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Bioorganic & Medicinal Chemistry 16 (2008) 4438–4456

Bioorganic & Medicinal Chemistry

Novel inhibitors of 17β-hydroxysteroid dehydrogenase type 1: Templates for design

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Received 19 November 2007; revised 12 February 2008; accepted 19 February 2008
Available online 7 March 2008

Abstract—The 17β-hydroxysteroid dehydrogenases (17β-HSDs) catalyze the interconversion between the oxidized and reduced forms of androgens and estrogens at the 17 position. The 17β-HSD type 1 enzyme (17β-HSD1) catalyzes the reduction of estrone (E1) to estradiol and is expressed in malignant breast cells. Inhibitors of this enzyme thus have potential as treatments for hormone dependent breast cancer. Syntheses and biological evaluation of novel non-steroidal inhibitors designed to mimic the E1 template are reported using information from potent steroidal inhibitors. Of the templates investigated biphenyl ethanone was promising and led to inhibitors with IC_{50} values in the low micromolar range.

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1. Introduction

Breast cancer is one of the most common cancers in women with an estimated global mortality of around 500,000 deaths per year. Of these breast tumors a large proportion are initially hormone-responsive with circulating estrogens playing a vital role in their growth. Steroidogenic enzyme inhibitors can reduce circulating and tissue levels of active estrogens by blocking their biosynthetic pathways and thus can represent an effective treatment for hormone dependent breast cancer (HDBC).

Aromatase inhibitors, which prevent the conversion of androgens into estrogens, are currently used as an adjuvant therapy to treat HDBC.[1] It has been proposed, however, that a more important source of estrone (E1) in breast tumors is the body's reservoir of estrone 3-*O*-sulfate (E1S), which can be converted to E1 by the action of estrone sulfatase.[2] Estrone sulfatase inhibitors have also been investigated and are now progressing into clinical trials.[3–5]

Estrone itself, however, is not the most potent human estrogen and, while inhibitors of E1 formation have reached an advanced stage of use and development, another attractive target for the treatment of HDBC is inhibition of 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1).

This enzyme is one of a class of enzymes known as the 17β-hydroxysteroid dehydrogenases (17β-HSDs) that catalyze the interconversion between the oxidized and reduced forms of androgens and estrogens at the 17 position. Although reversible, their activity is mainly unidirectional and thus they can be classified as oxidative or reductive. Thirteen members of this enzyme family have been identified to date, eleven of which exist in humans where they regulate the bioavailability of active androgens and estrogens.[6,7] While all require NAD(P)H or $NAD(P)^+$ as cofactor, each type has a selective substrate affinity, directional activity, and a particular tissue distribution.

Keywords: Hydroxysteroid dehydrogenase; 17β-HSD1; 17β-HSD2; Breast cancer.

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doi:10.1016/j.bmc.2008.02.059

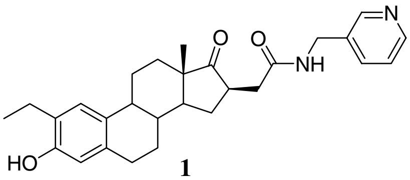
The 17β-HSD1 enzyme, which has a preferentially reductive activity using NADPH as cofactor,[8,9] is responsible for the reduction of the keto group of the weakly active E1 to give the most potent of the human estrogens, 17β estradiol (E2).

The enzyme is expressed in many steroidogenic tissues, including breast tissue, and has been found to be active in malignant breast cells.[10,11] Estradiol is known to stimulate the growth and development of HDBC[12]; therefore inhibition of the final step in the synthesis of E2, by the design of selective inhibitors of 17β-HSD1, is an attractive option for the treatment of HDBC. Some progress has recently been made by our group in proving the in vivo validity of this concept.[13]

The 17β-HSD1 enzyme consists of 327 amino acid residues, with a subunit mass of ~35 kDa, and exists as a homodimer.[14] Much crystallographic information has been determined, including that for the enzyme in its native form,[15] in complex with E2 and NADP,[16] with E2 alone,[17] with equilin and NADP,[18] and with the inhibitor EM-1745.[19] This structural information is a useful aid for identifying potential inhibitors of 17β-HSD1 using in silico techniques.

Inhibitors of 17β-HSD1 have been reported by several groups and this field has been reviewed by Poirier.[20] Common structural features can be identified which aid binding at the active site. These include a phenol, which can undergo bifurcated hydrogen bonding to His221 and Glu282 residues of the protein, and a hydrophobic scaffold which inhabits the hydrophobic area in the active site.

Most of the inhibitors of 17β-HSD1 reported to date are based on the steroid scaffold, with expansion from the 6, 15, 16, and 17 positions. Poirier et al. have reported a number of inhibitors. These include E2 derivatives bearing a short side chain at the C17α and C16α positions on the E2 skeleton,[21] novel hybrid inhibitors of 17β-HSD1[22] and data for C6-(*N*,*N*-butyl-methyl-heptanamide) derivatives of E1 and E2[23] with a 6β-E2 derivative, which shows 82% inhibition of 17β-HSD1 at 1 μM and 29% inhibition at 0.1 μM in an assay using intact T-47D cells. Patents detailing steroidal inhibitors have been published by our group,[24] Solvay Pharmaceuticals[25,26] and Schering AG.[27,28]



1

Figure 1. Potent steroidal inhibitor of 17β-HSD1.

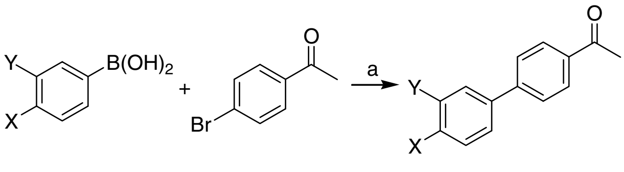
Less has been reported about non-steroidal inhibitors of 17β-HSD1. A patent filed by Solvay Pharmaceuticals details thiopyrimidone inhibitors,[29] of which the most potent has an IC_{50} of 0.6 μM in a purified enzyme assay. Recently, phenyl ketone- and biphenyl ketone-based compounds have been reported to show moderate inhibition of 17β-HSD1, with the best showing 46% inhibition at 100 μM in an enzyme-based assay.[30] As part of our approach to developing non-steroidal inhibitors, we have investigated different possible mimics of the E1 skeleton and different areas of expansion from these. We report here a study of various templates to develop this new and growing area. In particular, we envisaged synthesizing non-steroidal mimics of our most potent steroidal inhibitors such as **1** (Fig. 1), which has an IC_{50} of 27 nM in an assay using intact T-47D cells.[31–33] As steroids are quite hydrophobic a non-steroidal template may give inhibitors with an improved PK profile.

2. Results and discussion

2.1. Synthesis

Our search for non-steroidal inhibitors of 17β-HSD1 began with an investigation of possible scaffolds, which might replace the E1 skeleton. It was decided initially to keep the phenol and ketone functionalities, since these are known to be important for binding. An investigation of biphenyl ethanone-type systems with different linkers between the phenyl rings[34] showed that those with just the C–C linker (e.g., **2** Scheme 1) showed activity. This compound and the others evaluated in this paper are listed in Tables 1–4.

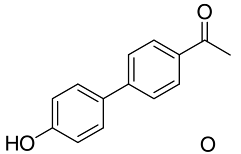
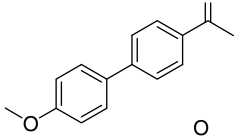
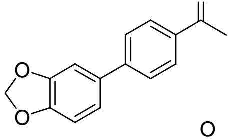
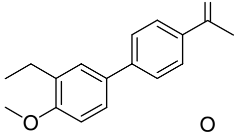
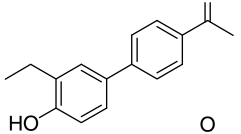
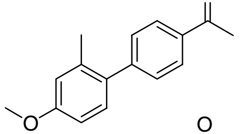
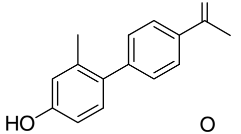
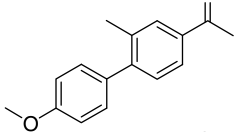
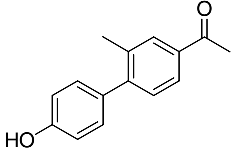
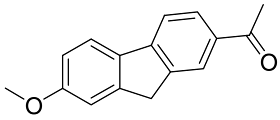
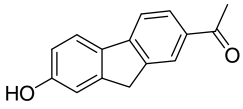
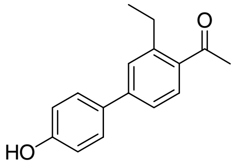
Compound **2** was synthesized by a Suzuki coupling of 4-hydroxyphenyl boronic acid to 4-bromoacetophenone (Scheme 1). This reaction was performed under microwave conditions at 150 °C for 10 min to give an unoptimized yield, after purification by flash chroma-



2 X=OH, Y=H
3 X=OMe, Y=H
4 X,Y=methylene dioxy

Scheme 1. Reagents and conditions: (a) $Pd(OAc)_2$, K_2CO_3, Bu_4NBr, $EtOH/H_2O$, μW 150 °C.

Table 1. Inhibition of 17β-HSD type 1 and type 2 by non-steroidal mimics of E1 based on the biphenyl ethanone template[a,b]

Structure	Compound	Inhibition of type 1 (% @ 10 μM)	Inhibition of type 2 (% @ 10 μM)	Type 1 (IC_{50} μM)
	**2**	97	nd	3.7
	**3**	Inactive	nd	nd
	**4**	Inactive	nd	nd
	**8**	Inactive	nd	nd
	**16**	73	51	5.4
	**9**	Inactive	nd	nd
	**17**	89	nd	3.7
	**24**	Inactive	nd	nd
	**25**	Inactive	nd	nd
	**27**	Inactive	nd	nd
	**28**	86	nd	4.8
	**31**	71	nd	9.9

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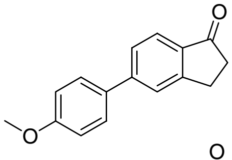
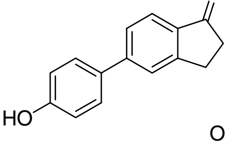
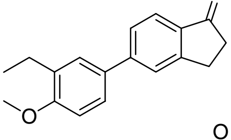
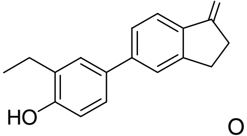
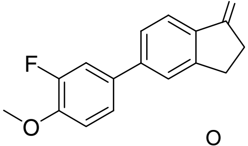
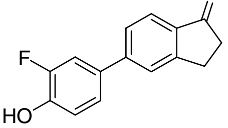
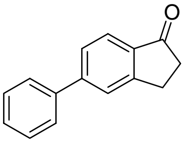
[a] Mean of at least two measurements with typically a SD or spread of ±14%.

[b] nd, not determined.

Table 2. Inhibition of 17β-HSD type 1 and type 2 by non-steroidal mimics of E1 based on the biphenyl indanone template[a,b]

Structure	Compound	Inhibition of type 1 (% @ 10 μM)	Inhibition of type 2 (% @ 10 μM)	Type 1 (IC_{50} μM)
	**10**	Inactive	nd	nd
	**18**	81	17	1.7
	**11**	Inactive	nd	nd
	**19**	86	48	2.0
	**12**	56	nd	nd
	**20**	75	24	2.9
	**32**	Inactive	nd	nd

[a] Mean of at least two measurements with typically a SD or spread of ±15%.

[b] nd, not determined.

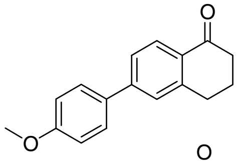
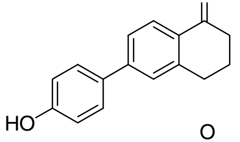
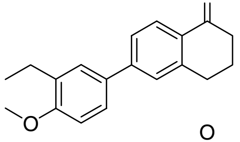
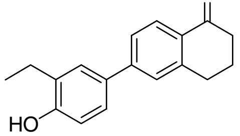
tography, of 28%. In the same manner compounds **3** and **4** were synthesized from 4-methoxyphenyl boronic acid and 3,4-(methylenedioxy)phenyl boronic acid in yields of 30% and 77%, respectively.

Alignment studies confirmed that molecule **2** is similar in length to E1, as can be seen in Figure 2, and a number of alignment and shape similarity studies were performed to investigate possible scaffolds.

Altogether, a number of substitutions from the biphenyl template were investigated: these are shown in Schemes 2 and 3. The indanone biphenyl systems were synthesized with the aim of the five-membered ring mimicking the D-ring on E1; tetralones were synthesized in view of the activities reported by Gege et al. for D-homo-estra-1,3,5(10)-trienes.[27] The boronic acids containing alkyl substituents which are not commercially available were synthesized from the corresponding bromophenyl compounds using *n*-butyl lithium and trimethyl borate. Having synthesized compounds **17** and **25** to investigate the effect of pushing the aromatic rings further out of plane from each other, the tricyclic compound **28**, known from the literature, was synthesized (Scheme 4), to investigate the effect of forcing the aromatic rings closer to planar. It was found that the acylation proceeded better using methyl protection of the phenol, rather than acetyl. The commercially available 2-hydroxyfluorene was therefore O-methylated, acylated, and then demethylated to give **28**.

Shape similarity studies also suggested that an ethyl substituent next to the ethanone moiety may be able to occupy the same area in space as the C-18 methyl group of E1. It was observed that a methyl substituent would not be in the correct orientation as it would be planar to the aromatic ring. An ethyl, however, being more flexible, might be able to occupy the C-18 niche in the active site. Molecule **31** was therefore synthesized as shown in Scheme 5. The Suzuki coupling of 4-methoxyphenylboronic acid to 1-bromo-3-ethyl benzene progressed well, giving a 75% yield after chromatography and recrystal-

Table 3. Inhibition of 17β-HSD type 1 by non-steroidal mimics of E1 based on the biphenyl tetralone template[a,b]

Structure	Compound	% @ 10 μM	IC_{50} (μM)
	**13**	Inactive	nd
	**21**	89	15.6
	**14**	71	8.3
	**22**	51	nd

[a] Mean of at least two measurements with typically a SD or spread of ±15%.

[b] nd, not determined.

lization. Acylation using acetic anhydride gave a mixture of products, which were not separated by chromatography. The mixture was then subjected to demethylation using BBr_3 to give the phenolic products, which were then separable from the mixture, with the desired product **31** being obtained in an unoptimized yield of 20% over the two steps.

Finally, compound **32** (Table 2) was also synthesized, to further investigate the necessity of a phenol for activity. This was prepared according to the method of Zhuang et al.[36]

From these scaffolds, two candidates were chosen from which to synthesize mimics of potent inhibitor **1**: template **16** and template **19**. It was decided that since the ethyl substituent adjacent to the phenol is not usually detrimental to activity and may hinder binding to the estrogen receptor, thus reducing estrogenicity, then this substituent could be incorporated from the outset. Although non-steroidal inhibitors may not be estrogenic an ethyl group next to the phenol moiety may retard potential metabolism at this site. A small library of amides was synthesized based on the biphenyl ethanone template, to investigate any possible effect of chain length, position of the pyridyl nitrogen, and comparison of pyridyl with the hydroxyethyl moiety. Two methyl substituted biphenyl amides, **52** and **53**, were also synthesized to investigate further the possibilities of expansion from this position. An additional two compounds containing a bis-methyl substituted side chain, **54** and **55**, were also prepared for comparison to determine whether rigidification of the side chain might be beneficial. The route to these amides is shown in Scheme 6. The acid side chains were incorporated by acylation of bromobenzene or bromotoluene with succinic anhydride or 2,2-dimethyl succinic anhydride in high yield. The resulting oxo-butyric acids were then subjected to Suzuki couplings, with the resulting biphenyl oxo-butyric acids being obtained in yields of about 60%. It was envisaged that the amide couplings would proceed as expected and, indeed for the straight side chain, amides were obtained in the region of 30% yield. For the bismethylated side chain, however, these conditions resulted in cyclization to give a lactone which was obtained in 27% yield, with no amide being isolated. This route was improved by using acetyl chloride to give the cyclic product in 56% yield, which could then be heated with amine to give the desired amide product. Demethylation using BBr_3 then gave the desired phenols in average yield of 47%.

In the indanone series the side chain was attached to **11** by the reaction with ethyl bromoacetate using LDA (Scheme 7). Saponification of the ester gave 16% yield of the acid **57** over two steps (the bis-alkylated product being separable at the acid stage). Amide coupling of **57** with selected amines gave amides in an average 42% yield and was followed by demethylation with an average yield of 36%. These compounds were evaluated biologically as mixtures of enantiomers.

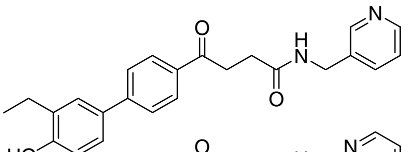
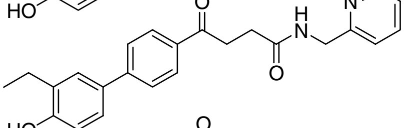
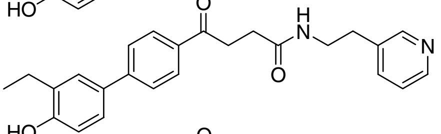
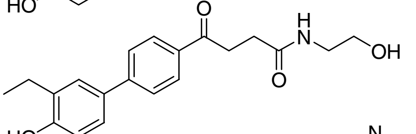
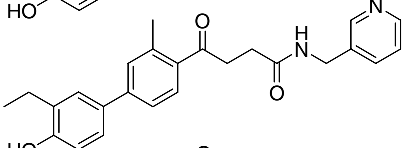
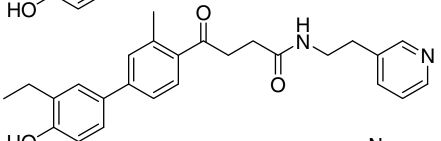
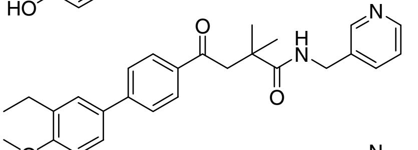
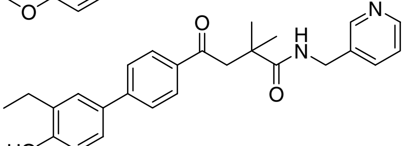
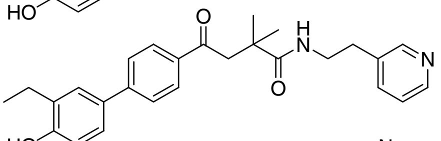
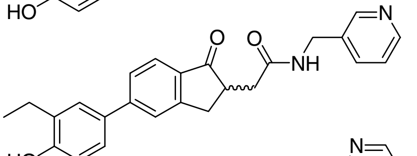
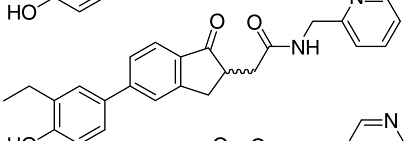
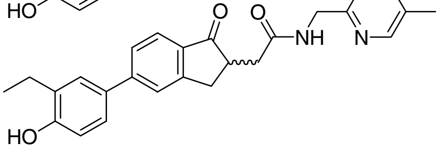
2.2. Biological results

The compounds shown in Tables 1–4 were assessed for their ability to inhibit 17β-HSD1 in an assay using intact T-47D human breast cancer cells, by measuring the amount of labeled E2 formed from the labelled natural substrate, E1 at a substrate concentration of 2 nM per well. The percentage of inhibition was then calculated by comparison of conversion in the absence and presence of inhibitor. The percentages of inhibition achieved for a 1 or 10 μM concentration of the inhibitors, as well as the IC_{50} values for some of the more potent compounds, are shown.

The results showed that the biphenyl ethanone-based molecules showed promising inhibition of 17β-HSD1, with the best having an IC_{50} of around 3.7 μM. It can be seen that methylation of the phenol was consistently detrimental to activity. Similarly, the methylene dioxy derivative **4** was found to be inactive. Incorporation of an ethyl substituent adjacent to the hydroxyl gave compound **16** of similar activity to **2**, with the IC_{50} for **16** being 5.4 μM. Compound **16** was found to possess some inhibitory activity against 17β-HSD2, showing 51% inhibition of this enzyme at 10 μM.

Attempts to investigate the effect of molecule planarity met with unexpected results. **17** Showed promising activity, with an IC_{50} of 3.7 μM; in contrast, **25** was shown to be inactive. Of course, it is not possible to tell in which orientation the rings are relative to each other or on which side the substituents are interacting in the active site. The tricyclic molecule **28**, in which the aromatic rings are fixed toward a more planar relative orienta-

Table 4. Inhibition of 17β-HSD type 1 and type 2 by non-steroidal mimics of potent inhibitor **1**[a,b]

Structure	Compound	Inhibition of type 1 (% at 1 μM)	Inhibition of type 2 (% @10 μM)	Type 1 (IC_{50} μM)
	**48**	24	12	3.7
	**49**	Inactive	nd	nd
	**50**	17	nd	nd
	**51**	23	nd	nd
	**52**	21	nd	nd
	**53**	15	nd	nd
	**46**	17	nd	nd
	**54**	38	nd	1.8
	**55**	15	nd	nd
	**61**	39	nd	4.7
	**62**	Inactive	nd	nd
	**63**	Inactive	nd	nd

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[a] Mean of at least two measurements with typically a SD or spread of ±19%.

[b] nd, not determined.

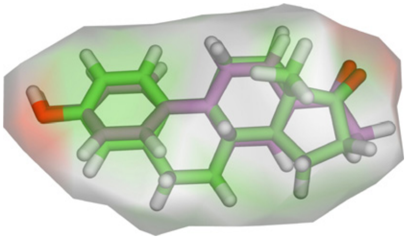
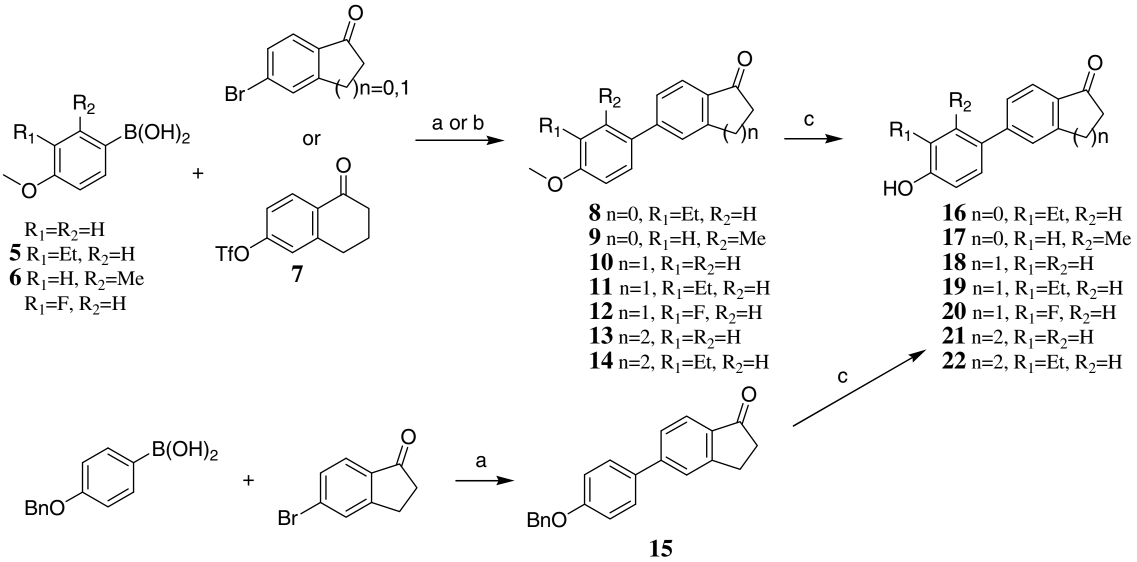


Figure 2. Alignment and shape similarity[35]: a comparison of E1 (green) with molecule **2** (purple).

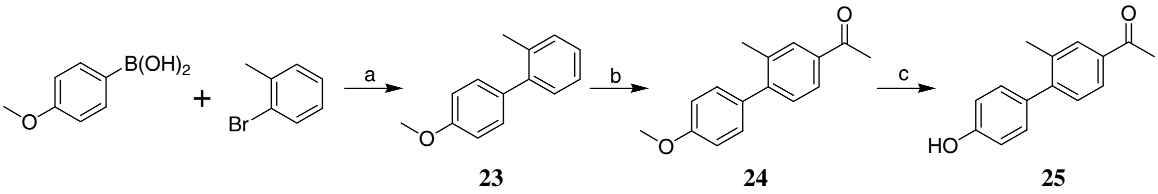
tion, showed similar activity to **2**, **16**, and **17**, with an IC_{50} of 4.8 μM. This, then, was not any better than with the aromatic rings untethered, and would add an extra point of oxidation and therefore metabolism onto the template.

It appears for **31** as though the ethyl substituent next to the acetyl is tolerated but with some loss of activity, suggesting that space around this area is limited. Rotation of the aromatic ring to place the ethyl on the bottom side of the molecule would mimic a tetralone (vide infra).

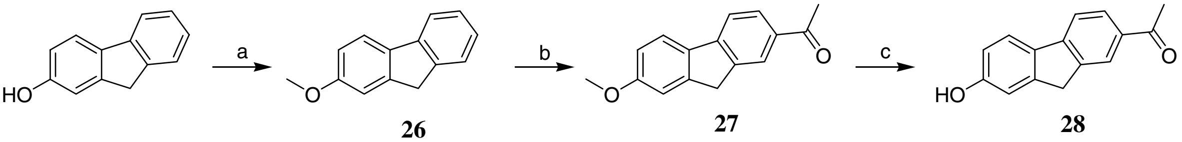
The indanone series proved promising, with the most potent compound being the unsubstituted biphenyl indanone **18**, which has an IC_{50} of 1.7 μM. This compound was also shown to be selective for 17β-HSD type 1 over type 2, showing only 17% inhibition of type 2 at 10 μM. Addition of the ethyl moiety to give **19** did not cause a significant decrease in potency (IC_{50} 2.0 μM), but did result in a slight decrease in selectivity (showing 48% inhibition of type 2 at 10 μM). Of the fluorinated compounds **12** and **20**, **12** was one of the few methylated phenols which showed some activity



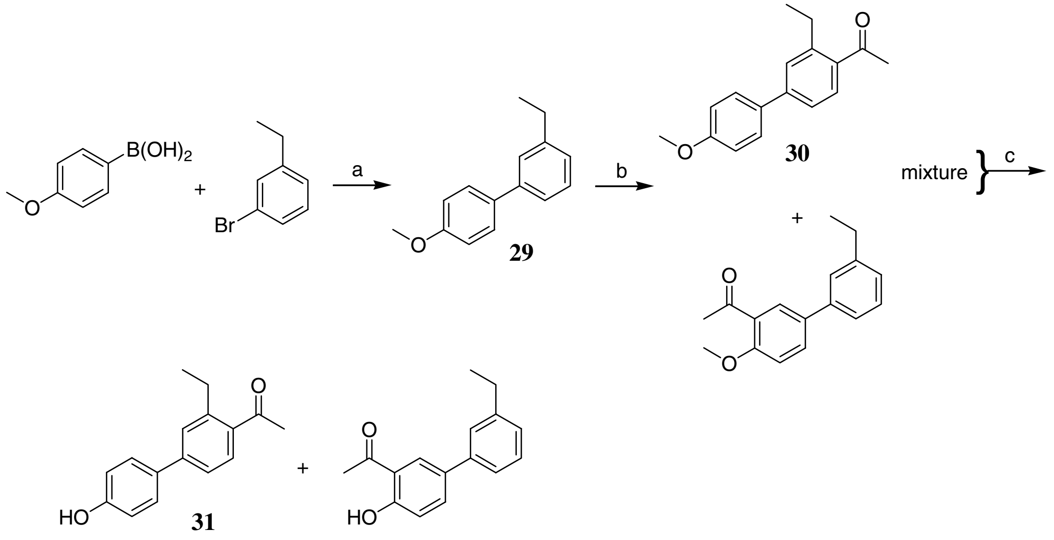
Scheme 2. Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, EtOH/PhMe, Δ; (b) $Pd(OAc)_2$, K_2CO_3, Bu_4NBr, $EtOH/H_2O$, μW 150 °C; (c) BBr_3, DCM, −78 °C–rt.



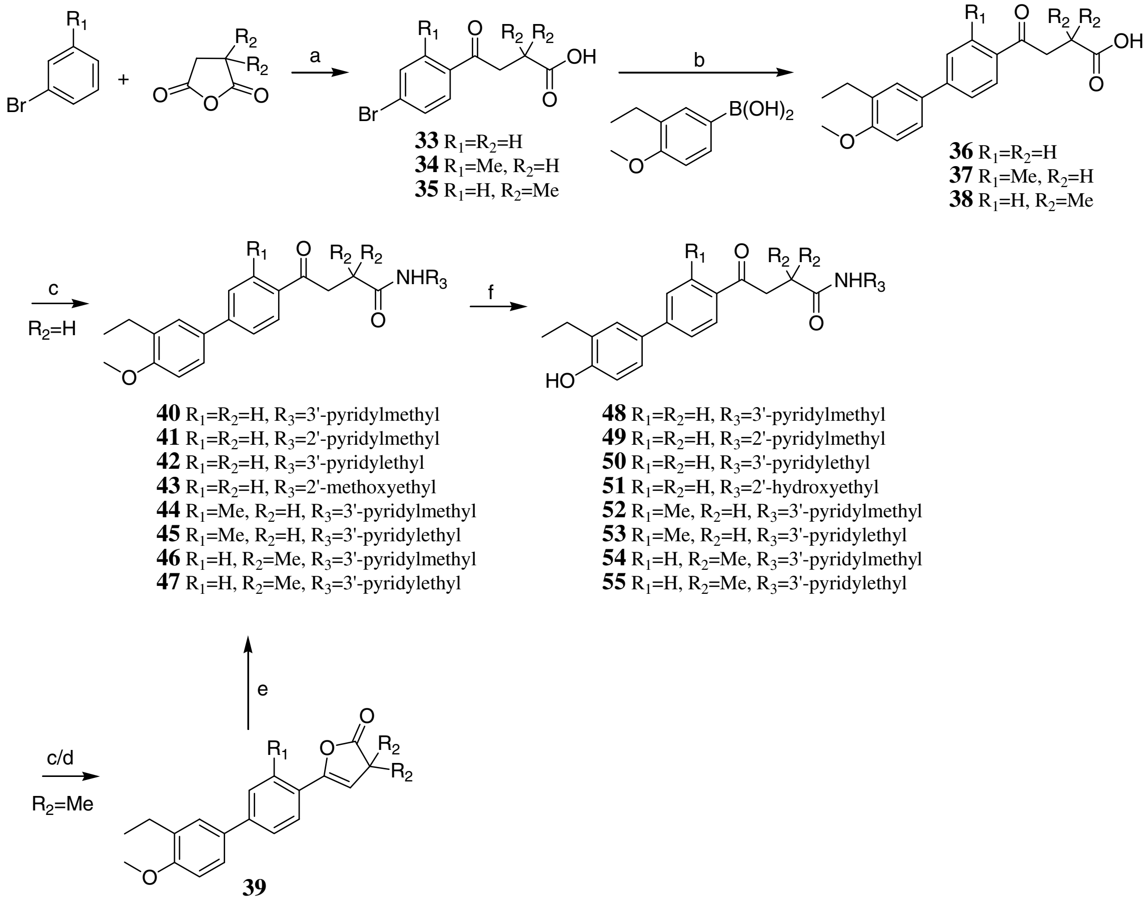
Scheme 3. Reagents and conditions: (a) $Pd(OAc)_2$, K_2CO_3, Bu_4NBr, $EtOH/H_2O$, μW 150 °C; (b) Ac_2O, $AlCl_3$, DCM, −10 °C–rt; (c) BBr_3, DCM, −78 °C–rt.



Scheme 4. Reagents and conditions: (a) MeI, K_2CO_3, DMF, rt; (b) Ac_2O, $AlCl_3$, DCE, rt; (c) BBr_3, DCM, −78 °C–rt.



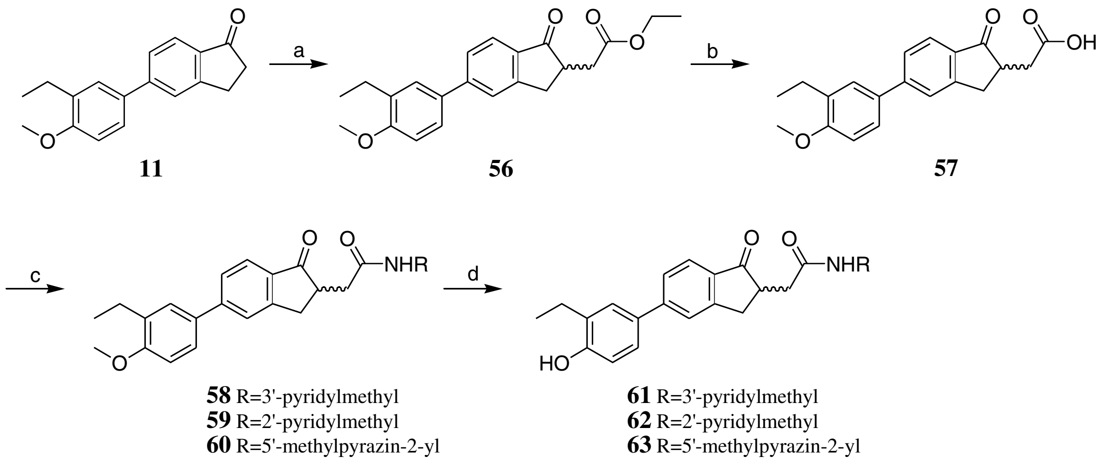
Scheme 5. Reagents and conditions: (a) $Pd(OAc)_2$, K_2CO_3, Bu_4NBr, $EtOH/H_2O$, μW 150 °C; (b) Ac_2O, $AlCl_3$, −10 °C–rt; (c) BBr_3, DCM, −78 °C–rt.



Scheme 6. Reagents and conditions: (a) $AlCl_3$, DCM, −10 °C–rt; (b) $Pd(PPh_3)_4$, Na_2CO_3, EtOH/PhMe, Δ; (c) amine, DMAP, EDCI, DCM, rt; (d) AcCl, NEt_3, DCM, rt; (e) Amine, DCM, Δ; (f) BBr_3, DCM, −78 °C–rt.

(55% at 10 μM). It was hoped, therefore, that the demethylated version might be highly potent; however, the IC_{50} of the phenol **20** was found to be a moderate 2.9 μM.

The tetralones showed diminished activity compared to the indanone and acetophenone series. This was a little surprising since the six-membered homo D ring derivatives of E1 are reported to be at least as active as the



Scheme 7. Reagents and conditions: (a) LDA, ethyl bromoacetate, THF, −60 °C–rt; (b) NaOH, THF/H_2O, rt; (c) amine, EDCI, DMAP, NEt_3, DCM, rt; (d) BBr_3, DCM, −78 °C–rt.

E1 scaffold itself.[27] It is possible, however, that the aromatic C ring mimic in our biphenyl series pushes the alkyl groups rigidly planar to the ring, in a direction which is unfavorable compared to those which would be occupied had such substituents been attached to a cyclohexyl ring. For the tetralones containing the larger cyclohexanone ring, these differences in orientation could cause more of a steric clash than for the indanone or ethanone systems. Another surprising result was obtained for the methylated biphenyl tetralone **14**: this was the only biphenyl template which was found to be more active than its phenolic counterpart (Table 3).

The results for the simple biphenyl-type templates **2**, **16**–**20** were thus all essentially similar, taking into account standard deviation or spread. For further elaboration, therefore, it was decided to use the simplest biphenyl ethanone template, since extension to mimic inhibitor **1** would not involve the creation of a chiral center. It was decided to incorporate the ethyl substituent immediately, with an intent to avoid problems of estrogenicity caused by binding to estrogen receptor-α. A few expanded indanones were also synthesized and tested as mixtures of enantiomers, with the plan being to synthesize single enantiomers of any particularly active molecule. The results for these are also shown in Table 4.

As in the steroidal series,[37] the length of the chain and position of the pyridyl nitrogen were investigated. Interestingly, the best results were for the 3-pyridyl methyl amides, as observed for the steroid series. However, the extended biphenyl template is much more flexible than molecule **1**. It was decided, therefore, to increase the rigidity of the side chain by incorporation of a bis-methylated link. This proved to be successful, with an increase in potency to give **54** with an IC_{50} of 1.8 μM. Once again, the 3-pyridyl methyl amide proved better than the 3-pyridyl ethyl motif. Compound **46**, the *O*-methyl intermediate of **54**, was however found to be much less active, showing only 17% inhibition of 17β-HSD1 at 10 μM. It can be seen that incorporation of a methyl substituent to give compounds **52** and **53** is not beneficial to activity. In the indanone series **61**–**63** the best result was again observed for the 3-pyridyl methyl amide **61**, with an IC_{50} of 4.7 μM for the mixture of enantiomers.

3. Summary and conclusions

We have identified biphenyl mimics of E1 and the potent steroidal inhibitor **1** that are promising inhibitors of 17β-HSD1 for further elaboration. Similar to our steroidal series we have attached an amide linker to the basic biphenyl scaffold to obtain improved activity. In the case of the biphenyl ethanone series, incorporation of a bis-methylated linker leads to increased potency, possibly due to increased rigidification of the side chain, or possibly due to beneficial hydrophobic interactions in the active site. In this series there is an optimum length for the side chain, and the 3-pyridyl amide seems consistently better than 2-pyridyl. O-Methylation of the phenol is usually detrimental to activity. This correlates very well with the results for the C16-amide derivatives of 2-ethyl E1, and thus implies that inhibitor **1** is being mimicked in the desired way. Further improvements from our steroidal series will be applied to these non-steroidal templates to improve potency.

4. Experimental

4.1. General methods

All chemicals were used as received. Reactions using anhydrous solvents were carried out under nitrogen. Thin layer chromatography (TLC) was performed on precoated plates (Merck TLC aluminum sheets silica gel 60 F_{254}). Product(s) and starting material(s) were detected by either viewing under UV light and/or treating with an ethanolic solution of phosphomolybdic acid followed by heating. Flash column chromatography was performed on silica gel (Sorbsil/Matrex C60) or using Argonaut prepacked columns with a Flashmaster™. ^1H NMR (270 MHz or 400 MHz) and *DEPT*-edited ^{13}C NMR (100.4 MHz) spectra were recorded with a

Jeol Delta 270 or a Varian Mercury VX 400 NMR spectrometer, and chemical shifts are reported in parts per million (ppm, δ). HPLC analyses were performed on a Waters Millennium 32 instrument equipped with a Waters 996 PDA detector, using a Symmetry C_{18} reverse phase column (4.6 × 150 mm) eluting with $MeCN/H_20$ at 0.5 mL/min. FAB low and high resolution mass spectra were recorded at the Mass Spectrometry Service Center, University of Bath, using *m*-nitrobenzyl alcohol (NBA) as the matrix; ES high resolution mass spectra were recorded on a Bruker MicroTOF. ES and APCI low resolution mass spectra were obtained on a Waters Micromass ZQ. Elemental analyses were performed by the Microanalysis Service, University of Bath. Melting points were determined using a Stanford Research Systems Optimelt and are uncorrected. Microwave syntheses were performed using a CEM Discover® instrument.

4.2. Molecular modeling

Alignment and shape similarity studies were carried out using The PyMOL Molecular Graphics System (2002), http://www.pymol.org.[35]

4.3. Biological assays

T-47D and MDA-MB-231 cells have previously been shown to possess predominantly reductive 17β-HSD type 1 or oxidative 17β-HSD type 2 activities, respectively.[38]

4.3.1. Measurement of inhibition of 17β-HSD type 1. T-47D human breast cancer cells were incubated with ^{3}H-E1 at a concentration of 2 nM per well, in a 24-well tissue culture plate, in the absence or presence of the inhibitor (0.1 nM–10 μM). After incubation of the substrate ± inhibitor for 30 min at 37 °C, the products were isolated from the mixture by extraction with Et_2O (4 mL), using ^{14}C-E2 (5000 dpm) to monitor procedural losses. Separation of ^{3}H-E2 from the mixture was achieved using TLC (DCM/EtOAc, 4:1 v/v) and the mass of ^{3}H-E2 produced was calculated from the ^{3}H counts detected and recovery of ^{14}C-E2.

4.3.2. Measurement of inhibition of 17β-HSD type 2. MDA-MB-231 human breast cancer cells were incubated with ^{3}H-E2 at a concentration of 2 nM per flask, in the absence or presence of the inhibitor (0.1 nM–10 μM). After incubation of the substrate ± inhibitor for 3 h at 37 °C, the products were isolated from the mixture by extraction with Et_2O (4 mL), using ^{14}C-E1 (5000 dpm) to monitor procedural losses. Separation of ^{3}H-E1 from the mixture was achieved using TLC (DCM/EtOAc, 4:1 v/v) and the mass of ^{3}H-E1 produced was calculated from the ^{3}H counts detected and recovery of ^{14}C-E1.

4.4. Chemical synthesis

Compounds **6**,[39] **7**,[40] **32**,[36] and **33**[41] were prepared according to the literature procedure, with physical and spectroscopic data in agreement with literature reported values.

4.4.1. General procedure 1: Suzuki coupling using microwave conditions. A mixture of bromo- or trifluoromethanesulfonyl-aromatic (0.5 mmol), the requisite boronic acid (0.75 mmol), K_2CO_3 (0.172 g, 1.25 mmol), Bu_4NBr (0.161 g, 0.5 mmol), and $Pd(OAc)_2$ (catalytic) in EtOH (1.5 mL) and water (3.5 mL) was heated under microwave conditions at 150 °C for 10 or 20 min. Water (20 mL) was added and the organics extracted into EtOAc (20 mL). Purification by flash chromatography using gradient elution of hexane/EtOAc gave the title compound.

4.4.2. General procedure 2: Suzuki coupling using conventional heating. A solution of bromo-aromatic (2.5 mmol) and the requisite boronic acid (2.8 mmol) in PhMe (18 mL), EtOH (2 mL), and 2 M aq Na_2CO_3 (2 mL) was degassed by bubbling N_2 through for 40 min. To this was added $Pd(PPh_3)_4$ (catalytic) and the reaction was heated to reflux under N_2 for 24 h. The reaction was allowed to cool to rt before water (100 mL) was added and the organics were extracted into EtOAc (2× 100 mL). The extracts were combined and concentrated under reduced pressure and the product purified by flash chromatography using gradient elution of hexane/EtOAc.

4.4.3. General procedure 3: demethylation using BBr_3. To a stirred solution of *O*-methyl starting material in dry DCM, cooled to −78 °C (dry ice/acetone bath) was added drop-wise BBr_3 (1 M in DCM, 3 equiv) and the reaction was allowed to warm slowly to rt overnight. Water was added and the organics extracted into DCM (2×). In cases where the product was soluble in DCM, the extracts were combined and concentrated under reduced pressure and the product purified by flash chromatography using either hexane/EtOAc or DCM/MeOH gradient elution. Where the product precipitated upon addition of water this was collected by filtration and washed with DCM and water. In cases where the product was not soluble in DCM and did not precipitate immediately (**52**–**55**), the aqueous layer was neutralized with $NaHCO_3$ to give a white powder, which was collected by filtration and washed with water before drying under high vacuum.

4.4.4. General procedure 4: amide coupling using a Greenhouse™ synthesizer. To a stirred solution of 4-(3′-ethyl-4′-methoxy-biphenyl)-4-oxo-butanoic acid **36** or 4-(3′-Ethyl-4′-methoxy-3-methyl-biphenyl-4-yl)-4-oxo-butyric acid **37** (0.32 mmol) and NEt_3 (60 μL) in dry DCM (2 mL) under N_2 was added a solution of EDCI (0.192 g, 1 mmol) and DMAP (catalytic) in dry DCM (2 mL) and the mixture was stirred for 40 min before addition of amine (0.06 mL). The reaction was stirred at rt for 24 h before quenching with $NaHCO_3$ (satd aq). The organic layer was separated and concentrated under reduced pressure and the product purified by flash chromatography using gradient elution of DCM to 5% MeOH in DCM, followed by recrystallization from DCM/hexane.

4.4.4.1. 1-(4′-Hydroxy-biphenyl-4-yl)-ethanone (2). Prepared according to the General Procedure 1, heating for 10 min (30 mg, 28%): mp 202–206 °C [lit. 205–

206 °C[42]]; ^{1}H NMR δ (400 MHz, CD_3OD) 2.59 (3H, s), 6.88 (2H, d, $J = 8.6$ Hz), 7.52 (2H, d, $J = 8.6$ Hz), 7.66 (2H, d, $J = 8.2$ Hz), 7.99 (2H, d, $J = 8.2$ Hz); ^{13}C NMR δ (100 MHz, CD_3OD) 24.6, 114.9, 125.4, 127.4, 128.1, 130.2, 134.3, 145.3, 157.2, 198.2; HPLC $t_R = 3.59$ min (>94%) 90% MeCN in H_2O; LC/MS (APCI) *m*/*z* 211.24 $(M-H)^-$; HRMS (ES+) *m*/*z* Calcd for $C_{14}H_{13}O_2$ 213.0910, found $(M+H)^+$ 213.0910.

4.4.4.2. 1-(4′-Methoxy-biphenyl-4-yl)-ethanone (3). Prepared according to the General Procedure 1, heating for 20 min (77 mg, 68%): mp 153–155 °C [lit. 153–154 °C[43]]; ^{1}H NMR δ (270 MHz, CD_3OD) 2.61 (3H, s), 3.84 (3H, s), 6.98 (2H, d, $J = 8.6$ Hz), 7.56 (2H, d, $J = 8.2$ Hz), 7.62 (2H, d, $J = 8.2$ Hz), 7.99 (2H, d, $J = 8.2$ Hz); HPLC $t_R = 2.93$ min (>96%) 90% MeCN in H_2O; LC/MS (APCI) *m*/*z* 227.0 $(M+H)^+$; HRMS (ES+) *m*/*z* Calcd for $C_{15}H_{15}O_2$ 227.1067, found $(M+H)^+$ 227.1077.

4.4.4.3. 1-(4-Benzo[1,3]dioxol-5-yl-phenyl)-ethanone (4). Prepared according to the General Procedure 1, heating for 10 min (90 mg, 75%): mp 132–134 °C [lit. 140–141 °C[44]]; ^{1}H NMR δ (400 MHz, $CDCl_3$) 2.59 (3H, s), 5.98 (2H, s), 6.87 (1H, d, $J = 7.8$ Hz), 7.06–7.09 (2H, m), 7.56 (2H, d, $J = 8.6$ Hz), 7.96 (2H, d, $J = 8.6$ Hz); ^{13}C NMR δ (100 MHz, $CDCl_3$) 26.5, 101.3, 107.4, 108.6, 120.9, 126.7, 128.8, 133.9, 135.3, 145.3, 147.8, 148.2, 197.6; HPLC $t_R = 4.34$ min (>97%) 90% MeCN in H_2O; LC/MS (APCI) *m*/*z* 241.36 $(M+H)^+$; HRMS (ES+) *m*/*z* Calcd for $C_{15}H_{13}O_3$ 241.0859, found $(M+H)^+$ 241.0858.

4.4.4.4. 3-Ethyl-4-methoxyphenylboronic acid (5). To a stirred solution of 4-bromo-2-ethyl-1-methoxybenzene[45] (4.59 g, 21 mmol) in dry THF (50 mL), cooled to −78 °C, was added slowly drop-wise (over 45 min) *n*-BuLi (15 mL of a 1.6 M solution in hexanes, 24 mmol). The solution was stirred at −78 °C for 2 h before trimethylborate (3.6 mL, 31.5 mmol) was added drop-wise and the reaction was allowed to warm slowly to rt with stirring overnight. The reaction was quenched with 2 M HCl (50 mL) and the products extracted with EtOAc (2× 50 mL). These extracts were combined and concentrated under reduced pressure to give an oily substance. To this was added hexane followed by a small amount of DCM and the resulting white precipitate was collected by filtration and washed with hexane (1.55 g, 41%); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.27 (3H, t, $J = 7.5$ Hz), 2.73 (2H, q, $J = 7.5$ Hz), 3.90 (3H, s), 6.60 (~1H, br s), 6.96 (1H, d, $J = 8.4$ Hz), 7.98 (1H, d, $J = 1.5$ Hz), 8.08 (1H, dd, $J = 8.2$, 1.7 Hz); HPLC $t_R = 2.71$ min (>99%) 90% MeCN in H_2O; LC/MS (APCI) *m*/*z* 179.04 $(M-H)^-$.

4.4.4.5. 2-Methyl-4-methoxyphenyl boronic acid (6). Preparation and ^{1}H NMR as described by Mello and Finney.[39]

HPLC $t_R = 1.27$ min (>99%) 90% MeCN in H_2O; LC/MS (APCI) *m*/*z* 164.76 $(M-H)^-$.

4.4.4.6. 1-(3′-Ethyl-4′-methoxy-biphenyl-4-yl)-ethanone (8). Prepared according to the General Procedure 2 using 3-ethyl-4-methoxyphenylboronic acid **5** (yield 88%): mp 69–72 °C; ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.23 (3H, t, $J = 7.5$ Hz), 2.62 (3H, s), 2.69 (2H, q, $J = 7.5$ Hz), 3.87 (3H, s), 6.92 (1H, d, $J = 8.2$ Hz), 7.43–7.47 (2H, m), 7.64 (2H, d, $J = 8.4$ Hz), 7.99 (2H, d, $J = 8.4$ Hz); ^{13}C NMR δ (100 MHz, $CDCl_3$) 14.2, 23.5, 26.7, 55.5, 110.5, 125.7, 126.7, 127.9, 128.9, 131.9, 132.0, 133.2, 135.1, 145.8, 157.8, 197.9; HPLC $t_R = 5.05$ min (>99%) 80% MeCN in H_2O; LC/MS (APCI) m/z 254.09 $(M+H)^+$; HRMS (FAB+) *m*/*z* Calcd for $C_{17}H_{19}O_2$ 255.1380, found $(M+H)^+$ 255.1384.

4.4.4.7. 1-(4′-Methoxy-2′-methyl-biphenyl-4-yl)-ethanone (9). Prepared according to the General Procedure 1 using 2-methyl-4-methoxyphenyl boronic acid **6**, heating for 10 min (yield 72%): mp 100–102 °C; ^{1}H NMR δ (270 MHz, $CDCl_3$) 2.26 (3H, s), 2.63 (3H, s), 3.83 (3H, s), 6.78–6.82 (2H, m), 7.15 (1H, d, $J = 8.4$ Hz), 7.39 (2H, d, $J = 8.4$ Hz), 7.98 (2H, d, $J = 8.4$ Hz); HPLC $t_R = 2.42$ min (>99%) 90% MeCN in H_2O; LC/MS (AP+) *m*/*z* 241.29 $(M+H)^+$.

4.4.4.8. 5-(4-Methoxyphenyl)-indan-1-one (10). This compound has been described in the literature.[46] Prepared according to the General Procedure 1, heating for 20 min (yield 62%): mp 147–150 °C; ^{1}H NMR δ (270 MHz, $CDCl_3$) 2.67–2.71 (2H, m), 3.12–3.16 (2H, m), 3.83 (3H, s), 6.97 (1H, d, $J = 8.8$ Hz), 7.51–7.59 (4H, m), 7.76 (1H, d, $J = 8.0$ Hz); HPLC $t_R = 3.04$ min (>98%) 90% MeCN in H_2O; LC/MS (APCI) *m*/*z* 239.0 $(M+H)^+$; HRMS (ES+) *m*/*z* Calcd for $C_{16}H_{15}O_2$ 239.1067, found $(M+H)^+$ 239.1071.

4.4.4.9. 5-(3-Ethyl-4-methoxyphenyl)-indan-1-one (11). Prepared according to the General Procedure 2 using 3-ethyl-4-methoxyphenylboronic acid **5** (yield 65%): mp 100–102 °C; ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.24 (3H, t, $J = 7.4$ Hz), 2.66–2.74 (4H, m), 3.14–3.19 (2H, m), 3.87 (3H, s), 6.92 (1H, d, $J = 9.1$ Hz), 7.43–7.46 (2H, m), 7.55–7.63 (2H, m), 7.78 (1H, d, $J = 8.0$ Hz); EtOAc/hexanes, 3:7, $R_f = 0.5$; HPLC $t_R = 2.80$ min (>97%) 90% MeCN in H_2O; LC/MS (ES+) *m*/*z* 267.4 $(M+H)^+$; HRMS (ES+) *m*/*z* Calcd for $C_{18}H_{19}O_2$ 267.1380, found $(M+H)^+$ 267.1380.

4.4.4.10. 5-(3-Fluoro-4-methoxyphenyl)-indan-1-one (12). Prepared according to the General Procedure 1, heating for 20 min (yield 25%): mp 130–131 °C; ^{1}H NMR δ (270 MHz, $CDCl_3$) 2.70–2.75 (2H, m), 3.15–3.20 (2H, m), 3.86 (3H, s), 6.90 (2H, d, $J = 8.8$ Hz), 7.54–7.62 (4H, m), 7.78 (1H, d, $J = 8.0$ Hz); HPLC $t_R = 2.05$ min (>95%) 90% MeCN in H_2O; HRMS (ES+) *m*/*z* 257.0981 $(M+H)^+$, Calcd 257.0972 for $C_{16}H_{14}FO_2$.

4.4.4.11. 6-(4-Methoxy-phenyl)-3,4-dihydro-2H-naphthalen-1-one (13). This compound has been described in the literature.[47] Prepared according to the General Procedure 1 from trifluoro-methanesulfonic acid 5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl ester **7**, heating for 10 min (yield 58%): mp 127–128 °C [lit. 126–127 °C[48]]; ^{1}H NMR δ (270 MHz, $CDCl_3$) 2.09–2.19 (2H, m), 2.63–2.68 (2H, m), 2.97–3.01 (2H, m), 3.84 (3H, s), 6.97 (2H, d, $J = 8.7$ Hz), 7.40 (1H, s), 7.48 (1H, dd,

J = 8.2, 1.7 Hz), 7.55 (2H, *d*, J = 8.7 Hz), 8.06 (1H, d, J = 8.2 Hz); HPLC t_R = 2.38 min (>99%) 90% MeCN in H_2O; LC/MS (ES+) m/z 252.95 $(M+H)^+$; HRMS (ES+) m/z calcd for $C_{17}H_{17}O_2$ 253.1223, found $(M+H)^+$ 253.1222.

4.4.4.12. 6-(3-Ethyl-4-methoxyphenyl)-3,4-dihydro-2H-naphthalen-1-one (14). Prepared according to the General Procedure 1 using 3-ethyl-4-methoxyphenylboronic acid **5**, heating for 10 min (yield 25%, oil); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.24 (3H, t, J = 7.4 Hz), 2.11–2.20 (2H, m), 2.64–2.74 (4H, m), 2.98–3.03 (2H, m), 3.87 (3H, s), 6.91 (1H, d, J = 8.9 Hz), 7.42–7.52 (4H, m), 8.07 (1H, d, J = 8.2 Hz); HPLC t_R = 3.40 min (>97%) 90% MeCN in H_2O; LC/MS (ES+) m/z 281.11 $(M+H)^+$; HRMS (ES+) m/z Calcd for $C_{19}H_{21}O_2$ 281.1536, found $(M+H)^+$ 281.1535.

4.4.4.13. 5-(-4-(Benzyloxy)-phenyl)-indan-1-one (15). Prepared according to the General Procedure 2 (yield 75%); ^{1}H NMR δ ($CDCl_3$, 270 MHz) 2.70–2.73 (2H, t, J = 4.2 Hz), 3.15–3.19 (2H, t, J = 5.6 Hz), 5.12 (2H, s), 7.07 (1H, d, J = 8.9 Hz), 7.28–7.37 (5H, m), 7.40–7.62 (4H, m), 7.77–7.80 (1H, d, J = 7.9 Hz); EtOAc/hexanes, 3:7, R_f = 0.5.

4.4.4.14. 1-(3′-Ethyl-4′-hydroxy-biphenyl-4-yl)-ethanone (16). Prepared according to the General Procedure 3 from 1-(3′-ethyl-4′-methoxy-biphenyl-4-yl)-ethanone **8** (yield 42%): mp 154–156 °C; ^{1}H NMR δ (400 MHz, $CDCl_3$) 1.29 (3H, t, J = 7.5 Hz), 2.65 (3H, s), 2.73 (2H, q, J = 7.5 Hz), 5.95 (1H, s), 6.91 (1H, d, J = 8.1 Hz), 7.34–7.37 (1H, m), 7.43 (1H, d, J = 2.1 Hz), 7.64 (2H, d, J = 8.4 Hz), 8.00 (2H, d, J = 8.4 Hz); ^{13}C NMR δ (100 MHz, $CDCl_3$) 14.0, 23.2, 26.6, 115.7, 125.8, 126.6, 128.3, 129.0, 130.7, 132.1, 134.9, 145.9, 154.2, 198.6; HPLC t_R = 2.24 min (>98%) 90% MeCN in H_2O; LC/MS(APCI) m/z 239.03 $(M-H)^-$; HRMS (FAB+) m/z Calcd for $C_{16}H_{17}O_2$ 241.1229, found (M^+) 241.1223.

4.4.4.15. 1-(4′-Hydroxy-2′-methyl-biphenyl-4-yl)-ethanone (17). Prepared according to the General Procedure 3 from 1-(4′-methoxy-2′-methyl-biphenyl-4-yl)-ethanone **9** (yield 13%): mp 117–119 °C; ^{1}H NMR δ (270 MHz, $CDCl_3$) 2.23 (3H, s), 2.64 (3H, s), 5.03 (1H, br s), 6.72–6.78 (2H, m), 7.10 (1H, d, J = 8.1 Hz), 7.39 (2H, d, J = 8.4 Hz), 7.98 (2H, d, J = 8.4 Hz); HPLC t_R = 1.72 min (>91%) 90% MeCN in H_2O; LC/MS (AP−) m/z 224.92 $(M-H)^-$; HRMS (ES+) m/z Calcd for $C_{15}H_{15}O_2$ 227.1067, found $(M+H)^+$ 227.1072.

4.4.4.16. 5-(4-Hydroxyphenyl)-indan-1-one (18). This compound has been described in the literature.[46] To a stirred suspension of 5-(4-benzyloxyphenyl)-indan-1-one **15** (0.100 g, 0.44 mmol), cooled to −78 °C, was added BBr_3 (1.0 M solution in DCM, 1.32 mL, 1.32 mmol) and the mixture stirred for 2 h until complete by TLC analysis (EtOAc/hexanes, 3:7, R_f = 0.19). The mixture was allowed to warm to room temperature, water (20 mL) was added and the organics extracted into EtOAc (2× 20 mL) and DCM (2× 20mL). The combined extracts were dried (Na_2SO_4) and concentrated to obtain pale yellow powder. This was purified by chromatography on SiO_2 (EtOAc/hexanes gradient elution) to afford the title compound (0.49 g, 50%) as a pale yellow solid; ^{1}H NMR δ (270 MHz, CD_3OD) 2.70 (2H, t, J = 5.6 Hz), 3.19 (2H, t, J = 5.4 Hz), 6.87–6.90 (2H, m), 7.53–7.63 (3H, m), 7.70–7.72 (2H, m); HPLC t_R = 1.70 min (>95%) 90% MeCN in H_2O; LRMS (FAB+) m/z 225 $(M+H)^+$.

4.4.4.17. 5-(3-Ethyl-4-hydroxyphenyl)-indan-1-one (19). Procedure as for **18**, from 5-(3-ethyl-4-methoxyphenyl)-indan-1-one **11** (0.178 g, 0.66 mmol) to give pale yellow solid (0.122 g, 72%); ^{1}H NMR δ (270 MHz, CD_3OD) 1.29 (3H, t, J = 7.4 Hz), 2.66–2.75 (4H, m), 3.17 (2H, t, J = 5.4 Hz), 6.86 (1H, d, J = 8.1 Hz), 7.36 (1H, dd, J = 8.1, 2.2 Hz), 7.41–7.42 (1H, m), 7.56 (1H, d, J = 7.9 Hz), 7.63 (1H, s), 7.78 (2H, d, J = 7.9 Hz); HPLC t_R = 1.70 min (>96%) 80% MeCN in H_2O; LC/MS (APCI) m/z 213 $(M+H)^+$.

4.4.4.18. 5-(3-Fluoro-4-hydroxyphenyl)-indan-1-one (20). Prepared according to the General Procedure 3 from 5-(3-fluoro-4-methoxyphenyl)-indan-1-one **12**. Flash chromatography (DCM/MeOH, gradient elution) followed by recrystallization from DCM/hexane gave the title compound as a pale yellow solid (yield 36%): mp >200 °C (dec); ^{1}H NMR δ (270 MHz, CD_3OD) 2.71 (2H, t, J = 3.9 Hz), 3.18–3.22 (2H, m), 7.01 (1H, t, J = 8.6 Hz), 7.37 (1H, dd, J = 9.1, 2.9 Hz), 7.45 (1H, dd, J = 12.6, 2.2 Hz), 7.62 (1H, d, J = 8.4 Hz), 7.71–7.74 (2H, m); HPLC t_R = 1.66 min (>94%) 90% MeCN in H_2O; LRMS (FAB+) m/z 242 $(M)^+$; HRMS (FAB+) m/z Calcd for $C_{15}H_{11}FO_2$ 243.0821, found $(M+H)^+$ 243.0820.

4.4.4.19. 6-(4-Hydroxy-phenyl)-3,4-dihydro-2H-naphthalen-1-one (21). This compound has been described in the literature.[40] Prepared according to the General Procedure 3 from 6-(4-methoxy-phenyl)-3,4-dihydro-2H-naphthalen-1-one **13**. Flash chromatography using DCM to 5% MeOH in DCM gave the product not fully separated from other fractions. The mixture was columned again using hexane to 30% EtOAc in hexane to give different fractions with approximately the same R_f. The first of these was found to be product (yield 22%): mp 208–211 °C [lit. 208–210 °C[40]]; ^{1}H NMR δ (270 MHz, $CDCl_3$) 2.03–2.08 (2H, m), 2.57–2.62 (2H, m), 2.97–3.01 (2H, t, J = 5.9 Hz), 6.87 (2H, d, J = 8.6 Hz), 7.55–7.60 (4H, m), 7.88 (1H, d, J = 8.9 Hz); 9.72 (1H, br s); HPLC t_R = 1.81 min (>95%) 90% MeCN in H_2O; LC/MS (ES−) m/z 236.95 $(M-H)^-$; HRMS (ES+) m/z Calcd for $C_{16}H_{15}O_2$ 239.1067, found $(M+H)^+$ 239.1065.

4.4.4.20. 6-(3-Ethyl-4-hydroxyphenyl)-3,4-dihydro-2H-naphthalen-1-one (22). Prepared according to the General Procedure 3 from 6-(3-ethyl-4-methoxyphenyl)-3,4-dihydro-2H-naphthalen-1-one **14**. Columned using DCM/MeOH then dissolved in MeOH, filtered, and filtrate concentrated (yield 23%): mp 202–206°C; ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.23 (3H, t, J = 7.5 Hz), 2.12–2.19 (2H, m), 2.63–2.71 (4H, m), 3.02–3.06 (2H, m), 6.83 (1H, d, J = 8.2 Hz), 7.34–7.37 (1H, m), 7.42 (1H, d, J = 1.5 Hz), 7.51–7.54 (4H, m), 7.97 (1H, d,

$J = 8.7$ Hz); HPLC $t_R = 1.99$ min (>92%) 90% MeCN in H_2O LC/MS (ES−) *m/z* 265.36 $(M-H)^-$; HRMS (ES+) *m/z* Calcd for $C_{18}H_{19}O_2$ 267.1380, found $(M+H)^+$ 267.1379.

4.4.4.21. 4′-Methoxy-2-methyl-biphenyl (23). This compound has been described in the literature.[49] A suspension of 4-methoxyphenyl boronic acid (0.57 g, 3.75 mmol), 2-bromotoluene (0.3 mL, 2.5 mmol), K_2CO_3 (0.86 g, 6.25 mmol), and Bu_4NBr (0.805 g, 2.5 mmol) in EtOH (7.5 mL) and water (17.5 mL) was degassed by bubbling N_2 through for 30 min while heating to 80 °C. To the resulting solution was added $Pd(OAc)_2$ (catalytic) and the reaction was heated at 80 °C for 1h with vigorous stirring. The reaction mixture was then allowed to cool before EtOAc (50 mL) was added and the mixture was washed with 1 M NaOH (aq) (2× 50 mL), water (2× 50 mL) ,and brine (2× 50 mL) before being concentrated under reduced pressure. Flash chromatography (20 g column, Flashmaster II) using a gradient elution of hexane to 10% EtOAc in hexane yielded the title compound (0.602 g, 80%); ^1H NMR δ (270 MHz, $CDCl_3$) 2.53 (3H, s), 4.01 (3H, s), 7.15–7.20 (2H, m), 7.43–7.51 (6H, m); HPLC $t_R = 2.51$ min (>92%) 90% MeCN in H_2O; LC/MS (ES−) *m/z* 197.28 $(M-H)^-$.

4.4.4.22. 1-(4′-Methoxy-2-methyl-biphenyl-4-yl)-ethanone (24). To a stirred solution of 4′-methoxy-2-methylbiphenyl **23** (06.00 g, 3 mmol) in dry DCM (5 mL) was added acetic anhydride (0.34 mL, 3.6 mmol) and the solution was cooled to −10 °C (ice/acetone bath). To this was then added $AlCl_3$ (0.800 g, 6 mmol) and the reaction was allowed to warm slowly to rt with stirring over 65 h. The reaction was quenched with 2 M HCl (aq) and the organics extracted into DCM and concentrated under reduced pressure. Purification by flash chromatography using hexane to 10% EtOAc in hexane gave the product as the second fraction in 33% yield: mp 89–92 °C; ^1H NMR δ (270 MHz, $CDCl_3$) 2.27 (3H, s), 2.66 (3H, s), 3.95 (3H, s), 7.02 (1H, d, $J = 8.7$ Hz), 7.19–7.25 (4H, m), 7.44 (1H, dd, $J = 8.5, 2.5$ Hz), 7.73 (1H, d, $J = 8.5$ Hz); HPLC $t_R = 2.20$ min (>99%) 90% MeCN in H_2O; LC/MS (ES+) *m/z* 263.45 $(M+Na)^+$.

4.4.4.23. 1-(4′-Hydroxy-2-methyl-biphenyl-4-yl)-ethanone (25). Prepared according to the General Procedure 3 from 1-(4′-methoxy-2-methyl-biphenyl-4-yl)-ethanone **24** to give the title compound as a pale yellow oil (yield 81%); ^1H NMR δ (400 MHz, CD_3OD) 2.25 (3H, s), 2.63 (3H, s), 6.98 (1H, d, $J = 8.6$ Hz), 7.19–7.27 (4H, m), 7.45 (1H, dd, $J = 8.6, 2.2$ Hz), 7.77 (1H, d, $J = 2.3$ Hz); ^{13}C NMR δ (100 MHz, CD_3OD) 20.6, 27.0, 118.7, 120.7, 127.0, 128.5, 130.8, 131.4, 132.5, 134.3, 136.5, 138.4, 141.9, 162.2, 206.4; HPLC $t_R = 2.75$ min (>99%) 90% MeCN in H_2O; LC/MS (AP−) *m/z* 224.99 $(M-H)^-$; HRMS (ES+) *m/z* Calcd for $C_{15}H_{15}O_2$ 227.1067, found (M+H)+ 227.1056.

4.4.4.24. 2-Methoxyfluorene (26). This compound is described in the literature.[50] To a stirred solution of 2-hydroxyfluorene (0.100 g, 0.55 mmol) in DMF (1.5 mL) was added K_2CO_3 (0.23 g, 1.65 mmol) followed by MeI (41 μL, 0.66 mmol) and the reaction was stirred at rt for 17 h. Water was added and the resulting beige precipitate was collected by filtration. Recrystallization from DCM/hexane gave a brown powder which was separated. The filtrate was columned using hexane to 20% EtOAc to give the title compound as the first fraction (yield 73%); ^1H NMR δ (270 MHz, $CDCl_3$) 3.88 (5H, s), 6.96 (1H, dd, $J = 8.3, 2.3$ Hz), 7.11–7.12 (1H, m), 7.26 (1H, dt, $J = 7.4, 1.3$ Hz), 7.34–7.40 (1H, m), 7.52 (1H, d, $J = 7.1$ Hz), 7.68–7.73 (2H, m); HPLC $t_R = 2.74$ min (>96%) 90% MeCN in H_2O.

4.4.4.25. 1-(7-Methoxy-9H-fluoren-2-yl)-ethanone (27). This compound is described in the literature.[51] To a stirred solution of **26** (78 mg, 0.4 mmol) and Ac_2O (0.1 mL) in 1,2-dichloroethane (10 mL) was added $AlCl_3$ (0.24 g) and the reaction was stirred at rt for 24 h. The reaction was quenched with 2 M HCl and the organic layer separated and concentrated under reduced pressure (yield 20%): mp 123–127 °C [lit. 131–132 °C[47]]; ^1H NMR δ (270 MHz, $CDCl_3$) 2.63 (3H, s), 3.86 (3H, s), 3.89 (2H, br s), 6.95 (1H, dd, $J = 8.4, 2.2$ Hz), 7.10–7.11 (1H, m), 7.70 (2H, d, $J = 8.2$ Hz), 7.72 (2H, d, $J = 8.4$ Hz), 7.94–7.98 (1H, m), 8.08 (1H, br s); HPLC $t_R = 2.31$ min (>99%) 90% MeCN in H_2O; LC/MS (AP−) *m/z* 237.27 $(M-H)^-$, 255.28; HRMS (ES+) *m/z* Calcd for $C_{16}H_{15}O_2$ 239.1067, found $(M+H)^+$ 239.1074.

4.4.4.26. 1-(6-Hydroxy-9H-fluoren-2-yl)-ethanone (28). Prepared according to the General Procedure 3 from 1-(7-methoxy-9H-fluoren-2-yl)-ethanone **27** (yield 36%): mp >190 °C (dec) [lit. 213–214 °C[52]]; ^1H NMR δ (270 MHz, $CDCl_3$) 2.63 (3H, s), 3.69 (2H, s), 5.43 (1H, s), 6.89 (1H, dd, $J = 8.3, 2.4$ Hz), 7.05 (1H, d, $J = 2.0$ Hz), 7.67–7.72 (2H, m), 7.95–7.986 (1H, m), 8.08 (1H, d, $J = 0.7$ Hz); HPLC $t_R = 1.70$ min (>95%) 90% MeCN in H_2O; LC/MS (AP−) *m/z* 222.91 $(M-H)^-$; HRMS (ES+) *m/z* Calcd for $C_{15}H_{13}O_2$ 225.0910, found $(M+H)^+$ 225.0921.

4.4.4.27. 3-Ethyl-4′-methoxy-biphenyl (29). Prepared according to the General Procedure 1, heating for 10 min. The product was purified by flash chromatography (20 g, Flashmaster) using hexane to 20% EtOAc in hexane followed by recrystallization from DCM/hexane (yield 75%); ^1H NMR δ (270 MHz, $CDCl_3$) 1.36 (3H, t, $J = 7.7$ Hz), 2.78 (2H, q, $J = 7.7$ Hz), 3.89 (3H, s), 7.04 (2H, d, $J = 8.9$ Hz), 7.23 (1H, d, $J = 5.1$ Hz), 7.38–7.47 (3H, m), 7.60 (2H, d, $J = 8.9$ Hz); HPLC $t_R = 2.35$ min (>97%) 90% MeCN in H_2O.

4.4.4.28. 1-(3-Ethyl-4′-methoxy-biphenyl-4-yl)-ethanone (30). To a stirred solution of 3-ethyl-4′-methoxybiphenyl **29** (0.16 g, 0.75 mmol) in 1,2-dichloroethane (4 mL) was added Ac_2O (0.2 mL) and the solution was cooled in an ice/acetone bath. To this was then added $AlCl_3$ (0.48 g) and the reaction was allowed to warm to rt with stirring over 24 h. The reaction was quenched with HCl (2 M, aq) and the organics extracted into DCM. This mixture containing the title compound and 1-(3′-ethyl-4-methoxy-biphenyl-3-yl)-ethanone was used for the demethylation step.

4.4.4.29. 1-(3-Ethyl-4′-hydroxy-biphenyl-4-yl)-ethanone (31). Prepared according to the General Procedure 3 from a mixture containing 1-(3-ethyl-4′-methoxy-biphenyl-4-yl)-ethanone **30** and 1-(3′-ethyl-4-methoxy-biphenyl-3-yl)-ethanone (yield over two steps 20%): mp 99–102 °C; ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.25 (3H, t, $J = 7.4$ Hz), 2.62 (3H, s), 2.97 (2H, q, $J = 7.4$ Hz), 6.94 (2H, d, $J = 8.7$ Hz), 7.38–7.45 (2H, m), 7.51 (2H, d, $J = 8.6$ Hz), 7.73 (1H, d, $J = 7.7$ Hz); HPLC $t_R = 1.80$ min (>95%) 90% MeCN in H_2O; LC/MS (ES−) *m/z* 239.03 $(M-H)^-$; HRMS (ES+) *m/z* Calcd for $C_{16}H_{17}O_2$ 241.1223, found $(M+H)^+$ 241.1228.

4.4.4.30. 2,3-Dihydro-5-phenylinden-1-one (32). Preparation and spectroscopic data as described by Zhuang et al.[36] HPLC $t_R = 2.25$ min (>99%) 90% MeCN in H_2O.

4.4.4.31. 4-(4-Bromophenyl)-4-oxo-butyric acid (33). Preparation and spectroscopic data as described by Sonpatki et al.[41] mp 148–149 °C [lit. 148–149 °C[53]].

4.4.4.32. 4-(4-Bromo-2-methylphenyl)-4-oxo-butyric acid (34). To a stirred mixture of succinic anhydride (0.50 g, 5.0 mmol) in 3-bromotoluene (3.74 mL, 30.85 mmol), cooled to −5 °C (ice/acetone bath) was added in one portion $AlCl_3$ (1.33 g, 10 mmol). The reaction temperature was maintained at −5 °C for 4 h before being slowly allowed to warm to rt overnight. The mixture was poured into cooled (ice bath) stirred aqueous HCl (15 mL, 18%) and stirring was continued for a further 30 min while the solution was allowed to warm to rt. No precipitate formed, therefore DCM (10 mL) was added and the organic layer was separated and concentrated under reduced pressure. To this was added hexane (5 mL) followed by a small amount of DCM (to mix the layers). The white needles obtained were shown by NMR to contain a small amount of the *ortho* product, therefore were recrystallized again from DCM/hexane (yield 63%); ^{1}H NMR δ (270 MHz, $CDCl_3$) 2.46 (3H, s), 2.75–2.80 (2H, m), 3.14–3.19 (2H, m), 7.39–7.42 (2H, m), 7.55–7.59 (1H, m); HPLC $t_R = 1.37$ min (>99%) 80% MeCN in H_2O; LRMS (FAB+) *m/z* 270.9, 272.9 $(M+H)^+$; HRMS (FAB+) *m/z* Calcd for $C_{11}H_{12}O_3\ ^{79}Br$ 270.9970, found $(M+H)^+$ 270.9967, Calcd for $C_{11}H_{12}O_3\ ^{81}Br$ 272.9949, found $(M+H)^+$ 272.9949.

4.4.4.33. 4-(4-Bromophenyl)-2,2-dimethyl-4-oxo-butyric acid (35). To a stirred suspension of 2,2-dimethylsuccinic anhydride (0.641 g, 5.0 mmol) in bromobenzene (3.3 mL), cooled to −10 °C (ice/acetone bath) was added $AlCl_3$ (1.34 g, 10 mmol) and the reaction was allowed to warm slowly to rt with stirring overnight. The resulting brown solution was poured into cooled (ice bath) aqueous HCl (10 mL, 18%) and stirred for a further 30 min while the solution was allowed to warm to rt. No precipitate formed therefore DCM (10 mL) was added and the organic layer was separated and concentrated under reduced pressure to give a solution of the product in PhBr. To this was added hexane followed by a small amount of DCM and the resulting white needles were collected by filtration (yield 51%): mp 137–138 °C; ^{1}H NMR δ (270 MHz, DMSO-d_6) 1.24 (6H, s), 3.29 (2H, s), 7.69 (2H, d, $J = 8.7$ Hz), 7.88 (2H, d, $J = 8.7$ Hz), 7.96 (1H, s); HPLC $t_R = 2.87$ min (>93%) 70% MeCN in H_2O; LC/MS (APCI) *m/z* 283.15, 285.10 $(M-H)^-$.

4.4.4.34. 4-(3′-Ethyl-4′-methoxy-biphenyl)-4-oxo-butanoic acid (36). Prepared from 3-ethyl-4-methoxyphenylboronic acid **5** and 4-(4-bromophenyl)-4-oxo-butanoic acid **33** according to the General Procedure 2 but purified by flash chromatography using gradient elution of DCM to 10% MeOH in DCM, followed by recrystallization from MeOH/H_2O to give the title compound as a pale pink powder (yield 64%): mp 91–94 °C; ^{1}H NMR δ (270 MHz, DMSO-d_6) 1.19 (3H, t, $J = 7.4$ Hz), 2.60–2.68 (4H, m), 3.27–3.30 (2H, m), 3.37 (1H, br s), 3.86 (3H, s), 7.08 (1H, d, $J = 8.6$ Hz), 7.57 (1H, d, $J = 2.3$ Hz), 7.60 (1H, dd, $J = 8.2, 2.3$ Hz), 7.80 (2H, d, $J = 8.6$ Hz), 8.04 (2H, d, $J = 8.6$ Hz); ^{13}C NMR δ (100 MHz, DMSO-d_6) 14.8, 23.4, 28.4, 33.5, 55.9, 111.6, 126.2, 126.7, 128.0, 129.0, 131.3, 132.7, 134.9, 145.0. 157.9, 174.4, 198.4; HPLC $t_R = 2.75$ min (>96%) 80% MeCN in H_2O; LC/MS (APCI) *m/z* 311.24 $(M-H)^-$; HRMS (FAB+) *m/z* Calcd for $C_{19}H_{20}O_4$ 312.1361, found (M^+) 312.1353.

4.4.4.35. 4-(3′-Ethyl-4′-methoxy-3-methyl-biphenyl-4-yl)-4-oxo-butyric acid (37). Prepared from 3-ethyl-4-methoxyphenylboronic acid **5** and 4-(4-bromo-2-methylphenyl)-4-oxo-butyric acid **34** according to the General Procedure 2 with purification as for **36** to give the title compound as white solid (yield 58%): mp >130 °C (dec); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.23 (3H, t, $J = 7.4$ Hz), 2.58 (3H, s), 2.69 (2H, q, $J = 7.4$ Hz), 2.78–2.83 (2H, m), 3.26–3.31 (2H, m), 3.87 (3H, s), 6.91 (1H, d, $J = 8.2$ Hz), 7.41–7.47 (4H, m), 7.81 (1H, d, $J = 7.9$ Hz); HPLC $t_R = 2.23$ min (>99%) 50% MeCN in H_2O; LRMS (FAB+) *m/z* 327.1 $(M+H)^+$; HRMS (FAB+) *m/z* Calcd for $C_{20}H_{23}O_4$ 327.1596, found $(M+H)^+$ 327.1585.

4.4.4.36. 4-(3′-Ethyl-4′-methoxy-biphenyl-4-yl)-2,2-dimethyl-4-oxo-butyric acid (38). Prepared from 3-ethyl-4-methoxyphenyl boronic acid **5** and 4-(4-bromophenyl)-2, 2-dimethyl-4-oxo-butyric acid **35** according to the General Procedure 3. Recrystallization from DCM/hexane gave colorless cubes (yield 60%); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.29 (3H, t, $J = 7.4$ Hz), 1.37 (6H, s), 2.69 (2H, q, $J = 7.4$ Hz), 3.33 (2H, s), 3.87 (3H, s), 6.92 (1H, d, $J = 8.4$ Hz), 7.42–7.46 (2H, m), 7.63 (2H, d, $J = 8.4$ Hz), 7.98 (2H, d, $J = 8.4$ Hz); HPLC $t_R = 2.68$ min (>99%) 90% MeCN in H_2O; LC/MS (APCI) *m/z* 339.17 $(M-H^+)$.

4.4.4.37. 5-(3′-Ethyl-4′-methoxy-biphenyl-4-yl)-3,3-dimethyl-4-oxo-3H-furan-2-one (39). From attempted amide coupling: to a stirred solution of 4-(3′-ethyl-4′-methoxy-biphenyl-4-yl)-2,2-dimethyl-4-oxo-butyric acid **38** (0.100 g, 0.3 mmol) in dry DCM (15 mL) was added DMAP (catalytic), EDCI (0.191 g, 1 mmol) and NEt_3 (0.06 mL) and the reaction was stirred at rt for 20 min before addition of 3-(2-aminoethyl) pyridine (0.06 mL). The solution was stirred at rt for 24 h before the solution was washed with satd aq bicarb. and the organic layer was separated and concentrated under reduced pressure. Flash chromatography (20g column, Flashmaster II) using a gradient elution of DCM to 5% MeOH in DCM yielded the title compound as the first fraction (yield 0.026g, 27%); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.23 (3H, t, $J = 7.5$ Hz), 1.41 (6H, s), 2.69 (2H, q, $J = 7.6$ Hz), 3.87 (3H, s), 5.81 (1H, s), 6.91 (1H, d, $J = 6.9$ Hz), 7.39–7.44 (2H, m), 7.55–7.65 (4H, m); HPLC $t_R = 2.91$ min (>99%) 90% MeCN in H_2O; LC/MS (APCI) *m*/*z* 323.29 $(M+H)^+$.

From reaction of 4-(3′-ethyl-4′-methoxy-biphenyl-4-yl)-2,2-dimethyl-4-oxo-butyric acid **38** with acetyl chloride: To a stirred solution of 4-(3′-ethyl-4′-methoxy-biphenyl-4-yl)-2,2-dimethyl-4-oxo-butyric acid **38** (0.055 g, 0.16 mmol) in dry DCM (5 mL) was added acetyl chloride (13 μL) and NEt_3 (30 μL) and the reaction was stirred at rt for 48 h. To this was added DCM (5 mL) and water (10 mL) and the organic layer was separated and concentrated under reduced pressure. Purification by flash chromatography (10 g column, Flashmaster II) using an elution gradient of hexane to 10% DCM in hexane yielded 0.029 g of product (56%); ^{1}H NMR and R_f as above.

4.4.4.38. 4-(3′-Ethyl-4′-methoxy-biphenyl)-4-oxo-*N*-pyridin-3-ylmethyl-butyramide (40). Prepared from 4-(3′-ethyl-4′-methoxy-biphenyl)-4-oxo-butanoic acid **36** according to the General Procedure 4, using 3-aminomethyl pyridine (yield 31%); ^{1}H NMR δ (270 MHz, CD_3OD) 1.21 (3H, t, $J = 7.5$ Hz), 2.65–2.73 (4H, m), 3.41–3.46 (2H, m), 3.87 (3H, s), 4.62 (2H, s), 7.02 (1H, d, $J = 8.7$ Hz), 7.45–7.55 (2H, m), 7.72 (2H, d, $J = 8.7$ Hz), 8.04–8.12 (3H, m), 8.64 (1H, d, $J = 8.2$ Hz), 8.76 (1H, d, $J = 5.7$ Hz), 8.89 (1H, s); HPLC $t_R = 2.29$ min (>99%) 90% MeCN in H_2O; LC/MS (APCI) *m*/*z* 403.25.

4.4.4.39. 4-(3′-Ethyl-4′-methoxy-biphenyl)-4-oxo-*N*-pyridin-2-ylmethyl-butyramide (41). Prepared from 4-(3′-ethyl-4′-methoxy-biphenyl)-4-oxo-butanoic acid **36** according to the General Procedure 4, using 2-aminomethylpyridine (yield 31%); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.23 (3H, t, $J = 7.5$ Hz), 2.65–2.76 (4H, m), 3.39–3.45 (2H, m), 3.87 (3H, s), 4.57 and 4.59 (2H, 2× s), 6.90–6.93 (2H, m), 7.16–7.21 (1H, m), 7.25–7.27 (1H, m), 7.42–7.47 (2H, m), 7.62–7.68 (3H, m), 8.03 (2H, d, $J = 8.4$ Hz), 8.53 (1H, d, $J = 4.5$ Hz); HPLC $t_R = 2.34$ min (>96%) 90% MeCN in H_2O; LC/MS (APCI) *m*/*z* 403.25 $(M+H)^+$.

4.4.4.40. 4-(3′-Ethyl-4′-methoxy-biphenyl)-4-oxo-*N*-pyridin-3-ylethyl-butyramide (42). Prepared from 4-(3′-ethyl-4′-methoxy-biphenyl)-4-oxo-butanoic acid **36** according to the General Procedure 4, using 2-(pyridin-3-yl)ethanamine (yield 30%); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.23 (3H, t, $J = 7.5$ Hz), 2.59 (2H, t, $J = 6.4$ Hz), 2.69 (2H, q, $J = 7.5$ Hz), 2.80–2.86 (2H, m), 3.36 (2H, t, $J = 6.4$ Hz), 3.48–3.56 (2H, m), 3.87 (3H, s), 5.90 (1H, br s), 6.92 (1H, d, $J = 8.7$ Hz), 7.16–7.25 (1H, m), 7.42–7.47 (2H, m), 7.52–7.56 (1H, m), 7.65 (2H, d, $J = 8.4$ Hz), 8.01 (2H, d, $J = 8.7$ Hz), 8.45–8.48 (2H, m); HPLC $t_R = 2.33$ min (>95%) 90% MeCN in H_2O; LC/MS (APCI) *m*/*z* 417.30 $(M+H)^+$.

4.4.4.41. 4-(3′-Ethyl-4′-methoxy-biphenyl)-4-oxo-*N*-(2-methoxyethyl)-butyramide (43). Prepared from 4-(3′-ethyl-4′-methoxy-biphenyl)-4-oxo-butanoic acid **36** according to the General Procedure 4, using 2-methoxyethanamine (yield 25%); 1H NMR δ (270 MHz, $CDCl_3$) 1.23 (3H, t, $J = 7.5$ Hz), 2.61–2.73 (4H, m), 3.30–3.56 (9H, m), 3.86 (3H, s), 6.10 (1H, br s), 6.91 (1H, d, $J = 8.7$ Hz), 7.42–7.46 (2H, m), 7.63 (2H, d, $J = 8.7$ Hz), 8.01 (2H, d, $J = 8.4$ Hz); HPLC $t_R = 2.34$ min (>99%) 90% MeCN in H_2O; LC/MS (APCI) *m*/*z* 370.30 $(M+H)^+$.

4.4.4.42. 4-(3′-Ethyl-4′-methoxy-3-methyl-biphenyl)-4-oxo-*N*-pyridin-3-ylmethyl-butyramide (44). Prepared from 4-(3′-ethyl-4′-methoxy-3-methyl-biphenyl-4-yl)-4-oxo-butyric acid **37** according to the General Procedure 4, using 3-aminomethyl pyridine (yield 87%); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.22 (3H, t, $J = 7.4$ Hz), 2.53 (3H, s), 2.60–2.72 (4H, m), 3.29 (2H, t, $J = 6.4$ Hz), 3.84 (3H, s), 4.42 (2H, d, $J = 5.9$ Hz), 6.88 (1H, d, $J = 9.2$ Hz), 6.93–6.97 (1H, m), 7.18–7.23 (1H, m), 7.37–7.43 (4H, m), 7.61–7.66 (1H, m), 7.78 (1H, d, $J = 8.9$ Hz), 8.43–8.45 (1H, m), 8.49 (1H, d, $J = 1.7$ Hz); HPLC $t_R = 2.49$ min (>98%) 80% MeCN in H_2O; LRMS (FAB+) *m*/*z* 417.1 $(M+H)^+$; HRMS (FAB+) *m*/*z* Calcd for $C_{26}H_{29}N_2O_3$ 417.2178, found $(M+H)^+$ 417.2175.

4.4.4.43. 4-(3′-Ethyl-4′-methoxy-3-methyl-biphenyl)-4-oxo-*N*-pyridin-3-ylethyl-butyramide (45). Prepared from 4-(3′-ethyl-4′-methoxy-3-methyl-biphenyl-4-yl)-4-oxo-butyric acid **37** according to the General Procedure 4, using 2-(pyridin-3-yl)ethanamine (yield 80%); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.21 (3H, t, $J = 7.4$ Hz), 2.53–2.57 (5H, m), 2.67 (2H, q, $J = 7.4$ Hz), 2.77–2.83 (2H, m), 3.23–3.28 (2H, m), 3.49 (2H, dd, $J = 13.1$, 6.9 Hz), 3.83 (3H, s), 6.49–6.53 (1H, m), 6.87 (1H, d, $J = 9.2$ Hz), 7.14–7.20 (1H, m), 7.38–7.44 (4H, m), 7.50–7.54 (1H, m), 7.79 (1H, d, $J = 8.4$ Hz), 8.38–8.43 (2H, m); HPLC $t_R = 2.52$ min (>98%) 80% MeCN in H_2O; LRMS (FAB)+ *m*/*z* 431.2 $(M+H)^+$; HRMS (FAB+) *m*/*z* Calcd for $C_{27}H_{31}N_2O_3$ 431.2335, found $(M+H)^+$ 431.2337.

4.4.4.44. 4-(3′-Ethyl-4′-methoxy-biphenyl)-2,2-dimethyl-4-oxo-*N*-pyridin-3-ylmethyl-butyramide (46). To a stirred solution of 5-(3′-ethyl-4′-methoxy-biphenyl-4-yl)-3,3-dimethyl-4-oxo-3*H*-furan-2-one **39** (0.0265 g, 0.08 mmol) in dry DCM (5 mL) was added 3-aminomethyl pyridine (0.01 mL) and the mixture was heated to reflux for 22 h before being cooled and concentrated under reduced pressure. The product was purified by flash chromatography using an elution gradient of DCM to 10% MeOH in DCM (yield 54%); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.20–1.27 (6H, m), 1.36 (3H, s), 2.35 (2H, s), 2.69 (2H, q, $J = 7.4$ Hz), 3.86 (3H, s), 3.97 (1H, d, $J = 15.1$ Hz), 4.68 (1H, d, $J = 15.1$ Hz), 4.97 (1H, br s), 6.91 (1H, d, $J = 9.2$ Hz), 7.06–7.11 (1H, m), 7.38–7.41 (4H, m), 7.53–7.61 (3H, m), 8.12–8.15 (2H, m); HPLC $t_R = 2.61$ min (>99%) 80% MeCN in H_2O; LC/MS (APCI) *m*/*z* 431.42 $(M+H)^+$; HRMS (FAB+) *m*/*z* Calcd for $C_{27}H_{31}N_2O_3$ 431.2335, found $(M+H)^+$ 431.2336.

4.4.4.45. 4-(3′-Ethyl-4′-methoxy-biphenyl)-2,2-dimethyl-4-oxo-*N*-pyridin-3-ylethyl-butyramide (47). To a stirred solution of 5-(3′-ethyl-4′-methoxy-biphenyl-4-yl)-3,3-dimethyl-4-oxo-3*H*-furan-2-one **39** (0.029 g, 0.09 mmol) in dry DCM (5 mL) was added 2-(pyridin-3-yl)ethanamine (0.01 mL) and the mixture was heated to reflux for 46 h before being cooled and concentrated under reduced pressure. The product was purified by flash chromatography using an elution gradient of DCM to 10% MeOH in DCM (yield 100%); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.19–1.24 (6H, m), 1.31 (3H, s), 2.30 (2H, s), 2.68 (2H, q, $J = 7.4$ Hz), 2.87–3.08 (3H, m), 3.54–3.65 (1H, m), 3.85 (3H, s), 6.89 (1H, d, $J = 9.2$ Hz), 7.08–7.13 (1H, m), 7.36–7.42 (4H, m), 7.48–7.55 (3H, m), 8.15 (2H, br s); HPLC $t_R = 3.11$ min (>96%) 90% MeCN in H_2O; LRMS (FAB+) *m/z* 445.2 $(M+H)^+$; HRMS (FAB+) *m/z* Calcd for $C_{28}H_{33}N_2O_3$ 445.2491, found $(M+H)^+$ 445.2490.

4.4.4.46. 4-(3′-Ethyl-4′-hydroxy-biphenyl)-4-oxo-*N*-pyridin-3-ylmethyl-butyramide (48). Prepared from 4-(3′-ethyl-4′-methoxy-biphenyl)-4-oxo-*N*-pyridin-3-ylmethyl-butyramide **27** according to the General Procedure 3 (yield 41%): mp >150 °C (dec); ^{1}H NMR δ (270 MHz, CD_3OD) 1.23 (3H, t, $J = 7.5$ Hz), 2.65–2.72 (4H, m), 3.37–3.42 (2H, m), 4.44 (2H, s), 6.83 (1H, d, $J = 8.2$ Hz), 7.35–7.43 (3H, m), 7.69 (2H, d, $J = 8.7$ Hz), 7.82 (1H, d, $J = 7.4$ Hz), 8.03 (2H, d, $J = 8.4$ Hz), 8.41–8.44 (1H, m), 8.52 (1H, s); HPLC $t_R = 1.83$ min (>96%) 90% MeCN in H_2O; LC/MS (APCI) *m/z* 389.20 $(M+H)^+$; HRMS (FAB+) *m/z* Calcd for $C_{24}H_{25}N_2O_3$ 389.1865, found $(M+H)^+$ 389.1867.

4.4.4.47. 4-(3′-Ethyl-4′-hydroxy-biphenyl)-4-oxo-*N*-pyridin-2-ylmethyl-butyramide (49). Prepared from 4-(3′-ethyl-4′-methoxy-biphenyl)-4-oxo-*N*-pyridin-2-ylmethyl-butyramide **28** according to the General Procedure 3 (yield 5%): mp 144–146 °C; ^{1}H NMR δ (270 MHz, CD_3OD) 1.23 (3H, t, $J = 7.5$ Hz), 2.64–2.75 (4H, m), 3.40–3.46 (2H, m), 4.51 (2H, s), 6.84 (1H, d, $J = 8.2$ Hz), 7.28–7.50 (4H, m), 7.69 (2H, d, $J = 8.7$ Hz), 7.79–7.86 (1H, m), 8.05 (2H, d, $J = 8.7$ Hz), 8.47 (1H, d, $J = 4.7$ Hz); HPLC $t_R = 1.89$ min (>90%) 90% MeCN in H_2O; LC/MS (APCI) *m/z* 389.14 $(M+H)^+$; HRMS (FAB+) *m/z* Calcd for $C_{24}H_{25}N_2O_3$ 389.1865, found $(M+H)^+$ 389.1871.

4.4.4.48. 4-(3′-Ethyl-4′-hydroxy-biphenyl)-4-oxo-*N*-pyridin-3-ylethyl-butyramide (50). Prepared from 4-(3′-ethyl-4′-methoxy-biphenyl)-4-oxo-*N*-pyridin-3-ylethyl-butyramide**29** according to the General Procedure 3 (yield 72%): mp 103–105 °C; ^{1}H NMR δ (270 MHz, CD_3OD) 1.22 (3H, t, $J = 7.5$ Hz), 2.55 (2H, t, $J = 6.2$ Hz), 2.67 (2H, q, $J = 7.5$ Hz), 3.08 (2H, t, $J = 6.2$ Hz), 3.27–3.32 (2H, m), 3.55–3.60 (2H, m), 6.84 (1H, d, $J = 8.2$ Hz), 7.35 (1H, dd, $J = 8.4,2.2$ Hz), 7.41 (1H, d, $J = 2.2$ Hz), 7.67 (2H, d, $J = 8.4$ Hz), 7.98–8.04 (3H, m), 8.60 (1H, d, $J = 8.2$ Hz), 8.73 (1H, d, $J = 5.7$ Hz), 8.88 (1H, s); HPLC $t_R = 1.85$ min (>99%) 90% MeCN in H_2O; LC/MS (APCI) *m/z* 403.19 $(M+H)^+$; HRMS (FAB+) *m/z* Calcd for $C_{25}H_{27}N_2O_3$ 403.2021, found $(M+H)^+$ 403.2026.

4.4.4.49. 4-(3′-Ethyl-4′-hydroxy-biphenyl)-4-oxo-*N*-(2-hydroxyethyl)-butyramide (51). Prepared from 4-(3′-ethyl-4′-methoxy-biphenyl)-4-oxo-*N*-(2-methoxyethyl)-butyramide **32** according to the General Procedure 3 (yield 41%): mp >110 °C (dec); ^{1}H NMR δ (270 MHz, CD_3OD) 1.22 (3H, t, $J = 7.5$ Hz), 2.61–2.71 (4H, m), 3.29–3.38 (4H, m), 3.59–3.63 (2H, m), 6.84 (1H, d, $J = 8.4$ Hz), 7.35 (1H, dd, $J = 8.2$, 2.5 Hz), 7.42 (1H, d, $J = 2.2$ Hz), 7.68 (2H, d, $J = 8.4$ Hz), 8.02 (1H, d, $J = 8.4$ Hz); HPLC $t_R = 1.76$ min (>93%) 90% MeCN in H_2O; LC/MS (APCI) *m/z* 342.13 $(M+H)^+$; HRMS (FAB+) *m/z* Calcd for $C_{20}H_{24}NO_4$ 342.1700, found $(M+H)^+$ 342.1700.

4.4.4.50. 4-(3′-Ethyl-4′-hydroxy-3-methyl-biphenyl)-4-oxo-*N*-pyridin-3-ylmethyl-butyramide (52). Prepared from 4-(3′-ethyl-4′-methoxy-3-methyl-biphenyl)-4-oxo-*N*-pyridin-3-ylmethyl-butyramide **44** according to the General Procedure 3 (yield 93%): mp 158–160 °C; ^{1}H NMR δ (270 MHz, CD_3OD) 1.23 (3H, t, $J = 7.5$ Hz), 2.50 (3H, s), 2.63–2.71 (4H, m), 3.28–3.34 (2H, m), 4.43 (2H, s), 6.82 (1H, d, $J = 8.4$ Hz), 7.30–7.49 (5H, m), 7.81–7.87 (2H, m), 8.41 (2H, d, $J = 4.2$ Hz), 8.52 (1H, s); ^{13}C NMR δ (100 MHz, DMSO-d_6) 14.8, 21.6, 23.4, 29.9, 36.4, 55.4, 115.8, 118.4, 123.6, 123.9, 125.7, 128.1, 129.4, 129.9, 130.1, 131.0, 135.4, 135.7, 138.4, 143.5, 148.5, 129.1, 156.2, 172.1, 202.7; HPLC $t_R = 1.91$ min (>97%) 90% MeCN in H_2O; FAB-LRMS (FAB+) *m/z* 403.0 $(M+H)^+$; HRMS (FAB+) *m/z* Calcd for $C_{25}H_{27}N_2O_3$ 403.20226, found $(M+H)^+$ 403.2026.

4.4.4.51. 4-(3′-Ethyl-4′-hydroxy-3-methyl-biphenyl)-4-oxo-*N*-pyridin-3-ylethyl-butyramide (53). Prepared from 4-(3′-ethyl-4′-methoxy-3-methyl-biphenyl)-4-oxo-*N*-pyridin-3-ylethyl-butyramide **45** according to the General Procedure 3 (yield 75%): mp 151–154 °C; ^{1}H NMR δ (400 MHz, CD_3OD) 1.27 (3H, t, $J = 7.5$ Hz), 2.56–2.57 (5H, m), 2.71 (2H, q, $J = 7.5$ Hz), 2.88 (2H, t, $J = 7.0$ Hz), 3.48 (2H, t, $J = 7.0$ Hz), 6.84 (1H, d, $J = 8.3$ Hz), 7.33–7.53 (5H, m), 7.90 (1H, dt, $J = 7.8$, 1.9 Hz), 7.87 (1H, d, $J = 8.0$ Hz), 8.41 (1H, dd, $J = 4.8$, 1.6 Hz), 8.48 (1H, d, $J = 1.6$ Hz); ^{13}C NMR δ (100 MHz, CD_3OD) 13.5, 20.6, 23.1, 29.5, 32.2, 40.0, 110.0, 115.5, 123.1, 123.8, 125.1, 127.4, 129.1, 129.6, 129.8, 131.3, 134.5, 135.8, 137.5, 138.7, 144.7, 146.6, 149.1, 157.1, 173.80; HPLC $t_R = 1.91$ min (>99%) 90% MeCN in H_2O; LRMS (FAB+) *m/z* 417.1 $(M+H)^+$; HRMS (FAB+) *m/z* Calcd for $C_{26}H_{29}N_2O_3$ 417.2178, found $(M+H)^+$ 417.2179.

4.4.4.52. 4-(3′-Ethyl-4′-hydroxy-biphenyl)-2,2-dimethyl-4-oxo-*N*-pyridin-3-ylmethyl-butyramide (54). Prepared from 4-(3′-ethyl-4′-methoxy-biphenyl)-2,2-dimethyl-4-oxo-*N*-pyridin-3-ylmethyl-butyramide **46** according to the General Procedure 3 (yield 72%); ^{1}H NMR δ (400 MHz, CD_3OD) 1.26 (3H, t, $J = 7.4$ Hz), 1.30 (3H, s), 1.41 (3H, s), 2.36–2.45 (2H, m), 2.70 (2H, q, $J = 7.6$ Hz), 4.32–4.42 (2H, m), 6.84 (1H, d, $J = 8.2$ Hz), 7.27–7.30 (2H, m), 7.35 (1H, d, $J = 2.1$ Hz), 7.40 (2H, d, $J = 8.7$ Hz), 7.50 (2H, d, $J = 8.5$ Hz), 7.67 (1H, d, $J = 7.9$ Hz) 8.30 (1H, s), 8.34 (1H, s); HPLC $t_R = 1.98$ min (>94%) 70% MeCN in H_2O; LRMS (FAB+) *m/z* 417.1 $(M+H)^+$; HRMS (FAB+) *m/z* Calcd for $C_{26}H_{29}N_2O_3$ 417.2178, found $(M+H)^+$ 417.2176.

4.4.4.53. 4-(3′-Ethyl-4′-hydroxy-biphenyl)-2,2-dimethyl-4-oxo-*N*-pyridin-3-ylethyl-butyramide (55). Prepared from 4-(3′-ethyl-4′-methoxy-biphenyl)-2,2-dimethyl-4-oxo-*N*-pyridin-3-ylethyl-butyramide **47** according to the General Procedure 3 (yield 52%): mp >130 °C (dec); ^{1}H NMR δ (270 MHz, CD_3OD) 1.19–1.24 (6H, m), 1.32 (3H, s), 2.26–2.36 (2H, m), 2.66 (2H, q, $J = 7.4$ Hz), 2.82–2.90 (2H, m), 3.05–3.16 (1H, m), 3.42–3.53 (1H, m), 6.80 (1H, d, $J = 8.2$ Hz), 7.26–7.30 (2H, m), 7.35 (1H, d, $J = 2.2$ Hz), 7.42 (2H, d, $J = 8.4$ Hz), 7.56–7.62 (3H, m), 8.28–8.32 (2H, m); ^{13}C NMR δ (100 MHz, CD_3OD) 13.5, 23.1, 25.1, 25.9, 31.5, 39.8, 41.7, 52.2, 90.9, 114.8, 124.9, 126.1, 127.5, 130.9, 131.4, 137.3, 141.3, 141.4, 146.5, 149.0, 154.9, 181.5; HPLC $t_R = 2.02$ min (>99%) 90% MeCN in H_2O; LRMS (FAB+) *m/z* 431.2 $(M+H)^+$; HRMS (FAB+) *m/z* Calcd for $C_{27}H_{31}N_2O_3$ 431.2335, found $(M+H)^+$ 431.2340.

4.4.4.54. [5-(3-Ethyl-4-methoxyphenyl)-1-oxo-indan-2-yl]-acetic acid ethyl ester (56). A solution of 5-(3-ethyl-4-methoxyphenyl)-indan-1-one **11** (0.312 g, 2.08 mmol) in dry THF (12 mL) under an inert atmosphere was cooled to −10 °C and stirred for 15 min. To this was added over 15 min at −10 °C a solution of LDA (1.8 M solution in heptane/THF/ethyl benzene, 0.711 mL, 1.28 mmol). The mixture was cooled to −60 °C and stirred at this temperature for 20 min before ethyl bromoacetate (0.155 mL, 1.40 mmol) was added drop-wise and the mixture stirred at −60 °C for 2–3 h and allowed to warm to rt overnight. The overall reaction time was 18 h. The reaction mixture was quenched with sat. NH_4Cl and the organics extracted into DCM (3× 20 mL). These extracts were combined, dried ($MgSO_4$), and concentrated to obtain a pale yellow solid. The solid was passed through a silica column (EtOAc/hexanes, gradient elution) to obtain the title compound mixed with the bis-alkylated product. This mixture was subjected to ester hydrolysis without further purification.

4.4.4.55. [5-(3-Ethyl-4-methoxyphenyl)-1-oxo-indan-2-yl]-acetic acid (57). To a suspension of [5-(3-ethyl-4-methoxyphenyl)-1-oxo-indan-2-yl]-acetic acid ethyl ester **56** (0.530 g, 1.56 mmol) in THF/water (1:1, 5 mL) was added NaOH (0.124 g, 3.12 mmol) and the mixture was stirred at rt for 2 days. Analysis by TLC showed two major products (DCM/MeOH, 95:5, $R_f = 0.02$ and 0.39). The resultant pale orange mixture was acidified to pH 2 with 2 M HCl and extracted with DCM (2× 20 mL) and EtOAc (2× 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated and the crude product was purified by chromatography (DCM/MeOH gradient elution). The compound with $R_f = 0.39$ was separated and shown to be the title compound (0.158 g, 16% over two steps); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.23 (3H, t, $J = 7.6$ Hz), 2.63–2.73 (3H, m), 2.89–3.17 (3H, m), 3.50 (1H, dd, $J = 17.3$, 7.6 Hz), 3.87 (3H, s), 6.92 (1H, d, $J = 8.4$ Hz), 7.42–7.45 (2H, m), 7.56–7.63 (2H, m), 7.79 (1H, d, $J = 7.9$ Hz); HPLC $t_R = 2.01$ min (>92%) 80% MeCN in H_2O; LRMS (FAB+) *m/z* 325 $(M+H)^+$.

4.4.4.56. 2-[5-(3-Ethyl-4-methoxyphenyl)-1-oxo-indan-2-yl]-*N*-pyridin-3-ylmethyl-acetamide (58). To a suspension of [5-(3-ethyl-4-methoxyphenyl)-1-oxo-indan-2-yl]-acetic acid **57** (0.070 g, 0.21 mmol) in DCM (12 mL) was added EDCI (0.123 g, 0.64 mmol) followed by DMAP (10 mg, cat. amount) and Et_3N (0.070 mL) and the mixture was stirred at rt for 20–30 min. To this was then added 3-aminomethyl pyridine (0.046 g, 0.43 mmol) and the resultant mixture was stirred for 25 h. The reaction was quenched with satd Na_2CO_3, the organics extracted into DCM (2× 20 mL) and the extracts were combined, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (DCM/MeOH, gradient elution) to give the title compound (20 mg, 23%) as a pale yellow solid; ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.23 (3H, t, $J = 7.6$ Hz), 2.59–3.20 (6H, m), 3.48 (1H, dd, $J = 16.8$, 8.6 Hz), 3.87 (3H, s), 4.43–4.46 (2H, m), 6.55 (1H, br t), 6.92 (1H, d, $J = 8.4$ Hz), 7.19–7.22 (1H, m), 7.42 (1H, s), 7.46 (1H, d, $J = 2.2$ Hz), 7.56–7.60 (3H, m), 7.75 (1H, d, $J = 7.6$ Hz), 8.48–8.51 (2H, m); LC/MS (APCI) *m/z* 415 $(M+H)^+$.

4.4.4.57. 2-[5-(3-Ethyl-4-methoxyphenyl)-1-oxo-indan-2-yl]-*N*-pyridin-2-ylmethyl-acetamide (59). To a suspension of [5-(3-ethyl-4-methoxyphenyl)-1-oxo-indan-2-yl]-acetic acid **57** (0.050 g, 0.15 mmol) in DCM (10 mL) was added EDCI (0.087 g, 0.46 mmol) followed by DMAP (10 mg, cat. amount) and Et_3N (0.050 mL) and the mixture stirred at rt for 20–30 min. To this was then added 2-aminomethyl pyridine (0.031 mL, 0.30 mmol) and the resultant mixture stirred for 25 h. The reaction was quenched with sat. Na_2CO_3 and the organics extracted into DCM (2× 20 mL). The extracts were combined, dried ($MgSO_4$), and concentrated and the crude product was purified by chromatography (DCM/MeOH, gradient elution) to give the title compound (40 mg, 63%) as a pale yellow solid; ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.23 (3H, t, $J = 7.4$ Hz), 2.59–3.20 (6H, m), 3.26 (1H, dd, $J = 17.8$, 7.9 Hz), 3.87 (3H, s), 4.56 (2H, d, $J = 4.9$ Hz), 6.92 (1H, d, $J = 8.4$ Hz), 7.17–7.20 (1H, m), 7.41–7.46 (3H, m), 7.55–7.66 (3H, m), 7.76–7.79 (1H, d, $J = 7.9$ Hz), 8.50–8.51 (1H, m); LC/MS (APCI) *m/z* 415 $(M+H)^+$.

4.4.4.58. 2-[5-(3-Ethyl-4-methoxyphenyl)-1-oxo-indan-2-yl]-*N*-(5-methyl-pyrazin-2-ylmethyl)-acetamide (60). To a stirred suspension of [5-(3-ethyl-4-methoxyphenyl)-1-oxo-indan-2-yl]-acetic acid **57** (0.050 g, 0.15 mmol) in DCM (10 mL) was added EDCI (0.087 g, 0.46 mmol) followed by DMAP (10 mg, catalytic amount) and Et_3N (0.050 mL) and the mixture stirred at rt for 20–30 min. To this was added 2-aminomethyl-5-methylpyrazine (0.037 g, 0.30 mmol) and the resultant mixture stirred for 25 h. The reaction was quenched with satd Na_2CO_3, the organics extracted into DCM (2× 20 mL), and the extracts were combined, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (DCM/MeOH, gradient elution) to give the title compound (28 mg, 42%) as a pale yellow solid; ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.23 (3H, t, $J = 7.4$ Hz), 2.53 (3H, s), 2.53–3.18 (5H, m), 3.44–3.50 (2H, m), 3.87 (3H, s), 4.55–4.66 (2H, m), 6.84 (1H, br s), 6.92 (1H, d, $J = 7.8$ Hz), 7.37–7.45 (2H, m), 7.55–7.59 (2H, m), 7.77 (1H, d, $J = 7.9$ Hz), 8.07–8.45 (2H, m); LC/MS (APCI) *m/z* 430 $(M+H)^+$.

4.4.4.59. 2-[5-(3-Ethyl-4-hydroxyphenyl)-1-oxo-indan-2-yl]-*N*-pyridin-3-ylmethyl-acetamide (61). Prepared from 2-[5-(3-ethyl-4-methoxyphenyl)-1-oxo-indan-2-yl]-*N*-pyridin-3-ylmethyl-acetamide **58** according to the General Procedure 3 (yield 31%); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.22 (3H, t, $J = 7.4$ Hz), 2.65–3.06 (6H, m), 3.38 (1H, dd, $J = 17.1$, 8.1 Hz), 4.44–4.47 (2H, m), 4.66 (1H, br s), 6.55 (1H, br t), 6.22 (1H, d, $J = 8.2$ Hz), 7.27–7.30 (1H, m), 7.39 (1H, m), 7.52–7.57 (3H, m), 7.74 (1H, d, $J = 7.9$ Hz), 8.07 (1H, s), 8.50–8.52 (2H, m); HPLC $t_R = 2.45$ min (>96%) 50% MeCN in H_2O; LC/MS (APCI) m/z 401 $(M+H)^+$.

4.4.4.60. 2-[5-(3-Ethyl-4-hydroxyphenyl)-1-oxo-indan-2-yl]-*N*-pyridin-2-ylmethyl-acetamide (62). Prepared from 2-[5-(3-ethyl-4-methoxyphenyl)-1-oxo-indan-2-yl]-*N*-pyridin-2-ylmethyl-acetamide **59** according to the General Procedure 3 (yield 37%); ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.19 (2H, t, $J = 7.4$ Hz), 2.51–2.63 (2H, m), 2.87 (1H, t, $J = 3.9$ Hz), 2.96 (2H, t, $J = 5.4$ Hz), 3.01–3.06 (1H, m), 3.38 (1H, dd, $J = 17.1$, 8.1 Hz), 4.51–4.53 (2H, m), 4.61 (1H, s), 6.73 (1H, d, $J = 8.2$ Hz), 6.93–6.94 (1H, br t), 7.12–7.18 (1H, m), 7.23 (1H, dd, $J = 8.2$, 2.3 Hz), 7.32 (1H, d, $J = 2.0$ Hz), 7.46–7.48 (2H, m), 7.59 (1H, dt, $J = 7.8$, 1.6 Hz), 7.70 (1H, d, $J = 8.6$ Hz), 8.02 (1H, s), 8.46 (1H, d, $J = 4.3$ Hz); HPLC $t_R = 2.39$ min (>99%) 50% MeCN in H_2O; LC/MS (APCI) m/z 401 $(M+H)^+$.

4.4.4.61. 2-[5-(3-Ethyl-4-hydroxyphenyl)-1-oxo-indan-2-yl]-*N*-(5-methyl-pyrazin-2-ylmethyl)-acetamide (63). Prepared from 2-[5-(3-ethyl-4-methoxyphenyl)-1-oxo-indan-2-yl]-*N*-(5-methyl-pyrazin-2-ylmethyl)-acetamide **60** according to the General Procedure 3 (yield 39%): according to ^{1}H NMR this compound exists as a mixture of rotamers. The analysis of the major rotamer; ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.27 (3H, t, $J = 7.4$ Hz), 2.58 (3H, s), 2.61–2.66 (1H, m), 2.74 (2H, q, $J = 7.4$ Hz), 2.95–3.06 (2H, m), 3.13–3.19 (1H, m), 3.54 (1H, dd, $J = 17.1$, 7.8 Hz), 3.92 (3H, s), 4.61 (2H, d, $J = 5.4$ Hz), 4.71 (2H, s), 6.89 (1H, br s), 6.96 (1H, d, $J = 8.1$ Hz), 7.46–7.52 (2H, m), 7.60–7.64 (2H, m), 7.82 (1H, d, $J = 8.1$ Hz), 8.12 (1H, s), 8.39 (1H, s), 8.50 (1H, s); HPLC $t_R = 2.43$ min (>84%) 80% MeCN in H_2O; LC/MS (APCI) m/z 416 $(M+H)^+$.

Acknowledgments

This research was supported by Sterix Ltd, a member of the Ipsen group. Alison Smith is thanked for expert technical assistance and Andrew Smith for molecular modeling discussions.

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