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Synthesis of a Series of Novel 3,9-Disubstituted Phenanthrenes as Analogues of Known NMDA Receptor Allosteric Modulators

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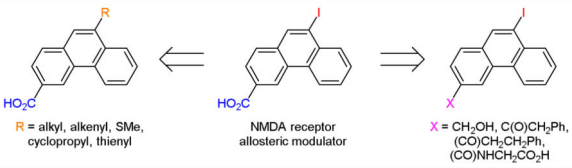
Abstract

9-Substituted phenanthrene-3-carboxylic acids have been reported to have allosteric modulatory activity at the NMDA receptor. This receptor is activated by the excitatory neurotransmitter L-glutamate and has been implicated in a range of neurological disorders such as schizophrenia, epilepsy and chronic pain and neurodegenerative disorders such as Alzheimer's disease. Herein, the convenient synthesis of a wide range of novel 3,9-disubstituted phenanthrene derivatives starting from a few common intermediates is described. These new phenanthrene derivatives will help to clarify the structural requirements for allosteric modulation of the NMDA receptor.

Graphical abstract

3,9-Disubstituted Phenanthrenes



Keywords

Phenanthrenes; NMDA receptor; allosteric modulators; palladium coupling; Wittig reaction

Phenanthrene is a naturally occurring polycyclic aromatic ring system which is found in a number of biologically active compounds.[2] Recently, we reported that phenanthrene derivatives such as **1**, **2**, and **3** (Figure 1) are allosteric modulators of the *N*-methyl-*D*-

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aspartate (NMDA) family of ionotropic glutamate receptors (*i*-GluRs).[3] NMDA receptors are tetrameric ligand-gated ion channels comprised of GluN1 and GluN2A-D subunits.[3] NMDA receptors have been implicated in a range of neurological disorders such as epilepsy, schizophrenia and chronic pain and neurodegenerative disorders such as ischaemia, Alzheimer's disease and Parkinson's disease.[3] Allosteric modulators have potential to treat these disorders, as they are less likely to interfere with the physiological roles of NMDA receptors compared to competitive antagonists or channel blockers.[3] A convenient synthetic route for 3-carboxyphenanthrenes with a wide range of hydrophobic and hydrophilic substituents at the 9-position was required to conduct a structure-activity relationship (SAR) study surrounding allosteric modulators **1**-**3**. A search of the literature revealed that with the exception of the 9-bromo, 9-chloro, and 9-carboxy derivatives, no 9-subtituted-3-carboxyphenanthrenes have previously been reported.[4,5] Herein, we report the synthesis of **1**-**3** and a novel series of their derivatives starting from a few common intermediates.

Initial studies suggested that 9-iodophenanthrene-3-carboxylic acid (**1**) had an interesting pharmacological profile[3] and so we investigated suitable methods for larger scale production of this compound. We recently reported a 2-step route to **1** in which an aromatic Finkelstein reaction[6] was utilized to convert 3-acetyl-9-bromophenanthrene (**4**) to its corresponding 9-iodo analogue (**9**).[7] A haloform reaction was then employed to oxidize the acetyl group and give the desired acid (Scheme 1). However, whilst our initial experiments led to complete conversion, subsequent attempts to resynthesize **9** led only to in-separable mixtures of **4** and **9** being isolated. Despite investigation (e.g. different amine ligands, alternative solvents, purification of copper (I) iodide catalyst), the exact reason for the non-reproducibility of the aromatic Finkelstein reaction could not be determined. With the halogen conversion route proving unreliable an alternative and robust pathway to **1** was sought. Unfortunately, attempts to directly iodinate the 9-position of phenanthrene-3-carboxylic acid (**5**) using either iodine monochloride or sodium iodide and sodium hypochlorite (Scheme 2) led only to the recovery of un-reacted starting material. As a consequence, we decided to focus on developing an alternative route to ketone **9**. The most obvious route to this compound is via Friedel-Crafts acylation. However, whilst Friedel-Crafts acylation can be used to synthesize the 3-acetyl derivatives of both 9-bromo and 9-chlorophenanthrene we found that employing the same reaction conditions on 9-iodophenanthrene (**6**) led only to the isolation of a black tar (Scheme 2).[4,5] Attempts to modify the reaction conditions by using aluminum iodide instead of aluminum chloride or acetic anhydride instead of acetyl chloride led only to the same outcome. With all previous routes proving unsuccessful we decided to investigate lithiation as a possible way of introducing the iodo substituent (Scheme 1). After protecting ketone **4** as an acetal (**7**), lithiation at the 9-position followed by quenching with (n-Bu)$_3$SnCl afforded stannane **8**. The 9-iodo group was then readily introduced by stirring with a saturated solution of iodine in DCM at 0 °C. Subsequent de-protection gave ketone **9** which was then easily converted to **1** using the haloform reaction described previously. In theory, the iodo group could have been introduced by quenching the lithiated species with iodine. However, we were concerned that employing this route would lead to the formation of side products which could not be easily separated from the desired product. Whilst it added an additional step, utilizing stannane **8** allowed **1** to be synthesized both cleanly and in high yield.

Attention was then turned to the synthesis of a structurally diverse series of 3-carboxyphenanthrenes bearing hydrophobic substituents at the 9-position as analogues of compounds **1**-**3**. Amongst the initial group of compounds generated was thioether **12** which was synthesized using an identical strategy to that described for **1** with the exception that after being lithiated, acetal **7** was quenched with dimethyl disulfide (Scheme 1). De-protection subsequently afforded acetyl **11** which was then readily converted to carboxylic acid **12** using a haloform reaction.

In addition to thioethers, compounds bearing alkyl substituents at the 9-position were synthesized. Initial attempts to generate these derivatives by reacting alkyl aldehydes with lithiated acetal **7** gave only a complex mixture of products. Consequently, an alternative route was devised to allow a range of alkyl chains to be introduced using common intermediates, which could be prepared both quickly and in high yield. With this in mind, the 9-formyl (**15**) and 9-bromo (**16**) substituted phenanthrenes were chosen as both functional groups could be easily manipulated using either Wittig or palladium coupling chemistry to afford a large variety of 9-alkylphenanthrenes from commercially available reagents. Both **15** and **16** were conveniently prepared from 9-bromo acid **13** (Scheme 3A).[7] Heck coupling of **13** with methyl acrylate followed by esterification with methyl iodide afforded di-ester **14**. Oxidation of alkene **14** using osmium tetroxide and cleavage of the resultant 1,2-diol with sodium periodate afforded the 9-formyl derivative **15**. Methyl ester **16** was generated in good yield by Fisher esterification of acid **13**.[4] Conducting either Wittig or Heck chemistry on **15** and **16** proceeded smoothly and led to the synthesis of alkene intermediates **17a-i** which, in the majority of cases, were hydrogenated immediately to their corresponding alkyl counterparts **18a-i** (Scheme 3B). Base hydrolysis subsequently afforded the desired 9-alkyl-3-carboxyphenanthrenes (**3**, **19a-d**, **f-h**, **j**). The 9-cyclopropyl derivative **2** was synthesized from vinyl **17a** in 2-steps. Firstly, the cyclopropyl ring was formed via a Simmons-Smith reaction to give **20**. Base hydrolysis of the ester subsequently afforded the desired acid (**2**). Initially, alkene **17a** was prepared from **15** via Wittig chemistry. Although this route proved successful we found that the compound was more conveniently prepared via Stille coupling between **16** and (tri-*n*-butyl)vinyl tin (Scheme 3B).

To investigate the introduction of a heteroaromatic moiety, Suzuki coupling was employed to react **16** and 3-thienyl boronic acid (Scheme 3B). Unfortunately, this reaction did not go to completion and led to a mixture of product and starting material (**21** and **16**) being isolated (~75:25 by ^{1}H-NMR). Despite investigation of different solvent systems it was not possible to separate the individual esters by silica gel chromatography. Consequently, the mixture was taken forward and hydrolyzed using base. By conducting multiple re-crystallizations from glacial acetic acid we were able to separate the mixture of acids and obtain a pure sample of **22** (Scheme 3B).

Synthesis of the branched 9-isopropyl derivative (**30**) required a different strategy to that described above (Scheme 4). This strategy had the added advantage of generating two intermediates (**24** and **28**) that could be pharmacologically characterized. Starting from diester **14**, 1,4-conjugate addition of methyl magnesium chloride afforded **23** in reasonable yield. Whilst a small amount of this compound was hydrolyzed with base to di-acid **24**, the

majority was reacted with 2-tosyl-3-phenyloxaziridine[8] to generate alcohol **25** (Scheme 4). Reduction of the alkyl ester with lithium borohydride and cleavage of the resultant 1,2-diol with sodium periodate led to the synthesis of aldehyde **26**. Reduction of the aldehyde with sodium borohydride gave alcohol **27** in good yield. A small amount of this ester was hydrolyzed to the corresponding acid, **28**, using base (Scheme 4). Alcohol **27** was then converted to the corresponding mesylate by reaction with methanesulfonyl chloride. The mesylate was then in turn converted to the corresponding iodo derivative via a Finkelstein reaction. Subsequent hydrogenation led to dehalogenation and yielded the 9-isopropyl derivative **29** which was readily hydrolyzed to the desired acid **30** (Scheme 4).

In addition to its use in the previously described Wittig chemistry, aldehyde **15** was utilized as a starting point for the synthesis of the 9-methyl derivative **35** (Scheme 5). Reduction of the aldehyde using sodium borohydride afforded 9-hydroxymethyl derivative **31**. Although a small portion of this compound was hydrolyzed to yield acid **32** for pharmacological characterization, the majority was taken forward and reacted with phosphorus tribromide to afford 9-bromomethyl **33**. Hydrogenation subsequently afforded 9-methyl derivative **34** which was readily hydrolyzed to the corresponding acid **35** (Scheme 5).

Whilst the introduction of hydrophobic substituents was our primary focus, we decided to synthesize some compounds with more polar groups at the 9-position in order to gather additional data on the requirements for biological activity. For example, aldehyde **15** was reacted with isopropylamine via reductive amination to afford ester **36** which was subsequently hydrolyzed to acid **37** (Scheme 5). Similarly, alkene **14** was hydrogenated to afford alkyl di-ester **38** which was then hydrolyzed to di-acid **39** (Scheme 6).

To identify the optimal 3-position substituent for biological activity, the 3-carboxy group in **1** was subjected to chemical modification (Scheme 7). Interestingly, attempts to reduce this moiety using lithium aluminium hydride led not only to reduction of the desired group but also de-halogenation. Consequently, a pathway was devised in which the acid chloride of **1** was generated via reaction with thionyl chloride and then reduced under mild conditions using sodium borohydride (Scheme 7). This route was successful and led to the synthesis of 3-hydroxymethyl **40** in good yield. Reaction of **40** with phosphorus tribromide afforded 3-bromomethyl **41** which was in turn converted to the corresponding nitrile **42** by reaction with sodium cyanide under phase transfer conditions. Hydrolysis of the nitrile under acidic conditions yielded the 3-acetic acid derivative **43** (Scheme 7).[9]

In a further modification to the 3-position, the acid chloride of **1** was reacted with benzylamine, phenethylamine and the *t*-butyl ester of glycine to afford amides **44a-b** and **45** (Scheme 8). De-protection of the *t*-butyl ester to afford acid **46** was achieved readily and in good yield by reaction with TFA (Scheme 8).

A previously described electrophysiological assay on GluN1 and GluN2A-D subunits individually expressed in Xenopus oocytes[3] was used to pharmacologically characterize a selection of the synthesized phenanthrenes. The compounds were tested at a concentration of 100 μM for their effects on GluN1/GluN2A-D receptor responses and percentage antagonism or potentiation of responses to glutamate (10 μM) and glycine (10 μM) was

determined (Table 1). Whilst only preliminary, these data suggest that: (a) an alkyl substituent at the 9-position promotes NMDA receptor potentiating activity, (b) as the length and/or size of the alkyl chain increases so does NMDA receptor potentiation (compare activity of **35** vs **2**, **3**, **19b**, **19d** & **19f**), (c) introduction of a polar group into the alkyl side chain promotes NMDA receptor antagonism over potentiation (**37** & **39**), (d) the 9-iodo group can be replaced by a 3-thienyl ring without adversely effecting activity (compare activity of **1** vs **22**), and (e) moving the carboxyl group away from the phenanthrene ring is beneficial for NMDA receptor antagonism (compare activity of **1** vs **43**).

In conclusion, we have developed an alternative and robust synthetic pathway to 9-iodophenanthrene-3-carboxylic acid (**1**), a novel allosteric NMDA receptor modulator. Starting from a few common intermediates, we have synthesized a series of novel phenanthrene derivatives with a variety of substituents at the 3- and 9-positions of the phenanthrene ring. It is hoped that these compounds will lead to a better understanding of the structural requirements for allosteric modulation of the NMDA receptor. The preliminary pharmacological data described here suggests that the new compounds have interesting profiles of activity on NMDA receptor subtypes. Further pharmacological characterization of these newly synthesized compounds is currently on-going and will be reported in due course.

Reagents were purchased from commercial suppliers and purified by standard techniques when necessary. All anhydrous solvents were obtained from either Acros or Sigma-Aldrich and used without further drying. All anhydrous reactions were conducted under an inert atmosphere. Melting points were determined using an Electrothermal IA9100 capillary apparatus and are uncorrected. ^{1}H-NMR spectra were measured on either a Jeol spectrometer at 270.18 MHz, a Jeol JNM-LA300 spectrometer at 300.53 MHz, a Jeol JNM-ECP400 spectrometer at 400.18 MHz, or a Varian 400MR spectrometer at 399.77 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, or a Varian 400MR spectrometer at 100.52 MHz. Chemical shifts (δ) are reported in parts per million (ppm) with 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt in D_2O, or tetramethylsilane in $CDCl_3$ or DMSO-d_6 used as internal standards. Mass spectrometry was performed in the mass spectroscopy laboratories of the Department of Chemistry, University of Bristol, UK. Elemental analyses were performed in the microanalytical laboratories of the Department of Chemistry, University of Bristol, UK. The purity of all novel compounds was determined by combustion analysis, which confirmed that they 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.

2-(9-Bromophenanthren-3-yl)-2-methyl-[1,3]dioxolane (7)

A stirred solution of **4**[4] (20.9 g, 70 mmol), ethylene glycol (8.68 g, 0.14 mol) and TsOH.H_2O (0.67 g, 3.5 mmol) in toluene (200 mL) was heated at reflux with a Dean-Stark trap in place overnight. After being allowed to cool to room temperature the reaction mixture was washed with saturated aqueous $NaHCO_3$ (50 mL) and H_2O (50 mL). The organic layer was then isolated, dried over $MgSO_4$ and concentrated in vacuo to ~ 50 mL.

At this point, the product precipitated out of solution as a white solid and was filtered off. Further concentration of the mother liquor to ~ 10 mL led to the precipitation of a second crop of product which was again collected by filtration. The mother liquor was then concentrated in vacuo and the remaining residue purified by flash chromatography (2% EtOAc in hexane) to give **7** as a white solid (23.4 g, 97%);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79 (s, 3H), 3.79-3.90 (m, 2H), 4.07-4.18 (m, 2H), 7.64-7.86 (m, 4H), 8.10-8.23 (m, 1H), 8.34-8.43 (m, 1H), 8.69-8.79 (m, 2H).

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{18}H_{15}O_2Br$: 343.0334; found 343.0338.

Tributyl-[3-(2-methyl-[1,3]dioxolan-2-yl)phenanthren-9-yl]stannane (8)

To a solution of **7** (22.2 g, 65 mmol) in anhydrous THF (350 mL) at −78 °C was added carefully and dropwise a 2.5 M solution of *n*-BuLi in hexane (31 mL, 78 mmol). The resultant mixture was allowed to stir for 1 h at −78 °C before being quenched with *n*-Bu_3SnCl (23 mL, 84.5 mmol). After complete addition, the solution was allowed to warm to room temperature. The reaction mixture was then diluted with diethyl ether (500 mL) and the organic layer isolated, washed with water (150 mL), dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was purified by flash chromatography (2% EtOAc in hexane) to afford **8** (31.9 g, 89%) which was utilized in the next step without further analysis.

3-Acetyl-9-iodophenanthrene (9)

8 (31.9 g, 57.7 mmol) was dissolved in DCM (150 mL) and a saturated iodine solution in DCM added slowly at 0 °C until the colour of the last drop of iodine did not disappear within 30 secs. The organic solution was then washed with saturated $NaHSO_3$ (50 mL), water (50 mL), dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was dissolved in acetone (200 mL) and aq 2 M HCl (4 mL) added dropwise. The ketone precipitated out of solution almost immediately and after stirring for 30 min **9** was collected by filtration as a white solid (17.0 g, 85%); mp: 149-151 °C (lit. 148-150 °C)[7];

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.78 (s, 3H), 7.67-7.75 (m, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 8.10 (dd, *J* = 8.4 & 1.8 Hz, 1H), 8.20-8.24 (m, 1H), 8.44 (s, 1H), 8.66-8.71 (m, 1H), 9.24 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.7, 102.4, 122.7, 123.8, 126.1, 127.9, 128.1, 128.4, 129.8, 130.7, 132.4, 133.5, 135.1, 135.3, 137.9, 197.8.

9-Iodophenanthrene-3-carboxylic acid (1)

Synthesized from **9** as described previously.[7]

2-Methyl-2-(9-methylsulfanylphenanthren-3-yl)-[1,3]dioxolane (10)

To a stirring solution of **7** (1.72 g, 5.00 mmol) in anhydrous THF (50 mL) at −78 °C was added dropwise a 2.5 M solution of *n*-BuLi (2.4 mL, 6.00 mmol). After complete addition the solution was allowed to stir for 1 h before being quenched by the dropwise addition of

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dimethyl disulfide (0.59 mL, 6.50 mmol). The reaction mixture was then allowed to warm to room temperature before being diluted with diethyl ether (50 mL). The organic layer was isolated, washed with H_2O (50 mL), dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash chromatography (2% EtOAc in hexane) to afford **10** which was utilized in the next step without further analysis.

1-[9-(Methylsulfanyl)phenanthren-3-yl]ethanone (11)

Concentrated HCl (0.4 mL) was added dropwise to a stirred solution of **10** in acetone (100 mL). The resultant solution was allowed to stir for 1 h during which time a precipitate formed. This solid was filtered off and washed with cold acetone (20 mL). Re-crystallization from acetone afforded **11** as an off-white solid (954 mg, 72%); mp: 135-137 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ = (s, 3H), 2.78 (s, 3H), 7.50 (s, 1H), 7.67-7.78 (m, 2H), 7.83 (d, *J* = 8.4 Hz, 1H), 8.12 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.31-8.35 (m, 1H), 8.77-8.81 (m, 1H), 9.25 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 26.9, 120.8, 123.2, 124.0, 124.8, 126.1, 127.4, 127.7, 127.7, 127.7 128.1, 130.5, 134.1, 134.9, 138.7, 198.0.

HRMS-EI: *m/z* $[M]^+$ calcd for $C_{17}H_{14}OS$: 266.0765; found: 266.0766.

Anal. calcd for $C_{17}H_{14}OS$: C, 76.66, H, 5.30; found: C, 76.60, H, 5.51.

(9-Methylsulfanyl)phenanthrene-3-carboxylic acid (12)

A stirred suspension of **11** (400 mg, 1.50 mmol) in dioxane (50 mL) was heated at 40 °C until complete dissolution of the solid. At the same time, a solution of sodium hypobromite was prepared by the dropwise addition of bromine (0.38 mL, 7.50 mmol) to an ice-cooled solution of sodium hydroxide (1.05 g, 26.3 mmol dissolved in 50 mL of H_2O). The sodium hypobromite solution was then added dropwise to the dioxane solution (complete addition took around 10 min) and stirring continued until TLC indicated complete conversion. The mixture was then allowed to cool to room temperature and a saturated sodium sulphite solution (10 mL) added to quench any excess hypobromite. The dioxane was removed in vacuo and the resultant suspension topped up with H_2O and acidified to pH 1 using conc HCl. Subsequent filtration yielded a yellow solid which was washed copiously with water (100 mL) and then dried over P_2O_5. Re-crystallization from a mixture of toluene and ethanol afforded **12** as a light yellow solid (104 mg, 26%); mp: 242-246 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ =2.72 (s, 3H), 7.72-7.83 (m, 3H), 8.02 (d, *J* = 8.0 Hz, 1H), 8.12 (dd, *J* = 8.0 & 1.2 Hz, 1H), 8.19-8.25 (m, 1H), 8.88 (d, *J* = 8.0 Hz, 1H), 9.29 (s, 1H), 13.09 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ =14.1, 120.3, 123.4, 123.9, 124.4, 127.0, 127.0, 127.6, 127.6, 127.9, 129.4, 129.4, 134.1, 137.4, 167.4.

HRMS-ESI: *m/z* $[M - H]^-$ calcd for $C_{16}H_{12}O_2S$: 267.0485; found 267.0489.

Anal. calcd for $C_{16}H_{12}O_2S \cdot 0.25H_2O$: C, 70.44, H, 4.62; found: C, 70.43, H, 4.53.

Methyl 9-(3-methoxy-3-oxoprop-1-en-1-yl)phenanthrene-3-carboxylate (14)

A flask was charged with **13** (30.1 g, 0.1 mol), palladium acetate (0.24 g, 0.1 mmol) and tri-*o*-tolylphosphine (1.28 g, 0.4 mmol). The flask was then briefly evacuated and backfilled with argon three times. A degassed solution of triethylamine (40 mL, 0.26 mol) and methyl acrylate (12 mL, 0.13 mol) in DMF (300 mL) was then cannulated into the flask and the resultant mixture heated at 100 °C for 18 h. After being allowed to cool to room temperature any remaining volatile compounds were removed in vacuo. Na_2CO_3 (10.6 g, 0.1 mol) was then added followed by methyl iodide (12.5 mL, 0.2 mol) and the reaction mixture stirred at room temperature overnight. The mixture was then diluted with diethyl ether (500 mL) and the organic layer isolated, washed with water (2 × 200 mL) and dried over $MgSO_4$. Concentration in vacuo gave **14** as a pale yellow solid (29.5 g, 92%) and a 1:1 mixture of *cis* and *trans* isomers; mp: 186-188 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 4.02 (s, 3H), 4.17 (d, *J* = 6.0 Hz, 1H), 5.45 (d, *J* = 6.0 Hz, 1H), 6.59 (d, *J* = 15.0 Hz, 1H), 7.38-7.51 (m, 4H), 7.65-7.75 (m, 2H), 7.84-7.89 (m, 2H), 7.99 (d, *J* = 7.8 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 8.14-8.17 (m, 2H), 8.46 (d, *J* = 15.0 Hz, 1H), 8.52 (d, *J* = 9.3 Hz, 1H), 8.74-8.78 (m, 1H), 9.12 (s, 1H), 9.33 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.0, 52.3, 52.5, 52.6, 122.1, 123.3, 123.5,124.0, 124.3, 124.6, 124.9, 125.1, 125.7, 126.6, 127.0, 127.6, 127.8, 128.4, 128.7, 129.0, 129.3, 130.2, 130.5, 130.7, 130.8, 133.4, 133.7, 133.9, 135.9, 142.2, 167.1, 167.2, 167.3, 172.7.

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{20}H_{16}O_4$: 321.1127; found, 321.1125.

Methyl 9-formylphenanthrene-3-carboxylate (15)

A solution of **14** in DCM (6.4 g, 20 mmol in 30 mL) was diluted with *t*-BuOH (150 mL) and water (50 mL) with vigorous stirring. TMAO (2.45 g, 22 mmol), OsO_4 (0.5 g, 0.2 mmol) and tartaric acid (4.2 g, 20 mmol) were added and the reaction monitored by TLC. Once all the starting material had been consumed $NaIO_4$ (21.3 g, 0.1 mol) was added. The aldehyde precipitated out of solution almost immediately. After stirring for an additional 20 min the solvent (mainly *t*-BuOH) was removed in vacuo, and **15** collected by filtration as a pale yellow solid (5.17 g, 98%); mp: 180-182 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.04 (s, 3H), 7.71-7.80 (m, 2H), 8.03 (d, *J* = 8.8 Hz, 1H), 8.20-8.24 (m, 2H), 8.74-8.77 (m, 1H), 9.29-9.34 (m, 2H), 10.38 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.7, 123.0, 125.2, 126.1, 127.2, 128.2, 128.4, 128.8, 130.5, 130.5, 132.2, 132.4, 132.8, 139.7, 166.9, 193.5.

MS (CI^+): *m/z* (%) = 265 (100) $[M + H]^+$.

Anal. calcd for $C_{17}H_{12}O_3$: C, 77.26, 4.58; found, C, 77.22, H, 4.49.

Methyl 9-bromophenanthrene-3-carboxylate (16)

A flask containing **13**[7] (10.0 g, 33.2 mmol) was briefly evacuated and backfilled with argon. Anhydrous methanol (300 mL) was then cannulated into the flask followed by a catalytic amount of concentrated H_2SO_4 (3 mL). The resultant mixture was heated under reflux for 48 h then allowed to cool to room temperature before being concentrated in vacuo. The resultant dark orange solid was dissolved in DCM (250 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3 × 50 mL), water (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to afford **16** as an orange solid (9.06 g, 87%); mp: 151-153 °C (lit. 155-155.5 °C)[4],

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.03 (s, 3H), 7.69-7.77 (m, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 8.07 (s, 1H), 8.17 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.33-8.37 (m, 1H), 8.71-8.75 (m, 1H), 9.32 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.4, 123.0, 124.6, 125.2, 127.1, 127.8, 128.0, 128.0, 128.2, 128.2, 129.1, 129.9, 130.5, 131.3, 134.7, 167.0.

General Procedure A (Wittig Reaction)

To a stirred suspension of the appropriate triphenylphosphonium salt (3.6 mmol) in THF (20 mL) was added dropwise potassium bis(trimethylsilyl)amide (0.5 M solution in toluene, 7.2 mL, 3.6 mmol). The resultant mixture was allowed to stir for 30 min before being added dropwise to a stirred solution of **15** (793 mg, 3 mmol) in THF (20 mL). After complete addition, the mixture was allowed to stir at room temperature for ~ 4 h before the reaction was quenched with a saturated NH_4Cl solution (10 mL). The mixture was then diluted with diethyl ether (25 mL) and the organic layer isolated and dried over $MgSO_4$. Concentration in vacuo yielded the crude product which was re-dissolved in diethyl ether (30 mL) and passed through a short silica plug. Concentration in vacuo subsequently afforded the alkene phenanthrenes (**17a-17c**) which were utilised immediately in the next step.

Methyl 9-vinylphenanthrene-3-carboxylate (17a)

Following general procedure A, methyltriphenylphosphonium iodide (1.46 g) afforded **17a** as a light yellow oil (677 mg, 86%).

Methyl 9-prop-1-en-1-ylphenanthrene-3-carboxylate (17b)

Following general procedure A, ethyltriphenylphosphonium bromide (1.34 g) afforded **17b** as a light yellow oil (729 mg, 88%).

Methyl 9-but-1-en-1-ylphenanthrene-3-carboxylate (17c)

Following general procedure A, propyltriphenylphosphonium bromide (1.38 g) afforded **17c** as a light yellow oil (793 mg, 91%).

General Procedure B (Heck Reaction)

A flask was charged with **16** (1.00 g, 3.17 mmol), palladium acetate (7.2 mg, 1 mol%), tri-*o*-tolylphosphine (39 mg, 4 mol%), and (if a solid) the appropriate alkene (3.96 mmol). The flask was then briefly evacuated and backfilled with argon three times. Degassed anhydrous DMF (25 mL) was then added followed by (if a liquid) the appropriate alkene (3.96 mmol) and triethylamine (1.11 mL, 7.93 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 × 30 mL). The organic extracts were pooled, washed with water (5 × 100 mL), brine (100 mL) and dried over $MgSO_4$. Concentration in vacuo afforded the crude alkene phenanthrenes (**17d**-**17i**) which were utilised immediately in the next step.

Methyl 9-pent-1-en-1-ylphenanthrene-3-carboxylate (17d)

Following general procedure B, 1-pentene (0.43 mL) afforded **17d** as a dark orange oil (850 mg, 88%).

9-(4-Methylpent-1-en-1-yl)phenanthrene-3-carboxylate (17e)

Following general procedure B, 4-methyl-1-pentene (0.50 mL) afforded **17e** as a dark orange oil (924 mg, 91%).

Methyl 9-hex-1-en-1-ylphenanthrene-3-carboxylate (17f)

Following general procedure B, 1-hexene (0.49 mL) afforded **17f** as a dark orange oil (950 mg, 94%).

Methyl 9-hept-1-en-1-ylphenanthrene-3-carboxylate (17g)

Following general procedure B, 1-heptene (0.56 mL) afforded **17g** as a dark orange oil (760 mg, 72%).

Methyl 9-(2-phenylethenyl)phenanthrene-3-carboxylate (17h)

Following general procedure B, styrene (0.45 ml) afforded **17h** as a yellow/brown solid (911 mg, 85%).

Methyl 9-[2-(4-methoxycarbonyl)phenylethenyl]phenanthrene-3-carboxylate (17i)

Following general procedure B, methyl 4-vinylbenzoate (642 mg) afforded **17i** as a yellow solid (1.02 g, 81%).

General Procedure C (Hydrogenation)

The appropriate alkene phenanthrene was dissolved in ethyl acetate (100 mL) and the resultant 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. Purification of the resultant residue

by flash chromatography (5 → 10% EtOAc in hexane) afforded the individual alkyl phenanthrenes.

Methyl 9-ethylphenanthrene-3-carboxylate (18a)

Following general procedure C, **17a** (677 mg, 2.58 mmol) afforded **18a** (613 mg, 90%) as a white solid; mp: 82-83 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (t, *J* = 7.6 Hz, 3H), 3.17 (q, *J* = 7.6 Hz, 2H), 4.02 (s, 3H), 7.61 (s, 1H), 7.64-7.73 (m, 2H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.11-8.15 (m, 1H), 8.17 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.81-8.85 (m, 1H), 9.39 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ =14.3, 26.3, 52.2, 123.4, 124.4, 124.4, 125.0, 126.5, 126.7, 127.0, 127.1, 128.1, 129.0, 130.8, 131.4, 134.9, 141.2, 167.5.

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}O_2$: 265.1229; found 265.1223.

Methyl 9-*n*-propylphenanthrene-3-carboxylate (18b)

Following general procedure C, **17b** (729 mg, 2.62 mmol) afforded **18b** (685 mg, 94%) as a clear oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.8 Hz, 3H), 1.81 (m, *J* = 7.8 Hz, 2H), 2.98 (t, *J* = 7.8 Hz, 2H), 3.23 (s, 3H), 7.43 (s, 1H), 7.57-7.66 (m, 2H), 7.71 (d, *J* = 9.0 Hz, 1H), 8.01-8.05 (m, 1H), 8.14 (d, *J* = 9.0 Hz, 1H), 8.72-8.75 (m, 1H), 9.32 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 22.9, 31.8, 52.2, 123.4, 124.5, 125.0, 125.4, 126.5,126.7, 127.0, 127.1, 128.1, 129.0, 130.9, 131.5, 134.8, 139.6, 167.5.

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{19}H_{18}O_2$: 279.1380; found 279.1373.

Methyl 9-*n*-butylphenanthrene-3-carboxylate (18c)

Following general procedure C, **17c** (793 mg, 2.71 mmol) afforded **18c** (729 mg, 92%) as a clear oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.8 Hz, 3H), 1.50-1.59 (m, 2H), 1.79-1.87 (m, 2H), 3.12 (t, *J* =7.8 Hz, 2H), 4.05 (s, 3H), 7.58-7.59 (m, 1H), 7.67-7.74 (m, 2H), 7.82-7.86 (m, 1H), 8.12-8.15 (m, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.82-8.85 (m, 1H), 9.41 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 23.1, 32.4, 33.4, 52.3, 123.5, 124.7, 125.1, 125.5, 126.6, 126.8, 127.1, 127.2, 128.2, 129.1, 131.0, 131.6, 135.0, 140.1, 167.6.

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{20}H_{20}O_2$: 293.1542; found 293.1553.

Methyl 9-*n*-pentylphenanthrene-3-carboxylate (18d)

Following general procedure C, **17d** (850 mg, 2.79 mmol) afforded **18d** (815 mg, 95%) as a viscous yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 6.8 Hz, 3H), 1.36-1.53 (m, 4H), 1.77-1.88 (m, 2H), 3.13 (t, *J* = 8.0 Hz, 2H), 4.02 (s, 3H), 7.61 (s, 1H), 7.64-7.75 (m, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 8.12-8.15 (m, 1H), 8.18 (dd, *J* = 8.0 & 1.6 Hz, 1H), 8.82-8.86 (m, 1H), 9.41 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 29.9, 32.1, 33.6, 52.2, 123.4, 124.6, 125.1, 125.4, 126.5, 126.7, 127.0, 127.0, 128.1, 129.0, 130.9, 131.4, 134.8, 140.0, 167.5.

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{21}H_{22}O_2$: 307.1698; found 307.1696.

Methyl 9-(4-methylpent-1-yl)phenanthrene-3-carboxylate (18e)

Following general procedure C, **17e** (924 mg, 2.90 mmol) afforded **18e** (886 mg, 95%) as a viscous yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.4 Hz, 6H), 1.36-1.44 (m, 2H), 1.58-1.70 (m, 1H), 1.78-1.87 (m, 2H), 3.11 (t, *J* = 7.6 Hz, 2H), 4.02 (s, 3H), 7.61 (s, 1H), 7.65-7.74 (m, 2H), 7.88-7.84 (d, *J* = 8.4 Hz, 1H), 8.11-8.15 (m, 1H), 8.18 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.82-8.86 (m, 1H), 9.41 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6, 28.0, 28.1, 33.9, 39.2, 52.5, 123.4, 124.6, 125.1, 125.4, 126.5, 126.7, 127.0, 127.1, 128.1, 129.0, 130.9, 131.4, 134.9, 140.1, 167.5.

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{22}H_{24}O_2$: 321.1855; found 321.1855.

Methyl 9-*n*-hexylphenanthrene-3-carboxylate (18f)

Following general procedure C, **17f** (950 mg, 2.98 mmol) afforded **18f** (899 mg, 94%) as a viscous yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3H), 1.30-1.42 (m, 4H), 1.43-1.55 (m, 2H), 1.77-1.87 (m, 2H), 3.12 (t, *J* = 7.6 Hz, 2H), 4.02 (s, 3H), 7.61 (s, 1H), 7.65-7.74 (m, 2H), 7.86 (d, *J* = 8.4 Hz, 1H), 8.11-8.15 (m, 1H), 8.18 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.82-8.86 (m, 1H), 9.40 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 29.6, 30.2, 31.8, 33.6, 52.2, 123.4, 124.6, 125.1, 125.4, 126.5, 126.7, 127.0, 127.0, 128.1, 129.0, 130.9, 131.4, 134.9, 140.1, 167.5.

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{22}H_{24}O_2$: 321.1855; found 321.1849.

Methyl 9-*n*-heptylphenanthrene-3-carboxylate (18g)

Following general procedure C, **17g** (760 mg, 2.29 mmol) afforded **18g** (500 mg, 65%) as a viscous pale yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.2 Hz, 3H), 1.24-1.54 (m, 8H), 1.83 (p, *J* = 7.6 Hz, 2H), 3.13 (t, *J* = 7.6 Hz, 2H), 4.02 (s, 3H), 7.61 (s, 1H), 7.65-7.74 (m, 2H), 7.86 (d, *J* = 8.4 Hz, 1H), 8.11-8.15 (m, 1H), 8.18 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.82-8.86 (m, 1H), 9.41 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 29.2, 29.8, 30.2, 31.9, 33.6, 52.2, 123.4, 124.6, 125.1, 125.4, 126.5, 126.7, 127.0, 127.1, 128.1, 129.0, 131.0, 131.4, 134.9, 140.1, 167.5.

HRMS-CI: *m/z* $[M + Na]^+$ calcd for $C_{23}H_{26}O_2$: 357.1831; found 357.1822.

Methyl 9-phenethylphenanthrene-3-carboxylate (18h)

Following general procedure C, **17h** (911 mg, 2.69 mmol) afforded **18h** as a viscous clear oil (599 mg, 64%);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.11-3.18 (m, 2H), 3.42-3.48 (m, 2H), 4.03 (s, 3H), 7.21-7.26 (m, 1H), 7.27-7.38 (m, 4H), 7.60 (s, 1H), 7.68-7.77 (m, 2H), 7.84 (d, *J* = 8.8 Hz, 1H), 8.18-8.22 (m, 1H), 8.19 (dd, *J* = 8.8 & 1.6 Hz, 1H), 8.85-8.89 (m, 1H), 9.42 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.5, 36.4, 52.3, 123.5, 124.4, 125.1, 125.7, 126.2, 126.6, 126.8, 127.2, 127.3, 128.2, 128.4, 128.5, 129.1, 130.9, 131.2, 134.7, 138.8, 141.7, 167.5.

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{24}H_{20}O_2$: 341.1542; found 341.1543.

Methyl 9-[2-(4-methoxycarbonylphenyl)ethyl]-phenanthrene-3-carboxylate (18i)

Following general procedure C, **17i** (1.02 g, 2.57 mmol) afforded **18i** as a viscous clear oil (625 mg, 61%);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.15-3.21 (m, 2H), 3.40-3.47 (m, 2H), 3.91 (s, 3H), 4.02 (s, 3H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.53 (s, 1H), 7.67-7.76 (m, 2H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.4Hz, 2H), 8.13-8.19 (m, 2H), 8.83-8.88 (m, 1H), 9.40 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.0, 36.4, 52.0, 52.3, 123.6, 124.2, 125.1, 125.8, 126.7, 126.9, 127.3, 127.4, 128.2, 128.5, 129.2, 129.9, 131.0, 131.1, 134.6, 138.2, 147.1, 167.1, 167.4.

HRMS-CI: *m/z* $[M]^+$ calcd for $C_{26}H_{22}O_4$: 398.1518; found 398.1511.

General Procedure D (Ester Hydrolysis)

The appropriate ester was dissolved in a mixture of either THF or dioxane (100 mL) and H_2O (20 mL). A NaOH or KOH solution (3 eqvs dissolved in 20 mL H_2O) was then added dropwise and the resulting solution heated either at reflux (THF) or 75 °C (dioxane) until TLC indicated complete hydrolysis. The reaction mixture was then allowed to cool to room temperature and the organic solvent removed in vacuo. The resulting aqueous suspension was topped up with water, extracted with diethyl ether (30 mL) and acidified to pH 1 using aq 1 M HCl. The solid that precipitated out of solution at this stage was filtered off, washed copiously with H_2O and then dried over P_2O_5 to afford the desired acid. Several compounds required purification and were re-crystallised from an appropriate solvent.

9-Ethylphenanthrene-3-carboxylic acid (19a)

Following general procedure D, **18a** (550 mg, 2.08 mmol), NaOH (250 mg, 6.24 mmol) and dioxane afforded **19a** as a white solid (495 mg, 95%); mp: 245-249 °C (dec);

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.39 (t, *J* = 7.6 Hz, 3H), 3.15 (q, *J* = 7.6 Hz, 2H), 7.72-7.79 (m, 3H), 8.02 (d, *J* = 8.4 Hz, 1H), 8.12 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.17-8.22 (m, 1H), 8.86-8.91 (m, 1H), 9.33 (s, 1H), 13.10 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.8, 26.0, 123.8, 124.7, 124.8, 124.9, 127.0, 127.6, 127.9, 128.6, 128.8, 130.5, 131.2, 134.7, 141.2, 168.0.

HRMS-ESI: *m/z* [M − H]$^-$ calcd for $C_{17}H_{14}O_2$: 249.0921; found 249.0929.

Anal. calcd for $C_{17}H_{14}O_2$: C, 81.58, H, 5.64; found, C, 81.75, H, 5.91.

9-*n*-Propylphenanthrene-3-carboxylic acid (19b)

Following general procedure D, **18b** (525 mg, 1.89 mmol), NaOH (227 mg, 5.67 mmol) and dioxane afforded **19b** as a white solid (465 mg, 93%); mp: 234-238 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.02 (t, *J* = 7.6 Hz, 3H), 1.77 (m, *J* = 7.6 Hz, 2H), 3.09 (t, *J* = 7.6 Hz, 2H), 7.71-7.78 (m, 3H), 8.00 (d, *J* = 8.4 Hz, 1H), 8.11 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.16-8.21 (m, 1H), 8.85-8.90 (m, 1H), 9.32 (s, 1H), 13.12 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.0, 22.9, 34.6, 123.3, 124.3, 124.6, 125.3, 126.5, 127.1, 127.3, 128.1, 128.2, 128.3, 130.1, 130.8, 134.1, 139.2, 167.5.

HRMS-ESI: *m/z* [M − H]$^-$ calcd for $C_{18}H_{16}O_2$: 263.1078; found 263.1085.

Anal. calcd for $C_{18}H_{16}O_2$: C, 81.79, H, 6.10; found, C, 82.05, H, 6.39.

9-*n*-Butylphenanthrene-3-carboxylic acid (19c)

Following general procedure D, **18c** (650 mg, 2.22 mmol), NaOH (266 mg, 6.66 mmol) and dioxane afforded **19c** as a white solid which was re-crystallised from a mixture of toluene and ethanol (248 mg, 40%); mp: 208-211 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.95 (t, *J* = 7.6 Hz, 3H), 1.45 (m, *J* = 7.6 Hz, 2H), 1.73 (p, *J* = 7.6 Hz, 2H), 3.12 (t, *J* = 7.2 Hz, 2H), 7.71-7.79 (m, 3H), 8.01 (d, *J* = 8.0 Hz, 1H), 8.11 (dd, *J* = 8.0 & 1.2 Hz, 1H), 8.16-8.21 (m, 1H), 8.85-8.90 (m, 1H), 9.32 (s, 1H), 13.08 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.8, 22.2, 31.9, 32.3, 123.3, 124.3, 124.6, 125.2, 126.5, 127.1, 127.3, 128.0, 128.2, 128.3, 130.1, 130.8, 134.1, 139.4, 167.5.

HRMS-ESI: *m/z* [M − H]$^-$ calcd for $C_{19}H_{18}O_2$: 277.1234; found 277.1232.

Anal. calcd for $C_{19}H_{18}O_2$: C, 81.99, H, 6.52; found, C, 81.85, H, 6.41.

9-*n*-Pentylphenanthrene-3-carboxylic acid (19d)

Following general procedure D, **18d** (573 mg, 1.88 mmol), NaOH (226 mg, 5.64 mmol) and dioxane afforded **19d** as a white solid which was re-crystallised from toluene (141 mg, 26%); mp: 194-197 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.87 (t, *J* = 7.2 Hz, 3H), 1.29-1.47 (m, 4H), 1.74 (p, *J* = 7.2 Hz, 2H), 3.10 (t, *J* = 7.2 Hz, 2H), 7.70-7.79 (m, 3H), 8.00 (d, *J* = 8.4 Hz, 1H), 8.11 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.15-8.20 (m, 1H), 8.84-8.92 (m, 1H), 9.33 (s, 1H), 13.13 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.5, 22.6, 30.0, 31.9, 33.2, 123.9, 124.9, 125.1, 125.8, 127.2, 127.6, 127.9, 128.6, 128.8, 128.9, 130.7, 131.4, 134.7, 140.0, 168.2.

MS (ESI$^-$): *m/z* (%) = 291 (100) [M−H]$^-$, 247 (46).

Anal. calcd for $C_{20}H_{20}O_2$: C, 82.16, H, 6.89; found, C, 82.00, H, 6.82.

9-(4-Methylpent-1-yl)phenanthrene-3-carboxylic acid (3)

Following general procedure D, **18e** (675 mg, 2.11 mmol), NaOH (253 mg, 6.33 mmol) and dioxane afforded **3** as a white solid which was re-crystallised from toluene (264 mg, 41%); mp: 193-196 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.82 (d, *J* = 6.4 Hz, 6H), 1.24-1.33 (m, 2H), 1.48-1.60 (m, 1H), 1.64-1.74 (m, 2H), 3.03 (t, *J* = 8.0 Hz, 2H), 7.66-7.77 (m, 3H), 7.97 (d, *J* = 8.4 Hz, 1H), 8.09-8.16 (m, 2H), 8.82-8.89 (m, 1H), 9.32 (s, 1H), 13.13 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.4, 27.3, 27.6, 32.8, 38.4, 123.2, 124.3, 124.5, 125.1, 126.5, 127.0, 127.3, 128.0, 128.2, 128.3, 130.1, 130.7, 134.1, 139.4, 167.5.

MS (ESI$^-$): *m/z* (%) = 305 (100) [M−H]$^-$, 261 (25).

Anal. calcd for $C_{21}H_{22}O_2$: C, 82.32, H, 7.24; found, C, 82.30, H, 7.17.

9-*n*-Hexylphenanthrene-3-carboxylic acid (19f)

Following general procedure D, **18f** (679 mg, 2.12 mmol), NaOH (254 mg, 6.36 mmol) and dioxane afforded **19f** as a white solid which was re-crystallised from toluene (221 mg, 34%); mp: 196-199 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85 (t, *J* = 7.2 Hz, 3H), 1.22-1.37 (m, 4H), 1.43 (p, *J* = 7.2 Hz, 2H), 1.73 (p, *J* = 7.2 Hz, 2H), 3.10 (t, *J* = 7.2 Hz, 2H), 7.71-7.79 (m, 3H), 8.00 (d, *J* = 8.4 Hz, 1H), 8.11 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.14-8.20 (m, 1H), 8.84-8.91 (m, 1H), 9.32 (s, 1H), 13.12 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.9, 22.1, 28.8, 29.7, 31.1, 32.7, 123.3, 124.3, 124.6, 125.2, 126.6, 127.1, 127.3, 128.1, 128.2, 128.3, 130.1, 130.8, 134.1, 139.4, 167.6.

MS (ESI$^-$): *m/z* (%) = 305 (100) [M−H]$^-$, 261 (20).

Anal. calcd for $C_{21}H_{22}O_2$: C, 82.32, H, 7.24; found, C, 82.01, H, 7.08.

9-*n*-Heptylphenanthrene-3-carboxylic acid (19g)

Following general procedure D, **18g** (450 mg, 1.35 mmol), NaOH (162 mg, 4.05 mmol) and dioxane afforded **19g** as a white solid which was re-crystallised from toluene (317 mg, 73%); mp: 185-188 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.83 (t, *J* = 7.2 Hz, 3H), 1.18-1.45 (m, 8H), 1.72 (p, *J* = 7.6 Hz, 2H), 3.08 (t, *J* = 7.6 Hz, 2H), 7.70-7.78 (m, 3H), 7.99 (d, *J* = 8.0 Hz, 1H), 8.11 (dd, *J* = 8.0 & 1.2 Hz, 1H), 8.14-8.19 (m, 1H), 8.85-8.90 (m, 1H), 9.32 (s, 1H), 13.09 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.9, 22.0, 28.5, 29.1, 29.8, 31.2, 32.6, 123.3, 124.2, 124.6, 125.2, 126.6, 127.0, 127.3, 128.2, 128.3, 130.1, 130.8, 134.1, 139.4, 167.6.

HRMS-ESI: *m/z* $[M - H]^-$ calcd for $C_{22}H_{24}O_2$: ; found .

Anal. calcd for $C_{22}H_{24}O_2$: C, 82.46, H, 7.55; found, C, 82.12, H, 7.50.

9-Phenethylphenanthrene-3-carboxylic acid (19h)

Following general procedure D, **18h** (512 mg, 1.50 mmol), NaOH (180 mg, 4.50 mmol) and dioxane afforded **19h** as a white solid which was re-crystallised from a mixture of toluene and ethanol (105 mg, 22%); mp: 236-237 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.07 (t, *J* = 8.0 Hz, 2H), 3.41 (t, *J* = 8.0 Hz, 2H), 7.18-7.24 (m, 1H), 7.27-7.37 (m, 4H), 7.73-7.81 (m, 3H), 7.98 (d, *J* = 8.4 Hz, 1H), 8.11 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.26-8.32 (m, 1H), 8.86-8.93 (m, 1H), 9.34 (s, 1H) 13.10 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 34.6, 35.7, 123.3, 124.3, 124.5, 125.4, 125.9, 126.6, 127.1, 127.5, 128.0, 128.1, 128.2, 128.3, 128.3, 130.1, 130.7, 134.0, 138.5, 141.4, 167.5.

MS (ESI^-): *m/z* (%) = 325 (100) $[M-H]^-$.

Anal. calcd for $C_{23}H_{18}O_2$: C, 84.64, H, 5.56; found, C, 84.53, H, 5.58.

9-[2-(4-Carboxyphenyl)ethyl]phenanthrene-3-carboxylic acid (19j)

Following general procedure D, **18i** (400 mg, 1.00 mmol), KOH (337 mg, 6.00 mmol) and THF afforded **19j** as an off-white solid (216 mg, 58%); mp: >250 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.15 (t, *J* = 8.0 Hz, 2H), 3.45 (t, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.75-7.81 (m, 3H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.11 (dd, *J* = 8.0 & 1.6 Hz, 1H), 8.27-8.32 (m, 1H), 8.87-8.93 (m, 1H), 9.34 (s, 1H), 12.97 (br s, 1H), 13.15 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 34.1, 35.6, 123.3, 124.3, 124.6, 125.5, 126.6, 127.2, 127.5, 128.2, 128.3, 128.4, 128.5, 128.6, 129.4, 130.1, 130.6, 134.0, 138.2, 146.7, 167.2, 167.5.

HRMS-ESI: *m/z* $[M - H]^-$ calcd for $C_{24}H_{18}O_4$: 369.1132; found 369.1142.

Anal. calcd for $C_{24}H_{18}O_4 \cdot 0.63H_2O$: C, 75.51, H, 5.09; found, C, 75.82, H, 5.48.

Methyl 9-vinylphenanthrene-3-carboxylate (17a)

A flask containing **16** (1.00 g, 3.17 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. $Pd(PPh_3)_4$ (109.9 mg, 3 mol%) was then added and the mixture de-gassed for a further 10 mins before vinyl(tri-*n*-butyl)tin (1.12 mL, 3.80 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 aq NH_4Cl (50 mL each). The organic layer was isolated and washed with aq 1 M KF (2 × 50 mL) to remove any tin byproducts. 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 afford a dark orange oil. Purification by flash chromatography (5% EtOAc in hexane) afforded a pale yellow oil which partially solidified on standing (550 mg, 66%);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.03 (s, 3H), 5.59 (dd, *J* = 10.8 & 1.6 Hz, 1H), 5.91 (dd, *J* = 17.2 & 1.6 Hz, 1H), 7.48 (ddd, *J* = 17.2, 10.8 & 0.8 Hz, 1H), 7.65-7.77 (m, 2H), 7.86 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.16-8.22 (m, 2H), 8.81-8.86 (m, 1H), 9.41 (d, *J* = 0.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.3, 118.7, 123.4, 124.1, 124.9, 125.2, 126.8, 127.3, 127.3, 127.8, 128.9, 129.8, 130.7, 130.8, 134.8, 134.9. 137.4, 167.5.

HRMS-ES: *m/z* $[M]^+$ calcd for $C_{18}H_{14}O_2$: 262.0994; found 262.0999.

Methyl 9-cyclopropylphenanthrene-3-carboxylate (20)

Diiodomethane (1.82 g, 6.8 mmol) was dissolved in anhydrous DCM (10 mL) and $ZnEt_2$ (1.0 M solution in hexane, 3.4 mL, 3.4 mmol) added to this solution at 0 °C followed by a solution of **17a** in DCM (450 mg, 1.7 mmol in 10 mL). The reaction mixture was then stirred vigorously overnight before being quenched with aq 1 M HCl. The mixture was extracted with diethyl ether (50 mL) and the organic layer isolated, dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was purified by flash chromatography (5% EtOAc in hexane) to afford **20** as a viscous clear oil (400 mg, 85%);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83-0.89 (m, 2H), 1.10-1.16 (m, 2H), 2.31-2.40 (m, 1H), 4.02 (s, 3H), 7.53 (s, 1H), 7.67-7.76 (m, 2H), 7.82 (d, *J* = 9.0 Hz, 1H), 8.16 (d, *J* = 9.0 Hz, 1H), 8.49-8.53 (m, 1H), 8.79-8.82 (m, 1H), 9.38 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.5, 6.5, 14.1, 52.3, 123.2, 123.9, 125.1, 125.3, 126.6, 127.0, 127.1, 127.3, 128.3, 129.1, 130.7, 132.9, 135.0, 140.4, 167.6.

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{19}H_{16}O_2$: 277.1229; found, 277.1231.

9-Cyclopropylphenanthrene-3-carboxylic acid (2)

20 (350 mg, 1.27 mmol) was dissolved in dioxane (10 mL) and saturated aqueous LiOH added dropwise until the reaction mixture became a slurry (~ 1 mL). The mixture was stirred at room temperature overnight, then extracted with diethyl ether (20 mL) before being acidified to pH 1 with aq 1 M HCl. The acid precipitated out of solution and was subsequently collected by filtration, washed with water and dried over P_2O_5 to afford **2** as a white solid (310 mg, 93%); mp: >250 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.81-0.85 (m, 2H), 1.10-1.15 (m, 2H), 2.41-2.49 (m, 1H), 7.69 (s, 1H), 7.77-7.80 (m, 2H), 8.02 (d, *J* = 8.8 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 8.52-8.54 (m, 1H), 8.85-8.88 (m, 1H), 9.31 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 7.0, 7.0, 13.9, 123.4, 123.5, 124.7, 125.5, 127.0, 127.8, 127.9, 128.6, 128.7, 129.0, 130.3, 132.6, 134.7, 140.4, 168.0.

MS (ESI$^-$): *m/z* (%) = 261 (100) $[M - H]^-$.

Anal. calcd for $C_{18}H_{14}O_2$: C, 82.42, H, 5.38; found, C, 82.84, H, 5.47.

Methyl 9-(thiophen-3-yl)phenanthrene-3-carboxylate (21)

A flame dried flask was successively charged with **16** (1.00 g, 3.17 mmol), 3-thienylboronic acid (573 mg, 4.48 mmol), K_2CO_3 (1.31 g, 9.51 mmol) and Pd(dppf)Cl_2.DCM (261 mg, 0.32 mmol). After each addition, the flask was briefly evacuated and backfilled with argon. Degassed anhydrous DME (75 mL) was then cannulated into the flask and the resultant mixture stirred at 80 °C for 24 h. After being allowed to cool to room temperature the reaction mixture was diluted with EtOAc (100 mL) and H_2O (20 mL). The organic layer was isolated and washed with water (2 × 25 mL) and then brine (2 × 25 mL). After drying over $MgSO_4$, concentration in vacuo afforded a dark brown/black residue which was partially purified by flash chromatography (10% EtOAc in hexane) to give a pale yellow solid (618 mg, 61%) which ^{1}H NMR showed was a mixture of **21** and **16** (~ 75:25). The mixture was taken forward to the next step without further purification.

21: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.04 (s, 3H), 7.35 (dd, *J* = 4.8 & 1.6 Hz, 1H), 7.49 (dd, *J* = 2.8 & 1.6 Hz, 1H), 7.51 (dd, *J* = 4.8 & 2.8 Hz, 1H), 7.59-7.64 (m, 1H), 7.71-7.76 (m, 1H), 7.77 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 8.08 (dd, *J* = 8.4 & 1.2, 1H), 8.21 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.87 (d, *J* = 8.4 Hz, 1H), 9.45 (s, 1H).

9-(Thiophen-3-yl)phenanthrene-3-carboxylic acid (22)

Following general procedure D, **21** (541 mg, 1.70 mmol), NaOH (204 mg, 5.10 mmol) and dioxane afforded a pale yellow solid which was re-crystallised 4 times from glacial acetic acid to give **22** (117 mg, 23%); mp: >250 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.42 (dd, *J* = 4.8 & 1.6 Hz, 1H), 7.68-7.73 (m, 1H), 7.77-7.83 (m, 3H), 7.94 (s, 1H), 8.04 (dd, *J* = 8.4 & 1.2 Hz, 1H), 8.11 (d, *J* = 8.4, 1H), 8.16 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.95 (d, *J* = 8.4 Hz, 1H), 9.39 (s, 1H), 13.15 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 123.7, 124.8, 125.3, 126.8, 127.0, 127.3, 128.0, 128.0, 129.1, 129.3, 129.4, 129.8, 130.7, 131.0, 134.2, 135.8, 140.3, 168.0.

HRMS-ESI: *m/z* [M − H]$^-$ calcd for $C_{19}H_{12}O_2S$: 303.0485; found 303.0495.

Anal. calcd for $C_{19}H_{12}O_2S{\cdot}0.55H_2O$: C, 72.61, H, 4.20; found, C, 72.61, H, 4.02.

Methyl 9-(4-methoxy-4-oxobutan-2-yl)phenanthrene-3-carboxylate (23)

To a cold (−78 °C) stirring mixture of CuI (25.2 g, 0.13 mol) and NaI (36 g, 0.24 mol) in Me_2S (79 mL) and DCM (72 mL) was added methylmagnesium chloride (3.0 M solution in THF, 41 mL, 0.12 mol) and TMSCl (31 mL, 0.24 mol). The mixture was then stirred for 30 min at −78 °C when a solution of **14** (7.7 g, 24 mmol) in DCM (72 mL) was added. The resultant mixture was stirred at −78 °C for 10 min and then slowly allowed to warm to room temperature. After stirring for 3 h the reaction was quenched with saturated aq NH_4Cl. The organic layer was isolated and the aqueous phase extracted with diethyl ether (100 mL). The organics were pooled, dried over $MgSO_4$, and concentrated in vacuo. Purification of the resultant residue by flash column chromatography (5% EtOAc in hexane) afforded **23** (4.83 g, 60%) as a light coloured oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 7.8 Hz, 3H), 2.69 (dd, J = 7.8 & 12.0 Hz, 1H), 2.89 (dd, J = 7.8 & 12.0 Hz, 1H), 3.87 (s, 3H), 3.93 (s, 3H), 4.06 (m, *J* = 7.8 Hz, 1H), 7.75-7.78 (m, 2H), 7.84 (s, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.94 (d, *J* = 8.7 Hz, 1H), 8.00-8.10 (m, 1H), 8.92-8.95 (m, 1H), 9.33 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 31.0, 41.6, 54.3, 56.7, 122.8, 124.0, 124.3, 124.7, 127.0, 127.6, 128.0, 128.7, 128.8, 129.1, 130.6, 130.7, 134.1, 143.4, 168.0, 173.8.

HRMS-CI: *m/z* [M + H]$^+$ calcd for $C_{21}H_{20}O_4$: 337.1440; found 337.1442.

9-(4-Methoxy-4-oxobutan-2-yl)phenanthrene-3-carboxylic acid (24)

Following general procedure D, **23** (508 mg, 1.51 mmol), NaOH (362.4 mg, 9.06 mmol) and dioxane afforded **24** as a white solid (377 mg, 81%); mp: >250 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.42 (d, *J* = 7.8 Hz, 3H), 2.68 (dd, J = 7.8 & 12.0 Hz, 1H), 2.87 (dd, J = 7.8 & 12.0 Hz, 1H), 4.07 (m, *J* = 7.8 Hz, 1H), 7.77-7.80 (m, 2H), 7.86 (s, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 8.27-8.30 (m, 1H), 8.90-8.93 (m, 1H), 9.33 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.7, 31.0, 41.6, 122.8, 124.0, 124.3, 124.7, 127.0, 127.6, 128.0, 128.7, 128.8, 129.1, 130.6, 130.7, 134.5, 143.4, 168.0, 173.8.

HRMS-ESI: *m/z* [M − H]$^-$ calcd for $C_{19}H_{16}O_4$: 307.0976; found 307.0969.

Anal. calcd for $C_{19}H_{16}O_4$: C, 74.01, H, 5.23; found, C, 74.07, H, 5.18.

Methyl 9-(3-hydroxy-2-methoxy-4-oxobutan-2-yl)phenanthrene-3-carboxylate (25)

To a stirring solution of **23** (2.74 g, 8.15 mmol) in anhydrous THF (40 mL) at −78 °C was added dropwise KHMDS (0.5 M solution in toluene, 17.3 mL, 8.65 mmol) followed by a solution of 2-tosyl-3-phenyloxaziridine[8] (3.2 g, 12.25 mmol) in THF (20 mL). After complete addition, the mixture was allowed to warm to room temperature and stirred for ~ 2 h. Water (30 mL) and diethyl ether (60 mL) were then added. The organic layer was subsequently isolated and washed with a saturated sodium sulphite solution (20 mL), aq 1 M HCl (20 mL), and brine (20 mL). Concentration in vacuo afforded 25 as an oil which was utilised in the next step without further purification or analysis.

Methyl 9-(1-oxopropan-2-yl)phenanthrene-3-carboxylate (26)

A stirred solution of **25** in anhydrous THF (20 mL) was cooled to 0 °C and $LiBH_4$ (227 mg, 12.3 mmol) added portionwise over a period of 10 min. After complete addition the mixture was stirred for 30 min at 0 °C and then at room temperature until TLC indicated complete conversion. The reaction was then quenched by the addition of aq 1 M HCl (5 mL) and extracted with diethyl ether (2 × 30 mL). The organic layers were pooled, dried over $MgSO_4$ and concentrated in vacuo to obtain the crude 1,2-diol as an orange oil. This intermediate was dissolved in a mixture of *t*-BuOH and water (30 mL, 4:1) and $NaIO_4$ (5.13 g, 24 mmol) added to the solution. The resultant mixture was stirred at room temperature for 30 min before the reaction was quenched by the addition of water (20 mL). The aqueous mixture was then extracted with diethyl ether (2 × 30 mL) and the organic layers pooled, dried over $MgSO_4$, and concentrated in vacuo. Purification of the resultant residue by flash chromatography (5% EtOAc in hexane) afforded **26** (1.55 g, 65%) as a viscous light orange oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (d, *J* = 7.2, 3H), 4.03 (s, 3H), 4.42 (q, *J* = 7.2 Hz, 1H), 7.57 (s, 1H), 7.68-7.79 (m, 2H), 7.89 (d, *J* = 8.4 Hz, 1H), 8.06-8.10 (m, 1H), 8.21 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.85-8.89 (m, 1H), 9.41 (s, 1H), 9.82 (d, *J* = 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 49.0, 52.3, 123.8, 123.9, 125.0, 126.0, 126.9, 127.3, 127.6, 128.1, 128.6, 129.5, 130.7, 131.2, 134.2, 135.3, 167.2, 200.9.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{19}H_{16}O_3$: 315.0997; found 315.0992.

Methyl 9-(1-hydroxypropan-2-yl)phenanthrene-3-carboxylate (27)

To a stirred solution of **26** (1.0 g, 3.42 mmol) in anhydrous THF (100 mL) was added portionwise $NaBH_4$ (388 mg, 10.26 mmol). *i*-PrOH (2 mL) was then added and the resultant suspension stirred at room temperature until TLC indicated complete reduction. Excess $NaBH_4$ was then destroyed via the dropwise addition of water. The solvent was then removed in vacuo and the resultant residue dissolved in a mixture of EtOAc and water (50 mL each). The organic layer was isolated and the aqueous layer further extracted with EtOAc (2 × 25 mL). The organic layers were pooled, washed with water (25 mL), brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification of the resultant residue by flash column chromatography (10% EtOAc in hexane) afforded **27** as a viscous pale yellow oil (985 mg, 98%);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 6.7 Hz, 3H), 3.85-3.91 (m, 2H), 4.00 (s, 3H), 4.05 (m, 1H), 7.64-7.73 (m, 3H), 7.87 (d, *J* = 8.8 Hz, 1H), 8.15-8.22 (m, 2H), 8.83 (d, J = 8.8 Hz, 1H), 9.37 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 21.1, 52.4, 67.7, 123.4, 123.7, 125.1, 126.7, 127.0, 127.3, 127.6, 128.6, 129.1, 131.1, 131.3, 134.5, 140.8, 167.5.

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{19}H_{18}O_3$: 295.1329; found 295.1320.

9-(1-Hydroxypropan-2-yl)phenanthrene-3-carboxylic acid (28)

Following general procedure D, **27** (301 mg, 1.02 mmol), NaOH (122 mg, 3.06 mmol), and dioxane afforded **28** as a white solid (213 mg, 75%); mp: >250 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.44 (d, *J* = 8.0 Hz, 3H), 3.54-3.64 (m, 1H), 3.69-3.78 (m, 1H), 3.79-3.87 (m, 1H), 4.82 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.27-8.34 (m, 1H), 8.86-8.93 (m, 1H), 9.33 (s, 1H), 13.14 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.8, 36.5, 66.3, 123.2, 123.4, 124.1, 124.3, 126.5, 127.0, 127.4, 128.1, 128.6, 130.1, 130.9, 134.1, 141.6, 167.6.

HRMS-ESI: *m/z* $[M - H]^-$ calcd for $C_{18}H_{16}O_3$: 279.1027; found 279.1019.

Anal. calcd for $C_{18}H_{16}O_3$: C, 77.12, H, 5.75; found, C, 77.37, H, 5.89.

Methyl 9-(propan-2-yl)phenanthrene-3-carboxylate (29)

To a stirred solution of **27** (505 mg, 1.72 mmol) in DCM (20 mL) at 0 °C was added triethylamine (0.25 mL, 1.80 mmol) followed by methanesulfonyl chloride (0.14 mL, 1.80 mmol). The resultant mixture was stirred at 0 °C for 1 h and then at room temperature for 3 h. After this time, the reaction was diluted with DCM and water (20 mL each) and the organic layer isolated, washed with aq 1 M HCl (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude mesylate thus obtained was dissolved in acetone (75 mL) and sodium iodide (645 mg, 4.3 mmol) added to the solution. The resultant mixture was refluxed for 24 h before being allowed to cool to room temperature. Filtration then removed any solids with the filter cake being rinsed with acetone. The filtrate and washes were combined and concentrated in vacuo. The resultant residue was dissolved in diethyl ether (40 mL) and washed with water (20 mL), a saturated sodium sulfite solution (15 mL), water (20 mL), and dried over $MgSO_4$. Concentration in vacuo afforded the crude iodo compound which was then dissolved in dioxane (100 mL). Triethylamine (0.25 mL, 1.80 mmol) was added and the resultant 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. The resultant residue was taken-up in DCM (50 mL) and washed successively with aq 1M HCl, H_2O, and brine (25 mL each). Drying over $MgSO_4$ followed by concentration in vacuo yielded a residue which was purified by flash column chromatography (10% EtOAc in hexane) to afford **29** as a pale yellow oil (349 mg, 73%);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 7.2 Hz, 6H), 3.74 (sep, *J* = 7.2 Hz, 1H), 3.85 (s, 3H), 7.66-7.72 (m, 3H), 7.86 (d, *J* = 8.7 Hz, 1H), 8.18-8.20 (m, 2H), 8.82-8.86 (m, 1H), 9.40 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2, 28.8, 52.2, 121.7, 123.5, 124.1, 124.9, 126.5, 126.6, 127.0, 127.1, 128.3, 128.8, 131.0, 134.9, 145.5, 167.5.

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{19}H_{18}O_2$: 279.1380; found 279.1371.

9-(Propan-2-yl)phenanthrene-3-carboxylic acid (30)

Following general procedure D, **29** (205 mg, 0.74 mmol), NaOH (89 mg, 2.22 mmol) and dioxane afforded **30** as a white solid (166 mg, 85%); mp: 226-230 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.42 (d, *J* = 6.8 Hz, 6H), 3.78 (sep, *J* = 6.8 Hz, 1H), 7.72-7.79 (m, 2H), 7.83 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 8.12 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.24-8.31 (m, 1H), 8.86-8.92 (m, 1H), 9.33 (s, 1H), 13.06 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.0, 28.1, 121.6, 123.4, 124.1, 124.2, 126.5, 127.0, 127.3, 128.1, 128.1, 128.5, 130.1, 130.3, 134.1, 145.0, 167.5.

HRMS-ESI: *m/z* $[M - H]^-$ calcd for $C_{18}H_{16}O_2$: 263.1078; found 263.1070.

Anal. calcd for $C_{18}H_{16}O_2$: C, 81.79, H, 6.10; found, C, 81.65, H, 6.01.

Methyl 9-(hydroxymethyl)phenanthrene-3-carboxylate (31)

To a stirred solution of **15** (1.10 g, 4.16 mmol) in anhydrous THF (150 mL) was added slowly and portionwise $NaBH_4$ (472 mg, 12.48 mmol). *i*-PrOH (2 mL) was then added and the resultant suspension stirred at room temperature until TLC indicated complete reduction. Excess $NaBH_4$ was destroyed by the dropwise addition of H_2O. Concentration in vacuo afforded a solid which was dissolved in a mixture of EtOAc and H_2O (50 mL each). The organic layer was isolated and the aqueous layer further extracted with EtOAc (2 × 25 mL). The organic layers where pooled, washed with water (25 mL), brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo to afford **31** as a pale yellow solid (1.05 g, 95%); mp: 179-182 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.96 (s, 3H), 5.05 (d, *J* = 5.6 Hz, 2H), 5.52 (t, *J* = 5.6 Hz, 1H), 7.69-7.81 (m, 2H), 7.96 (s, 1H), 8.07-8.18 (m, 3H), 8.85-8.91 (m, 1H), 9.34 (s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.2, 61.2, 123.2, 123.3, 124.3, 124.3, 126.3, 127.2, 127.2, 127.4, 128.7, 128.9, 129.7, 129.8, 134.2, 139.1, 166.4.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{17}H_{14}O_3$: 289.0835; found 289.0832.

Anal. calcd for $C_{17}H_{14}O_3$: C, 76.68, H, 5.30; found, C, 76.35, H, 5.31.

9-(Hydroxymethyl)phenanthrene-3-carboxylic acid (32)

Following general procedure D, **31** (500 mg, 1.88 mmol), NaOH (226 mg, 5.64 mmol) and dioxane afforded **32** as a light yellow solid which was re-crystallised from a mixture of toluene and ethanol (180 mg, 38%); mp: >250 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.04 (s, 2H), 7.67-7.78 (m, 2H), 7.93 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.13 (dd, *J* = 8.4 & 0.8 Hz, 2H), 8.85 (d, *J* = 8.0 Hz, 1H), 9.32 (s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 61.4, 123.2, 123.6, 124.5, 126.8, 127.4, 127.5, 128.5, 128.8, 128.9, 130.0, 134.1, 138.9, 167.7.

MS (ESI$^-$): *m/z* (%) = 251 (100) [M − H]$^-$.

Anal. calcd for $C_{16}H_{12}O_3 \cdot 0.25H_2O$: C, 74.84, H, 4.91; found, C, 74.82, H, 4.83.

Methyl 9-(bromomethyl)phenanthrene-3-carboxylate (33)

A flask containing **31** (1.17 g, 4.39 mmol) was briefly evacuated and backfilled with argon. Anhydrous DCM (100 mL) was cannulated into the flask and the resulting solution cooled to 0 °C. Phosphorus tribromide (1.65 mL, 17.56 mmol) was then added dropwise to the stirring solution. After complete addition, the reaction mixture was stirred at 0 °C for 30 min and then at room temperature until TLC confirmed complete conversion. After ~ 2 h the reaction mixture was again cooled to 0 °C and excess PBr_3 destroyed by the dropwise addition of a saturated $NaHCO_3$ solution. The organic layer was subsequently isolated, dried over $MgSO_4$ and concentrated in vacuo to afford an off-white solid which was dissolved in diethyl ether (100 mL) and washed successively with H_2O (40 mL) and brine (40 mL). Drying over $MgSO_4$ followed by concentration in vacuo yielded **33** as an off-white solid (994 mg, 69%); mp: 135-139 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.03 (s, 3H), 5.00 (s, 2H), 7.73-7.78 (m, 2H), 7.86 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 8.20 (dd, *J* = 8.4 & 1.8 Hz, 1H), 8.22-8.27 (m, 1H), 8.80-8.87 (m, 1H), 9.39 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ =31.8, 52.4, 123.5, 124.7, 125.1, 126.9, 127.4, 127.5, 128.1, 128.6, 128.8, 129.6, 130.3, 131.2, 134.0, 134.3, 167.2.

MS (CI$^+$): *m/z* (%) = 328/330 (69/67) [M$^+$], 249 (100).

Anal. Calcd for $C_{17}H_{13}O_2Br$: C, 62.03, H, 3.98; Found, C, 62.31, H, 4.31.

Methyl 9-methylphenanthrene-3-carboxylate (34)

33 (500 mg, 1.52 mmol) and triethylamine (0.21 mL, 1.52 mmol) were dissolved in dioxane (100 mL) and the resultant 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. The resultant solid was taken-up in DCM (50 mL) and washed successively with aq 1M HCl, H_2O, and brine (25 mL each). Drying over $MgSO_4$ followed by concentration in vacuo afforded **34** as an off-white solid (344 mg, 91%); mp: 152-156 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.74 (s, 3H), 4.02 (s, 3H), 7.58 (s, 1H), 7.65-7.75 (m, 2H), 7.81 (d, *J* = 8.4 Hz, 1H), 8.04-8.09 (m, 1H), 8.43 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.78-8.83 (m, 1H), 9.38 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ =20.2, 52.2, 123.2, 124.7, 125.0, 126.2, 126.5, 126.8, 127.0, 127.0, 127.8, 129.0, 130.5, 132.1, 134.8, 135.5, 167.5.

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}O_2$: 251.1067; found 251.1059.

9-Methylphenanthrene-3-carboxylic acid (35)

Following general procedure D, **34** (310 mg, 1.24 mmol), NaOH (149 mg, 3.72 mmol) and dioxane afforded **35** as an off-white solid (199 mg, 68%); mp: >250 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.70 (s, 3H), 7.69-7.78 (m, 3H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.09 (dd, *J* = 8.0 & 1.2 Hz, 1H), 8.09-8.12 (m, 1H), 8.82-8.86 (m, 1H), 9.33 (s, 1H), 13.01 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.7, 123.1, 124.3, 124.9, 125.9, 126.6, 127.2, 127.4, 128.0, 128.0, 128.3, 130.0, 131.5, 134.2, 135.2, 167.5.

MS (ESI^-): *m/z* (%) = 235 (100) $[M - H]^-$.

Anal. calcd for $C_{16}H_{12}O_2$: C, 81.34, H, 5.12; found, C, 81.08, H, 5.40.

9-(Isopropylaminomethyl)phenanthrene-3-carboxylic acid methyl ester (36)

To a stirred mixture of **15** (750 mg, 2.84 mmol) and isopropylamine (0.41 mL, 4.97 mmol) in anhydrous DCE (100 mL) was added sodium triacetoxyborohydride (843 mg, 3.98 mmol). The resultant suspension was stirred at room temperature for 24 h. At this point TLC indicated incomplete conversion so 12 drops of glacial acetic acid were added to help catalyse the reaction. Stirring was continued for another 24 h when excess sodium triacetoxyborohydride was destroyed via the dropwise addition of a saturated aqueous $NaHCO_3$ solution. EtOAc (40 mL) was added and the organic phase isolated, washed with brine (40 mL), dried over $MgSO_4$ and concentrated in vacuo to yield an orange oil. Purification by flash chromatography (EtOAc followed by 20% MeOH in EtOAc) afforded **36** as a golden coloured oil (779 mg, 89%);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.4 Hz, 6H), 2.98-3.09 (m, 1H), 4.02 (s, 3H), 4.27 (s, 2H), 7.65-7.74 (m, 2H), 7.77 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 8.18 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.80-8.84 (m, 1H), 9.38 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1, 49.1, 49.6, 52.3, 123.4, 124.3, 125.0, 125.5, 126.6, 126.9, 127.2, 127.5, 128.4, 129.4, 130.9, 130.9, 134.5, 137.3, 167.4.

HRMS-ESI: *m/z* $[M]^+$ calcd for $C_{20}H_{21}NO_2$: 305.1572; found 305.1598.

9-(Isopropylaminomethyl)phenanthrene-3-carboxylic acid (37)

To a stirring solution of **36** (740 mg, 2.41 mmol) in a mixture of dioxane (80 mL) and H_2O (20 mL) was added dropwise a NaOH solution (289 mg, 7.23 mmol dissolved in 20 mL H_2O). The resultant mixture was stirred at 75 °C until TLC indicated complete hydrolysis. After 4 h the reaction mixture was allowed to cool to room temperature and the dioxane removed in vacuo. The resultant aqueous solution was topped up with H_2O and acidified to pH 3 using aq 1M HCl. No product precipitated from solution so the pH was re-adjusted to 7 using aq 1 M NaOH and the solution concentrated in vacuo to afford a white solid. The crude product was dissolved in a minimum volume of water and then absorbed onto AG-50 resin. The column was first eluted with water until the pH of the aqueous fractions was neutral. The product was then eluted using aq 1 M pyridine. Concentration of the aqueous pyridine fractions in vacuo afforded **37** as a white solid which was azeotroped with water to remove any remaining pyridine and then dried over P_2O_5 (496 mg, 70%); mp: >250 °C;

^{1}H NMR (400 MHz, D_2O/NaOD, pH 11): δ = 0.99 (d, *J* = 6.4 Hz, 6H), 2.61-2.72 (m, 1H), 3.46 (s, 2H), 6.99 (s, 1H), 7.33-7.39 (m, 1H), 7.42-7.52 (m, 3H), 7.91 (dd, *J* = 8.0 & 1.2 Hz, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 8.88 (s, 1H).

^{13}C NMR (125 MHz, D_2O/NaOD, pH 11): δ = 21.2, 47.1, 47.9, 122.8, 123.1, 123.5, 124.5, 126.5, 126.6, 126.7, 127.8, 128.4, 129.5, 129.8, 132.4, 133.6, 134.1, 175.1.

HRMS-ESI: *m/z* $[M - H]^-$ calcd for $C_{19}H_{19}NO_2$: 292.1343; found: 292.1352.

Anal. calcd for $C_{19}H_{19}NO_2 \cdot 0.55H_2O$: C, 73.93, H, 6.76, N, 4.54. found, C, 73.90, H, 6.41, N, 4.45.

Methyl 9-(3-methoxy-3-oxopropyl)phenanthrene-3-carboxylate (38)

14 (1.00g, 3.12 mmol) was dissolved in ethyl acetate (150 mL) with the aid of stirring and heating. The resultant solution 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 to afford a viscous pale yellow oil. Purification by flash column chromatography (5 → 30% EtOAc in hexane) afforded **38** as a light coloured oil which solidified on standing (536 mg, 53%); mp: 88-92 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.84 (t, *J* = 8.0 Hz, 2H), 3.48 (t, *J* = 8.0 Hz, 2H), 3.72 (s, 3H), 4.02 (s, 3H), 7.63 (s, 1H), 7.66-7.76 (m, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 8.10 (dd, *J* = 8.0 & 1.6 Hz, 1H), 8.15-8.21 (m, 1H), 8.80-8.87 (m, 1H), 9.39 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5, 34.3, 51.8, 52.3, 123.6, 124.1, 125.0, 125.7, 126.6, 127.0, 127.3, 127.5, 128.2, 129.2, 130.9, 130.9, 134.6, 137.5, 167.4, 173.3.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{20}H_{18}O_4$: 345.1097; found 345.1095.

Anal. calcd for $C_{20}H_{18}O_4$: C, 74.52, H, 5.63; found, C, 74.34, H, 6.04.

9-(3-Methoxy-3-oxopropyl)phenanthrene-3-carboxylic acid (39)

Following general procedure D, **38** (350 mg, 1.09 mmol), NaOH (262 mg, 6.54 mmol) and THF afforded **39** as an off-white solid (156 mg, 49%); mp: >250 °C;

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.75 (t, J = 7.5 Hz, 2H), 3.39 (t, J = 7.5 Hz, 2H), 7.73-7.81 (m, 3H), 8.01 (d, J = 8.0 Hz, 1H), 8.12 (dd, J = 8.0 & 1.5 Hz, 1H), 8.17-8.22 (m, 1H), 8.87-8.92 (m, 1H), 9.33 (s, 1H), 12.60 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.3, 34.4, 123.9, 124.8, 124.8, 125.7, 127.1, 127.7, 128.0, 128.8, 128.9, 128.9, 130.6, 131.0, 134.4, 138.2, 168.0, 174.2.

HRMS-ESI: *m/z* $[M - H]^-$ calcd for $C_{18}H_{14}O_4$: 293.0819; found 293.0821.

Anal. calcd for $C_{18}H_{14}O_4 \cdot 0.25H_2O$: C, 72.35, H, 4.89; found, C, 72.36, H, 5.02.

(9-Iodophenanthren-3-yl)methanol (40)

A stirred suspension of **1** (3.00 g, 8.62 mmol) and thionyl chloride (10 mL) in anhydrous dioxane (150 mL) was heated under reflux for 12 h. The solution was then allowed to cool to room temperature and the solvent removed in vacuo. The product was then dissolved in anhydrous THF and again concentrated in vacuo to remove any traces of thionyl chloride. The crude acid chloride was then dissolved in anhydrous THF (100 mL) and the resulting solution cooled to 0 °C using an ice water bath. Sodium borohydride (571 mg, 15.09 mmol) was then added portionwise over a period of 10 minutes. After complete addition the suspension was stirred at 0 °C for 30 minutes and then at room temperature for 12 h. Excess sodium borohydride was destroyed via the dropwise addition of H_2O. The solvent was then removed in vacuo and the resultant solid suspended between EtOAc and H_2O (100 mL each). The aqueous layer was further extracted with EtOAc (2 × 50 mL) and the organics pooled, washed with H_2O (50 mL), brine (50 mL), and dried over $MgSO_4$. Concentration in vacuo yielded a yellow solid. Purification by flash chromatography (10 → 40% EtOAc in hexane) afforded **40** as a yellow solid (2.45 g, 85%); mp: 164-168 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.77 (s, 2H), 5.44 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.72-7.81 (m, 2H), 7.92 (d, J = 8.0 Hz, 1H), 8.10-8.17 (m, 1H), 8.59 (s, 1H), 8.75 (s, 1H), 8.78-8.83 (m, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 63.1, 97.9, 120.0, 123.2, 126.3, 127.5, 127.7, 128.1, 129.4, 130.1, 131.4, 131.5, 132.4, 138.0, 142.1.

HRMS-CI: *m/z* $[M^+]$ calcd for $C_{15}H_{11}OI$: 333.9855; found 333.9862.

Anal. calcd for $C_{15}H_{11}OI$: C, 53.92, H, 3.32; found, C, 53.63, H, 3.54.

3-(Bromomethyl)-9-iodophenanthrene (41)

A flask containing **40** (2.43 g, 7.27 mmol) was briefly evacuated and backfilled with argon. Anhydrous DCM (200 mL) was cannulated into the flask and the resulting suspension cooled to 0 °C. Phosphorus tribromide (2.73 mL, 29.08 mmol) was then added dropwise to the stirred suspension. After complete addition the solution was stirred at 0 °C for 30 min

and then at room temperature until TLC confirmed complete conversion. After 1 h the reaction mixture was again cooled to 0 °C and excess PBr_3 destroyed by the dropwise addition of a saturated $NaHCO_3$ solution. The organic layer was subsequently isolated, dried over $MgSO_4$ and concentrated in vacuo to afford a light yellow solid which was dissolved in diethyl ether (100 mL) and washed successively with H_2O (40 mL) and brine (40 mL). Drying over $MgSO_4$ followed by concentration in vacuo yielded **41** as a pale yellow solid (1.87 g, 65%); mp: 124-128 °C;

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.75 (s, 2H), 7.61 (dd, *J* = 8.0 & 1.5 Hz, 1H), 7.66-7.72 (m, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 8.20-8.23 (m, 1H), 8.41 (s, 1H), 8.59-8.62 (m, 1H), 8.63 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.1, 99.7, 122.9, 123.3, 127.8, 128.1, 128.3, 128.4, 130.4, 130.5, 132.4, 132.8, 133.5, 136.7, 138.2.

HRMS-CI: *m/z* [M^+] cald for $C_{15}H_{10}BrI$: 395.9011; found 395.9012.

(9-Iodophenanthren-3-yl)acetonitrile (42)

41 (1.00 g, 2.52 mmol) was dissolved in anhydrous DCM (75 mL) and stirred vigorously with a solution of sodium cyanide (136 mg, 2.77 mmol) and tetra-*n*butylammonium bromide (89 mg, 0.28 mmol) in H_2O (75 mL). After 5 days TLC indicated complete conversion. The organic layer was subsequently isolated and the aqueous phase extracted with DCM (2 × 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo to afford a brown oil. Purification by flash chromatography (10 → 20% EtOAc in hexane) yielded **42** as a yellow solid (492 mg, 57%); mp: 141-145 °C;

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.00 (s, 2H), 7.50 (dd, *J* = 8.5 & 2.0 Hz, 1H), 7.68-7.74 (m, 2H), 7.77 (d, *J* = 8.5 Hz, 1H), 8.20-8.25 (m, 1H), 8.41 (s, 1H), 8.59-8.63 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 99.5, 122.1, 122.8, 126.6, 127.8, 128.3, 128.5, 128.7, 130.0, 130.6, 132.4, 132.4, 133.4, 137.9.

HRMS-ESI: *m/z* [M + Na] + cald for $C_{16}H_{10}NI$: 365.9743; found 365.9750.

(9-Iodophenanthren-3-yl)acetic acid (43)

A stirred mixture of **42** (471 mg, 1.37 mmol), glacial acetic acid (15 mL), conc H_2SO_4 (3 mL) and H_2O (3 mL) was heated under reflux until TLC indicated complete consumption of the starting material. After 3 h the mixture was allowed to cool to room temperature and then diluted with H_2O (100 mL). The aqueous mixture was extracted with diethyl ether (100 mL then 2 × 50 mL) and the organic layers pooled and extracted with aq 1 M NaOH (3 × 50 mL). The alkaline phases were combined and acidified to pH 1 using aq 2 M HCl. The aqueous solution was then extracted with diethyl ether (100 mL then 2 × 50 mL) and the organic layers pooled, dried over Na_2SO_4 and concentrated in vacuo to afford **43** as a straw coloured solid (355 mg, 72%); mp: 218-222 °C (dec);

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.87 (s, 2H), 7.58 (dd, *J* = 8.0 & 1.6 Hz, 1H), 7.73-7.80 (m, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 8.11-8.16 (m, 1H), 8.59 (s, 1H), 8.73 (s, 1H), 8.78-8.83 (m, 1H), 12.48 (br s, 1H);

^{13}C NMR (100 MHz, DMSO-d_6): δ = 40.9, 98.1, 123.3, 123.6, 127.4, 127.7, 128.2, 129.1, 129.5, 129.9, 131.2, 131.4, 132.4, 134.6, 137.9, 172.5.

HRMS-ESI: *m/z* $[M-H]^-$ cald for $C_{16}H_{11}O_2I$: 360.9735; found 360.9731.

Anal. calcd for $C_{16}H_{11}O_2I$: C, 53.06, H, 3.06; found, C, 52.85, H, 3.17.

9-Iodophenanthrene-3-carboxylic acid benzylamide (44a)

A stirred suspension of **1** (1.00 g, 2.87 mmol) and thionyl chloride (5 mL) in anhydrous benzene (45 mL) was heated under reflux for 12 h. The solution was then allowed to cool to room temperature and the solvent removed in vacuo. The product was dissolved in a second aliquot of anhydrous benzene and again concentrated in vacuo to remove any traces of thionyl chloride. The crude acid chloride was then dissolved in anhydrous dioxane (20 mL) and added dropwise to a rapidly stirring solution of benzylamine (0.31 mL, 2.87 mmol) and triethylamine (0.40 mL, 2.87 mmol) in anhydrous dioxane (30 mL). After complete addition the solution was allowed to stir for 3 h at room temperature. The solvent was then removed in vacuo and the resultant solid dissolved in a mixture of DCM (100 mL) and H_2O (40 mL). The organic layer was isolated and washed successively with aq 1M HCl (2 × 30 mL), aq 1M NaOH (2 × 30 mL), and H_2O (40 mL). Drying over $MgSO_4$ followed by concentration in vacuo afforded **44a** as an off-white solid (459.2 mg, 37%); mp: 208-212 °C (dec);

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.61 (d, *J* = 6.0 Hz, 2H), 7.23-7.24 (m, 1H), 7.33-7.38 (m, 2H), 7.38-7.43 (m, 2H), 7.78-7.87 (m, 2H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.16-8.20 (m, 1H), 8.17 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.68 (s, 1H), 8.91-8.95 (m, 1H), 9.38 (s, 1H), 9.42 (t, *J* = 6.0 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 42.8, 101.0, 122.0, 123.6, 126.1, 126.8, 127.3, 127.7, 128.1, 128.3, 128.6, 129.1, 130.2, 131.6, 132.6, 132.7, 134.0, 137.7, 139.5, 165.8.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{22}H_{16}NOI$: 460.0169; found 460.0164.

Anal. calcd for $C_{22}H_{16}NOI$: C, 60.43, H, 3.69, N, 3.20; found, C, 60.14, H, 3.81, N, 2.85.

9-Iodophenanthrene-3-carboxylic acid 2-phenethyl amide (44b)

The procedure was identical to that described for **44a** with the exception that phenethylamine (0.36 mL, 2.87 mmol) was used. The reaction afforded **44b** as light brown solid (430.8 mg, 33%); mp: 194-197 °C (dec);

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.94 (t, *J* = 7.6 Hz, 2H), 3.56-3.63 (m, 2H), 7.19-7.24 (m, 1H), 7.28-7.34 (m, 4H), 7.79-7.88 (m, 2H), 8.03 (d, *J* = 8.4 Hz, 1H), 8.09 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.16-8.20 (m, 1H), 8.67 (s, 1H), 8.88-8.92 (m, 1H), 8.95 (t, *J* = 6.0 Hz, 1H), 9.26 (s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 35.1, 41.0, 100.7, 121.8, 123.3, 125.9, 127.5, 128.0, 128.2, 128.4, 128.5, 129.0, 130.2, 131.6, 132.5, 132.9, 133.8, 137.7, 139.4, 165.8.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{23}H_{18}NOI$: 474.0325; found 474.0318.

Anal. calcd for $C_{23}H_{18}NOI \cdot 0.39H_2O$: C, 60.27, H, 4.13, N, 3.06; found, C, 60.27, H, 4.40, N, 2.96.

[(9-Iodophenanthrene-3-carbonyl)amino]acetic acid tert-butyl ester (45)

Initial synthesis and purification of acid chloride was as described for **44a** with the exception that **1** (600 mg, 1.72 mmol), thionyl chloride (3 mL) and anhydrous benzene (45 mL) were used. The crude acid chloride was then dissolved in anhydrous dioxane (20 mL) and added dropwise to a rapidly stirring suspension of glycine *t*-butyl ester hydrochloride (301.7 mg, 1.80 mmol) and triethylamine (0.48 mL, 3.44 mmol) in anhydrous dioxane (30 mL) which had been pre-stirred for 30 mins. After complete addition the mixture was allowed to stir at room temperature for 3 h. The dioxane was then removed in vacuo and the resulting solid dissolved in a mixture of DCM (100 mL) and H_2O (30 mL). The organic layer was isolated and washed successively with aq 1 M HCl (2 × 30 mL), aq 1 M NaOH (2 × 30 mL), H_2O (30 mL) and brine (30 mL). Subsequent drying over $MgSO_4$ followed by concentration in vacuo afforded **45** as an orange/yellow oil (576.3 mg, 73%);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55 (s, 9H), 4.24 (d, *J* = 4.8 Hz, 2H), 7.05 (t, *J* = 4.8 Hz, 1H), 7.66-7.74 (m, 3H), 7.89 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.14-8.20 (m, 1H), 8.36 (s, 1H), 8.58-8.64 (m, 1H), 9.08 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 42.7, 82.7, 101.4, 122.6, 123.0, 124.6, 127.8, 128.0, 128.3, 129.9, 130.4, 131.9, 132.2, 133.3, 134.5, 137.8, 167.1, 169.5.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{20}NO_3I$: 484.0380; found 484.0371.

[(9-Iodophenanthrene-3-carbonyl)amino]acetic acid (46)

To a stirred solution of **45** (565.9 mg, 1.23 mmol) and *m*-dimethoxybenzene (0.81 mL, 6.15 mmol) in DCM (30 mL) was added dropwise TFA (4.57 mL, 61.5 mmol). The resulting mixture was stirred at room temperature until TLC confirmed complete deprotection. The solvent was then removed in vacuo and the resulting solid azeotroped with toluene (3 × 30 mL) to remove any traces of TFA. The solid was then suspended in diethyl ether (30 mL) and stirred for 10 mins before being filtered off and washed thoroughly with diethyl ether. Air drying subsequently afforded **46** as a light yellow solid (346.4 mg, 70%); mp: 241-244 °C (dec);

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.06 (d, *J* = 5.6 Hz, 2H), 7.79-7.88 (m, 2H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.14 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.16-8.20 (m, 1H), 8.69 (s, 1H), 8.90-8.94 (m, 1H), 9.26 (t, *J* = 5.6 Hz, 1H), 9.36 (s, 1H), 12.71 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 41.3, 101.2, 122.1, 123.5, 126.0, 127.8, 128.2, 128.7, 129.1, 130.2, 131.7, 132.1, 132.6, 134.1, 137.7, 166.1, 171.3.

HRMS-ESI: *m/z* $[M - H]^-$ calcd for $C_{17}H_{12}NO_3I$: 403.9789; found 403.9803.

Anal. calcd for $C_{17}H_{12}NO_3I$: C, 50.39, H, 2.99, N, 3.46; found, C, 50.73, H, 2.93, N, 3.11.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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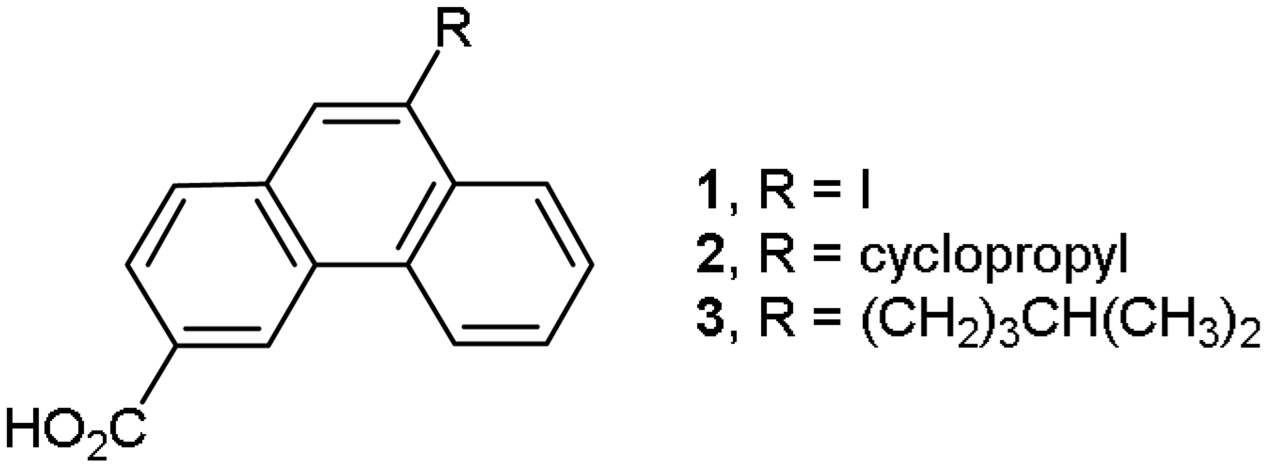

Figure 1.
NMDA receptor allosteric modulators

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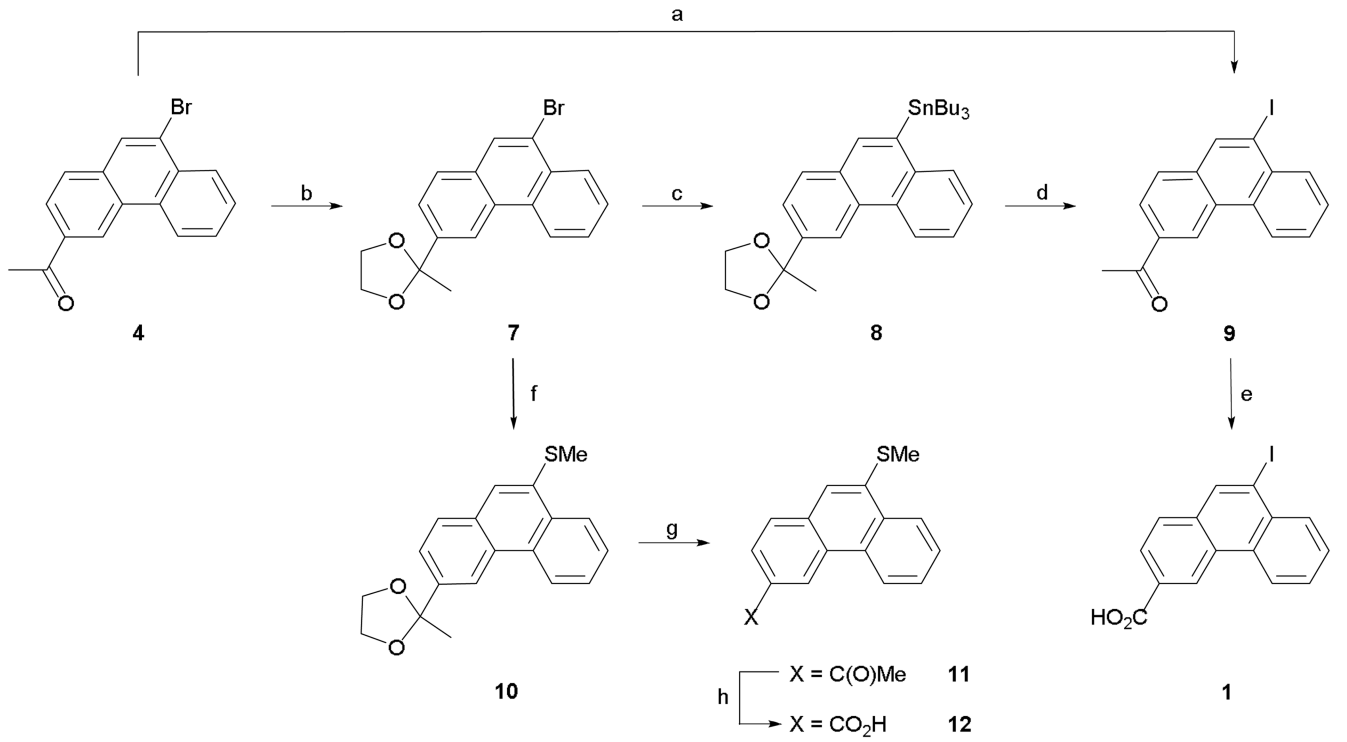

Scheme 1.

Reagents and conditions: (a) NaI, CuI, *N*,*N*'-dimethylethylenediamine, dioxane, 110 °C, 65 h; (b) Ethylene glycol, TsOH, toluene, 110 °C, 18 h; (c) (i) *n*-BuLi, THF, −78 °C, 1 h, (ii) $(n\text{-Bu})_3SnCl$, −78 °C; (d) (i) I_2, DCM, 0 °C, (ii) 2 M HCl (aq), acetone, 0.5 h; (e) (i) Br_2, NaOH (aq), dioxane, 70 °C, 1 h, (ii) conc HCl (aq); (f) (i) *n*-BuLi, THF, −78 °C, 1 h, (ii) MeSSMe, −78 °C, then rt; (g) HCl/acetone, 1 h, rt; (h) (i) Br_2, NaOH, dioxane, 40 °C, 1 h, (ii) conc HCl.

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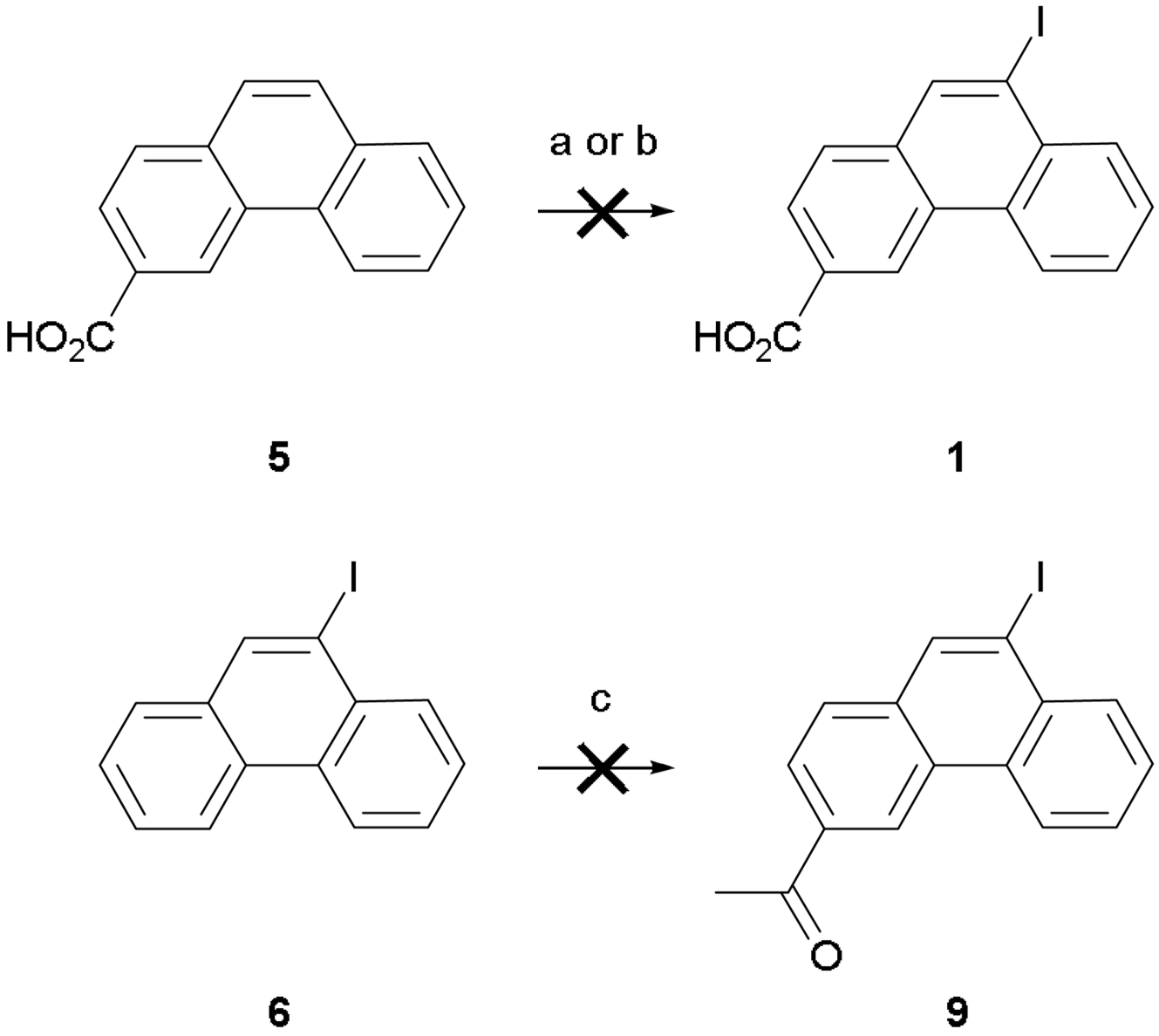
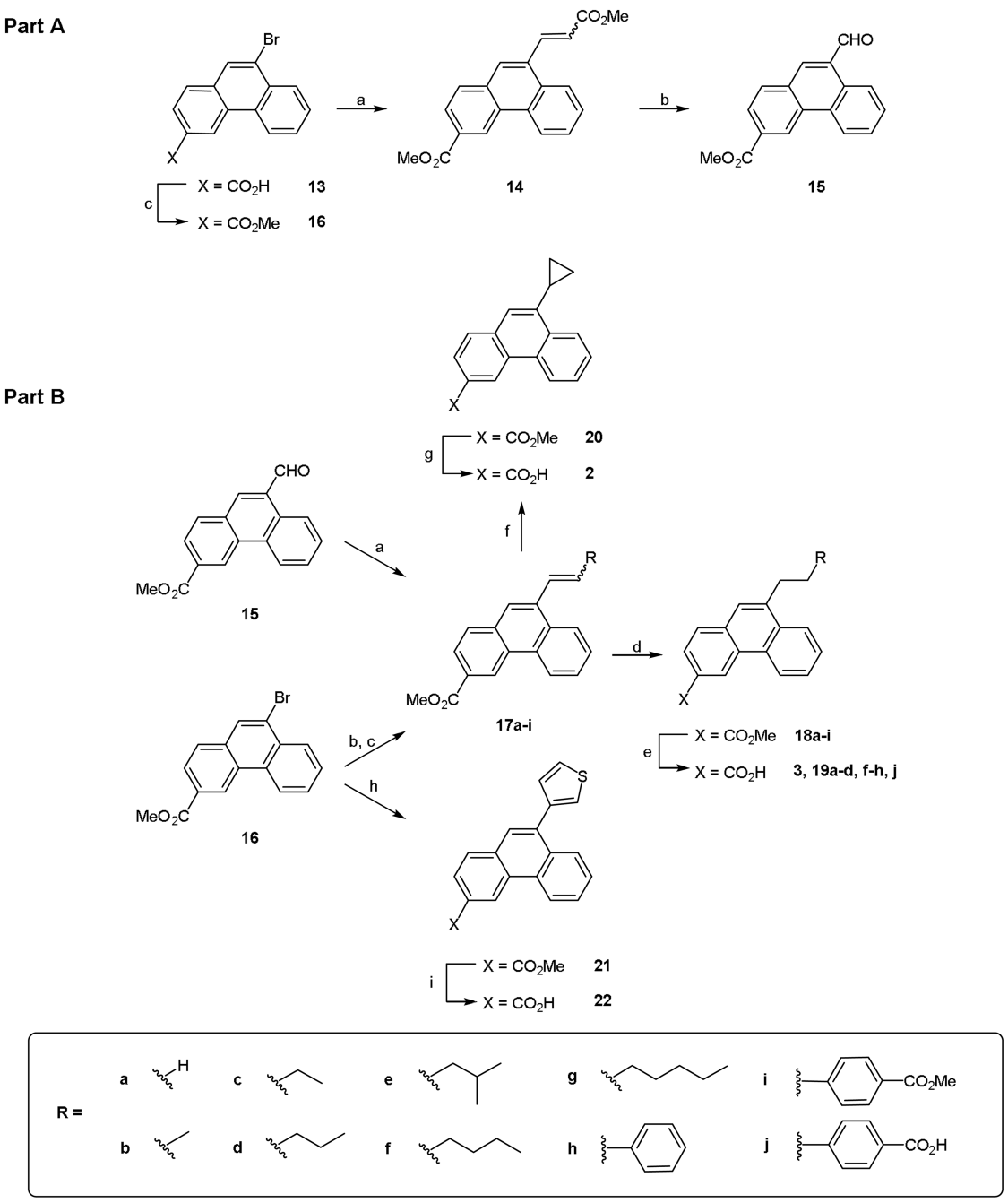


Scheme 2.

Reagents and conditions: (a) ICl, AcOH, 118 °C, 18 h; (b) NaI, NaClO, NaOH, MeOH, 0 °C then rt, 1 h; (c) AcCl, $AlCl_3$, CS_2, 5 °C then rt, 18 h.



Scheme 3.

Reagents and conditions: **Part A** (a) (i) Methyl acrylate, P(*o*-tolyl)$_3$, TEA, Pd(OAc)$_2$, DMF, 100 °C, 18 h, (ii) MeI, K_2CO_3, DMF, rt, 18 h; (b) (i) OsO_4, TMAO, *t*-BuOH/H_2O, rt, 2 days, (ii) $NaIO_4$; (c) MeOH, H_2SO_4, reflux, 48 h. **Part B** (a) RCH_2PPh_3X, KHMDS, THF, 4 h, rt; (b) alkene, P(*o*-tolyl)$_3$, TEA, Pd(OAc)$_2$, DMF, 100 °C, 18 h; (c) (*n*-Bu)$_3$SnCH=CH$_2$, Pd(PPh$_3$)$_4$, toluene, reflux, 4 h; (d) H_2, 10% Pd/C, EtOAc, rt, 18 h; (e) (i) NaOH or KOH (aq), THF, reflux or dioxane, 75 °C, (ii) 1 M HCl (aq); (f) **17a**, CH_2I_2, $ZnEt_2$, DCM, 0 °C, 18 h; (g) (i) LiOH (aq), dioxane, rt, 18 h, (ii) 1 M HCl (aq); (h) 3-thienylboronic acid,

K_2CO_3, Pd(dppf)Cl_2.DCM, DME, 80 °C, 24 h; (i) (i) NaOH (aq), dioxane, 75 °C, (ii) 1 M HCl (aq), (iii) crystallisation (AcOH).

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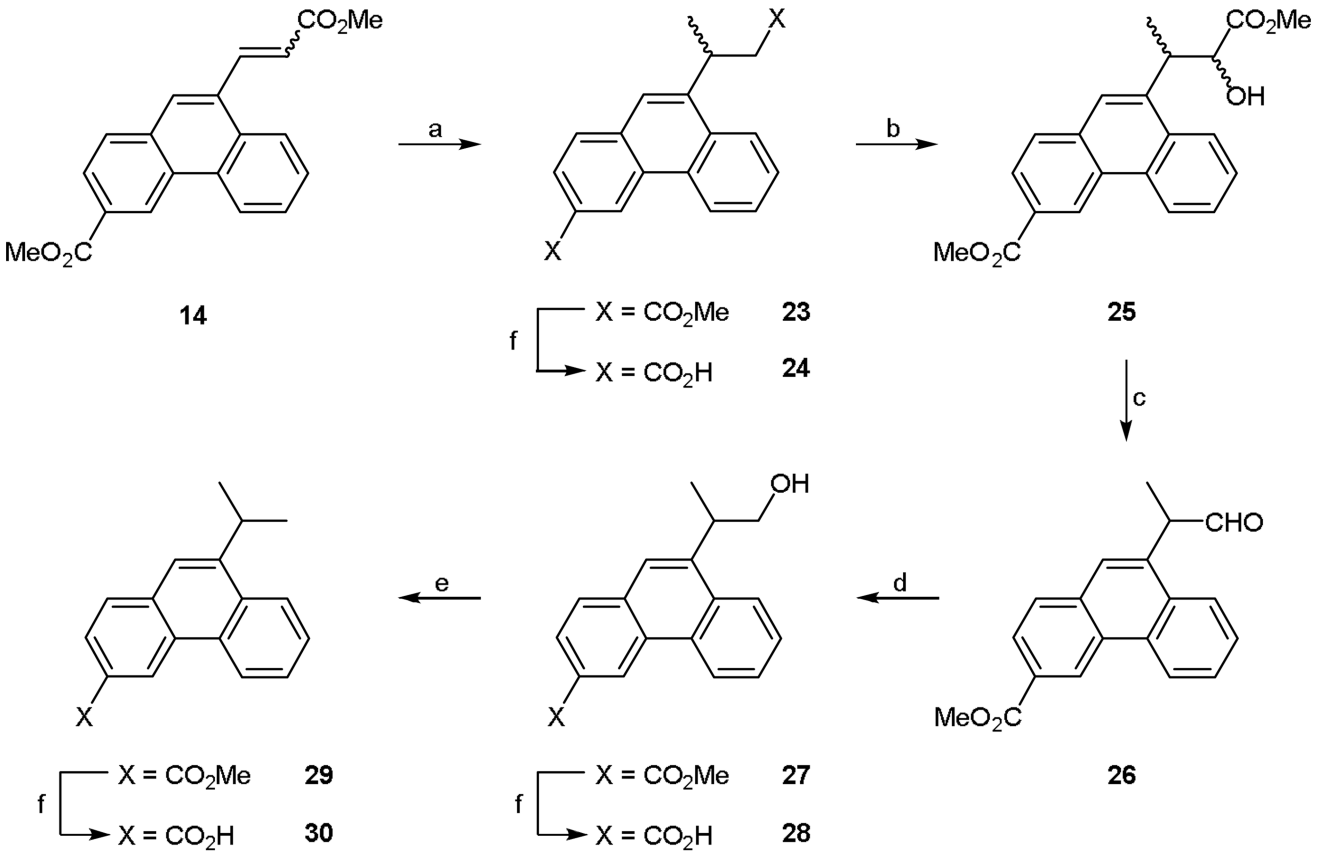

Scheme 4.

Reagents and conditions: (a) CuI, NaI, MeMgCl, TMSCl, DCM/Me_2S, −78 °C then rt, 3h; (b) KHMDS, THF, 2-tosyl-3-phenyloxaziridine, −78 °C then rt, 2h; (c) (i) $LiBH_4$, THF, 0 °C, 30 min then rt, 4h, (ii) *t*-BuOH/H_2O (4:1), $NaIO_4$, rt, 30 min; (d) $NaBH_4$, THF, rt, 4h; (e) (i) MsCl, TEA, 0 °C, 1 h then rt, 3h, (ii) NaI, acetone, reflux, 24 h, (iii) H_2, TEA, 10% Pd/C, rt, 18 h; (f) (i) NaOH (aq), dioxane, 75 °C, (ii) 1 M HCl (aq).

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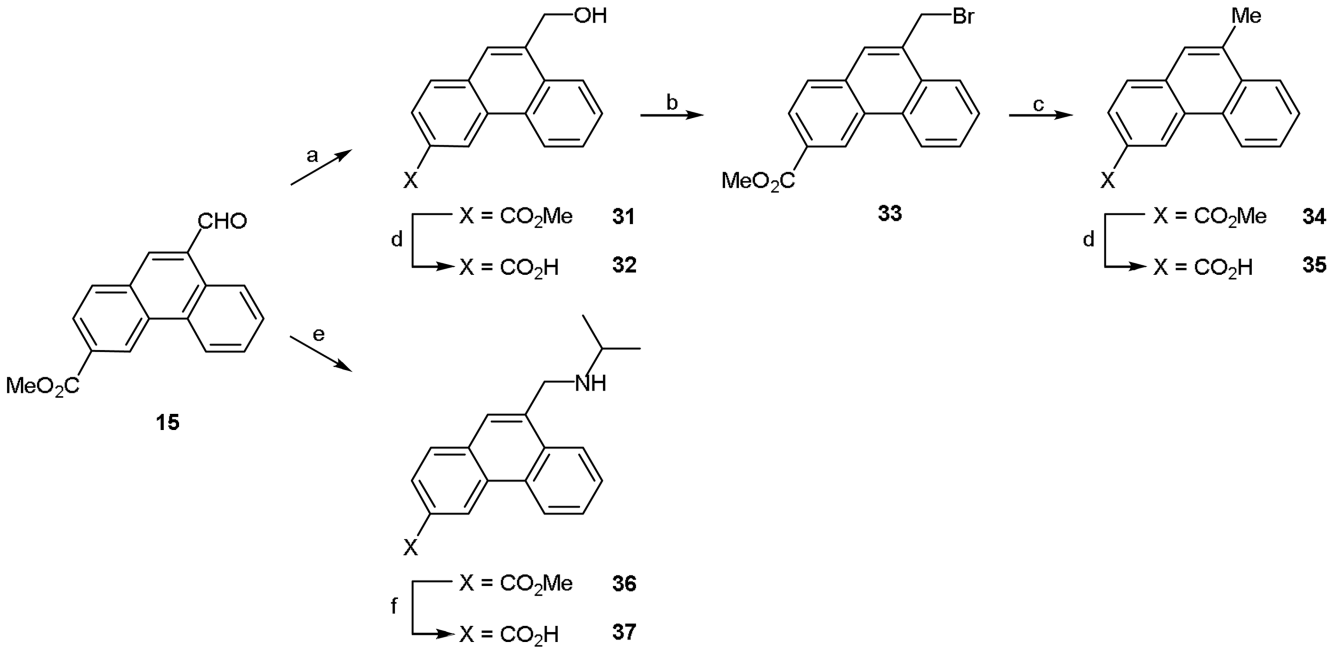

Scheme 5.

Reagents and conditions: (a) $NaBH_4$, THF, rt, 4 h; (b) PBr_3, DCM, 0 °C then rt, 2 h; (c) H_2, 10% Pd/C, rt, 18 h; (d) (i) NaOH (aq), dioxane, 75 °C, (ii) 1 M HCl (aq); (e) isopropylamine, $NaBH(OAc)_3$, DCE, rt, 40 h; (f) (i) NaOH (aq), dioxane, 75 °C, 4 h, (ii) 1 M HCl (aq), (iii) ion exchange chromatography.

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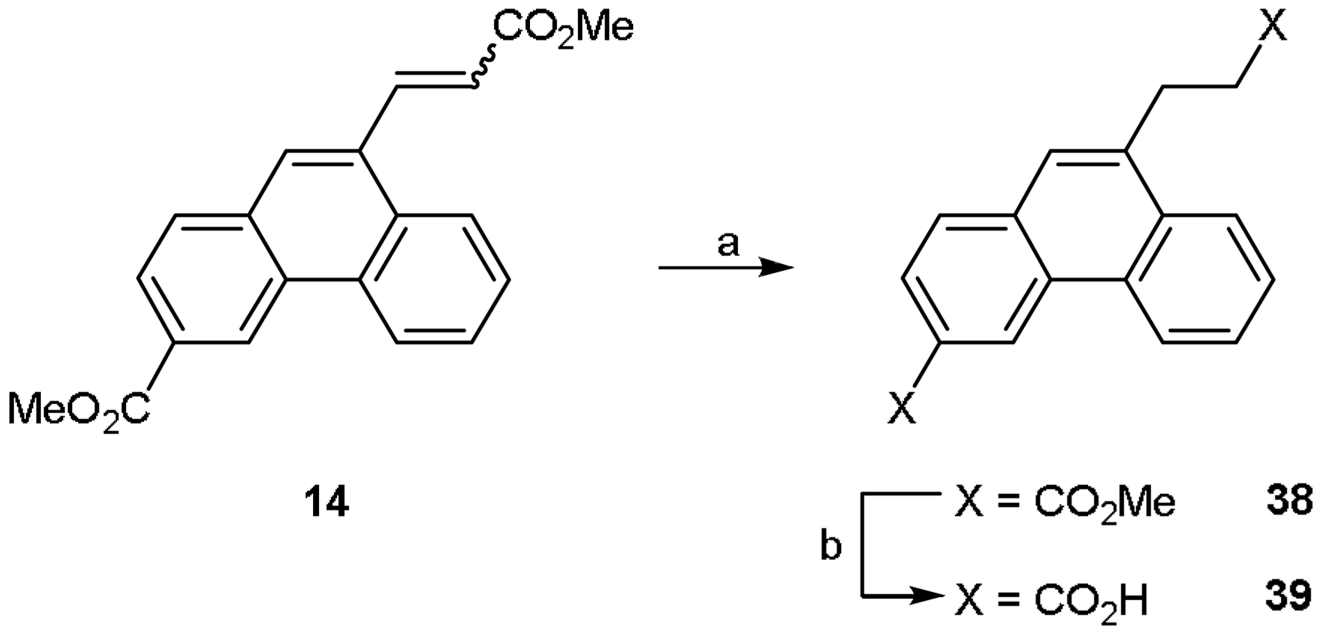

Scheme 6.

Reagents and conditions: (a) H_2, 10% Pd/C, EtOAc, rt, 18 h; (b) (i) NaOH (aq), THF, reflux, 4 h, (ii) 1 M HCl (aq).

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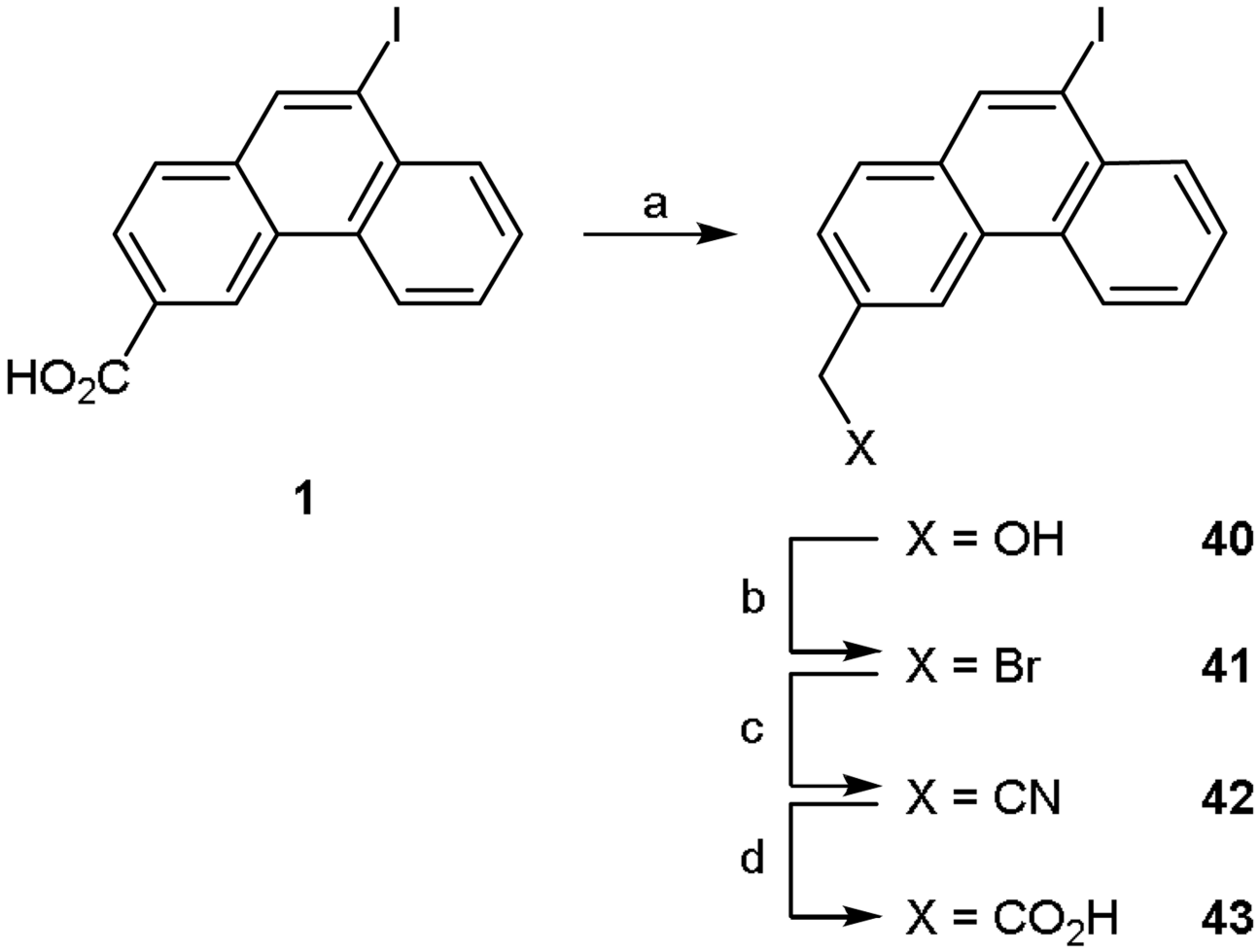
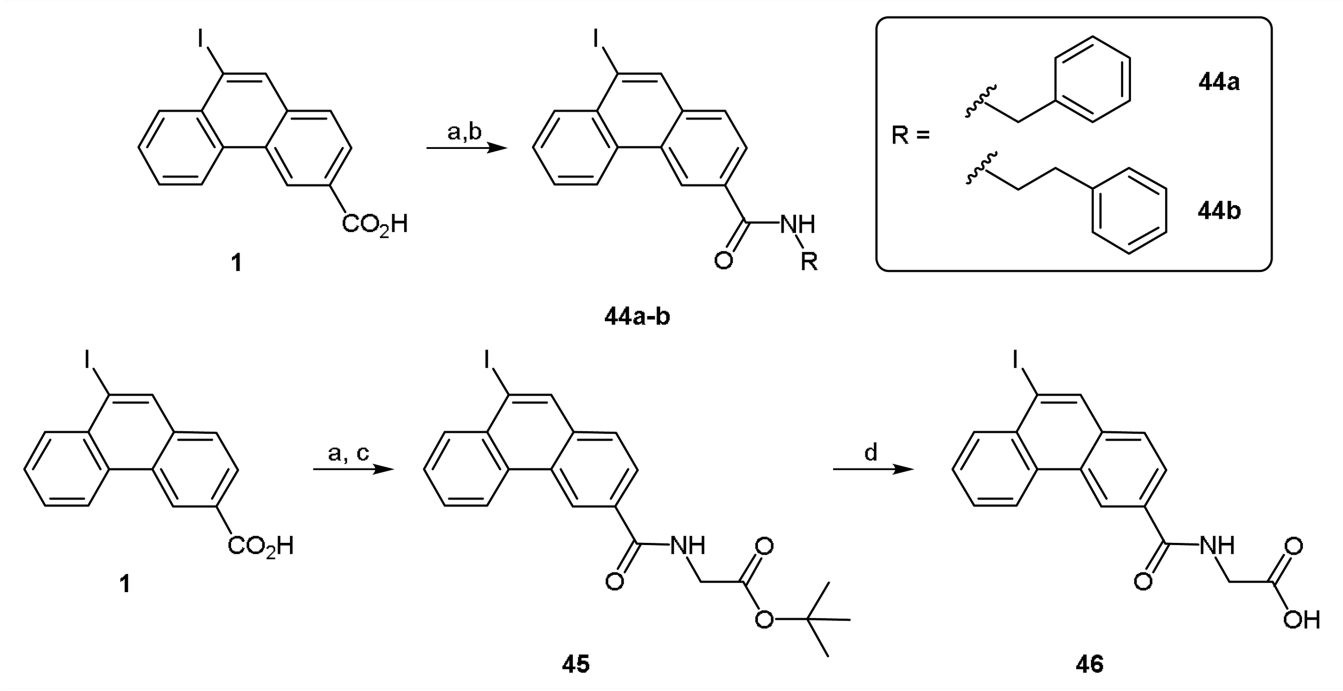


Scheme 7.

Reagents and conditions: (a) (i) $SOCl_2$, dioxane, reflux, 12 h, (ii) $NaBH_4$, THF, 0 °C, 0.5 h then rt, 12 h; (b) PBr_3, DCM, 0 °C then rt, 1 h; (c) NaCN, TBAB, H_2O/DCM (1:1), rt, 5 days; (d) AcOH, H_2SO_4, H_2O, 118 °C, 3 h.



Scheme 8.

Reagents and conditions: (a) $SOCl_2$, C_6H_6, 80 °C, 12 h; (b) R-NH_2, TEA, dioxane, rt, 3 h; (c) H-Gly-O*t*Bu.HCl, TEA, dioxane, rt, 3 h; (d) TFA, DCM, rt, 18 h.

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Table 1

Activity of selected 3,9-disubstituted phenanthrene derivatives at recombinant NMDA receptor subtypes[a]

	NMDAR (n≥4)[b]			
Compound[c]	**GluN2A**	**GluN2B**	**GluN2C**	**GluN2D**
1	8.6 ± 4.8	0.9 ± 0.1	−34.1 ± 8.3	−52.3 ± 3.0
2	36.0 ± 7.4	51.2 ± 13.2	−7.3 ± 0.4	5.6 ± 4.7
3	31.5 ± 10.0	34.0 ± 8.5	21.8 ± 8.1	24.3 ± 3.6
35	−4.8 ± 4.6	−3.2 ± 0.3	−15.1 ± 0.3	−4.1 ± 0.9
19b	6.6 ± 1.2	30.0 ± 1.8	5.2 ± 4.0	7.8 ± 1.8
19d	42.6 ± 9.6	42.1 ± 14.3	26.4 ± 5.4[d]	20.3 ± 5.3
19f	28.2 ± 11.4	20.5 ± 7.5	19.6 ± 3.0	24.6 ± 7.3
22	10.7 ± 6.4	3.9 ± 12.6	−52.7 ± 9.1	−45.2 ± 8.7
37	−21.9 ± 9.2	−0.3 ± 1.8	−13.0 ± 2.5	−2.6 ± 0.8
39	−48.1 ± 6.5	−51.1 ± 3.4	−17.8 ± 2.7	−15.1 ± 0.7
43	−23.5 ± 3.9	−30.9 ± 3.8	−46.7 ± 4.3	−66.6 ± 4.1

[a] ND = not determined; All compounds tested at a concentration of 100 μM

[b] % inhibition (negative number) or potentiation (positive number) of the responses of recombinant rat NMDA receptors (GluN1 expressed with the indicated GluN2 subunit) expressed in *Xenopus* oocytes (means ± s.e.m.).

[c] All of the compounds were made up as stocks solutions in DMSO and were soluble up to a concentration of 100 μM in the buffer used in these assays.

[d] **19d** inhibited 22% in one experiment, this value was not included in the average shown.