^+$ ($C_{47}H_{60}N_2O_6Na$) m/z = 771.4344 (Calc. 771.4349); IR (ATR) *v*/cm^{-1}: 3345, 2960, 1696, 1596, 1514, 1265, 1168, 1100, 755.

*4.2.20. Preparation of methyl 3-(3-((4-butylphenyl)amino)phenyl)propanoate **(30)***

Methyl 3-(3-bromophenyl)propanoate **31** (1.00 g, 4.11 mmol) and 4-butylaniline **16** (0.78 mL, 4.93 mmol) were added to $Pd(OAc)_2$ (0.02 g, 0.08 mmol), BINAP (0.10 g, 0.16 mmol) and Cs_2CO_3 (1.87 g, 5.75 mmol) and were allowed to react according to the general Buchwald-Hartwig amination procedure. The crude residue was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.41) to afford 0.43 g (34%) of **30** as an orange oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.93 (t, 3H, *J* = 8 Hz, -*CH*$_3$$CH_2CH_2CH_2$Ar), 1.36 (*sex*., 2H, *J* = 8 Hz, -CH_3*CH*$_2$$CH_2CH_2$Ar), 1.58 (*quin.*, 2H, *J* = 8 Hz, -CH_3CH_2*CH*$_2$$CH_2$Ar), 2.56 (t, 2H, *J* = 8 Hz, -$CH_3CH_2CH_2$*CH*$_2$Ar), 2.61 (t, 2H, *J* = 8 Hz, ArC-*CH*$_2$$CH_2$-$COOCH_3$), 2.89 (t, 2H, *J* = 8 Hz, ArC-CH_2*CH*$_2$-$COOCH_3$), 3.67 (s, 3H,-COO*CH*$_3$), 5.60 (s, 1H, -NH), 6.71 (*app*. d, *app*. *J* = 8 Hz, 2H, HN-CH-C(CH_2CH_2($COOCH_3$))-CHCH*CH*-), 6.86 (*app*. d, *app*. *J* = 8 Hz, 2H, HN-*CH*-C(CH_2CH_2($COOCH_3$))-*CH*CHCH-), 7.00 (*app*. d, 2H, *app. J* = 8 Hz, HN-Ar*CHCH*), 7.09 (*app*. d, 2H, *app. J* = 8 Hz, C_4H_9-Ar*CHCH*), 7.14 (*app*. d, 1H, *app. J* = 8 Hz, HN-CH-C($COOCH_3$)-CHCH*CH*-NH); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 14.0, 22.4, 31.0, 33.8, 35.0, 35.7, 51.7, 114.8, 116.7, 118.8, 120.2, 129.2, 129.4, 136.1, 140.4, 141.8, 144.1, 173.4; Found $[M+H]^+$ ($C_{20}H_{26}NO_2$) m/z = 312.1958 (Calc. 312.1964); IR (ATR) *v*/cm^{-1}: 3380, 2925, 1725, 1591, 1514, 1166, 778.

*4.2.21. Preparation of ethyl 2-(4-((4-butylphenyl)amino)phenyl)acetate **(32)***

Ethyl 2-(4-(bromophenyl)acetate **33** (0.50 g, 2.06 mmol) and 4-butylaniline **16** (0.39 mL, 2.47 mmol) were added to $Pd(OAc)_2$ (0.01 g, 0.04 mmol), BINAP (0.05 g, 0.08 mmol) and Cs_2CO_3 (0.94 g, 2.88 mmol) and were allowed to react according to the general Buchwald-Hartwig amination procedure. The crude residue was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (85:15) (R_f = 0.33) to afford 0.43 g (67%) of **32** as an orange oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.92 (t, 3H, *J* = 8 Hz, -*CH*$_3$$CH_2CH_2CH_2$Ar), 1.25 (t, 3H, *J* = 8 Hz, ArC-CH_2-$COOCH_2$*CH*$_3$), 1.35 (*sex*., 2H, *J* = 8 Hz, -CH_3*CH*$_2$$CH_2CH_2$Ar), 1.57 (*quin*, 2H, *J* = 8 Hz, -CH_3CH_2*CH*$_2$$CH_2$Ar), 2.55 (t, 2H, *J* = 8 Hz, -$CH_3CH_2CH_2$*CH*$_2$Ar), 3.53 (s, 2H, ArC-*CH*$_2$-$COOCH_2CH_3$), 4.14 (q, 2H, *J* = 8 Hz, ArC-CH_2-COO*CH*$_2$$CH_3$), 5.62 (s, 1H, -NH), 6.97 (m, 4H, HN-Ar*CH*$_4$-CH_2($COOCH_2CH_3$)), 7.00 (*app*. d, 2H, *app. J* = 8 Hz, HN-Ar*CHCH*), 7.07 (*app*. d, 2H, *app. J* = 8 Hz, C_4H_9-Ar*CHCH*); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 14.0, 14.3, 22.4, 33.9, 35.0, 40.7, 60.8, 117.1, 118.6, 125.8, 129.2, 130.1, 136.0, 140.6, 142.9, 172.1; Found $[M+H]^+$ ($C_{20}H_{26}NO_2$) m/z = 312.1958 (Calc. 312.1964); IR (ATR) *v*/cm^{-1}: 3385, 2928, 1725, 1608, 1514, 1308, 1140, 750.

*4.2.22. Preparation of methyl 3-(4-((4-butylphenyl)amino)phenyl)propanoate **(34)***

Methyl 3-(4-(bromophenyl)propanoate **35** (1.01 g, 4.11 mmol) and 4-butylaniline **16** (0.78 mL, 4.93 mmol) were added to $Pd(OAc)_2$ (0.02 g, 0.08 mmol), BINAP (0.10 g, 0.16 mmol) and Cs_2CO_3 (1.87 g, 5.75 mmol) and were allowed to react according to the general Buchwald-Hartwig amination procedure. The crude residue was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.37) to afford 1.61 g (91%) of **34** as a waxy yellow solid; M.p. 48-50 °C; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.93 (t, 3H, *J* = 8 Hz, -*CH*$_3$$CH_2CH_2CH_2$Ar), 1.36 (*sex*., 2H, *J* = 8 Hz, -CH_3*CH*$_2$$CH_2CH_2$Ar), 1.57 (*quin*, 2H, *J* = 8 Hz, -CH_3CH_2*CH*$_2$$CH_2$Ar), 2.55 (t, 2H, *J* = 8 Hz, -$CH_3CH_2CH_2$*CH*$_2$Ar), 2.61 (t, 2H, Ar-*CH*$_2$$CH_2$-($COOCH_3$)), 2.89 (t, 2H, Ar-$CH_2$*CH*$_2$-($COOCH_3$)), 3.67 (s, 3H, -$COO$*CH*$_3$), 5.56 (s, 1H, -NH), 6.97 (m, 4H, HN-Ar*CH*$_4$-CH_2($COOCH_2CH_3$)), 7.07 (*app*. d, 2H, *app. J* = 8

Hz, C_4H_9-Ar*CH*$_4$); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 14.0, 22.4, 30.2, 33.9, 34.9, 36.0, 51.6, 117.5, 118.2, 129.1, 129.2, 132.5, 135.7, 140.8, 142.0, 173.5; Found $[M+H]^+$ ($C_{20}H_{26}NO_2$) m/z = 312.1958 (Calc. 312.1964); IR (ATR) *v*/cm^{-1}: 3384, 2960, 1726, 1514, 1191, 823.

*4.2.23. Preparation of 3-(3-((4-butylphenyl)amino)phenyl)propanoic acid **(36)***

Aqueous potassium hydroxide (11 mL, 2.24 mmol) was added to **30** (0.35 g, 1.12 mmol) in ethanol (6 mL) at room temperature and allowed to react according to the general ester hydrolysis procedure to yield 0.25 g (70%) of **36** as a waxy red solid; M.p. 45-47 °C; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.93 (t, 3H, *J* = 8 Hz, -*CH*$_3$CH$_2$CH$_2$CH$_2$Ar), 1.38 (*sex.*, 2H, *J* = 8 Hz, -CH$_3$*CH*$_2$CH$_2$CH$_2$Ar), 1.58 (*quin*., 2H, *J* = 8 Hz, -CH$_3$CH$_2$*CH*$_2$CH$_2$Ar), 2.56 (t, 2H, *J* = 8 Hz, -CH$_3$CH$_2$CH$_2$*CH*$_2$Ar), 2.67 (t, 2H, *J* = 8 Hz, ArC-*CH*$_2$CH$_2$-COOCH$_3$), 2.89 (t, 2H, *J* = 8 Hz, ArC-CH$_2$*CH*$_2$-COOCH$_3$), 6.72 (*app*. d, 1H, HN-CH-C(CH$_2$CH$_2$(COOH))-*CH*CHCH), 6.86 (m, 2H, HN-*CH*-C(CH$_2$CH$_2$(COOH))-CHCH*CH*), 7.00 (*app*. d, 2H, *app. J* = 8 Hz, HN-Ar*CHCH*), 7.09 (*app*. d, 1H, *app. J* = 8 Hz, C_4H_9-Ar*CHCH*), 7.16 (*app*. t, 2H, *J* = 8 Hz, HN-CH-C(CH$_2$CH$_2$(COOH))-CH*CH*CH); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 14.0, 22.4, 30.6, 33.8, 34.9, 35.5, 114.8, 116.6, 118.9, 120.1, 129.2, 129.5, 136.2, 140.3, 141.4, 144.1, 178.8; Found $[M+Na]^+$ ($C_{19}H_{23}NO_2Na$) m/z = 320.1622 (Calc. 320.1626); IR (ATR) *v*/cm^{-1}: 3407, 3102-2601 (br), 2960, 1687, 1605, 1519, 1303, 792.

*4.2.24. Preparation of 2-(4-((4-butylphenyl)amino)phenyl)acetic acid **(37)***

Aqueous potassium hydroxide (41 mL, 8.16 mmol) was added to **32** (1.27 g, 4.08 mmol) in ethanol (20 mL) at room temperature and allowed to react according to the general ester hydrolysis procedure to yield 0.73 g (63%) of **37** as a pale orange solid; M.p. 105-108 °C; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.93 (t, 3H, *J* = 8 Hz, -*CH*$_3$CH$_2$CH$_2$CH$_2$Ar), 1.38 (*sex*., 2H, *J* = 8 Hz, -CH$_3$*CH*$_2$CH$_2$CH$_2$Ar), 1.58 (*quin*, 2H, *J* = 8 Hz, -CH$_3$CH$_2$*CH*$_2$CH$_2$Ar), 2.56 (t, 2H, *J* =

8 Hz, -$CH_3CH_2CH_2CH_2$Ar), 3.58 (s, 2H, ArC-CH_2-COOH), 6.99 (m, 4H, HN-ArCH_4-CH_2(COOCH)), 7.08 (*app*. d, 2H, *app. J* = 8 Hz, HN-Ar*CHCH*), 7.14 (*app*. d, 2H, *app. J* = 8 Hz, C_4H_9-Ar*CHCH*); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 14.0, 22.4, 33.8, 34.9, 40.2, 117.0, 118.8, 124.8, 129.2, 130.3, 136.2, 140.3, 143.2, 177.4; Found $[M+H]^+$ ($C_{18}H_{22}NO_2$) m/z = 284.1645 (Calc. 284.1651); IR (ATR) *v*/cm^{-1}: 3374, 3088-2535 (br), 2923, 1696, 1611, 1515, 1177, 803.

*4.2.25. Preparation of 3-(4-((4-butylphenyl)amino)phenyl)propanoic acid **(38)***

Aqueous potassium hydroxide (32 mL, 6.42 mmol) was added to **34** (1.00 g, 3.21 mmol) in ethanol (16 mL) at room temperature and allowed to react according to the general ester hydrolysis procedure to yield 0.91 g (95%) of **38** as a pale orange solid; M.p. 118-120 °C; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.93 (t, 3H, *J* = 8 Hz, -$CH_3$$CH_2CH_2CH_2$Ar), 1.39 (*sex*., 2H, *J* = 8 Hz, -$CH_3CH_2$$CH_2CH_2$Ar), 1.58 (*quin*, 2H, *J* = 8 Hz, -$CH_3CH_2CH_2$$CH_2$Ar), 2.55 (t, 2H, *J* = 8 Hz, -$CH_3CH_2CH_2CH_2$Ar), 2.66 (t, 2H, Ar-$CH_2$$CH_2$-($COOCH_3$)), 2.90 (t, 2H, Ar-$CH_2CH_2$-($COOCH_3$)), 6.97 (m, 4H, HN-Ar$CH_4$-$CH_2$($COOCH_2CH_3$)), 7.08 (m, 4H, C_4H_9-ArCH_4); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 14.0, 22.4, 30.0, 33.8, 34.9, 35.8, 117.4, 118.3, 129.1, 129.2, 132.1, 135.8, 140.7, 142.2, 178.5; Found $[M+Na]^+$ ($C_{19}H_{23}NO_2Na$) m/z = 320.1622 (Calc. 320.1626); IR (ATR) *v*/cm^{-1}: 3402, 3090-2607 (br), 2920, 1689, 1514, 1305, 818.

*4.2.26. Preparation of mixed amine-phenol **(39)***

The mono-phenolic linker **5** (0.40 g, 0.79 mmol), 3-(3-((4-butylphenyl)amino)phenyl)propanoic acid **36** (0.35 g, 1.18 mmol), DPTS (60%) and DCC (0.24 g, 1.18 mmol) were allowed to react according to the general mixed amine-phenol procedure. The crude product was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.39) to afford 0.52 g (84%) of **39** as a dark orange oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.87 (m, 6H, -CH_2CH_3), 0.93 (t, 3H, *J* = 8 Hz, -

CH$_3$CH$_2$CH$_2$CH$_2$Ar), 1.16 (s, 3H, -CH$_3$), 1.26-1.35 (m, 10H, -*CH*$_2$CH$_3$), 1.42 (s, 18H, -CH$_3$ *tert*-butyl), 1.58 (m, 3H, -CH$_3$CH$_2$*CH*$_2$CH$_2$Ar and -*CH*(CH$_2$CH$_3$)), 2.59 (m, 6H, Ph-CH$_2$*CH*$_2$-COO-, -C$_3$H$_7$*CH*$_2$Ar, ArC-*CH*$_2$CH$_2$-COO), 2.85 (m, 4H, Ph-*CH*$_2$CH$_2$-COO-, ArC-CH$_2$*CH*$_2$-COO), 4.03 (m, 2H, COO-*CH*$_2$-CH(CH$_2$CH$_3$)-C$_4$H$_9$), 4.21 (s, 4H, COO-*CH*$_2$-C), 5.07 (s, 1H, -OH), 5.69 (s, 1H, -NH), 6.69 (*app*. d, 1H, HN-ArCH^2-C(CH$_2$CH$_3$COO-)-*CH*^{4}CH^{5}CH^6-), 6.82 (*app*. s, 1H, HN-Ar*CH*^{2}-C(CH$_2$CH$_3$COO-)), 6.87 (*app*. d, 1H, HN-ArCH^2-C(CH$_2$CH$_3$COO-)-CH^{4}CH^5*CH*^{6}-), 6.97 (s, 2H, Ph-*CH*), 7.00 (*app*. d, 2H, Ar*CHCH*C-NH), 7.08 (*app*. d, 2H, C$_4$H$_9$-Ar*CHCH*), 7.14 (*app*. t, 1H, HN-ArCH^2-C(CH$_2$CH$_3$COO-)-CH^4*CH*^{5}CH^6-); ^{13}C NMR (100 MHz/CDCl$_3$)/ppm, δ =11.0, 14.0, 17.8, 22.4, 22.9, 23.7, 28.9, 30.2, 30.3, 30.8, 33.8, 34.3, 34.9, 36.2, 38.7, 46.4, 65.4, 65.6, 67.4, 114.6, 116.7, 118.7, 124.7, 126.1, 129.2, 129.4, 130.8, 135.9, 136.0, 140.4, 141.5, 144.1, 152.2, 172.4, 172.7, 172.9; Found [M+H]$^+$ (C$_{49}$H$_{72}$NO$_7$) m/z = 786.5303 (Calc. 786.5309); IR (ATR) *ν*/cm^{-1}: 3634, 3380, 2960, 1731, 1515, 1135, 752.

*4.2.27. Preparation of mixed amine-phenol **(40)***

The mono-phenolic linker **5** (0.51 g, 1.01 mmol), 2-(4-((4-butylphenyl)amino)phenyl)acetic acid **37** (0.43 g, 1.52 mmol), DPTS (60%) and DCC (0.31 g, 1.52 mmol) were allowed to react according to the general mixed amine-phenol procedure. The crude product was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (85:15) (R$_f$ = 0.33) to afford 0.42 g (54%) of **40** as an orange oil; ^{1}H NMR (400 MHz/CDCl$_3$)/ppm, δ = 0.87 (m, 6H, -CH$_2$*CH*$_3$), 0.93 (t, 3H, *J* = 8 Hz, -*CH*$_3$CH$_2$CH$_2$CH$_2$Ar), 1.16 (s, 3H, -CH$_3$), 1.26-1.36 (m, 10H, -*CH*$_2$CH$_3$), 1.42 (s, 18H, -CH$_3$ *tert*-butyl), 1.57 (m, 3H, -CH$_3$CH$_2$*CH*$_2$CH$_2$Ar and -*CH*(CH$_2$CH$_3$)), 2.56 (m, 4H, Ph-CH$_2$*CH*$_2$-COO- and -C$_3$H$_7$*CH*$_2$Ar), 2.82 (t, 2H, *J* = 8 Hz, Ph-*CH*$_2$CH$_2$-COO-), 3.53 (s, 2H, ArC-*CH*$_2$-COO), 4.00 (m, 2H, COO-*CH*$_2$-CH(CH$_2$CH$_3$)-C$_4$H$_9$), 4.21 (m, 4H, COO-*CH*$_2$-C), 5.07 (s, 1H, -OH), 5.60 (s, 1H, -NH), 6.97 (m, 6H, Ph-*CH* and Ar*CH*-CNH), 7.10 (m, 4H, Ar*CH*-CCH$_2$); ^{13}C NMR (100 MHz/CDCl$_3$)/ppm, δ = 11.0, 14.0,

14.1, 17.8, 22.4, 22.9, 23.7, 28.9, 30.3, 30.8, 33.8, 34.3, 34.9, 36.2, 38.7, 40.4, 46.4, 65.4, 65.8, 67.4, 117.0, 118.6, 124.7, 125.3, 129.2, 130.1, 130.8, 135.9, 136.1, 140.4, 143.0, 152.2, 171.4, 172.6, 172.8; Found $[M+H]^+$($C_{48}H_{70}NO_7$) m/z = 772.5147 (Calc. 771.5152); IR (ATR) *v*/cm^{-1}: 3632, 3382, 2960, 1730, 1514, 1132, 753.

*4.2.28. Preparation of mixed amine-phenol **(41)***

The mono-phenolic linker **5** (0.46 g, 0.90 mmol), 3-(4-((4-butylphenyl)amino)phenyl)propanoic acid **38** (0.40 g, 1.34 mmol), DPTS (60%) and DCC (0.28 g, 1.34 mmol) were allowed to react according to the general mixed amine-phenol procedure. The crude product was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.37) to afford 0.64 g (90%) of **41** as a purple oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.87 (m, 6H, -CH_2*CH_3*), 0.93 (t, 3H, *J* = 8 Hz, -*CH_3*$CH_2CH_2CH_2$Ar), 1.16 (s, 3H, -CH_3), 1.27-1.36 (m, 10H, -*CH_2*CH_3), 1.42 (s, 18H, -CH_3 *tert*-butyl), 1.57 (m, 3H, -CH_3CH_2*CH_2*CH_2Ar and -*CH*(CH_2CH_3)), 2.59 (m, 6H, Ph-CH_2*CH_2*-COO-, -C_3H_7*CH_2*Ar, ArC-*CH_2*CH_2-COO), 2.85 (m, 4H, Ph-*CH_2*CH_2-COO-, ArC-CH_2*CH_2*-COO), 4.03 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.21 (s, 4H, COO-*CH_2*-C), 5.07 (s, 1H, -OH), 5.56 (s, 1H, -NH), 6.96 (m, 6H, Ph-*CH* and Ar*CH*-CNH), 7.06 (m, 4H, Ar*CH*-CCH_2); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 11.0, 14.0, 17.8, 22.4, 22.9, 23.7, 28.9, 30.3, 30.8, 33.8, 34.3, 34.9, 35.9, 36.2, 38.7, 46.4, 65.5, 67.3, 117.5, 118.2, 124.7, 126.1, 129.0, 129.2, 130.8, 132.2, 135.7, 136.0, 140.8, 142.1, 152.2, 172.5, 172.7, 172.9; Found $[M+H]^+$($C_{49}H_{72}NO_7$) m/z = 786.5303 (Calc. 786.5309); IR (ATR) *v*/cm^{-1}:3633, 3384, 2960, 1731, 1514, 1136, 753.

*4.2.29. Preparation of bis(diphenylamine) **(42)***

The first generation hydroxyl linker **6** (0.08 g, 0.35 mmol), 3-(3-((4-butylphenyl)amino)phenyl)propanoic acid **36** (0.24 g, 0.81 mmol), DPTS (60%) and DCC (0.17 g, 0.81 mmol) were allowed to react according to the general bis(diphenylamine)

procedure. The crude product was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.38) to afford 0.21 g (75%) of **42** as a pale orange oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.86 (m, 6H, -CH_2*CH_3*), 0.93 (t, 6H, *J* = 8 Hz, -*CH_3*$CH_2CH_2CH_2$Ar), 1.15 (s, 3H, -CH_3), 1.26-1.39 (m, 12H, -*CH_2*CH_3), 1.58 (m, 5H, -CH_3CH_2*CH_2*CH_2Ar and -*CH*(CH_2CH_3)), 2.55 (t, 4H, *J* = 8 Hz, -C_3H_7*CH_2*Ar), 2.60 (t, 4H, *J* = 8 Hz, ArC-*CH_2*CH_2-COO), 2.86 (t, 4H, *J* = 8 Hz, ArC-CH_2*CH_2*-COO), 4.02 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.19 (m, 4H, COO-*CH_2*-C), 5.67 (s, 2H, -NH), 6.68 (app. d, 2H, *J* = 8 Hz, HN-ArCH^2-C(CH_2CH_3COO-)-*CH^4*CH^5CH^6-), 6.80 (m, 2H, HN-Ar*CH^2*-C(CH_2CH_3COO-)), 6.87 (m, 2H, HN-ArCH^2-C(CH_2CH_3COO-)-CH^4CH^5*CH^6*-), 6.99 (*app*. d, 4H, *app*. *J* = 8 Hz, Ar*CHCH*C-NH), 7.10 (*app*. d, 4H, *app*. *J* = 8 Hz, C_4H_9-Ar*CHCH*), 7.13 (*app*. t, 2H, *app*. *J* = 8 Hz, HN-ArCH^2-C(CH_2CH_3COO-)-CH^4*CH^5*CH^6-); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 11.0, 14.0, 17.8, 22.4, 22.9, 23.7, 28.9, 30.3, 30.8, 31.5, 33.8, 34.9, 35.5, 38.7, 46.3, 65.5, 67.4, 114.6, 116.8, 118.7, 120.1, 129.2, 129.4, 136.0, 140.4, 141.5, 144.1, 172.4, 172.9; Found $[M+H]^+$($C_{51}H_{69}N_2O_6$) m/z = 805.5155 (Calc. 805.5156); IR (ATR) *v*/cm^{-1}: 3382, 2960, 1730, 1514, 1134, 776.

4.2.30. Preparation of bis(diphenylamine) ***(43)***

The first generation hydroxyl linker **6** (0.19 g, 0.86 mmol), 2-(4-((4-butylphenyl)amino)phenyl)acetic acid **37** (0.56 g, 1.98 mmol), DPTS (60%) and DCC (0.41 g, 1.98 mmol) were allowed to react according to the general bis(diphenylamine) procedure. The crude product was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.41) to afford 0.46 g (68%) of **43** as a dark red oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.87 (m, 6H, -CH_2*CH_3*), 0.93 (t, 6H, *J* = 8 Hz, -*CH_3*$CH_2CH_2CH_2$Ar), 1.15 (s, 3H, -CH_3), 1.25-1.30 (m, 8H, -*CH_2*CH_3), 1.36 (m, 4H, -CH_3*CH_2*CH_2CH_2Ar), 1.58 (m, 5H, -CH_3CH_2*CH_2*CH_2Ar and -*CH*(CH_2CH_3)), 2.55 (t, 4H, *J* = 8 Hz, -$CH_3CH_2CH_2$*CH_2*Ar), 3.50 (s, 4H, ArC-*CH_2*-COO-), 3.98 (m, 2H, COO-*CH_2*-

CH(CH_2CH_3)-C_4H_9), 4.16 (d, 2H, *J* = 12 Hz, COO-*CH_2*-C), 4.22 (d, 2H, *J* = 12 Hz, COO-*CH_2*-C), 5.59 (s, 2H, -NH), 6.94 (*app*. d, 4H, Ar*CH*-CNH), 6.98 (*app*. d, 4H, Ar*CH*-CNH), 7.07 (m, 8H, Ar*CH*-CCH_2); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 10.9, 14.0, 17.9, 22.4, 23.0, 28.9, 30.3, 31.5, 33.8, 34.9, 38.6, 40.4, 46.3, 65.6, 67.4, 117.1, 118.6,125.3, 129.2, 130.1, 136.0, 140.4, 142.9, 171.4, 172.8; Found $[M+H]^+$($C_{49}H_{65}N_2O_6$) m/z = 777.4839 (Calc. 777.4843); IR (ATR) *v*/cm^{-1}:3379, 2960, 1730, 1607, 1514, 1131.

4.2.31. Preparation of bis(diphenylamine) ***(44)***

The first generation hydroxyl linker **6** (0.13 g, 0.58 mmol), 3-(4-((4-butylphenyl)amino)phenyl)propanoic acid **38** (0.40 g, 1.34 mmol), DPTS (60%) and DCC (0.28 g, 1.34 mmol) were allowed to react according to the general bis(diphenylamine) procedure. The crude product was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (80:20) (R_f = 0.42) to afford 0.45 g (96%) of **44** as a pale yellow oil; ^{1}H NMR (400 MHz/$CDCl_3$)/ppm, δ = 0.87 (m, 6H, -CH_2*CH_3*), 0.92 (t, 6H, *J* = 8 Hz, -*CH_3*$CH_2CH_2CH_2$Ar), 1.17 (s, 3H, -CH_3), 1.27-1.38 (m, 12H, -*CH_2*CH_3 and -CH_3*CH_2*CH_2CH_2Ar), 1.57 (m, 8H, -CH_3CH_2*CH_2*CH_2Ar and -*CH*(CH_2CH_3)), 2.57 (m, 8H, -$CH_3CH_2CH_2$*CH_2*Ar and Ar-*CH_2*CH_2-(COO-)), 2.85 (t, 4H, J=8 Hz, Ar-CH_2*CH_2*-($COOCH_3$)), 4.03 (m, 2H, COO-*CH_2*-CH(CH_2CH_3)-C_4H_9), 4.19 (s, 4H, COO-*CH_2*-C), 5.55 (s, 2H, -NH), 6.95 (m, 8H, Ar*CH*-CCH_2), 7.05 (m, 8H, Ar*CH*-CNH); ^{13}C NMR (100 MHz/$CDCl_3$)/ppm, δ = 11.0, 14.0, 17.8, 22.4, 22.9, 23.7, 28.9, 30.1, 30.3, 33.8, 34.9, 35.9, 38.7, 46.3, 65.5, 67.4, 117.5, 118.2, 129.0, 129.2, 132.2, 135.7, 140.8, 142.0, 172.5, 172.9; Found $[M+H]^+$($C_{51}H_{69}N_2O_6$) m/z = 805.5150 (Calc. 805.5156); IR (ATR) *v*/cm^{-1}: 3384, 2960, 1730, 1514, 1137, 752.

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References

[1] Santos JCO, Santos IMG., Sinfrônio FSM, Silva MA, Sobrinho EV, *J. Therm. Anal. Calorim.* 2005; 79:461.

[2] Dantas TNC, Dantas MSG, Dantas AAN, Ornellas CVD, Queiroz LR, *Fuel* 2003; 82:1465.

[3] Rios MADS, *J. Therm. Anal. Calorim.* 2013; 111:553.

[4] Sevim ZE, Svajus A, *Ind. Crop. Prod.* 2000; 11:277.

[5] Keating MY, Howell JL, J. *Therm. Anal. Calorim.* 2011; 106:213.

[6] Ren D, Gellman AJ, *Tribol. Int.* 2001; 34:353.

[7] Duangkaewmanee S, Petsom A, *Tribol. Int.* 2011; 44:266.

[8] Rios MADS, Mazzetto SE, *J. Therm. Anal. Calorim.* 2013; 111:553.

[9] Du D, Kim SS, Moon WS, Jin SB, Kwon WS, *Thermochim. Acta.* 2003; 407:17.

[10] He JB, Shi H, Wang Y, Gao XL, *Molecules* 2018; 23:401.

[11] Jing Y, Diao Y, Yu X, *React. Funct. Polym.* 2019; 135:16.

[12] Ingold KU, *Chem. Rev.* 1961; 61:563.

[13] Ingold KU, Pratt DA, *Chem. Rev.* 2014; 114:9022.

[14] Shah R, Haidasz EA, Valgimigli L, Pratt DA, *J. Am. Chem. Soc.* 2015; 137:2440.

[15] Czochara R, Kusio J, Symonowicz M, Litwinienko G, *Ind. Eng. Chem. Res.* 2016; 55:9887.

[16] Bolbukh Y, Kuzema P, Tertykh V, Laguta I, *J. Therm. Anal. Calorim.* 2008; 94:727.

[17] Gensler R, Plummer CJG, Kausch HH, Kramer E, Pauquet JR, Zweifel H, *Polym. Degrad. Stab.* 2000; 67:195.

[18] Miao C, Zhang L, Zheng K, Cui Y, Zhang S, Yu L, Zhang P, *Tribol. Int.* 2015; 88:95.

[19] Gatto VJ, Elnagar HY, Moehle WE, Schneller ER, *Lubr. Sci.* 2007; 19:25.

[20] Valgimigli L, Pratt DA, *Acc. Chem. Res.* 2015; 48:966.

[21] Hanthorn JJ, Valgimigli L, Pratt DA, *J. Org. Chem.* 2012; 77:6908.

[22] Feng J, Zhao H, Yue S, Liu S, *ACS Sustainable Chem. Eng.* 2017; 5:3399.

[23] Duangkaewmanee S, Petsom A, *Tribol. Int.* 2011; 44:266.
[24] Chao TS, Hutchison DA, Kjonaas M, *Ind. Eng. Chem. Prod. Res. Dev.* 1984; 23:21.
[25] Fotty R, Rakovsky S, Marchevsky P, Popov AA, *Oxid. Commun.* 1997; 20:208.
[26] Gatto VJ, Grina MA, *Lubr. Eng.* 1999; 55:11.
[27] Sharma BK, Perez JM, Erhan SZ, *Energy Fuels* 2007; 21:2408.
[28] Kassler A, Pittenauer E, Doerr N, Allmaier G, *Rapid Commun. Mass Spectrum.* 2014; 28:63.
[29] Higgins CL, Fillip SV, Afsar A, Hayes W, *React. Funct. Polym.* 2019; 142:119.
[30] Kumar S, Johansson H, Kanda T, Engman L, Müller T, Jonsson M, Pedulli GF, Petrucci S, Valgimigli L, *Org. Lett.* 2008; 10:4895.
[31] Gatto VJ, Elnagar HY, Moehle WE, Schneller ER, *lubrication Science* 2007; 19:25.
[32] Hanthorn JJ, Valgimigli L, Pratt DA, *J. Am. Chem. Soc.* 2012; 134:8306.
[33] Valgimigli L, Brigati G, Pedulli GF, DiLabio GA, Mastragostino M, Arbizzani C, Pratt DA, *Chem. Eur. J.* 2003; 9:4997.
[34] Miao C, Zhang Y, Yang G, Zhang S, Yu L, Zhang P, *Ind. Eng. Chem. Res.* 2016; 55:12703.
[35] Li C, Sun P, Guo S, Zhang Z, Wang J, *J. Appl. Polym. Sci.* 2017; 134:45095.
[36] Yu S, Feng J, Cai T, Liu S, *Ind. Eng. Chem. Res.* 2017; 56:4196.
[37] Louie J, Hartwig JF, *Tetrahedron Lett.* 1995; 36:3609.
[38] Driver MS, Hartwig JF, *J. Am. Chem. Soc.* 1996; 118:7217.
[39] Guram AS, Rennels RA, Buchwald SL, *Angew. Chemie Int. Ed.* 1995; 34:1348.
[40] Suarez-Pantiga S, Hernandez-Ruiz R, Virumbrales C, Pedrosa MR, Sanz R, *Angew. Chemie Int. Ed.* 2019; 58:2129.
[41] Vantourout JC, Law RP, Isidro-Llobet A, Atkinson SJ, Watson AJB, *J. Org. Chem.* 2016; 81:3942.
[42] Park NH, Teverovskiy G, Buchwald SL, *Org. Lett.* 2014; 16:220.
[43] Graboyes H, Anderson EL, Levinson SH, Resnick TM, *J. Heterocycl. Chem.* 1975; 12:1225.
[44] Acheson RM, Bolton RG, *J. Chem. Soc. Perkin 1* 1975; 1975:650.
[45] Huang X, Anderson KW, Zim D, Jiang L, Klapars A, Buchwald SL, *J. Am. Chem. Soc.* 2003; 125:6653.

Tables, Figures and schemes captions

Figure 1. Structure of Schiff base bridged phenolic diphenylamine (SPD) antioxidants **SPD1** and **SPD2** [37].

Figure 2. Commercial antioxidants a) Irganox L135 and b) L57.

Scheme 1. The statistical reaction between 3-(3,5 di-tert-butyl-4-hydroxyphenyl)propionic acid **7**, **4** and **6** to yield the mixed amine-phenol **8**.

Figure 3. Potential products from the statistical reaction shown in Scheme 1.

Scheme 2. Synthesis of the mono-phenolic hydroxyl linker **5** and mixed amine-phenol **8**.

Table 1. Structure of the meta substituted amine-phenol **8** and *bis*(diphenylamine) **9** for comparison against the para substituted amine-phenol **11** and *bis*(diphenylamine) **13**.

Scheme 3. General scheme for the synthesis of **Series 2** diphenylamine derivatives.

Table 2. Structure of the *ortho*, *meta* and *para* substituted amine-phenols **24**-**26** and the *bis*(diphenylamines) **27**-**29** for comparison.

Scheme 4 General scheme for the synthesis of **Series 3** diphenylamine derivatives.

Table 3. Structure of the mixed amine-phenols **39**-**41** and the *bis*(diphenylamines) **42**-**44** for comparison

Figure 4. Average Oxidation induction time of 0.5% w/w antioxidant-base oil samples (tested in duplicate).

Figure 5. Average Oxidation onset temperature of 0.5% w/w antioxidant-base oil samples (tested in duplicate).

Figure 6. Average Oxidation induction time of **Series 2**, mixed amine-phenol base oil samples (tested in duplicate).

Figure 7. Comparison of oxidation induction time analysis from **Series 1** and **2**.

Figure 8. Oxidation onset temperature analysis of **Series 2**, mixed amine-phenol base oil samples.

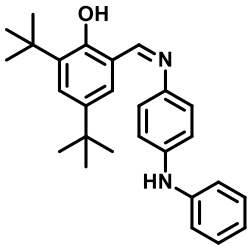
Figure 9. Oxidation induction time analysis of *bis*(diphenylamines) **27**-**29**.

Figure 10. Oxidation induction time analysis of **Series 3**, mixed amine-phenol base oil samples.

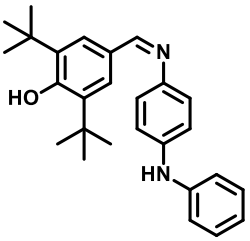
Figure 11. Comparison of average oxidation induction time analysis from **Series 1** (**8**), **Series 2** (**25**) and **Series 3** (**39**).

Figure 12. Average Oxidation onset temperature analysis of **Series 3**, mixed amine-phenol base oil samples (tested in duplicate).

Figures and Schemes

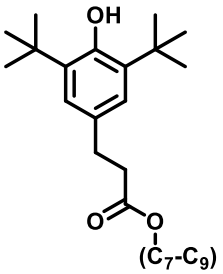


SPD1

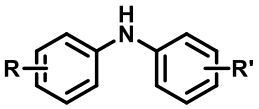


SPD2

Figure 1

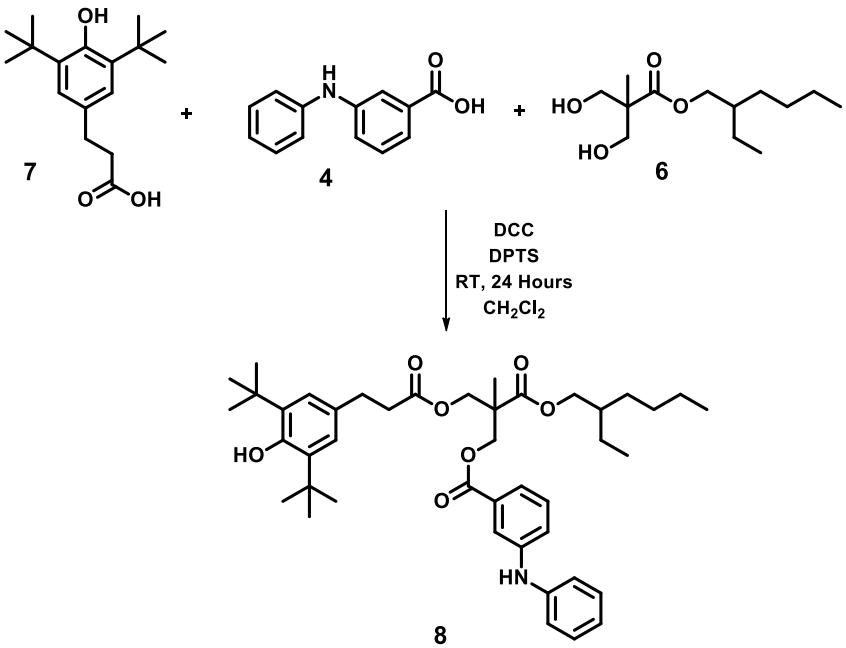


a)



b)

Figure 2



Scheme 1

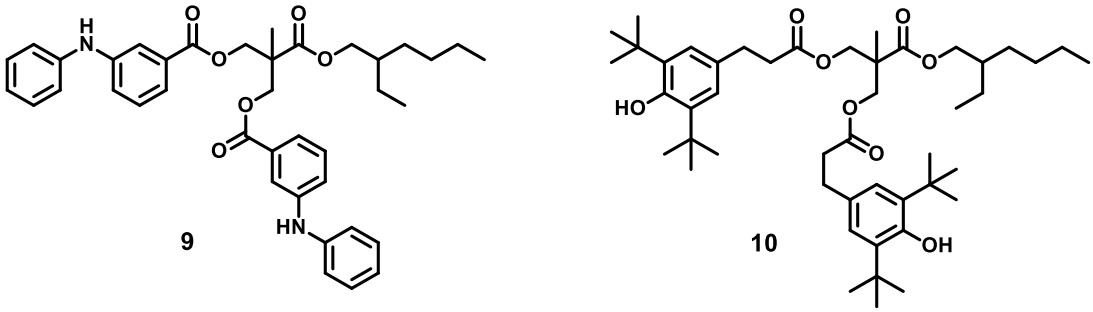
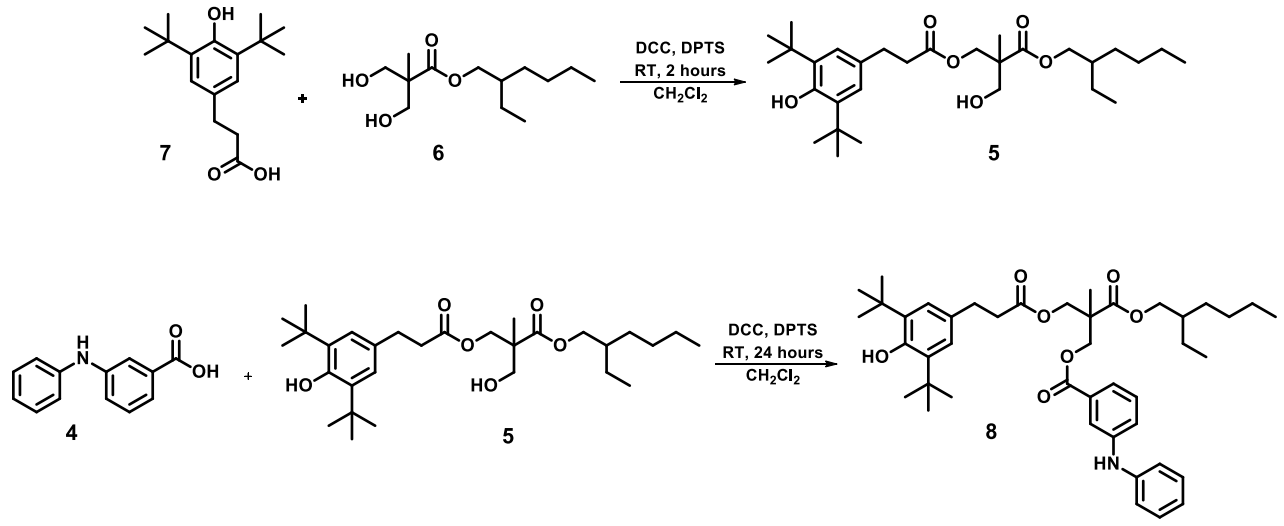
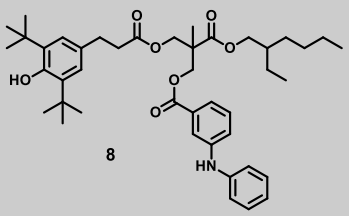
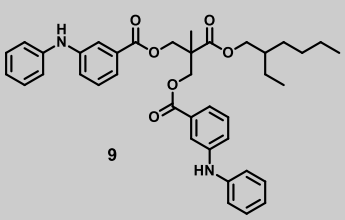
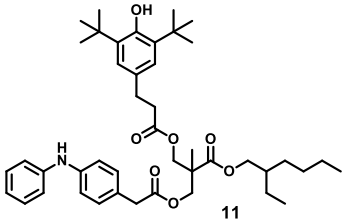
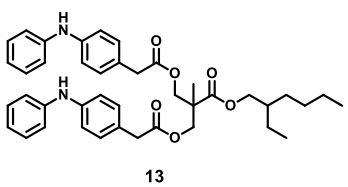


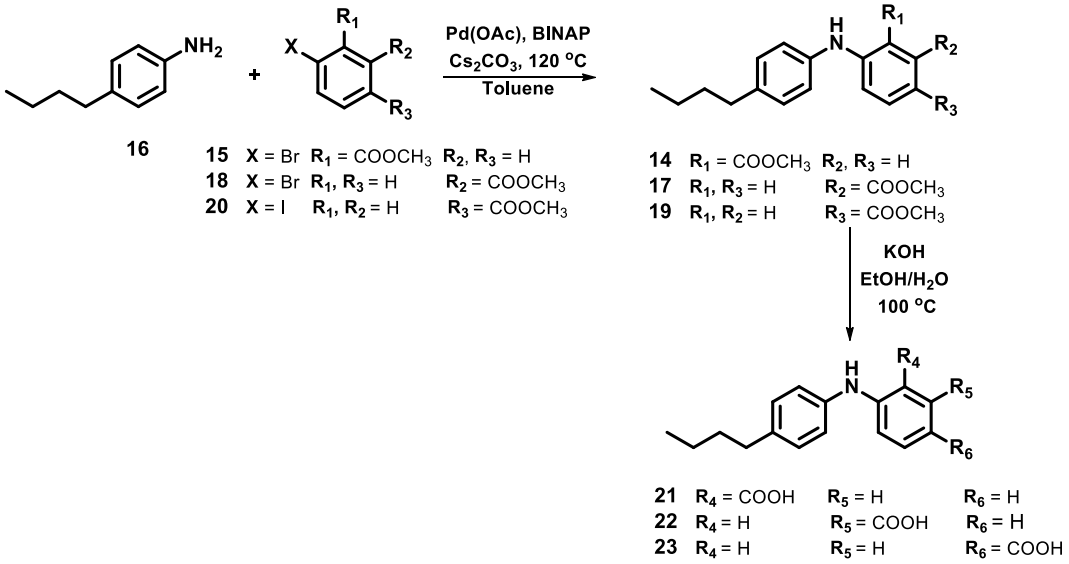
Figure 3



Scheme 2

Table 1

Mixed Amine-Phenol	*Bis*(diphenylamine)
	
	



16

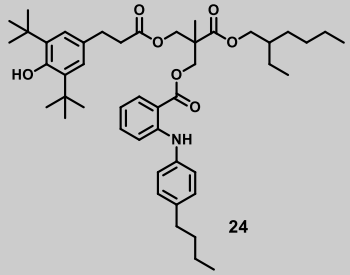
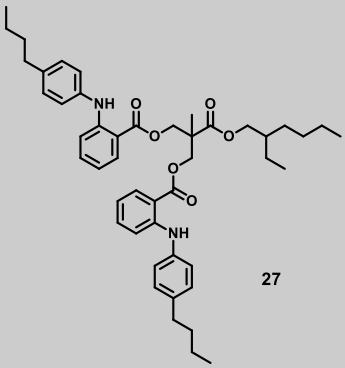
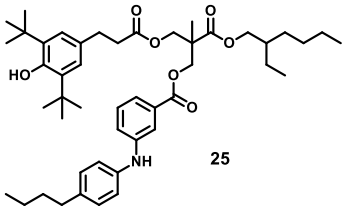
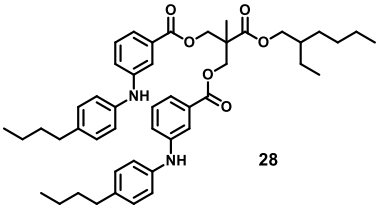
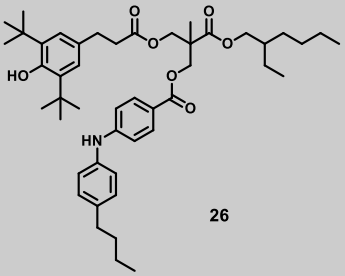
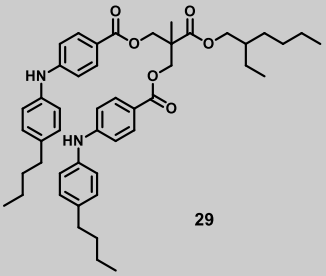
15 X = Br R_1 = $COOCH_3$ R_2, R_3 = H
18 X = Br R_1, R_3 = H R_2 = $COOCH_3$
20 X = I R_1, R_2 = H R_3 = $COOCH_3$

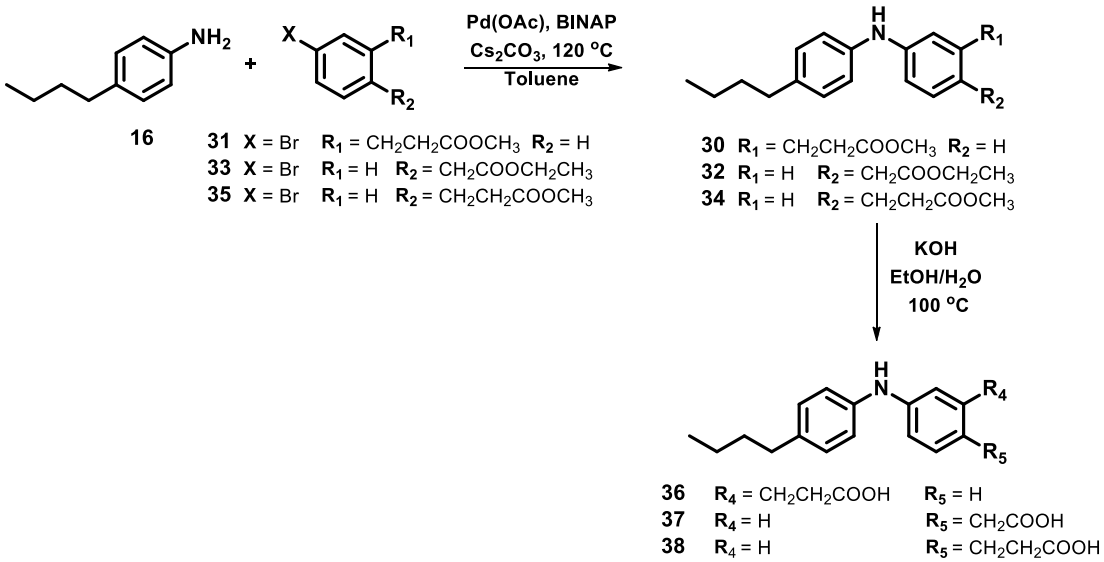
14 R_1 = $COOCH_3$ R_2, R_3 = H
17 R_1, R_3 = H R_2 = $COOCH_3$
19 R_1, R_2 = H R_3 = $COOCH_3$

21 R_4 = COOH R_5 = H R_6 = H
22 R_4 = H R_5 = COOH R_6 = H
23 R_4 = H R_5 = H R_6 = COOH

Scheme 3

Table 2

Mixed Amine-Phenol	*Bis*(diphenylamine)
 24	 27
 25	 28
 26	 29



16

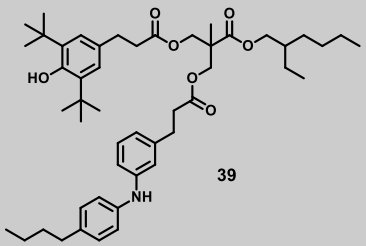
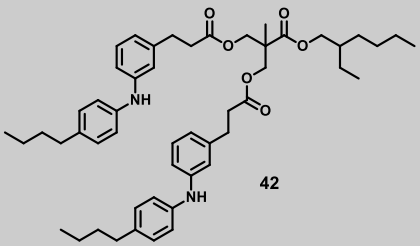
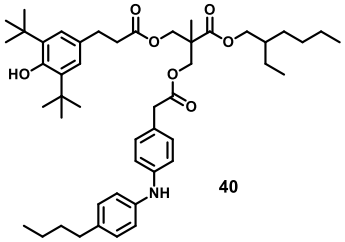
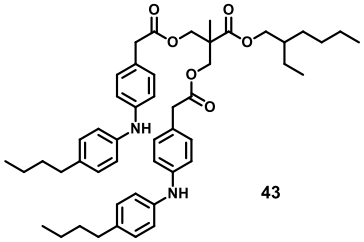
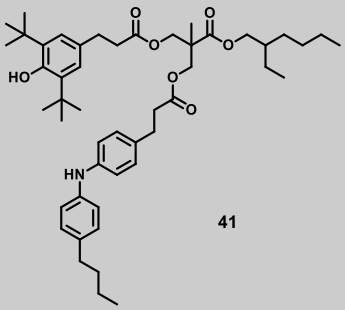
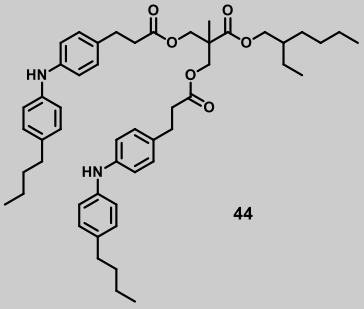
31 X = Br $R_1 = CH_2CH_2COOCH_3$ R_2 = H
33 X = Br R_1 = H $R_2 = CH_2COOCH_2CH_3$
35 X = Br R_1 = H $R_2 = CH_2CH_2COOCH_3$

30 $R_1 = CH_2CH_2COOCH_3$ R_2 = H
32 R_1 = H $R_2 = CH_2COOCH_2CH_3$
34 R_1 = H $R_2 = CH_2CH_2COOCH_3$

36 $R_4 = CH_2CH_2COOH$ R_5 = H
37 R_4 = H $R_5 = CH_2COOH$
38 R_4 = H $R_5 = CH_2CH_2COOH$

Scheme 4

Table 3

Mixed Amine-Phenol	*Bis*(diphenylamine)
 39	 42
 40	 43
 41	 44

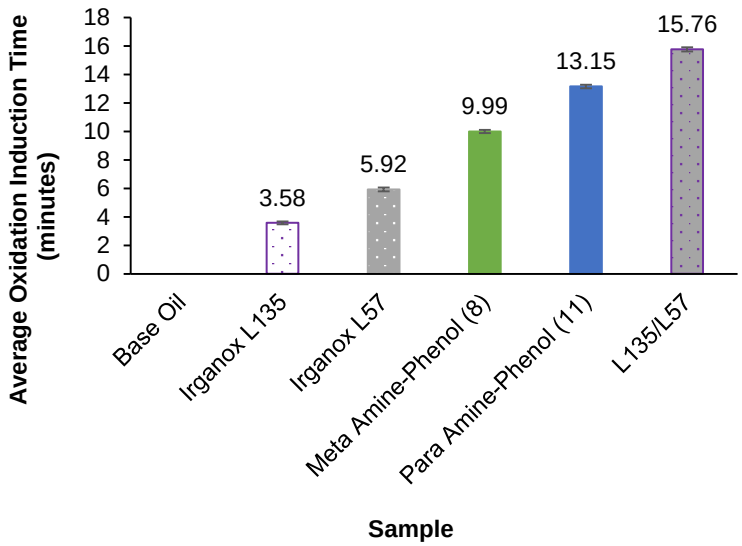
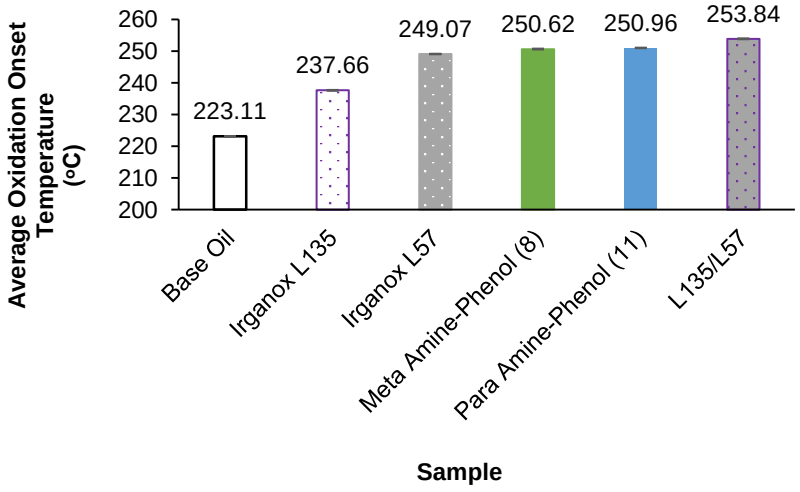


Figure 4



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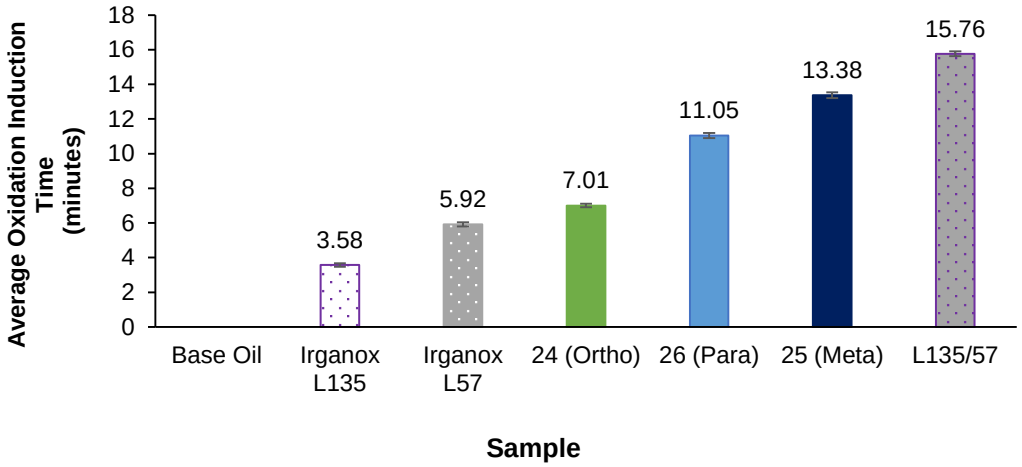

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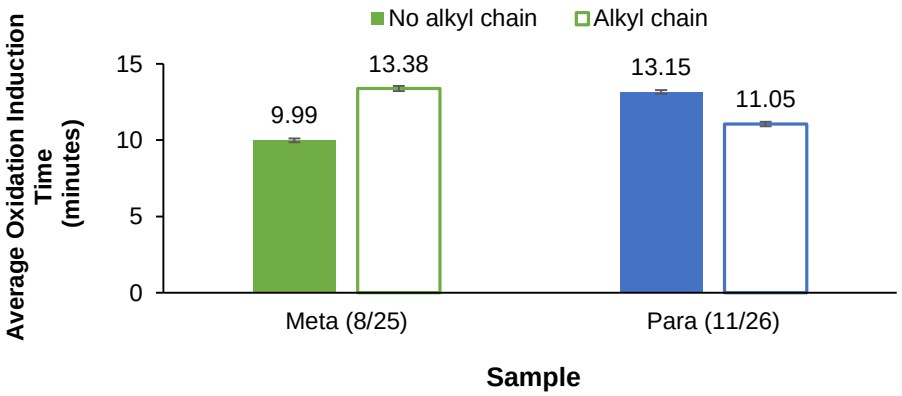


Figure 7

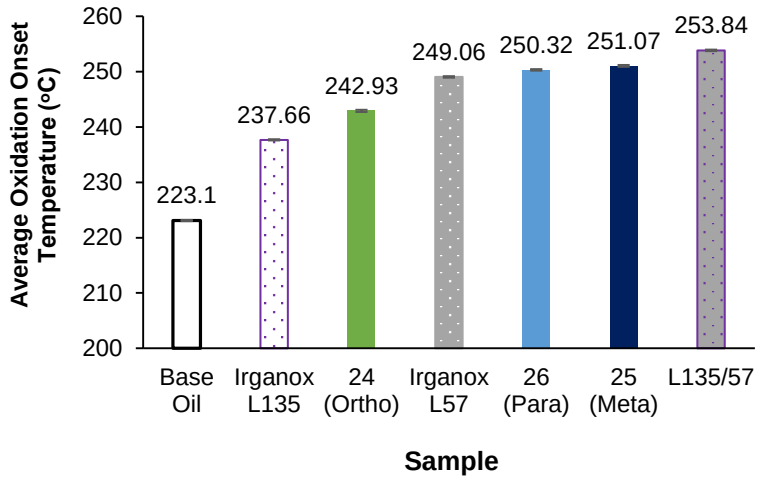
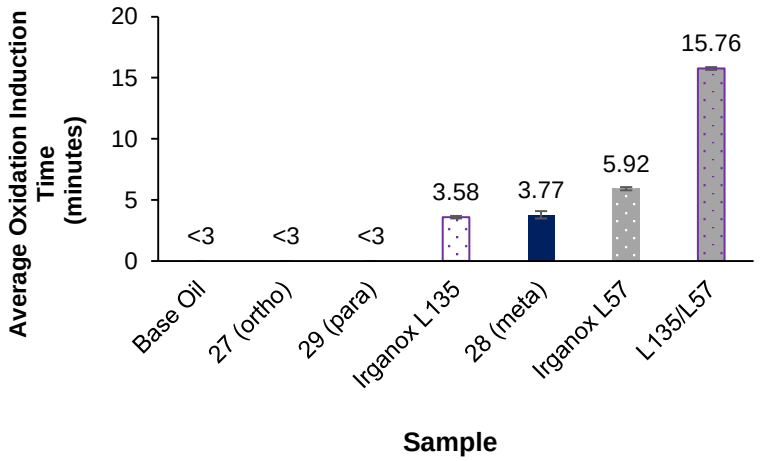


Figure 8



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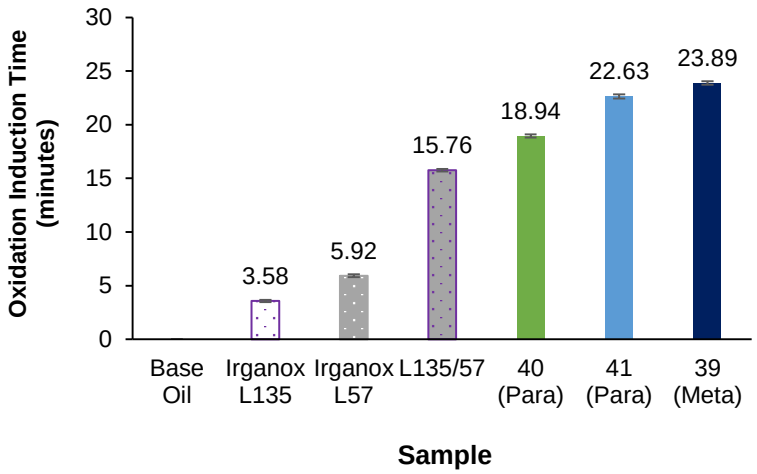

Figure 10

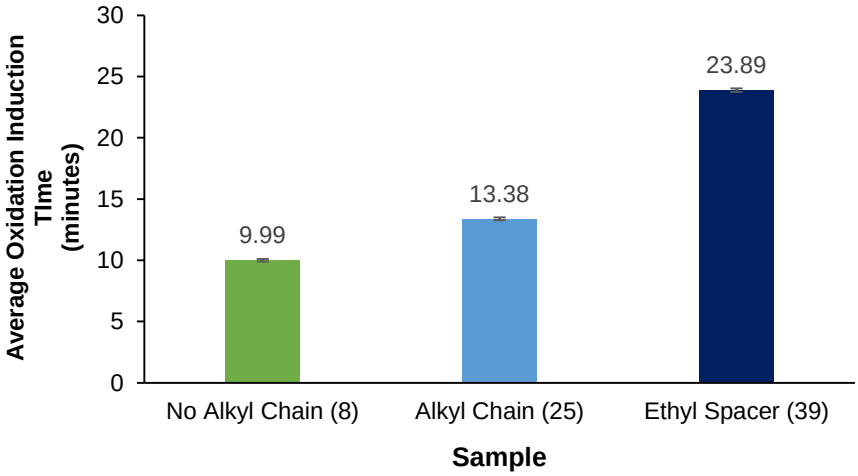

Figure 11

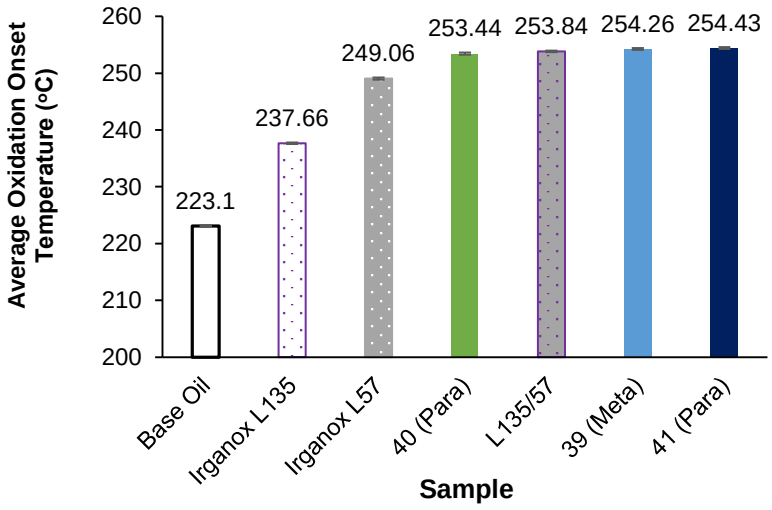
Average Oxidation Onset Temperature (°C)
260
250
240
230
220
210
200
223.1
237.66
249.06
253.44
253.84
254.26
254.43
Base Oil
Irganox L135
Irganox L57
40 (Para)
L135/57
39 (Meta)
41 (Para)
Sample

Figure 12