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The Design, Synthesis, and Evaluation of Novel 9-Arylxanthenedione-Based Allosteric Modulators for the δ-Opioid Receptor

Owindeep Deo, Sadia Alvi, Vi Pham, Arthur Christopoulos, David M. Thal, Manuela Jörg, Ben Capuano, Celine Valant,* and Peter J. Scammells*

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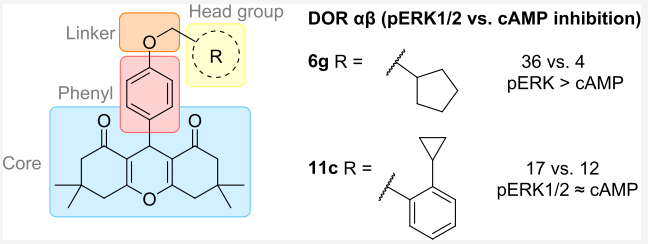
ABSTRACT: Chronic pain and depression are both widely prevalent comorbid medical conditions. While efficient, μ-opioid receptor-based medications are associated with life-threatening side effects, including respiratory depression, dependence, and addiction. The δ-opioid receptor is a promising alternative biological target for chronic pain and depression due to its significantly reduced on-target side effects compared to the μ-opioid receptor. A previous study identified two δ-opioid receptor positive allosteric modulators. Herein, we report the design of five series of compounds targeting previously unexplored regions of the originally described SAR. Analogs were assessed for their ability to potentiate the agonist response of Leu-enkephalin. Of the 30 analogs, compound **6g** displayed trends toward enhancing the ERK1/2 phosphorylation signaling compared to the cAMP inhibition, while compound **11c** exhibited a trend in shifting the signaling bias toward cAMP inhibition. Both **6g** and **11c** emerged as promising tool compounds toward the design of prospective therapeutics requiring specific downstream signaling attributes.



INTRODUCTION

Chronic pain and depression are both recognized medical conditions that account for an increasing number of clinical consultations each year, with an increase of over 60% within the past two decades for chronic pain alone. Both these conditions are comorbid, whereby 35% of the population who suffer from chronic pain also report depressive symptoms.[1] Opioids have been regarded as one of the most effective drugs for the treatment of pain and have also shown to be effective in alleviating depressive symptoms.[2] The majority of prescribed opioids such as morphine, hydrocodone, and oxymorphone are agonists for the μ-opioid receptor (MOR), which belong to a larger pool of G protein-coupled opioid receptors and are considered as the gold standard for the treatment of acute pain.[3] However, the long-term administration of such opioids have serious adverse effects, including respiratory depression; tolerance; and, more significantly, dependence and abuse liability, which questions the integrity of MOR agonists for treating chronic pain and depression, two long-term disorders.[4]

To circumvent the more significant side effects attributed to MOR activation, there has been a growing body of research investigating the ability of δ-opioid receptor (DOR) activation to promote similar beneficial effects with reduced on-target side effects. Preclinical models involving rodent and nonhuman primates have demonstrated the effectiveness of DOR agonists in addressing chronic pain and depression,[5,6] propelling the DOR as a therapeutically viable alternative, with significantly less respiratory depression, dependence, and abuse liabilities compared to MOR agonists.[7] However, the development of DOR agonists has been hindered by their own set of on-target side effects observed in preclinical studies, which primarily consisted of the development of tolerance and the propensity to cause convulsions.[2,8] Current DOR agonists such as SNC-80 and TAN-67 are small molecules that bind and activate the receptor via the orthosteric site, which is the site enkephalins, the endogenous ligands, bind. When considering DOR agonists, a primary drawback to their effectiveness resides in the DORs' constant exposure to the agonist resulting in receptor desensitization and consequentially the development of tolerance, paving the way for alternative therapeutically favorable strategies to be pursued. Allosteric modulators on the other hand bind to a topographically distinct site of the receptor relative to the orthosteric site, known as the allosteric site.[9] Allosteric modulators can be categorized into positive allosteric modulators (PAMs), negative allosteric modulators (NAMs), and neutral allosteric ligands (NALs), either

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increasing or decreasing the affinity and/or efficacy of the orthosteric ligand or having no influence on orthosteric agonist activity but preventing the binding of other ligands to the allosteric site, respectively. Allosteric ligands can also possess direct intrinsic activity themselves, thereby being termed allosteric agonists. Additionally, allosteric ligands are capable of both modulation and intrinsic agonism concurrently, being referred to as PAM-agonists or NAM-agonists.[10,11] The rationale behind utilizing PAMs is to minimize the constant activation of DOR, a major drawback of traditional orthosteric agonists. A DOR PAM with limited efficacy in its own right would typically only act in the presence of an endogenous ligand and hence maintain the temporal and spatial fidelity of opioid signaling *in vivo*, potentially reducing receptor desensitization and resulting in the attenuation of the development of tolerance. Additionally, allosteric modulators of G protein-coupled receptors (GPCRs) may present another key feature termed biased modulation.[12,13] Indeed, allosteric modulators, when co-bound to a GPCR with its cognate endogenous ligand, may impart bias by stabilizing specific subsets of receptor conformations that are distinct from the ones stabilized by the endogenous ligand alone, leading to different cellular outcomes.

A previous high-throughput screen of a Bristol-Myers-Squibb (BMS) library led to the discovery of the xanthenedione-based DOR PAM chemotype.[10] This ultimately led to the identification and evaluation of two highly potent and selective lead compounds that established the foundation of this study: 3,3,6,6-tetramethyl-9-(4-((2-methylbenzyl)oxy)-phenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (BMS-986187, **1**) and 9-(4-((2-bromobenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (BMS-986188, **2**) (Figure 1). In competition

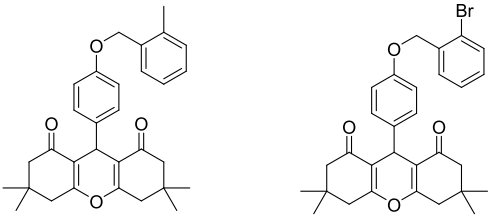
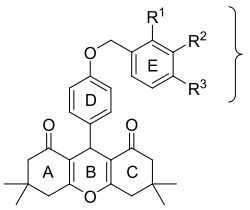


Figure 1. Lead DOR PAMs identified by BMS. EC_{50} concentrations were acquired through β-arrestin recruitment assays in the presence of a fixed EC_{20} concentration of Leu-enkephalin (n = 3).[10]

binding assays with DOR agonists, 10 μM of **1** enhanced the ability for orthosteric agonists Leu-enkephalin, SNC-80, and TAN-67 to displace [^{3}H]-DPN, suggesting that **1** is, at least partly, an affinity-based PAM of DOR agonists.[10] Additionally, while **1** has been identified as a PAM for the DOR, it is further capable of eliciting activity in the absence of an orthosteric ligand in certain pathways, thereby acting as an allosteric agonist in some conditions. Finally, **1** was also found to be biased toward G protein activation relative to β-arrestin 2 recruitment, thereby functioning as a biased PAM-agonist.[14]

The current structure–activity relationship (SAR) based on β-arrestin recruitment assay data (Figure 2) available for the BMS-based scaffold is limited and solely based on alterations



- *ortho* substitution where R^1 = Me, Br increased activity
- disubstitution where R^1, R^2 = Cl increased activity modestly
- *meta/para* substitution had minimal effect, except *para*-fluoro which gave a 2-fold increase

Figure 2. SAR profile of the current scaffold derived from the 15 compounds of the BMS study.[10]

to the benzyl moiety, with the consensus being that *ortho*-substitution with a methyl or bromo group produced the greatest increase in activity and selectivity.[10] Interestingly, when comparing the *ortho*-fluoro analog to its unsubstituted counterpart, it was found to be notably less active, suggesting that the increase in potency observed for the *ortho*-methyl and *ortho*-bromo analogs resulted from steric rather than electronic effects. The activity gains due to steric effects on *ortho*-substitution, however, were not observed in analogs containing the *ortho*-OCF_3, *ortho*-$OCHF_2$, *ortho*-SO_2CH_3, *ortho*-CH_2OH, and *ortho*-CF_3 groups, where a loss of activity was discerned. Substitutions along the *meta*- and *para*-positions were typically found to have negligible influence on both activity and selectivity. However, certain intricacies were observed. In the instance of the *para*-fluoro analog, a twofold increase in activity was observed relative to its unsubstituted benzyl counterpart. A similar finding was also apparent for the doubly substituted *ortho*-chloro and *meta*-chloro analog where a threefold gain in DOR activity was seen relative to the monosubstituted *ortho*-Cl analog. The inherently small sample size, on which the SAR is currently based, presents an opportunity for a more comprehensive study on the scaffold to take place, investigating previously uncharted territories of the BMS-scaffold and thus forming the basis for the work presented in this study.

Herein, this study reports the synthesis and SAR of an extended series of allosteric modulators based on the two previously identified leads, **1** and **2**. An array of targets for evaluation were devised on account of alterations made to the lead BMS-scaffold, which can be distinctly divided into five separate series (Figure 3): series 1 investigated alterations to

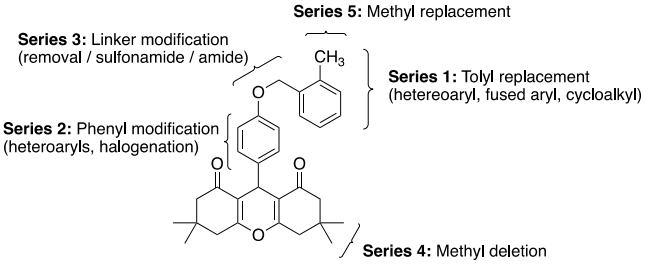


Figure 3. Overview of modifications to the BMS-scaffold explored within the premise of this work.

the tolyl head group, series 2 explored modifications to the D-ring between the xanthenedione base and benzyloxy head group, series 3 consisted of alterations made to the oxymethylene linker of the head group, series 4 introduced minor modifications to the xanthenedione base, and series 5 further probed the *ortho*-position of the benzyloxy head group. Several potent DOR-PAMs were identified in a preliminary dual screen using both an ERK 1/2 phosphorylation assay and

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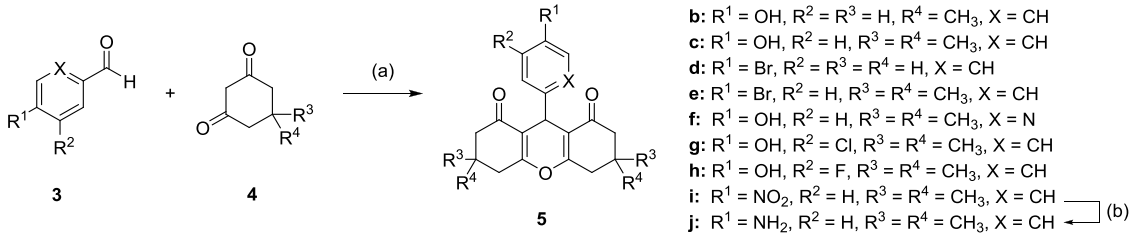
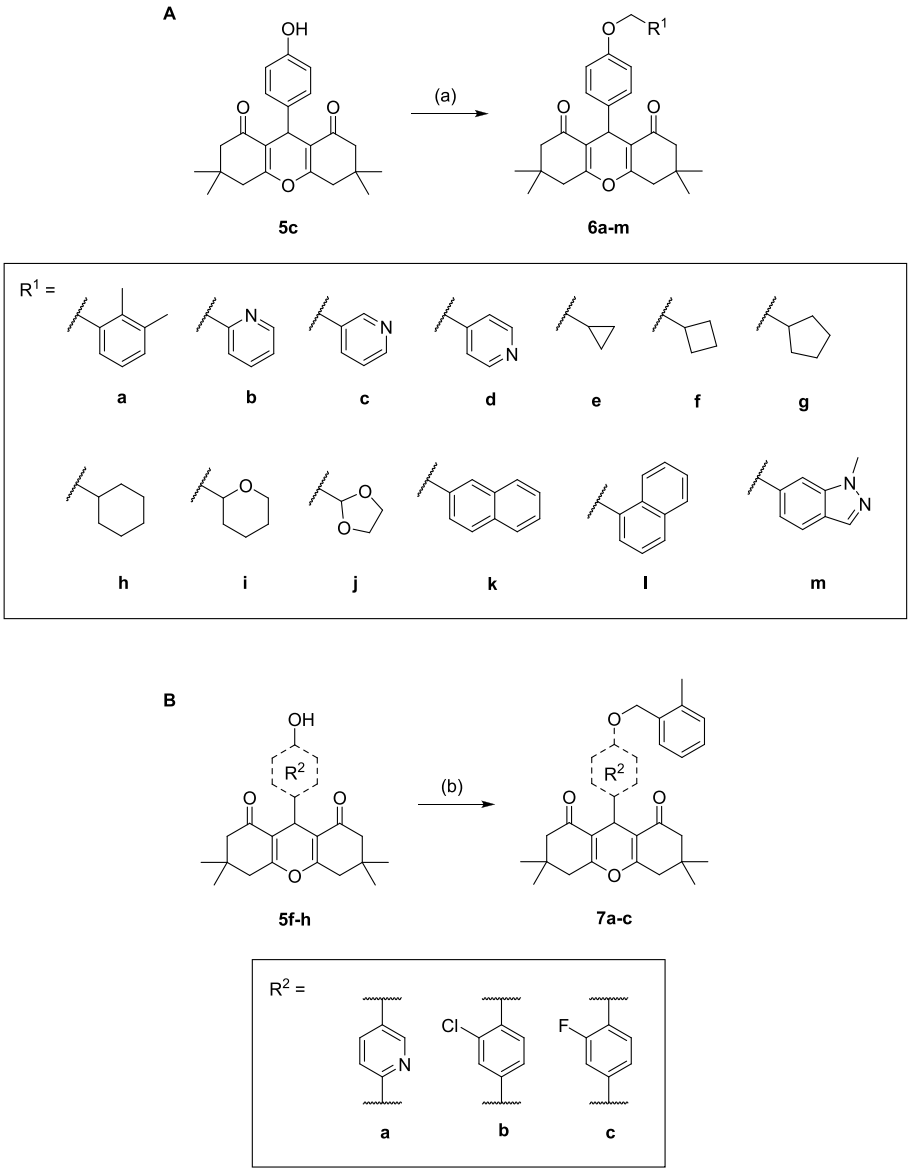
Scheme 1. Tandem Knoevenagel Condensation and Michael Addition Obtaining Key 9-Arylxanthenedione Precursors 5a−j[a]



[a]Reagents and conditions: (a) MeOH, 98% H_2SO_4, reflux, overnight, 21−74%; (b) (i) Sn/HCl, EtOH, reflux, 1 h; (ii) 0.5 M NaOH, pH 7−8, 63%.

Scheme 2. (A) *O*-Alkylation of 5c for the Synthesis of Series 1 Analogs; (B) *O*-Alkylation of 5f−h for the Synthesis of Series 2 Analogs[a]



[a]Reagents and conditions: (a) respective alkyl halide, DMF, Cs_2CO_3, rt, 18−87 h, 15−79%; (b) 1-(chloromethyl)-2-methylbenzene, DMF, Cs_2CO_3, rt, 18−66 h, **7a** (78%), **7b** (64%) and **7c** (67%).

a cyclic AMP (cAMP) inhibition assay to provide an initial assessment of potential biased modulation within G protein pathways. Subsequently, full allosteric interaction assays were carried out on the most chemically and pharmacologically interesting PAMs to better understand the modulatory profile of the compounds. A family of concentration−response curves

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in the absence or presence of increasing concentrations of selected PAMs in both functional assays was constructed and analyzed using the operational model of allosterism, which provided quantitative insight into the SAR of the modulators for the most potent PAMs, based on their affinity (pK_B), allosteric effect ($\alpha\beta$), and efficacy in our system (τ_B). We found that subtle chemical changes can alter the balance between cAMP inhibition and ERK1/2 phosphorylation and therefore allow for the rational design of differentially biased modulators for the DOR.

RESULTS AND DISCUSSION

Chemistry. To access all proposed target compounds across each of the five outlined series, key precursors containing the 9-aryl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione scaffold **10a−j** were synthesized. These precursors were prepared *via* a tandem Knoevenagel condensation and Michael addition between select commercially available aryl aldehydes **3** and 1,3-cyclohexanediones **4** in a 1:2 ratio, respectively (Scheme 1).

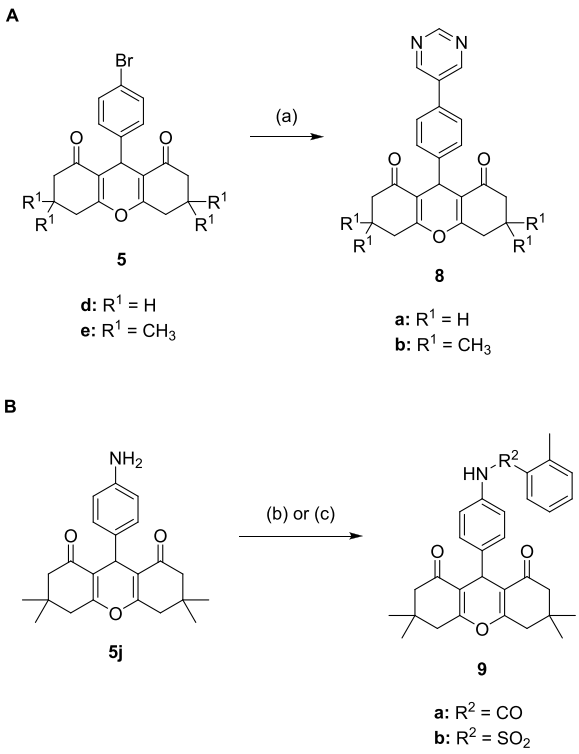
Reaction conditions to synthesize precursors **5a−i** were adapted from Arora *et al.*[15] whereby the reaction was conducted under reflux, employing MeOH as the solvent. An equivalent of the aryl aldehyde first reacted with a single equivalent of cyclohexanedione through the Knoevenagel condensation, forming the benzylidene reaction intermediate, which reacted with a second equivalent of cyclohexanedione, forming the open ring intermediate. Preliminary attempts from our work found that the conditions described by Arora *et al.* were not sufficient for progressing the open ring intermediate to the target 9-arylxanthenedione **5** and therefore required catalytic amounts of concentrated H_2SO_4 (98%) for complete conversion. The reactions did not require any additional workup beyond filtration of the formed precipitate, and the precursors **5a−h** were obtained in moderate yields of 21−74%.

A slightly modified route was required to obtain the 9-(4-aminophenyl)xanthenedione **5j**. Reacting 5,5-dimethyl-1,3-cyclohexanedione with *p*-aminobenzaldehyde in the method described in Scheme 1 resulted in the formation of an insoluble powder, hampering the ability for both LCMS analysis and NMR characterization to confirm product formation. As a result, an alternative route to form the desired precursor **5j** was devised based on reducing the 9-(4-nitrophenyl)-xanthenedione **5i** to the corresponding aniline in 63% yield by utilizing a tin/HCl in ethanol mixture followed by neutralization as described by Kaya *et al.*[16]

Series 1 compounds targeted modifications to the head group of the scaffold and were primarily designed to investigate the importance of the sp^2 hybridized aryl ring system to the BMS leads' pharmacological activity by incorporating alternative monocyclic and fused ring systems. Series 2 analogs alternatively probed minor alterations to the D-ring of the scaffold, previously unexplored in its influence on DOR modulation, through substitution on the ring and replacement of the phenyl ring with pyridine. All series 1 (**6a−m**) and series 2 (**7a−c**) compounds were synthesized in a similar manner through the *O*-alkylation of select precursors **5c** and **5f−h** with the appropriate alkyl halide containing the desirable head group (Scheme 2). The alkylation reactions were performed in DMF with the use of the mild inorganic base Cs_2CO_3. An additional equivalent of Cs_2CO_3 was added when the reacting alkyl halide was present in its salt form. In total, 13 *O*-alkylated compounds were synthesized for series 1 and three for series 2 according to Scheme 2. Yields of approximately 60−80% were observed for most compounds, with lesser yields below being attributed to the incomplete conversion of the starting phenol precursor **5**. It was also observed that alkylations involving sp^3 hybridized ring systems, such as **6e−j**, often required additional time (>20 h) to achieve maximal conversion. To counter this, an additional equivalent of the alkyl halide and inorganic base was added after 18 h to increase the conversion rate of precursor **5c** to product.

Series 3 compounds were synthesized to investigate the importance of the oxymethylene linker of the scaffold to its activity. This series comprises three distinct modifications to the linker making up four analogs (Scheme 3). The first involved the removal of the oxymethylene unit by coupling the 9-bromophenyl precursors **5d** and **5e** to a pyrimidine directly to form a biaryl motiff. The remaining two analogs involved replacing the oxymethylene linker with an amide and a sulfonamide linker by coupling with the aniline **5j**. The first two compounds of the series, **8a** and **8b**, were synthesized *via* the Suzuki coupling reaction of pyrimidine-5-boronic acid with key precursors **5d** and **5e**, respectively. These reactions proceeded in the presence of $PdCl_2(PPh_3)_2$ as the catalyst in a degassed solution of THF and 1 M Na_2CO_3 (aq) (3:1 ratio). Flash column chromatography was conducted to remove any remaining organic impurities. In the instance of **8a**, trace amounts of triphenylphosphine oxide (TPPO) were still

Scheme 3. (A) Synthesis of Pyrimidine Containing Analogs; (B) Coupling of Aniline Precursor to Form Amide and Sulfonamide Linked Head Group[a]



[a]Reagents and conditions: (a) pyrimidine-5-boronic acid, $PdCl_2(PPh_3)_2$, THF/1 M Na_2CO_3 (aq) (3:1), reflux, overnight, **8a** (27%) and **8b** (22%); (b) (i) 2-methylbenzoic acid, DCM, DMF, $(COCl)_2$, rt, 1 h; (ii) dry THF, rt-reflux, overnight, **9a** (23%); (c) 2-methylbenzenesulfonyl chloride, dry THF, rt-reflux, overnight, **9b** (53%).

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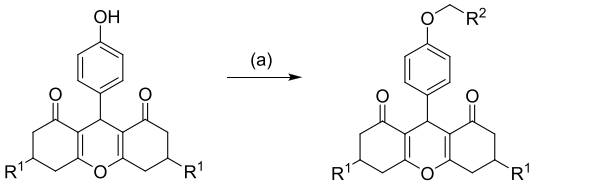
present post-chromatography. The TPPO was subsequently removed by concentrating the eluates and subsequently recrystallizing the resultant solids. However, both compounds **8a** and **8b** were obtained in suboptimal yields (27 and 22%, respectively). The carboxamide **9a** was synthesized from the aniline **5j** and 2-methylbenzoyl chloride, which was first prepared from the corresponding carboxylic acid and oxalyl chloride. The sulfonamide **9b** was also prepared from **5j** using a commercially available 2-methylbenzenesulfonyl chloride conditions were adapted from Kaya *et al.*[16]

Series 4 compounds aimed to examine the importance of the xanthenedione core to the activity of the lead BMS compounds. This series incorporated minor modifications, which maintained the tricyclic xanthenedione core but altered the substitution of methyl groups at positions C3 and C6. Three compounds were synthesized that maintain the xanthenedione core of the scaffold, with subtle variance through the C3 and C6 position, namely, replacing the tetramethyl core for a dimethyl core, as well as an unsubstituted core. Forming these three compounds was carried out in the same manner as those formed in series 1 and 2, with the core alterations emerging from the unique precursors used (**5a** or **5b**). These reactions proceeded through the *O*-alkylation of desired precursor with either 1-(chloromethyl)-2-methylbenzene or (bromomethyl)-cyclohexane to synthesize compounds **10a** (58%), **10b** (31%), and **10c** (72%) (Scheme 4). Each reaction was

Scheme 4. Synthesis of Compounds 10a−c through the *O*-Alkylation of Select Precursor with the Respective Alkyl Halide[a]



[a]Reagents and conditions: (a) 1-(chloromethyl)-2-methylbenzene (for **10a** and **10b**) or (bromomethyl)cyclohexane (for **10c**), DMF, Cs_2CO_3, rt, overnight, **10a** (58%), **10b** (31%) and **10c** (72%).

conducted at room temperature overnight in DMF with the presence of inorganic base Cs_2CO_3. A lower yield for **10b** was observed as the reaction did not proceed to completion.

One interesting aspect of the SAR from the lead BMS study was the close to 10-fold reduction in activity observed when the *ortho*-methylbenzyl head group of BMS-986187 (EC_{50} = 0.03 μM) was replaced with the unsubstituted benzyl head group (EC_{50} = 0.2 μM). It was therefore of interest to further probe the *ortho*-position of the benzyl head group in series 5. This was done by incorporating slightly extended aliphatic substituents as well as introducing thiophenes as an isosteric replacement for the bromine of lead **2**. These modifications were primarily achieved by first forming and utilizing the *ortho*-bromo precursor **2** in good yield (83%) from **5c** and subsequently performing Suzuki couplings to introduce the desired substituents **11a−f** (Scheme 5). In the instance of **11f**, it was not possible to source a supply of isopropylboronic acid that was stable; hence, the alternative route through the direct *O*-alkylation of **5c** with 1-(bromomethyl)-2-isopropylbenzene was utilized.

The Suzuki coupling to introduce alternative groups to the benzyl *ortho*-position was first trialed with cyclopropylboronic acid utilizing previously used conditions from the Suzuki couplings of series 3 compounds. Tracking the LCMS profile of this reaction concluded that there was no observable product formation. Alternative conditions optimized toward aryl bromides and alkyl boronic acids were hence referred to as described by Wallace and Chen.[17] It was concluded that the reaction performed best in toluene in the presence of catalytic amounts of water, which produced a significant accelerating effect. The choice of palladium(II) acetate in conjunction with the bulky ligand tricyclohexylphosphine resulted in the best conversion. The couplings were also found to be applicable to the thiophene-based boronic acids. Formation of products typically proceeded with a high degree of conversion; however, traces of dehalogenated starting material were at times present. A low yield of 8% for **11d** and 13% for **11a** was attributed to both the suboptimal conversion of aryl bromide to the product as well as the difficulty in chromatographically separating the product from the aryl bromide **2** and the traces of dehalogenated starting material.

Compound **2** was also used to introduce an ethynyl to the benzyl *ortho*-position, in this instance attempting a Sonogashira coupling to TMS acetylene followed by deprotection of the TMS protecting group. Several relevant literature conditions were trialed; however, suboptimal conversion (<50%) to the product was commonly observed, likely due to the poor solubility of **2** in various reaction solvents. To overcome the poor conversion of **2** to the ethynyl **15**, an alternative pathway was devised (Scheme 6). The idea behind the pathway was to introduce the TMS acetylene to the smaller (2-iodophenyl)-methanol building block **12**, which was much more soluble in the reaction solvent. Iodo groups are also known to be more reactive in Sonogashira couplings, which helped promote the attachment of the TMS acetylene. The newly formed TMS acetylene benzyl alcohol **13** underwent conversion to the corresponding TMS acetylene benzyl bromide **14** using *N*-bromosuccinimide. The last step in the pathway involved alkylating phenol precursor **5c** with newly formed **14** using previously described *O*-alkylation conditions, which were consequentially strong enough to favorably deprotect the TMS group, leading to an excellent average yield of ∼80% across the three steps. In addition, ethynyl **15** was hydrogenated to the corresponding ethyl **11a** *via* H_2 on Pd/C chemistry as an alternative method to the previously described Suzuki coupling, with significantly improved yields (95 vs 13%).

Pharmacology. The DOR is known to be predominantly coupled to Gαi/o proteins, leading to the inhibition of adenylate cyclases (ACs) located at the cell membrane and reduction in intracellular cAMP production. In contrast, the phosphorylation of extracellular signal-regulated protein kinases (ERK) 1/2 is a far more complex cellular process that can originate from (i) Gαi/o-mediated through AC inactivation and/or Rap1-GAPII activation and (ii) Gβγ-mediated Ras activation via PLCβ and/or PI3K and is therefore convergent from multiple downstream signaling pathways and not a linearly amplified signaling pathway from cAMP. To validate the origins of DOR-mediated pERK1/2

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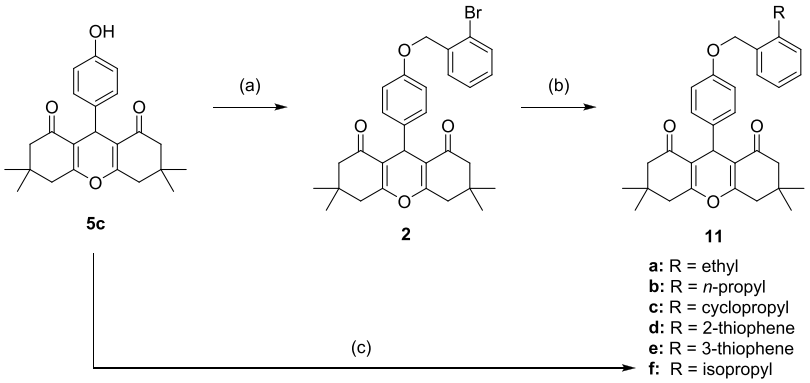
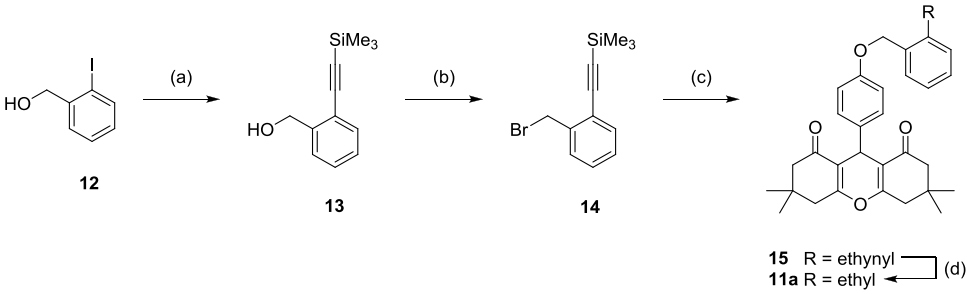
Scheme 5. Formation of *Ortho*-Substituted Compounds *via* Suzuki Couplings with 2 or through Direct *O*-Alkylation with 5c[a]



[a]Reagents and conditions: (a) 1-bromo-2-(bromomethyl)benzene, DMF, Cs_2CO_3, rt, 20 h, 83%; (b) respective boronic acid, $Pd(OAc)_2$, PCy_3, K_3PO_4, toluene/H_2O (95:5), 100 °C, 1−3 h, **11a−e** (8−99%); (c) 1-(bromomethyl)-2-isopropylbenzene, DMF, Cs_2CO_3, rt, 17 h, **11f** (73%).

Scheme 6. Multistep Pathway to Produce *Ortho*-Ethynyl Analog 15 and Successive Reduction to the *Ortho*-Ethyl 11a[a]



[a]Reagents and conditions: (a) ethynyltrimethylsilane, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 0 °C−rt, 5 h, 91%; (b) NBS, PPh_3, DCM, 0 °C, 1.5 h, 87%; (c) **5c**, DMF, Cs_2CO_3, rt, 42 h, 65%; (d) H_2, Pd/C, EtOAc, rt, 1.5 h, 95%.

response, we determined concentration−response curves of three structurally distinct DOR agonists, Leu-enkephalin, SNC-80, and TAN-67, in the absence or presence of pertussis toxin (PTX), a protein known to prevent Gαi/o protein activation, in CHO cells stably expressing the DOR (Figure S1). In the presence of 100 ng/mL of PTX, all DOR agonist-mediated pERK1/2 responses were abolished, suggesting that, in CHO cells at least, pERK1/2 responses mediated by DOR agonists are almost completely driven by events following Gαi/o protein activation. Of note, all three agonists appeared to display potency values (Leu-enkephalin: pEC_{50} = 9.00 ± 0.17, SNC-80: pEC_{50} = 7.36 ± 0.13, and TAN-67: pEC_{50} = 7.50 ± 0.14) similar to their reported affinities,[18] suggesting a low level of receptor reserve in this specific functional assay. Indeed, by performing a [^{3}H]-DPN saturation binding assay on our CHO cell line stably expressing the human DOR, we were able to quantify the expression level of the DOR, B_{max} = 103,296 ± 24 sites per cell (Figure S2).

However, while being both Gαi/o protein-dependent pathways, the activity of DOR PAMs in the inhibition of cAMP and pERK1/2 may nonetheless not necessarily track, and bias may occur between these two pathways. To identify if our newly synthesized DOR PAMs may display some degree of biased modulation between these two Gαi/o-mediated signaling pathways, all synthesized compounds were preliminarily screened for PAM activity by measuring the potentiation of the endogenous ligand Leu-enkephalin *via* both an ERK 1/2 phosphorylation assay and a cAMP inhibition assay using CHO cells stably expressing the human DOR. In the preliminary screens, we constructed two concentration−response curves of Leu-enkephalin, one in the absence and one in the presence of 10 μM of each of the 30 newly synthesized compounds, to allow the quantification of the shift in agonist potency (ΔpEC_{50}) between the two curves. Results for all 30 analogs from the dual screen are reported in the heat map (Figure 4). The shift in pEC_{50} values was used to capture the extent of the allosteric effect as an initial surrogate for functional cooperativity ($\alpha\beta$), with the PAM effect reflected by a shift into the red color, while a potential NAM or antagonist effect was reflected by a shift into the blue color.

The data gained from the primary screen allowed us to gain some insight in the associated SAR of the BMS-scaffold beyond the benzyl head group from the original BMS study, particularly in terms of biased modulation within G protein-coupled pathways. While care must be taken as these interpretations are based on effects observed at a single, high concentration (10 μM) of the modulator, nonetheless, we have been able to observe some trends in the activity of our newly synthesized DOR PAMs. First, the two reference compounds appeared to display subtle differences in their preference between ERK1/2 and cAMP pathways, with **1** potentially displaying stronger modulation of Leu-enkephalin-mediated ERK1/2 phosphorylation response versus cAMP inhibition response. In contrast, **2** appeared to behave as a more "balanced" PAM, equipotently potentiating Leu-enkephalin responses in both signaling assays. When investigating replacements to the benzyl head group **6a−m**, the major observation was an obvious loss of PAM activity displayed at 10 μM for the majority of compounds in both pathways, including all pyridine derivatives **6b−d**, the heterocyclic

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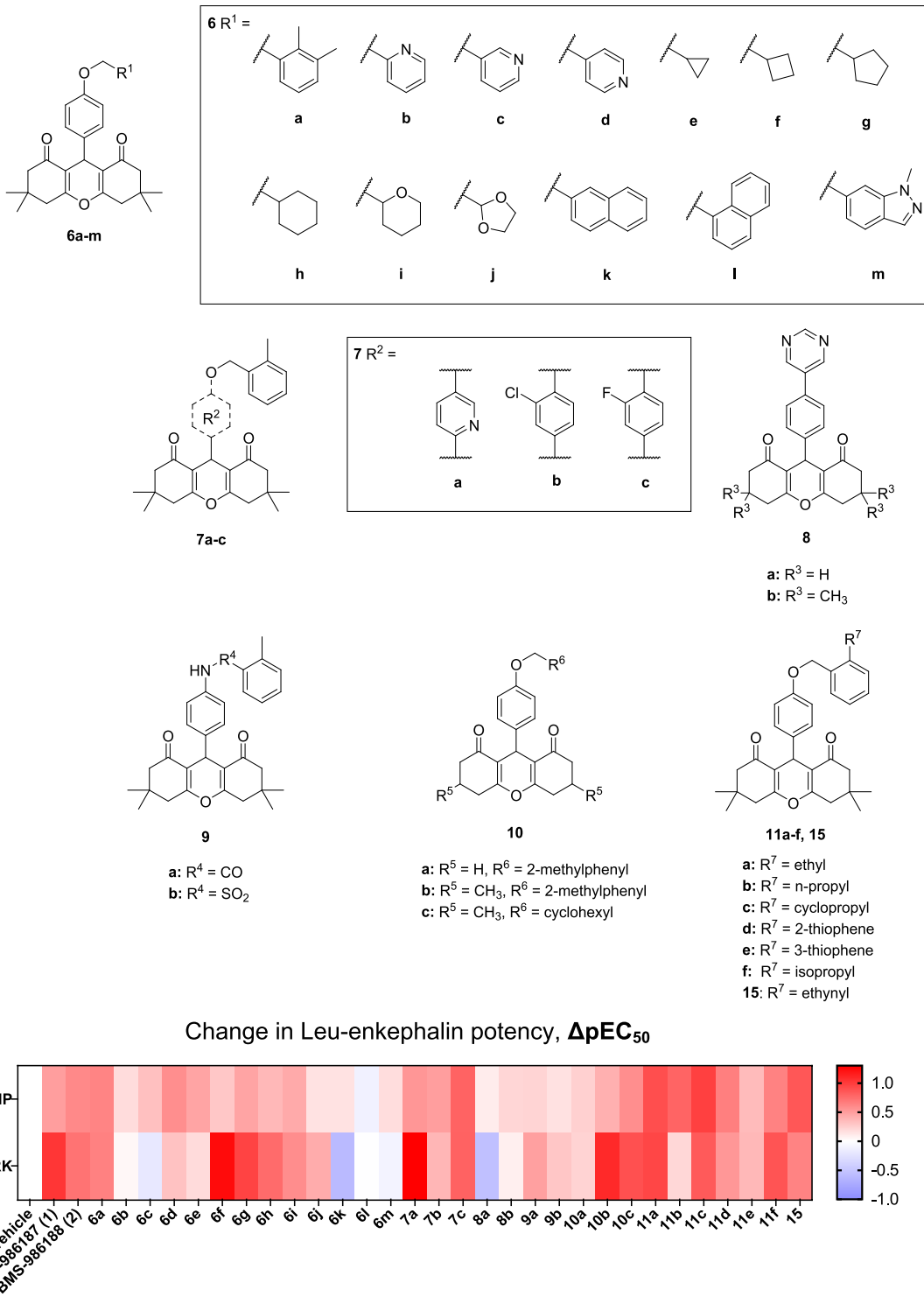

Figure 4. Structures of the 30 analogs synthesized in this study and heat map representation of the shift in pEC_{50} elicited by 10 μM of the compound (ΔpEC_{50}) in preliminary ERK1/2 phosphorylation and cAMP inhibition screen. Data for the heat map were obtained by determining concentration−response curves in the absence or presence of 10 μM of each compound, normalized to the positive controls, 10% FBS for pERK1/2, and 10 μM forskolin for cAMP inhibition, from at least three experiments performed in duplicate. Data were analyzed with a three-parameter logistic equation to define pEC_{50}; ΔpEC_{50} values were quantified by subtracting the pEC_{50} of Leu-enkephalin in the absence of a modulator to the one in the presence of 10 μM of the modulator (Table S1). Color shifts to red are indicative of PAM effects, while shifts to blue are indicative of NAM or antagonist effects.

dioxolane **6j**, and all fused-bicyclics **6k−m**. Of the remaining compounds, the cycloalkyl derivatives **6f** and **6g** showed comparable activity to **1** and **2**, particularly in terms of the ERK1/2 phosphorylation response. Each of the D-ring alternatives **7a−c** displayed PAM activity across both functional assays, with **7a** favoring pERK1/2 over cAMP inhibition and **7b** and **7c** exhibiting a more "balanced" profile. Of note, the pyridine linked analog **7a** appeared to be the best

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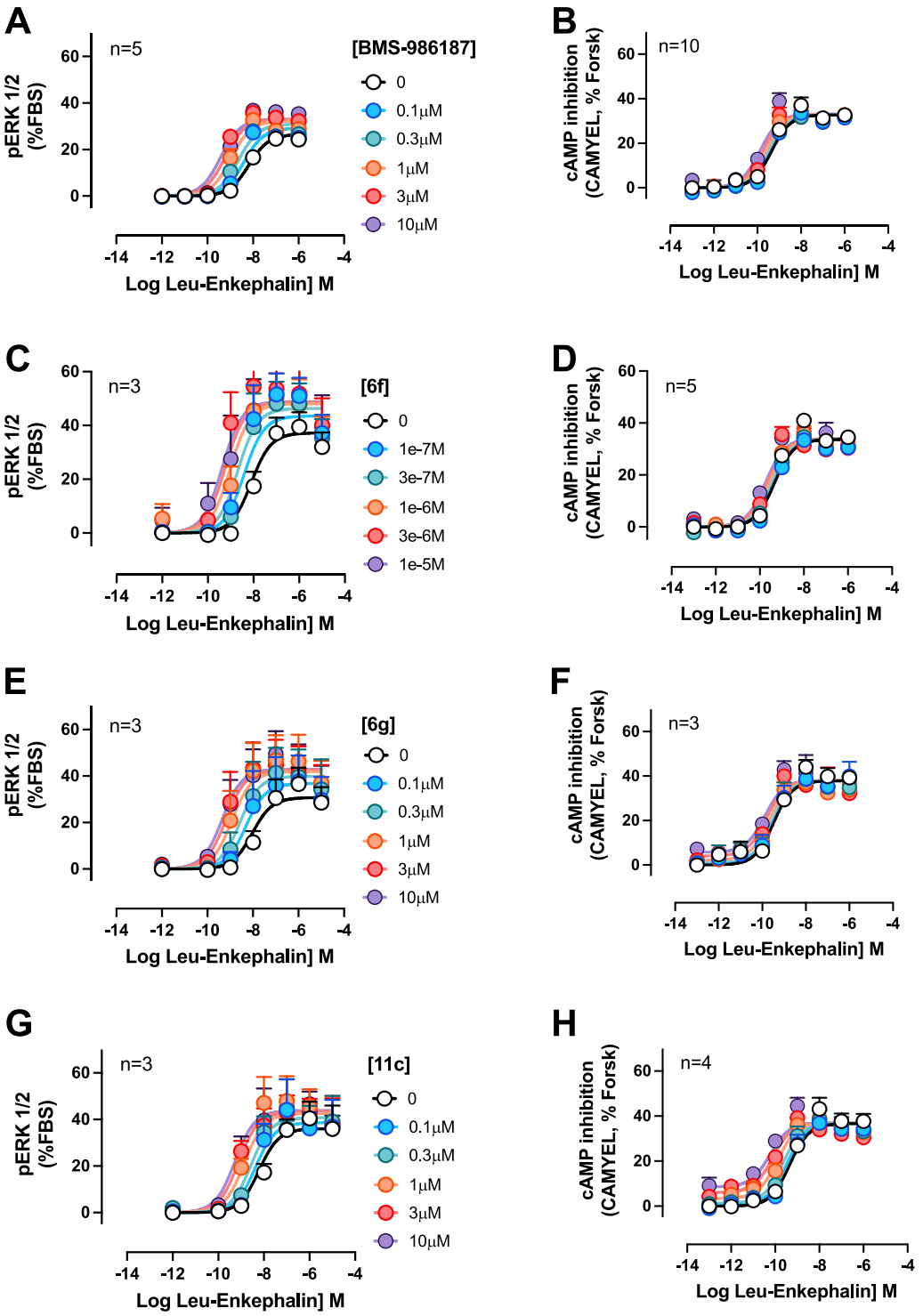

Figure 5. Effect of increasing concentrations of allosteric modulators on Leu-enkephalin concentration−response curves in both ERK1/2 phosphorylation (left) and cAMP inhibition (right) assays performed in CHO cells stably expressing the DOR for reference compounds BMS-986187 **1** (A, B) as well as the novel modulators **6f** (C, D), **6g** (E, F), and **11c** (G, H). Data represent the mean ± SEM of at least three experiments performed in duplicate, n = 3−10, normalized to 10% FBS or 10 μM forskolin.

performing analog of the pERK1/2 screen compared to both the BMS leads **1** and **2**. The activity of the fluoro-substituted linker indicates that substitution around the phenyl ring as in **7c** was tolerated, and furthermore, the presence of the fluorine-substituted ring may also be pharmacokinetically advantageous as it may promote reduced metabolism compared to the phenyl ring. Attempts at replacing the oxymethylene linker of the scaffold in the pursuit of an improved profile proved to be fruitless. The pyrimidine bound structure with an unsubstituted (**8a**) or substituted xanthenedione core (**8b**) displayed reduced activity relative to the control. Similarly, introducing an amide linker, as in **9a**, and sulfonamide, as in **9b**, reduced activity relative to the reference BMS compounds **1** and **2**, suggesting detrimental interactions to the binding site. While

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Table 1. Pharmacological Parameters for BMS Leads and Selected Modulators at the DOR[a]

		pERK 1/2		cAMP inhibition	
PAM	pK_B[a]	log $\alpha\beta$ ($\alpha\beta$)[b]	log τ_B (τ_B)[c]	log $\alpha\beta$ ($\alpha\beta$)	log τ_B (τ_B)
1	5.47 ± 0.26	1.46 ± 0.18 (29)[f]	−3 (0.001)[d]	0.63 ± 0.13 (4.3)[e]	−3 (0.001)
2	5.90 ± 0.33	0.72 ± 0.18 (5.2)[g]	−3 (0.001)	0.85 ± 0.24 (7.1)	−0.78 ± 0.21 (0.17)
6f	5.72 ± 0.27	1.46 ± 0.18 (29)[f]	−3 (0.001)	0.46 ± 0.32 (2.9)[e]	−3 (0.001)
6g	5.57 ± 0.36	1.56 ± 0.26 (36)[f]	−3 (0.001)	0.56 ± 0.34 (3.5)[e]	−0.65 ± 0.31 (0.22)
7a	4.89 ± 0.45	1.66 ± 0.36 (46)[f]	−0.21 ± 0.29 (0.62)	0.86 ± 0.63 (7.2)	−0.45 ± 0.68 (0.35)
7c	6.01 ± 0.36	0.79 ± 0.16 (6.2)[g]	−3 (0.001)	0.46 ± 0.33 (2.9)	−3 (0.001)
10c	5.83 ± 0.18	1.08 ± 0.21 (12)	−3 (0.001)	0.62 ± 0.37 (4.2)	−3 (0.001)
11a	5.50 ± 0.20	1.63 ± 0.17 (43)[f]	−3 (0.001)	0.79 ± 0.19 (6.2)[e]	−0.27 ± 0.12 (0.54)
11c	5.53 ± 0.27	1.24 ± 0.19 (17)[f]	−3 (0.001)	1.09 ± 0.25 (12)	−0.42 ± 0.18 (0.38)
11f	6.08 ± 0.59	0.45 ± 0.19 (2.8)[g]	−3 (0.001)	0.69 ± 0.34 (4.9)	−3 (0.001)
15	6.18 ± 0.37	0.69 ± 0.15 (4.9)[g]	−3 (0.001)	0.30 ± 0.20 (2.0)	−3 (0.001)

[a]Negative logarithm of the binding affinity estimate for the unoccupied allosteric binding site of the DOR and therefore taken as a shared parameter between both functional assays. [b]Logarithm of the functional cooperativity between the allosteric modulator and the endogenous ligand Leu-enkephalin, reflecting the ability of the modulator to alter the pEC_{50} and E_{max} of the orthosteric agonist. [c]Logarithm of the operational efficacy parameter of the allosteric ligand, reflecting its ability to induce an agonist response in its own right. [d]Parameter estimate not significantly different from −3 (τ_B = 0.001), as per *F* test, and therefore constrained as such in the analysis, reflecting the absence of agonism in our system. [e]Denotes $P < 0.05$ when comparing functional cooperativity values of a given allosteric modulator from ERK1/2 phosphorylation assay to cAMP inhibition as per unpaired Student's *t* test with the Holm−Sidak post hoc test. [f]Denotes $P < 0.05$ when comparing functional cooperativity values of a given allosteric modulator in ERK1/2 phosphorylation compared to BMS-986187 (**1**) performing a one-way ANOVA statistical analysis with Dunnett's post hoc test. [g]Denotes $P < 0.05$ when comparing functional cooperativity values of a given allosteric modulator in ERK1/2 phosphorylation compared to BMS-986188 (**2**) performing a one-way ANOVA statistical analysis with Dunnett's post hoc test.

this series was by no means exhaustive, it appears that the oxymethylene linker is important for maintaining activity. The loss of all methyl groups on the xanthenedione core as in **10a** displayed near to no PAM activity in our dual screen, but the simple reintroduction of one methyl on each side of the xanthenedione core as in **10b** recovered the original activity as seen in **1**, with a similar pERK1/2 > cAMP profile. The replacement of the tolyl group for a cyclohexyl as in **10c** did not seem to alter the PAM activity. Probing the *ortho*-position of the head group yielded interesting results. In general, it appears that aliphatic extensions beyond the methyl of **1** were in most instances detrimental in potentiating the Leu-enkephalin-mediated pERK1/2 assays with only marginal effects on the cAMP inhibition responses, therefore potentially shifting the transduction pathways to favor cAMP inhibition over ERK phosphorylation. Neither of the thiophene containing analogs **11d** or **11e** produced notable activity relative to the BMS lead.

Since the parameters from our dual-screen approach relied on only a single concentration (10 μM) of each modulator, we selected nine of the newly synthesized analogs, along with both BMS reference compounds **1** and **2**, for full interaction studies in the aforementioned functional assays to fully characterize their allosteric properties. The basis of compound selection was both PAM activity and chemical diversity, thus leading to the cycloalkyl derivatives **6f** and **6g**; the D-ring alternatives **7a** and **7c**; the combined hexyl and alternative core **10c**; and the extended *ortho*-substituted analogs **11a**, **11c**, **11f**, and **15** being selected. Results from the full interaction studies are shown in Figure 5, highlighting the effect of increasing concentrations of PAM against concentration−response curves of Leu-enkephalin in both cAMP inhibition and ERK1/2 phosphorylation for reference compound **1** and three of the novel modulators (**6f**, **6g**, and **11c**) identified in this study.

For BMS-986187 (**1**), there was an evident leftward shift of the concentration−response curves in ERK1/2 phosphorylation as the concentration of **1** increased, as well as an increase in the E_{max} response of the endogenous agonist. Such dual effects are consistent with PAMs being capable of both affinity and efficacy modulation and are only separately detectable when the orthosteric agonist is a partial agonist in the system. Indeed, in our system, the potency of Leu-enkephalin in cAMP inhibition was not dissimilar to its reported affinity.[10] This feature was less observable in cAMP inhibition, with a limited left-shift of Leu-enkephalin potency and no detectable effect on its E_{max}. Consistent with our initial dual screen, the PAM effect of **1** was validated as being more pronounced in the ERK1/2 phosphorylation assay than in the cAMP inhibition assay (pERK1/2 > cAMP) in our cell background. Conversely, for the *ortho*-bromo substituted analog **2**, the degree to which Leu-enkephalin was potentiated in ERK1/2 phosphorylation is diminished relative to its *ortho*-CH_3 counterpart **1** yet maintained for cAMP inhibition, suggesting that the bulkier bromo substituent is detrimental for ERK1/2 phosphorylation, rendering **2** equipotent in both functional assays (pERK1/2 = cAMP), as was observed in our preliminary screening. Analyzing the data with an operational model of allosterism allowed us to provide estimates of affinity (pK_B) for the unoccupied allosteric site of the DOR; the functional cooperativity ($\alpha\beta$) exerted by each modulator on the signaling response of the endogenous ligand Leu-enkephalin in both assays; and, when possible, the efficacy of the modulator (τ_B) in our systems (i.e., allosteric agonist effect) (Table 1).[19] As the affinity of modulators for the unoccupied allosteric site is independent of the functional assays investigated, we globally fit the two functional assays, sharing affinity estimates across both ERK1/2 phosphorylation and cAMP inhibition assays. Reference analog **1** displayed micromolar affinity and significantly higher functional cooperativity in the ERK1/2 phosphorylation assay (log $\alpha\beta$ = 1.46 ± 0.18) compared to the cAMP inhibition assay (log $\alpha\beta$ = 0.63 ± 0.13), as per *t* test statistical analysis. In contrast, **2** displayed similar micromolar affinity but appeared to equipotently modulate Leu-enkephalin-mediated ERK1/2 phosphorylation and cAMP inhibition

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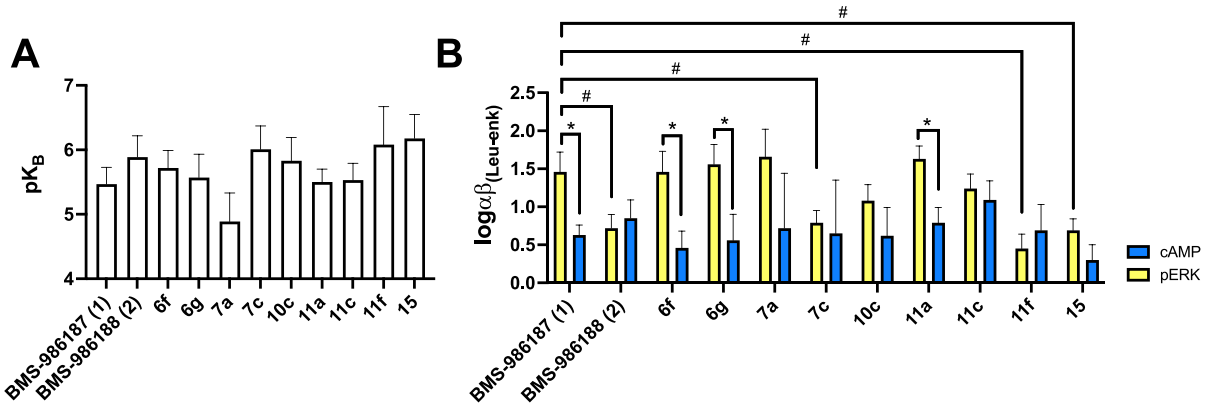

Figure 6. Global affinity estimates (pK_B) for selected analogs (A) and functional cooperativity ($\log\alpha\beta$) (B) between endogenous orthosteric ligand Leu-enkephalin and reference compounds **1** and **2**, as well as selected PAMs for cAMP inhibition (blue) and pERK 1/2 (yellow). $^*P < 0.05$ when comparing functional cooperativity values of a given allosteric modulator from the ERK1/2 phosphorylation assay to cAMP inhibition as per unpaired Student's *t* test with the Holm−Sidak post hoc test. $^{\#}P < 0.05$ when comparing functional cooperativity values of a given allosteric modulator in ERK1/2 phosphorylation compared to BMS-986187 (**1**) performing a one-way ANOVA statistical analysis with Dunnett's post hoc test.

responses with log $\alpha\beta$ = 0.72 ± 0.18 and 0.85 ± 0.24, respectively. This switch in the balance between the two functional assays appears to be predominantly driven by a reduction in the PAM effect mediated by **2**. Indeed, one-way ANOVA statistical analysis shows that the functional cooperativity exerted by **1** is significantly greater in the ERK1/2 phosphorylation assay than the one in the cAMP inhibition assay (Table 1). Of note, the degree of allosteric modulation observed in our study in cAMP inhibition was noticeably reduced for compound **1** compared to the one reported in the original study.[10] Such discrepancies may be explained by the use of different detection methods. We used the BRET-based cAMP biosensor (CAMYEL) that relies on local levels of cAMP for its activation/inactivation, while Burford and colleagues used the HTF-based cAMP detection reagent, which detects the global alteration in intracellular cAMP production/inhibition.

Identical full pharmacological characterizations were performed for all selected nine analogs. Overall, there was no significant observable difference in binding affinities between the reference compounds **1** and **2** and the nine analogs selected from this study. The pyridine-based D-ring **7a** appeared to have a marginally weaker binding affinity (pK_B = 4.89 ± 0.45), while the *ortho*-ethynyl substituted analog **15** had a slight increase in binding affinity (pK_B = 6.18 ± 0.37); however, these differences were not statistically significant. Similarly, none of the functional cooperativity estimates in cAMP inhibition differed from the BMS compounds. In contrast, the functional cooperativity in ERK1/2 phosphorylation was the only assay that appeared to be readily affected by our chemical modifications. All parameters from these experiments are listed in Table 1, and the global affinity and cooperativity values between each assay are shown in Figure 6. Overall, the modulators appeared to present in clusters, with some that were more similar to **1**, with a preference for PAM effect in ERK1/2 phosphorylation, and others behaving more like **2**, displaying more balanced PAM activity across the two signaling pathways. For instance, the two unsubstituted cycloalkane analogs **6f**,**g**, the D-ring alternative **7a**, and the *ortho*-substituted **11a** and **11c** all seemed to behave in a similar manner to BMS-986187 (**1**), with **6f**,**g** and **11a** displaying a statistically significant higher PAM effect in ERK1/2 phosphorylation than in cAMP inhibition (Table 1). All five analogs displayed strong PAM effects in ERK1/2 phosphorylation (significantly higher than **2** but similar to **1**) with marginal effects on cAMP inhibition, with perhaps **11c** as an exception. The *ortho*-cyclopropyl substituted analog exhibited a trend for increased PAM effect in cAMP inhibition (log $\alpha\beta$ = 1.09 ± 0.25) compared to the two BMS leads; however, this did not reach significance in our statistical analysis (Table 1). The second cluster of analogs is **7c**, **10c**, **11f**, and **15**, which displayed significantly reduced PAM effects in ERK1/2 phosphorylation compared to **6** but maintained a PAM effect in cAMP inhibition. These analogs were more similar to **2** in terms of their PAM activity, with a more balanced profile between the two signaling pathways.

Finally, it is important to note that some of the PAMs were also modest allosteric agonists. This feature is common to GPCR PAMs in that the PAMs stabilize the active conformation of the receptor. With the exception of **7a**, no PAM analogs were able to promote any agonist response in ERK1/2 phosphorylation assays; however, in cAMP inhibition assays, the PAMs **2**, **6g**, **7a**, **11a**, and **11c** triggered a modest agonist response, as seen by an increase in the baseline activity (Figure 5D,F,H). It is important to note that this discrepancy in allosteric agonism between the two pathways is not necessarily indicative of bias. Indeed, in our systems, the potency of the endogenous ligand Leu-enkephalin is significantly lower in the ERK1/2 phosphorylation assay compared to the cAMP inhibition assay (pEC_{50} = 8.25 ± 0.06 vs 9.42 ± 0.13, respectively). In these conditions, the cAMP inhibition pathway detected is ∼10-fold more amplified, and consequently, the degree of allosteric agonism is expected to be more readily detectable. Nonetheless, the overall degree of allosteric agonism in our assays was low, suggesting that our PAM analogs display low allosteric agonist efficacy.

CONCLUSIONS

In this study, we reported a wide variety of synthetic approaches that were expanded upon the scaffold of the reference compounds BMS-986187 (**1**) and BMS-986188 (**2**). A total of 30 analogs were synthesized across five unique series, namely, series 1: replacement of the benzyl head group with a heteroaromatic, cycloalkyl, and fused bicyclic structures; series

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2: modifications to the D-ring with heterocycles; series 3: interchanging the oxymethylene linker with an amide and sulfonamide, as well as the direct C−C bond between the 9-aryl xanthenedione and pyrimidine; series 4: modifying the xanthenedione core by either altering substitution of the C3 and C6 position; and series 5: probing the *ortho*-position of the scaffolds' aromatic head group with hydrocarbon extensions as well as isosteric replacements for the bromine of **2**. All 30 synthesized analogs were screened for PAM activity in a dual pERK 1/2 and cAMP inhibition assay at a fixed concentration of 10 μM of the modulator against increasing concentrations of the orthosteric ligand Leu-enkephalin to measure activity potentiation. Globally, 13 analogs appeared to have lost most of their PAM activity in both assays, and the remaining 17 analogs could be clustered into two pharmacological behaviors: pERK1/2 > cAMP, with **6f−h**, **7a**, and **10b**,**c**, versus pERK1/2 = cAMP, with **6a**, **6i**, **7b**,**c**, **11a−f**, and **15**. A selection of nine analogs from these two clusters was further investigated in full interaction studies to provide further information surrounding the SAR of the scaffold and information on iterations that favored specific binding or functional capabilities. What was most profoundly validated from these extended studies was the potential to shift the signaling bias between the downstream pathways of ERK1/2 phosphorylation and cAMP inhibition. This phenomenon was perhaps best observed with the cyclopentyl analog **6g** (pERK1/2 > cAMP) and the *ortho*-cyclopropyl **11c** (pERK1/2 = cAMP) and will prove to be useful tool compounds toward future iterations around the scaffold that may require specific downstream signaling.

One caveat of our study is that we have not determined how the new BMS analogs bind to DOR. Prior MD simulations and docking studies have suggested that DOR PAMs bind in an extracellular pocket near the orthosteric site.[20,21] A new NMR spectroscopy study on the μ-opioid receptor has shown that BMS-986122 binds to an extrahelical pocket outside of the receptor near TM3.[22] Prior pharmacological evidence suggested that BMS-986122 and BMS-986187 bind to a common allosteric site on opioid receptors.[23] Therefore, it is not clear where or how these BMS analogs bind to DOR, and answering this question will likely require the determination of a PAM bound DOR structure. Notably, there are currently no PAM bound opioid receptor structures, and such a structure would be pivotal to understanding the binding mechanism of opioid receptor PAMs.

■ EXPERIMENTAL SECTION

All reagents and solvents used were obtained from standard suppliers and used without additional purification. Reaction progress was monitored *via* thin-layer chromatography (TLC) utilizing Merck Millipore TLC silica gel 60 F_{254} aluminum plates, which were visualized under ultraviolet light (254 nm). Flash column chromatography (FCC) was performed using either isocratic or gradient solvent ratios through Merck silica gel 60, particle size 40−63 μm. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded using a Bruker Avance III Nanobay 400 MHz spectrometer equipped with a BACS 60 automatic sample changer at 400, 101, and 377 MHz, respectively. All chemical shifts (δ) are recorded in parts per million (ppm), with all peaks being referenced through the residual deuterated solvent peak. Experimental data were recorded in the following format: chemical shift (multiplicity, coupling constant, integration) whereby multiplicity is denoted by singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), heptet (hept), doublet of doublets (dd), triplet of doublets (td), doublet of doublets of doublets (ddd), and multiplet (m). Coupling constants were recorded as J in hertz (Hz). ^{13}C NMR assignments were based on the spectral phasing of carbon environments in regard to the APT test where C = quaternary carbon, CH = methine carbon, CH_2 = methylene carbon, and CH_3 = methyl carbon. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. LC−MS analysis was conducted on an Agilent 1260 LCMS SQ equipped with a 1260 Infinity G1312B Binary pump and a 1260 Infinity G1367E 1260 HiP ALS autosampler. Detection of UV reactive compounds was performed at wavelengths of 214 and 254 nm and was recorded by a 1290 Infinity G4212A 1290 DAD variable wavelength detector. LC−MS data were processed through the LC/MSD Chemstation Rev.B.04.03 SP2 coupled with the MassHunter Easy Access Software. The LC component was run as a reverse phase HPLC using a Raptor C18 2.7 μm 50 × 3.0 mm column at 35 °C. Solvents comprised of buffer A was 0.1% formic acid in H_2O, and buffer B was 0.1% formic acid in MeCN. The gradient was as follows: 0−1 min 95% buffer A and 5% buffer B, from 1 to 2.5 min up to 0% buffer A and 100% buffer B, held at this composition until 3.8 min, 3.8−4 min 95% buffer A and 5% buffer B, held until 5 min at this composition. The flow rate was 0.5 mL/min, and total run time was 5 min The mass spectrum section was acquired in positive and negative ion mode using a scan range of 100−1000 m/z. HR-MS analysis was conducted with an Agilent 6224 TOF LC/MS Mass Spectrometer coupled to an Agilent 1290 Infinity (Agilent, Palo Alto, CA). All data were acquired, and reference mass was corrected via a dual-spray electrospray ionization (ESI) source. Each scan or data point on the total ion chromatogram (TIC) is an average of 13,700 transients, producing a spectrum every second. Mass spectra were created by averaging the scans across each peak and background subtracted against the first 10 s of the TIC. Mass spectrometer conditions used were as follows: electrospray ionization mode, 11 L/min drying gas flow, 45 psi nebulizer, 325 °C drying gas temperature, 4000 V capillary voltage, 160 V fragmentor, 65 V skimmer, 750 V OCT RFV, and a scan range of 100−1500 m/z. The internal reference ions were m/z = 121.050873 and 922.009798 in the positive ion mode. Analytical HPLC was performed on an Agilent 1260 analytical HPLC system through a Zorbax Eclipse Plus C18 Rapid Resolution 4.6 × 100 mm 3.5 μm column using a flow rate of 20 mL/min and a gradient of 5−100% B over 12 min followed by 100% B over 3 min where A = Milli-Q water and B = HPLC-grade MeCN.

General Procedure A: Tandem Knoevenagel Condensation and Michael Condensation to Form 9-Arylxanthenediones. To a solution of cyclohexanedione (2.0 equiv) in MeOH were added aryl aldehyde (1.0 equiv) and 98% H_2SO_4 (10 μL). The reaction mixture was left to stir under reflux overnight. The formed precipitate was collected by suction filtration and washed with cold MeOH (∼20 mL) to afford the desired product without further purification.

General Procedure B: *O*-Alkylation. To a solution of 9-arylxanthenedione (1.0 equiv) in DMF (4 mL/100 mg intermediate) were added the associated alkyl halide (2.0−3.0 equiv) and Cs_2CO_3 (2.0−5.0 equiv). The reaction mixture was stirred at room temperature for a specified period of time. The reaction mixture was partitioned between EtOAc (40 mL) and water (40 mL), and the phases were separated. The organic phase was further washed with water (2 × 40 mL) followed by brine (40 mL), dried over $MgSO_4$, gravity filtered, and then concentrated *in vacuo* before being purified *via* FCC. The collected eluates were reduced *in vacuo* to afford the desired product.

*9-(4-Hydroxyphenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**5a**).* 1,3-Cyclohexanedione (5.00 g, 44.6 mmol, 2.0 equiv) and *p*-hydroxybenzaldehyde (2.72 g, 22.3 mmol, 1.0 equiv) in MeOH (20 mL) were reacted for 22 h as per general procedure A. The desired product was afforded as a beige powder (4.26 g, 62%). LCMS (m/z): 217.1 $[M - C_6H_5O]^+$. TLC R_f = 0.38 (PET/EtOAc, 1:1). ^{1}H NMR (DMSO-d_6) δ 9.16 (s, 1H), 7.00−6.91 (m, 2H), 6.61−6.52 (m, 2H), 4.47 (s, 1H), 2.71−2.51 (m, 4H), 2.36−2.18 (m, 4H), 2.02−1.89 (m, 2H), 1.89−1.75 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 196.4 (C), 164.5 (C), 155.6 (C), 135.1 (C), 128.9 (CH), 116.0 (C), 114.7 (CH), 36.5 (CH_2), 29.8 (CH), 26.5 (CH_2), 19.9 (CH_2).

*9-(4-Hydroxyphenyl)-3,6-dimethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**5b**).* 5-Methyl-1,3-cyclohexanedione (1.00

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g, 7.93 mmol, 2.0 equiv) and *p*-hydroxybenzaldehyde (484 mg, 3.96 mmol, 1.0 equiv) in MeOH (4 mL) were reacted for 19 h as per general procedure A. The desired product was afforded as a white crystalline solid (536 mg, 40%). LCMS (*m/z*): 245.1 $[M - C_6H_5O]^+$, 337.1 $[M - H]^-$. TLC R_f = 0.40 (PET/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$) δ 9.16 (s, 1H), 6.93 (dt, J = 8.4, 2.9 Hz, 2H), 6.57 (dt, J = 8.5, 1.8 Hz, 2H), 4.43 (t, J = 7.9 Hz, 1H), 2.67−2.59 (m, 2H), 2.48−2.41 (m, 1H), 2.39−2.18 (m, 4H), 2.16−1.92 (m, 3H), 1.06−0.89 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 196.9 (C), 163.6 (C), 154.3 (C), 136.2 (C), 129.4 (CH), 116.7 (C), 115.1 (CH), 45.2 (CH_2), 35.2 (CH_2), 30.9 (CH), 27.8 (CH), 20.8 (CH_3).

9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**5c**). 5,5-Dimethyl-1,3-cyclohexanedione (5.00 g, 35.7 mmol, 2.0 equiv) and *p*-hydroxybenzaldehyde (2.18 g, 17.8 mmol, 1.0 equiv) in MeOH (4 mL) were reacted for 18 h as per general procedure A. The desired product was afforded as a white solid (2.03 g, 31%). LC−MS (*m/z*): 273.1 $[M - C_6H_5O]^+$, 390.2 $[M + Na]^+$ and 755.3 $[2M + Na]^+$. TLC R_f = 0.45 (PET/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$) δ 7.16−7.04 (m, 2H), 6.64−6.52 (m, 2H), 5.91 (s, 1H), 4.67 (s, 1H), 2.45 (br s, 4H), 2.24 (d, J = 16.3 Hz, 2H), 2.18 (d, J = 16.3 Hz, 2H), 1.09 (s, 6H), 1.00 (s, 6H). ^{13}C NMR (DMSO-d_6) δ 196.6 (C), 163.1 (C), 156.0 (C), 135.3 (C), 129.4 (CH), 115.3 (C), 115.1 (CH), 50.5 (C), 39.9 (CH_2), 32.3 (CH_2), 30.6 (CH), 29.2 (CH_3), 26.9 (CH_3).

9-(4-Bromophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**5d**). 1,3-Cyclohexanedione (2.00 g, 17.8 mmol, 2.0 equiv) and *p*-bromobenzaldehyde (1.65 g, 8.92 mmol, 1.0 equiv) in MeOH (8 mL) were reacted for 18 h as per general procedure A. The desired product was afforded as a beige powder (1.84 g, 55%). LC−MS (*m/z*): 217.1 $[M - C_6H_5{}^{79}Br]^+$ and 373.1 $[M + H]^+$. TLC R_f = 0.46 (PET/EtOAc, 1:1). ^{1}H NMR (DMSO-d_6) δ 7.45−7.35 (m, 2H), 7.17−7.09 (m, 2H), 4.53 (s, 1H), 2.71−2.54 (m, 4H), 2.36−2.18 (m, 4H), 2.00−1.89 (m, 2H), 1.89−1.78 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 196.4 (C), 165.1 (C), 144.0 (C), 130.9 (CH), 130.4 (CH), 119.3 (C), 115.1 (C), 36.4 (CH_2), 30.8 (CH), 26.5 (CH_2), 19.9 (CH_2).

9-(4-Bromophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**5e**). 5,5-Dimethyl-1,3-cyclohexanedione (5.00 g, 35.7 mmol, 2.0 equiv) and *p*-bromobenzaldehyde (3.30 g, 17.8 mmol, 1.0 equiv) in MeOH (20 mL) were reacted for 19 h as per general procedure A. The desired product was afforded as a white crystalline solid (4.11 g, 54%). LC−MS (*m/z*): 429.1 $[M + H]^+$ and 452.0 $[M + Na]^+$. TLC R_f = 0.49 (PET/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$) δ 7.45−7.38 (m, 2H), 7.15−7.08 (m, 2H), 4.47 (s, 1H), 2.52 (br s, 4H), 2.26 (d, J = 16.2 Hz, 2H), 2.07 (d, J = 16.0 Hz, 2H), 1.03 (s, 6H), 0.89 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.5 (C), 162.6 (C), 143.4 (C), 131.3 (CH), 130.3 (CH), 120.4 (C), 115.3 (C), 50.8 (C), 40.9 (CH_2), 32.4 (CH_2), 31.7 (CH), 29.4 (CH_3), 27.4 (CH_3).

9-(5-Hydroxypyridin-2-yl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**5f**). 5,5-Dimethylcyclohexane-1,3-dione (200 mg, 1.43 mmol, 2.0 equiv) and 5-hydroxypicolinaldehyde (88 mg, 713 μmol, 1.0 equiv) in MeOH (2 mL) were reacted for 18 h as per general procedure A. The desired product was afforded as a white powder (54 mg, 21%). LC−MS (*m/z*): 368.2 $[M + H]^+$, 390.2 $[M + Na]^+$, 757.3 $[2M + Na]^+$. TLC R_f = 0.55 (PET/EtOAc, 1:1). ^{1}H NMR (CD_3OD) δ 7.18 (d, J = 2.8 Hz, 1H), 6.69 (d, J = 8.7 Hz, 1H), 6.60 (dd, J = 2.8, 8.7 Hz, 1H), 3.95 (s, 1H), 1.78 (br s, 4H), 1.50 (d, J = 16.2 Hz, 2H), 1.35 (d, J = 16.2 Hz, 2H), 0.30 (s, 6H), 0.20 (s, 6H). ^{13}C NMR (CD_3OD) δ 198.0 (C), 164.7 (C), 153.7 (C), 151.0 (C), 131.7 (CH), 127.1 (CH), 125.8 (CH), 112.3 (C), 49.9 (CH_2), 39.9 (CH_2), 32.5 (CH), 31.8 (C), 27.5 (CH_3), 26.1 (CH_3).

9-(3-Chloro-4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**5g**). 5,5-Dimethylcyclohexane-1,3-dione (400 mg, 2.85 mmol, 2.0 equiv) and 3-chloro-4-hydroxybenzaldehyde (223 mg, 1.43 mmol, 1.0 equiv) in MeOH (2 mL) were reacted for 20 h as per general procedure A. The desired product was afforded as a white powder (220 mg, 38%). LC−MS (*m/z*): 273.2 $[M - C_6H_4{}^{35}ClO]^+$. TLC R_f = 0.60 (PET/EtOAc, 1:1). ^{1}H NMR (DMSO-d_6) δ 9.94 (s, 1H), 7.05 (d, J = 2.2 Hz, 1H), 6.89 (dd, J = 2.2, 8.4 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 4.39 (s, 1H), 2.59−2.46 (m, 4H), 2.26 (d, J = 16.2 Hz, 2H), 2.09 (d, J = 16.1 Hz, 2H), 1.03 (s, 6H), 0.91 (s, 6H). ^{13}C NMR (DMSO-d_6) δ 196.1 (C), 162.8 (C), 151.2 (C), 136.1 (C), 129.2 (CH), 127.3 (CH), 118.8 (C), 116.1 (CH), 114.1 (C), 50.0 (CH_2), 39.6 (CH_2), 31.8 (C), 30.2 (CH), 28.6 (CH_3), 26.4 (CH_3).

9-(3-Fluoro-4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**5h**). 5,5-Dimethylcyclohexane-1,3-dione (400 mg, 2.85 mmol, 2.0 equiv) and 3-fluoro-4-hydroxybenzaldehyde (200 mg, 1.43 mmol, 1.0 equiv) in MeOH (2 mL) were reacted for 20 h as per general procedure A. The desired product was afforded as a white powder (204 mg, 37%). LC−MS (*m/z*): 273.1 $[M - C_6H_4FO]^+$. TLC R_f = 0.65 (PET/EtOAc, 1:1). ^{1}H NMR (DMSO-d_6) δ 9.95 (s, 1H), 7.06 (d, J = 2.1 Hz, 1H), 6.90 (dd, J = 2.2, 8.4 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 4.40 (s, 1H), 2.62−2.47 (m, 4H), 2.27 (d, J = 16.2 Hz, 2H), 2.10 (d, J = 16.1 Hz, 2H), 1.04 (s, 6H), 0.92 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.8 (C), 162.5 (C), 150.8 (d, J_{CF} = 237.9 Hz, C), 142.2 (d, J_{CF} = 14.2 Hz, C), 137.1 (d, J_{CF} = 5.0 Hz, C), 124.4 (d, J_{CF} = 3.2 Hz, CH), 116.9 (d, J_{CF} = 2.0 Hz, CH), 115.7 (d, J_{CF} = 18.4 Hz, CH), 115.5 (C), 50.8 (CH_2), 40.9 (CH_2), 32.3 (C), 31.1 (CH), 29.3 (CH_3), 27.5 (CH_3). ^{19}F NMR (DMSO-d_6) δ −137.15.

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**5i**). 5,5-Dimethyl-1,3-cyclohexanedione (1.00 g, 7.13 mmol, 2.0 equiv) and *p*-nitrobenzaldehyde (539 mg, 3.57 mmol, 1.0 equiv) in MeOH (4 mL) were reacted for 19 h as per general procedure A. The desired product was afforded as a white powder (590 mg, 42%). LC−MS (*m/z*): 396.2 $[M + H]^+$. TLC R_f = 0.42 (PET/EtOAc, 1:1). ^{1}H NMR (DMSO-d_6) δ 8.20−8.05 (m, 2H), 7.51−7.40 (m, 2H), 4.61 (s, 1H), 2.65−2.47 (m, 4H), 2.28 (d, J = 16.2 Hz, 2H), 2.08 (d, J = 16.1 Hz, 2H), 1.03 (s, 6H), 0.89 (s, 6H). ^{13}C NMR (DMSO-d_6) δ 196.6 (C), 163.9 (C), 152.3 (C), 146.4 (C), 129.9 (CH), 123.6 (CH), 113.8 (C), 50.3 (C), 40.2 (CH_2), 32.4 (CH_2), 32.4 (CH), 29.0 (CH_3), 27.0 (CH_3).

9-(4-Aminophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**5j**). To a solution of 3,3,6,6-tetramethyl-9-(4-nitrophenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5i**) (100 mg, 253 μmol, 1.0 equiv) in EtOH (1 mL) were added granulated tin (300 mg, 2.53 mmol, 10.0 equiv) and 1 M HCl (1 mL). The mixture was stirred under reflux for 1 h; thereafter, LC−MS analysis showed complete consumption of the starting material. The reaction mixture was gravity filtered to remove any remaining granulated tin. An aqueous solution of NaOH (0.5 M) was subsequently added dropwise to the collected filtrate until a pH of 7−8 was attained. The EtOH within the solution was evaporated *in vacuo*. The resultant mixture was partitioned between EtOAc (40 mL) and water (40 mL), and the phases were separated. The organic phase was further washed with water (2 × 40 mL) followed by brine (40 mL), dried over $MgSO_4$, gravity filtered, and then concentrated *in vacuo* to afford the desired product as a white solid (58 mg, 63%). LC−MS (*m/z*): 273.1 $[M - C_6H_6N]^+$, 366.2 $[M + H]^+$, 389.2 $[M + Na]^+$, 638.4 $[2M - C_6H_6N]^+$ and 754.4 $[2M + Na]^+$. TLC R_f = 0.42 (PET/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$) δ 7.11−7.00 (m, 2H), 6.59−6.47 (m, 2H), 4.63 (s, 1H), 3.51 (s, 2H), 2.44 (br s, 4H), 2.22 (d, J = 16.3 Hz, 2H), 2.16 (d, J = 16.3 Hz, 2H), 1.09 (s, 6H), 0.99 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.5 (C), 161.9 (C), 144.6 (C), 134.7 (C), 129.2 (CH), 115.9 (C), 115.0 (CH), 50.8 (C), 40.9 (CH_2), 32.2 (CH_2), 30.8 (CH), 29.3 (CH_3), 27.4 (CH_3).

9-(4-((2,3-Dimethylbenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**6a**). 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (100 mg, 273 μmol, 1.0 equiv), 1-(bromomethyl)-2,3-dimethylbenzene (109 mg, 546 μmol, 2.0 equiv), and Cs_2CO_3 (178 mg, 546 μmol, 2.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 18 h. The desired product was isolated *via* FCC (PET/EtOAc 4:1), resulting in a white solid (98 mg, 74%) following concentration. LC−MS (*m/z*): 273.2 $[M - C_{15}H_{15}O]^+$ and 507.2 $[M + Na]^+$. TLC R_f = 0.22 (PET/EtOAc, 4:1). HPLC: t_R 7.21 min, >95% purity (254 nm). HRMS: calcd for $C_{32}H_{36}NaO_4^+$ $[M + Na]^+$ 507.2506, found 507.2517. ^{1}H NMR ($CDCl_3$) δ 7.26−7.22 (m, 3H), 7.16 (d, J = 7.6 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 6.89−6.85 (m, 2H), 4.97 (s, 2H), 4.73 (s, 1H), 2.48 (br s, 4H), 2.33 (s, 3H), 2.26 (s,

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3H), 2.26 (d, J = 16.3 Hz, 2H), 2.20 (d, J = 16.3 Hz, 2H), 1.13 (s, 6H), 1.03 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.5 (C), 162.0 (C), 157.4 (C), 137.1 (C), 136.6 (C), 135.6 (C), 134.7 (C), 130.0 (CH), 129.3 (CH), 127.0 (CH), 125.5 (CH), 115.7 (C), 114.2 (CH), 69.1 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 31.02 (CH), 29.2 (CH_3), 27.4 (CH_3), 20.3 (CH_3), 14.9 (CH_3).

3,3,6,6-Tetramethyl-9-(4-(pyridin-2-ylmethoxy)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**6b**). 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (61 mg, 166 μmol, 1.0 equiv), 2-(bromomethyl)-pyridine hydrobromide (82 mg, 333 μmol, 2.0 equiv), and Cs_2CO_3 (163 mg, 499 μmol, 3.0 equiv) in DMF (3 mL) were reacted as per general procedure B for 18 h. The desired product was isolated *via* FCC (PET/EtOAc 1:1), resulting in an off-white solid (50 mg, 66%) following concentration. LC−MS (m/z): 273.2 [M − $C_{12}H_{10}NO]^+$, 458.2 [M + H]$^+$, and 480.2 [M + Na]$^+$. TLC R_f = 0.31 (PET/EtOAc, 1:1). HPLC: t_R 5.39 min, >95% purity (254 nm). HRMS: calcd for $C_{29}H_{31}NO_4^+$ [M + H]$^+$ 458.2326, found 458.2338. ^{1}H NMR ($CDCl_3$) δ 8.63−8.53 (m, 1H), 7.69 (td, J = 7.7, 1.8 Hz, 1H), 7.55−7.44 (m, 1H), 7.24−7.16 (m, 3H), 6.90−6.78 (m, 2H), 5.12 (s, 2H), 4.70 (s, 1H), 2.45 (br s, 4H), 2.23 (d, J = 16.3 Hz, 2H), 2.16 (d, J = 16.3 Hz, 2H), 1.09 (s, 6H), 0.99 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.6 (C), 162.2 (C), 157.6 (C), 157.0 (C), 149.2 (CH), 137.1 (C), 136.9 (CH), 129.5 (CH), 122.6 (CH), 121.4 (CH), 115.9 (C), 114.5 (CH), 70.7 (CH_2), 50.9 (C), 41.0 (CH_2), 32.4 (CH_2), 31.1 (CH), 29.4 (CH_3), 27.5 (CH_3).

3,3,6,6-Tetramethyl-9-(4-(pyridin-3-ylmethoxy)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**6c**). 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (100 mg, 273 μmol, 1.0 equiv), 3-(chloromethyl)pyridine hydrochloride (90 mg, 546 μmol, 2.0 equiv), and Cs_2CO_3 (267 mg, 819 μmol, 3.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 18 h. The desired product was isolated *via* FCC (PET/EtOAc 1:1), resulting in an off-white solid (49 mg, 39%) following concentration. LC−MS (m/z): 458.2 [M + H]$^+$. TLC R_f = 0.3 (PET/EtOAc, 1:1). HPLC: t_R 5.35 min. HRMS: calcd for $C_{29}H_{31}NO_4^+$ [M + H]$^+$ 458.2326, found 458.2337. ^{1}H NMR ($CDCl_3$) δ 8.64 (d, J = 1.4 Hz, 1H), 8.56 (dd, J = 4.8, 1.7 Hz, 1H), 7.74 (dt, J = 7.9, 2.0 Hz, 1H), 7.30 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 7.25−7.19 (m, 2H), 6.87−6.80 (m, 2H), 4.99 (s, 2H), 4.70 (s, 1H), 2.46 (br s, 4H), 2.24 (d, J = 16.3 Hz, 2H), 2.17 (d, J = 16.3 Hz, 2H), 1.10 (s, 6H), 0.99 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.5 (C), 162.1 (C), 156.8 (C), 149.3 (CH), 148.9 (CH), 137.2 (C), 135.3 (CH), 132.7 (C), 129.4 (CH), 123.5 (CH), 115.6 (C), 114.3 (CH), 67.4 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 31.0 (CH), 29.2 (CH_3), 27.3 (CH_3).

3,3,6,6-Tetramethyl-9-(4-(pyridin-4-ylmethoxy)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**6d**). 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (100 mg, 273 μmol, 1.0 equiv), 4-(bromomethyl)pyridine hydrobromide (207 mg, 819 μmol, 3.0 equiv), and Cs_2CO_3 (445 mg, 1.36 mmol, 5.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 4 days. The desired product was isolated *via* FCC (PET/EtOAc 1:2), resulting in a light-yellow solid (28 mg, 22%) following concentration. LC−MS (m/z): 458.2 [M + H]$^+$. TLC R_f = 0.31 (PET/EtOAc, 1:1). HPLC: t_R 5.34 min, >95% purity (254 nm). HRMS: calcd for $C_{29}H_{31}NO_4^+$ [M + H]$^+$ 458.2326, found 458.2340. ^{1}H NMR ($CDCl_3$) δ 8.64−8.56 (m, 2H), 7.38−7.32 (m, 2H), 7.27−7.21 (m, 2H), 6.90−6.78 (m, 2H), 5.03 (s, 2H), 4.73 (s, 1H), 2.45 (br s, 4H), 2.23 (d, J = 16.3 Hz, 2H), 2.16 (d, J = 16.3 Hz, 2H), 1.12 (s, 6H), 1.01 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.4 (C), 162.1 (C), 156.7 (C), 149.8 (CH), 146.5 (C), 137.4 (C), 129.5 (CH), 121.5 (CH), 115.7 (C), 114.3 (CH), 68.1 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 31.0 (CH), 29.2 (CH_3), 27.3 (CH_3).

9-(4-(Cyclopropylmethoxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**6e**). 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (100 mg, 273 μmol, 1.0 equiv), (bromomethyl)-cyclopropane (53.0 μL, 546 μmol, 2.0 equiv), and Cs_2CO_3 (178 mg, 546 μmol, 2.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 21 h. The desired product was isolated *via* FCC (PET/EtOAc 4:1), resulting in a white solid (71 mg, 62%) following concentration. LC−MS (m/z): 273.2 [M − $C_{10}H_{11}O]^+$, 443.2 [M + Na]$^+$, and 693.4 [2M − $C_9H_{11}O]^+$. TLC R_f = 0.27 (PET/EtOAc, 4:1). HPLC: t_R 6.52 min, >95% purity (254 nm). HRMS: calcd for $C_{27}H_{32}NaO_4^+$ [M + Na]$^+$ 443.2193, found 443.2203. ^{1}H NMR ($CDCl_3$) δ 7.24−7.14 (m, 2H), 6.80−6.73 (m, 2H), 4.71 (s, 1H), 3.74 (d, J = 6.9 Hz, 2H), 2.47 (br s, 4H), 2.23 (d, J = 16.3 Hz, 2H), 2.16 (d, J = 16.3 Hz, 2H), 1.27−1.22 (m, 1H), 1.12 (s, 6H), 1.01 (s, 6H), 0.66−0.57 (m, 2H), 0.36−0.28 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 196.4 (C), 162.0 (C), 157.3 (C), 136.3 (C), 129.2 (CH), 115.8 (C), 114.0 (CH), 72.5 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 30.9 (CH), 29.3 (CH_3), 27.3 (CH_3), 10.3 (CH), 3.1 (CH_2).

9-(4-(Cyclobutylmethoxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**6f**). 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (100 mg, 273 μmol, 1.0 equiv), (bromomethyl)-cyclobutane (61.0 μL, 546 μmol, 2.0 equiv), and Cs_2CO_3 (178 mg, 546 μmol, 2.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 3 days. The desired product was isolated *via* FCC (PET/EtOAc 5:1), resulting in an off-white solid (81 mg, 68%) following concentration. LC−MS (m/z): 273.2 [M − $C_{11}H_{13}O]^+$ and 457.3 [M + Na]$^+$. TLC R_f = 0.24 (PET/EtOAc, 5:1). HPLC: t_R 6.94 min, >95% purity (254 nm). HRMS: calcd for $C_{28}H_{34}NaO_4^+$ [M + Na]$^+$ 457.2349, found 457.2362. ^{1}H NMR ($CDCl_3$) δ 7.21−7.14 (m, 2H), 6.77−6.72 (m, 2H), 4.69 (s, 1H), 3.84 (d, J = 6.7 Hz, 2H), 2.70 (hept, J = 7.3 Hz, 1H), 2.45 (br s, 4H), 2.23 (d, J = 16.3 Hz, 2H), 2.16 (d, J = 16.3 Hz, 2H), 2.13−2.04 (m, 2H), 1.98−1.86 (m, 2H), 1.86−1.74 (m, 2H), 1.09 (s, 6H), 0.99 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.4 (C), 161.9 (C), 157.6 (C), 136.2 (C), 129.2 (CH), 115.8 (C), 114.0 (CH), 71.8 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 34.6 (CH), 32.2 (C), 30.9 (CH), 29.3 (CH_3), 27.3 (CH_3), 24.8 (CH_2), 18.6 (CH_2).

9-(4-(Cyclopentylmethoxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**6g**). 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (100 mg, 273 μmol, 1.0 equiv), (bromomethyl)-cyclopentane (103 μL, 819 μmol, 3.0 equiv), and Cs_2CO_3 (267 mg, 819 μmol, 3.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 4 days. The desired product was isolated *via* FCC (PET/EtOAc 5:1), resulting in an off-white solid (85 mg, 69%) following concentration. LC−MS (m/z): 273.1 [M − $C_{12}H_{15}O]^+$, 471.3 [M + Na]$^+$, and 919.4 [2M + Na]$^+$. TLC R_f = 0.20 (PET/EtOAc, 5:1). HPLC: t_R 7.22 min, >95% purity (254 nm). HRMS: calcd for $C_{29}H_{36}NaO_4^+$ [M + Na]$^+$ 471.2506, found 471.2518. ^{1}H NMR ($CDCl_3$) δ 7.23−7.15 (m, 2H), 6.79−6.72 (m, 2H), 4.71 (s, 1H), 3.76 (d, J = 7.0 Hz, 2H), 2.47 (br s, 4H), 2.33 (hept, J = 7.3 Hz, 1H), 2.23 (d, J = 16.3 Hz, 2H), 2.16 (d, J = 16.3 Hz, 2H) 1.89−1.73 (m, 2H), 1.70−1.48 (m, 4H), 1.40−1.29 (m, 2H), 1.12 (s, 6H), 1.01 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.4 (C), 161.9 (C), 157.7 (C), 136.2 (C), 129.2 (CH), 115.8 (C), 114.0 (CH), 72.0 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 39.1 (CH), 32.2 (C), 30.9 (CH), 29.5 (CH_2), 29.3 (CH_3), 27.3 (CH_3), 25.4 (CH_2).

9-(4-(Cyclohexylmethoxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**6h**). 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (100 mg, 273 μmol, 1.0 equiv), (bromomethyl)-cyclohexane (76 μL, 546 μmol, 2.0 equiv), and Cs_2CO_3 (178 mg, 546 μmol, 2.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 20 h. The desired product was isolated *via* FCC (PET/EtOAc 3:1), resulting in a white solid (48 mg, 38%) following concentration. LC−MS (m/z): 273.1 [M − $C_{13}H_{17}O]^+$. TLC R_f = 0.33 (PET/EtOAc, 3:1). HPLC: t_R 7.56 min, >95% purity (254 nm). HRMS: calcd for $C_{30}H_{38}NaO_4^+$ [M + Na]$^+$ 485.2662, found 485.2671. ^{1}H NMR ($CDCl_3$) δ 7.22−7.13 (m, 2H), 6.77−6.68 (m, 2H), 4.68 (s, 1H), 3.66 (d, J = 6.3 Hz, 2H), 2.44 (br s, 4H), 2.23 (d, J = 16.3 Hz, 2H), 2.16 (d, J = 16.3 Hz, 2H), 1.86−1.78 (m, 2H), 1.77−1.61 (m, 4H), 1.33−81.14 (m, 5H), 1.09 (s, 6H), 0.99 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.5 (C), 162.0 (C), 157.7 (C), 136.2 (C), 129.3 (CH), 115.9 (C), 113.9 (CH), 73.3 (CH_2), 50.8 (C), 40.9 (CH_2),

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37.7 (CH), 32.2 (CH_2), 30.9 (CH), 29.9 (CH_2), 29.3 (CH_3), 27.4 (CH_3), 26.6 (CH_2), 25.8 (CH_2).

*3,3,6,6-Tetramethyl-9-(4-((tetrahydro-2H-pyran-2-yl)methoxy)-phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**6i**).* 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (100 mg, 273 μmol, 1.0 equiv), 2-(bromomethyl)tetrahydro-2*H*-pyran (105 μL, 819 μmol, 3.0 equiv), and Cs_2CO_3 (267 mg, 819 μmol, 3.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 4 days, with the reaction vessel heated to 40 °C for the final 5 h. The desired product was isolated *via* FCC (toluene/EtOAc 8:1), resulting in a yellow solid (44 mg, 35%) following concentration. LC−MS (*m/z*): 273.1 $[M - C_{12}H_{15}O_2]^+$ and 487.2 $[M + Na]^+$. TLC R_f = 0.29 (toluene/EtOAc, 8:1). HPLC: t_R 6.46 min, >95% purity (254 nm). HRMS: calcd for $C_{29}H_{36}NaO_5^+$ $[M + Na]^+$ 487.2455, found 487.2468. ^{1}H NMR ($CDCl_3$) δ 7.20−7.14 (m, 2H), 6.81−6.69 (m, 2H), 4.68 (s, 1H), 4.02 (ddt, *J* = 11.4, 3.8, 1.6 Hz, 1H), 3.90 (dd, *J* = 9.8, 6.1 Hz, 1H), 3.79 (dd, *J* = 9.8, 4.4 Hz, 1H), 3.65 (dddd, *J* = 10.7, 6.3, 4,4, 2.2 Hz, 1H), 3.48 (td, *J* = 11.6, 2.4 Hz, 1H), 2.44 (br s, 4H), 2.22 (d, *J* = 16.3 Hz, 2H), 2.15 (d, *J* = 16.3 Hz, 2H), 1.91−1.82 (m, 1H), 1.73−1.46 (m, 4H), 1.44−1.29 (m, 1H), 1.09 (s, 6H), 0.98 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.4 (C), 162.0 (C), 157.2 (C), 136.5 (C), 129.2 (CH), 115.8 (C), 114.1 (CH), 75.9 (CH), 71.2 (CH_2), 68.5 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 30.9 (CH), 29.3 (CH_3), 28.4 (CH_2), 27.2 (CH_3), 25.9 (CH_2), 23.0 (CH_2).

*9-(4-((1,3-Dioxolan-2-yl)methoxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**6j**).* 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (100 mg, 273 μmol, 1.0 equiv), 2-(bromomethyl)-1,3-dioxolane (84.0 μL, 819 μmol, 3.0 equiv), and Cs_2CO_3 (267 mg, 819 μmol, 3.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 4 days, with the reaction vessel heated to 40 °C for the final 5 h. The crude mixture was purified *via* FCC (toluene/EtOAc 4:1) followed by preparative reverse-phase HPLC to afford the desired product as a white crystalline solid (30 mg, 24%) following concentration. LC−MS (*m/z*): 273.1 $[M - C_{10}H_{11}O_3]^+$ and 475.2 $[M + Na]^+$. TLC R_f = 0.62 (PET/EtOAc, 1:1). HPLC: t_R 5.99 min, >95% purity (254 nm). HRMS: calcd for $C_{27}H_{32}NaO_6^+$ $[M + Na]^+$ 475.2091, found 475.2104. ^{1}H NMR ($CDCl_3$) δ 7.22−7.15 (m, 2H), 6.83−6.73 (m, 2H), 5.24 (t, *J* = 4.1 Hz, 1H), 4.69 (s, 1H), 4.08−4.00 (m, 2H), 3.99−3.89 (m, 4H), 2.45 (br s, 4H), 2.23 (d, *J* = 16.3 Hz, 2H), 2.16 (d, *J* = 16.3 Hz, 2H), 1.09 (s, 6H), 0.98 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.4 (C), 162.0 (C), 156.9 (C), 136.9 (C), 129.3 (CH), 115.7 (C), 114.1 (CH), 101.9 (CH), 68.6 (CH_2), 65.2 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 30.9 (CH), 29.3 (CH_3), 27.3 (CH_3).

*3,3,6,6-Tetramethyl-9-(4-(naphthalen-2-ylmethoxy)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**6k**).* 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (100 mg, 273 μmol, 1.0 equiv), 2-(bromomethyl)naphthalene (121 mg, 546 μmol, 2.0 equiv), and Cs_2CO_3 (178 mg, 546 μmol, 2.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 18 h. The desired product was isolated *via* FCC (PET/EtOAc 5:1), resulting in off-white solid (109 mg, 79%) following concentration. LC−MS (*m/z*): 273.1 $[M - C_{17}H_{13}O]^+$ and 529.3 $[M + Na]^+$. TLC R_f = 0.21 (PET/EtOAc, 5:1). HPLC: t_R 7.18 min, >95% purity (254 nm). HRMS: calcd for $C_{34}H_{34}NaO_4^+$ $[M + Na]^+$ 529.2349, found 529.2358. ^{1}H NMR ($CDCl_3$) δ 7.88−7.78 (m, 4H), 7.55−7.40 (m, 3H), 7.24−7.17 (m, 2H), 6.91−6.83 (m, 2H), 5.14 (s, 2H), 4.71 (s, 1H), 2.45 (br s, 4H), 2.23 (d, *J* = 16.3 Hz, 2H), 2.16 (d, *J* = 16.3 Hz, 2H), 1.10 (s, 6H), 0.99 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 192.4 (C), 162.0 (C), 157.4 (C), 136.8 (C), 134.7 (C), 133.3 (C), 133.0 (C), 129.3 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 126.3 (CH), 126.1 (CH), 125.9 (CH), 125.4 (CH), 115.8 (C), 114.4 (CH), 70.1 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 31.0 (CH), 29.2 (CH_3), 27.4 (CH_3).

*3,3,6,6-Tetramethyl-9-(4-(naphthalen-1-ylmethoxy)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**6l**).* 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (100 mg, 273 μmol, 1.0 equiv), 1-(chloromethyl)naphthalene (96 mg, 546 μmol, 2.0 equiv), and Cs_2CO_3 (178 mg, 546 μmol, 2.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 18 h. The crude mixture was purified *via* FCC (cyclohexane/EtOAc 4:1) followed by preparative reverse-phase HPLC to afford the desired product as a light blue solid (20 mg, 15%) following concentration. LC−MS (*m/z*): 273.1 $[M - C_{17}H_{13}O]^+$ and 529.2 $[M + Na]^+$. TLC R_f = 0.70 (PET/EtOAc, 1:1). HPLC: t_R 7.18 min, >95% purity (254 nm). HRMS: calcd for $C_{34}H_{34}NaO_4^+$ $[M + Na]^+$ 529.2349, found 529.2355. ^{1}H NMR ($CDCl_3$) δ 8.06−7.97 (m, 1H), 7.90−7.85 (m, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.56 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.53−7.49 (m, 2H), 7.45 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.26−7.21 (m, 2H), 6.95−6.86 (m, 2H), 5.40 (s, 2H), 4.73 (s, 1H), 2.46 (br s, 4H), 2.23 (d, *J* = 16.3 Hz, 2H), 2.16 (d, *J* = 16.3 Hz, 2H), 1.11 (s, 6H), 1.01 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.5 (C), 162.0 (C), 157.4 (C), 136.9 (C), 133.7 (C), 132.5 (C), 131.6 (C), 129.4 (CH), 128.9 (CH), 128.6 (CH), 126.7 (CH), 126.4 (CH), 125.8 (CH), 125.3 (CH), 123.9 (CH), 115.7 (C), 114.4 (CH), 68.5 (CH_2), 50.8 (CH_2), 40.9 (CH_2), 32.2 (C), 31.0 (CH), 29.2 (CH_3), 27.4 (CH_3).

*3,3,6,6-Tetramethyl-9-(4-((1-methyl-1H-indazol-6-yl)methoxy)-phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**6m**).* 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (100 mg, 273 μmol, 1.0 equiv), 6-(bromomethyl)-1-methyl-1*H*-indazole hydrobromide (167 mg, 546 μmol, 2.0 equiv), and Cs_2CO_3 (178 mg, 546 μmol, 2.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 18 h. The desired product was isolated *via* FCC (PET/EtOAc 2:1), resulting in a light-yellow solid (105 mg, 75%) following concentration. LC−MS (*m/z*): 273.1 $[M - C_{15}H_{13}N_2O]^+$, 511.3 $[M + H]^+$, 533.3 $[M + Na]^+$, and 783.4 $[2M - C_{15}H_{13}N_2O]^+$. TLC R_f = 0.24 (PET/EtOAc, 2:1). HPLC: t_R 6.54 min, >95% purity (254 nm). HRMS: calcd for $C_{32}H_{34}N_2O_4^+$ $[M + H]^+$ 511.2591, found 511.2600. ^{1}H NMR ($CDCl_3$) δ 7.95 (d, *J* = 1.0 Hz, 1H), 7.70 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.45 (d, *J* = 1.1 Hz, 1H), 7.24−7.19 (m, 2H), 7.15 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.90−6.83 (m, 2H), 5.13 (s, 2H), 4.71 (s, 1H), 4.07 (s, 3H), 2.45 (br s, 4H), 2.23 (d, *J* = 16.3 Hz, 2H), 2.16 (d, *J* = 16.3 Hz, 2H), 1.10 (s, 6H), 0.99 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.5 (C), 162.1 (C), 157.2 (C), 140.0 (C), 136.9 (C), 135.7 (C), 132.6 (CH), 129.4 (CH), 123.6 (C), 121.2 (CH), 120.2 (CH), 115.7 (C), 114.4 (CH), 107.6 (CH), 70.2 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 35.6 (CH_3), 32.2 (C), 31.0 (CH), 29.2 (CH_3), 27.3 (CH_3).

*3,3,6,6-Tetramethyl-9-(5-((2-methylbenzyl)oxy)pyridin-2-yl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**7a**).* 9-(5-Hydroxypyridin-2-yl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5f**) (110 mg, 299 μmol, 1.0 equiv), 1-(chloromethyl)-2-methylbenzene (77.0 μL, 599 mmol, 2.0 equiv), and Cs_2CO_3 (195 mg, 599 μmol, 2.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 66 h. The desired product was isolated *via* FCC (PET/EtOAc 2:1), resulting in a white crystalline solid (110 mg, 78%) following concentration. LC−MS (*m/z*): 472.3 $[M + H]^+$, 494.2 $[M + Na]^+$, 965.4 $[2M + Na]^+$. TLC R_f = 0.35 (PET/EtOAc, 2:1). HPLC: t_R 5.40 min, >95% purity (254 nm). HRMS: calcd for $C_{30}H_{33}NO_4^+$ $[M + H]^+$ 472.2482, found 472.2482. ^{1}H NMR ($CDCl_3$) δ 8.15 (d, *J* = 2.9 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.25−7.15 (m, 4H), 4.97 (s, 2H), 4.83 (s, 1H), 2.52 (d, *J* = 17.6 Hz, 2H), 2.45 (d, *J* = 17.5 Hz, 2H), 2.34 (s, 3H), 2.24 (d, *J* = 16.2 Hz, 2H), 2.16 (d, *J* = 17.2 Hz, 2H), 1.10 (s, 6H), 1.01 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 197.5 (C), 163.6 (C), 154.7 (C), 153.8 (C), 137.7 (CH), 137.3 (C), 134.7 (C), 130.9 (CH), 129.2 (CH), 128.9 (CH), 126.5 (CH), 125.4 (CH), 121.4 (CH), 114.9 (C), 69.3 (CH_2), 51.2 (CH_2), 41.3 (CH_2), 33.9 (C), 32.7 (CH), 29.7 (CH_3), 27.6 (CH_3), 19.3 (CH_3).

*9-(3-Chloro-4-((2-methylbenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**7b**).* 9-(3-Chloro-4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5g**) (110 mg, 274 μmol, 1.0 equiv), 1-(chloromethyl)-2-methylbenzene (71.0 μL, 549 μmol, 2.0 equiv), and Cs_2CO_3 (179 mg, 549 μmol, 2.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 18 h. The desired product was isolated *via* FCC (PET/EtOAc 3:1), resulting in a white solid (89 mg, 64%) following concentration. LC−MS (*m/z*): 273.1 $[M - C_{14}H_{12}ClO]^+$.

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TLC R_f = 0.26 (PET/EtOAc, 3:1). HPLC: t_R 6.85 min, >95% purity (254 nm). HRMS: calcd for $C_{31}H_{33}{}^{35}ClNaO_4{}^+$ $[M + Na]^+$ 527.1974, found 527.1960. ^1H NMR ($CDCl_3$) δ 7.43 (dd, J = 2.3, 6.9 Hz, 1H), 7.28−7.16 (m, 5H), 6.88 (d, J = 8.5 Hz, 1H), 5.02 (s, 2H), 4.68 (s, 1H), 2.47 (br s, 4H), 2.36 (s, 3H), 2.24 (d, J = 16.3 Hz, 2H), 2.19 (d, J = 16.3 Hz, 2H), 1.10 (s, 6H), 1.02 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.4 (C), 162.3 (C), 152.8 (C), 137.8 (C), 136.5 (C), 134.5 (C), 130.2 (CH), 129.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 125.9 (CH), 122.7 (C), 115.2 (C), 113.2 (CH), 69.4 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 30.9 (CH_3), 29.2 (CH_3), 27.4 (CH_3), 18.9 (CH_3).

*9-(3-Fluoro-4-((2-methylbenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**7c**).* 9-(3-Fluoro-4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5h**) (110 mg, 0.286 mmol, 1.0 equiv) and 1-(chloromethyl)-2-methylbenzene (74.0 μL, 599 μmol, 2.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 18 h. The desired product was isolated *via* FCC (PET/EtOAc 4:1), resulting in a white solid (94 mg, 67%) following concentration. LC−MS (*m/z*): 273.1 $[M - C_{14}H_{12}FO]^+$. TLC R_f = 0.3 (PET/EtOAc, 4:1). HPLC: t_R 6.68 min, >95% purity (254 nm). HRMS: calcd for $C_{31}H_{33}FNaO_4{}^+$ $[M + Na]^+$ 511.2266, found 511.2255. ^1H NMR ($CDCl_3$) δ 7.44−7.37 (m, 1H), 7.27−7.18 (m, 3H), 7.15−7.06 (m, 1H), 7.00−6.89 (m, 2H), 5.04 (s, 2H), 4.72 (s, 1H), 2.46 (br s, 4H), 2.38 (s, 3H), 2.25 (d, J = 16.3 Hz, 2H), 2.19 (d, J = 16.3 Hz, 2H), 1.13 (s, 6H), 1.03 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.4 (C), 162.3 (C), 152.6 (d, J_{CF} = 245.6 Hz, C), 145.3 (d, J_{CF} = 10.9 Hz, C), 137.8 (d, J_{CF} = 5.3 Hz, C), 136.7 (C), 134.5 (C), 130.3 (CH), 128.7 (CH), 128.2 (CH), 125.9 (CH), 124.4 (d, J_{CF} = 3.3 Hz, C), 115.7 (d, J_{CF} = 18.7 Hz, CH), 115.3 (C), 114.9 (C), 69.9 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 31.0 (CH), 29.2 (CH_3), 27.4 (CH_3), 18.9 (CH_3). ^{19}F NMR ($CDCl_3$) δ − 134.20.

*9-(4-(Pyrimidin-5-yl)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**8a**).* To a solution of 9-(4-bromophenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5d**) (500 mg, 1.34 mmol, 1.0 equiv) and pyrimidine-5-boronic acid (498 mg, 4.02 mmol, 3.0 equiv) in degassed THF/1 M $Na_2CO_{3(aq)}$ (3:1, 20 mL) was added $PdCl_2(PPh_3)_2$ (188 mg, 268 μmol, 0.2 equiv). The reaction mixture was stirred at reflux overnight; thereafter, LC−MS analysis showed complete consumption of the starting material. The THF was evaporated *in vacuo*, and the resultant mixture was partitioned between EtOAc (40 mL) and water (40 mL). The organic phase was separated and further washed with water (2 × 40 mL) followed by brine (40 mL), dried over $MgSO_4$, gravity filtered, and then concentrated *in vacuo*. The residue was purified *via* FCC (MeOH/DCM 2:98). The desired eluates were concentrated *in vacuo* to yield a white solid that was recrystallized from MeOH to afford the desired product as a white crystalline solid (136 mg, 27%). LC−MS (*m/z*): 373.2 $[M + H]^+$. TLC R_f = 0.25 (MeOH/DCM, 2:98). HPLC: t_R 4.87 min, >95% purity (254 nm). HRMS: calcd. for $C_{23}H_{20}N_2O_3{}^+$ $[M + H]^+$ 373.1547, found 373.1556. ^1H NMR ($CDCl_3$) δ 9.16 (s, 1H), 8.88 (s, 2H), 7.52−7.38 (m, 4H), 4.86 (s, 1H), 2.77−2.52 (m, 4H), 2.45−2.28 (m, 4H), 2.14−1.91 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 196.7 (C), 164.3 (C), 157.3 (CH), 154.9 (CH), 145.7 (C), 134.4 (C), 132.4 (C), 129.7 (CH), 126.9 (CH), 116.6 (C), 37.1 (CH_2), 31.9 (CH), 27.3 (CH_2), 20.4 (CH_2).

*3,3,6,6-Tetramethyl-9-(4-(pyrimidin-5-yl)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**8b**).* To a solution of 9-(4-bromophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5e**) (200 mg, 465 μmol, 1.0 equiv) and pyrimidine-5-boronic acid (173 mg, 1.40 mmol, 3.0 equiv) in degassed THF/1 M $Na_2CO_{3(aq)}$ (3:1, 8 mL) was added $PdCl_2(PPh_3)_2$ (65 mg, 93 μmol, 0.2 equiv). The reaction mixture was stirred at reflux overnight; thereafter, LC−MS analysis showed conversion of the starting material to a single product. The THF within the mixture was evaporated *in vacuo*. The resultant mixture was partitioned between EtOAc (40 mL) and water (40 mL), and the phases were separated. The organic phase was further washed with water (2 × 40 mL) followed by brine (40 mL), dried over $MgSO_4$, gravity filtered, and then concentrated *in vacuo* before purification *via* FCC (PET/EtOAc 1:1), whereby the eluates were reduced *in vacuo* to afford the desired product as a white crystalline solid (43 mg, 22%). LC−MS (*m/z*): 429.2 $[M + H]^+$. TLC R_f = 0.32 (PET/EtOAc, 1:1). HPLC: t_R 5.91 min, >95% purity (254 nm). HRMS: calcd for $C_{27}H_{28}N_2O_3{}^+$ $[M + H]^+$ 429.2173, found 429.2185. ^1H NMR ($CDCl_3$) δ 9.15 (s, 1H), 8.89 (s, 2H), 7.53−7.39 (m, 4H), 4.80 (s, 1H), 2.49 (br s, 4H), 2.26 (d, J = 16.3 Hz, 2H), 2.19 (d, J = 16.3 Hz, 2H), 1.12 (s, 6H), 1.01 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.5 (C), 162.6 (C), 157.2 (CH), 154.8 (CH), 145.3 (C), 134.3 (C), 132.2 (C), 129.6 (CH), 126.8 (CH), 115.2 (CH_2), 50.7 (C), 40.9 (CH_2), 32.2 (CH_2), 31.9 (CH), 29.3 (CH_3), 27.4 (CH_3).

*2-Methyl-N-(4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenyl)benzamide (**9a**).* To a solution of 2-methylbenzoic acid (30 mg, 220 μmol, 1.0 equiv) in DCM (2 mL) were added DMF (1 drop) and oxalyl chloride (25.0 μL, 286 μmol, 1.3 equiv). The solution was stirred at room temperature for 1 h before TLC analysis (PET/EtOAc, 1:1) showed complete conversion of the starting material. The solution was reduced *in vacuo* to afford 2-methylbenzoyl chloride as a yellow oil, which was subsequently used without further purification. To a solution of the crude 2-methylbenzoyl chloride (29.0 μL, 226 μmol, 1.1 equiv) in anhydrous THF (9 mL) was added 9-(4-aminophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5j**) (75 mg, 205 μmol, 1.0 equiv). The solution was stirred under reflux for 3 h before being cooled to rt and left to stir overnight. The reaction mixture was reduced *in vacuo* to afford an oily residue that was partitioned between EtOAc (40 mL) and water (40 mL), and the phases were separated. The organic phase was further washed with water (2 × 40 mL) followed by brine (40 mL), dried over $MgSO_4$, gravity filtered, and then concentrated *in vacuo*. The residue was purified *via* FCC (PET/EtOAc 3:2), whereby the desired eluates were reduced *in vacuo* to afford the desired product as a thick brown oil (23 mg, 23%). LC−MS (*m/z*): 273.1 $[M - C_{14}H_{12}NO]^+$, 482.2 $[M - H]^-$, 506.2 $[M + Na]^+$, and 967.4 $[2M + H]^+$. TLC R_f = 0.23 (PET/EtOAc, 3:2). HPLC: t_R 6.18 min, >95% purity (254 nm). HRMS: calcd for $C_{31}H_{33}NaNO_4{}^+$ $[M + Na]^+$ 506.2302, found 506.2315. ^1H NMR ($CDCl_3$) δ 7.67 (s, 1H), 7.11−7.00 (m, 2H), 6.59−6.47 (m, 2H), 4.63 (s, 1H), 3.51 (s, 2H), 2.44 (br s, 7H), 2.22 (d, J = 16.3 Hz, 2H), 2.15 (d, J = 16.3 Hz, 2H), 1.09 (s, 6H), 0.99 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.6 (C), 167.9 (C), 162.3 (C), 140.4 (C), 136.7 (C), 136.4 (C), 136.3 (C), 131.2 (CH), 130.1 (CH), 129.1 (CH), 126.7 (CH), 125.9 (CH), 119.5 (CH), 115.5 (C), 50.7 (C), 40.9 (CH_2), 32.2 (CH_2), 31.5 (CH), 29.2 (CH_3), 27.5 (CH_3), 19.8 (CH_3).

*2-Methyl-N-(4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenyl)benzenesulfonamide (**9b**).* To an oven-dried 10 mL microwave vial were added 9-(4-aminophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5j**) (75 mg, 205 μmol, 1.0 equiv) and 2-methylbenzenesulfonyl chloride (59.0 μL, 410 μmol, 2.0 equiv) in anhydrous THF (5 mL). The reaction was left to stir at reflux for 21 h, after which TLC analysis (PET/EtOAc, 1:1) showed complete consumption of the starting material. The reaction mixture was reduced *in vacuo* to afford an oily residue, which was partitioned between EtOAc (40 mL) and water (40 mL), and the phases were separated. The organic phase was further washed with water (2 × 40 mL) followed by brine (40 mL), dried over $MgSO_4$, gravity filtered, and then concentrated *in vacuo* before purification *via* FCC (MeOH/DCM 5:95), whereby the desired eluates were reduced *in vacuo* to afford the desired product as a light-yellow solid (56 mg, 53%). LC−MS (*m/z*): 273.1 $[M - C_{13}H_{12}NO_2S]^+$ and 542.2 $[M + Na]^+$. TLC R_f = 0.33 (MeOH/DCM, 5:95). HPLC: t_R 6.23 min, >95% purity (254 nm). HRMS: calcd for $C_{30}H_{33}NaNO_5S^+$ $[M + Na]^+$ 542.1972, found 542.1982. ^1H NMR ($CDCl_3$) δ 7.88 (dd, J = 7.9, 1.4 Hz, 1H), 7.39 (td, J = 7.5, 1.4 Hz, 1H), 7.25−7.17 (m, 2H), 7.14−7.09 (m, 2H), 6.88−6.79 (m, 2H), 6.68 (s, 1H), 4.65 (s, 1H), 2.53 (s, 3H), 2.43 (br s, 4H), 2.22 (d, J = 16.3 Hz, 2H), 2.15 (d, J = 16.3 Hz, 2H), 1.09 (s, 6H), 0.94 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.4 (C), 162.4 (C), 141.1 (C), 137.5 (C), 137.2 (C), 134.4 (C), 132.9 (CH), 132.5 (CH), 129.8 (CH), 129.2 (CH), 126.1 (CH), 120.7 (CH), 115.3 (C), 50.6 (CH_2), 40.8 (CH_2), 32.2 (C), 31.1 (CH), 29.2 (CH_3), 27.2 (CH_3), 20.3 (CH_3).

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*9-(4-((2-Methylbenzyl)oxy)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**10a**).* 9-(4-Hydroxyphenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5a**) (75 mg, 241 μmol, 1.0 equiv), 1-(chloromethyl)-2-methylbenzene (64.0 μL, 483 μmol, 2.0 equiv), and Cs_2CO_3 (157 mg, 483 μmol, 2.0 equiv) in DMF (3 mL) were reacted as per general procedure B for 18 h. The desired product was isolated *via* FCC (PET/EtOAc 2:1), resulting in a white solid (58 mg, 58%) following concentration. LC−MS (*m/z*): 217.1 $[M - C_{14}H_{13}O]^+$ and 437.2 $[M + Na]^+$. TLC R_f = 0.24 (PET/EtOAc, 2:1). HPLC: t_R 6.23 min, >95% purity (254 nm). HRMS: calcd for $C_{27}H_{26}NaO_4^+$ $[M + Na]^+$ 437.1723, found 437.1738. ^{1}H NMR ($CDCl_3$) δ 7.36 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.27−7.15 (m, 5H), 6.89−6.81 (m, 2H), 4.95 (s, 2H), 4.77 (s, 1H), 2.72−2.48 (m, 4H), 2.44−2.25 (m, 4H), 2.34 (s, 3H), 2.10−1.91 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 196.8 (C), 163.9 (C), 157.6 (C), 137.1 (C), 136.9 (C), 135.1 (C), 130.5 (CH), 129.5 (CH), 128.9 (CH), 128.3 (CH), 126.1 (CH), 117.1 (C), 114.4 (CH), 68.6 (CH_2), 37.1 (CH_2), 30.9 (CH), 27.3 (CH_2), 20.4 (CH_2), 19.0 (CH_3).

*3,6-Dimethyl-9-(4-((2-methylbenzyl)oxy)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**10b**).* 9-(4-Hydroxyphenyl)-3,6-dimethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5b**) (100 mg, 296 mmol, 1.0 equiv), 1-(chloromethyl)-2-methylbenzene (78.0 μL, 591 μmol, 2.0 equiv), and Cs_2CO_3 (193 mg, 591 μmol, 2.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 18 h. The desired product was isolated *via* FCC (PET/EtOAc 4:1), resulting in a white crystalline solid (41 mg, 31%) following concentration. LC−MS (*m/z*): 245.1 $[M - C_{14}H_{13}O]^+$ and 465.2 $[M + Na]^+$. TLC R_f = 0.23 (PET/EtOAc, 4:1). HPLC: t_R 6.69 min, >95% purity (254 nm). HRMS: calcd for $C_{29}H_{30}O_4$ $[M + Na]^+$ 465.2036, found 465.2044. ^{1}H NMR ($CDCl_3$) δ 7.40−7.33 (m, 1H), 7.24−7.16 (m, 5H), 6.87−6.79 (m, 2H), 4.94 (s, 2H), 4.76−4.70 (m, 1H), 2.70−2.53 (m, 2H), 2.48−2.36 (m, 3H), 2.31−2.15 (m, 3H), 2.12−1.96 (m, 2H), 1.14−1.01 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 196.6 (C), 163.5 (C), 157.4 (C), 136.9 (C), 136.8 (C), 134.9 (C), 130.3 (CH), 129.3 (CH), 128.8 (CH), 128.2 (CH), 126.0 (CH), 116.7 (C), 114.2 (CH), 68.5 (CH_2), 45.3 (CH_2), 35.3 (CH_2), 30.9 (CH), 29.7 (C), 27.9 (CH), 20.8 (CH_3), 18.9 (CH_3).

*9-(4-(Cyclohexylmethoxy)phenyl)-3,6-dimethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**10c**).* 9-(4-Hydroxyphenyl)-3,6-dimethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5b**) (100 mg, 296 μmol, 1.0 equiv), (bromomethyl)cyclohexane (105 mg, 591 μmol, 2.0 equiv), and Cs_2CO_3 (193 mg, 591 μmol, 2.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 20 h. The desired product was isolated *via* FCC (PET/EtOAc 5:1), resulting in an off-white solid (92 mg, 72%) following concentration. LC−MS (*m/z*): 245.1 $[M - C_{13}H_{17}O]^+$, 457.3 $[M + Na]^+$, and 891.4 $[2M + Na]^+$. TLC R_f = 0.26 (PET/EtOAc, 5:1). HPLC: t_R 7.19 min, >95% purity (254 nm). HRMS: calcd for $C_{28}H_{34}NaO_4^+$ $[M + Na]^+$ 457.2349, found 457.2361. ^{1}H NMR ($CDCl_3$) δ 7.22−7.15 (m, 2H), 6.78−6.70 (m, 2H), 4.80−4.61 (m, 1H), 3.68 (d, *J* = 6.3 Hz, 2H), 2.72−2.55 (m, 2H), 2.52−2.37 (m, 3H), 2.37−2.15 (m, 3H), 2.13−1.95 (m, 2H), 1.90−1.80 (m, 2H), 1.79−1.66 (m, 4H), 1.39−1.13 (m, 5H), 1.13−1.05 (m, 6H), 1.05−0.95 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 196.5 (C), 163.4 (C), 157.7 (C), 136.3 (C), 129.2 (CH), 116.6 (C), 113.9 (CH), 73.3 (CH_2), 45.2 (CH_2), 37.6 (CH), 35.3 (CH_2), 30.9 (CH), 29.9 (CH_2), 28.5 (CH), 27.8 (CH), 26.5 (CH_2), 25.8 (CH_2), 20.8 (CH_3).

*9-(4-((2-Bromobenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**2**).* 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (400 mg, 1.09 mmol, 1.0 equiv), 1-bromo-2-(bromomethyl)benzene (546 mg, 2.18 mmol, 2.0 equiv), and Cs_2CO_3 (711 mg, 2.18 mmol, 2.0 equiv) in DMF (16 mL) were reacted as per general procedure B for 20 h. The desired product was isolated *via* FCC (PET/EtOAc 5:1), resulting in a white solid (486 mg, 83%) following concentration. LC−MS (*m/z*): 273.1 $[M - C_{13}H_{10}{}^{79}BrO]^+$ and 557.2 $[M + Na]^+$. TLC R_f = 0.22 (PET/EtOAc, 5:1). HPLC: t_R 7.10 min, >95% purity (254 nm). HRMS: calcd for $C_{30}H_{31}{}^{79}BrNaO_4$ $[M + Na]^+$ 557.1298, found 557.1308. ^{1}H NMR ($CDCl_3$) δ 7.58 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.54 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.33 (td, *J* = 7.5, 1.2 Hz, 1H), 7.27−7.21 (m, 2H), 7.18 (td, *J* = 7.7, 1.8 Hz, 1H), 6.90−6.83 (m, 2H), 5.07 (s, 2H), 4.73 (s, 1H), 2.45 (br s, 4H), 2.23 (d, *J* = 16.3 Hz, 2H), 2.17 (d, *J* = 16.3 Hz, 2H), 1.12 (s, 6H), 1.02 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.5 (C), 162.1 (C), 156.9 (C), 137.0 (C), 136.5 (C), 132.5 (CH), 129.4 (CH), 129.0 (CH), 128.9 (CH), 127.5 (CH), 122.2 (C), 115.7 (C), 114.4 (CH), 69.3 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 31.0 (CH), 29.2 (CH_3), 27.4 (CH_3).

*9-(4-((2-Ethylbenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**11a**).* Method A: To a solution of 9-(4-((2-bromobenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**2**) (100 mg, 187 μmol, 1.0 equiv), ethylboronic acid (18 mg, 0.243 mmol, 1.3 equiv), K_3PO_4 (139 mg, 654 μmol, 3.5 equiv), and tricyclohexylphosphine (5.2 mg, 18.7 μmol, 0.1 equiv) in toluene (2 mL) and water (100 μL) under a nitrogen atmosphere was added $Pd(OAc)_2$ (2.1 mg, 9.34 μmol, 0.05 equiv). The mixture was heated to 100 °C for 3 h and then cooled to room temperature. The crude mixture was partitioned between water (40 mL) and EtOAc (40 mL), and the phases were separated. The organic phase was further washed with water (2 × 40 mL) followed by brine (40 mL), dried over $MgSO_4$, gravity filtered, and then concentrated *in vacuo*. The residue was purified *via* FCC (PET/EtOAc 3:1). The desired eluates were concentrated *in vacuo* to afford the product as an off-white solid (12 mg, 13%).

Method B: A three-neck round-bottom flask was charged with 9-(4-((2-ethynylbenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**15**) (125 mg, 260 μmol, 1.0 equiv) and Pd/C (10 mg) in EtOAc (10 mL). The mixture was left to stir under constant H_2 pressure for 1.5 h after which the starting material was fully consumed. The reaction mixture was filtered through a pad of Celite that was washed with EtOAc. The filtrate was concentrated *in vacuo* to afford the desired product as an off-white solid (120 mg, 95%).

LC−MS (*m/z*): 273.1 $[M - C_{15}H_{14}O]^+$ and 507.3 $[M + Na]^+$. TLC R_f = 0.34 (PET/EtOAc, 3:1). HPLC: t_R 7.10 min, >95% purity (254 nm). HRMS: calcd for $C_{32}H_{36}NaO_4^+$ $[M + Na]^+$ 507.2506, found 507.2517. ^{1}H NMR ($CDCl_3$) δ 7.30 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.21 (td, *J* = 7.3, 1.5 Hz, 1H), 7.18−7.09 (m, 4H), 6.81−6.75 (m, 2H), 4.89 (s, 2H), 4.64 (s, 1H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.46 (br s, 4H), 2.24 (d, *J* = 16.3 Hz, 2H), 2.18 (d, *J* = 16.3 Hz, 2H), 1.16 (t, *J* = 7.6 Hz, 3H), 1.03 (s, 6H), 0.93 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.5 (C), 162.0 (C), 157.4 (C), 142.8 (C), 136.7 (C), 134.3 (C), 129.3 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH), 125.9 (CH), 115.8 (C), 114.2 (CH), 68.1 (CH_2), 50.8 (CH_2), 40.9 (CH_2), 32.2 (C), 31.0 (CH), 29.2 (CH_3), 27.4 (CH_3), 25.3 (CH_2), 15.2 (CH_3).

*3,3,6,6-Tetramethyl-9-(4-((2-propylbenzyl)oxy)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**11b**).* To a solution of 9-(4-((2-bromobenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**2**) (80 mg, 149 μmol, 1.0 equiv), propylboronic acid (17 mg, 194 μmol, 1.3 equiv), K_3PO_4 (111 mg, 523 μmol, 3.5 equiv), and tricyclohexylphosphine (4.2 mg, 15.0 μmol, 0.1 equiv) in toluene (1.5 mL) and water (70 μL) under a nitrogen atmosphere was added palladium acetate (1.7 mg, 7.47 μmol, 0.05 equiv). The mixture was heated to 100 °C for 3 h and then cooled to room temperature. The crude mixture was partitioned between water (40 mL) and EtOAc (40 mL), and the phases were separated. The organic phase was further washed with water (2 × 40 mL) followed by brine (40 mL), dried over $MgSO_4$, gravity filtered, and then concentrated *in vacuo*. The residue was purified *via* FCC (PET/EtOAc 4:1). The desired eluates were concentrated *in vacuo* to afford the product as an off-white solid (41 mg, 56%). LC−MS (*m/z*): 273.2 $[M - C_{16}H_{17}O]^+$ and 521.3 $[M + Na]^+$. TLC R_f = 0.28 (PET/EtOAc, 4:1). HPLC: t_R 7.10 min, >95% purity (254 nm). HRMS: calcd for $C_{33}H_{38}NaO_4^+$ $[M + Na]^+$ 521.2662, found 521.2673. ^{1}H NMR ($CDCl_3$) (DMSO-d_6) δ 7.39 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.31−7.15 (m, 3H), 7.12−7.04 (m, 2H), 6.93−6.83 (m, 2H), 5.00 (s, 2H), 4.48 (s, 1H), 2.63−2.57 (m, 2H), 2.56−2.48 (m, 4H), 2.27 (d, *J* = 16.2 Hz, 2H), 2.09 (d, *J* = 16.1 Hz, 2H), 1.57 (h, *J* = 7.3 Hz, 2H), 1.04 (s, 6H), 0.91 (s, 6H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) (DMSO-d_6) δ 196.6 (C), 163.1 (C), 157.2 (C), 141.5 (C), 137.1 (C), 134.9 (C), 129.7 (CH), 129.7 (CH), 129.5 (CH),

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128.6 (CH), 126.2 (CH), 115.0 (C), 114.4 (CH), 67.9 (CH_2), 50.5 (CH_2), 34.2 (CH_2), 32.3 (C), 30.7 (CH), 29.1 (CH_3), 26.9 (CH_3), 24.2 (CH_2), 14.4 (CH).

*9-(4-((2-Cyclopropylbenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**11c**).* To a solution of 9-(4-((2-bromobenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**2**) (150 mg, 280 μmol, 1.0 equiv), cyclopropylboronic acid (31 mg, 364 μmol, 1.3 equiv), K_3PO_4 (208 mg, 980 μmol, 3.5 equiv), and tricyclohexylphosphine (7.9 mg, 28.0 μmol, 0.1 equiv) in toluene (2.5 mL) and water (125 μL) under a nitrogen atmosphere was added $Pd(OAc)_2$ (3.1 mg, 14.0 μmol, 0.05 equiv). The mixture was heated to 100 °C for 3 h and then cooled to room temperature. The crude mixture was partitioned between water (40 mL) and EtOAc (40 mL), and the phases were separated. The organic phase was further washed with water (2 × 40 mL) followed by brine (40 mL), dried over $MgSO_4$, gravity filtered, and then concentrated *in vacuo* to afford the desired product as a an off-white solid (137 mg, 99%). LC−MS (*m*/*z*): 273.2 $[M - C_{16}H_{15}O]^+$ and 519.3 $[M + Na]^+$. TLC R_f = 0.67 (PET/EtOAc, 1:1). HPLC: t_R 7.18 min, >95% purity (254 nm). HRMS: calcd for $C_{33}H_{36}NaO_4^+$ $[M + Na]^+$ 519.2506, found 519.2516. ^{1}H NMR ($CDCl_3$) δ 7.39 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.24−7.13 (m, 4H), 7.03 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.91−6.83 (m, 2H), 5.14 (s, 2H), 4.71 (s, 1H), 2.46 (br s, 4H), 2.23 (d, *J* = 16.3 Hz, 2H), 2.16 (d, *J* = 16.3 Hz, 2H), 1.97 (tt, *J* = 8.4, 5.4 Hz, 1H), 1.10 (s, 6H), 1.00 (s, 6H), 0.95−0.88 (m, 2H), 0.71−0.64 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 196.5 (C), 162.0 (C), 157.5 (C), 141.4 (C), 136.6 (C), 136.2 (C), 129.3 (CH), 128.4 (CH), 128.1 (CH), 125.8 (CH), 125.6 (CH), 115.8 (C), 114.3 (CH), 68.0 (CH_2), 50.8 (CH_2), 40.9 (CH_2), 32.2 (C), 31.0 (CH), 29.2 (CH_3), 27.4 (CH_3), 12.3 (CH), 7.1 (CH_2).

*3,3,6,6-Tetramethyl-9-(4-((2-(thiophen-2-yl)benzyl)oxy)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**11d**).* To a solution of 9-(4-((2-bromobenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**2**) (100 mg, 187 μmol, 1.0 equiv), 2-thiopheneboronic acid (31 mg, 243 μmol, 1.3 equiv), K_3PO_4 (139 mg, 654 μmol, 3.5 equiv), and tricyclohexylphosphine (5.2 mg, 18.7 μmol, 0.1 equiv) in toluene (2 mL) and water (100 μL) under a nitrogen atmosphere was added $Pd(OAc)_2$ (2.1 mg, 9.34 μmol, 0.05 equiv). The mixture was heated to 100 °C for 1 h and then cooled to room temperature. The crude mixture was partitioned between water (40 mL) and EtOAc (40 mL), and the phases were separated. The organic phase was further washed with water (2 × 40 mL) followed by brine (40 mL), dried over $MgSO_4$, gravity filtered, and then concentrated *in vacuo*. The residue was purified *via* preparative reverse-phase HPLC to afford the desired product as a yellow solid (8 mg, 8%). LC−MS (*m*/*z*): 273.2 $[M - C_{16}H_{11}SO]^+$, 561.2 $[M + Na]^+$. TLC R_f = 0.32 (PET/EtOAc, 4:1). HPLC t_R: 7.00 min, >95% purity (254 nm). HRMS: calcd for $C_{34}H_{34}SO_4$ $[M + Na]^+$ 561.2089, found 561.2070. ^{1}H NMR ($CDCl_3$) δ 7.60−7.54 (m, 1H), 7.50−7.46 (m, 1H), 7.40−7.31 (m, 3H), 7.22−7.15 (m, 2H), 7.11 (dd, *J* = 1.2, 3.6 Hz, 1H), 7.05 (dd, *J* = 3.5, 5.1 Hz, 1H), 6.81−6.75 (m, 2H), 4.98 (s, 2H), 4.70 (s, 1H), 2.45 (br s, 4H), 2.24 (d, *J* = 16.3 Hz, 2H), 2.18 (d, *J* = 16.3 Hz, 2H), 1.10 (s, 6H), 1.00 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.6 (C), 162.1 (C), 156.9 (C), 136.7 (C), 134.6 (C), 134.2 (C), 130.7 (CH), 129.9 (CH), 129.3 (CH), 128.2 (CH), 128.1 (CH), 127.5 (CH), 127.1 (CH), 125.8 (CH), 115.7 (C), 114.4 (CH), 68.2 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 30.9 (CH), 29.2 (CH_3), 27.4 (CH_3).

*3,3,6,6-Tetramethyl-9-(4-((2-(thiophen-3-yl)benzyl)oxy)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**11e**).* To a solution of 9-(4-((2-bromobenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**2**) (100 mg, 187 μmol, 1.0 equiv), 3-thiopheneboronic acid (31 mg, 243 μmol, 1.3 equiv), K_3PO_4 (139 mg, 654 μmol, 3.5 equiv), and tricyclohexylphosphine (5.2 mg, 18.7 μmol, 0.1 equiv) in toluene (2 mL) and water (100 μL) under a nitrogen atmosphere was added $Pd(OAc)_2$ (2.1 mg, 9.34 μmol, 0.05 equiv). The mixture was heated to 100 °C for 1 h and then cooled to room temperature. The crude mixture was partitioned between water (40 mL) and EtOAc (40 mL), and the phases were separated. The organic phase was further washed with water (2 × 40 mL) followed by brine (40 mL), dried over $MgSO_4$, gravity filtered, and then concentrated *in vacuo*. The residue was purified *via* FCC (PET/EtOAc 4:1). The desired eluates were concentrated *in vacuo* to afford the product as a light-yellow solid (84 mg, 84%). LC−MS (*m*/*z*): 273.2 $[M - C_{16}H_{11}SO]^+$, 561.2 $[M + Na]^+$. TLC R_f = 0.29 (PET/EtOAc, 4:1). HPLC t_R: 6.87 min, >95% purity (254 nm). HRMS: calcd for $C_{34}H_{34}NaSO_4^+$ $[M + Na]^+$ 561.2092, found 561.2070. ^{1}H NMR ($CDCl_3$) δ 7.64−7.51 (m, 1H), 7.45−7.41 (m, 1H), 7.41−7.35 (m, 3H), 7.33 (dd, *J* = 3.0, 1.4 Hz, 1H), 7.24−7.18 (m, 3H), 6.84−6.76 (m, 2H), 4.92 (s, 2H), 4.73 (s, 1H), 2.45 (br s, 4H), 2.24 (d, *J* = 16.3 Hz, 2H), 2.18 (d, *J* = 16.3 Hz, 2H), 1.13 (s, 6H), 1.03 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.5 (C), 162.1 (C), 157.0 (C), 140.6 (C), 136.8 (C), 136.7 (C), 134.1 (C), 130.1 (CH), 129.9 (CH), 129.3 (CH), 128.9 (CH), 128.2 (CH), 127.6 (CH), 125.4 (CH), 123.2 (CH), 115.7 (C), 114.3 (CH), 68.3 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 30.9 (CH), 29.2 (CH_3), 27.4 (CH_3).

*9-(4-((2-Isopropylbenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**11f**).* 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2*H*)-dione (**5c**) (80 mg, 218 μmol, 1.0 equiv), 1-(bromomethyl)-2-isopropylbenzene (72.0 μL, 437 μmol, 2.0 equiv), and Cs_2CO_3 (142 mg, 437 μmol, 2.0 equiv) in DMF (4 mL) were reacted as per general procedure B for 17 h. The desired product was isolated *via* FCC (PET/EtOAc 5:1), resulting in a white crystalline solid (79 mg, 73%) following concentration. LC−MS (*m*/*z*): 273.3 $[M - C_{16}H_{17}O]^+$, 521.3 $[M + Na]^+$. TLC R_f = 0.25 (PET/EtOAc, 5:1). HPLC t_R: 6.91 min, >95% purity (254 nm). HRMS: calcd for $C_{33}H_{38}NaO_4^+$ $[M + Na]^+$ 521.2676, found 521.2662. ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 3H), 7.25−7.14 (m, 3H), 6.94−6.63 (m, 2H), 4.98 (s, 2H), 4.71 (s, 1H), 3.15 (h, *J* = 6.9 Hz, 1H), 2.46 (br s, 4H), 2.24 (d, *J* = 16.3 Hz, 2H), 2.18 (d, *J* = 16.3 Hz, 2H), 1.24 (d, *J* = 6.8 Hz, 6H), 1.10 (s, 6H), 1.01 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.6 (C), 162.0 (C), 157.3 (C), 147.9 (C), 136.6 (C), 133.4 (C), 129.5 (CH), 129.3 (CH), 128.7 (CH), 125.7 (CH), 125.5 (CH), 115.7 (C), 114.2 (CH), 68.2 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 31.0 (CH), 29.2 (CH_3), 28.8 (CH), 27.4 (CH_3), 23.9 (CH_3).

*(2-((Trimethylsilyl)ethynyl)phenyl)methanol (**13**).* To a solution of (2-iodophenyl)methanol (500 mg, 2.14 mmol, 1.0 equiv) in Et_3N (5 mL) at 0 °C were added ethynyltrimethylsilane (440 μL, 3.2 mmol, 1.5 equiv), $PdCl_2(PPh_3)_2$ (75 mg, 107 μmol, 0.05 equiv), and CuI (41 mg, 214 μmol, 0.1 equiv) successively. The mixture was stirred at rt for 5 h, after which TLC analysis (PET/EtOAc, 1:1) showed complete consumption of the starting material. The reaction mixture was filtered through a pad of Celite that was washed with EtOAc. The organic solution was concentrated *in vacuo* before purification *via* FCC (PET/EtOAc 4:1). The desired eluates were reduced *in vacuo* to afford the desired product as a yellow oil (398 mg, 91%). TLC R_f = 0.30 (PET/EtOAc, 4:1). ^{1}H NMR ($CDCl_3$) δ 7.48−7.45 (m, 1H), 7.41 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H), 7.33 (td, *J* = 7.6, 1.4 Hz, 1H), 7.26−7.21 (m, 1H), 4.82 (d, *J* = 6.6 Hz, 2H), 2.20 (t, *J* = 6.6 Hz, 1H), 0.27 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 143.2 (C), 132.5 (CH), 129.0 (CH), 127.4 (CH), 127.2 (CH), 121.2 (C), 102.6 (C), 99.6 (C), 64.1 (CH_2), 0.0 (CH_3).

*((2-(Bromomethyl)phenyl)ethynyl)trimethylsilane (**14**).* To a solution of (2-((trimethylsilyl)ethynyl)phenyl)methanol (**13**) (231 mg, 1.13 mmol, 1.0 equiv) in chloroform (5 mL) at 0 °C were added Ph_3P (385 mg, 1.47 mmol, 1.3 equiv) and NBS (262 mg, 1.47 mmol, 1.3 equiv) successively. The mixture was stirred at 0 °C for 1.5 h before LC−MS analysis confirmed complete consumption of the starting material. The reaction mixture was partitioned between EtOAc (40 mL) and water (40 mL), and the phases were separated. The organic phase was further washed with water (2 × 40 mL) followed by brine (40 mL), dried over $MgSO_4$, gravity filtered, and then concentrated *in vacuo*. The residue was purified *via* FCC (PET/EtOAc 10:1). The desired eluates were concentrated *in vacuo* to afford the product as a colorless oil (263 mg, 87%). TLC R_f = 0.28 (PET/EtOAc, 10:1). ^{1}H NMR (DMSO-d_6) δ 7.58−7.52 (m, 1H), 7.50−7.45 (m, 1H), 7.40 (td, *J* = 7.6, 1.6 Hz, 1H), 7.34 (td, *J* = 7.5, 1.4 Hz, 1H), 4.76 (s, 2H), 0.27 (s, 9H). ^{13}C NMR (DMSO-d_6) δ

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139.7 (C), 132.0 (CH), 130.0 (CH), 129.4 (CH), 128.8 (CH), 122.2 (C), 102.1 (C), 100.4 (C), 32.4 (CH_2), −0.2 (CH_3).

*9-(4-((2-Ethynylbenzyl)oxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**15**).* 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5c**) (130 mg, 355 μmol, 1.0 equiv), ((2-(bromomethyl)phenyl)ethynyl)trimethylsilane (**14**) (190 mg, 710 μmol, 2.0 equiv), and Cs_2CO_3 (231 mg, 710 μmol, 2.0 equiv) in DMF (5 mL) were reacted as per general procedure B for 42 h. The desired product was isolated *via* FCC (PET/EtOAc 4:1), resulting in a white solid (127 mg, 65%) following concentration. LC−MS (*m/z*): 273.1 $[M - C_{15}H_{11}O]^+$, 503.2 $[M + Na]^+$ and 753.3 $[2M - C_{15}H_{11}O]^+$. TLC R_f = 0.27 (PET/EtOAc, 4:1). HPLC: t_R 6.83 min, >95% purity (254 nm). HRMS: calcd for $C_{32}H_{32}NaO_4^+$ $[M + Na]^+$ 503.2193, found 503.2205. ^{1}H NMR ($CDCl_3$) δ 7.55−7.47 (m, 2H), 7.35 (td, *J* = 7.6, 1.4 Hz, 1H), 7.29−7.23 (m, 1H), 7.23−7.16 (m, 2H), 6.87−6.81 (m, 2H), 5.17 (s, 2H), 4.71 (s, 1H), 3.30 (s, 1H), 2.45 (br s, 4H), 2.23 (d, *J* = 16.3 Hz, 2H), 2.16 (d, *J* = 16.3 Hz, 2H), 1.10 (s, 6H), 1.00 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 196.4 (C), 162.0 (C), 157.2 (C), 139.6 (C), 136.8 (C), 132.6 (CH), 129.3 (CH), 129.1 (CH), 127.4 (CH), 127.3 (CH), 120.2 (C), 115.7 (C), 114.4 (CH), 82.2 (C), 80.9 (CH), 67.9 (CH_2), 50.7 (CH_2), 40.8 (CH_2), 32.2 (C), 30.9 (CH), 29.2 (CH_3), 27.4 (CH_3).

Pharmacology. *ERK 1/2 Phosphorylation Assay.* All compounds that underwent pharmacological evaluation were >95% pure as assessed by analytical HPLC. Leu-Enk was dissolved at 10 mM in water, and putative DOR PAMs at 10 mM in DMSO. All compounds were then diluted in assay buffers. Human DOR FlpIn Chinese hamster ovary cells (CHO-hDOR) were seeded into 96-well plates at a density of 20, 000 cells/well. After 4−6 h, cells were washed with phosphate-buffered saline (PBS) and incubated overnight in serum-free DMEM. Initially, time-course experiments were conducted at least twice for each ligand to determine the time required to maximally promote ERK1/2 phosphorylation via the DOR (Figure S3). Concentration−response experiments were performed for the orthosteric ligands in the absence or presence of increasing concentrations of the allosteric modulator at 37 °C. Stimulation of the cells was terminated by the removal of the media and addition of 50 μL of SureFire lysis buffer (PerkinElmer) to each well. The plate was shaken for 5 min at room temperature before transferring 5 μL of the lysates to a white 384-well Proxiplate (PerkinElmer). Then, 8.5 μL of the detection buffer (reaction buffer/activation buffer/acceptor beads/donor beads, 60:10:0.3:0.3) was added to the samples and incubated in the dark at 37 °C for 1 h. Fluorescence signal was measured using the Envision multilabel plate reader with AlphaScreen settings. Data were expressed as a percentage of the pERK1/2 mediated by 10% FBS response. For pertussis toxin treated experiments, cells were incubated overnight with 100 ng/mL of PTX prior to performing concentration−response curve experiments.

cAMP Inhibition Assay. To measure $G_{\alpha i}$-mediated cAMP inhibition, FlpIn CHO 3HA_hDOR cells were transfected with a BRET-based cAMP biosensor (CAMYEL = **cAM**P sensor using **Y**FP-**E**pac-R**L**uc). Briefly, 20,000 cells/well were seeded in 96-well white CulturPlates (Sigma Aldrich) and incubated overnight at 37 °C and 5% CO_2 followed by transient transfection with 60 ng/well of CAMYEL DNA and linear polyethylenimine PEI (DNA:PEI ratio of 1:6). Forty-eight hours post transfection, cells were washed twice with phosphate-buffered saline (PBS) and equilibrated with Hanks' balanced salt buffer containing10 mM HEPES. After 30 min incubation at 37 °C, a final concentration of 5 μM coelenterazine H (Nanolight Technology, Pinetop, AZ) was added to each well for 5 min. Cells were then incubated for 5 min with various concentrations of Leu-enkephalin in the absence or presence of increasing concentrations of each allosteric modulator followed by 3 μM of forskolin. Cells were further incubated for 5 min at 37 °C before BRET measurements were performed on a LUMIstar FS instrument (BMG Labtech) using 445−505 nm/505−565 nm filters. The BRET signals were determined by quantifying the ratio of light emitted at 505/565 nm by YFP over the light emitted at 430/475 nm by Renilla luciferase. The kinetics was initially performed to determine the time point to achieve the optimal BRET signals (data not shown). Concentration−response curves were constructed with the data point at 10 min after the addition of the ligands and were normalized to the response mediated by 3 μM forskolin (0%) or buffer (100%) alone.

Data Analysis. All data were analyzed using GraphPad Prism 9 (San Diego, CA). Allosteric interactions of the modulator with the agonist were analyzed by fitting the curves to the operational model of allosterism[19] as follows:

$$E = \text{basal} + \frac{(E_m - \text{basal})\,([A](K_B + \alpha\beta[B]) + \tau_B[B]EC_{50})^n}{EC_{50}{}^n(K_B + [B])^n + ([A](K_B + \alpha\beta[B]) + \tau_B[B]EC_{50})^n}$$

where K_A and K_B denote the equilibrium dissociation constants for orthosteric and allosteric ligands, respectively, and α refers to the cooperativity factor that each ligand exerts on the affinity of the other. In addition to allosteric effects on binding affinity (governed by α), allosteric effects on efficacy are incorporated by the use of an additional parameter, β. The parameters τ_A and τ_B denote the capacity of orthosteric and allosteric ligands, respectively, to exhibit agonism and incorporate the intrinsic efficacy of each ligand.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.2c01061.

Purity data for all compounds that underwent pharmacological evaluation; change in Leu-enkephalin potency; agonist-mediated ERK1/2 phosphorylation responses are Gαi/o protein dependent; expression level of DOR at the cell surface; expression level of DOR at the cell surface; and ligand-mediated ERK1/2 phosphorylation responses over the course of 20 min (PDF)

Molecular formula strings (CSV)

■ AUTHOR INFORMATION

Corresponding Authors

Celine Valant − *Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia;* orcid.org/0000-0002-2509-7465; Phone: +613 9903 9091; Email: celine.valant@monash.edu

Peter J. Scammells − *Medicinal Chemistry, Monash University, Parkville, VIC 3052, Australia;* orcid.org/0000-0003-2930-895X; Phone: +613 9903 9542; Email: peter.scammells@monash.edu

Authors

Owindeep Deo − *Medicinal Chemistry, Monash University, Parkville, VIC 3052, Australia*

Sadia Alvi − *Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia*

Vi Pham − *Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia*

Arthur Christopoulos − *Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia*

David M. Thal − *Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia;* orcid.org/0000-0002-0325-2524

Manuela Jörg − *Medicinal Chemistry, Monash University, Parkville, VIC 3052, Australia; School of Natural and*

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Environmental Sciences, Newcastle University, Newcastle upon Tyne NE1 7RU, U.K.; orcid.org/0000-0002-3116-373X

Ben Capuano − *Medicinal Chemistry, Monash University, Parkville, VIC 3052, Australia;* orcid.org/0000-0001-5434-0180

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jmedchem.2c01061

Notes

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■ ABBREVIATIONS USED

cAMP, cyclic adenosine monophosphate; $CDCl_3$, deuterated chloroform; CD_3OD, deuterated methanol; DCM, dichloromethane; DMSO-d_6, deuterated dimethyl sulfoxide; DMF, dimethylformamide; DOR, δ-opioid receptor; ERK, extracellular signal-related kinase; EtOAc, ethyl acetate; Et_3N, triethylamine; MeCN, acetonitrile; MeOH, methanol; MOR, μ-opioid receptor; PET, petroleum spirits; SAR, structure−activity relationship; SEM, standard error of mean; THF, tetrahydrofuran; TMS, trimethylsilyl

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