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Abstract: The N-methyl-D-aspartate receptor (NMDAR), a ligand-gated ion channel activated by L-glutamate and glycine, plays a major role in the synaptic plasticity underlying learning and memory. NMDARs are involved in neurodegenerative disorders such as Alzheimer's and Parkinson's disease and NMDAR hypofunction is implicated in schizophrenia. Herein we describe structure-activity relationship (SAR) studies on 2-naphthoic acid derivatives to investigate structural requirements for positive and negative allosteric modulation of NMDARs. These studies identified compounds such as UBP684 (14b), which act as pan potentiators by enhancing NMDAR currents in diheteromeric NMDAR tetramers containing GluN1 and GluN2A-D subunits. 14b and derivatives thereof are useful tools to study synaptic function and have potential as leads for the development of drugs to treat schizophrenia and disorders that lead to a loss of cognitive function. In addition, SAR studies have identified a series of styryl substituted compounds with partial NAM activity and a preference for inhibition of GluN2D versus the other GluN2 subunits. In particular, the 3-and 2-nitrostyryl derivatives UBP783 (79i) and UBP792 (79h) had IC50s of 1.4 μM and 2.9 μM, respectively, for inhibition of GluN2D but showed only 70-80% maximal inhibition. GluN2D has been shown to play a role in excessive pain transmission due to nerve injury and potentially in neurodegenerative disorders. Partial GluN2D inhibitors may be leads for the development of drugs to treat these disorders without the adverse effects observed with full NMDAR antagonists.

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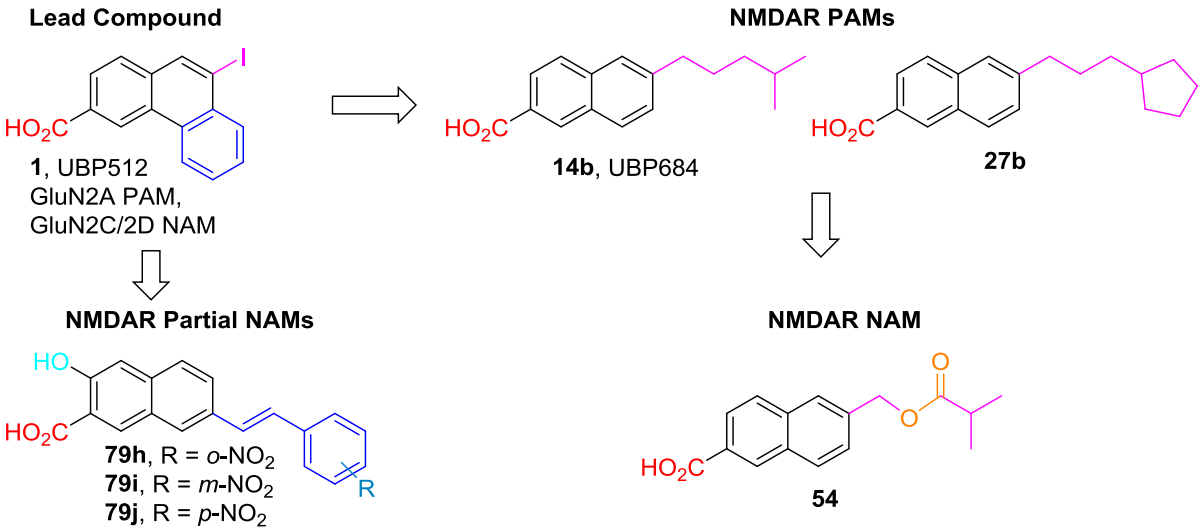

Highlights

SAR studies on 2-naphthoic acid derivatives revealed a series of NMDAR PAMs and NAMs.

6-Alkyl substituted 2-naphthoic acid derivatives such as **14b** are NMDAR PAMs.

Adding heteroatoms into the 6-alkyl chain generally led to NMDAR NAMs.

7-(Nitrostyryl)-3-hydroxy-2-naphthoic acids (**79h-j**) are GluN2D preferring partial NMDAR NAMs.

NMDAR NAMs and PAMs may treat chronic pain and cognitive disorders, respectively.

Investigation of the Structural Requirements for *N*-Methyl-D-Aspartate Receptor Positive and Negative Allosteric Modulators Based on 2-Naphthoic Acid

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Abstract

The *N*-methyl-D-aspartate receptor (NMDAR), a ligand-gated ion channel activated by L-glutamate and glycine, plays a major role in the synaptic plasticity underlying learning and memory. NMDARs are involved in neurodegenerative disorders such as Alzheimer's and Parkinson's disease and NMDAR hypofunction is implicated in schizophrenia. Herein we describe structure-activity relationship (SAR) studies on 2-naphthoic acid derivatives to investigate structural requirements for positive and negative allosteric modulation of NMDARs. These studies identified compounds such as **UBP684** (**14b**), which act as pan potentiators by enhancing NMDAR currents in diheteromeric NMDAR tetramers containing GluN1 and GluN2A-D subunits. **14b** and derivatives thereof are useful tools to study synaptic function and have potential as leads for the development of drugs to treat schizophrenia and disorders that lead to a loss of cognitive function. In addition, SAR studies have identified a series of styryl substituted compounds with partial NAM activity and a preference for inhibition of GluN2D versus the other GluN2 subunits. In particular, the 3-and 2-nitrostyryl derivatives **UBP783** (**79i**) and **UBP792** (**79h**) had IC_{50}s of 1.4 µM and 2.9 µM, respectively, for inhibition of GluN2D but showed only 70-80% maximal inhibition. GluN2D has been shown to play a role in excessive pain transmission due to nerve injury and potentially in neurodegenerative disorders. Partial GluN2D inhibitors may be leads for the development of drugs to treat these disorders without the adverse effects observed with full NMDAR antagonists.

Keywords: *N*-Methyl-D-aspartate receptor; NMDA; GluN2; positive allosteric modulator; negative allosteric modulator; 2-naphthoic acid

Introduction

N-Methyl-D-aspartic acid receptors (NMDARs) are members of the ionotropic glutamate receptor family, which are L-glutamate-gated ion channels that mediate fast excitatory synaptic transmission in the central nervous system (CNS). NMDARs are tetramers assembled from two GluN1 subunits, each containing a binding site for the co-agonist glycine and two GluN2A-D subunits, containing a binding site for L-glutamate in the ligand binding domain (LBD) region on each subunit. In some areas of the CNS, GluN3A and GluN3B subunits are incorporated into the tetramer [1-3]. An important function of NMDARs is to initiate the synaptic plasticity that occurs during CNS development and in learning and memory [4].

NMDARs have been the subject of intense investigations into the development of drugs that can modulate their activity. This is due to the involvement of these receptors in neurological disorders such as epilepsy, chronic pain, depression and schizophrenia and neurodegenerative disorders such as ischemia, Alzheimer's and Parkinson's diseases [5]. Very few compounds have made it into the clinic, with low affinity channel blockers such as memantine, which is used to treat moderate to severe Alzheimer's disease, being the exception. Antagonists interacting with the glutamate binding site on GluN2 subunits, the glycine binding site on GluN1 subunits, the ion channel with high affinity and the *N*-terminal domain of the GluN2B subunit have so far failed in clinical trials for stroke, head injury and epilepsy [1,5,6]. This is largely due to lack of efficacy and/or intolerable side effects such as amnesia, ataxia and psychotomimetic effects. More recently, attention has focused on the development of allosteric modulators, which may be able to treat neurological disorders without interfering with the normal physiological functions of NMDARs, thereby reducing side effects [6]. Furthermore, most efforts in NMDAR drug development have focused on inhibitors of activity. However, for treating schizophrenia, which is associated with NMDAR hypofunction, NMDAR positive allosteric modulators (PAMs) may have therapeutic benefits over currently available antipsychotics [6].[6] NMDAR PAMs may also have a role in treating the cognitive deficits observed in patients with other disorders such as Alzheimer's and Parkinson's disease [6].

We have reported a series of phenanthrene derivatives that can act as negative allosteric modulators (NAMs) and/or PAMs by binding to a site(s) distinct from those known for previous NMDAR ligands [7]. For example, UBP512 (**1**) (Figure 1) potentiated NMDARs containing GluN2A, had no effect on GluN2B and inhibited GluN2C and GluN2D in an

electrophysiological assay. Others have reported compounds that potentiate GluN2C and GluN2D (**2**, CIQ) [8] or specifically potentiate GluN2C (**3**) [9] (Figure 1). Recently, a GluN2A selective PAM (**6**) has been reported, which was developed from the lead compounds GNE-6901 (**4**) and GNE-8324 (**5**) (Figure 1) [10]. X-ray crystallography has revealed that these compounds bind at the dimer interface of the ligand binding domains (LBDs) of GluN1 and GluN2A [10]. Endogenous neurosteroids such as pregnenolone sulfate and synthetic derivatives thereof also potentiate NMDAR responses [11,12].

Removal of the terminal aromatic ring in **1** and modification of the resultant 2-naphthoic acid core afforded a series of derivatives, such as **UBP617** (**7**) (Figure 1), which non-selectively inhibited receptors containing different GluN2 subunits [13]. Interestingly, **7** and several structurally realated analogues showed submaximal inhibition of NMDARs making them potential leads for neurological conditions associated with overactivation of the receptor, such as neuropathic pain, where a complete block of activity could have adverse effects due to inhibition of essential brain functions. Others have reported compounds that selectively antagonise GluN2C and GluN2D (**QNZ46**, **8**, Figure 1) [14] and a series of compounds that act as partial negative allosteric modulators (NAMs) [15]. NAMs that specifically inhibit GluN2A (TCN-201, **MPX-004**, **9**, Figure 1) have been reported [16,17]. Inhibition of GluN1/GluN2A by **9** has been shown to be dependent on the glycine concentration and X-ray crystallography has revealed that it binds to the dimer interface of the ligand binding domains of GluN1 and GluN2A [17].

Herein we describe structure-activity relationship (SAR) studies on 2-naphthoic acid derivatives as analogues of our previously reported phenanthrene [7] and naphthalene series [7a,13] with the aim of understanding the structural requirements for NMDAR NAMs and PAMs.

Results

Chemistry

The synthesis of the naphthalene derivatives described in this report is outlined in Schemes 1-10. Heck coupling between methyl 6-bromo-2-naphthoate (**10**) and the appropriate alkene afforded **11a-b** (Scheme 1). To aid SAR studies, a small amount of the *trans*-alkene (**11a-b**) was hydrolysed to its corresponding acid (**12a-b**) using base. However, the majority was taken forward and hydrogenated before being hydrolysed with base to yield saturated acids **14a-b**. The 6-cyclopropyl derivative (**17**) was synthesized from **10** in three steps (Scheme 1). Firstly, Stille coupling between **10** and tri-*n*-butyl(vinyl)tin afforded **15**.

The cyclopropyl ring was then formed via a Simmons-Smith reaction and the resultant ester (**16**) hydrolysed to the desired acid (**17**) using base.

In order to gather SAR information, several analogues of **14a** were synthesized (Scheme 2). Reduction of the 3-carboxy moiety using $LiAlH_4$ proceeded smoothly, giving the 3-hydroxymethyl derivative **18** in good yield. Reaction of **18** with PBr_3 afforded 3-bromomethyl derivative **19** which was in turn converted to nitrile **20** by reaction with NaCN under phase transfer conditions. Acidic hydrolysis of the nitrile yielded the corresponding 3-acetic acid derivative **21**. The 5-bromo analogue **22** was readily synthesized by reacting **14a** with a solution of bromine in glacial acetic acid (Scheme 2). Alkylation of 6-hydroxy-2-naphthoic acid (**23**) with 1-bromobutane afforded the 6-butoxy derivative **24** in good yield (Scheme 2).

Methyl 6-bromo-2-naphthoate (**10**) was utilised as a starting material in the synthesis of various analogues of **14b** (Schemes 3 and 4). Heck coupling between **10** and the appropriate alkene led to the synthesis of *trans* alkene intermediates **25a-b** and **30** (Scheme 3). To aid SAR studies, a sample of **30** was hydrolysed using base to yield unsaturated acid **31**. Hydrogenation of **25a-b** and **30** gave the corresponding alkyl esters which were subjected to base hydrolysis to give acids **27a-b** and **33** (Scheme 3). Sonogashira coupling between **10** and 4-methylpent-1-yne afforded ester **28** which was readily hydrolysed to acid **29** (Scheme 3). Using transesterification under acidic conditions, **10** was converted to isobutyl ester **34** in reasonable yield. Palladium catalysed carboxylation using carbon monoxide subsequently afforded acid **35** (Scheme 4). A Claisen condensation between **10** and ethyl 4-methylvalerate followed by intramolecular decarboxylation yielded ketone **36**. Palladium catalysed carboxylation using carbon monoxide gave ester **37** which was hydrolysed using base to afford acid **38** (Scheme 4). Sonogashira coupling between **10** and 4-pentyn-2-ol led to the synthesis of alcohol **39**. Hydrogenation of the alkyne bond followed by oxidation of the alcohol using Dess-Martin periodinane (DMP) afforded ketone **40** in good yield (Scheme 4). The introduction of a carboxymethyl group was achieved by reacting ketone **40** with methyl diethylphosphonoacetate under Wittig reaction conditions. Hydrogenation of the resultant alkene gave ester (**41**) which was readily hydrolysed to di-acid **42** using base (Scheme 4).

To gather additional SAR information, ketone **37** was subjected to further chemical modification (Scheme 4). Using Wittig reaction chemistry, methylenation of ketone **37** afforded alkene **43** in good yield. Although the majority of alkene **43** was taken forward and hydrogenated to give ester **45**, some was held back and hydrolysed using base to give

unsaturated acid **44**. Ester **45** was hydrolysed to acid **46** in good yield under basic conditions (Scheme 4).

Thioether, amide and ester analogues of **14b** were also synthesised during the course of SAR studies (Scheme 5). The reaction between 6-bromomethyl derivative **47** and 2-methylpropan-1-thiol in the presence of sodium yielded thioether **48** which was readily converted to corresponding acid **49** by base hydrolysis (Scheme 5). Coupling of acid chloride **50** with isobutylamine under standard conditions afforded amide **51** which was hydrolysed to acid **52** using base (Scheme 5). Using identical conditions, 6-hydroxymethyl **53** and isobutyryl chloride were coupled to yield ester **54** (Scheme 5).

Further modifications to the 6-isohexyl side chain in **14b** were investigated using 6-bromomethyl derivative **55** as a starting material (Scheme 6). The reaction between **55** and 2-methylpropan-1-ol in the presence of sodium yielded ether **56**. Palladium catalysed carboxylation using carbon monoxide subsequently afforded acid **57** (Scheme 6). Base promoted nucleophilic substitution between **55** and ethyl 4-methylvalerate generated ester **58**. Palladium catalysed carboxylation using carbon monoxide yielded di-ester **59**. Base hydrolysis subsequently afforded di-acid **60** (Scheme 6).

3-Hydroxy-2-naphthoic acid derivatives of **14b** were also the subject of investigation (Schemes 7). The starting material required for these compounds (**63**) was synthesised in two steps from 7-bromo-3-hydroxy-2-naphthoic acid **69**. Firstly, the 2-carboxy group was esterified using K_2CO_3 and methyl iodide to afford methyl ester **62**. The 3-hydroxy group was in turn acetylated using acetic anhydride to afford **63** (Scheme 7). Heck coupling between **63** and 4-methylpent-1-ene and hydrogenation of the resulting alkene yielded **64**. Base hydrolysis was used to deprotect a sample of this compound giving **65** (Scheme 7). The majority of **64** was deprotected at the 3-position using dimethylamine to afford phenol **66** which was in turn reacted with triflic anhydride under classical conditions to give triflate **67**. Removal of the triflate group using formic acid and $Pd(PPh_3)_4$ yielded ester **68** which was subsequently hydrolysed in the presence of base to acid **69** (Scheme 7).

Swapping the respective positions of the carboxy and hydroxy groups in compound **65** was desirable for investigating the SAR surrounding this compound (Scheme 8). Sonogashira coupling between triflate **70** and 4-methylpent-1-yne led to the synthesis of alkyne **71**. Hydrogenation of the triple bond followed by *t*-BuLi promoted carboxylation afforded ester **72**. Acidic deprotection of the 3-hydroxy group yielded **73** which was readily hydrolysed using base to give acid **74** (Scheme 8). Replacing the hydroxy group in **65** with a carboxy moiety was also of interest for SAR studies (Scheme 8). Heck coupling between

commercially available **75** and 4-methylpent-1-ene afforded alkene **76**. Subsequent hydrolysis of the nitrile groups under acidic conditions and hydrogenation of the alkene bond afforded di-acid **77** (Scheme 8).

Heck coupling between **63** and the appropriately substituted styrene afforded a series of 7-substituted styryl derivatives (**78a-j**) (Scheme 9). The majority of these compounds were taken forward and de-protected under basic conditions to give **79a-j**. However, to gather additional SAR information, **78a**, **78b** and **78d** were hydrogenated to their saturated counterparts (**80a-c**) and then hydrolysed using base to afford phenethyl derivatives **81a-c** (Scheme 9). In order to investigate it's importance, the 3-hydroxy moiety of **79a** was subjected to modification. De-acetylation of **78a** using dimethylamine afforded phenol **82** which was in turn reacted with triflic anhydride under classical conditions to give triflate **83** (Scheme 9). Palladium catalysed carboxylation using carbon monoxide gave di-ester **84** which was hydrolysed using base to afford di-acid **85** in moderate yield (Scheme 9).

The coumarin UBP608 has previously been reported as a moderately potent NAM that fully inhibited GluN2A responses with an IC_{50} of 18.6 ± 1.4 µM and 23-fold selectivity over GluN2D [7a]. It was thought, given styryl group addition to the naphthalene series (see **78a-j** in Table 5) gave a series of interesting NMDAR NAMs, that the same strategy could be applied to create the coumarin analogue of **78a**. It was hoped that by using commercially available ethyl 6-bromo-3-coumarincarboxylate (**86**), a range of analogues could be accessed in a similar way to the naphthalene series, through palladium catalysed cross-coupling with a variety of substituted benzene derivatives. In our hands, however, negligible yields of the desired styryl-coupled coumarin (**88**) were achieved under standard Heck and Suzuki conditions (Scheme 10). Instead of attempting to functionalise an existing coumarin, the next strategy was to synthesise a coumarin with the desired functional groups in place, in this case, a styryl group. A Knoevenagel condensation of Meldrum's acid [18] with known intermediate (E)-2-hydroxy-5-styrylbenzaldehyde (**87**) (synthesised using a literature procedure [19]) gave the desired coumarin **88** in a moderate yield (Scheme 10).

Biological evaluation and SAR studies

Compounds were initially evaluated at a concentration of 100 µM for their effects on agonist-induced NMDAR currents using a two-electrode voltage clamp (TEVC) electrophysiological assay [7]. Although the test concentration is high even for screening it allowed us to detect any weak NMDAR PAM effects. Compounds with significant activity

were investigated more thoroughly using full concentration response curves. cRNA coding for the four GluN1/GluN2A-D diheteromeric NMDARs were individually injected into *Xenopus laevis* oocytes. After 2 to 5 days, NMDAR currents were induced by L-glutamate (Glu) (10 μM) and glycine (Gly) (10 μM) and after a steady-state response was obtained, the test compounds were co-applied with agonist. Data from these studies are shown in Tables 1-3 and 5. Full concentration-response curves (Figures 2 and 3) and EC_{50} or IC_{50} values across GluN2A-D were then generated for compounds with significant NMDAR potentiating or inhibitory activity identified in the initial screen (Tables 4 and 6). All compounds were soluble and showed no visible signs of precipitation at the concentrations tested in these assays. The origianlly described compounds (e.g. **1** and **7**, Figure 1) did not display glutamate-site or glycine-site NMDAR agonist activity nor were they active in the absence of agonists [7,13]. In this study, compounds with the greatest PAM activity (**14b** and **46**, Tables 1, 2 and 4) were similarly evaluated and found to have no NMDAR agonist activity or effect on the holding current (Saptoka et al., 2017).

SAR studies to identify novel NMDAR positive allosteric modualtors.

SAR studies were focused on identifying novel NMDAR PAMs and investigating their structural requirements. The following structural changes were investigated: 1. Effect of removing the unsubstituted aromatic ring from the phenanthrene based compounds such as UBP512 (**1**) to form naphthalene derivatives, 2. Effect of changing the 6-substituent on the naphthyl ring, 3. Effect of changing the position of the carboxylic acid group attached to the naphthalene ring, 4. Effect of adding substituents to the naphthyl ring system, 5. Effect of adding substituents to the alkyl chain attached to the 6-position of the naphthalene ring, 6. Effect of adding heteroatoms to the alkyl chain attached to the 6-position of the naphthalene ring.

Effect of removing unsubstitued aromatic ring from phenanthrene lead compounds.

Previous studies have shown that 9-substituted phenanthrene-3-carboxylic acids such as UBP512 (**1**, Figure 1) and 9-alkyl derivatives have potentiating effects on NMDARs [7]. The 9-iodo derivative (**1**) weakly potentiated the GluN2A response, had no effect on GluN2B and inhibited GluN2C/GluN2D [7] (Table 1).

Removal of the unsubstituted aromatic ring from **1** (Figure 1) to afford 6-iodo-2-naphthoic acid eliminated NMDAR PAM activity on GluN2A (at 100 μM it inhibited the agonist response on GluN2A by 26 ± 2% and had 9-12% inhibitory activity on GluN2B-D). 2-

Naphthoic acid analogues with short chain alkyl substituents at the 6-position (e.g. ethyl or *n*-propyl) were found to have no NMDAR PAM activity. The 6-ethyl derivative (100 µM) instead inhbited GluN2A-D with perecentage values in the range of 17-52%, while the 6-*n*-propyl derivative (100 µM) had percentage inhibition values on GluN2A-D in the range of 0-14%). A similar outcome was observed for the 6-cyclopropyl derivative (**17**, Table 1). In contrast, the corresponding 9-ethyl, 9-*n*-propyl and 9-cyclopropyl phenanthrene-3-carboxylic acid derivatives showed weak to moderate NMDAR PAM activity [7]. Like the parent phenanthrenes [7], the 6-*n*-pentyl (**14a**) and 6-isohexyl (**14b**, UBP684) derivatives of 2-naphthoic acid showed potentiating effects on NMDARs. The 6-*n*-pentyl derivative (**14a**) showed potentiating activity on NMDARs containing GluN2A, GluN2C and GluN2D (Tables 1 and 4) but not GluN2B. When tested at a concentration of 100 µM, the 6-isohexyl naphthyl derivative (**14b**) showed potentiation in excess of 170% across GluN2A-D. This was higher than that of the 6-*n*-pentyl derivative (**14a**) (Table 1), suggesting that **14b** was better at increasing the efficacy of L-glutamate/and or glycine. The pan-potentiator **14b** (EC_{50} values ranging from 28.0-37.2 µM across GluN2A-D) had similar potency to that of **14a** on GluN2A but was a more potent PAM on GluN2B-D (Tables 1 and 4, Figure 2). These data suggest that the unsubstituted aromatic ring of the phenanthrene series is not needed for NMDAR PAM activity when long chain alkyl substituents are present at the 6-position of the naphthalene ring.

Effect of changes to the 6-alkyl substituent on the naphthalene ring.

Conformational restriction of the isohexyl side chain in **14b** by incorporation of a *trans* double bond gave **12b**, which displayed an increase in potentiation of agonist response on GluN2C and GluN2D compared to **14b** (Table 1). However, a similar conformational restriction of the *n*-pentyl side chain of **14a** to give **12a** resulted in weak inhibitory activity across the GluN2 subunits (Table 1). Incorporation of a triple bond into the isohexyl side chain to give **29**, led to the loss of the potentiating effect on GluN2A and GluN2B and a much reduced potentiating effect on GluN2C and GluN2D compared to **14b** (Table 1). Although restricting conformational freedom by incorporating a double or triple bond was detrimental for PAM activity on GluN2A and GluN2B, adding a *trans* double bond into the side chain of **14b** can be used to increase selectivity for GluN2C/GluN2D versus GluN2A/GluN2B.

Adding a 4-phenylbut-1-yl substituent to the 6-position of the naphthalene ring (Figure 2, Table 1) to give **27a** reduced potentiation compared to **14b**. Adding a 3-cyclopentylprop-1-yl

substituent to the 6-position of the naphthalene ring to give **27b** (Tables 1 and 4) led to a similar level of potentiating activity on GluN2A-D to that of **14b**, with the former being more potent on GluN2A (Table 4). Thus, incorporating the two methyl groups at the end of the isohexyl chain of **14b** into a cyclopentyl ring enhances PAM potency and selectivity for GluN2A.

Effect of changing the nature and position of the carboxylic acid group attached to the naphthalene ring.

Reduction of the carboxylic acid group in **14a** to give the corresponding hydroxymethyl derivative **18** replaced potentiating activity with weak inhibitory activity at GluN2A-D (Table 1). A similar observation was made when a CH_2 linker was introduced between the naphthalene ring and the carboxylic acid group in **14a**. The resultant acetic acid derivative, **21**, had weak to moderate inhibitory activity at GluN2A-D (Table 1). Taken together, the activities of **18** and **21** suggest that the carboxylic acid group is necessary for potentiating activity and that this group must be directly attached to the naphthalene ring. Furthermore, moving the carboxylic acid of **14b** to an adjacent position on the naphthalene ring to give 7-isohexyl-2-naphthoic acid (**69**) resulted in weak inhibitory activity at GluN2D and a weaker potentiating effect on GluN2A-C compared to the parent compound (Table 1). Thus, switching the position of the carboxylic acid group relative to the alkyl substituent is detrimental for NMDAR PAM activity, especially for GluN2D.

Effect of adding substituents to the naphthalene ring.

Adding a bromo substituent to the 5-position of the naphthalene ring of **14a** to give **22** (Table 1) resulted in weak inhibitory activity on GluN2A and GluN2B and no activity on GluN2C and GluN2D, suggesting the bromo group is in an area of excluded volume in the NMDAR PAM binding site or that this addition prevents the PAM's allosteric action. The 2,3-dicarboxy analogue (**77**) of **14b** resulted in little or no activity on GluN2A and GluN2B but weak to moderate inhibitory activity on GluN2C and GluN2D (Table 1).

Adding a hydroxyl group to the 3-position of the naphthalene ring of **14b** to give **74** produced a pan-potentiator with similar, or possibly enhanced activity on GluN2B-D compared to **14b** (Table 1). Thus, it may be possible to reduce the hydrophobicity and increase water solubility of the NMDAR PAMs described here by adding a hydroxyl group to the 3-position of the 2-naphthoic acid derivatives. Switching the placement of the hydroxyl and carboxyl groups on the naphthalene ring of **74** to give **65** resulted in weak inhibitory

activity on GluN2A and weaker potentiating activity on GluN2B-D compared to that observed for **14b** and **74** (Table 1). However, unlike the 7-isohexyl derivative **69**, which showed weak inhibitory activity on GluN2D, **65** potentiated GluN2D activity (Table 1), suggesting that the 3-hydroxyl group is required for this activity. Interestingly, replacing the isohexyl group of **65** with a bromo [13], phenyl (**7**, Figure 1) [13], styryl (**79a**, Table 5) or phenethyl (**81a**, Table 5) group leads to moderate NMDAR NAM activity on GluN2A-D.

Effect of adding substituents to the 6-alkyl chain.

Substitution at the 1-position of the isohexyl side chain of **14b** with a methyl group to give **46** resulted in a pan-potentiator with similar potency on GluN2A-D (EC_{50} values ranged from 25.0 to 39.4 μM) to that of **14b** (Tables 2 and 4, Figure 2). However, the maximum potentiating effect of **46** across GluN2A-D was greater than that observed for **14b** (Figure 2). Conformational restriction of **46** by incorporating a double bond to give **44** (Table 3) produced a pan-potentiator with similar potency to its parent compound on GluN2C but weaker potency on the other GluN2 subunits (EC_{50} values ranged from 26.1 to 116.4 μM across GluN2A-D, Table 4). Interestingly, **44** showed different degrees of maximal potentiation across GluN2A-D and the value for GluN2B was higher than for any other compound that was tested (Figure 2E, Table 4). Adding a carboxylic acid at the 4-position of the *n*-pent-1-yl side chain of **14a** to give **33** resulted in little or no activity at GluN2B or GluN2C and very weak potentiating activity on GluN2A and GluN2D (Table 2). Conformational restriction of **33** by including a *trans* double bond to give **31** (Table 2) resulted in little or no activity across GluN2A-D. Furthermore, adding a CH_2CO_2H group to the 4-position of the *n*-pent-1-yl side chain of **14a** to give **42** removed potentiating activity and instead weak inhibition was observed on GluN2A, GluN2B and GluN2D (Table 2). Adding a carboxylic acid at the 2-position of the isohexyl side chain of **14b** to give **60** resulted in selective weak potentiation of GluN2C with little or no activity on GluN2A and weak inhibition of GluN2B and GluN2D (Table 2). Thus, it appears that polar substituents on the alkyl chain cannot be accommodated, while methylene substitution (**44**) at the 1-position of the alkyl chain of **14b** reduces PAM potency on GluN2A and GluN2B but increases agonist efficacy to a greater degree than **14b**.

Effect of adding heteroatoms to the 6-alkyl chain.

A SAR study was undertaken to investigate the effect of adding heteroatoms to the isohexyl side chain of **14b**, with the aim of reducing hydrophobicity. Adding a ketone group

to the isohexyl chain of **14b** to produce **38** (Table 3) led to a loss of potentiating activity on GluN2B-D and a weak potentiating effect on GluN2A. Replacing the CH_2 group adjacent to the naphthalene ring of **14a** with an oxygen atom to give **24** (Table 1) resulted in inhibitory activity across GluN2A-D. Similarly, replacing the second CH_2 group in the isohexyl chain of **14b** with either a sulphur atom (**49**) or an oxygen atom (**57**) resulted in either loss of potentiating activity or weak inhibitory effects (Table 3). Incorporating either an amide or ester group into the isohexyl chain of **14b** to give **52** and **54** respectively, led to either inhibitory effects or loss of activity on GluN2A-D. However, incorporating an ester group at a different position in the isohexyl chain of **14b** to give **35** resulted in a pan-potentiator with similar levels of activity across GluN2A-D to that observed with **14b** (Table 3). The potentiating activity of the ester **35** was unexpected given that the ketone **38** and the ether derivative **57** lacked potentiating activity. A possible explanation is that both oxygen atoms of the ester group are required for potentiating activity.

SAR studies on 2-naphthoic acid derivatives as NMDAR negative allosteric modulators

In the preceding SAR studies, NMDAR NAM activity was observed for some 2-naphthoic acid derivatives. For example, the 6-pentyl compound (**21**, Table 1) and 6-isohexyl derivatives with heteroatoms in the side chain (**24** Table 1, **52**, **54** and **57** Table 3) showed 50% or greater inhibition on at least one of the GluN1/GluN2 subtypes when tested at a concentration of 100 μM. These data show that inserting heteroatoms into the 6-alkyl chain such as an O atom (**24** and **57**), a carboxamide (**52**) or an ester (**54**) converts PAMs into NMDAR NAMs. This suggests that the PAM and NAM binding sites for 6-substituted 2-naphthoic acid derivatives differ in that the NAM binding site appears to be much more polar in the area where the 6-substituent binds. Chain extension of the carboxylic acid in **14a** by insertion of a CH_2 group leads to preferential GluN2D NAM activity for compound **21**, while adding a carboxy group to the 3-position of **14b** leads to preferential GluN2C and GluN2D NAM activity for compound **77** (Table 1). Thus, while acidic group chain extension and 2,3-dicarboxy substitution is acceptable for NMDAR NAMs it is detrimental to PAM activity.

The 7-styryl substituted 2-naphthoic acid **79a** (Tables 5 and 6) showed greater NMDAR NAM activity than any of the 6-substituted 2-naphthoic acid derivatives. This 2,7 relationship between the carboxy group and styryl side chain favours NAM activity but the 2,7 relationship of the 7-alkyl derivatives **65** and **69** was detrimental to PAM activity (Table 1). Compound **79a** is structurally similar to the previously reported NMDAR NAM **7**, (Figure 1) [13], which has a phenyl substituent at the position occupied by the styryl group. Compared

to **7**, (Figure 1), the parent styryl-substituted compound, **79a** was found to have similar activity on GluN2A, ~10-fold greater inhibitory activity on GluN2B and 3-5 fold greater inhibitory on GluN2C and GluN2D (Table 6). In addition, **79a** showed 83-94% maximal inhibition across GluN2A-D, whereas **7** showed only 57-72% maximal inhibition of GluN2A and GluN2B (Table 6) [13].

Given that **79a** showed interesting NMDAR NAM activity, a SAR study was undertaken with the aim of improving NAM potency and GluN2 subunit selectivity. When the hydroxyl group of **79a** was replaced by a carboxyl group to give compound **85** (formula C, Table 5) inhibitory activity was reduced. Similarly, replacement of the naphthalene ring of **79a** with a coumarin ring to give compound **88** (formula D, Table 5) dramatically reduced inhibitory activity and indeed led to potentiating activity on GluN2C and GluN2D. This suggests that the hydroxyl group of **79a** is necessary for optimal NAM activity. Next, the effect of saturating the double bond linking the phenyl ring of **79a** to the naphthalene ring was studied. The saturated analogue, compound **81a** (Table 5) had weaker inhibitory activity than the parent compound **79a**, suggesting a degree of conformational restriction is necessary for optimal NMDAR NAM activity.

Having established that the core structure was necessary for NMDAR NAM activity of **79a**, a study was undertaken to investigate the effect of substitutions on the phenyl ring. Carboxyl group substitution at the *ortho*, *meta* or *para* positions (compounds **79b**, **79c** and **79d**, Table 5) led to much reduced inhibitory activity compared to the parent compound. Saturation of the double bond in the *ortho* and *para* carboxy derivatives to give compounds **81b** and **81c**, respectively, did not improve upon the already weak inhibitory activity of the parent compounds. Interestingly, *ortho* methoxy substitution (compound **79e**, Table 5) led to weak potentiation of GluN2A responses and weak inhibition of GluN2B-D. Either *meta* or *para* methoxy substitution to give compounds **79f** and **79g** (Table 5), respectively, led to improved inhibitory activity compared to the *ortho* derivative. *Ortho* nitro substitution (**79h**, Table 5) improved inhibitory activity compared to the corresponding methoxy derivative, especially on GluN2C and GluN2D. *Meta* and *para* nitro substitution (**79i** and **79j**, Table 5) had a similar effect on inhibitory activity to that observed with the corresponding methoxy substituted compounds.

Full concentration response curves were obtained for the inhibitory activity of **79h**, **79i** and **79j** across GluN1/GluN2A-D (Figure 3B-D). Surprisingly, unlike the parent compound **79a** (Figure 3A**)**, all three compounds failed to produce 100% maximal inhibition of GluN2A-D responses. The ortho nitro derivative **79h** only maximally inhibited GluN2A by

30% and GluN2B-D by 60-80% (Table 6). Similar findings were observed with the meta (**79i**) and para (**79j**) nitro derivatives in terms of their maximal inhibition. Regarding inhibitory activity, IC_{50} values for **79h** were 3-fold lower on GluN2A and GluN2D and 4-fold higher on GluN2B compared to **79a** (Table 6). A similar trend was observed for **79i** and **79j**, with the former having the most potent inhibitory activity on GluN2D of all the analogues tested (IC_{50} value 1.4 µM). Compared to the previously reported 7-phenyl derivative UBP617 (**7**, Table 6) (Costa et al., 2012), the meta-nitrostyryl derivative **79i** had similar activity on GluN2A and 10-fold, 5-fold and 35-fold higher inhibitory activity on GluN2B, GluN2C and GluN2D, respectively (Table 6). Thus, meta-nitrostyryl substitution produced a NAM that was more potent than the parent compound **79a** and was selective for inhibiting NMDARs containing GluN2D. In addition, unlike **79a**, **79i** was a partial NAM on GluN2D.

Testing **79h** at two different agonist concentrations (10/10 µM Glu/Gly and 300/300 µM Glu/Gly) showed that the degree of inhibition of the agonist response was not reduced at higher agonist concentrations (Figure 4). This suggests that **79h** is not competing with either Glu or Gly for their binding sites on the GluN1 or GluN2 LBD, respectively.

Discussion

Structure-activity relationship studies on 2-naphthoic acid derivatives based on the lead phenanthrene UBP512 (**1**, Table 1) [7] have led to the discovery of novel series of both NMDAR PAMs and NAMs. We have shown that 6-alkyl substitued 2-naphthoic acid derivatives such as **14b** (UBP684) can act as pan potentiators of agonist-induced currents through NMDARs (i.e. they potentiate regardless of the type of GluN2 subunit incorporated into the NMDAR). The NMDAR PAM **27b** (Table 1) showed a preference for the GluN2A subunit and further modification of this compound may lead to GluN2A selective NMDAR potentiators. In contrast to 6-alkyl derivatives such as **14b**, the 7-styryl derivative **79a** and analogues thereof were found to be NMDAR NAMs. NAM activity and selectivity for GluN2D could be enhanced by 3-nitro substitution to produce **79i** (Table 6), which unlike the parent compound **79a**, was a partial NAM.

Our SAR studies revealed different structural requirements for NMDAR NAMs and PAMs based on 2-naphthoic acid. Whilst 6-alkyl substituents were required for optimal PAM activity, NAM activity was predominantly observed when heteroatoms were added to the 6-alkyl chain. In addition, with regards to relative positioning of the carboxy and alkyl or alkenyl groups, a 2,6-substitution pattern favours PAM activity (e.g. **14a** and **14b**, Table 1), whereas a 2,7-substitution pattern was either detrimental for PAM activity (e.g. **65** and **69**) or

produced moderately potent NAM activity (e.g. **79a**, Table 5). These differences in the structural requirements suggest that either there are distinct binding sites for PAMs and NAMs or that they contact different areas within the same binding site on the NMDAR complex.

Experiments with structurally related analogues of the NMDAR PAM **14b** (Table 1) and the NAM **79a** showed that they are not binding to the known sites for glutamate antagonists, glycine site antagonists, channel blockers or at the *N*-terminal domain site where NMDAR NAMs such as ifenprodil bind [7,13]. The NMDAR PAM **14b** (UBP684) has been shown to slow deactivation upon glutamate removal and increases open channel probability by stabilizing the NMDAR LBDs in an active conformation [20,21]. It has been proposed that **14b** may be binding at the LBD dimer interface [6d,20,21], as has been observed for the GluN2A selective PAM GNE-6901 (**4**, Figure 1) [10a] or at the LBD/transmembrane domain linker region as proposed for neurosteroids that act as NMDAR PAMs [22]. A feasible binding mode for **14b** was observed when it was docked into the GluN1/GluN2A LBD dimer interface using the Induced Fit module in Maestro (Schrodinger LLC) [21]. The 6-isohexyl side chain of **14b** interacts with a number of hydrophobic residues in the dimer interface in agreement with the current SAR study, which showed that a 6-alkyl substituent is preferred for NMDAR PAM activity. However, structural studies are required to definitively show that **14b** is binding to the LBD dimer interface.

It has been reported that the GluN2A selective NAM MPX-004 (**9**, Figure 1) binds at a similar site to the GluN2A PAM GNE-6901 at the dimer interface of the LBDs of GluN1/GluN2A. The major diffrences between these two binding sites is the conformation of Y535 in GluN1 and the position of V783 in GluN2A, which is displaced upon MPX-004 but not PAM binding [10a,17]. It is possible that the 2-naphthoic acid based NAMs and PAMs bind at these sites. However, the inhibitory activity of NMDAR NAMs structurally related to **79h** were not dependent on glycine concentration [13] in the same way as MPX-004 [17]. In the case of **79h** it did not show dependence on glycine concentration for its inhibitory activity (Figure 4) and so it is unlikely that **79h** and derivatives thereof are binding to the NMDAR LBD dimer interface or the glycine binding site on the GluN1 LBD. Further studies are needed to definitively identify the binding sites on the NMDAR for the NAMs based on 2-naphthoic acid. This will enable computer modelling studies to gain an understanding of the binding modes of the NMDAR NAMs we have identified.

The NMDAR PAMs described herein are useful tools to study synaptic function and represent possible leads for the development of drugs for disorders that involve NMDAR

hypofunction, such as schizophrenia. Since NMDARs are involved in mechanisms that have been proposed to underlie learning and memory processes in the hippocampus, NMDAR potentiators may have application in the treatment of disorders that involve a loss of cognitive function, such as Alzheimer's disease.

A new class of partial NMDAR NAMs that show some selectivity for GluN2D has been identified. NMDAR inhibitors have been proposed as treatments for disorders which arise from NMDAR overactivation such as neuropathic pain, epilepsy, depression and for neurodegenerative disorders such as ischaemia. However, inhibition of NMDARs involved in normal CNS activity causes adverse effects such as psychotomimetic effects, ataxia and cognitive dysfunction. The use of partial NAMs, together with improved subtype-selectivity, may be a way of counteracting overactivation of NMDARs in CNS disorders whilst allowing essential physiological signalling, thus avoiding adverse CNS effects.

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Abbreviations

AMPAR, (*S*)-2-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid receptor; CNS, central nervous system; GFP, green fluorescent protein; HEK, human embryonic kidney; HEPES, 4-(2-hydroxethyl)-1-piperazineethanesulfonic acid); LBD, ligand binding domain; LTP, long-term potentiation; NAM, negative allosteric modulator; NMDAR, *N*-methyl-D-aspartic acid receptor; PAM, positive allosteric modulator; STP, short-term potentiation; TEVC, two electrode voltage clamp

Experimental Methods

Chemistry experimental

General Procedures

Melting points were determined using an Electrothermal IA9100 capillary apparatus and are uncorrected. ^{1}H-NMR spectra were measured on either a Jeol JNM-LA300 spectrometer at 300.53 MHz, a Jeol JNM-ECP400 spectrometer at 400.18 MHz, a Varian 400MR

spectrometer at 399.77 MHz, or a Varian 500 spectrometer at 500 MHz. ^{13}C-NMR spectra were recorded on either a Jeol JNM-LA300 spectrometer at 75.57 MHz, a Jeol JNM-ECP400 spectrometer at 100.63 MHz, a Varian 400MR spectrometer at 100.52 MHz or a Varian 500 spectrometer at 125 MHz. Chemical shifts (δ) are reported in parts per million (ppm) with tetramethylsilane in $CDCl_3$ or DMSO-d_6 used as internal standards. Mass spectrometry was performed in the mass spectroscopy laboratories of the School of Chemistry, University of Bristol, UK. Elemental analyses were performed in the microanalytical laboratories of the School of Chemistry, University of Bristol, UK. The purity of all compounds sent for biological testing was determined by combustion analysis, which confirmed that there were ≥ 95% pure. Thin layer chromatography was performed on Merck silica gel 60 F_{254} plastic sheets. Flash chromatography was performed on Merck silica gel 60 (220-440 mesh) from Fisher. All anhydrous reactions were conducted under argon. All anhydrous solvents were obtained from Sigma-Aldrich, UK or Acros Organics, UK. **47** [23] (methyl 6-(bromomethyl)-2-naphthoate), **50** [24] (methyl 6-(chlorocarbonyl)-2-naphthoate), **53** [25] (6-(hydroxymethyl)-2-naphthoic acid), **55** [26] (2-bromo-6-(bromomethyl)naphthalene), **61** [27] (7-bromo-3-hydroxy-2-naphthoic acid) and **70** [28,29] (6-(methoxymethoxy)naphthalen-2-yl trifluoromethane-sulfonate) were synthesized according to literature procedures.

(*E*)-Methyl 6-(pent-1-en-1-yl)-2-naphthoate (11a). A flask was charged with **10** (3.00 g, 11.3 mmol), palladium acetate (25 mg, 1 mol%) and tri-*o*-tolylphosphine (138 mg, 4 mol%). The flask was then briefly evacuated and backfilled with argon three times. Degassed anhydrous DMF (100 mL) was added followed by pent-1-ene (1.55 mL, 14.1 mmol) and triethylamine (1.97 mL, 14.1 mmol). The resultant mixture was heated at 100 °C overnight. After being allowed to cool to room temperature the reaction mixture was filtered through a celite pad to remove any precipitated Pd(0) and then poured into a stirred solution of EtOAc (100 mL), water (100 mL) and aqueous 1 M HCl (10 mL). The organic layer was subsequently isolated and the aqueous phase further extracted with EtOAc (2 × 50 mL). The organic extracts were pooled, washed with water (5 × 100 mL), brine (100 mL) and dried over $MgSO_4$. Concentration in vacuo afforded a light brown solid which was purified by flash chromatography (2 → 5% EtOAc in hexane) to afford **11a** as a clear oil (2.62 g, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.02 (dd, *J* = 8.4 & 1.6 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H, ArH), 7.81 (d, *J* = 8.4 Hz, 1H, ArH), 7.70 (s, 1H, ArH), 7.63 (dd, *J* = 8.8 & 2.0 Hz, 1H, ArH), 6.56 (d, *J* = 16.0 Hz, 1H, Ar**CH**=CH-), 6.42 (dt, *J* = 16.0 & 6.8 Hz, 1H,

ArCH=**CH**-), 3.97 (s, 3H, -CO_2**CH_3**), 2.32-2.23 (m, 2H, -**CH_2**CH_2CH_3), 1.55 (sex, *J* = 7.2 Hz, 2H, -CH_2**CH_2**CH_3), 0.99 (t, *J* = 7.2 Hz, 3H, -CH_2CH_2**CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 137.8, 135.9, 133.1, 131.6, 130.7, 129.7, 129.4, 127.9, 126.8, 125.6, 125.0, 124.4, 52.2, 35.3, 22.5, 13.8; HRMS-ESI calcd for $C_{17}H_{18}O_2$ $[M + H]^+$ 255.1385; found 255.1392.

(*E*)-Methyl 6-(4-methylpent-1-en-1-yl)-2-naphthoate (11b). Method identical to that described for **11a**. **10** (4.00 g, 15.1 mmol), palladium acetate (34 mg, 1 mol%), tri-*o*-tolylphosphine (184 mg, 4 mol%), 4-methylpent-1-ene (2.39 mL, 18.9 mmol) and triethylamine (2.63 mL, 18.9 mmol) afforded a light brown solid which was purified by flash chromatography (2 → 5% EtOAc in hexane) to afford **11b** as a as a clear oil (3.61 g, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H, ArH), 8.02 (dd, *J* = 8.8 & 2.0 Hz, 1H, ArH), 7.87 (d, *J* = 8.8 Hz, 1H, ArH), 7.81 (d, *J* = 8.4 Hz, 1H, ArH), 7.70 (s, 1H, ArH), 7.64 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 6.54 (d, *J* = 15.6 Hz, 1H, Ar**CH**=CH-), 6.42 (dt, *J* = 15.6 & 7.2 Hz, 1H, ArCH=**CH**-), 3.97 (s, 3H, -CO_2**CH_3**), 2.20-2.15 (m, 2H, -**CH_2**$CH(CH_3)_2$), 1.84-1.70 (m, 1H, -CH_2**CH**$(CH_3)_2$), 0.98 (d, *J* = 6.8 Hz, 6H, -CH_2CH(**CH_3**)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 137.8, 135.9, 132.0, 131.6, 130.7, 130.6, 129.4, 128.0, 126.8, 125.6, 125.0, 124.4, 52.2, 42.6, 28.6, 22.4; HRMS-ESI calcd for $C_{18}H_{20}O_2$ $[M + H]^+$ 269.1536; found 269.1540.

(*E*)-6-(Pent-1-en-1-yl)-2-naphthoic acid (12a). To a stirring solution of **11a** (1.29 g, 5.1 mmol) in a THF/water mix (3:1, 100 mL) was added LiOH (486 mg, 20.3 mmol) dissolved in water (10 mL). The resultant mixture was stirred at room temperature overnight. In the morning, TLC indicated incomplete hydrolysis so the mixture was heated at 65 °C until all the ester had been consumed. After 2 h the mixture was allowed to cool to room temperature before the THF was removed in vacuo. The resultant aqueous solution was topped up with water (40 mL) and then acidified to pH 1 using aqueous 2 M HCl. The solid which precipitated out of solution was filtered off, washed copiously with water and then dried over P_2O_5 overnight. Recrystallisation from toluene (twice) afforded **12a** as a white solid (507 mg, 42%); mp: 157-160 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.00 (br s, 1H, -**CO_2H**), 8.53 (s, 1H, ArH), 8.02 (d, *J* = 8.5 Hz, 1H, ArH), 7.94 (dd, *J* = 8.5 & 1.5 Hz, 1H, ArH), 7.92 (d, *J* = 8.5 Hz, 1H, ArH), 7.86 (s, 1H, ArH), 7.74 (dd, *J* = 8.5 & 1.5 Hz, 1H, ArH), 6.59 (d, *J* = 16.0 Hz, 1H, Ar**CH**=CH-), 6.53 (dt, *J* = 16.0 & 6.5 Hz, 1H, ArCH=**CH**-), 2.23 (q, *J* = 7.0 Hz, 2H, -**CH_2**CH_2CH_3), 1.50 (sex, *J* = 7.5 Hz, 2H, -CH_2**CH_2**CH_3), 0.94 (d, *J* = 7.5 Hz, 3H, -CH_2CH_2**CH_3**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.3, 137.1, 135.3, 132.7, 131.2, 130.1,

129.4, 129.4, 127.9, 127.5, 125.4, 124.6, 124.3, 34.6, 21.8, 13.5; HRMS-ESI calcd for $C_{16}H_{16}O_2$ [M - H]$^-$ 239.1078; found 239.1081; Anal. ($C_{16}H_{16}O_2$) C, H.

(*E*)-6-(4-Methylpent-1-en-1-yl)-2-naphthoic acid (12b). To a stirring solution of **11b** (889 mg, 3.31 mmol) in a dioxane/water mix (3:1, 80 mL) was added aqueous 1 M NaOH (13.2 mL, 13.2 mmol). The resultant mixture was stirred at 80 °C until TLC indicated complete hydrolysis of the ester. The mixture was then allowed to cool to room temperature before the dioxane was removed in vacuo. The resultant aqueous solution was topped up with water (40 mL), extracted with diethyl ether (25 mL), and then acidified to pH 1 using aqueous 2 M HCl. The solid which precipitated out of solution was filtered off, washed copiously with water and then dried over P_2O_5 overnight. Recrystallisation from toluene afforded **12b** as a white solid (376 mg, 45%); mp: 178-182 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (br s, 1H, **-CO_2H**), 8.54 (s, 1H, ArH), 8.03 (d, *J* = 8.8 Hz, 1H, ArH), 7.95 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 7.92 (d, *J* = 8.8 Hz, 1H, ArH), 7.87 (s, 1H, ArH), 7.76 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 6.58 (d, *J* = 16.0 Hz, 1H, Ar**C**H=CH-), 6.52 (dt, *J* = 16.0 & 6.4 Hz, 1H, Ar**C**H=**C**H-), 2.14 (t, *J* = 6.4 Hz, 2H, -**CH_2**CH(CH_3)$_2$), 1.75 (sep, *J* = 6.8 Hz, 1H, -CH_2**C**H(CH_3)$_2$), 0.94 (d, *J* = 6.8 Hz, 6H, -CH_2CH(**CH_3**)$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.3, 137.1, 135.3, 131.7,131.2, 130.4, 130.1, 129.4, 127.9, 127.5, 125.5, 124.7, 124.4, 41.9, 27.9, 22.2; HRMS-ESI calcd for $C_{17}H_{18}O_2$ [M - H]$^-$ 253.1234; found 253.1235; Anal. ($C_{17}H_{18}O_2$·0.34C_7H_8) C, H.

Methyl 6-*n*-pent-1-yl-2-naphthoate (13a). A solution of **11a** (1.30 g, 5.1 mmol) in EtOAc (100 mL) was hydrogenated under 3 bar of hydrogen in the presence of 10 wt % palladium on activated carbon (50 mg) for 18 h. The reaction mixture was then filtered through a celite pad before being concentrated in vacuo to afford **13a** as a clear oil (1.28 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, ArH), 8.03 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 7.87 (d, *J* = 8.4 Hz, 1H, ArH), 7.81 (d, *J* = 8.4 Hz, 1H, ArH), 6.64 (s, 1H, ArH), 7.40 (dd, *J* = 8.4 & 2.0 Hz, 1H, ArH), 3.98 (s, 3H, -CO_2**CH_3**), 2.79 (t, *J* = 7.6 Hz, 2H, Ar**CH_2**-), 1.76-1.67 (m, 2H, -**CH_2**CH_2 CH_2-), 1.38-1.31 (m, 4H, -CH_2**CH_2CH_2**-), 0.90 (t, *J* = 7.2 Hz, 3H, -**CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 143.4, 135.8, 130.9, 130.8, 129.2, 128.3, 127.6, 126.5, 126.2, 125.2, 52.1, 36.2, 31.5, 30.9, 22.5, 14.0; HRMS-CI calcd for $C_{17}H_{20}O_2$ [M + H]$^+$ 257.1542; found 257.1550.

Methyl 6-(4-methylpent-1-yl)-2-naphthoate (13b). Method identical to that described for **13a**. **11b** (2.70 g, 10.1 mmol) and 10 wt % palladium on activated carbon (100 mg) afforded **13b** as a clear oil (2.68 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, ArH,), 8.03 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 7.87 (d, *J* = 8.8 Hz, 1H, ArH), 7.81 (d, *J* = 8.8 Hz, 1H, ArH), 6.55 (s, 1H, ArH), 7.40 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 3.98 (s, 3H, -CO_2**CH_3**), 2.77 (t, *J* = 7.6 Hz, 2H, Ar**CH_2**-), 1.76-1.67 (m, 2H, -CH_2CH_2-), 1.64-1.55 (m, 1H, -**CH**$(CH_3)_2$), 1.32-1.23 (m, 2H, -CH_2CH_2-), 0.89 (d, *J* = 6.8 Hz, 6H, -CH(**CH_3**$)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 143.4, 135.8, 130.9, 130.8, 129.2, 128.3, 127.6, 126.6, 126.2, 125.3, 52.1, 38.6, 36.5, 29.1, 27.9, 22.6; HRMS-CI calcd for $C_{18}H_{22}O_2$ $[M + H]^+$ 271.1698; found 271.1703.

6-*n*-Pent-1-yl-2-naphthoic acid (14a). To a stirring solution of **13a** (1.14 g, 4.5 mmol) in a THF/water mix (3:1, 80 mL) was added aqueous 1 M NaOH (22.5 mL, 22.5 mmol). The resultant mixture was stirred at 65 °C until TLC indicated complete hydrolysis of the ester. The mixture was then allowed to cool to room temperature before the THF was removed in vacuo. The resultant aqueous solution was topped up with water (40 mL) and then acidified to pH 1 using aqueous 2 M HCl. The solid which precipitated out of solution was filtered off, washed copiously with water and then dried over P_2O_5 overnight to afford **13a** as an off-white solid (913 mg, 84%); mp: 128-132 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.00 (br s, 1H, -**CO_2H**), 8.54 (s, 1H, ArH), 8.01 (d, *J* = 9.0 Hz, 1H, ArH), 7.94 (dd, *J* = 9.0 & 1.5 Hz, 1H, ArH), 7.91 (d, *J* = 8.5 Hz, 1H, ArH), 7.76 (s, 1H, ArH), 7.46 (dd, *J* = 8.5 & 1.5 Hz, 1H, ArH), 2.76 (t, *J* = 7.5 Hz, 2H, Ar**CH_2**-), 1.66 (pent, *J* = 7.5 Hz, 2H, -**CH_2**CH_2CH_2-), 1.37-1.25 (m, 4H, -CH_2**CH_2CH_2**-), 0.86 (t, *J* = 7.0 Hz, 3H, -**CH_3**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5, 142.8, 135.1, 130.6, 130.2, 129.1, 128.2, 127.6, 127.2, 125.9, 125.1, 35.3, 30.9, 30.3, 21.9, 13.9; HRMS-ESI calcd for $C_{16}H_{18}O_2$ $[M - H]^-$ 241.1234; found 241.1235; Anal. ($C_{16}H_{18}O_2 \cdot 0.2H_2O$) C, H.

6-(4-Methylpent-1-yl)-2-naphthoic acid (14b). To a stirring solution of **13b** (2.66 g, 9.84 mmol) in a dioxane/water mix (3:1, 80 mL) was added NaOH (1.58 g, 39.5 mmol) dissolved in water (20 mL). The resultant mixture was stirred at 80 °C until TLC indicated complete hydrolysis of the ester. The mixture was then allowed to cool to room temperature before the dioxane was removed in vacuo. The resultant aqueous solution was topped up with water (40 mL) and then acidified to pH 1 using aqueous 2 M HCl. The solid which precipitated out of solution was filtered off, washed copiously with water and then dried over P_2O_5 overnight.

Recrystallisation from acetonitrile afforded **14b** as a fluffy white solid (1.67 g, 66%); mp: 149-153 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (br s, 1H, -**CO$_2$H**), 8.55 (s, 1H, ArH), 8.02 (d, *J* = 8.4 Hz, 1H, ArH), 7.95 (dd, *J* = 8.4 & 2.0 Hz, 1H, ArH), 7.91 (d, *J* = 8.4 Hz, 1H, ArH), 7.76 (s, 1H, ArH), 7.47 (dd, *J* = 8.4 & 2.0 Hz, 1H, ArH), 2.74 (t, *J* = 7.6 Hz, 2H, Ar**CH$_2$**-), 1.71-1.61 (m, 2H, -CH$_2$CH$_2$-), 1.56 (sep, *J* = 6.8 Hz, 1H, -**CH**(CH$_3$)$_2$), 1.24-1.17 (m, 2H, CH$_2$CH$_2$-), 0.85 (d, *J* = 6.8 Hz, 6H, -CH(**CH$_3$**)$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.4, 142.7, 135.1, 130.5, 130.2, 129.1, 128.2, 127.5, 127.2, 125.9, 125.1, 38.0, 35.5, 28.4, 27.2, 22.4; HRMS-ESI calcd for $C_{17}H_{20}O_2$ [M - H]$^-$ 255.1391; found 255.1396; Anal. ($C_{17}H_{20}O_2 \cdot 0.13H_2O$) C, H.

Methyl 6-vinyl-2-naphthoate (15). A flask containing **10** (2.00 g, 7.6 mmol) was evacuated and backfilled with argon three times. Anhydrous toluene (50 mL) was cannulated into the flask and the resultant solution de-gassed with argon for approx. 30 mins. Pd(PPh$_3$)$_4$ (266 mg, 3 mol%) was then added and the mixture de-gassed for a further 10 mins before vinyl(tri-*n*-butyl)tin (2.55 mL, 8.7 mmol) was added. The resultant mixture was refluxed for 4 h before being allowed to cool to room temperature and filtered through celite to remove any precipitated Pd(0). The filtrate was then poured into a stirring mixture of EtOAc and saturated aqueous NH_4Cl (50 mL each). The organic layer was isolated and washed with aqueous 1M KF (2 × 50 mL) to remove any tin by-products. The white solid (Bu_3SnF) which precipitated from solution after the first wash was removed via filtration through celite. The organic layer was then isolated, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo to yield a light peach coloured residue. Purification by flash chromatography (5% EtOAc in hexane) afforded **15** as a viscous clear oil which partially solidified on standing to a white solid (1.01 g, 63%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H, ArH), 8.05 (d, *J* = 8.7 & 1.8 Hz, 1H, ArH), 7.90 (d, *J* = 8.7 Hz, 1H, ArH), 7.85 (d, *J* = 8.7 Hz, 1H, ArH), 7.78 (s, 1H, ArH), 7.69 (dd, *J* = 8.7 & 1.8 Hz, 1H, ArH), 6.89 (dd, *J* = 17.4 & 10.8 Hz, 1H, Ar**CH**=CH$_2$), 5.93 (d, *J* = 17.4 Hz, 1H, ArCH=**CH$_2$**), 5.41 (d, *J* = 10.8 Hz, 1H, ArCH=**CH$_2$**), 3.98 (s, 3H, -CO$_2$**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 137.3, 136.5, 135.8, 132.2, 130.7, 129.6, 128.2, 127.3, 126.0, 125.7, 124.0, 115.6, 52.2; HRMS-ESI calcd for $C_{14}H_{12}O_2$ [M + H]$^+$ 213.0910; found 213.0915.

Methyl 6-cyclopropyl-2-naphthoic acid (17). Diiodomethane (0.91 mL, 11.32 mmol) was dissolved in anhydrous DCM (30 mL) and $ZnEt_2$ (1.0 M solution in hexane, 5.66 mL, 5.66 mmol) added to this solution at 0 °C followed by a solution of **15** in DCM (600 mg, 2.83

mmol in 10 mL). The reaction mixture was then stirred vigorously overnight before being quenched with aqueous saturated NH_4Cl. The mixture was diluted with diethyl ether (50 mL) and the organic layer isolated, washed with water (25 mL), brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was purified by flash chromatography (5% EtOAc in hexane) to afford the ester (**16**) as a viscous clear oil (465 mg, 73%) which was taken forward and hydrolysed without further characterisation. To a mixture of the **16** (465 mg, 2.05 mmol) in a THF/water mix (3:1, 40 mL) was added aqueous 1 M NaOH (8.2 mL, 8.2 mmol). The resultant mixture was stirred at 65 °C until TLC indicated complete hydrolysis of the ester. The mixture was then allowed to cool to room temperature before the THF was removed in vacuo. The resultant aqueous solution was topped up with water (40 mL), extracted with diethyl ether (25 mL) and then acidified to pH 1 using aqueous 2 M HCl. The solid which precipitated out of solution was filtered off, washed copiously with water and then dried over P_2O_5 overnight to yield a white solid. Recrystallisation from toluene afforded **17** as a white solid (179 mg, 41%); mp: 125-129 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 12.96 (br s, 1H, **-CO_2H**), 8.52 (s, 1H, ArH), 7.98 (d, *J* = 8.4 Hz, 1H, ArH), 7.92 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 7.87 (d, *J* = 8.4 Hz, 1H, ArH), 7.68 (s, 1H, ArH), 7.31 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 2.16-2.08 (m, 1H, Ar**CH**$(CH_2)_2$), 1.09-1.03 (m, 2H, ArCH(**CH_2**$)_2$), 0.87-0.81 (m, 2H, ArCH(**CH_2**$)_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.9, 144.8, 135.6, 130.9, 130.7, 129.7, 127.8, 127.4, 125.8, 125.6, 123.5, 16.0, 10.4; HRMS-ESI calcd for $C_{14}H_{12}O_2$ $[M - H]^-$ 211.0765; found 211.0770; Anal. ($C_{14}H_{12}O_2$) C, H.

2-Hydroxymethyl-6-*n*-pent-1-yl-naphthalene (18). A flask was charged with **14a** (4.50 g, 18.6 mmol) before being briefly evacuated and backfilled with argon. Anhydrous THF (100 mL) was cannulated into the flask and the resultant solution cooled to 0 °C. A 1 M $LiAlH_4$ solution in THF (27.9 mL, 27.9 mmol) was then added dropwise with care. After complete addition the solution was allowed to warm to room temperature before being refluxed for 4 h. After being allowed to cool to room temperature the solution was further cooled to 0 °C and excess $LiAlH_4$ destroyed via the dropwise addition of saturated aqueous NH_4Cl. The THF was then removed in vacuo and the resultant residue partitioned between EtOAc and water (100 mL each). The organic layer was isolated, dried over $MgSO_4$ and concentrated in vacuo to yield a cream coloured solid which was purified by flash chromatography (20 → 30% EtOAc in hexane) to afford **18** as a white solid (3.20 g, 75%); mp: 72-76 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.73 (m, 3H, ArH), 7.61 (s, 1H, ArH), 7.45 (dd, *J* = 8.4 & 2.0 Hz, 1H,

ArH), 7.35 (dd, *J* = 8.4 & 2.0 Hz, 1H, ArH), 4.84 (s, 2H, -**CH$_2$**OH), 2.77 (t, *J* = 7.6 Hz, 2H, Ar**CH$_2$**-), 1.77-1.67 (m, 2H, -$CH_2CH_2CH_2$-), 1.39-1.32 (m, 4H, $CH_2CH_2CH_2$-), 0.91 (t, *J* = 7.2 Hz, 3H, -**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 137.4, 133.1, 131.8, 127.9, 127.8, 127.7, 126.1, 125.3, 125.2, 65.6, 36.1, 31.5, 31.0, 22.6, 14.0; HRMS-CI calcd for $C_{16}H_{20}O$ $[M]^+$ 228.1514; found 228.1516; Anal. ($C_{16}H_{20}O$) C, H.

2-Bromomethyl-6-*n*-pent-1-yl-naphthalene (19). A flask containing **18** (3.00 g, 13.1 mmol) was briefly evacuated and backfilled with argon. Anhydrous DCM (100 mL) was then cannulated into the flask and the resultant solution cooled to 0 °C. PBr_3 (4.92 mL, 52.4 mmol) was added dropwise and after complete addition the solution was allowed to warm to room temperature and stirred until TLC showed complete conversion. After 1 h the solution was cooled to 0 °C and excess PBr_3 destroyed via the dropwise addition of saturated aqueous $NaHCO_3$. The DCM was removed in vacuo to afford an oily residue which was diluted with diethyl ether (100 mL). The organic layer was isolated, dried over $MgSO_4$ and concentrated in vacuo to yield an amber oil which solidified on standing. Dissolving the crude product in hexane and passing it through a short silica plug (10 cm) afforded **19** as an oil which partially solidified on standing to a light brown solid (2.98 g, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H, ArH), 7.76 (d, *J* = 8.4 Hz, 1H, ArH), 7.73 (d, *J* = 8.4 Hz, 1H, ArH), 7.59 (s, 1H, ArH), 7.47 (dd, *J* = 8.4 & 2.0 Hz, 1H, ArH), 7.35 (dd, *J* = 8.4 & 2.0 Hz, 1H, ArH), 4.67 (s, 2H, -**CH$_2$**Br), 2.76 (t, *J* = 7.6 Hz, 2H, Ar**CH$_2$**-), 1.74-1.66 (m, 2H, -$CH_2CH_2CH_2$-), 1.38-1.31 (m, 4H, -$CH_2CH_2CH_2$-), 0.90 (t, *J* = 7.2 Hz, 3H, -**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 134.2, 133.3, 131.6, 128.3, 128.1, 127.8, 127.6, 126.7, 126.2, 36.1, 34.3, 31.5, 31.0, 22.6, 14.0; HRMS-CI calcd for $C_{16}H_{19}Br$ $[M + H]^+$ 291.0748; found 291.0746.

(6-*n*-Pent-1-ylnapthalen-2-yl)acetonitrile (20). 19 (1.90 g, 6.5 mmol) was dissolved in anhydrous DCM (25 mL) and stirred vigorously with a solution of sodium cyanide (480 mg, 9.8 mmol) and tetra-*n*-butylammonium bromide (316 mg, 0.98 mmol) in water (25 mL). After 48 hours TLC indicated complete conversion. The organic layer was subsequently isolated and the aqueous phase extracted with DCM (2 × 20 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo to afford a golden brown oil. Purification by flash chromatography (10% EtOAc in hexane) yielded **20** as a yellow oil (1.20 g, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.77 (m, 2H, ArH), 7.75 (d, *J* = 8.4 Hz, 1H, ArH), 7.61 (s, 1H, ArH), 7.38 (dd, *J* = 8.4 & 2.0, 1H, ArH), 7.35 (dd, *J* = 8.0 & 2.0 Hz,

1H, ArH), 3.90 (s, 2H, -**CH$_2$**CN), 2.77 (t, *J* = 7.6 Hz, 2H, Ar**CH$_2$**-), 1.71 (pent, *J* = 7.6 Hz, 2H, -$CH_2CH_2CH_2$-), 1.40-1.30 (m, 4H, -$CH_2CH_2CH_2$-), 0.90 (t, *J* = 7.2 Hz, 3H, -**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 132.9, 131.8, 128.6, 128.4, 127.5, 126.6, 126.2, 126.2, 125.4, 118.0, 36.1, 31.5, 31.0, 23.8, 22.6, 14.0; HRMS-ESI cald for $C_{17}H_{19}N$ $[M + Na]^+$ 260.1410; found 260.1420.

(6-*n*-Pent-1-ylnaphthalen-2-yl)acetic acid (21). A stirring mixture of **20** (1.17 g, 4.9 mmol) in glacial acetic acid (20 mL), conc H_2SO_4 (10 mL) and water (10 mL) was heated under reflux for 18 h. The mixture was then allowed to cool to room temperature before being diluted with water (100 mL). The aqueous mixture was extracted with EtOAc (100 mL then 2 × 50 mL) and the organic layers pooled, washed with water (3 × 100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated in vacuo to afford a light brown solid. The crude product was dissolved in diethyl ether (100 mL) and the resultant organic solution extracted with aqueous 2 M NaOH (30 mL). The sodium salt which formed had poor solubility so additional water (approximately 150 mL) was added in order to get it fully into solution. The aqueous phase was isolated and the organic solution further extracted with aqueous 2 M NaOH (2 × 30 mL). The alkaline phases were combined and acidified to pH 1 using aqueous 2 M HCl. The aqueous solution was then extracted with diethyl ether (2 × 100 mL) and the organic layers pooled, washed with water (4 × 100 mL), brine (100 mL), dried over $MgSO_4$ and concentrated in vacuo to afford **21** as a light brown solid (994 mg, 79%); mp: 120-124 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (br s, 1H, -CH_2**CO$_2$H**), 7.79 (d, *J* = 6.0 Hz, 1H, ArH), 7.77 (d, *J* = 6.0 Hz, 1H, ArH), 7.71 (s, 1H, ArH), 7.65 (s, 1H, ArH), 7.38 (dd, *J* = 6.0 & 2.0 Hz, 1H, ArH), 7.36 (dd, *J* = 6.0 & 2.0 Hz, 1H, ArH), 3.71 (s, 2H, -**CH$_2$**CO_2H), 2.73 (d, *J* = 7.2 Hz, 2H, Ar**CH$_2$**-), 1.66 (pent, *J* = 7.2 Hz, 2H, -**CH$_2$**CH_2CH_2-), 1.39-1.25 (m, 4H, -CH_2**CH$_2$CH$_2$**-), 0.86 (t, *J* = 7.2 Hz, 3H, -**CH$_3$**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.7, 139.6, 131.9, 131.7, 131.4, 127.8, 127.4, 127.3, 127.2, 127.1, 125.7, 40.7, 35.1, 30.8, 30.4, 21.9, 13.8; HRMS-ESI cald for $C_{17}H_{20}O_2$ $[M + Na]^+$ 279.1356; found 279.1360; Anal. ($C_{17}H_{20}O_2$) C, H.

5-Bromo-6-*n*-pent-1-yl-2-naphthoic acid (22). To a stirring solution of **14a** (1.00 g, 4.1 mmol) in glacial acetic acid (65 mL) at 50 °C was added dropwise a solution of bromine (0.21 mL, 4.1 mmol) in glacial acetic acid (5 mL). The resultant mixture was stirred at 50 °C until TLC showed complete consumption of the starting material. The mixture was then

allowed to cool to room temperature before being diluted with water (100 mL), causing precipitation of a solid. Excess bromine was destroyed via the dropwise addition of a saturated aqueous Na_2SO_3 solution. Filtration of the suspension afforded an off-white solid which was washed copiously with water and then dried over P_2O_5 overnight. Re-crystallisation from glacial acetic acid (three times) afforded **22** as a white solid (293 mg, 22%); mp: 193-196 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 13.18 (br s, 1H, -**CO_2H**), 8.61 (d, *J* = 1.6 Hz, 1H, ArH), 8.27 (d, *J* = 8.8 Hz, 1H, ArH), 8.12-8.08 (m, 2H, ArH), 7.58 (d, *J* = 8.4 Hz, 1H, ArH), 2.95 (t, *J* = 7.2 Hz, 2H, Ar**CH_2**-), 1.65 (pent, *J* = 7.2 Hz, 2H, -**CH_2**CH_2CH_2-), 1.40-1.29 (m, 4H, -CH_2**CH_2CH_2**-), 0.88 (t, *J* = 7.2 Hz, 3H, -**CH_3**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5, 143.1, 134.1, 132.5, 131.2, 129.7, 129.6, 128.6, 127.4, 127.4, 122.8, 37.1, 31.5, 29.7, 22.4, 14.3; HRMS-ESI calcd for $C_{16}H_{17}O_2Br$ $[M + Na]^+$ 343.0304; found 343.0312; Anal. ($C_{16}H_{17}O_2Br$) C, H.

6-Butoxy-2-naphthoic acid (24). Method adapted from the literature.[30] To a stirring solution of **23** (1.00 g, 5.3 mmol) in an EtOH/water mix (3:1, 40 mL) was added 1-bromobutane (0.86 mL, 8.0 mmol). The resultant mixture was refluxed for 18 h and then allowed to cool to room temperature before a 10% aqueous NaOH solution (10 mL) was added. The mixture was then refluxed for a further 2 h before being allowed to cool to room temperature. After being diluted with water (150 mL) the solution was acidified to pH 1 using aqueous 2 M HCl. The solid which precipitated out of solution was filtered off, washed copiously with water and then dried over P_2O_5 overnight to afford **24** as a white solid (1.10 g, 85%); mp: 188-192 ^oC (lit[30]: 198 ^oC); ^1H NMR (400 MHz, DMSO-d_6) δ 12.93 (br s, 1H, -**CO_2H**), 8.51 (s, 1H, ArH), 8.00 (d, *J* = 8.8 Hz, 1H, ArH), 7.92 (dd, *J* = 8.8 & 2.0 Hz, 1H, ArH), 7.86 (d, *J* = 8.8 Hz, 1H, ArH), 7.39 (d, *J* = 2.4 Hz, 1H, ArH), 7.23 (dd, *J* = 8.8 & 2.4 Hz, 1H, ArH), 4.12 (t, *J* = 6.4 Hz, 2H, ArO**CH_2**-), 1.81-1.73 (m, 2H, -**CH_2**CH_2CH_3), 1.48 (sex, *J* = 7.2 Hz, 2H, -CH_2**CH_2**CH_3), 0.96 (t, *J* = 7.2 Hz, 3H, -CH_2CH_2**CH_3**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5, 158.4, 136.7, 130.8, 130.3, 127.3, 126.8, 125.6, 125.5, 119.6, 106.5, 67.4, 30.6, 18.7, 13.6.

(*E*)-Methyl 6-(4-phenylbut-1-en-1-yl)-2-naphthoate (25a). Method identical to that described for **11a**. **10** (1.50 g, 5.7 mmol), palladium acetate (13 mg, 1 mol%), tri-*o*-tolylphosphine (70 mg, 4 mol%), 4-phenylbut-1-ene (1.06 mL, 7.1 mmol) and triethylamine

(0.99 mL, 7.1 mmol) afforded **25a** as a light brown solid (1.75 g, 98%) which was utilised immediately in the next step.

(*E*)-Methyl 6-(3-cyclopentylprop-1-en-1-yl)naphthalene-2-carboxylate (25b). Method identical to that described for **11a**. **10** (1.50 g, 5.7 mmol), palladium acetate (13 mg, 1 mol%), tri-*o*-tolylphosphine (70 mg, 4 mol%), allyl cyclopentane (0.99 mL, 7.1 mmol) and triethylamine (0.99 mL, 7.1 mmol) afforded **25b** as a light brown solid (1.60 g, 96%) which was utilised immediately in the next step.

Methyl 6-(4-phenylbut-1-yl)-2-naphthoate (26a). Method identical to that described for **13a**. **25a** (1.75 g, 5.5 mmol) and 10 wt % palladium on activated carbon (100 mg) yielded a viscous golden coloured oil which was purified by flash chromatography (5% EtOAc in hexane) to afford **26a** as a viscous clear oil (1.29 g, 73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, ArH), 8.03 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 7.87 (d, *J* = 8.4 Hz, 1H, ArH), 7.80 (d, *J* = 8.4 Hz, 1H, ArH), 7.63 (s, 1H, ArH), 7.38 (dd, *J* = 8.4 & 2.0 Hz, 1H, ArH), 7.31-7.25 (m, 2H, ArH), 7.21-7.15 (m, 3H, ArH), 3.98 (s, 3H, -CO_2**CH_3**), 2.83 (t, *J* = 7.2 Hz, 2H, Ar**CH_2**-), 2.67 (m, 2H, -$CH_2CH_2CH_2Ph$), 1.82-1.67 (m, 4H, -$CH_2CH_2CH_2Ph$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 142.9, 142.4, 135.8, 131.0, 130.8, 129.2, 128.4, 128.3, 128.2, 127.6, 126.6, 126.2, 125.7, 125.3, 52.1, 36.1, 35.8, 31.1, 30.7; HRMS-CI calcd for $C_{22}H_{22}O_2$ $[M + H]^+$ 319.1698; found 319.1705; Anal. ($C_{22}H_{22}O_2$) C, H.

Methyl 6-(3-cyclopentylprop-1-yl)naphthalene-2-carboxylate (26b). Method identical to that described for **13a**. **25b** (1.60 g, 5.4 mmol) and 10 wt % palladium on activated carbon (100 mg) yielded a golden coloured oil which was purified by flash chromatography (1 → 5% EtOAc in hexane) to afford **26b** as a viscous clear oil (1.10 g, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, ArH), 8.03 (dd, *J* = 8.8 & 2.0 Hz, 1H, ArH), 7.87 (d, *J* = 8.4 Hz, 1H, ArH), 7.81 (d, *J* = 8.8 Hz, 1H, ArH), 7.44 (s, 1H, ArH), 7.40 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 3.98 (s, 3H, -CO_2**CH_3**), 2.79 (t, *J* = 7.6 Hz, 2H, Ar**CH_2**-), 1.84-1.68 (m, 5H, -CH_2CH_2cPe), 1.65-1.45 (m, 4H, CH_2CH_2cPe), 1.43-1.34 (m, 2H, CH_2CH_2cPe), 1.13-1.02 (m, 2H, CH_2CH_2cPe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 143.4, 135.8, 130.9, 130.8, 129.2, 128.3, 127.6, 126.5, 126.2, 125.2, 52.1, 40.1, 36.5, 35.9, 32.7, 30.4, 25.2; HRMS-ESI calcd for $C_{20}H_{24}O_2$ $[M + Na]^+$ 319.1669; found 319.1674.

6-(4-Phenylbut-1-yl)naphthalene-2-carboxylic acid (27a). Method identical to that described for **14a**. **26a** (1.29 g, 4.1 mmol) and aqueous 1 M NaOH (12.3 mL, 12.3 mmol) afforded **27a** as a white solid (1.17 g, 95%); mp: 151-155 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (br s, 1H, **-CO_2H**), 8.53 (s, 1H, ArH), 8.00 (d, *J* = 8.4 Hz, 1H, ArH), 7.94 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 7.89 (d, *J* = 8.4 Hz, 1H, ArH), 7.74 (s, 1H, ArH), 7.44 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 7.28-7.22 (m, 2H, ArH), 7.19-7.12 (m, 3H, ArH), 2.79 (d, *J* = 7.2 Hz, 2H, Ar**CH_2**CH_2-), 2.61 (d, *J* = 7.2 Hz, 2H, ArCH_2**CH_2**-), 1.73-1.56 (m, 4H, **-CH_2CH_2**Ph); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.6, 142.4, 142.1, 135.0, 130.6, 130.0, 129.1, 128.2, 128.2, 128.1, 127.4, 125.9, 125.6, 125.3, 35.1, 34.9, 30.6, 30.2; HRMS-ESI calcd for $C_{21}H_{20}O_2$ [M - H]$^-$ 303.1385; found 303.1393; Anal. ($C_{21}H_{20}O_2$) C, H.

6-(3-Cyclopentylprop-1-yl)-2-naphthoic acid (27b). Method identical to that described for **14a**. **26b** (1.10 g, 3.7 mmol) and aqueous 1 M NaOH (11.1 mL, 11.1 mmol) yielded a white solid which was recrystallised from acetonitrile to afford **27b** as an off-white solid (476 mg, 45%); mp: 147-150 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (br s, 1H, **-CO_2H**), 8.53 (s, 1H, ArH), 8.01 (d, *J* = 8.4 Hz, 1H, ArH), 7.94 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 7.91 (d, *J* = 8.4 Hz, 1H, ArH), 7.75 (s, 1H, ArH), 7.46 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 2.75 (t, *J* = 7.6 Hz, 2H, Ar**CH_2**-), 1.81-1.61 (m, 5H, -CH_2CH_2cPe), 1.57-1.41 (m, 4H, CH_2CH_2cPe), 1.36-1.27 (m, 2H, CH_2CH_2cPe), 1.08-0.97 (m, 2H, CH_2CH_2cPe); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.4, 142.8, 135.1, 130.5, 130.2, 129.1, 128.2, 127.5, 127.2, 125.9, 125.1, 39.4, 35.6, 35.2, 32.1, 29.8, 24.6; HRMS-ESI calcd for $C_{19}H_{22}O_2$ [M - H]$^-$ 281.1547; found 281.1552; Anal. ($C_{19}H_{22}O_2$) C, H.

Methyl 6-(4-methylpent-1-yn-1-yl)-2-naphthoate (28). A stirring solution of **10** (1.32g, 5.0 mmol), $PdCl_2(Ph_3)_2$ (211 mg, 0.3 mmol) and CuI (57 mg, 0.3 mmol) in anhydrous THF (15 mL) was briefly evacuated and backfilled with argon. An identical procedure was conducted on a solution of 4-methylpent-1-yne (0.71 mL, 6.0 mmol) and diethylamine (1.0 mL, 10 mmol) in anhydrous THF (5 mL). The alkyne solution was then added to the bromide solution and the resultant mixture stirred at 50 ^{o}C overnight. The reaction was then quenched with saturated NH_4Cl (10 mL) and extracted with diethyl ether (2 × 40 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was purified by flash chromatography (10% EtOAc in hexane) to afford **28** as a clear oil (1.25 g, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H, ArH), 8.01 (d, *J* = 8.2 Hz, 1H, ArH), 7.90 (s, 1H, ArH), 7.82 (d, *J* = 8.2 Hz, 1H, ArH), 7.76 (d, *J* = 8.2 Hz, 1H, ArH), 7.49

(d, *J* = 8.2 Hz, 1H, ArH), 3.95 (s, 3H, -CO_2**CH_3**), 2.34 (d, *J* = 6.4 Hz, 2H, -**CH_2**$CH(CH_3)_2$), 1.99-1.89 (m, 1H, -CH_2**CH**$(CH_3)_2$), 1.07 (d, *J* = 6.4 Hz, 6H, -CH_2CH(**CH_3**$)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 135.1, 131.4, 130.7, 129.6, 129.1, 127.7, 125.8, 124.1, 91.5, 81.6, 52.2, 28.7, 28.2, 22.1; HRMS-ESI calcd for $C_{18}H_{19}O_2$ $[M + H]^+$ 267.1386; found 267.1380.

6-(4-Methylpent-1-yn-1-yl)-2-naphthoic acid (29). To a stirring solution of **28** (1.25 g, 4.7 mmol) in dioxane (10 mL) was added LiOH (562 mg, 23.5 mmol) dissolved in a few mL of water. The resultant mixture was stirred at room temperature until TLC indicated complete hydrolysis. The dioxane was then removed in vacuo and the resultant residue dissolved in water (40 mL), extracted with diethyl ether (10 mL), and acidified to pH 1 using aqueous 2 M HCl. The solid which precipitated from solution was filtered off, washed copiously with water and then dried over P_2O_5 overnight to afford **29** as white solid (1.05 g, 88%); mp: 125-129 ^{o}C; ^{1}H NMR (300 MHz, DMSO-*d_6*) δ 8.54 (s, 1H, ArH), 8.06-8.03 (m, 2H, ArH), 7.95-7.94 (m, 2H, ArH), 7.49 (dd, *J* = 7.6 & 1.5 Hz, 1H, ArH), 2.36 (d, *J* = 6.5 Hz, 2H, -**CH_2**$CH(CH_3)_2$), 1.92-1.79 (m, 1H, -CH_2**CH**$(CH_3)_2$), 1.01 (d, *J* = 6.6 Hz, 6H, -CH_2CH(**CH_3**$)_2$); ^{13}C NMR (75 MHz, DMSO-*d_6*) δ 167.8, 135.1, 131.7, 131.0, 130.8, 130.1, 129.6, 129.1, 128.4, 126.4, 123.5, 92.0, 82.1, 28.3, 28.2, 22.4; HRMS-ESI calcd for $C_{17}H_{15}O_2$ $[M-H]^-$ 251.1074; found 251.1077; Anal. ($C_{17}H_{16}O_2$) C, H.

(*RS*)-(*E*)-Ethyl 6-(4-ethylcarbonylpent-1-en-1-yl)-2-naphthoate (30). Method identical to that described for **11a**. **10** (3.00 g, 11.3 mmol), palladium acetate (25 mg, 1 mol%), tri-*o*-tolylphosphine (138 mg, 4 mol%), ethyl 2-methyl-4-pentenoate (2.28 mL, 14.1 mmol) and triethylamine (1.97 mL, 14.1 mmol) yielded a dark orange oil which was purified by flash chromatography (5 → 20% EtOAc in hexane) to afford **30** as a viscous light yellow oil (3.35 g, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H, ArH), 8.03 (dd, *J* = 8.4 & 2.0 Hz, 1H, ArH), 7.86 (d, *J* = 8.4 Hz, 1H, ArH), 7.81 (d, *J* = 8.8 Hz, 1H, ArH), 7.70 (s, 1H, ArH), 7.61 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 6.60 (d, *J* = 15.6 Hz, 1H, -**CH**=$CHCH_2$-), 6.35 (dt, *J* = 15.6 & 7.2Hz, 1H, -CH=**CH**CH_2-), 4.15 (q, *J* = 7.2 Hz, 2H, -$CH(CH_3)CO_2$**CH_2**CH_3), 3.97 (s, 3H, -CO_2**CH_3**), 2.69-2.58 (m, 2H, -CH=CH**CH_2**-), 2.47-2.37 (m, 1H, -**CH**$(CH_3)CO_2CH_2CH_3$), 1.28-1.22 (m, 6H, -CH(**CH_3**$)CO_2CH_2$**CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 167.2, 137.2, 135.8, 131.8, 131.8, 130.7, 129.5, 129.3, 128.0, 127.0, 125.6, 125.3, 124.4, 60.4, 52.2, 39.6, 37.2, 16.8, 14.3; HRMS-ESI calcd for $C_{20}H_{22}O_4$ $[M + Na]^+$ 349.1410; found 349.1423.

(*RS*)-(*E*)-6-(4-Carboxypent-1-en-1-yl)-2-naphthoic acid (31). Method identical to that described for **14b** with the exception that the reaction mixture was stirred at room temperature until TLC indicated complete hydrolysis of the ester. **30** (1.41 g, 4.3 mmol) and NaOH (1.04 g, 25.9 mmol) afforded **31** as an off-white solid (1.19 g, 96%); mp: 226-230 ^{o}C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (br s, 2H, -**CO_2H**), 8.53 (s, 1H, ArH), 8.03 (d, *J* = 8.4 Hz, 1H, ArH), 7.96-7.93 (m, 2H, ArH), 7.87 (s, 1H, ArH), 7.73 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 6.63 (d, *J* = 16.0 Hz, 1H, -**CH**=CHCH_2-), 6.47 (dt, *J* = 16.0 & 6.8 Hz, 1H, -CH=**CH**CH_2-), 2.59-2.51 (m, 2H, -CH=CH**CH_2**-), 2.39-2.29 (m, 1H, -**CH**(CH_3)CO_2H), 1.13 (d, *J* = 6.8 Hz, 3H, -CH(**CH_3**)CO_2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.7, 167.3, 136.8, 135.2, 131.3, 131.1, 130.1, 129.9, 129.5, 128.0, 127.6, 125.5, 124.9, 124.3, 38.7, 36.6, 16.5; HRMS-ESI calcd for $C_{17}H_{16}O_4$ $[M - H]^-$ 283.0976; found 283.0982; Anal. ($C_{17}H_{16}O_4$) C, H.

(*RS*)-Ethyl 6-(4-ethoxycarbonylpent-1-yl)-2-naphthoate (32). Method identical to that described for **13a**. **30** (1.91 g, 5.9 mmol) and 10 wt % palladium on activated carbon (100 mg) afforded **32** as a viscous light yellow oil (1.90 g, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, ArH), 8.03 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 7.87 (d, *J* = 8.4 Hz, 1H, ArH), 7.80 (d, *J* = 8.4 Hz, 1H, ArH), 7.64 (s, 1H, ArH), 7.38 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 4.12 (q, *J* = 7.2 Hz, 2H, -CH(CH_3)CO_2**CH_2**CH_3), 3.97 (s, 3H, -CO_2**CH_3**), 2.80 (t, *J* = 7.2 Hz, 2H, Ar**CH_2**-), 2.47 (sex, *J* = 7.2 Hz, 1H, -**CH_2**CH_2-), 1.81-1.68 (m, 3H, -**CH_2CH_2**-), 1.54-1.46 (m, 1H, -**CH**(CH_3)$CO_2CH_2CH_3$), 1.24 (t, *J* = 7.2 Hz, 3H, -CH(CH_3)CO_2CH_2**CH_3**), 1.15 (d, *J* = 7.2 Hz, 3H, -CH(**CH_3**)$CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 167.3, 142.6, 135.8, 131.0, 130.8, 129.3, 128.1, 127.6, 126.7, 126.3, 125.3, 60.2, 52.2, 39.4, 36.0, 33.4, 28.8, 17.1, 14.3; HRMS-ESI calcd for $C_{20}H_{24}O_4$ $[M + Na]^+$ 351.1567; found 351.1558.

(*RS*)-6-(4-Carboxypent-1-yl)-2-naphthoic acid (33). Method identical to that described for **14b** with the exception that the reaction mixture was stirred at room temperature until TLC indicated complete hydrolysis of the ester. **32** (1.90 g, 5.8 mmol) and NaOH (1.39 g, 34.8 mmol) afforded **33** as a white solid (1.60 g, 95%); mp: 195-199 ^{o}C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.51 (br s, 2H, **CO_2H**), 8.55 (s, 1H, ArH), 8.02 (d, *J* = 8.4 Hz, 1H, ArH), 7.94 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 7.91 (d, *J* = 8.8 Hz, 1H, ArH), 7.76 (s, 1H, ArH), 7.46 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 2.77 (t, *J* = 6.8 Hz, 2H, Ar**CH_2**-), 2.36 (sex, *J* = 6.8 Hz, 1H, -**CH_2**CH_2-), 1.72-1.55 (m, 3H, -**CH_2CH_2**-), 1.44-1.34 (m, 1H, -**CH**(CH_3)CO_2H), 1.04 (d, *J* = 6.8 Hz, 3H, -CH(**CH_3**)CO_2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.3, 167.4, 142.4, 135.1,

130.6, 130.2, 129.2, 128.1, 127.6, 127.2, 125.9, 125.2, 38.5, 35.2, 32.8, 28.3, 16.9; HRMS-ESI calcd for $C_{17}H_{18}O_4$ $[M - H]^-$ 285.1132; found 285.1125; Anal. ($C_{17}H_{18}O_4$) C, H.

6-(Isobutoxycarbonyl)-2-naphthoic acid (35). A stirring mixture of **10** (2.65g, 10.0 mmol), 2-methylpropan-1-ol (20 mL) and concentrated H_2SO_4 (0.5 mL) was heated at 70 ^oC overnight. After cooling to room temperature, the reaction was diluted with diethyl ether (50 mL) and the solution washed with water (2 × 20 mL) and dried over $MgSO_4$. Concentration in vacuo yielded a tacky solid which was re-crystallised from EtOAc to afford the crude bromo (**34**) as an off-white solid (1.24 g, 40%) which was taken forward without further purification or characterisation.

A flask was charged with **34** (920 mg, 3.0 mmol), $Pd(OAc)_2$ (67 mg, 0.3 mmol) and DPPP (161 mg, 0.39 mmol). The flask was then evacuated and backfilled with carbon monoxide three times. A solution of triethylamine (2.09 mL, 15 mmol) and water (5.4 mL, 0.3 mol) in anhydrous DMF (20 mL) was then added and the resultant mixture stirred at 85 ^oC for 24 h. After cooling to room temperature the reaction was diluted with water (25 mL) and EtOAc (50 mL). The organic layer was isolated and washed with aqueous 1 M NaOH (3 × 15 mL). The aqueous extracts were combined and acidified to pH 2 with aqueous 2 M HCl. The solid which precipitated from solution was filtered off, washed copiously with water and then dried over P_2O_5 overnight to afford **35** as a white solid (678 mg, 83%); mp: 210-212 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 8.53 (br s, 2H), 8.01 (dd, J = 8.0 & 1.6 Hz, 1H), 8.00 (dd, J = 8.4 & 1.6 Hz, 1H), 7.96 (d, J = 8.8 Hz, 2H), 4.07 (d, J = 6.4 Hz, 2H, -$\mathbf{CH_2}$CH$(CH_3)_2$), 2.10-2.00 (m, 1H, -CH_2**CH**$(CH_3)_2$), 0.98 (d, J = 6.8 Hz, 6H, -$CH_2CH(\mathbf{CH_3})_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 166.0, 134.5, 134.4, 130.6, 130.5, 130.3, 129.6, 129.6, 129.5, 126.3, 125.8, 71.2, 27.9, 19.3; MS (ESI) 273 (MH^+), 295 (MNa^+); Anal. ($C_{16}H_{16}O_4$) C, H.

1-(6-Bromonaphthalen-2-yl)-4-methylpentan-1-one (36). To a stirring solution of ethyl 4-methylvalerate (6.64 mL, 40.0 mmol) in anhydrous THF (20 mL) at -78 ^oC was added LiHMDS (1.0 M in THF, 40.0 mL, 40.0 mmol). The resultant mixture was stirred at -78 ^oC for 30 min before a solution of **10** (5.30g, 20.0 mmol) in anhydrous THF (100 mL) was added. After complete addition, the reaction was stirred at room temperature for 3 h. The THF was then removed in vacuo and hexane (50 mL) added to the remaining residue. The solid which precipitated from solution was filtered off, re-dissolved in aqueous 1 M NaOH

(40 mL) and stirred at 50 ^{o}C overnight. After cooling to room temperature, the pH was adjusted to 1 using conc aqueous HCl and the mixture heated at 60 ^{o}C for 1 h. After cooling to room temperature, the reaction was extracted with diethyl ether (3 × 30 mL). The organic extracts were combined, washed with water (25 mL), brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was purified by flash chromatography (10% EtOAc in hexane) to afford **36** as a light brown oil (4.57 g, 75%); ^{1}H NMR (400 Mz, $CDCl_3$) δ 8.39 (s, 1H, ArH), 8.03-8.00 (m, 2H, ArH), 7.79 (d, *J* = 8.8 Hz, 1H, ArH), 7.76 (d, *J* = 8.8 Hz, 1H, ArH), 7.58 (dd, *J* = 8.4 & 2.0 Hz, 1H, ArH), 2.36 (t, *J* = 7.6 Hz, 2H, ArCO**CH$_2$**-), 1.54-1.39 (m, 3H, -**CH$_2$CH**(CH_3)$_2$), 0.85 (d, *J* = 6.4 Hz, 6H, -CH_2CH(**CH$_3$**)$_2$); ^{13}C NMR (100 Mz, $CDCl_3$) δ 211.7, 136.3, 134.7, 131.0, 131.0, 130.2, 129.9, 129.3, 127.4, 125.1, 122.6, 40.7, 32.7, 27.7, 22.3.

Methyl 6-(4-methylpentanoyl)-2-naphthoate (37). A flask was charged with $Pd(OAc)_2$ (225 mg, 1.0 mmol) and DPPP (536 mg, 1.3 mmol) before being briefly evacuated and backfilled with carbon monoxide three times. A degassed solution of **36** (3.05g, 10.0 mmol) and triethylamine (3.1 mL, 22.0 mmol) in a mixture of anhydrous MeOH (9 mL) and DMF (27 mL) was added and the resultant mixture heated at 90 ^{o}C for 18 h. After cooling to room temperature, the reaction mixture was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, washed with aqueous 1 M HCl (25 mL), water (25 mL), brine (25 mL) dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was purified via flash chromatography (10% EtOAc in hexane) to afford **37** as a colourless oil (2.07 g, 73%); ^{1}H NMR (400 Mz, $CDCl_3$) δ 8.62 (s, 1H, ArH), 8.48 (s, 1H, ArH), 8.12 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 8.07 (dd, *J* = 1.6 Hz, 1H, ArH), 8.02-7.99 (m, 2H, ArH), 3.99 (s, 3H, -CO_2**CH$_3$**), 3.10 (t, *J* = 7.6 Hz, 2H, ArCO**CH$_2$**-), 1.71-1.67 (m, 3H, -**CH$_2$CH**(CH_3)$_2$), 0.97 (d, *J* = 6.4 Hz, 6H, -CH_2CH(**CH$_3$**)$_2$); ^{13}C NMR (100 Mz, $CDCl_3$) δ 200.4, 166.8, 136.2, 134.7, 134.5, 130.6, 129.8, 129.7, 129.5, 129.0, 126.0, 124.7, 52.4, 36.8, 30.9, 27.9, 22.5; MS (ESI) 285 (MH^+), 307 (MNa^+); HRMS (ESI) for $C_{18}H_{21}O_3$ required 285.1485; found 285.1481.

6-(4-Methylpentanoyl)-2-naphthoic acid (38). Method as that described for **29**. **37** (1.50 g, 5.3 mmol) and LiOH (634 mg, 26.5 mmol) afforded **38** as an off-white solid (1.17 g, 82%); mp: 202-204 ^{o}C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.73 (s, 1H, ArH), 8.63 (s, 1H, ArH), 8.20 (d, *J* = 7.6 Hz, 1H, ArH), 8.19 (d, *J* = 8.4 Hz, 1H, ArH), 8.04 (d, *J* = 7.6 Hz, 1H, ArH), 8.02 (d, *J* = 8.4 Hz, 1H, ArH), 3.16 (t, *J* = 7.6 Hz, 2H, ArCO**CH$_2$**-), 1.66-1.53 (m, 3H, -**CH$_2$CH**(CH_3)$_2$), 0.92 (d, *J* = 6.4 Hz, 6H, -CH_2CH(**CH$_3$**)$_2$); ^{13}C NMR (100 MHz, DMSO-*d*$_6$)

δ 200.7, 167.7, 136.1, 134.7, 134.6, 130.4, 130.4, 130.3, 130.2, 129.7, 126.5, 124.7, 36.6, 33.2, 27.7, 22.9; MS (ESI) 270 (M^-); Anal. ($C_{17}H_{18}O_3$) C, H.

Methyl 6-(4-hydroxypent-1-yn-1-yl)-2-naphthoate (39). A flask was charged with **10** (1.33 g, 5.0 mmol), $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) and CuBr (43 mg, 0.30 mmol). The flask was then briefly evacuated and backfilled with argon three times. A degassed solution of 4-pentyn-2-ol (0.57 mL, 6.0 mmol) in triethylamine (15 mL) was then added and the reaction heated at 65 ^oC overnight. The mixture was then concentrated in vacuo and the residue re-dissolved in diethyl ether (30 mL) and aqueous 1 M HCl (10 mL). The organic layer was isolated, washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was purified via flash chromatography (30% EtOAc in hexane) to afford **39** as colourless oil (1.12 g, 84%); ^1H NMR (400 Mz, $CDCl_3$) δ 8.55 (s, 1H, ArH), 8.06 (dd, *J* = 8.4 & 2.0 Hz, 1H, ArH), 7.95 (s, 1H, ArH), 7.86 (d, *J* = 8.4 Hz, 1H, ArH), 7.80 (d, *J* = 8.4 Hz, 1H, ArH), 7.51 (dd, *J* = 8.4 & 2.0 Hz, 1H, ArH), 4.14-4.06 (m, 1H, -CH_2**CH**$(OH)CH_3$), 3.96 (s, 3H, -CO_2**CH_3**), 2.69 (dd, *J* = 16.8 & 5.6 Hz, 1H, -**CH_2**$CH(OH)CH_3$), 2.61 (dd, *J* = 16.9 & 6.4 Hz, 1H, -**CH_2**$CH(OH)CH_3$), 1.36 (d, *J* = 6.4 Hz, 3H, -$CH_2CH(OH)$**CH_3**); ^{13}C NMR (100Mz, $CDCl_3$) δ 167.0, 135.0, 131.6, 131.0, 130.7, 129.4, 129.3, 127.8, 127.9, 125.9, 123.2, 88.1, 83.0, 66.6, 52.3, 30.1, 22.5.

Methyl 6-(4-oxopent-1-yl)-2-naphthoate (40). A solution of **39** (1.34g, 5.0 mmol) in ethanol (100 mL) was hydrogenated under 3 bar pressure of hydrogen in the presence of 10 wt % palladium on carbon (100 mg) for 18 h. The reaction mixture was then filtered through a celite pad before being concentrated in vacuo to afford the crude alcohol which was taken up in anhydrous DCM (20 mL) and treated with Dess-Martin periodinane (2.12 g, 5 mmol). The resultant mixture was stirred at room temperature for 2 h and then extracted with diethyl ether (30 mL). The organic layer was isolated, washed with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. The resultant residue was purified via flash chromatography (10% EtOAc in hexane) to give **40** as a viscous oil (1.24 g, 92% over two steps); ^1H NMR (400 Mz, $CDCl_3$) δ 8.53 (s, 1H, ArH), 8.00 (d, *J* = 8.4 Hz, 1H, ArH), 7.83 (d, *J* = 8.4 Hz, 1H, ArH), 7.76 (d, *J* = 8.4 Hz, 1H, ArH), 7.59 (s, 1H, ArH), 7.33 (d, *J* = 8.4 Hz, 1H, ArH), 3.93 (s, 3H, -CO_2**CH_3**), 2.75 (t, *J* = 7.6 Hz, 2H, Ar**CH_2**-), 2.43 (t, *J* = 7.6 Hz, 2H, -CH_2**CH_2**$COCH_3$), 2.08 (s, 3H, -CH_2CH_2CO**CH_3**),

1.99-1.92 (m, 2H, -**CH$_2$**CH$_2$COCH$_3$); ^{13}C NMR (100Mz, CDCl$_3$) δ 208.4, 167.2, 142.0, 135.7, 131.0, 130.8, 129.4, 128.0, 127.6, 126.7, 126.4, 125.4, 52.1, 42.6, 35.2, 29.9, 24.8.

(*RS*)-Methyl 6-(6-methoxy-4-methyl-6-oxohex-1-yl)-2-naphthoate (41). To a stirring solution of methyl diethylphosphonoacetate (841 mg, 4.0 mmol) in anhydrous THF (20 mL) at 0 ^{o}C was added dropwise KHMDS (0.5 M in toluene, 8.0 mL, 4.0 mmol). The resultant mixture was stirred at room temperature for 1 h before a solution of **40** (830 mg, 3.1 mmol) dissolved in anhydrous THF (5 mL) was added dropwise. The reaction was then stirred for 4 h at room temperature before being quenched by the addition of aqueous 1 M HCl (10 mL). The reaction was extracted with diethyl ether (2 × 20 mL) and the organic layers combined, washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo to afford the crude alkene which was subsequently dissolved in ethanol (20 mL) and hydrogenated under 3 bar of hydrogen in the presence of 10 wt % palladium on carbon (50 mg) for 18 h. The reaction mixture was then filtered through a celite pad before being concentrated in vacuo to afford **41** as a colourless oil (763 mg, 75%); ^{1}H NMR (400 Mz, CDCl$_3$) δ 8.56 (s, 1H, ArH), 8.03 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 7.85 (d, *J* = 8.4 Hz, 1H, ArH), 7.79 (d, *J* = 8.8 Hz, 1H, ArH), 7.62 (s, 1H, ArH), 7.37 (d, *J* = 8.4 Hz, 1H, ArH), 3.96 (s, 3H, -CO$_2$**CH$_3$**), 3.63 (s, 3H, -CO$_2$**CH$_3$**), 2.79-2.74 (m, 2H, -CH$_2$CH$_2$CH$_2$CH-), 2.29 (dd, *J* = 14.8 & 6.4 Hz, 1H, -CH(CH$_3$)**CH$_2$**CO$_2$CH$_3$), 2.12 (dd, *J* = 14.8 & 7.6 Hz, 1H, -CH(CH$_3$)**CH$_2$**CO$_2$CH$_3$), 2.05-1.96 (m, 1H, -CH$_2$CH$_2$CH$_2$CH-), 1.81-1.63 (m, 2H, -CH$_2$CH$_2$CH$_2$CH-), 1.45-1.36 (m, 1H, -CH$_2$CH$_2$CH$_2$-), 1.31-1.22 (m, 1H, -CH$_2$CH$_2$CH$_2$CH-), 0.94 (d, *J* = 6.8 Hz, 3H, -CH(**CH$_3$**)CH$_2$CO$_2$CH$_3$); ^{13}C NMR (100Mz, CDCl$_3$) δ 173.6, 167.3, 142.9, 135.7, 131.0, 130.8, 129.2, 128.1, 127.6, 126.6, 126.2, 125.3, 52.3, 51.1, 41.5, 36.2, 36.2, 30.2, 28.5, 19.7; HRMS-ESI calcd for $C_{20}H_{24}O_4$ $[M + H]^+$ 329.1675; found 329.1677.

(*RS*)-6-(5-Carboxy-4-methylpent-1-yl)-2-naphthoic acid (42). Method as that described for **29**. **41** (763 mg, 2.3 mmol) and LiOH (275 mg, 11.5 mmol) afforded **42** as a white solid (551 mg, 79%); mp: 146-148 ^{o}C; ^{1}H NMR (400 MHz, DMSO-*d$_6$*) δ 8.51 (s, 1H, ArH), 7.98 (d, *J* = 8.4 Hz, 1H, ArH), 7.93 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 7.87 (d, *J* = 8.8 Hz, 1H, ArH), 7.74 (s, 1H, ArH), 7.46 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 2.73 (t, *J* = 7.2 Hz, 2H, Ar**CH$_2$**-), 2.19 (dd, *J* = 14.8 & 6.0 Hz, 1H, -CH(CH$_3$)**CH$_2$**CO$_2$H), 1.99 (dd, *J* = 14.8 & 7.6 Hz, 1H, -CH(CH$_3$)**CH$_2$**CO$_2$H), 1.90-1.82 (m, 1H, -CH$_2$CH$_2$CH-), 1.71-1.58 (m, 2H, -CH$_2$CH$_2$CH-), 1.39-1.29 (m, 1H, -CH$_2$CH$_2$CH-), 1.24-1.15 (m, 1H, -CH$_2$CH$_2$CH-), 0.87 (d, *J* = 6.8 Hz, 3H, -CH(**CH$_3$**)CH$_2$CO$_2$H); ^{13}C NMR (100 MHz, DMSO-*d$_6$*) δ 174.4, 168.1, 142.9, 135.5, 131.1,

130.53, 129.6, 128.6, 128.5, 127.9, 126.4, 125.8, 41.8, 36.2, 36.0, 30.0, 28.6, 20.0; MS (ESI) 300 (M^+), 256; Anal. ($C_{18}H_{20}O_4$) C, H.

Methyl 6-(5-methylhex-1-en-2-yl)-2-naphthoate (43). KHMDS (0.5 M in toluene, 4.4 mL, 2.2 mmol) was added dropwise to a stirring -78 ^oC solution of methyl triphenylphosphonium bromide (643 mg, 1.8 mmol) in anhydrous THF (15 mL). The resultant mixture was stirred at room temperature for 1 h before a solution of **37** (427 mg, 1.5 mmol) dissolved in anhydrous THF (5 mL) was added dropwise. After complete addition, the reaction mixture was stirred for 2 h at room temperature before being quenched with aqueous 1 M HCl (2 mL). The reaction mixture was extracted with diethyl ether (3 × 20 mL) and the organic extracts combined, washed with water (25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated in vacuo. The resultant residue was purified via flash chromatography (10% EtOAc in hexane) to afford **43** as a colourless oil (380 mg, 90%); ^1H NMR (400 Mz, $CDCl_3$) δ 8.58 (s, 1H, ArH), 8.06 (d, *J* = 8.8 Hz, 1H, ArH), 7.90 (d, *J* = 8.4 Hz, 1H, ArH), 7.87 (d, *J* = 8.8 Hz, 1H, ArH), 7.86 (s, 1H, ArH), 7.64 (d, *J* = 8.4 Hz, 1H, ArH), 5.44 (s, 1H, =$\mathbf{CH_2}$), 5.22 (s, 1H, =$\mathbf{CH_2}$), 3.98 (s, 3H, -$CO_2\mathbf{CH_3}$), 2.62 (t, *J* = 8.0 Hz, 2H, -$\mathbf{CH_2}CH_2CH(CH_3)_2$), 1.67-1.59 (m, 1H, -$CH_2CH_2\mathbf{CH}(CH_3)_2$), 1.43-1.37 (m, 2H, -$CH_2\mathbf{CH_2}CH(CH_3)_2$), 0.93 (d, *J* = 6.8 Hz, 6H, -$CH_2CH_2CH(\mathbf{CH_3})_2$); ^{13}C NMR (100 Mz, $CDCl_3$) δ 167.3, 148.5, 141.2, 135.6, 131.8, 130.6, 129.2, 128.3, 125.5, 125.5, 125.3, 124.4, 113.5, 52.2, 37.6, 33.1, 27.8, 22.5; HRMS-ESI calcd for $C_{19}H_{22}O_2$ $[M + H]^+$ required 283.1693; found 283.1683.

6-(5-Methylhex-1-en-2-yl)-2-naphthoic acid (44). Method as that described for **29**. **43** (185 mg, 0.66 mmol) and LiOH (79 mg, 3.30 mmol) afforded **44** as a white solid (147 mg, 83%); mp: 178-180 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H, ArH), 8.05 (d, *J* = 8.8 Hz, 1H, ArH), 8.01-7.99 (m, 2H, ArH), 7.95 (d, *J* = 8.8 Hz, 1H, ArH), 7.70 (d, *J* = 8.4 Hz, 1H, ArH), 5.49 (s, 1H, =$\mathbf{CH_2}$), 5.22 (s, 1H, =$\mathbf{CH_2}$), 2.60 (t, *J* = 8.0 Hz, 2H, -$\mathbf{CH_2}CH_2CH(CH_3)_2$), 1.62-1.52 (m, 1H, -$CH_2CH_2\mathbf{CH}(CH_3)_2$), 1.33-1.28 (m, 2H, -$CH_2\mathbf{CH_2}CH(CH_3)_2$), 0.86 (d, *J* = 6.8 Hz, 6H, -$CH_2CH_2CH(\mathbf{CH_3})_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.9, 148.2, 140.6, 135.5, 131.9, 130.5, 129.7, 128.9, 128.5, 125.9, 125.7, 124.6, 114.2, 37.6, 27.6, 22.8; MS (ESI) 268 (M^-), 228; Anal. ($C_{18}H_{20}O_2$) C, H.

(*RS*)-Methyl 6-(5-methylhexan-2-yl)-2-naphthoate (45). A solution of **43** (175 mg, 0.62 mmol) in ethanol (50 mL) was hydrogenated under 3 bar of hydrogen in the presence of 10 wt % palladium on activated carbon (50 mg) for 18 h. The reaction mixture was then filtered

through a celite pad before being concentrated in vacuo to afford **45** as a colourless oil (170 mg, 96%); ^{1}H NMR (400 Mz, $CDCl_3$) δ 8.59 (s, 1H, ArH), 8.05 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 7.89 (d, *J* = 8.4 Hz, 1H, ArH), 7.84 (d, *J* = 8.4 Hz, 1H, ArH), 7.64 (s, 1H, ArH), 7.42 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 3.98 (s, 3H, -CO_2**CH_3**), 2.88-2.79 (m, 1H, -$CHCH_2CH_2CH$-), 1.75-1.60 (m, 2H, -$CHCH_2CH_2CH$-), 1.57-1.47 (m, 1H, -$CHCH_2CH_2CH$-), 1.33 (d, *J* = 6.8 Hz, 3H, ArCH(**CH_3**)-), 1.24-1.15 (m, 1H, -$CHCH_2CH_2CH$-), 1.10-1.01 (m, 1H, -$CHCH_2CH_2CH$-), 0.85 (d, *J* = 6.8 Hz, 6H, -CH(**CH_3**)$_2$); ^{13}C NMR (100Mz, $CDCl_3$) δ 167.4, 148.3, 135.8, 131.2, 130.8, 129.3, 127.2, 126.7, 126.6, 125.2, 125.0, 52.1, 40.5, 37.0, 35.9, 28.1, 22.6, 22.5, 22.2; HRMS-ESI calcd for $C_{19}H_{24}O_2$ $[M + H]^+$ 285.1776; found 285.1768.

(*RS*)-6-(5-Methylhexan-2-yl)-2-naphthoic acid (46). Method as that described for **29**. **45** (170 mg, 0.60 mmol) and LiOH (72 mg, 3.0 mmol) afforded **46** as a white solid (143 mg, 88%); mp: 151-153 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H, ArH), 8.01 (d, *J* = 8.4 Hz, 1H, ArH), 7.94-7.90 (m, 2H, ArH), 7.74 (s, 1H, ArH), 7.48 (d, *J* = 8.4 Hz, 1H, ArH), 2.85-2.79 (m, 1H, -$CHCH_2CH_2CH$-), 1.65-1.57 (m, 2H, -$CHCH_2CH_2CH$-), 1.49-1.42 (m, 1H, -$CHCH_2CH_2CH$-), 1.26 (d, *J* = 6.8 Hz, 3H, ArCH(**CH_3**)-), 1.16-1.07 (m, 1H, -$CHCH_2CH_2CH$-), 0.99-0.90 (m, 1H, -$CHCH_2CH_2CH$-), 0.78 (d, *J* = 6.4 Hz, 6H, -CH(**CH_3**)$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.0, 148.2, 135.6, 131.3, 130.9, 129.8, 128.2, 127.7, 127.0, 125.6, 125.2, 37.0, 35.7, 28.0, 23.0, 22.9, 22.6; MS (ESI) 270 (M^-); Anal. ($C_{18}H_{22}O_2$) C, H.

Methyl 6-((Isobutylthio)methyl)-2-naphthoate (48). To a solution of sodium (58 mg, 2.5 mmol) dissolved in anhydrous ethanol (20 mL) was added isobutyl mercaptan (0.76 mL, 7.0 mmol). The resultant mixture was stirred for 10 mins at room temperature before **47** (650 mg, 2.3 mmol) was added. After complete addition the reaction was stirred at room temperature for 30 mins before being diluted with diethyl ether (100 mL). The organic solution was washed with aqueous 1 M HCl (10 mL), water (20 mL), brine (10 mL) and dried over $MgSO_4$. Concentration in vacuo afforded a viscous oil which was purified by flash chromatography (5% EtOAc in hexane) to give the **48** as a colourless oil (623 mg, 94%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H, ArH), 8.05 (dd, *J* = 8.4 & 1.5 Hz, 1H, ArH), 7.90 (d, *J* = 8.4 Hz, 1H, ArH), 7.81 (d, *J* = 8.4 Hz, 1H, ArH), 7.71 (s, 1H, ArH), 7.54 (d, *J* = 8.4 & 1.8 Hz, 1H, ArH), 3.97 (s, 3H, -CO_2**CH_3**), 3.84 (s, 2H, Ar**CH_2**-), 2.30 (d, *J* = 4.8 Hz, 2H, -**CH_2**$CH(CH_3)_2$), 1.85-1.71 (m, 1H, -CH_2**CH**$(CH_3)_2$), 0.94 (d, *J* = 6.6 Hz, 6H, -

$CH_2CH(\mathbf{CH_3})_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 139.0, 135.5, 131.6, 130.9, 129.8, 128.1, 127.9, 127.3, 127.1, 125.7, 52.3, 40.6, 37.1, 28.3, 22.1.

6-((Isobutylthio)methyl)-2-naphthoic acid (49). Method identical to that described for **29**. **48** (550 mg, 1.9 mmol) and LiOH (227 mg, 9.5 mmol) afforded **49** as an off-white solid (454 mg, 87%); mp: 170-172 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H, ArH), 8.04 (d, *J* = 8.4 Hz, 1H, ArH), 7.97-7.90 (m, 2H, ArH), 7.83 (s, 1H, ArH), 7.55 (d, *J* = 8.4 Hz, 1H, ArH), 3.87 (s, 2H, Ar$\mathbf{CH_2}$-), 2.27 (d, *J* = 6.8 Hz, 2H, -$\mathbf{CH_2}CH(CH_3)_2$), 1.75-1.65 (m, 1H, -$CH_2\mathbf{CH}(CH_3)_2$), 0.86 (d, *J* = 6.8 Hz, 6H, -$CH_2CH(\mathbf{CH_3})_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 139.6, 135.2, 131.5, 130.7, 129.9, 128.6, 128.3, 128.3, 127.2, 125.9, 40.2, 36.3, 28.1, 22.2; MS (ESI) 274 (M^-), 230; Anal. ($C_{16}H_{18}O_2S$) C, H, S.

Methyl 6-(isobutylcarbamoyl)-2-naphthoate (51). 50 (500 mg, 2.0 mmol) was added to a stirring mixture of isobutylamine (0.22 mL, 2.2 mmol) and triethylamine (0.84 mL, 6.0 mmol) in anhydrous DCM (20 mL) at 0 ^oC. After complete addition the reaction mixture was stirred at room temperature overnight. The reaction was then concentrated in vacuo and the resultant residue was taken up in EtOAc (20 mL) and washed sequentially with water (10 mL), aqueous 1 M HCl (5 mL), water (10 mL), aqueous 1 M NaOH (5 mL), water (10 mL), brine (10 mL) and dried over $MgSO_4$. Concentration in vacuo afforded a tacky residue which was purified by flash chromatography (10% EtOAc in hexane) to afford **51** as a clear oil (540 mg, 94%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H, ArH), 8.28 (s, 1H, ArH), 8.08 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 7.98 (d, *J* = 8.8 Hz, 1H, ArH), 7.93 (d, *J* = 8.8 Hz, 1H, ArH), 1H, 7.86 (dd, *J* = 8.8 & 2.0 Hz, 1H, ArH), 3.98 (s, 3H, -$CO_2\mathbf{CH_3}$), 3.34 (t, *J* = 6.0 Hz, 2H, -$\mathbf{CH_2}CH(CH_3)_2$), 1.99-1.89 (m, 1H, -$CH_2\mathbf{CH}(CH_3)_2$), 1.00 (d, *J* = 6.8 Hz, 6H, -$CH_2CH(\mathbf{CH_3})_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 166.9, 134.8, 134.4, 133.7, 130.7, 129.9, 129.1, 128.9, 126.8, 126.1, 124.4, 52.4, 47.5, 28.7, 20.2; HRMS-EI calcd for $C_{17}H_{19}NO_3$ $[M]^+$ 285.1367; found: 285.1365.

6-(Isobutylcarbamoyl)-2-naphthoic acid (52). Method identical to that described for **29**. **51** (540 mg, 1.9 mmol) and LiOH (227 mg, 9.5 mmol) afforded **52** as an off-white solid (439 mg, 85%); mp: >250 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H, ArH), 8.46 (s, 1H, ArH), 8.14 (d, *J* = 8.4 Hz, 1H, ArH), 8.09 (d, *J* = 8.8 Hz, 1H, ArH), 7.98 (dd, *J* = 8.8 & 2.0 Hz, 1H, ArH), 7.97 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 3.11 (t, *J* = 6.8 Hz, 2H, -$\mathbf{CH_2}CH(CH_3)_2$), 1.90-1.80 (m, 1H, -$CH_2\mathbf{CH}(CH_3)_2$), 0.88 (d, *J* = 6.8 Hz, 6H, -

$CH_2CH(\mathbf{CH_3})_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 166.5, 134.7, 134.6, 133.6, 130.6, 129.8, 129.8, 129.6, 127.5, 126.2, 125.47, 47.3, 28.6, 20.7; MS (ESI) 270 (M^-), 226; Anal. ($C_{16}H_{17}NO_3$) C, H, N.

6-((Isobutyryloxy)methyl)-2-naphthoic acid (54). To a stirring solution of **53** (405 mg, 2.0 mmol) and triethylamine (0.70 mL, 5.0 mmol) in anhydrous DCM (10 mL) at 0 ^oC was added isobutyryl chloride (0.52 mL, 5.0 mmol) dissolved in 3 mL of anhydrous DCM. After complete addition the reaction mixture was stirred at room temperature for 1 h. The DCM was then removed in vacuo and aqueous 2 M $NaHCO_3$ (40 mL) added to the resultant residue. The mixture was stirred vigorously at 0 ^oC for 3 h and then extracted with diethyl ether (15 mL). The aqueous phase was isolated and then acidified with aqueous 1 M HCl. The solid which precipitated from solution was filtered off, washed copiously with water and then dried over P_2O_5 overnight to afford **54** as a white solid 457 mg, 84%); mp: 152-154 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H, ArH), 8.05 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 7.88 (d, *J* = 8.8 Hz, 1H, ArH), 7.80 (d, *J* = 8.8 Hz, 1H, ArH), 7.78 (s, 1H, ArH), 7.45 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 5.23 (s, 2H, Ar$\mathbf{CH_2}$-), 2.13-2.06 (m, 1H -$\mathbf{CH}(CH_3)_2$), 0.91 (d, *J* = 6.4 Hz, 6H, -CH($\mathbf{CH_3}$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 171.1, 136.5, 135.6, 132.0, 131.6, 129.8, 128.2, 127.0, 126.7, 126.4, 125.8, 65.7, 25.7, 20.8; MS (ESI): 273 (MH^+), 295 (MNa^+); Anal. ($C_{16}H_{16}O_4$) C, H.

2-Bromo-6-(isobutoxymethyl)naphthalene (56). To a stirring suspension of 60% NaH (1.2 g, 30.0 mmol) in anhydrous DMF (150 mL) was added 2-methylpropan-1-ol (5.5 mL, 60.0 mmol). The mixture was stirred at room temperature for 4 h before **55** (3.0 g, 10.0 mmol) was added. After complete addition, the reaction was stirred at room temperature for 3 h before being quenched with water (50 mL) and extracted with hexane (100 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo. The resultant residue was purified by flash chromatography (2% EtOAc in hexane) to afford **56** as a colourless oil (2.7 g, 92%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 2.0 Hz, 1H, ArH), 7.75 (s, 1H, ArH), 7.73 (d, *J* = 8.8 Hz, 1H, ArH), 7.69 (d, *J* = 8.8 Hz, 1H, ArH), 7.54 (dd, *J* = 8.8 & 2.0 Hz, 1H, ArH), 7.49 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 4.65 (s, 2H, Ar$\mathbf{CH_2}$-), 3.29 (d, *J* = 7.8 Hz, 2H, -$\mathbf{CH_2}CH(CH_3)_2$), 2.00-1.90 (m, 1H, -$CH_2\mathbf{CH}(CH_3)_2$), 0.97 (d, *J* = 6.4 Hz, 6H, -$CH_2CH(\mathbf{CH_3})_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 133.9, 131.7, 129.7, 129.5, 129.4, 127.1, 126.7, 126.0, 119.6, 72.8, 28.56, 22.7, 19.4.

6-(Isobutoxymethyl)-2-naphthoic acid (57). A flask was charged with **56** (1.8 g, 6.14 mmol), $Pd(OAc)_2$ (138 mg, 0.61 mmol) and DPPP (327 mg, 0.79 mmol). The flask was then briefly evacuated and backfilled with carbon monoxide three times. A solution of triethylamine (4.28 mL, 30.7 mmol) and water (11.0 mL, 0.61 mmol) in anhydrous DMF (30 mL) was added and the resultant mixture heated at 80 ^oC for 24 h. After cooling to room temperature the reaction was diluted with water (30 mL) and EtOAc (100 mL). The organic layer was isolated and washed with aqueous 1 M NaOH (3 × 20 mL). The aqueous extracts were combined and acidified to pH 2 with aqueous 2 M HCl. The solid which precipitated from solution was filtered off, washed copiously with water and then dried over P_2O_5 overnight to afford **57** as an off-white solid (1.14 g, 72%); mp: 160-162 ^oC; ^1H NMR (300 MHz, DMSO-d_6) δ 8.55 (s, 1H, ArH), 8.05 (d, J = 8.4 Hz, 1H, ArH), 7.97-7.91 (m, 2H, ArH), 7.87 (s, 1H, ArH), 7.51 (dd, J = 8.4 & 1.5 Hz, 1H, ArH), 4.61 (s, 2H, Ar**CH$_2$**-), 3.21 (d, J = 6.6 Hz, 2H, -**CH$_2$**CH$(CH_3)_2$), 1.91-1.76 (m, 1H, -CH_2**CH**$(CH_3)_2$), 0.85 (d, J = 6.9 Hz, 6H, -$CH_2CH($**CH$_3$**$)_2$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.8, 139.6, 135.3, 132.0, 130.7, 129.8, 128.5, 128.4, 126.8, 125.9, 125.8, 77.0, 72.3, 28.5, 19.8; MS (ESI): 259 (HM^+); Anal. ($C_{16}H_{18}O_3$) C, H.

(*RS*)-Methyl 6-(2-(ethoxycarbonyl)-4-methylpent-1-yl)-2-naphthoate (59). KHMDS (0.5 M in toluene, 12.0 mL, 6.0 mmol) was added dropwise to a stirred -78 ^oC solution of ethyl 4-methylvalerate (1.00 mL, 6.0 mmol) in anhydrous THF (10 mL). The mixture was stirred at -78 ^oC for 30 min before **55** (900 mg, 3.0 mmol) in THF (10 mL) was added. After complete addition, the mixture was allowed to warm to room temperature and stirred overnight. The reaction was then quenched with water (20 mL) and extracted with diethyl ether (2 × 30 mL). The organic extracts were combined, washed with aqueous 2 M HCl (10 mL), water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was dissolved in ethyl acetate and passed through a short silica plug (10 cm). After concentration in vacuo the crude bromide (**58**) was dissolved in a mixture of anhydrous methanol (3 mL) and DMF (9 mL). Triethylamine (0.92 mL, 6.6 mmol) was added and the solution subsequently de-gassed. A flask containing $Pd(OAc)_2$ (67 mg, 0.3 mmol) and DPPP (136 mg, 0.33 mmol) was briefly evacuated and backfilled with carbon monoxide three times. The de-gassed bromide solution was then added and the resultant mixture heated at 80 ^oC for 24 h. The reaction was then quenched with water (20 mL) and extracted with ethyl acetate (30 mL). The organic phase was washed with aqueous 2 M HCl (10 mL), water (10 mL), brine

(10 mL), dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was purified by flash chromatography (10% EtOAc in hexane) to afford **59** as a colourless oil (690 mg, 67% over two steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H, ArH), 8.03 (d, *J* = 8.6 Hz, 1H, ArH), 7.86 (d, *J* = 8.6 Hz, 1H, ArH), 7.80 (d, *J* = 8.6 Hz, 1H, ArH), 7.64 (s, 1H, ArH), 7.37 (d, *J* = 8.6 Hz, 1H, ArH), 4.01-3.98 (m, 2H, -CH(CO_2**CH_2**CH_3)), 3.97 (s, 3H, -CO_2**CH_3**), 3.07 (dd, *J* = 13.5 & 8.8 Hz, 1H, Ar**CH_2**-), 2.98-2.80 (m, 2H, Ar**CH_2CH**-), 1.74-1.67 (m, 1H, -**CH_2**CH(CH_3)$_2$), 1.65-1.55 (m, 1H, -**CH_2**CH(CH_3)$_2$), 1.36-1.30 (m, 1H, -CH_2**CH**(CH_3)$_2$), 1.05 (t, *J* = 7.1 Hz, 3H, -CH(CO_2CH_2**CH_3**)), 0.91-0.89 (m, 6H, -CH(**CH_3**)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 167.3, 139.8, 135.6, 131.2, 130.8, 129.3, 128.2, 127.7, 127.1, 126.9, 125.3, 60.1, 52.2, 45.6, 41.6, 39.3, 26.1, 23.0, 22.0, 14.1; HRMS-ESI calcd for $C_{21}H_{26}O_4$ [M + H]$^+$ 243.1831; found 243.1832.

(*RS*)-6-(2-Carboxy-4-methylpent-1-yl)-2-naphthoic acid (60). Method identical to that described for **29**. **59** (650 mg, 1.90 mmol) and LiOH (227 mg, 9.50 mmol) afforded **60** as an off-white solid (405 mg, 71%); mp: 197-199 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H, ArH), 8.00 (d, *J* = 8.4 Hz, 1H, ArH), 7.93 (d, *J* = 8.4 Hz, 1H, ArH), 7.90 (d, *J* = 8.4 Hz, 1H, ArH), 7.75 (s, 1H, ArH), 7.45 (d, *J* = 8.4 Hz, 1H, ArH), 2.95 (dd, *J* = 13.6 & 9.2 Hz, 1H, Ar**CH_2**-), 2.87 (dd, *J* = 13.6 & 5.6 Hz, 1H, Ar**CH_2**-), 2.76-2.68 (m, 1H, -CHCH_2CH-), 1.58-1.53 (m, 2H, -CHCH_2CH-), 1.28-1.21 (m, 1H, -CHCH_2CH-), 0.84 (d, *J* = 6.4 Hz, 6H, -CH(**CH_3**)$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.8, 167.9, 140.4, 135.4, 131.3, 130.7, 129.6, 128.8, 128.1, 128.0, 127.3, 125.7, 45.5, 41.7, 39.1, 26.2, 23.5, 22.3; MS (ESI) 300 (M$^-$); Anal. ($C_{18}H_{20}O_4$) C, H.

Methyl 7-bromo-3-hydroxy-2-naphthoate (62). 61 (500 mg, 1.87 mmol) was added to a suspension of K_2CO_3 (129 mg, 0.94 mmol) in anhydrous DMF (18 mL). The reaction was stirred for 1 h, and then methyl iodide (174 μL, 2.81 mmol) was added. The reaction was stirred for 12 h at room temperature, and then concentrated under reduced pressure. The solid was taken up in a 1:1 mixture of ethyl acetate and water (50 ml each). The aqueous layer was removed and the organic layer was washed with water (2 × 10 mL) and then brine (10 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure, and the product obtained by flash chromatography (0 → 25% EtOAc in hexane) to give **62** as white crystals (525 mg, 99%); mp: 153-155 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.46 (s, 1H, -**OH**), 8.39 (d, *J* = 0.7 Hz, 1H, ArH), 7.95 (dd, *J* = 1.4 & 0.7 Hz, 1H, ArH), 7.57-7.54 (m, 2H, ArH), 7.29 (s, 1H, ArH), 4.03 (s, 3H, -CO_2**CH_3**); ^{13}C (125 MHz, $CDCl_3$) δ 170.0, 156.7, 136.2, 132.3,

131.3, 130.9, 128.0, 127.9, 117.4, 115.0, 111.9, 52.7; HRMS-CI calcd for $C_{12}H_{10}O_3Br$ $[M + H]^+$ 279.9727; found 279.9735.

Methyl 3-acetoxy-7-bromo-2-naphthoate (63). To a solution of **62** (184 mg, 0.65 mmol) in $CHCl_3$ (6.5 mL), was added acetic anhydride (100 μL, 0.98 mmol), followed by pyridine (80 μL, 0.98 mmol), and then a catalytic amount of DMAP. The reaction was stirred for 12 h, and then diluted with DCM (50 mL). The organic layer was washed with water (2 × 10 mL), and then brine (10 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure, to give **63** as an amber oil (168 mg, 80%) which was used without further purification; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H, ArH), 8.08 (d, *J* = 1.4 Hz, 1H, ArH), 7.68 (d, *J* = 8.8 Hz, 1H, ArH), 7.65 (dd, *J* = 8.8 & 1.4 Hz, 1H, ArH), 7.50 (s, 1H, ArH), 3.93 (s, 3H, -CO_2**CH_3**), 2.40 (s, 3H, -**OAc**); ^{13}C (125 MHz, $CDCl_3$) δ 170.1, 164.6, 147.0, 133.1, 132.6, 132.2, 131.6, 130.9, 128.8, 122.9, 121.2, 120.5, 52.4, 21.0; HRMS-CI calcd for $C_{14}H_{11}O_4Br$ $[M + H]^+$ 321.9841; found 321.9838.

Methyl 3-acetoxy-7-(4-methylpent-1-yl)-2-naphthoate (64). A flask was charged with **63** (7.95g, 24.6 mmol), palladium acetate (55 mg, 1 mol%), and tri-*o*-tolylphosphine (30 mg, 4 mol%). The flask was then briefly evacuated and backfilled with argon three times. A degassed mixture of 4-methylpent-1-ene (4.67 mL, 36.9 mmol) and triethylamine (8.57 mL, 61.5 mmol) in anhydrous DMF (80 mL) was added and the resultant mixture heated at 100 ^{o}C overnight. After cooling to room temperature the mixture was diluted with diethyl ether (200 mL). The organic layer was isolated, washed with water (100 mL), aqueous 2M HCl (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo to afford the crude alkene which was taken forward to the next step without further characterisation or purification.

A solution of the crude alkene in ethanol (40 mL) was hydrogenated under 3 bar of hydrogen in the presence of 10 wt % palladium on activated carbon (100 mg) for 18 h. The reaction mixture was then filtered through a celite pad before being concentrated in vacuo. The resultant residue was purified by flash chromatography (10% ethyl acetate in hexane) to afford **64** as a colourless oil (7.0 g, 87% over two steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H, ArH), 7.72 (d, *J* = 8.4 Hz, 1H, ArH), 7.68 (s, 1H, ArH), 7.48 (s, 1H, ArH), 7.43 (d, *J* = 8.4 Hz, 1H, ArH), 3.92 (s, 3H, -CO_2**CH_3**), 2.74 (t, *J* = 6.6 Hz, 2H, Ar**CH_2**-), 2.39 (s, 3H, -**OAc**), 1.72-1.64 (m, 2H, -CH_2CH_2CH-), 1.60-1.54 (m, 1H, -CH_2CH_2CH-), 1.29-1.20 (m, 2H, -CH_2CH_2CH-), 0.87 (d, *J* = 6.8 Hz, 6H, -CH(**CH_3**)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5,

165.2, 146.3, 141.4, 134.2, 133.4, 131.0, 130.7, 127.5, 127.2, 121.6, 120.9, 52.3, 38.6, 36.3, 29.1, 28.0, 22.7, 21.2; HRMS-ESI calcd for $C_{20}H_{24}O_4$ $[M + Na]^+$ 351.1572; found 351.1567.

3-Hydroxy-7-(4-methylpent-1-yl)-2-naphthoic acid (65). Method identical to that described for **29**. **64** (3.50 g, 10.7 mmol) and LiOH (1.28 g, 53.5 mmol) afforded **65** as a yellow solid (2.62 g, 90%); mp: 150-152 ^oC; ^1H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H, ArH), 7.68 (br s, 1H, ArH), 7.65 (d, J = 8.4 Hz, 1H, ArH), 7.36 (dd, J = 8.4 & 1.5 Hz, 1H, ArH), 7.23 (s, 1H, ArH), 2.61 (t, J = 7.5 Hz, 2H, Ar**CH$_2$**-), 1.63-1.44 (m, 3H, -CH_2CH_2CH-), 1.18-1.11 (m, 2H, -CH_2CH_2CH-), 0.80 (d, J = 0.6 Hz, 6H, -CH(**CH$_3$**)$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.9, 135.2, 131.8, 131.0, 130.8, 130.1, 129.7, 129.2, 128.4, 126.4, 123.5, 92.0, 82.1, 28.3, 28.1, 22.4; HRMS-ESI calcd for $C_{17}H_{20}O_3$ $[M-H]^-$ 271.1340; found 271.1335. Anal. ($C_{17}H_{20}O_3$) C, H.

Methyl 3-hydroxy-7-(4-methylpent-1-yl)-2-naphthoate (66). To a stirring solution of **64** (3.28g, 10.0 mmol) in methanol (50 mL) at 0 ^oC was added dimethylamine (2.0 M in methanol, 10.0 mL, 20.0 mmol). After 1 h the reaction mixture was diluted with diethyl ether (100 mL) and aqueous 1 M HCl (30 mL). The organic phase was separated and washed with water (25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated in vacuo to afford **66** (1.45 g, 51%) as a tacky solid which was utilised without further purification; ^1H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H, -**OH**), 8.43 (s, 1H, ArH), 7.61 (d, J = 8.8 Hz, 1H, ArH), 7.56 (s, 1H, ArH), 7.27 (d, J = 8.8 Hz, 1H, ArH), 7.26 (s, 1H, ArH), 4.02 (s, 3H, -CO_2**CH$_3$**), 2.70 (t, J = 7.6 Hz, 2H, Ar**CH$_2$**-), 1.72-1.64 (m, 2H, -CH_2CH_2CH-), 1.62-1.54 (m, 1H, -CH_2CH_2CH-), 1.28-1.23 (m, 2H, -CH_2CH_2CH-), 0.89 (d, J = 7.6 Hz, 6H, -CH(**CH$_3$**)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 155.8, 138.4, 136.4, 131.8, 131.0, 127.3, 127.2, 126.2, 114.0, 111.4, 52.5, 38.6, 36.0, 29.0, 27.9, 22.6.

Methyl 7-(4-methylpent-1-yl)-3-(((trifluoromethyl)sulfonyl)oxy)-2-naphthoate (67). To a stirring solution of **66** (1.45 g, 5.1 mmol) and triethylamine (1.42 mL, 10.2 mmol) in anhydrous DCM (10 mL) at -5 ^oC was added Tf_2O (1.1 mL, 6.5 mmol). The resultant mixture was stirred at -5 ^oC for 1.5 h and then quenched by the addition of aqueous 2 M HCl (5 mL). The organic phase was separated, dried over Na_2SO_4 and concentrated in vacuo. The resultant residue was dissolved in ethyl acetate and passed through a short silica plug (10 cm) to give **67** (1.92g, 90%) which was utilised without further purification or characterisation.

Methyl 7-(4-methylpent-1-yl)-2-naphthoate (68). A flask was charged with **67** (418 mg, 1.0 mmol) and $Pd(PPh_3)_4$ (12 mg, 1 mol%) before being evacuated and backfilled with argon three times. A degassed mixture of formic acid (0.11 mL, 3.0 mmol) and triethylamine (0.42 mL, 3.0 mmol) in anhydrous DMF (10 mL) was then added and the resultant mixture heated at 80 ^oC overnight. After cooling to room temperature, the reaction was diluted with water (40 mL) and extracted with diethyl ether (3 × 20 mL). The organic extracts were combined, washed with aqueous 1 M HCl (20 mL), water (20 mL), brine (25 mL), and dried over Na_2SO_4. Concentration in vacuo yielded a viscous oil which was purified by flash chromatography (5% ethyl acetate in hexane) to afford **68** as a colourless oil (232 mg, 86%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H, ArH), 7.99 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 7.83 (d, *J* = 8.8 Hz, 1H, ArH), 7.79 (d, *J* = 8.4 Hz, 1H, ArH), 7.71 (s, 1H, ArH), 7.44 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 3.97 (s, 3H, -CO_2**CH_3**), 2.76 (t, *J* = 7.6 Hz, 2H, Ar**CH_2**-), 1.75-1.66 (m, 2H, -CH_2CH_2CH-), 1.64-1.54 (m, 1H, -CH_2CH_2CH-), 1.29-1.23 (m, 2H, -CH_2CH_2CH-), 0.88 (d, *J* = 6.8 Hz, 6H, -CH(**CH_3**)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 141.4, 134.0, 132.7, 130.6, 129.9, 127.8, 127.7, 127.6, 127.3, 124.39, 52.2, 38.6, 36.2, 29.1, 27.9, 22.6; HRMS-ESI calcd for $C_{18}H_{22}O_2$ [M^+] 270.1620; found 270.1618.

7-(4-Methylpent-1-yl)-2-naphthoic acid (69). Method identical to that described for **29**. **68** (232 mg, 0.86 mmol) and LiOH (103 mg g, 4.3 mmol) afforded **69** as a white solid (203 mg, 92%); mp: 140-142 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H, ArH), 7.94-7.85 (m, 4H, ArH), 7.50 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 2.72 (t, *J* = 8.0 Hz, 2H, Ar**CH_2**-), 1.64-1.61 (m, 2H, -CH_2CH_2CH-), 1.58-1.50 (m, 1H, -CH_2CH_2CH-), 1.22-1.17 (m, 2H, -CH_2CH_2CH-), 0.83 (d, *J* = 6.4 Hz, 6H, -CH(**CH_3**)$_2$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.9, 141.5, 133.9, 132.8, 130.4, 130.1, 128.7, 128.2, 128.0, 127.8, 124.8, 38.4, 35.9, 29.0, 27.8, 22.9; MS (ESI): 257 (MH^+), 279 (MNa^+); Anal. ($C_{17}H_{20}O_2$) C, H.

2-(Methoxymethoxy)-7-(4-methylpent-1-yn-1-yl)naphthalene (71). A flask was charged with CuI (248 mg, 1.3 mmol) and $Pd(PPh_3)_2Cl_2$ (913 mg, 1.3 mmol) before being briefly evacuated and backfilled with argon three times. A degassed solution of **70** (10.4 g, 30.9 mmol), 4-methylpent-1-yne (4.36 mL, 37.1 mmol) and diethylamine (6.39 mL, 61.8 mmol) in anhydrous THF (100 mL) was added and the resultant mixture heated at 45 ^oC for 18 h. The reaction was then extracted with diethyl ether (3 × 75 mL) and the organic layer isolated and washed with saturated aqueous NH_4Cl (40 mL), water (50 mL) and brine (50 mL). After drying over Na_2SO_4, concentration in vacuo yielded a viscous oil which was purified by flash

chromatography (5% EtOAc in hexane) to afford **71** as a colourless oil (7.97 g, 96%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H, ArH), 7.70 (d, *J* = 9.3 Hz, 1H, ArH), 7.66 (d, *J* = 8.7 Hz, 1H, ArH), 7.34 (dd, *J* = 9.3 & 1.2 Hz, 1H, ArH), 7.32 (s, 1H, ArH), 7.18 (dd, *J* = 8.7 & 2.4 Hz, 1H, ArH), 5.28 (s, 2H, ArO**CH$_2$**OCH$_3$), 3.51 (s, 3H, ArOCH$_2$O**CH$_3$**), 2.34 (d, *J* = 8.8 Hz, 2H, -**CH$_2$**CH(CH$_3$)$_2$), 1.94 (m, 1H, -CH$_2$**CH**(CH$_3$)$_2$), 1.07 (d, *J* = 8.8 Hz, 6H, -CH$_2$CH(**CH$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 134.2, 130.3, 129.3, 128.6, 127.6, 127.1, 122.1, 119.3, 109.7, 94.6, 89.9, 82.0, 56.2, 28.8, 28.4, 22.2.

Methyl 3-(methoxymethoxy)-6-(4-methylpent-1-yl)-2-naphthoate (72). A solution of **71** (7.97 g, 29.7 mml) in ethanol (100 mL) was hydrogenated under 3 bar pressure of hydrogen in the presence of 10 wt % palladium on carbon (200 mg) for 18 h. The reaction mixture was then filtered through a celite pad before being concentrated in vacuo. The resultant residue was purified by flash chromatography (5% EtOAc in hexane) to afford the saturated alkyl as a viscous colourless oil which was taken forward without further characterisation.

t-Butyl lithium (1.9 M in pentene, 20.3 mL, 38.6 mmol) was added dropwise to a stirring 0 ^{o}C solution of the hydrogenation product (8.08 g, 29.7 mmol) in a mixture of diethyl ether and hexane (1:1, 200 mL). After complete addition, the mixture was stirred at 0 ^{o}C for 1 h before being cooled to -78 ^{o}C. Methyl chloroformate (3.44 mL, 44.6 mmol) was added dropwise and the resultant mixture stirred at room temperature for 1 hour before being quenched with methanol (10 mL). The organic mixture was washed with water (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The resultant residue was purified by flash chromatography (DCM/hexane from 3:5 to 4:5 to 6:5) to afford **72** as a colourless oil (5.49 g, 56% over two steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H, ArH), 7.73 (d, *J* = 8.4 Hz, 1H, ArH), 7.52 (s, 1H, ArH), 7.44 (s, 1H, ArH), 7.24 (d, *J* = 8.4 Hz, 1H, ArH), 5.36 (s, 2H, ArO**CH$_2$**OCH$_3$), 3.95 (s, 3H, -CO$_2$**CH$_3$**), 3.57 (s, 3H, ArOCH$_2$O**CH$_3$**), 2.73 (t, *J* = 7.6 Hz, 2H, Ar**CH$_2$**-), 1.73-1.65 (m, 2H, -CH$_2$CH$_2$CH-), 1.62-1.53 (m, 1H, -CH$_2$CH$_2$CH-), 1.28-1.19 (m, 2H, -CH$_2$CH$_2$CH-), 0.89 (d, *J* = 6.8 Hz, 6H, -CH(**CH$_3$**)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 153.2, 143.4, 136.2, 132.4, 128.5, 126.7, 126.6, 125.3, 121.3, 111.2, 95.2, 56.3, 52.1, 38.6, 36.5, 29.0, 27.9, 22.6; HRMS-EI calcd for $C_{20}H_{26}O_4$ [M^+] 330.1834; found 330.1831.

Methyl 3-hydroxy-6-(4-methylpent-1-yl)-2-naphthoate (73). To a stirring solution of **72** (5.28 g, 16.0 mmol) in methanol (40 mL) was added aqueous 2 M HCl (5 mL). The mixture was stirred at room temperature for 4 h before being extracted with diethyl ether (2 × 50 mL).

The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ (6 ml), water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The resultant residue was purified via flash chromatography (20% EtOAc in hexane) to give **73** as a viscous oil (4.48 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H, -**OH**), 8.42 (s, 1H, ArH), 7.70 (d, *J* = 8.4 Hz, 1H, ArH), 7.44 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.18 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 4.00 (s, 3H, -CO_2**CH_3**), 2.71 (t, *J* = 8.0 Hz, 2H, Ar**CH_2**-), 1.74-1.66 (m, 2H, -CH_2CH_2CH-), 1.64-1.55 (m, 1H, -CH_2CH_2CH-), 1.30-1.25 (m, 2H, -CH_2CH_2CH-), 0.91 (d, *J* = 6.8 Hz, 6H, -CH(**CH_3**)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 156.5, 144.3, 138.3, 132.1, 129.1, 125.7, 124.6, 113.3, 111.1, 52.4, 38.7, 36.6, 28.9, 27.9, 22.6; HRMS-EI for $C_{18}H_{22}O_3$ [M^+] 286.1566; found 286.1569.

3-Hydroxy-6-(4-methylpent-1-yl)-2-naphthoic acid (74). Method as that described for **29**. **73** (3.50 g, 12.2 mmol) and LiOH (1.46 g, 61.0 mmol) afforded **74** as a pale yellow solid (2.36 g, 71%); mp: 168-170 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H, ArH), 7.85 (d, *J* = 8.4 Hz, 1H, ArH), 7.51 (s, 1H, ArH), 7.21 (s, 1H, ArH), 7.19 (d, *J* = 8.4 Hz, 1H, ArH), 2.65 (t, *J* = 7.6 Hz, 2H, Ar**CH_2**-), 1.65-1.47 (m, 3H, -CH_2CH_2CH-), 1.20-1.14 (m, 2H, -CH_2CH_2CH-), 0.82 (d, *J* = 6.4 Hz, 6H, -CH(**CH_3**)$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.1, 156.7, 144.1, 138.0, 132.7, 129.6, 125.9, 125.7, 124.6, 114.7, 110.7, 38.5, 36.2, 28.8, 27.8, 22.9; MS (ESI) 271 (M^-), 227; Anal. ($C_{17}H_{20}O_3$) C, H.

(*E*)-(6-(4-Methylpent-1-en-1-yl)naphthalene-2,3-dicarbonitrile (76). A flask was charged with **75** (1.00 g, 3.89 mmol), palladium acetate (8.7 mg, 1 mol%) and tri-*o*-tolylphosphine (47.4 mg, 4 mol%). The flask was then briefly evacuated and backfilled with argon three times. Degassed anhydrous DMF (20 mL) was added followed by 4-methylpent-1-ene (0.62 mL, 4.86 mmol) and triethylamine (0.68 mL, 4.86 mmol). The resultant mixture was heated at 100 °C overnight. After being allowed to cool to room temperature the reaction mixture was filtered through a celite pad to remove any precipitated Pd(0) and then poured into a stirred solution of EtOAc (100 mL), water (100 mL) and aqueous 1 M HCl (10 mL). The organic layer was subsequently isolated and the aqueous phase further extracted with EtOAc (2 × 50 mL). The organic extracts were pooled, washed with water (2 × 100 mL), brine (100 mL) and dried over $MgSO_4$. Concentration in vacuo afforded a clay coloured solid which was purified by flash chromatography (10% EtOAc in hexane) to afford **76** as a light yellow oil (773 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29-8.25 (m, 2H, ArH), 7.90-7.86 (m, 2H,

ArH), 7.77 (s, 1H, ArH), 6.59-6.47 (m, 2H, -**CH**=**CH**-), 2.20 (t, *J* = 6.4 Hz, 2H, -**CH$_2$**CH(CH$_3$)$_2$), 1.81 (sep, *J* = 6.4 Hz, 1H, -CH$_2$**CH**(CH$_3$)$_2$), 0.98 (d, *J* = 6.4 Hz, 6H, -CH$_2$CH(**CH$_3$**)$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 140.5, 135.5, 135.5, 135.0, 133.8, 132.2, 129.4, 128.7, 128.6, 125.3, 116.1, 116.0, 110.4, 109.1, 42.6, 28.5, 22.4; HRMS-ESI calcd for $C_{18}H_{16}N_2$ $[M + Na]^+$ 283.1206; found 283.1214.

6-(4-Methylpent-1-yl)naphthalene-2,3-dicarboxylic acid (77). To a stirring suspension of **76** (400 mg, 1.54 mmol) in a 3:1 glacial acetic acid/water mix (40 mL) was added concentrated sulphuric acid (5 mL). The resultant mixture was heated at reflux until TLC indicated complete hydrolysis. After 24 h the now solution was allowed to cool to room temperature before being poured into a stirring mix of EtOAc and water (75 mL each). The organic layer was isolated and the aqueous phase further extracted with EtOAc (2 × 25 mL). The organics were pooled, washed with water (2 × 25 mL), brine (2 × 25 mL), dried over $MgSO_4$ and concentrated in vacuo to afford an orange residue. The crude product was then suspended in water (50 mL) and basified using aqueous 1 M NaOH. The resultant aqueous solution was extracted with diethyl ether (25 mL) and then acidified with aqueous 1 M HCl before being extracted with EtOAc (3 × 30 mL). The organic extracts were combined, washed with water (25 mL), brine (25 mL), dried over $MgSO_4$ and concentrated in to afford the di-acid as a viscous orange oil which used without further purification or characterisation. A solution of the crude alkene (427 mg, 1.43 mmol) in EtOAc (100 mL) was hydrogenated under 3 bar of hydrogen in the presence of 10 wt % palladium on activated carbon (50 mg) for 18 h. The reaction mixture was then filtered through a celite pad before being concentrated in vacuo to afford **77** as a glassy yellow solid (275 mg, 60%); mp: >250 ^{o}C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98 (s, 1H, ArH), 7.93-7.89 (m, 2H, ArH), 7.79 (s, 1H, ArH), 7.52 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 2.80 (t, *J* = 7.6 Hz, 2H, Ar**CH$_2$**-), 1.73 (quin, *J* = 7.6 Hz, 2H, -**CH$_2$**CH$_2$CH(CH$_3$)$_2$), 1.58 (sep, *J* = 6.8 Hz, 1H, -CH$_2$CH$_2$**CH**(CH$_3$)$_2$), 1.26-1.19 (m, 2H, -CH$_2$**CH$_2$**CH(CH$_3$)$_2$), 0.85 (d, *J* = 6.8 Hz, 6H, -CH(**CH$_3$**)$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.8, 167.7, 141.0, 133.9, 132.5, 131.1, 129.1, 129.1, 128.3, 127.1, 126.9, 38.9, 35.9, 28.3, 27.8, 22.8; HRMS-ESI calcd for $C_{18}H_{20}O_4$ $[M - H]^-$ 299.1289; found 299.1283; Anal. ($C_{18}H_{20}O_4$) C, H.

Methyl (*E*)-3-Acetoxy-7-styryl-2-naphthoate (78a). Method identical to that described for **11a**. **63** (1.00 g, 3.1 mmol), palladium acetate (7 mg, 1 mol%), tri-*o*-tolylphosphine (38 mg, 4 mol%), styrene (0.45 mL, 3.9 mmol), triethylamine (0.54 mL, 3.9 mmol) and anhydrous

DMF (25 mL) yielded an orange/yellow solid which was re-crystallized from toluene to afford **78a** (843 mg, 79 %) as an off-white solid; mp: 195-197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.93 (s, 1H), 7.86 (dd, *J* = 8.8 & 2.0 Hz, 1H, ArH), 7.79 (d, *J* = 9.0 Hz, 1H, ArH), 7.59-7.55 (m, 2H, ArH), 7.51 (s, 1H, ArH), 7.42-7.37 (m, 2H, ArH & -CH=CH-), 7.33-7.27 (m, 1H, -CH=CH-), 7.25 (s, 2H, ArH), 3.94 (s, 3H, -CO_2**CH_3**), 2.41 (s, 3H, -**OAc**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 165.0, 146.8, 137.0, 135.7, 135.2, 133.7, 131.0, 130.0, 128.8, 128.0, 127.9, 127.6, 127.3, 126.7, 126.6, 122.2, 121.0, 52.3, 21.1; MS (ESI^+) *m/z* 369 (M + Na, 100 %); HRMS-ESI calcd for $C_{22}H_{18}O_4$ $[M + Na]^+$ 369.1097; found 369.1107; Anal ($C_{22}H_{18}O_4.0.3C_7H_8$) C, H.

(*E*)-3-Hydroxy-7-styryl-2-naphthoic acid (79a). To a stirring suspension of **78a** (250 mg, 0.72 mmol) in a dioxane/water mix (2:1, 60 mL) was added aqueous 1 M NaOH (2.88 mL, 2.88 mL). The resultant mixture was stirred at room temperature until TLC indicated complete de-protection. After 18 h, the dioxane was removed in vacuo causing precipitation of an orange solid. The aqueous mixture was topped up with water and acidified to pH 1 using aqueous 2 M HCl. The precipitate was filtered off, washed copiously with water and then dried over P_2O_5 overnight to afford **79a** as an orange solid (199 mg, 95 %); mp: >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 1H, ArH), 7.92 (s, 1H, ArH), 7.78 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 7.67-7.60 (m, 3H, ArH), 7.41-7.33 (m, 3H, ArH & -CH=CH-), 7.31-7.23 (m, 2H, ArH & -CH=CH-), 7.05 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.8, 159.3, 137.3, 136.0, 131.0, 130.8, 128.6, 128.6, 127.7, 127.2, 126.9, 126.2, 126.2, 125.9, 124.6, 121.5, 109.3; MS (ESI^-) *m/z* 289 (M - H, 100 %), 245 (25); HRMS-ESI calcd for $C_{19}H_{14}O_3$ $[M - H]^+$ 289.0870; found 289.0874; Anal. ($C_{19}H_{14}O_3.0.75H_2O$) C, H.

(*E*)-7-(2-carboxystyryl)-3-hydroxy-2-naphthoic acid (79b). Method identical to that described for **11a**. **63** (600 mg, 1.86 mmol), palladium acetate (4.2 mg, 1 mol%), tri-*o*-tolylphosphine (22.6 mg, 4 mol%), methyl 2-vinylbenzoate (378 mg, 2.33 mmol), triethylamine (0.33 mL, 2.33 mmol) and anhydrous DMF (25 mL) yielded a viscous orange oil. Purification by flash chromatography (2 % EtOAc in hexane) afforded the protected styryl intermediate **78b** as a white solid (752 mg) which was taken forward without further characterisation.

To a stirring suspension of **78b** (752 mg, 1.86 mmol), in a THF/water mix (3:1, 80 mL) was added aqueous 1 M NaOH (11.16 mL, 11.16 mmol). The resultant mixture was heated at

reflux until TLC indicated complete de-protection. After 4 h the reaction was allowed to cool to room temperature and the THF removed in vacuo. The resultant aqueous solution was topped up with water and acidified to pH 1 using aqueous 2 M HCl. The solid which precipitated from solution was filtered off, washed copiously with water and dried over P_2O_5 overnight to afford **79b** (187 mg, 30%) as a yellow solid; mp: >250 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.52 (s, 1H, ArH), 8.05 (s, 1H, ArH), 7.99 (d, *J* = 16.5 Hz, 1H, -CH=CH-), 7.87 (m, 2H, ArH), 7.81 (m, 2H, ArH), 7.60 (m, 1H, ArH), 7.40 (m, 1H, ArH), 7.33 (s, 1H, ArH), 7.28 (d, *J* = 16.5 Hz, 1H, -CH=CH-); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.4, 168.6, 156.5, 137.9, 136.9, 132.8, 132.5, 131.9, 130.4, 130.3, 129.7, 128.1, 127.4, 127.0, 126.8, 126.6, 126.6, 126.5, 115.9, 111.1; MS (ESI⁻) *m/z* 333 (M – H, 100 %); HRMS-ESI calcd for $C_{20}H_{13}O_5$, 333.0768; found, 333.0766; Anal. ($C_{20}H_{14}O_5 \cdot 0.89H_2O$) C, H.

(*E*)-7-(3-carboxystyryl)-3-hydroxy-2-naphthoic acid (79c). Method identical to that described for **11a**. **63** (500 mg, 1.55 mmol), palladium acetate (3.5 mg, 1 mol%), tri-*o*-tolylphosphine (18.9 mg, 4 mol%), methyl 3-vinylbenzoate (315 mg, 1.94 mmol) [32] (Erdelyi et al, 2008), triethylamine (0.27 mL, 1.94 mmol) and anhydrous DMF (25 mL) yielded the crude protected styryl intermediate **78c** (627 mg) as a viscous orange oil which was taken forward without further purification or characterization.
De-protection was carried out in an identical fashion to **79b**. **78c** (627 mg, 1.55 mmol), THF/water (3:1, 80 mL) and aqueous 1 M NaOH (9.30 mL, 9.30 mmol) afforded **79c** as a yellow solid (278 mg, 53 %); mp: >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H, ArH), 8.14 (s, 1H, ArH), 8.06 (s, 1H, ArH), 7.94-7.72 (m, 4H, ArH & -CH=CH-), 7.49 (t, *J* = 7.6 Hz, 1H, ArH), 7.41 (s, 2H, ArH), 7.28 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.4, 167.1, 156.4, 137.5, 136.9, 132.5, 132.4, 131.3, 130.4, 129.2, 129.1, 128.3, 128.1, 127.4, 127.2, 126.8, 126.7, 126.5, 115.7, 111.1; MS (ESI⁻) *m/z* 333 (M - H, 100 %); HRMS-ESI calcd for $C_{20}H_{13}O_5$, 333.0768; found, 333.0772; Anal. ($C_{20}H_{14}O_5 \cdot H_2O$) C, H.

Methyl (*E*)-3-Acetoxy-7-(4-(methoxycarbonyl)styryl)-2-naphthoate (78d). Method identical to that described for **11a**. **63** (1.00 g, 3.10 mmol), palladium acetate (7 mg, 1 mol%), tri-*o*-tolylphosphine (38 mg, 4 mol%), methyl 4-vinylbenzoate (629 mg, 3.88 mmol), triethylamine (0.54 mL, 3.88 mmol) and anhydrous DMF (25 mL) yielded a yielded a yellow solid which was re-crystallized from toluene to afford **78d** (891 mg, 71 %) as a pale yellow solid; mp: 185-189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H, ArH), 8.06 (d, *J* = 8.4 Hz,

2H, ArH), 7.95 (s, 1H, ArH), 7.86 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 7.81 (d, *J* = 8.8 Hz, 1H, ArH), 7.62 (d, *J* = 8.4 Hz, 2H, ArH), 7.52 (s, 1H, ArH), 7.36, (d, *J* = 16.4 Hz, 1H, -CH=CH-), 7.26 (d, *J* = 16.4 Hz, 1H, -CH=CH-), 3.94 (s, 3H, -CO_2**CH_3**), 3.94 (s, 3H, -CO_2**CH_3**), 2.41 (s, 3H, -**OAc**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 166.8, 164.9, 147.1, 141.4, 135.4, 135.1, 133.8, 130.9, 130.4, 130.1, 129.2, 128.8, 127.9, 127.7, 126.5, 126.4, 122.4, 121.1, 52.4, 52.1, 21.0; MS (ESI^+) *m/z* 427 (M + Na, 100 %); HRMS-ESI calcd for $C_{24}H_{20}O_6$ $[M + Na]^+$ 427.1152; found 427.1143; Anal. ($C_{24}H_{20}O_6$) C, H.

(*E*)-7-(4-Carboxystyryl)-3-hydroxy-2-naphthoic acid (79d). Method identical to that described for **79b**. **78d** (250 mg, 0.62 mmol), THF/water (3:1, 80 mL) and aqueous 1 M NaOH (3.72 mL, 3.72 mmol) afforded **79d** (141 mg, 68%) as a yellow/orange solid; mp: >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (br s, 1H, -**CO_2H**), 11.25 (br s, 1H), 8.52 (s, 1H, ArH), 8.10 (s, 1H, ArH), 7.98-7.92 (m, 3H, ArH), 7.80 (d, *J* = 8.4 Hz, 1H, ArH), 7.74 (d, *J* = 8.4 Hz, 2H, ArH), 7.51 (d, *J* = 16.4 Hz, 1H, -CH=CH-), 7.42 (d, *J* = 16.4 Hz, 1H, -CH=CH-), 7.34 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 167.0, 156.5, 141.4, 136.9, 132.4, 132.2, 130.6, 129.7, 129.3, 128.3, 127.2, 126.7, 126.5, 126.5, 126.3, 115.8, 111.0; MS (ESI^-) *m/z* 333 (M - H, 96 %), 289 (75), 245 (100); HRMS-ESI calcd for $C_{20}H_{14}O_5$ $[M - H]^+$ 333.0768; found 333.0767; Anal. ($C_{20}H_{14}O_5.0.4H_2O$) C, H.

(***E*)-3-hydroxy-7-(2-methoxystyryl)-2-naphthoic acid (79e).** Method identical to that described for **11a**. **63** (1.00 g, 3.10 mmol), palladium acetate (7 mg, 1 mol%), tri-*o*-tolylphosphine (38 mg, 4 mol%), 2-vinylanisole (521 mg, 3.88 mmol), triethylamine (0.54 mL, 3.88 mmol) and anhydrous DMF (25 mL) yielded the crude protected styryl intermediate **78e** (1.17 g) as a viscous yellow oil which was taken forward without further purification or purification.

De-protection was carried out in an identical fashion to **79b**. **78e** (1.17 g, 3.10mmol), THF/water (3:1, 80 mL) and aqueous 1 M NaOH (12.4 mL, 12.4 mmol) afforded **79e** (100 mg, 10 %) as a yellow solid; mp: >235 °C (dec); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.52 (s, 1H, ArH), 8.03 (br.s, 1H, ArH), 7.86 (dd, *J* = 9.0 & 1.5 Hz, 1H, ArH), 7.77 (d, *J* = 9.0 Hz, 1H, ArH), 7.69 (dd, *J* = 8.0 & 1.5 Hz, 1H, ArH), 7.51 (d, *J* = 16.5 Hz, 1H, -CH=CH-), 7.34 (d, *J* = 16.5 Hz, 1H, -CH=CH-), 7.32 (br s, 1H, ArH), 7.28 (m, 1H, ArH), 7.05 (d, *J* = 8.0 Hz, 1H, ArH), 6.99 (pt, *J* = 7.0 Hz, 1H, ArH), 3.88 (s, 3H, -**OMe**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.5, 156.5, 156.3, 136.7, 133.1, 132.4, 128.9, 128.6, 127.5, 126.9, 126.7, 126.5,

126.3, 125.5, 122.9, 120.7, 115.7, 111.5, 111.0, 55.5; MS (ESI⁻) *m/z* 319 (100 %); Anal. ($C_{20}H_{16}O_4$) C, H.

(*E*)-3-Hydroxy-7-(3-methoxystyryl)-2-naphthoic acid (79f). Method identical to that described for **11a**. **63** (500 mg, 1.55 mmol), palladium acetate (3.5 mg, 1 mol%), tri-*o*-tolylphosphine (19 mg, 4 mol%), 3-vinylanisole (260 mg, 1.94 mmol), triethylamine (0.27 mL, 1.94 mmol) and anhydrous DMF (25 mL) yielded the crude protected styryl intermediate **78f** (583 mg) as a viscous orange oil which was taken forward without further purification or characterisation.

De-protection was carried out in an identical fashion to **79b**. **78f** (583 g, 1.55 mmol), THF/water (3:1, 80 mL) and aqueous 1 M NaOH (6.20 mL, 6.20 mmol) afforded **79f** as a yellow solid (391 mg, 79%); mp: > 250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (br s, 1H, ArH), 7.89 (br s, 1H, ArH), 7.74 (dd, *J* = 8.8 & 1.6 Hz, 1H, ArH), 7.61 (d, *J* = 8.8 Hz, 1H, ArH), 7.36 (d, *J* = 16.4 Hz, 1H, -CH=CH-), 7.29 (m, 1H, ArH), 7.23 (d, *J* = 16.4 Hz, 1H, -CH=CH-), 7.19 (m, 2H, ArH), 6.99 (br s, 1H, ArH), 6.83 (m, 1H, ArH), 3.81 (s, 3H, -**OMe**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.8, 160.1, 159.6, 138.9, 136.0, 130.7, 130.6, 129.7, 129.2, 127.9, 126.7, 126.2, 125.9, 124.3, 122.9, 118.9, 113.2, 111.2, 109.1, 55.1; MS (ESI⁻) *m/z* 319 (M – Na, 100 %); Anal. ($C_{20}H_{15}NaO_4$) C, H.

(*E*)-3-hydroxy-7-(4-methoxystyryl)-2-naphthoate (79g). Method identical to that described for **11a**. **63** (500 mg, 1.55 mmol), palladium acetate (3.5 mg, 1 mol%), tri-*o*-tolylphosphine (19 mg, 4 mol%), 4-vinylanisole (260 mg, 1.94 mmol), triethylamine (0.27 mL, 1.94 mmol) and anhydrous DMF (25 mL) yielded the crude protected styryl intermediate **78g** (583 mg) as a viscous yellow/orange oil which was taken forward without further purification or characterisation.

De-protection was carried out in an identical fashion to **79b**. **78g** (583 g, 1.55 mmol), THF/water (3:1, 80 mL) and aqueous 1 M NaOH (6.20 mL, 6.20 mmol) afforded **79g** as a yellow solid (140 mg, 28%); mp: > 250 °C; ^{1}H NMR (400 MHz, DMSO-d_6,) δ 8.43 (s, 1H, ArH), 7.94 (s, 1H, ArH), 7.83 (d, *J* = 8.5 Hz, 1H, ArH), 7.71 (d, *J* = 8.5 Hz, 1H, ArH), 7.56 (d, *J* = 8.5 Hz, 2H, ArH), 7.27 (d, *J* = 16.0 Hz, 1H, -CH=CH-), 7.21 (s, 1H, ArH), 7.19 (d, *J* = 16.0 Hz, 1H, -CH=CH-), 6.96 (d, *J* = 8.5 Hz, 2H, ArH), 3.78 (s, 3H, -**OMe**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 158.9, 157.4, 136.3, 132.4, 131.7, 129.8, 127.7, 127.5, 127.1, 126.7, 126.2, 126.1, 125.9, 114.2, 110.4, 55.1; MS (ESI⁻) *m/z* 319 (100 %); Anal. ($C_{20}H_{15}NaO_4$) C, H.

(*E*)-3-Hydroxy-7-(2-nitrostyryl)-2-naphthoic acid (79h). Method identical to that described for **11a**. **63** (737 mg, 2.28 mmol), palladium acetate (5 mg, 1 mol%), tri-*o*-tolylphosphine (28 mg, 4 mol%), 2-nitrostyrene (425 mg, 2.85 mmol), triethylamine (0.40 mL, 2.85 mmol) and anhydrous DMF (25 mL) yielded the crude protected styryl intermediate **78h** (892 mg) as a viscous dark orange oil which was taken forward without further purification or characterisation.

De-protection was carried out in an identical fashion to **79b**. **78h** (892 mg, 2.28 mmol), THF/water (3:1, 80 mL) and aqueous 1 M NaOH (9.12 mL, 9.12 mmol) afforded **79h** as a yellow solid (343 mg, 45%); mp: > 250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (br s, 1H, ArH), 8.13 (br.s, 1H, ArH), 8.01 (m, 2H, ArH), 7.88 (dd, *J* = 9.0 & 1.5 Hz, 1H, ArH), 7.81 (d, *J* = 9.0 Hz, 1H, ArH), 7.76 (m, 1H, ArH), 7.56 (m, 2H, ArH & -CH=CH-), 7.44 (d, *J* = 16.5 Hz, 1H, -CH=CH-), 7.34 (br s, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.4, 156.7, 147.9, 137.1, 133.5, 133.1, 132.7, 132.0, 131.8, 128.8, 128.5, 128.0, 126.7, 126.7, 126.7, 124.5, 122.6, 116.0, 111.1; MS (ESI$^-$) *m/z* 334 (M – H, 100 %); HRMS-ESI calcd for $C_{19}H_{12}NO_5$, 414.0948; found, 414.0941; Anal. ($C_{19}H_{13}NO_5$.0.1H_2O) C, H, N.

(*E*)-3-Hydroxy-7-(3-nitrostyryl)-2-naphthoic acid (79i). Method identical to that described for **11a**. **63** (1.00 g, 3.10 mmol), palladium acetate (7 mg, 1 mol%), tri-*o*-tolylphosphine (38 mg, 4 mol%), 3-nitrostyrene (521 mg, 3.88 mmol), triethylamine (0.54 mL, 3.88 mmol) and anhydrous DMF (25 mL) yielded the crude protected styryl intermediate **78i** (1.21 g) as a viscous yellow oil which was taken forward without further purification or purification.

De-protection was carried out in an identical fashion to **79b**. **78i** (1.21 g, 3.10 mmol), THF/water (3:1, 80 mL) and aqueous 1 M NaOH (12.4 mL, 12.4 mmol) afforded **79i** as a brown solid (120 mg, 12 %); mp: > 250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (pt, *J* = 1.5 Hz, 1H, ArH), 8.34 (s, 1H, ArH), 8.09 (dd, *J* = 8.0 & 2.0 Hz, 2H, ArH), 7.98 (br s, 1H, ArH), 7.80 (dd, *J* = 9.0 & 1.5 Hz, 1H, ArH), 7.67 (m, 2H, ArH), 7.58 (d, *J* = 16.5 Hz, 1H, -CH=CH-), 7.44 (d, *J* = 16.5 Hz, 1H, -CH=CH-), 7.04 (br s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.8, 160.0, 148.4, 139.5, 136.4, 132.3, 131.8, 131.0, 130.4, 130.2, 128.7, 126.2, 126.1, 124.7, 124.5, 122.2, 121.6, 120.5, 109.4; MS (ESI$^-$) *m/z* 334 (100 %); Anal. ($C_{19}H_{13}NO_5$.0.38H_2O) C, H, N.

(*E*)-3-Hydroxy-7-(4-nitrostyryl)-2-naphthoic acid (79j). Method identical to that described for **11a**. **63** (500 mg, 1.55 mmol), palladium acetate (3.5 mg, 1 mol%), tri-*o*-tolylphosphine

(19 mg, 4 mol%), 4-nitrostyrene (289 mg, 1.94 mmol), triethylamine (0.27 mL, 1.94 mmol) and anhydrous DMF (25 mL) yielded the crude protected styryl intermediate **78j** (607 mg) as a viscous yellow/orange oil which was taken forward without further purification or characterisation.

De-protection was carried out in an identical fashion to **79b**. **78j** (607 mg, 1.55 mmol), THF/water (3:1, 80 mL) and aqueous 1 M NaOH (6.20 mL, 6.20 mmol) afforded **79j** as a yellow solid (154 mg, 30%); mp: >250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (s, 1H, ArH), 8.25 (d, *J* = 8.5 Hz, 2H, ArH), 8.13 (br s, 1H, ArH), 7.96 (d, *J* = 8.5 Hz, 1H, ArH), 7.89 (d, *J* = 8.5 Hz, 2H, ArH), 7.82 (d, *J* = 8.5 Hz, 1H, ArH), 7.64 (d, *J* = 16.0 Hz, 1H, -CH=CH-), 7.51 (d, *J* = 16.0 Hz, 1H, -CH=CH-), 7.35 (s, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.4, 156.8, 146.1, 144.1, 137.2, 133.0, 132.7, 132.0, 129.1, 127.2, 126.7, 126.6, 126.2, 124.1, 115.9, 111.2; MS (ESI$^-$) *m/z* 334 (M – H, 100 %); HRMS-ESI calcd for $C_{19}H_{12}NO_5$, 334.0721; found, 334.0727; Anal. ($C_{19}H_{13}NO_5$) C, H, N.

3-Hydroxy-7-phenethyl-2-naphthoic acid (81a). 78a (450 mg, 1.30 mmol) was dissolved in dioxane (100 mL) and the resulting solution hydrogenated under 3 bar of hydrogen in the presence of 10 wt % palladium on activated carbon (50 mg) for 18 h. The reaction mixture was then filtered through a Celite pad before being concentrated in vacuo to yield a clear oil which solidified on standing. Purification by flash chromatography (10 → 20% EtOAc in hexane) afforded the protected phenethyl intermediate **80a** (300 mg, 66%) as a white solid which was utilised in the next step without further characterisation.

De-protection was carried out in an identical fashion to **79b. 80a** (300 mg, 0.86 mmol), THF/water (3:1, 80 mL) and aqueous 1 M NaOH (3.44 mL, 3.44 mmol) afforded **81a** (238 mg, 95%) as a pale yellow/green solid; mp: >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H, ArH), 7.70 (s, 1H, ArH), 7.65 (d, *J* = 8.4 Hz, 1H, ArH), 7.41 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 7.30-7.22 (m, 4H, ArH), 7.20-7.14 (m, 2H, ArH), 3.03-2.91 (m, 4H, -$\mathbf{CH_2CH_2}$-); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 156.4, 141.4, 136.2, 135.5, 131.2, 129.9, 128.3, 128.1, 127.2, 126.5, 125.7, 125.6, 117.2, 110.0, 36.8, 36.7; MS (ESI$^-$) *m/z* 291 (M - H, 100 %); HRMS-ESI calcd for $C_{19}H_{16}O_3$ [M - H]$^+$ 291.1027; found 291.1038; Anal. ($C_{19}H_{16}O_3$.0.1H_2O) C, H.

3-Hydroxy-7-(2-carboxyphenethyl)-2-naphthoic acid (81b). Method identical to that described for **80a** with the exception that EtOAc (100 mL) was used instead of dioxane.**78b**

(336 mg, 0.83 mmol) and 10 wt % palladium on activated carbon (50 mg) yielded the protected phenethyl intermediate **80b** as a tacky white solid (337 mg) which was taken forward without further purification or characterization.

De-protection was carried out in an identical fashion to **79b**. **80b** (337 mg, 0.83 mmol), THF/water (3:1, 80 mL), and aqueous 1 M NaOH (4.98 mL, 4.98 mmol) yielded a light brown solid that ^{1}H-NMR indicated was a mixture of the desired product and the methyl ester. As base hydrolysis was not sufficient to bring the reaction to completion, the crude product was suspended in a mixture of glacial acetic acid and water (25 mL each), and 6 M HCl added (50 mL). The resulting suspension was heated at reflux for 18 hours before being allowed to cool to room temperature. The solid which precipitated from solution was filtered off, washed with plenty of water and then dried over P_2O_5 overnight to yield a yellow/mustard coloured solid. Re-crystallisation from methanol (H_2O was added to precipitate the product) afforded **81b** as a pale yellow solid (191 mg, 68 %); mp: >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (br s, 1H, -**CO_2H**), 10.97 (br s, 1H, -**OH**), 8.43 (s, 1H, ArH), 7.83 (dd, *J* = 8.0 & 1.2 Hz, 1H, ArH), 7.73 (s, 1H, ArH), 7.71 (d, *J* = 8.8 Hz, 1H, ArH), 7.49-7.42 (m, 2H, ArH), 7.34-7.29 (m, 2H, ArH), 7.28 (s, 1H, ArH), 3.30-3.24 (m, 2H, -CH_2CH_2-), 2.92-2.90 (m, 2H, -CH_2CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.5, 168.7, 155.5, 142.5, 137.1, 135.8, 131.7, 131.6, 130.9, 130.5, 130.3, 127.2, 126.6, 126.1, 125.9, 115.1, 110.6, 37.2, 35.6; MS (ESI$^+$) *m/z* 335 (M - H, 100 %); HRMS-ESI calcd for $C_{20}H_{16}O_5$ $[M - H]^+$ 335.0925; found 335.0928.

7-(4-Carboxyphenethyl)-3-hydroxy-2-naphthoic acid (81c). Method identical to that described for **80a** with the exception that THF (100 mL) was used instead of dioxane. **78d** (500 mg, 1.24 mmol) and 10 wt % palladium on activated carbon (50 mg) yielded the protected phenethyl intermediate **80c** (504 mg) as a white solid which was taken forward without further characterisation or purification.

De-protection was carried out in an identical fashion to **79b**. **80c** (504 mg, 1.24 mmol), THF/water (3:1, 80 mL) and aqueous 1 M NaOH (1.24 mL, 1.24 mmol) afforded **81c** (388 mg, 93 %) as a yellow solid; mp: >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.5 (br s, 1H, -CO_2H), 8.36 (s, 1H, ArH), 7.85 (d, *J* = 8.4 Hz, 2H, ArH), 7.70 (s, 1H, ArH), 7.63 (d, *J* = 8.4 Hz, 1H, ArH), 7.42-7.34 (m, 3H, ArH), 7.16 (s, 1H, ArH), 3.02 (s, 4H, -**CH_2CH_2**-); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 167.2, 156.7, 146.8, 135.8, 135.4, 131.1, 129.7, 129.3, 128.6,

128.4, 127.3, 126.5, 125.6, 109.8, 36.6, 36.3; MS (ESI$^-$) *m/z* 335 (M - H, 100 %); HRMS-ESI calcd for $C_{20}H_{16}O_5$ $[M - H]^+$ 335.0925; found 335.0928; Anal. ($C_{20}H_{16}O_5.0.25H_2O$) C, H.

Dimethyl 6-Styrylnaphthalene-2,3-dicarboxylate (84). Methylamine (2.0 M in methanol, 3.2 mL, 6.4 mmol) was added dropwise to a stirring 0 ^oC solution of **78a** (1.10 g, 3.2 mmol) in toluene (20 mL). The resultant mixture was stirred at 0 ^oC for 2 hours. The solid which precipitated from solution was filtered off, washed with methanol (20 mL) and dried under vacuum to afford the crude phenol (**82**) as a pale yellow solid which was taken forward without further purification or characterisation.

To a solution of **82** (974 mg, 3.2 mmol) in anhydrous DCM (20 mL) at -10 ^oC was added triethylamine (0.89 mL, 6.4 mmol) and Tf_2O (0.7 mL, 4.2 mmol). The resultant mixture was stirred at room temperature for 2 h before aqueous 1 M HCl (10 mL) was added. The organic layer was separated, washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was passed through a short silica plug to afford the crude triflate (**83**) which was taken forward without further purification or characterisation.

A flask was charged with $Pd(OAc)_2$ (72 mg, 0.32 mmol) and DPPP (172 mg, 0.42 mmol) before being briefly evacuated and backfilled with carbon monoxide. A degassed mixture of **83** (1.39 g, 3.2 mmol) and triethylamine (0.89 mL, 6.4 mmol) in a mixture of anhydrous DMF and methanol (3:1, 12 mL) was added. The resultant mixture was heated at 80 ^oC for 24 h. After being allowed to cool to room temperature, the reaction was diluted with aqueous 1 M HCl (10 mL) and then extracted with ethyl acetate (2 × 25 mL). The organic phase was isolated, washed with water (15 mL), brine (15 mL), dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was purified via flash chromatography (20% EtOAc in hexane) to afford a white solid which was further purified by re-crystallisation from toluene to give **84** (459 mg, 41% over 3 steps); ^1H NMR (400 MHz, $CDCl_3$) 8.24 (s, 1H, ArH), 8.21 (s, 1H, ArH), 7.91-7.86 (m, 3H, ArH), 7.59-7.57 (m, 2H, ArH), 7.42-7.38 (m, 2H, ArH & -CH=CH-), 7.33-7.28 (m, 3H, ArH & -CH=CH-), 3.97 (s, 3H, -CO_2**CH_3**), 3.96 (s, 3H, -CO_2**CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$) 168.3, 168.0, 137.7, 137.8, 133.9, 132.8, 130.9, 130.0, 129.9, 129.2, 129.0, 128.8, 128.2, 128.0, 127.7, 126.8, 126.7, 126.2, 52.7, 52.7; MS (ESI) 347 (MH^+), 369 (MNa^+), 315; HRMS (ESI) for $C_{22}H_{19}O_4$ required 347.1278, obtained 347.1283.

(*E*)-6-Styrylnaphthalene-2,3-dicarboxylic acid (85). Method identical to that described for **29**. **84** (415 mg, 1.2 mmol) and LiOH (144 mg, 6.0 mmol) afforded **85** as an off-white solid

(329 mg, 86%); mp: >250 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) 8.28 (s, 1H, ArH), 8.24 (s, 1H, ArH), 8.16 (s, 1H, ArH), 8.08 (d, *J* = 8.4 Hz, 1H, ArH), 8.01 (d, *J* = 8.4 Hz, 1H, ArH), 7.67-7.64 (m, 2H, ArH), 7.46-7.38 (m, 4H, ArH & -CH=CH-), 7.31-7.28 (m, 1H, -CH=CH-); ^{13}C NMR (100 MHz, DMSO-d_6) 169.2, 169.0, 137.6, 137.2, 133.7, 132.7, 131.1, 130.9, 130.0, 129.6, 129.4, 129.4, 129.3, 128.5, 128.3, 127.2, 127.1, 126.5; MS (ESI) 318 (M^-), 374; Anal. ($C_{20}H_{14}O_4$) C, H.

(*E*)-2-oxo-6-styryl-2H-chromene-3-carboxylic acid (88). (*E*)-2-hydroxy-5-styrylbenzaldehyde [19] (64 mg, 0.29 mmol), Meldrum's acid (41 mg, 1.34 mmol) and piperidinium acetate (1mg, 0.01 mmol) were mixed in ethanol (5 mL) and stirred at rt for 20 min before heating at reflux for 2 h. The mixture was then cooled to 0 °C for 1 h and the resulting precipitate was filtered, washed with ethanol and dried under vacuum to give **88** as a white solid (50 mg, 60%); mp: >250 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.28 (br s, 1H, -**CO_2H**), 8.71 (s, 1H, ArH), 8.09 (d, *J* = 2.0 Hz, 1H, ArH), 7.99 (dd, *J* = 8.5 & 2.0 Hz, 1H, ArH), 7.62 (br d, *J* = 7.0 Hz, 2H, ArH), 7.46 (d, *J* = 8.5 Hz, 1H, ArH), 7.40 (m, 2H, ArH & -CH=CH-), 7.30 (m, 3H, ArH & -CH=CH-); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.0, 156.6, 153.8, 148.2, 136.7, 133.9, 129.5, 128.8, 128.0, 127.5, 126.6, 126.5, 118.7, 118.2, 116.6; MS (ESI$^-$) *m/z* 291 (100 %); Anal. $C_{18}H_{12}O_4$: C, H.

Biology Experimental

Expression and electrophysiological analysis of NMDAR activity.

cDNA encoding the rat NMDAR subunits was generously provided by Dr. Shigetada Nakanishi, Kyoto, Japan (GluN1a), Dr. Peter Seeburg, Heidelburg, Germany (GluN2A, GluN2C, and GluN2D) and Drs. Dolan Pritchett and David Lynch, Philadelphia, USA (GluN2B). Plasmids were linearized with Not I (GluN1a, GluN2C, and GluN2D), EcoR I (GluN2A) or Sal I (GluN2B) and transcribed *in vitro* with T7 (GluN1a, GluN2A, GluN2C, and GluN2D) or SP6 (GluN2B) RNA polymerase using mMessage mMachine transcription kits (Ambion, Austin, TX, USA).

Oocytes from mature female *Xenopus laevis* (Xenopus One, Ann Arbor, MI, USA) were removed and isolated.[31] GluN1a and GluN2 RNAs were mixed in a molar ratio of 1:1-3 and microinjected (50 nl, 15-30 ng total) into the oocyte cytoplasm. Oocytes were incubated in ND-96 solution at 17°C prior to electrophysiological assay (1-5 days). Electrophysiological responses were measured using a standard two-electrode voltage clamp (TEVC) using a

Warner Instruments (Hamden, CT, U.S.A.) model OC-725B Oocyte Clamp amplifier and a Digidata 1440 data acquisition system with pClamp 10 software (Molecular Devices, Sunnyvale, CA, USA). The recording buffer contained 116 mM NaCl, 2 mM KCl, 0.3 mM $BaCl_2$ and 5 mM HEPES, pH 7.4. Response magnitude was determined by the steady plateau response elicited by bath application of 10 μM L-glutamate plus 10 μM glycine at a holding potential of -60 mV. Dose-response results were fit using GraphPad Prism (ISI Software, San Diego, CA, U.S.A.) (Costa et al., 2010).

Supporting Information Available.

Proton and carbon NMR spectra for final compounds. Elemental analyses for intermediates and final compounds.

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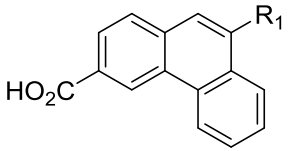
Table 1. SAR studies on naphthalene derivatives and comparsion to corresponding phenanthrene deriavtives. Values are percentage response for agonist (10 μM L-glutamate/10 μM glycine) in presence of test compound (100 μM) compared to agonist alone.



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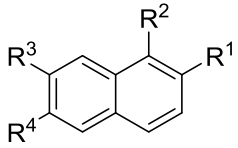
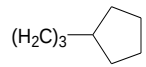


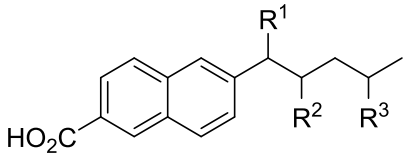
B

						NMDAR (n≥4)[a]			
Compound	**Formula**	**R^1**	**R^2**	**R^3**	**R^4**	**GluN2A**	**GluN2B**	**GluN2C**	**GluN2D**
1	A	I	-	-	-	108.6 ± 4.8	100.9 ± 0.1	65.9 ± 0.1	47.7 ± 3.0
12a	B	Pent-1-ene-1-yl	H	H	CO_2H	51 ± 18	58 ± 5	82 ± 9	68 ± 6
12b	B	$CH=CHCH_2CH(CH_3)_2$	H	H	CO_2H	135 ± 11	152 ± 9	264 ± 41	220 ± 40
14a	B	$(CH_2)_4CH_3$	H	H	CO_2H	131 ± 5	102 ± 2	126 ± 3	110 ± 4
14b	B	$(CH_2)_3CH(CH_3)_2$	H	H	CO_2H	171 ± 6	171 ± 9	192 ± 6	207 ± 15
17	B	Cyclopropyl	H	H	CO_2H	97.0 ± 3.4	97.0 ± 1.6	97.0 ± 0.6	94.0 ± 3.2
18	B	$(CH_2)_4CH_3$	H	H	CH_2OH	89 ± 3	84 ± 8	76 ± 3	85 ± 2
21	B	$(CH_2)_4CH_3$	H	H	CH_2CO_2H	67 ± 18	67 ± 10	60 ± 3	37 ± 2
22	B	$(CH_2)_4CH_3$	Br	H	CO_2H	73 ± 11	52 ± 15	97.0 ± 4.3	99.0 ± 2.8
24	B	$O(CH_2)_3CH_3$	H	H	CO_2H	55 ± 7	46 ± 3	63 ± 15	57 ± 3
27a	B	$(CH_2)_4Ph$	H	H	CO_2H	118 ± 13	120 ± 4	123 ± 10	115 ± 5
27b	B		H	H	CO_2H	136 ± 7	175 ± 13	171 ± 13	161 ± 11

29	B	4-methylpent-1-yn-1-yl	H	H	CO_2H	104 ± 12	99 ± 7	125± 15	110 ± 20
74	B	$(CH_2)_3CH(CH_3)_2$	H	OH	CO_2H	178 ± 30	309 ± 107	357 ± 93	301 ± 113
69	B	$(CH_2)_3CH(CH_3)_2$	H	CO_2H	H	123 ± 36	120 ± 12	115 ± 22	80 ± 21
65	B	$(CH_2)_3CH(CH_3)_2$	H	CO_2H	OH	78 ± 23	113 ± 18	113 ± 38	180 ± 51
77	B	$(CH_2)_3CH(CH_3)_2$	H	CO_2H	CO_2H	92.0 ± 7.9	88 ± 6	47 ± 2	24 ± 1

[a]Compounds were tested by TEVC for activity at recombinant NMDA receptors (GluN1a and the indicated GluN2 subunit) expressed in *Xenopus* oocytes. After obtaining a steady state NMDAR response evoked by 10 μM L-glutamate and 10 μM glycine, test compounds (100 μM) were co-applied with agonists. Values (mean ± s.e.m.) represent the % response in the presence of the test compound compared to response in the presence of agonists alone. Values >100 represent potentiation and those < 100 represent inhibition of the agonist response.

Table 2. SAR studies to probe the effect of substitution of the alkyl chain at the 6-position of the naphthalene ring. Values are percentage response for agonist (10 µM L-glutamate/10 µM glycine) in presence of test compound (100 µM) compared to agonist alone.



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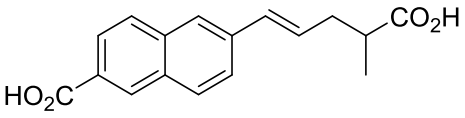
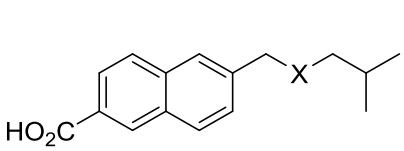


B

					NMDAR (n≥4)[a]			
Compound	**Formula**	**R^1**	**R^2**	**R^3**	**GluN2A**	**GluN2B**	**GluN2C**	**GluN2D**
33	A	H	H	CO_2H	110 ± 6	85 ± 6	98 ± 2	107 ± 12
31	B	-	-	-	107 ± 4	97 ± 4	105 ± 0.5	97 ± 1
42	A	H	H	CH_2CO_2H	60 ± 10	64 ± 8	96 ± 10	71 ± 13
46	A	CH_3	H	CH_3	281 ± 42	225 ± 25	337 ± 55	317 ± 37
60	A	H	CO_2H	CH_3	104 ± 6	78 ± 6	118 ± 10	85 ± 5

[a]Compounds were tested by TEVC for activity at recombinant NMDA receptors (GluN1a and the indicated GluN2 subunit) expressed in Xenopus oocytes. After obtaining a steady state NMDAR response evoked by 10 µM L-glutamate and 10 µM glycine, test compounds (100 µM) were co-applied with agonists. Values (mean ± s.e.m.) represent the % response in the presence of the test compound compared to response in the presence of agonists alone. Values >100 represent potentiation and those < 100 represent inhibition of the agonist response.

Table 3. SAR studies to probe the effect of heteroatom or methylene substitution of the alky chain. Values are percentage response for agonist (10 µM L-glutamate/10 µM glycine) in presence of test compound (100 µM) compared to agonist alone.



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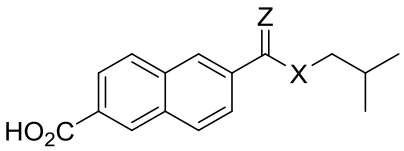

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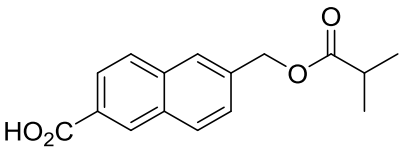


C

				NMDAR (n≥4)[a]			
Compound	**Formula**	**X**	**Z**	**GluN2A**	**GluN2B**	**GluN2C**	**GluN2D**
38	B	CH_2	O	128 ± 10	82 ± 9	99 ± 12	79 ± 12
44	B	CH_2	CH_2	163 ±1 2	265 ± 29	349 ± 45	310 ± 49
49	A	S	-	113 ± 15	77 ± 11	105 ± 13	100.2 ± 7
52	B	NH	O	65 ± 17	65 ± 10	46 ± 14	99 ± 5
54	C	-	-	73 ± 12	45 ± 10	56 ± 12	42 ± 10
57	A	O	-	83 ± 14	49 ± 10	83 ± 9	72 ± 8
35	B	O	O	159 ± 21	179 ± 35	144 ± 17	169 ± 30

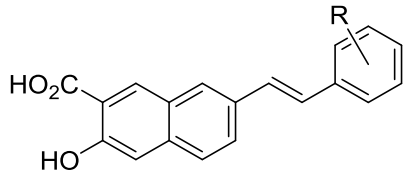
[a]Compounds were tested by TEVC for activity at recombinant NMDA receptors (GluN1a and the indicated GluN2 subunit) expressed in Xenopus oocytes. After obtaining a steady state NMDAR response evoked by 10 µM L-glutamate and 10 µM glycine, test compounds (100 µM) were co-applied with agonists. Values (mean ± s.e.m.) represent the % response in the presence of the test compound compared to response in the presence of agonists alone. Values >100 represent potentiation and those < 100 represent inhibition of the agonist response.

Table 4. EC_{50} (μM, n≥4) values for potentiation of GluN1/GluN2 NMDAR subtypes[a]

Compounds	GluN2A	GluN2B	GluN2C	GluN2D
14a	26.7 ± 5.6	ND	113 ± 66	61 ± 33
	(39.0 ± 5.9)		(42.7 ± 16.1)	(17.3 ± 16.2)
14b	28.0 ± 4.6	34.6 ± 3	37.2 ± 2.8	28.9 ± 4.1
	(68.6 ± 16.2)	(102.0 ± 17.8)	(117.2 ± 22.3)	(88.4 ±9.6)
27b	7.5 ± 2.8	27.0 ± 6.3	22.4 ± 3.6	34.7 ± 10.3
	(38.4 ±4.7)	(61.9 ± 10.9)	(105.3 ± 26.1)	(65.6 ± 18.4))
44	114.4 ± 7.2	116.4 ± 19.8	26.1 ± 4.5	72.3 ± 15.5
	(230.4 ± 84.6)	(416.6 ± 70.9)	(136.6 ± 11.6)	(277.2 ± 36.8)
46	39.4 ± 27.5	25.0 ± 11.6	36.2± 5.7	30.6 ± 7.5
	(277.2 ± 36.8)	(192.3 ± 46.6)	(262.6 ± 33.9)	(240.3 ± 63.6)

[a]EC_{50} values (mean ± s.e.m.) for the potentiation of GluN1/GluN2 NMDAR responses responses. Values in parenthesis are the maximum potentiation expressed as a percentage (± s.e.m.) above the agonist alone response (L-glutamate, 10 μM and glycine, 10 μM). ND = not determined.

Table 5. SAR studies on naphthalene derivatives as NMDAR NAMs. Values are percentage response for agonist (10 μM L-glutamate/10 μM glycine) in presence of test compound (100 μM) compared to agonist alone.



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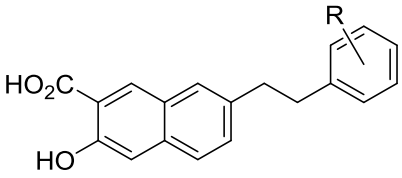

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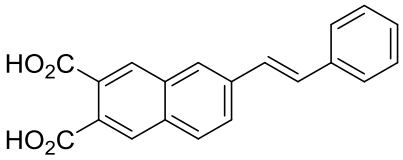

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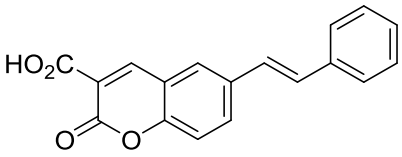


D

			NMDAR (n≥4)[a]			
Compound	**Formula**	**R**	**GluN2A**	**GluN2B**	**GluN2C**	**GluN2D**
7	**-**	**-**	28.4 ± 2.6	49.9 ± 9.0	26.1 ± 1.7	26.1 ± 4.6
79a	A	H	32.7 ± 3.8	7.3 ± 1.6	21.7 ± 0.7	11.3 ± 3.3
85	C	-	55.0 ± 12.6	66.7 ± 14.2	37.1 ± 6.8	38.6 ± 6.1
88	D	-	95.1 ± 12.4	92.0 ± 5.6	114.3 ± 8.6	118.9 ± 7.9
81a	B	H	71.4 ± 14.3	54.3 ± 9.0	46.8 ± 5.7	32.1 ± 2.9
79b	A	*o*-CO_2H	92.1 ± 5.9	84.5 ± 2.8	83.7 ± 3.1	102.6 ± 5.0
81b	B	*o*-CO_2H	91.8 ± 15.7	85.2 ± 2.4	94.1 ± 1.5	80.7 ± 1.7
79c	A	*m*-CO_2H	90.3 ± 4.3	70.0 ± 5.7	76.8 ± 3.7	61.4 ± 2.1
79d	A	*p*-CO_2H	89.7 ± 3.2	89.0 ± 6.0	85.2 ± 2.7	67.0 ± 11.0
81c	B	*p*-CO_2H	101.9 ± 4.3	95.8 ± 7.6	114.6 ± 6.1	92.6 ± 2.2
79e	A	*o*-OMe	105.0 ± 12.3	74.0 ± 18.3	61.7 ± 15.6	71.0 ± 9.3
79f	A	*m*-OMe	52.4 ± 10.2	24.9 ± 3.7	30.8 ± 4.9	29.9 ± 5.1
79g	A	*p*-OMe	42.7 ± 20.6	36.0 ± 6.6	39.6 ± 7.2	39.0 ± 10.0
79h	A	*o*-NO_2	80.5 ± 4.7	56.1 ± 7.8	35.1 ± 3.2	26.8 ± 3.4
79i	A	*m*-NO_2	50.5 ± 11.0	28.8 ± 5.5	24.4 ± 5.3	30.7 ± 7.0
79j	A	*p*-NO_2	47.4 ± 5.7	53.2 ± 6.7	43.3 ± 5.1	34.4 ± 2.0

[a]Compounds were tested by TEVC for activity at recombinant NMDA receptors (GluN1a and the indicated GluN2 subunit) expressed in Xenopus oocytes. After obtaining a steady state

NMDAR response evoked by 10 µM L-glutamate and 10 µM glycine, test compounds (100 µM) were co-applied with agonists. Values (mean ± s.e.m.) represent the % response in the presence of the test compound compared to response in the presence of agonists alone. Values >100 represent potentiation and those < 100 represent inhibition of the agonist response.

Table 6. IC_{50} (μM, n≥4) values for inhbition of GluN1/GluN2 NMDAR subtypes[a]

Compounds	GluN2A	GluN2B	GluN2C	GluN2D
7[b]	11.0 ± 5.2	97.8 ± 20.9	41.8 ± 8.4	49.6 ± 6.0
	(71.5 ± 6.4)	(56.8 ± 5.2)	(105.5 ± 4.4)	(98.6 ± 3.2)
79a	17.8 ± 4.6	7.5 ± 2.0	13.8 ± 3.3	8.6 ± 1.9
	(83.2 ± 11.4)	(93.9 ± 7.3)	(86.3 ± 4.7)	(93.6 ±4.2)
79h	6.0 ± 4.1	32.2 ± 16.0	8.2 ± 1.2	2.9 ± 0.4
	(30.5 ± 6.3)	(61.3 ± 18.1)	(80.1 ± 4.1)	(79.7 ± 2.8)
79i	9.7 ± 3.8	9.2 ± 5.3	7.9 ± 4.2	1.4 ± 0.4
	(49.7 ± 6.8)	(66.3 ± 5.2)	(74.4 ± 6.9)	(70.0 ± 4.6)
79j	5.8 ± 1.1	11.1 ± 2.9	6.5 ± 2.8	2.9 ± 0.3
	(54.1 ± 5.5)	(48.4± 6.0)	(55.9 ± 3.9)	(72.3 ± 2.1)

[a]IC_{50} values (mean ± s.e.m.) for the inhibition of GluN1/GluN2 NMDAR responses. Values in parenthesis are the percentage maximum inhibition (± s.e.m.) of the agonist response (L-glutamate, 10 μM and glycine, 10 μM).

[b]Values taken from Costa et al., 2012.

Figure 1 Structures of known NMDAR positive and negative allosteric modulators.

Figure 2 Potentiation of NMDAR responses by 2-naphthoic acid derivatives. Select PAMs identified in Table 1 were tested for activity at various concentrations to determine potency and efficacy. Compounds were tested on NMDA receptors containing GluN1a and the indicated GluN2 subunit expressed in *Xenopus* oocytes. After obtaining a steady state NMDAR response evoked by 10 µM L-glutamate and 10 µM glycine, test compounds were co-applied with agonists at various concentrations. Values (mean ± s.e.m.) represent the % potentiation of the response above the agonist-alone response.

Figure 3 Inhibition of NMDAR responses by 2-naphthoic acid derivatives. **A. 7**, **B. 79h**, **C. 79i**, **D. 79j**. NAMs described in Table 6 were tested for activity at various concentrations to determine inhibitory potency and the percentage of maximum inhibition. Compounds were tested on NMDA receptors containing GluN1a and the indicated GluN2 subunit expressed in *Xenopus* oocytes. After obtaining a steady state NMDAR response evoked by 10 µM L-glutamate and 10 µM glycine, test compounds were co-applied with agonists at various concentrations. Values (mean ± s.e.m.) represent the % response in the presence of the test compound compared to response in the presence of agonists alone.

Figure 4 79h does not compete with L-glutamate or glycine at NMDARs. 30 µM **79h** did not display reduced inhibition of GluN1/GluN2C (blue) and GluN1/GluN2D (gray) NMDAR responses evoked by high concentrations of agonists (300 µM glutamate / 300 µM glycine; dark blue/gray) than by low agonist concentrations (10 µM glutamate / 10 µM glycine; light blue/gray).

Figure 1

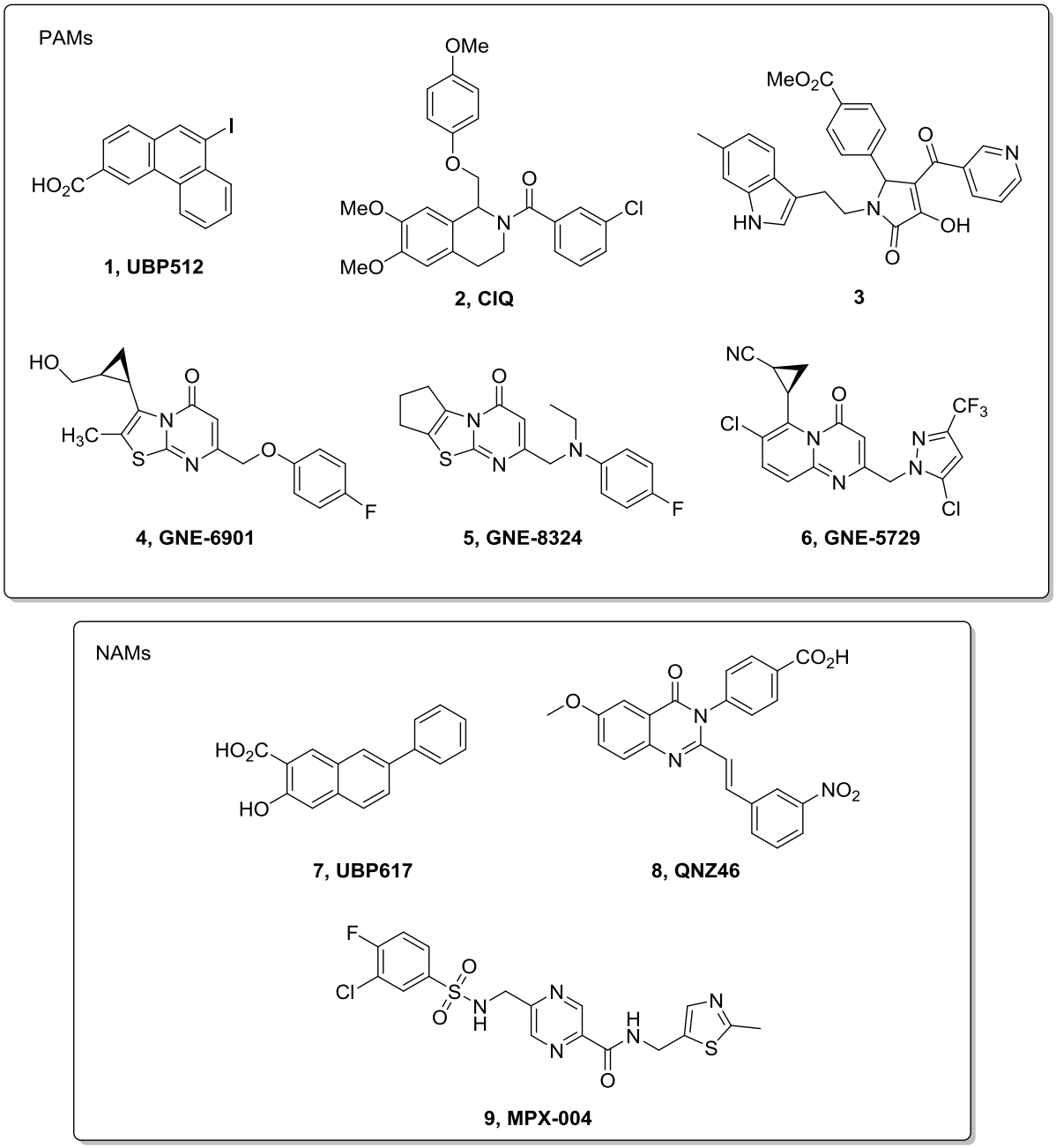

PAMs
1, UBP512
2, CIQ
3
4, GNE-6901
5, GNE-8324
6, GNE-5729
NAMs
7, UBP617
8, QNZ46
9, MPX-004

Figure 2

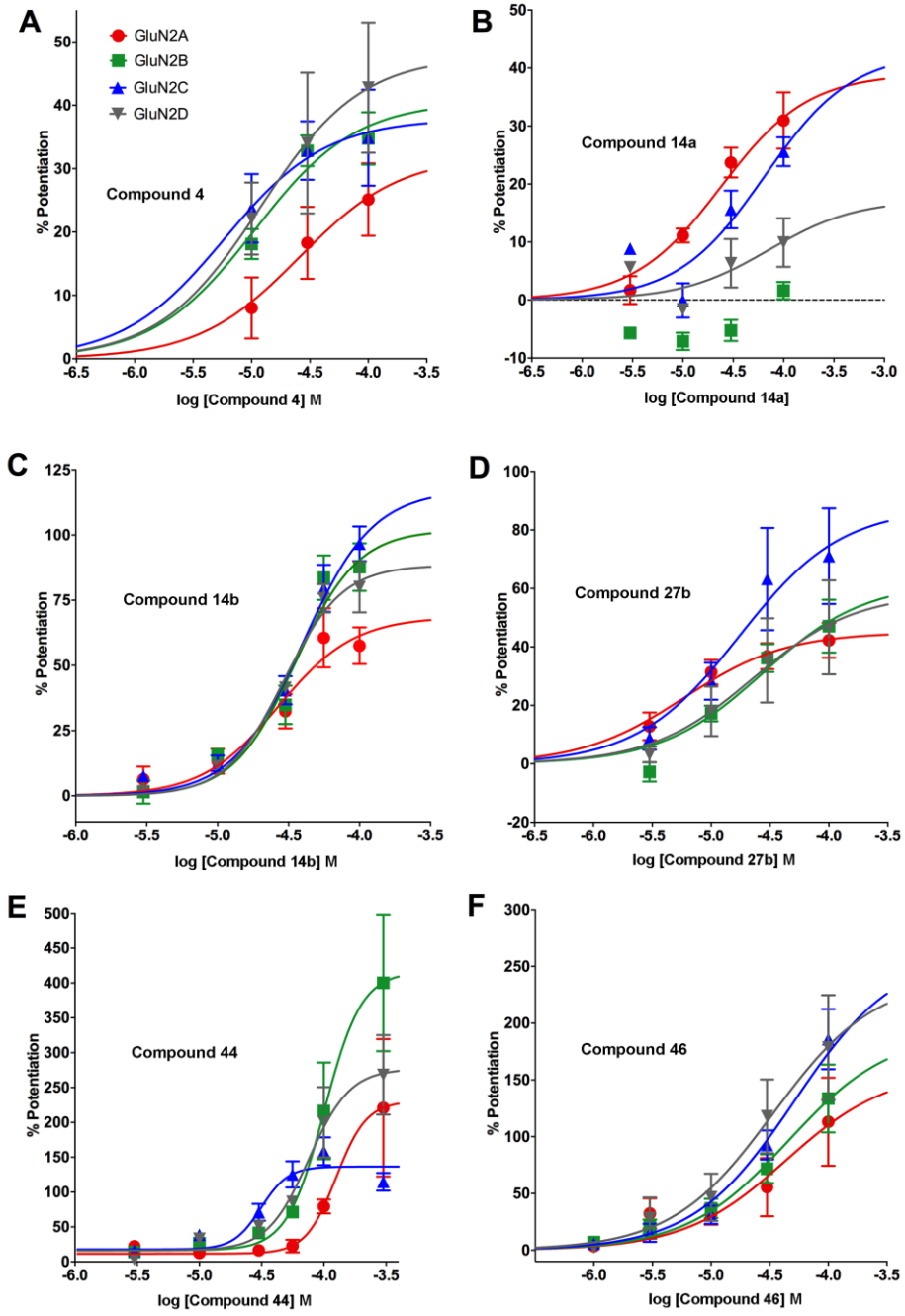

A
GluN2A
GluN2B
GluN2C
GluN2D
Compound 4
% Potentiation
log [Compound 4] M
B
Compound 14a
% Potentiation
log [Compound 14a]
C
Compound 14b
% Potentiation
log [Compound 14b] M
D
Compound 27b
% Potentiation
log [Compound 27b] M
E
Compound 44
% Potentiation
log [Compound 44] M
F
Compound 46
% Potentiation
log [Compound 46] M

Figure 3

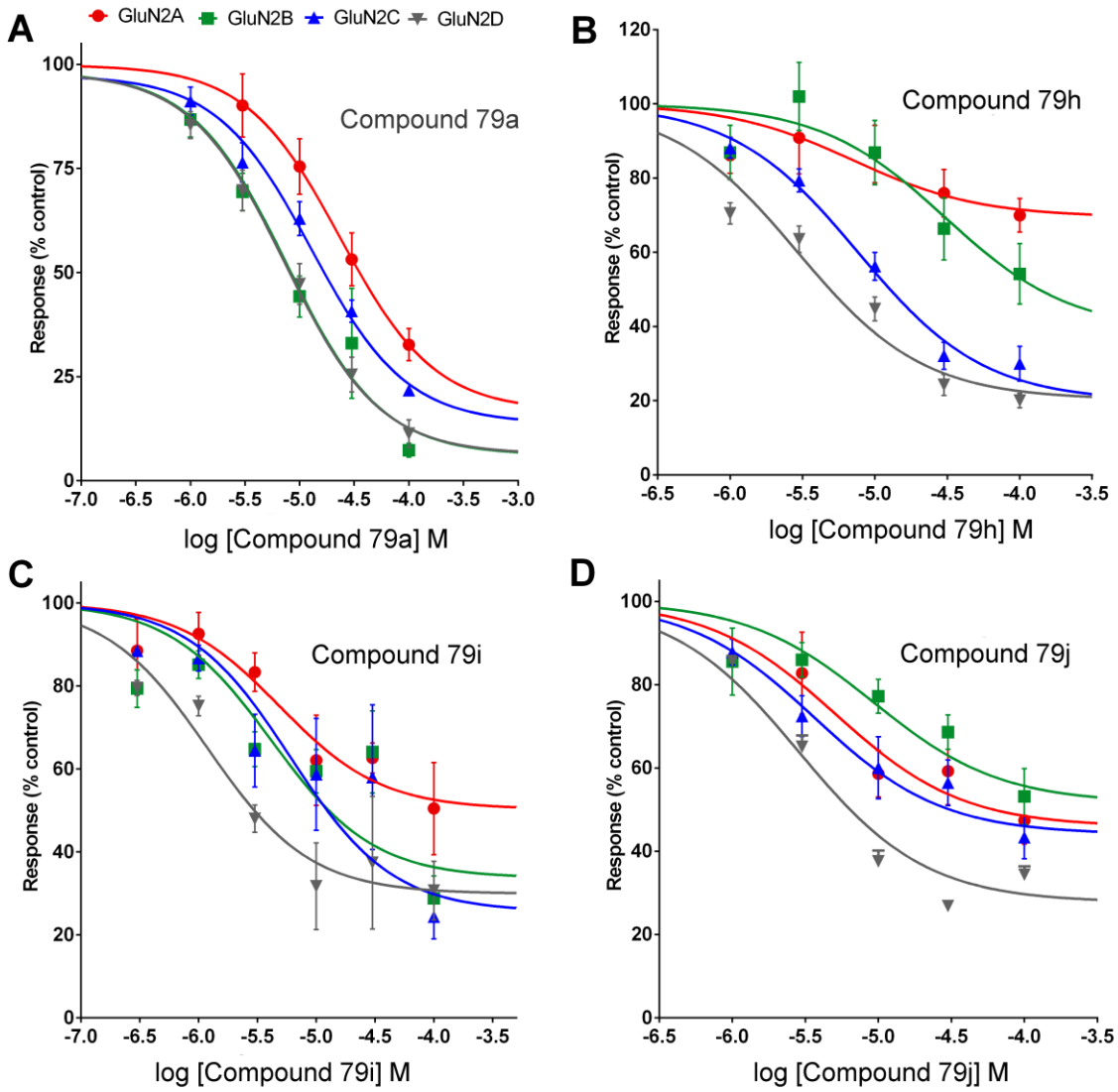
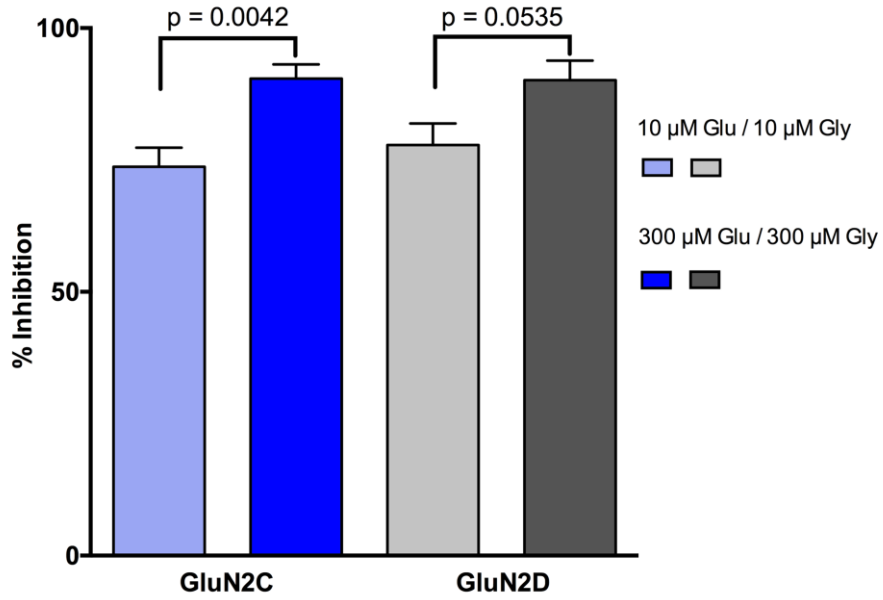
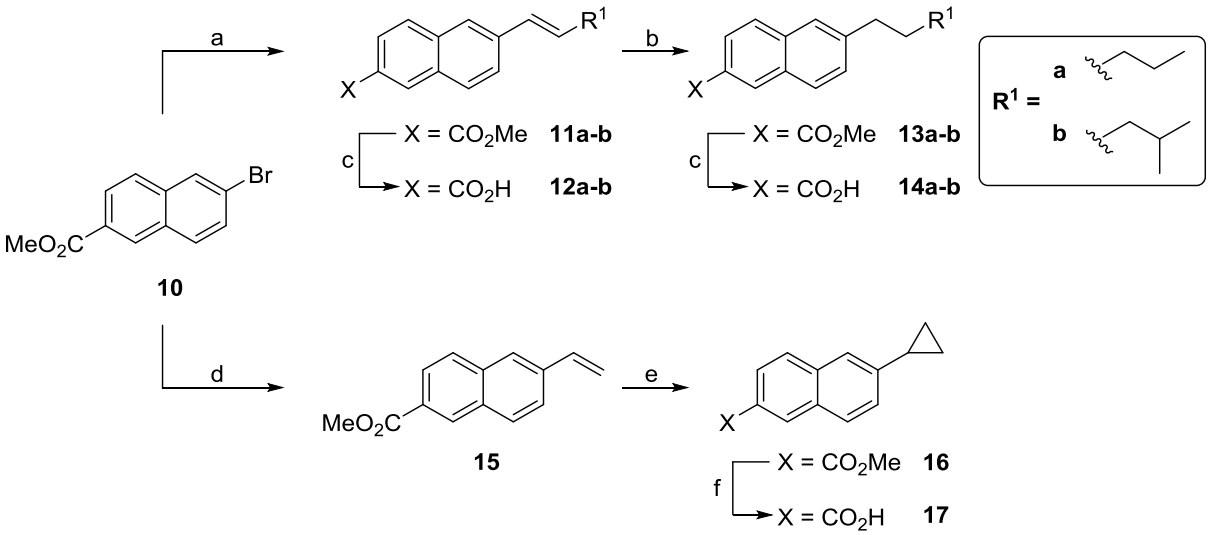

A
GluN2A
GluN2B
GluN2C
GluN2D
Compound 79a
Response (% control)
log [Compound 79a] M
B
Compound 79h
Response (% control)
log [Compound 79h] M
C
Compound 79i
Response (% control)
log [Compound 79i] M
D
Compound 79j
Response (% control)
log [Compound 79j] M

Figure 4

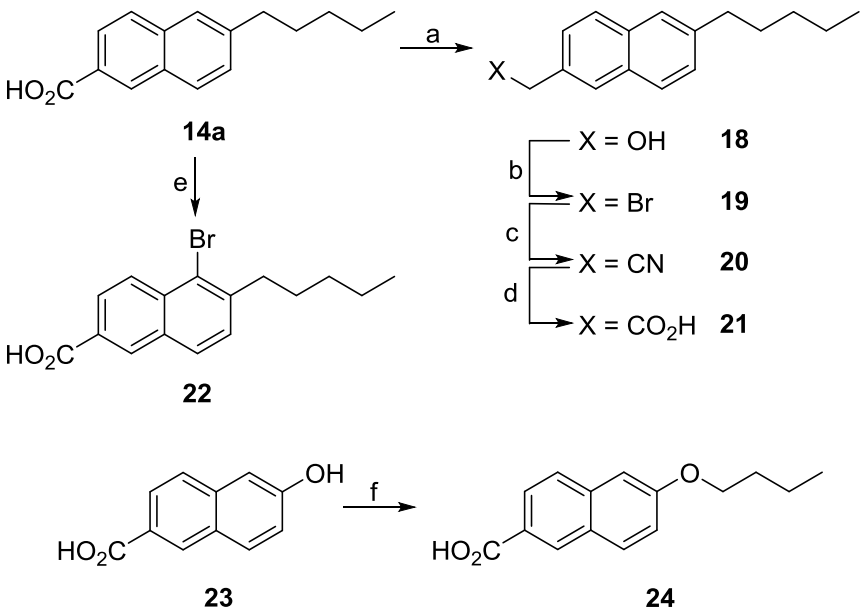

p = 0.0042
p = 0.0535
100
50
0
% Inhibition
GluN2C
GluN2D
10 µM Glu / 10 µM Gly
300 µM Glu / 300 µM Gly

Scheme 1[a]



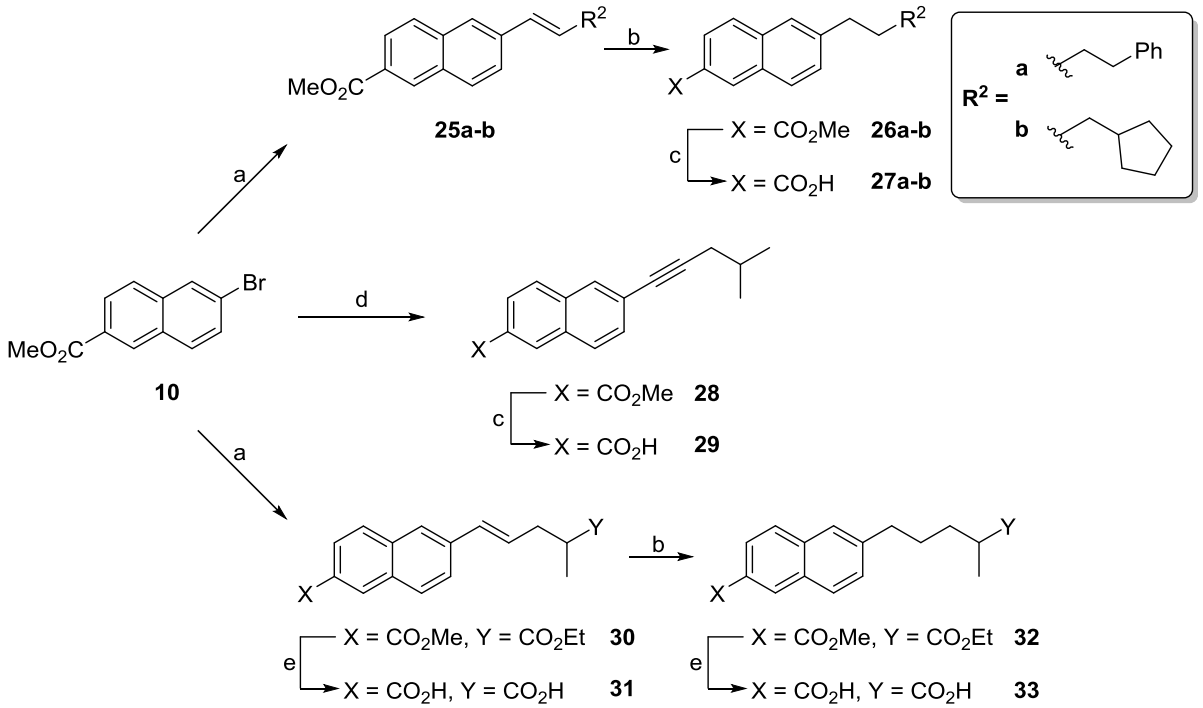
[a]Reagents and conditions: (a) Alkene, P(*o*-tolyl)$_3$, TEA, Pd(OAc)$_2$, DMF, 100 ^{o}C, 18 h; (b) H_2, 10% Pd/C, rt, 18 h; (c) (i) LiOH or NaOH (aq), THF, 65 ^{o}C or dioxane, 80 ^{o}C, (ii) 1 M HCl (aq); (d) (*n*-Bu)$_3$SnCH=CH$_2$, Pd(PPh$_3$)$_4$, toluene, reflux, 4 h; (e) CH_2I_2, Et_2Zn, DCM, 0 ^{o}C, 18 h; (f) (i) NaOH (aq), THF/H_2O, rt, 18 h, (ii) 1 M HCl (aq).

Scheme 2[a]



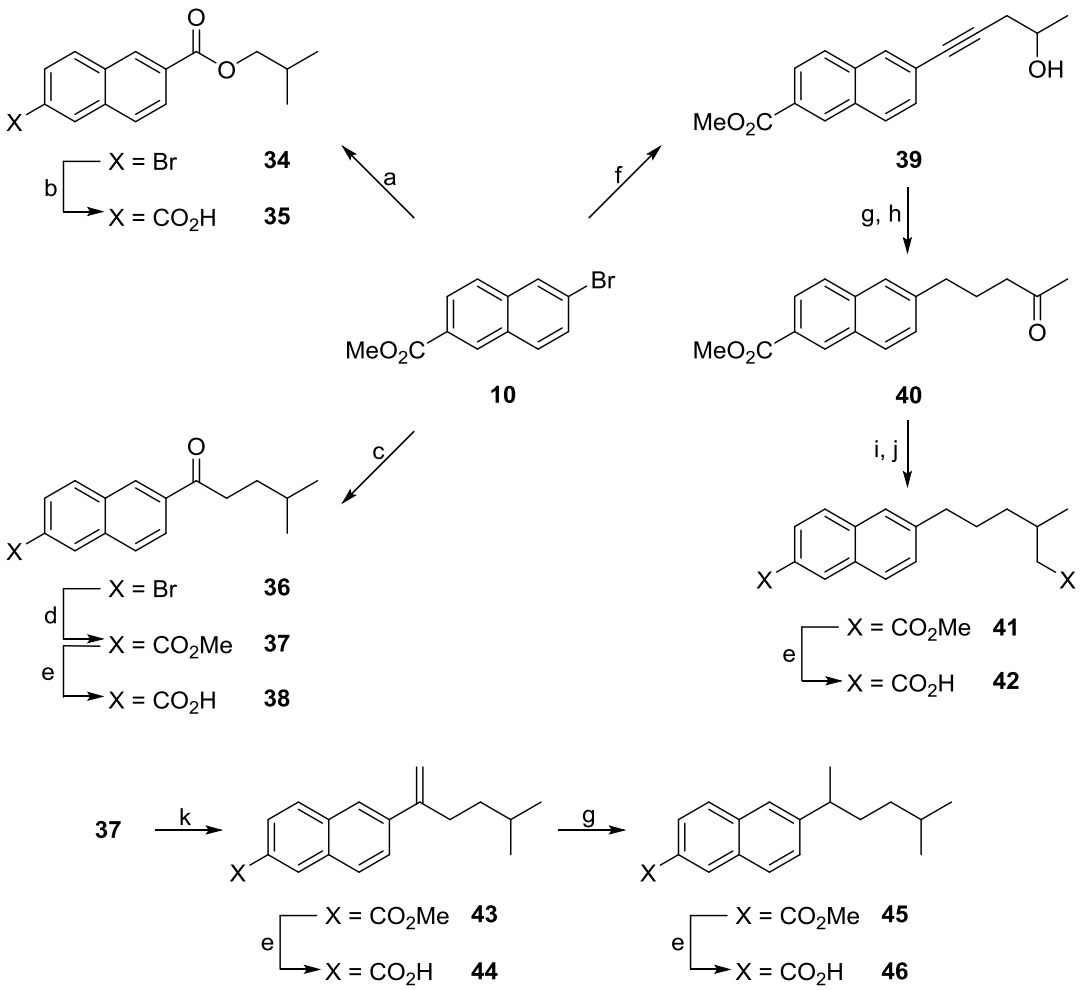
[a]Reagents and conditions: (a) $LiAlH_4$, THF, 0 ^oC then 65 ^oC, 4 h; (b) PBr_3, 0 ^oC then rt, 1 h; (c) NaCN, TBAB, H_2O/DCM (1:1), rt, 48 h; (d) H_2SO_4, AcOH/H_2O (1:1), 118 ^oC, 18 h; (e) Br_2, AcOH, 50 ^oC; (f) (i) 1-Bromobutane, NaOH, EtOH/H_2O (3:1), 78 ^oC, 18 h, (ii) 10% NaOH, 78 ^oC, 2 h, (iii) 2 M HCl (aq).

Scheme 3[a]



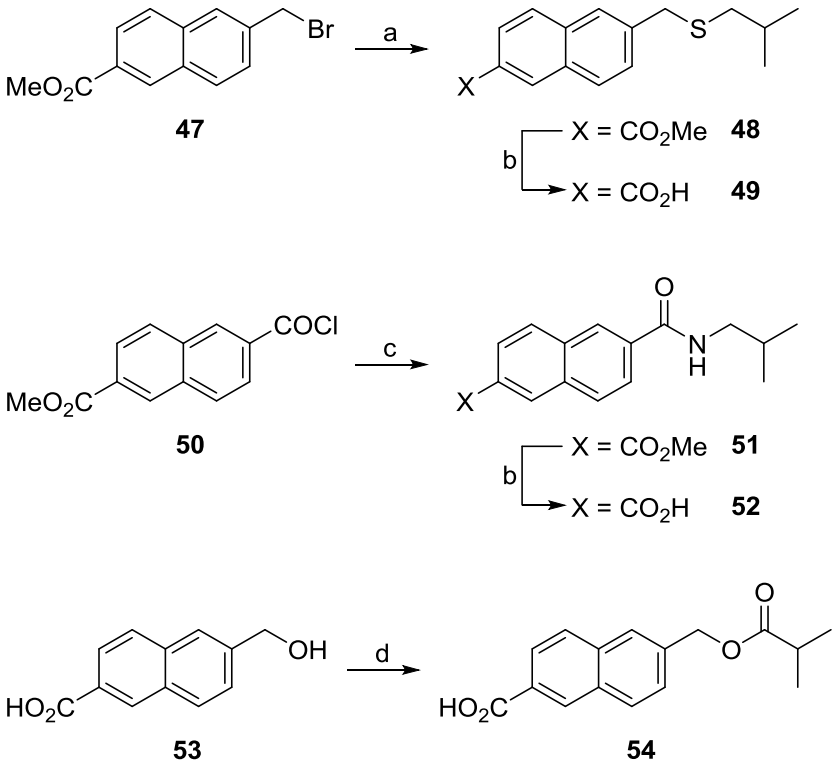
[a]Reagents and conditions: (a) Alkene, P(*o*-tolyl)$_3$, TEA, Pd(OAc)$_2$, DMF, 100 ^{o}C, 18 h; (b) H_2,10% Pd/C, rt, 18 h; (c) (i) NaOH, THF/H_2O, 65 ^{o}C, (ii) 1 M HCl (aq); (d) 4-methylpent-1-yne, $NHEt_2$, CuI, $Pd(Ph_3)_2Cl_2$, THF, 50 ^{o}C, 18 h; (e) (i) LiOH, dioxane/H_2O, rt, 18 h, (ii) 1 M HCl (aq); (f) (i) NaOH, dioxane/H_2O, rt, 18 h, (ii) 1 M HCl (aq).

Scheme 4[a]



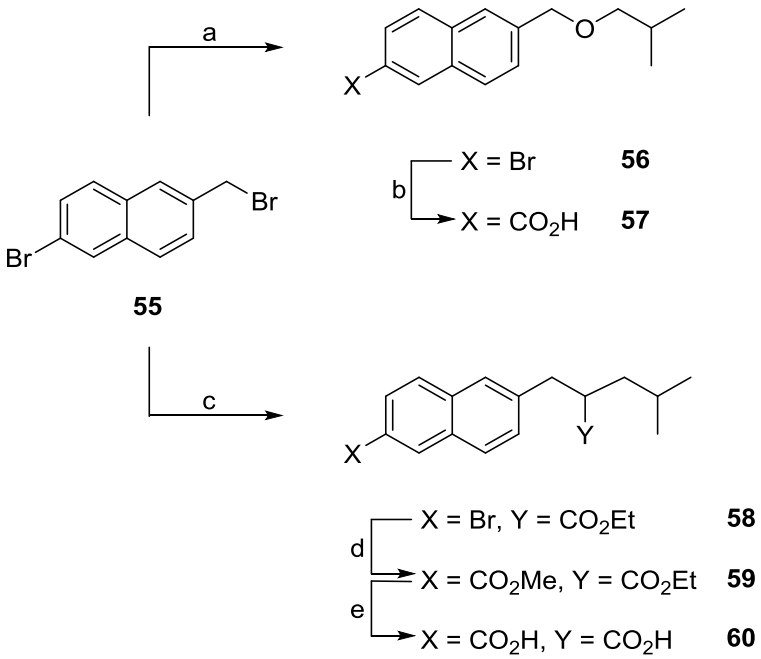
[a]Reagents and conditions: (a) Isobutanol, H_2SO_4, reflux, 18 h; (b) CO, DPPP, NEt_3, $Pd(OAc)_2$, H_2O/DMF, 85 ^oC, 24 h; (c) (i) ethyl 4-methylvalerate, LiHMDS, THF, -78 ^oC then rt 3 h, (ii) 1 M NaOH (aq), 50 ^oC, 18 h, (iii) conc HCl (aq), 60 ^oC, 1 h; (d) CO, DPPP, NEt_3, $Pd(OAc)_2$, MeOH/DMF, 90 ^oC, 18 h; (e) (i) LiOH, dioxane/H_2O, rt, 18 h, (ii) 1 M HCl (aq); (f) 4-pentyn-2-ol, NEt3, CuBr, $Pd(PPh_3)4$, 65 ^oC, 18 h; (g) H_2, 10% Pd/C, EtOH, rt, 1 h; (h) DMP, DCM, rt, 2 h; (i) methyl diethylphosphonoacetate, KHMDS, THF, 0 ^oC 1 h then rt 4 h; (j) H_2, 10% Pd/C, EtOH, rt, 1 h; (k) CH_3PPh_3Br, KHMDS, THF, -78 ^oC 1 h then rt 2 h.

Scheme 5[a]



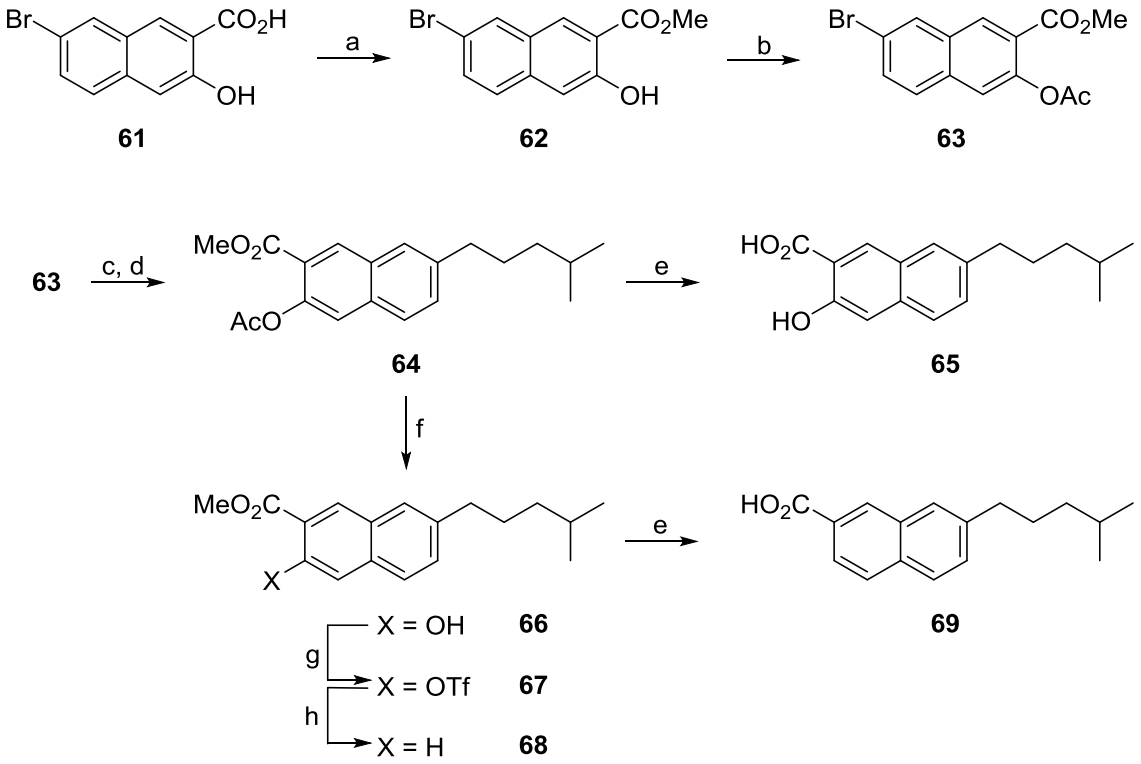
[a]Reagents and conditions: (a) 2-Methylpropan-1-thiol, Na, EtOH; (b) (i) LiOH, dioxane/H_2O, rt, 18 h, (ii) 1 M HCl (aq); (c) Isobutylamine, NEt_3, DCM, 0 ^oC then rt, 18 h; (d) Isobutyryl chloride, NEt_3, DCM, 0 ^oC then rt, 1 h, (ii) 2 M $NaHCO_3$ (aq), 0 ^oC, 3 h, (iii) 1 M HCl (aq).

Scheme 6[a]



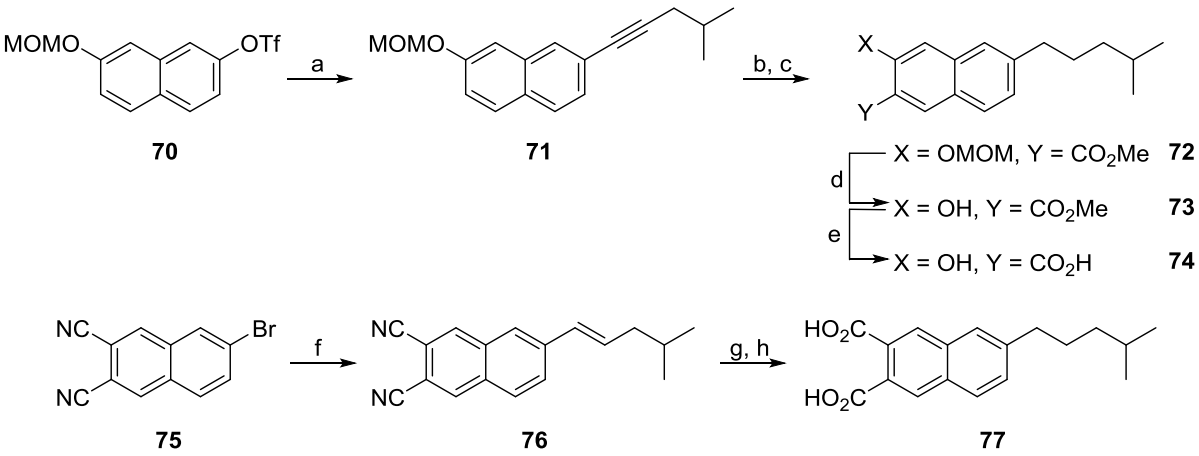
[a]Reagents and conditions: (a) 2-Methylpropan-1-ol, Na, DMF, rt, 7 h; (b) CO, DPPP, NEt_3, $Pd(OAc)_2$, H_2O/DMF, 85 ^oC, 24 h; (c) ethyl 4-methylvalerate, KHMDS, THF, -78 ^oC 0.5 h then rt, 18 h; (d) CO, DPPP, NEt_3, $Pd(OAc)_2$, MeOH/DMF, 80 ^oC, 18 h; (e) (i) LiOH, dioxane/H_2O, rt, 18 h, (ii) 1 M HCl (aq).

Scheme 7[a]



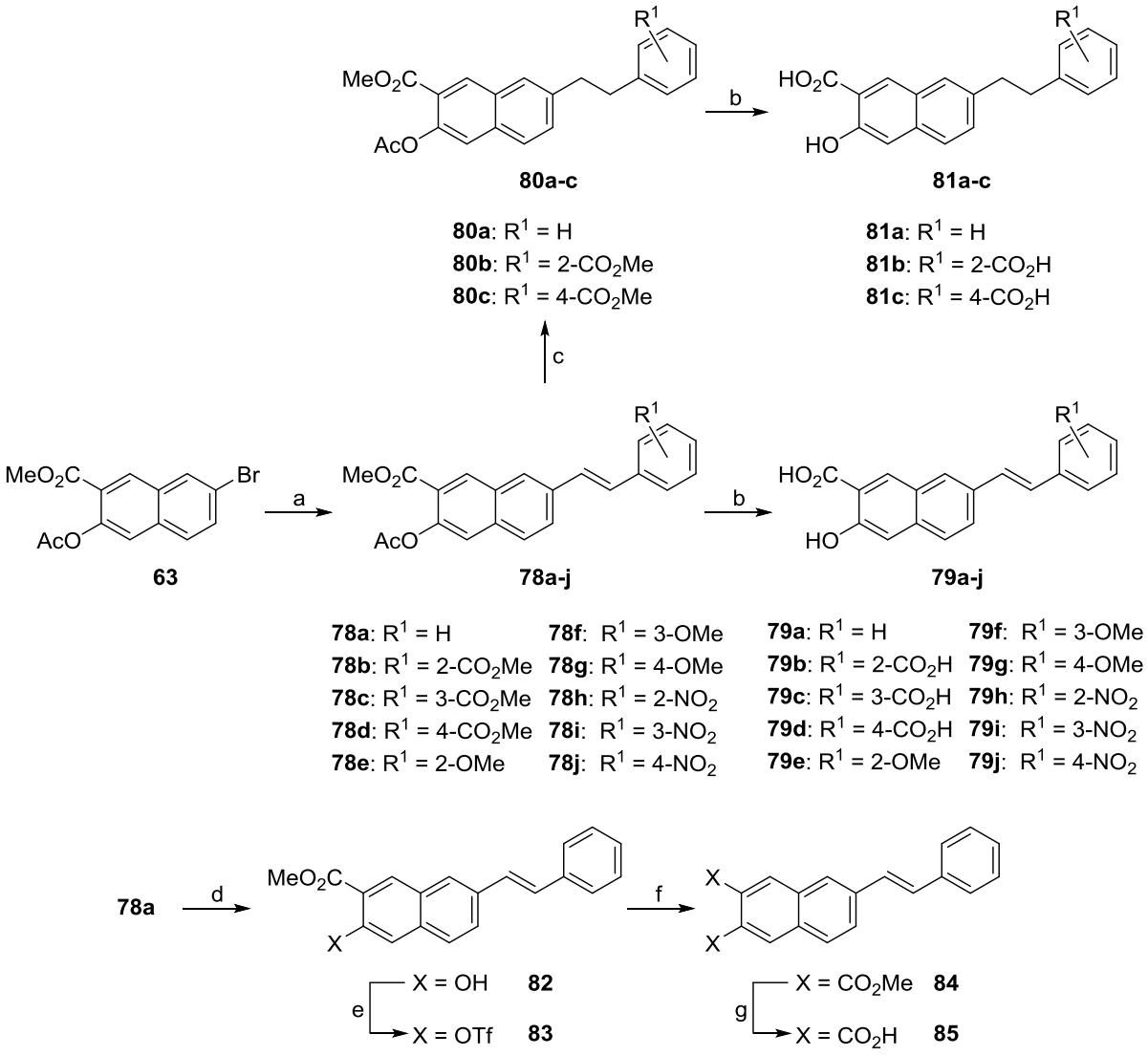
[a]Reagents and conditions: (a) MeI, K_2CO_3, DMF, rt, 12 h; (b) Ac_2O, TEA, DMAP, DCM, rt, 12 h; (c) 4-methylpent-1-ene, P(*o*-tolyl)$_3$, Pd(OAc)$_2$, NEt_3, DMF, 100 ^oC, 18 h; (d) H_2, 10% Pd/C, EtOH, rt, 1 h; (e) (i) LiOH, dioxane/H_2O, rt, 18 h, (ii) 1 M HCl (aq); (f) $(CH_3)_2NH$, MeOH, 0 ^oC then rt 1 h; (g) Tf_2O, NEt_3, DCM, -10 ^oC, 2 h; (h) HCOOH, NEt_3, Pd$(PPh_3)_4$, DMF, 80 ^oC, 18 h.

Scheme 8[a]



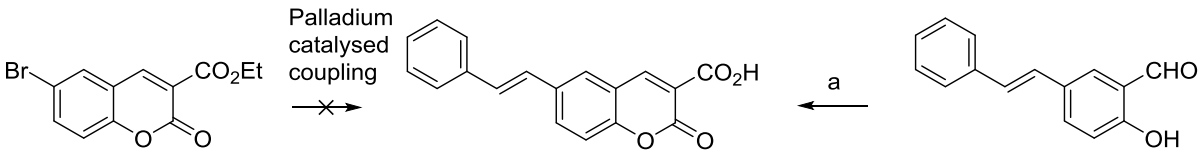
[a]Reagents and conditions: (a) 4-Methylpent-1-yne, $NHEt_2$, CuI, $Pd(PPh_3)_2Cl_2$, 45 ^oC, 18 h; (b) H_2, 10% Pd/C, rt, 18 h; (c) (i) *t*-BuLi, 0 ^oC, 1h, (ii) methyl chloroformate, -78 ^oC then rt 1h; (d) 2 M HCl (aq), MeOH; (e) (i) LiOH, dioxane/H_2O, rt, 18 h, (ii) 1 M HCl (aq); (f) 4-Methylpent-1-ene, P(*o*-tolyl)$_3$, $Pd(OAc)_2$, NEt_3, DMF, 100 ^oC, 18 h; (g) H_2SO_4, AcOH/H_2O (3:1), 118 ^oC, 24 h; (h) H_2, 10% Pd/C, EtOAc, rt, 18 h.

Scheme 9[a]



[a]Reagents and conditions: (a) Styrene, P(*o*-tolyl)$_3$, NEt$_3$, Pd(OAc)$_2$, DMF, 100 ^{o}C, 18 h; (b) (i) NaOH (aq), THF/H$_2$O, reflux or dioxane/H$_2$O, rt, (ii) 2 M HCl (aq); (c) H$_2$, 10% Pd/C, THF or dioxane, rt, 18 h; (d) NHMe$_2$, 0 ^{o}C, 2 h; (e) Tf$_2$O, NEt$_3$, DCM, -10 ^{o}C, 2 h; (f) CO, DPPP, NEt$_3$, Pd(OAc)$_2$, MeOH/DMF, 80 ^{o}C, 24 h; (g) (i) LiOH, dioxane/H$_2$O, rt, 18 h, (ii) 1 M HCl (aq).

Scheme 10[a]



86 **88** **87**

[a]Reagents and conditions: (a) Meldrum's acid, piperidinium acetate, EtOH, rt 20 min, then reflux 2 h.

TOC Graphic

Figure(s)

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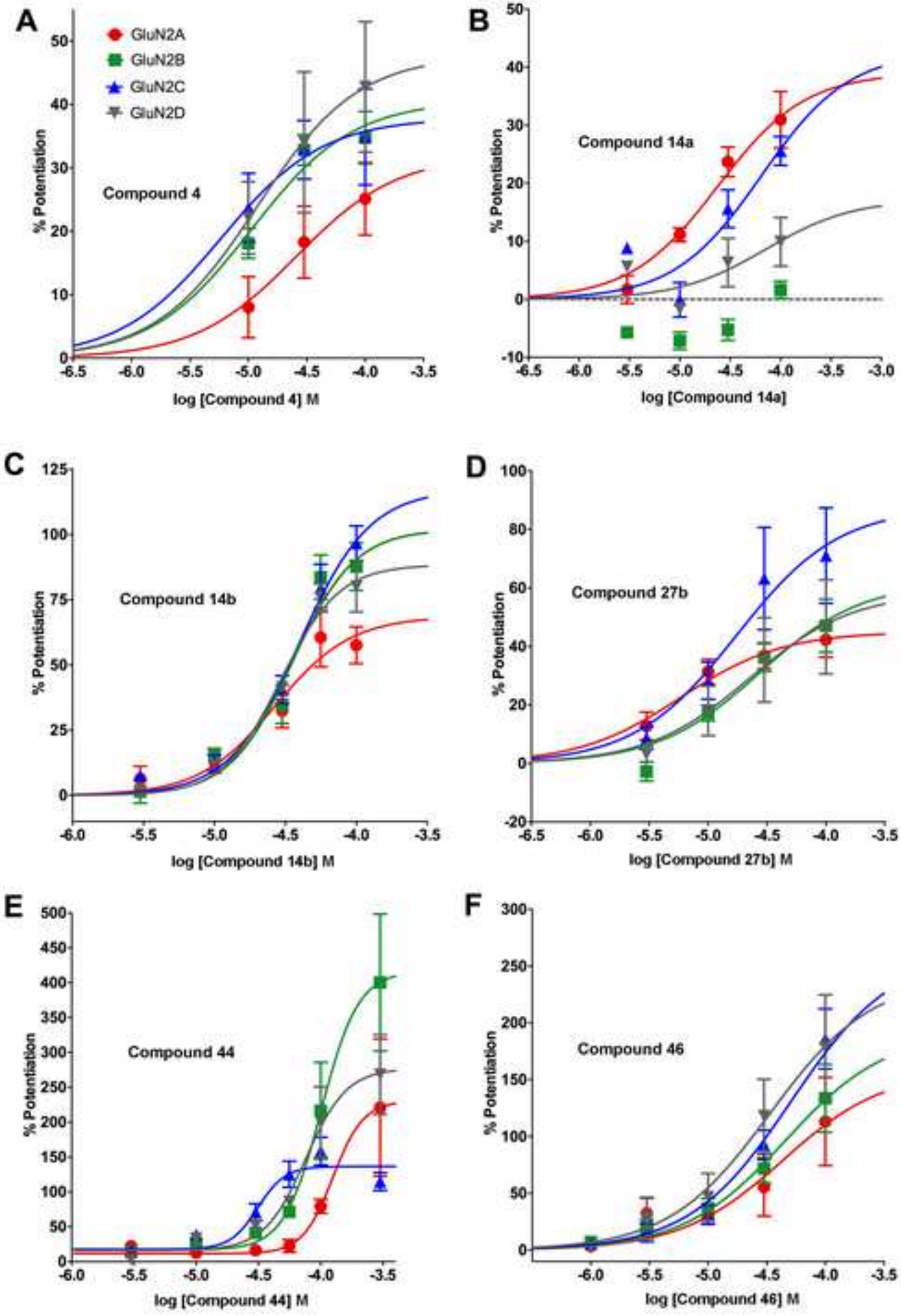

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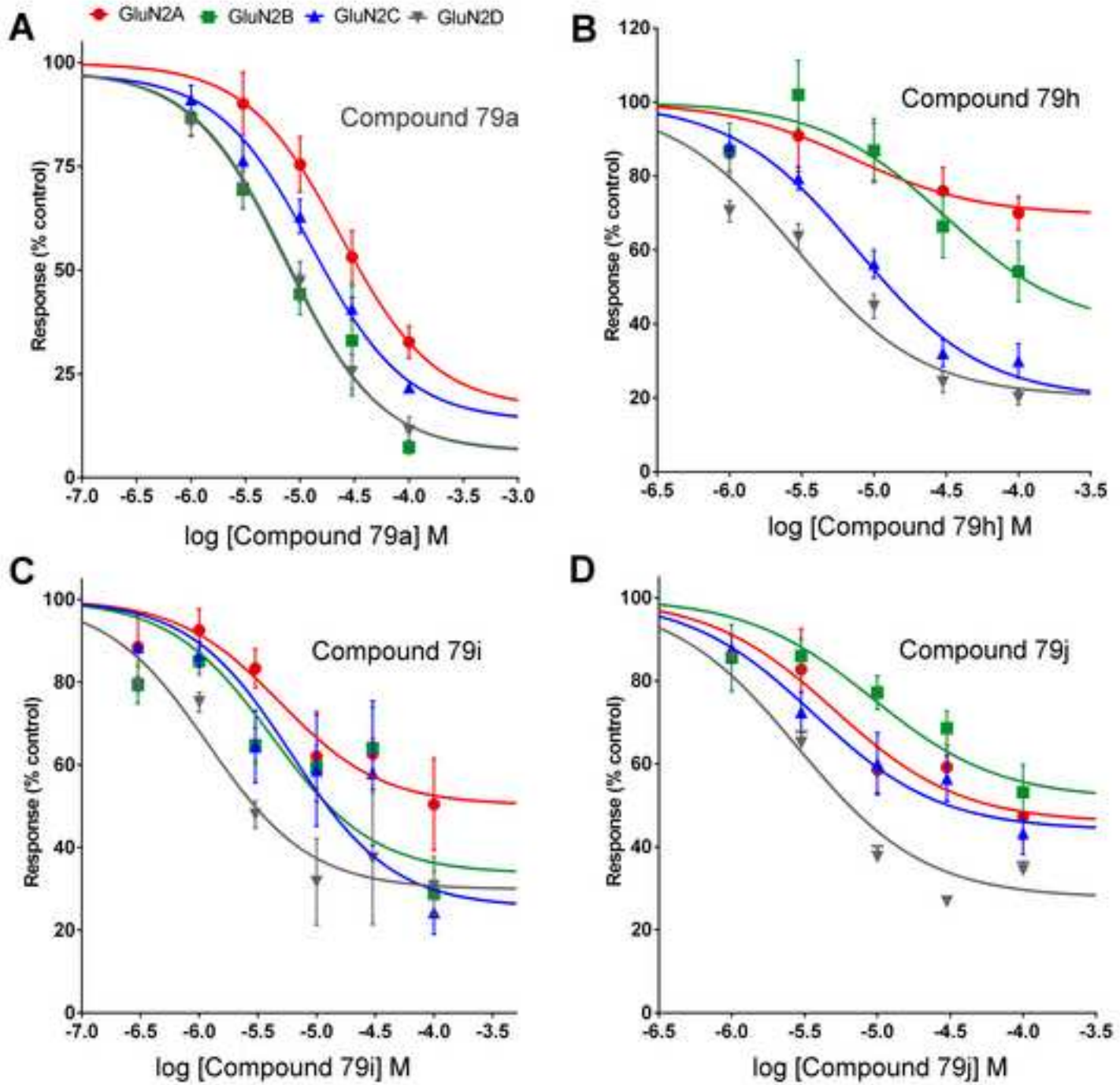

Figure(s)

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