

## Article

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# Structure-Kinetic Profiling of Haloperidol Analogues at the Human Dopamine D<sub>2</sub> Receptor

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## ▪ ABSTRACT

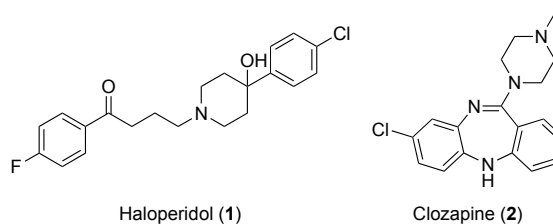
Haloperidol is a typical antipsychotic drug (APD) associated with an increased risk of extrapyramidal side-effects (EPS) and hyperprolactinemia relative to atypical APDs such as clozapine. Both drugs are dopamine D<sub>2</sub> receptor (D<sub>2</sub>R) antagonists, with contrasting kinetic profiles. Haloperidol displays fast association/slow dissociation at the D<sub>2</sub>R whereas clozapine exhibits relatively slow association/fast dissociation. Recently, we have provided evidence that slow dissociation from the D<sub>2</sub>R predicts hyperprolactinemia, whereas fast association predicts EPS. Unfortunately, clozapine can cause severe side-effects independent of its D<sub>2</sub>R action. Our results suggest an optimal kinetic profile for D<sub>2</sub>R antagonist APDs that avoids EPS. To begin exploring this hypothesis, we conducted a structure-kinetic relationship study of haloperidol and reveal that subtle structural modifications dramatically change binding kinetic rate constants, affording compounds with a clozapine-like kinetic profile. Thus, optimisation of these kinetic parameters may allow development of novel APDs based on the haloperidol scaffold with improved side-effect profiles.

## ▪ INTRODUCTION

Haloperidol (**1**, Figure 1) is an effective, typical antipsychotic drug (APD) used in the treatment of schizophrenia (SCZ). As for all current APDs, its mechanism of action is primarily through antagonism of dopamine (DA) D<sub>2</sub> receptors (D<sub>2</sub>R) in the mesolimbic pathway, where excessive DA activity is thought to underlie the positive symptoms of schizophrenia.<sup>1-3</sup> Unfortunately, **1** along with

1  
2  
3 other typical APDs, are associated with severe on-target side effects including EPS (e.g., Parkinsonian  
4 symptoms such as bradykinesia and tremor) and hyperprolactinemia.<sup>3,4</sup> These symptoms are mediated  
5 by blockade of D<sub>2</sub>R signalling in the nigrostriatal and tuberoinfundibular DA pathways,  
6 respectively.<sup>2-7</sup> Tardive dyskinesia is also associated with long-term exposure to typical APDs such  
7 as **1**.<sup>8</sup>

10  
11 Atypical APDs display a diminished incidence of EPS and hyperprolactinemia relative to typical  
12 APDs.<sup>9-11</sup> While the primary distinction between typicality and atypicality is based on such clinical  
13 observations, the mechanism(s) that might drive this distinction remain unclear. Clozapine (**2**, Figure  
14 **1**) is a prototypical atypical antipsychotic. It has a complex pharmacological profile with high affinity  
15 for other members of the biogenic amine receptor family and, in particular, a relatively high affinity  
16 for the serotonin 2A receptor (5-HT<sub>2A</sub>R).<sup>12</sup> Many atypical APDs have similar pharmacology leading  
17 to the hypothesis that a relatively high affinity for the 5HT<sub>2A</sub>R as compared to the D<sub>2</sub>R confers  
18 atypicality.<sup>13-16</sup> However, not all atypical APDs share this profile suggesting that this theory cannot  
19 account for all examples of atypicality.<sup>13,17</sup> Unfortunately, this lack of selectivity across aminergic  
20 receptors is associated with off-target side-effects, including sedation, metabolic disorders, weight  
21 gain, urinary incontinence and constipation.<sup>18</sup> **2** can also cause acute agranulocytosis, a potentially  
22 life-threatening white blood cell disorder.



**Figure 1.** Typical APD haloperidol (**1**) and atypical APD clozapine (**2**).

The relatively fast rate at which **2**, and other related APDs, dissociate from the D<sub>2</sub>R has also been suggested to be the basis for an atypical profile.<sup>17</sup> Rapid dissociation of an antagonist might allow a fraction of D<sub>2</sub>Rs to be occupied by transiently high concentrations of DA released into the synapse whereas an antagonist with a slow dissociation rate would cause insurmountable antagonism. Central to this hypothesis was the consensus that APDs exhibit similar association rates ( $k_{on}$ ) for the D<sub>2</sub>R meaning that affinity is largely mediated by differences in dissociation rate ( $k_{off}$ ).<sup>19</sup> Olanzapine, however, which has a similar high affinity for the D<sub>2</sub>R as many typical antipsychotics, displays an atypical profile.<sup>4</sup>

The incorporation of drug-receptor kinetic binding parameters into drug discovery programs is seen as increasingly important for the development of next generation therapeutics.<sup>20-28</sup> Previous efforts to derive estimates of APD kinetic rate constants have used radiometric detection methods with limited

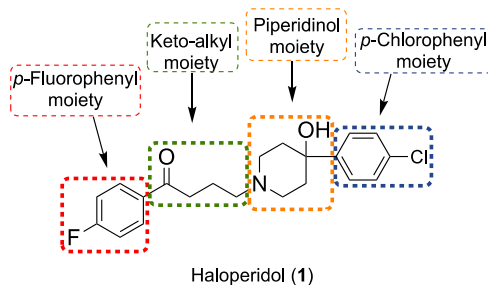
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3 assay throughput.<sup>19,29,30</sup> We have recently developed a competition association assay using TR-FRET  
4 to determine ligand kinetic parameters of unlabelled D<sub>2</sub>R agonists,<sup>31,32</sup> and profiled an extensive  
5 series of APDs in order to explore the kinetic basis for on-target side effects.<sup>33</sup> We found that the  
6 association rates of the APDs varied over three orders of magnitude and that association rates, rather  
7 than dissociation rates, correlated with EPS. These observations led us to propose a revised kinetic  
8 hypothesis whereby rapid association rate leads to drug rebinding at the D<sub>2</sub>R, maintaining a higher  
9 concentration of APD in the synaptic compartment. This causes increased competition with DA  
10 leading to EPS. In contrast, hyperprolactinaemia was correlated with APD dissociation rate.<sup>33</sup>  
11 Optimising D<sub>2</sub>R binding kinetics may permit the design of novel tools to test this kinetic hypothesis,  
12 as well as facilitate the generation of new APDs with an improved therapeutic profile.

13  
14 Although clozapine (**2**) appears to possess the desired slow on/fast off kinetic profile for reduced on-  
15 target side effects ( $k_{\text{on}} = 8.23 \pm 1.42 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 1.67 \pm 0.25 \text{ min}^{-1}$ ),<sup>33</sup> it displays affinity  
16 for many aminergic GPCRs, contributing to its off-target side effects. Haloperidol (**1**), in contrast,  
17 has a better off-target selectivity profile, but an undesirable fast on/slow off kinetic profile at the D<sub>2</sub>R  
18 ( $k_{\text{on}} = 1.29 \pm 0.21 \times 10^9 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 0.61 \pm 0.04 \text{ min}^{-1}$ ) that contributes to its on-target side effects.  
19 The aim of the current study was to optimise the kinetic binding parameters of the more selective  
20 scaffold of haloperidol towards a slow on/fast off profile. To this end, we herein describe the design  
21 and synthesis of 50 analogues of **1**, focusing on structural modification of four key moieties (figure  
22 2) and use competition association kinetic binding methodology to determine their association and  
23 dissociation rates, and equilibrium affinities at the D<sub>2</sub>R. We reveal that both the association and  
24 dissociation kinetics of this scaffold can vary considerably with subtle structural modification.  
25 Interestingly, we have identified previous analogues of **1**, among others, that may have been  
26 overlooked on the basis of affinity-driven scaffold optimisation, that possess favourable kinetic  
27 profiles. These data reveal the structure-kinetic relationships (SKR) of **1**, as well identify novel tool  
28 compounds with which to interrogate the relationship between APD kinetic binding parameters and  
29 on-target side-effect profiles. Although the structure-activity relationships (SAR) surrounding the  
30 butyrophenone scaffold of APDs have been extensively studied in previous years,<sup>34-39</sup> to our  
31 knowledge, these data represent the first reported SKR relating to analogues of **1**.

## 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 ■ RESULTS AND DISCUSSION

54  
55 **Chemistry.** To begin our structure-kinetic study, we focused on modifying four distinct regions of  
56 **1**, namely the *para*-fluorophenyl (red box), ketone and alkyl linker (green box), piperidinol (orange  
57 box), and *para*-chlorophenyl (blue box) moieties, as depicted in **figure 2**. For completeness, we  
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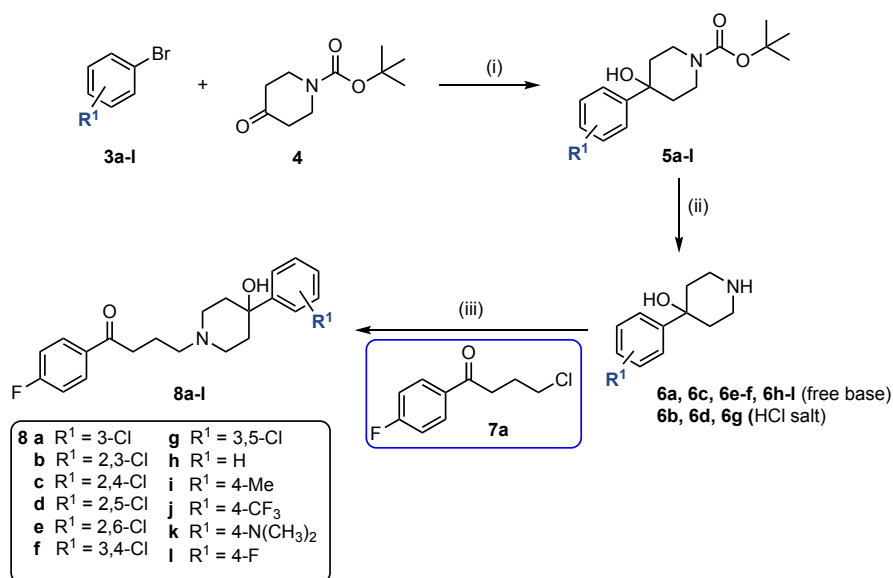
1  
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3 included both established and novel analogues of **1** in our approach, covering 50 compounds in  
4  
5 totality.



**Figure 2.** Structural regions of haloperidol (**1**) investigated as part of the SKR study.

*Variation of para-chlorophenyl moiety of 1.* In evaluating the positional effects of halogen substitution on the *p*-chlorophenyl moiety, we initially synthesised analogues bearing the chloro-substituent in the *ortho* (**8n**) and *meta* (**8a**) positions, as well as incorporation of all possible dichloro substitution patterns (2,3-diCl (**8b**); 2,4-diCl (**8c**); 2,5-diCl (**8d**); 2,6-diCl (**8e**); 3,4-diCl (**8f**);<sup>40</sup> and 3,5-diCl (**8g**)). In addition, we wanted to assess the effects of halogen removal through the proteo analogue (**8h**),<sup>41</sup> as well as alternative *para*-substituents, including methyl (**8i**),<sup>41</sup> trifluoromethyl (**8j**), *N,N*-dimethylamino (**8k**) and fluoro (**8l**).<sup>41</sup> The synthesis of these compounds is summarised in **scheme 1**. Firstly, the appropriately substituted bromobenzene (**3a-l**) underwent lithiation using *n*-BuLi, followed by treatment with commercially available *tert*-butyl 4-oxopiperidine-1-carboxylate (**4**) to afford the corresponding *N*-Boc-protected phenylpiperidinols (**5a-l**). HCl-mediated *N*-Boc-deprotection afforded the corresponding hydrochloride salts or free amines following basic work-up (**6a-l**). Finally, nucleophilic displacement of key intermediate 4-chloro-1-(4-fluorophenyl)butan-1-one (**7a**) with the appropriate substituted phenylpiperidinol (**6a-l**) was achieved by refluxing in toluene in the presence of KI and NaHCO<sub>3</sub>, to afford the desired final analogues (**8a-l**).

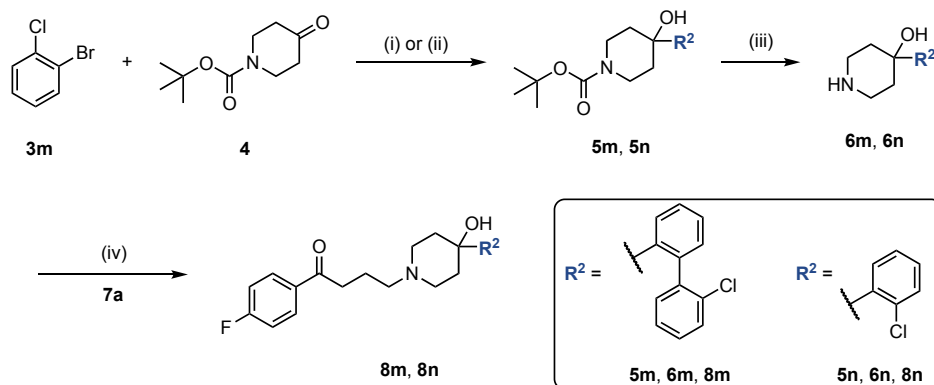
**Scheme 1. Synthesis of haloperidol (1) analogues with modification to *para*-chlorophenyl moiety<sup>a</sup>**



<sup>a</sup>Reagents and conditions: (i) *n*-BuLi, THF, -78 °C, 3-8 h, 50-88% (**5a-l**); (ii) HCl (4 M), 1,4-dioxane, 1-3 h, 75-98% (**6a**, **6c**, **6e-f**, **6h-l** (free base) **6b**, **6d**, **6g** (HCl salt)); (iii) NaHCO<sub>3</sub>, KI, toluene, reflux, 24 h, 45-70% (**8a-l**).

Though established, the employed lithiation chemistry proved to be problematic towards the synthesis of the *o*-chloro analogue (**8n**, **scheme 2**). Standard conditions failed to deliver the desired *N*-Boc-protected piperidinol intermediate from **3m**, instead producing the biphenyl piperidinol (**5m**). Whilst unintended, this molecule would still provide additional information to our study and was *N*-Boc deprotected to give **6m**, followed by *N*-alkylation with **7a** using conditions outlined previously, to furnish biphenyl analogue (**8m**). In contrast, the desired *o*-chloro analogue was accessed in three steps using an alternative approach (**scheme 2**). Grignard addition of **3m** to **4** yielded *o*-chlorophenyl piperidinol intermediate **5n**, which underwent *N*-Boc deprotection to give **6n**. Final *N*-alkylation with **7a**, furnished **8n**.

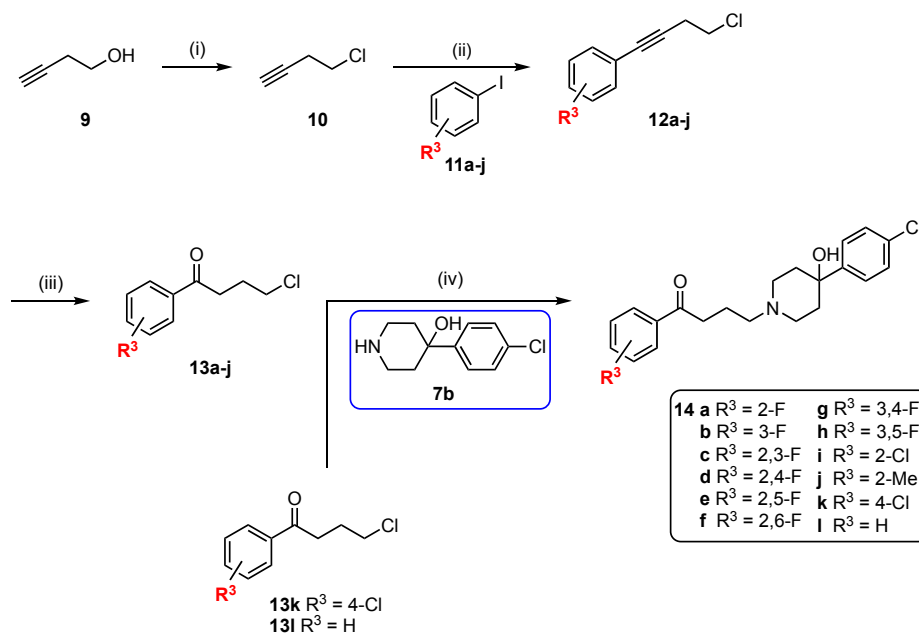
**Scheme 2. Synthesis of biphenyl side-product and *ortho*-Cl analogues of **1**<sup>a</sup>**



<sup>a</sup>Reagents and conditions: (i) *n*-BuLi, THF, -78 °C, 6 h, 55% (**5m**); (ii) Mg, I<sub>2</sub>(cat.), Et<sub>2</sub>O, 0 °C – reflux, 3 h, 54% (**5n**); (iii) HCl, 1,4-dioxane, rt, 2 h, 72-96% (**6m**, **6n**); (iii) NaHCO<sub>3</sub>, KI, toluene, reflux, 24 h, 62-76% (**8m**, **8n**).

*Variation of the *p*-fluorophenyl moiety of 1.* To investigate positional effects of fluorine substitution on the butyrophenone phenyl ring on the kinetics of **1**, we generated analogues with all possible mono and di-fluoro substituents (2-F (**14a**);<sup>42</sup> 3-F (**14b**);<sup>42</sup> 2,3-diF (**14c**); 2,4-diF (**14d**); 2,5-diF (**14e**); 2,6-diF (**14f**); 3,4-diF (**14g**);<sup>42</sup> 3,5-diF (**14h**), as well as two *ortho*-substituted analogues (2-Cl (**14i**) and 2-Me (**14j**)), a *para*-substituted analogue (4-Cl (**16k**))<sup>43</sup> and a *des*-fluoro variant (**14l**).<sup>41</sup> As detailed in **scheme 3**, commercially available 3-butynol (**9**) was treated with SOCl<sub>2</sub> and catalytic pyridine at reflux temperature, followed by distillation to afford 4-chlorobut-1-yne (**10**).<sup>42</sup> The appropriate iodobenzene (**11a-j**) was then employed in a Pd-catalysed Sonogashira cross-coupling reaction<sup>42</sup> with **10**, affording the corresponding internal aryl alkynes (**12a-j**). Next, we utilised a TfOH-catalysed metal-free regioselective Markovnikov-type hydration protocol<sup>44</sup> with 2,2,2-trifluoroethanol as solvent in the presence of H<sub>2</sub>O, furnishing the corresponding aryl ketones (**13a-j**). Finally, *N*-alkylation of commercially available key intermediate **7b** with each synthesised alkyl chloride (**13a-b**, **13d-e**, **13g-j**) furnished final analogues **14a-b**, **14d-e**, and **14g-j**. Alternatively, 4-chloro-1-(4-chlorophenyl)butan-1-one (**13l**) was accessed via Friedel-Crafts acylation, followed by *N*-alkylation of **7b** to afford **14k**. Finally, commercially available 4-chloro-1-phenylbutan-1-one (**13l**) was aminated with **7b** to afford the *des*-fluoro analogue **14l**.

**Scheme 3. Synthesis of analogues of 1 with modification to *p*-fluorophenyl moiety<sup>a</sup>**

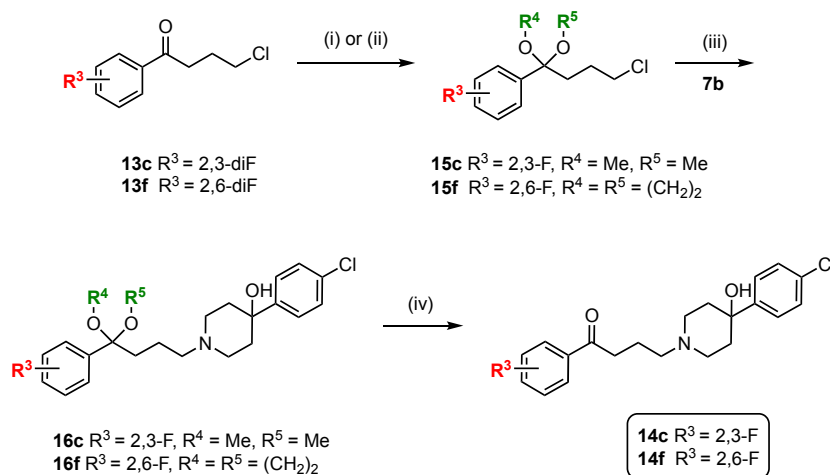


<sup>a</sup>Reagents and conditions: (i) SOCl<sub>2</sub>, pyridine, 0 °C – reflux, 30 min, 82%; (ii) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, CuI, Et<sub>3</sub>N, 1,4-dioxane, 50 °C, 1-3 h, 45-85% (**12a-j**); (iii) TfOH, H<sub>2</sub>O, CF<sub>3</sub>CH<sub>2</sub>OH, 60 °C, 3-8 h, 50-90% (**13a-j**); (iv) NaHCO<sub>3</sub>, KI, toluene, reflux, 24 h, 50-82% (**14a-b, d-e, g-l**); **14c** and **14f** were detected but unable to be isolated in appreciable yield.

The synthesis of analogues containing 2,3-difluorophenyl (**14c**) and 2,6-difluorophenyl (**14f**) substituents were problematic. When attempting to *N*-alkylate key intermediate **7b** with the corresponding alkyl halides (**13c**, **13f**) major side-products due to a competing S<sub>N</sub>Ar reaction were observed, making purification of the target compounds by FCC and preparative HPLC extremely challenging. These side-products are believed to arise due to activation of the position *ortho* to the ketone moiety, when a fluoro-substituent is present. To circumvent the S<sub>N</sub>Ar reaction, syntheses of the affected analogues were modified to incorporate ketal protection/deprotection of the ketone, permitting nucleophilic displacement of the alkyl halide only (**scheme 4**). Beginning with ketal protection of **13c**, we employed a *p*TsOH-catalysed reaction with trimethyl orthoformate in MeOH at room temperature, to afford the corresponding dimethyl ketal (**15c**). Alternatively, **13f** was reacted with 1,2-ethanediol in the presence of catalytic *p*TsOH in toluene under Dean-Stark conditions, to afford the corresponding 1,3-dioxolane (**15f**). These compounds were then subjected to nucleophilic displacement using **7b** to furnish **16c** and **16f**, followed by acid-catalysed hydrolysis in acetone at reflux, affording final compounds **14c** and **14f**.

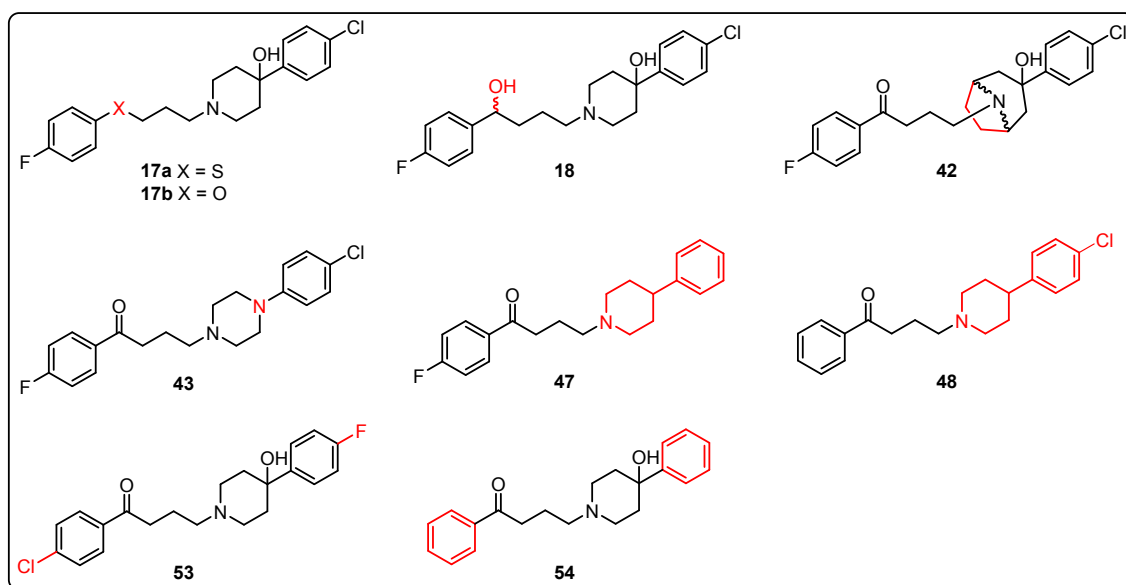


**Scheme 4. Synthesis of 2,3- and 2,6-difluoro analogues of 1 using various protection strategies<sup>a</sup>**



<sup>a</sup>Reagents and conditions: (i) trimethylorthoformate, *p*-TsOH.H<sub>2</sub>O, MeOH, rt, 12 h, 77% (**15c**); (ii) ethylene glycol, *p*-TsOH.H<sub>2</sub>O, toluene, reflux (Dean-Stark), 16 h, 83% (**15f**); (iii) NaHCO<sub>3</sub>, KI, toluene, reflux, 24 h, 71-77% (**16c**, **16f**); (iv) *p*-TsOH.H<sub>2</sub>O, 15:1 acetone/H<sub>2</sub>O, reflux, 48 h, 76-82% (**14c**, **14f**).

*Variation of ketone and linker moiety of 1.* We focused on replacement of the ketone group of **1** with a range of moieties, including ether, thioether and the corresponding carbinol (racemic). The ether- and thioether-variants of **1** were accessed using a literature procedure in three steps<sup>45</sup> (**17a-b**, Figure 3, Supplementary Scheme 1), whilst the corresponding secondary alcohol was afforded in two-steps also through literature procedure (**18**, Figure 3)<sup>46</sup> (Supplementary Scheme 2).

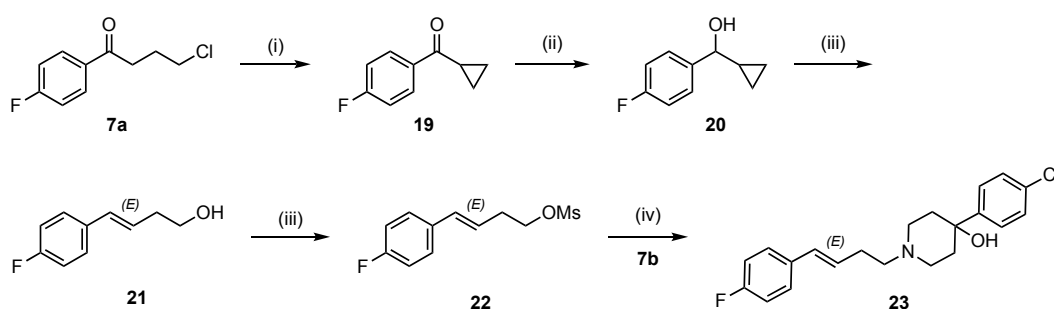


**Figure 3. Literature analogues of 1 synthesised using various methodologies.** Ether- and thioether analogues<sup>45</sup> (**17a-b**, respectively); racemic alcohol analogue<sup>46</sup> (**18**); tropanyl analogue<sup>34</sup> (**42**);

piperazinyl analogue<sup>34</sup> (**43**); phenyl- and *p*-chlorophenylpiperidine analogues<sup>38,47</sup> (**47-48**, respectively); reverse substitution analogue<sup>48</sup> (**53**); *des*-halo analogue<sup>41</sup> (**54**).

Our subsequent focus was to further understand the effect and importance of geometry on the kinetics of conformationally restricted analogues of **1**, via synthesis of both olefin geometric isomers. The *trans*-olefin **23** was accessed through a five step chemical synthesis as outlined in **scheme 5**, beginning with a one-pot base-mediated intramolecular enolate alkylation of key intermediate **7a**, to furnish cyclopropyl(4-fluorophenyl)methanone (**19**) in quantitative yield. Subsequent reduction with NaBH<sub>4</sub> afforded secondary alcohol **20**, followed by a vanadyl acetylacetonate-catalysed stereoselective isomerisation in chlorobenzene to yield (*E*)-4-(4-fluorophenyl)but-3-en-1-ol (**21**) as the exclusive geometric isomer. Compound **21** was subsequently activated with methanesulfonyl chloride to give mesylate **22**. This was followed by *N*-alkylation of **7b** using standard conditions, affording final olefin analogue **23**.

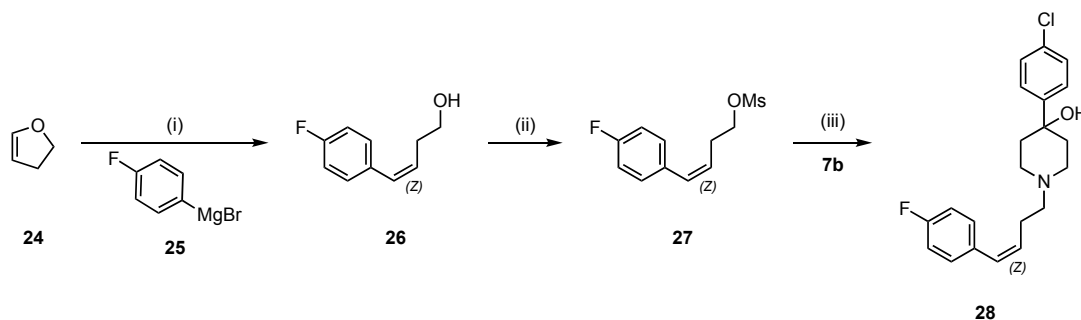
#### Scheme 5. Synthesis of *trans*-olefin analogue of **1**<sup>a</sup>



<sup>a</sup>Reagents and conditions: (i) NaOH, MeOH, 60 °C, 5 h, quantitative; (ii) NaBH<sub>4</sub>, MeOH, 0 °C – rt, 3 h, 99%; (iii) VO(acac)<sub>2</sub>, BHT, PhCl, 80 °C, 48 h, 35%; (iv) MsCl, DCM, Et<sub>3</sub>N, rt, 3h, 88%; (v) NaHCO<sub>3</sub>, KI, toluene, reflux, 24 h, 82%.

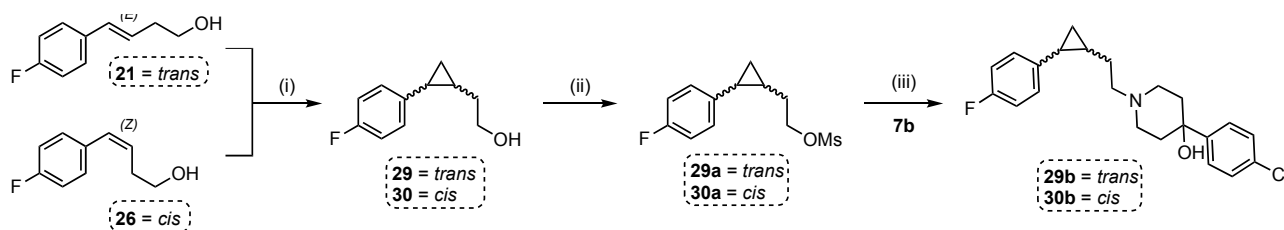
The *cis*-isomer **28**, was accessed through a three-step synthesis as outlined in **scheme 6**. Initially, Ni-catalysed stereoselective arylation of 2,3-dihydrofuran **24** with (4-fluorophenyl)magnesium bromide (**25**) at -30 °C, successfully afforded the *cis*-olefin **26**<sup>49</sup> as the exclusive isomer. This compound was then mesylated using standard conditions to afford **27**, followed by *N*-alkylation of **7b** using conditions outlined previously, furnishing **28**. As outlined in **scheme 7**, both *trans* and *cis*-isomers (**21** and **26**, respectively) were treated with diethylzinc and diiodomethane using Simmons-Smith<sup>50</sup> conditions to access the corresponding racemic *trans*- and *cis*-cyclopropanes (**29** and **30**, respectively). This was followed by mesylation to give **29a** and **30a**, and subsequent *N*-alkylation of **7b** to afford racemic **29b** and **30b**.

**Scheme 6. Synthesis of *cis*-olefin analogue of **1**<sup>a</sup>**



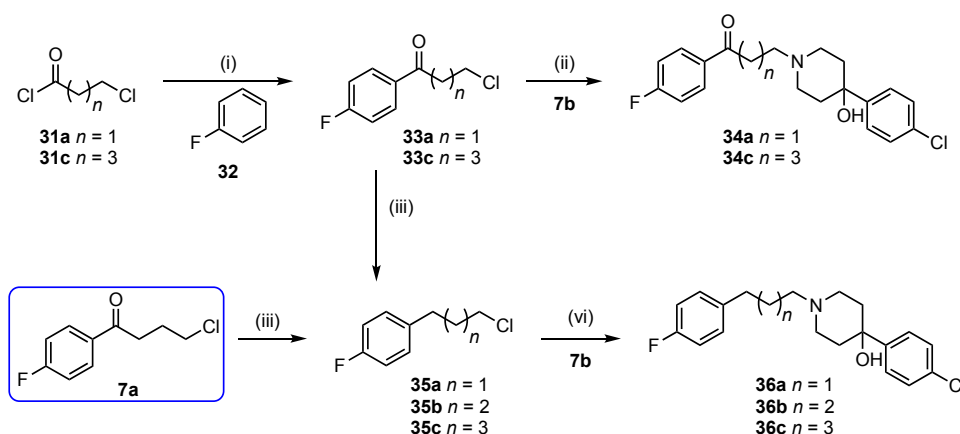
<sup>a</sup>Reagents and conditions: (i) Ni[COD]<sub>2</sub>, 1,3-bis-(2,6-diisopropylphenyl)imidazolium chloride, LiCl, THF, -30 °C, 8 h, 31%; (ii) MsCl, Et<sub>3</sub>N, DCM, rt, 24 h, 90%; (iii) NaHCO<sub>3</sub>, KI, toluene, reflux, 24 h, 75%.

**Scheme 7. Synthesis of both *trans*- and *cis*-cyclopropane enantiomers of **1**<sup>a</sup>**



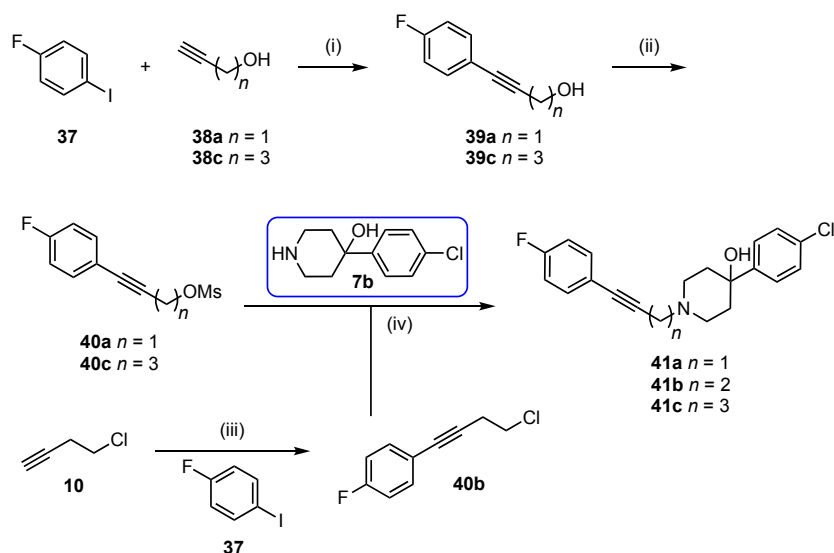
<sup>a</sup>Reagents and conditions: (i) Et<sub>2</sub>Zn, CH<sub>2</sub>I<sub>2</sub>, DCM, 0 °C – rt, 24 h, 95-98% (**29**, **30**); (ii) MsCl, Et<sub>3</sub>N, DCM, rt, 90-95% (**29a**, **30a**); (iii) NaHCO<sub>3</sub>, KI, toluene, reflux, 24 h, 67-70% (**29b**, **30b**).

Next, we focused on the synthesis of both propiophenone and valerophenone analogues of **1** that maintained the ketone functionality (**scheme 8**). Beginning with Friedel-Crafts acylation chemistry, the appropriate commercially available acyl chloride (**31a**, **31c**) was reacted with fluorobenzene **32** in the presence of stoichiometric AlCl<sub>3</sub> to afford the corresponding phenones (**33a**,<sup>51</sup> **33c**<sup>52</sup>). This was followed by *N*-alkylation of **7b** to afford final analogues (**34a**, **34c**<sup>53</sup>). In addition, we wanted to access the 1,3-propylene, 1,4-butylene and 1,5-pentylene analogues of **1** (**scheme 8**). To achieve this, phenones **33a**, **7a**, and **33c** were treated with triethylsilane in TFA, followed by evaporation and direct chromatographic purification to furnish the corresponding reduced intermediates **35a-c**. Lastly, *N*-alkylation of key intermediate **7b** furnished alkane analogues **36a-c**.

Scheme 8. Synthesis of ketone and alkane analogues of 1<sup>a</sup>

<sup>a</sup>Reagents and conditions: (i) AlCl<sub>3</sub>, DCM, 0 °C – rt, 6 h, 85% (**33a**, **33c**); (ii) NaHCO<sub>3</sub>, KI, toluene, reflux, 24 h, 75-90% (**34a**, **34c**); (iii) triethylsilane, trifluoroacetic acid, 0 °C, 2-3 h, 75-85% (**35a-c**); (iv) NaHCO<sub>3</sub>, KI, toluene, reflux, 24 h, 72-91% (**36a-c**).

To assess analogues of **1** incorporating internal aromatic alkynes (**scheme 9**), 1-fluoro-4-iodobenzene (**37**) was initially subjected to modified Sonagashira conditions<sup>54</sup> using commercially available alcohols (**38a**, **38c**), affording aryl alkynes (**39a**,<sup>55</sup> **39c**). Next, the alcohols were converted to their corresponding mesylates (**40a**,<sup>56</sup> **40c**), followed by *N*-alkylation of **7b** with the appropriate mesylate to afford the corresponding final propynyl and pentynyl analogues (**41a** and **41c**, respectively). The butynyl analogue **41b** was accessed via the cross-coupling reaction between key intermediate **10** and 1-fluoro-4-iodobenzene (**37**), providing aryl alkyne intermediate **40b**, which underwent amination with **7b**.

Scheme 9. Synthesis of internal alkyne analogues of 1<sup>a</sup>

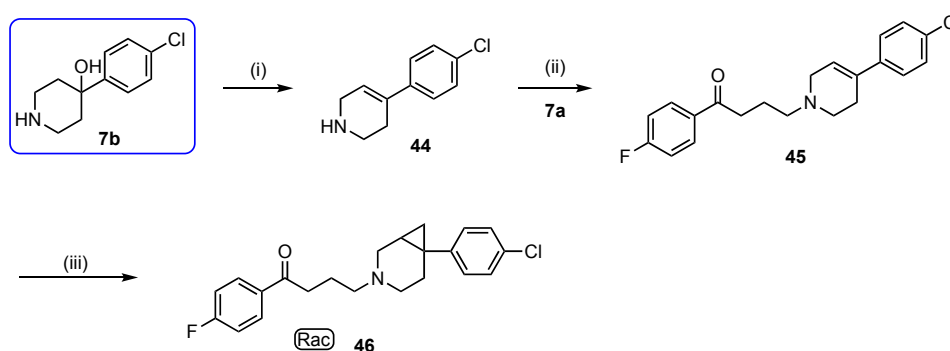
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<sup>a</sup>Reagents and conditions: (i) Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, CuI, Et<sub>3</sub>N, MeCN, rt, 5 h, 94% (**39a**, **39c**); (ii) methanesulfonyl chloride, Et<sub>3</sub>N, DCM, 24 h, 93% (**40a**, **40c**); (iii) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Et<sub>3</sub>N, 1,4-dioxane, 50 °C, 3 h, 75% (**40b**); (iii) NaHCO<sub>3</sub>, KI, toluene, reflux, 24 h, 68-74% (**41a-c**).

*Variation of the piperidinol moiety of 1.* Modification to the piperidinol moiety of **1** was another key interest in our SKR investigation. To observe the kinetic effect of introducing an ethylene bridge on the piperidinol, we synthesised tropanyl analogue **42** according to a literature procedure<sup>36</sup> (Figure 3, Supplementary Scheme 3), utilising *n*-BuLi in place of Grignard chemistry. We then sought to modify the tertiary alcohol group, beginning with synthesis of piperazinyl analogue **43** (Figure 3). This compound was accessed in two steps *via* the construction of the piperazine ring and subsequent *N*-alkylation with **7a**<sup>34</sup> (Supplementary Scheme 4).

Removing the tertiary alcohol within **1** to generate the corresponding 3,6-dihydropyridine (**45**) was our next focus, as well as further elaboration of the olefin to yield the corresponding cycloalkane derivative (**46**) (**scheme 10**). Key piperidinol intermediate **7b** was firstly dehydrated using neat concentrated HCl followed by an alkaline work-up to afford the 1,2,3,6-tetrahydropyridine (**44**). Displacement of **7a** with **44** furnished olefin **45**.<sup>57</sup> This molecule was subsequently treated using Simmons-Smith<sup>50</sup> conditions, as outlined previously, to afford the corresponding cyclopropane analogue **46**.

### Scheme 10. Synthesis of dihydropyridyl and fused cyclopropane analogues of **1**<sup>a</sup>

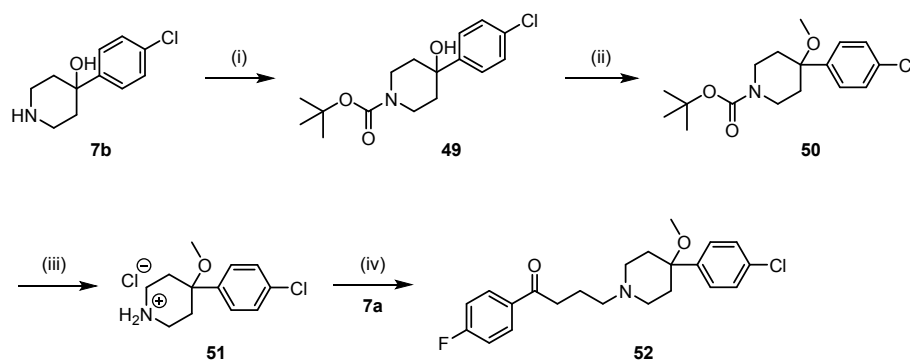


Reagents and conditions: (i) HCl (conc.), reflux, 5 h, quantitative; (ii) NaHCO<sub>3</sub>, KI, toluene, reflux, 24 h, 65% (**45**); (iii) Et<sub>2</sub>Zn, CH<sub>2</sub>I<sub>2</sub>, DCM, 0 °C – rt, 24 h, 75% (**46**).

In addition, we synthesised two analogues of **1** containing modified phenyl piperidine (**47**)<sup>47</sup> and *p*-chlorophenyl piperidine (**48**)<sup>38</sup> cores (Figure 3), of which their synthesis is detailed in Supplementary Scheme 5.

Further emphasis was placed on the tertiary alcohol contained within **1**, where we sought to assess the impact of *O*-methylation (**scheme 11**). *N*-Boc-protection of key intermediate **7b** gave **49**, followed by *O*-alkylation with methyl iodide to afford the corresponding methyl ether **50**. This was followed by *N*-Boc-deprotection to give the secondary amine hydrochloride **51**. Final *N*-alkylation with key intermediate **7a** afforded compound **52**.

### Scheme 11. Synthesis of methyl ether analogue of **1**<sup>a</sup>



<sup>a</sup>Reagents and conditions: (i) Boc<sub>2</sub>O, Et<sub>3</sub>N, DCM, rt, 4 h, 85%; (ii) NaH, MeI, DMF, rt, 24 h, 80%; (iii) HCl, 1,4-dioxane, rt, 2 h, 95%; (iv) NaHCO<sub>3</sub>, KI, toluene, reflux, 24 h, 70%.

*Dual modification to halo-aryl moieties of 1.* Recent molecular dynamics (MD) simulations by Thomas *et al.*<sup>58</sup> were used to understand the ligand binding pathways of **1** and **2** at the D<sub>2</sub>R/D<sub>3</sub>R. The final stable pose of **1** was shown to occupy the same space as predicted in a number of molecular docking studies;<sup>59-61</sup> however, the molecular orientation was contradictory to these data by 180°, with the butyrophenone moiety buried most deeply in the receptor. Therefore, and due to confounding studies regarding the orientation of **1** at the D<sub>2</sub>R, it was of interest to investigate the kinetic effects of modifying both phenyl moieties of **1** simultaneously. Accordingly, we synthesised a further two structural analogues of **1** (Figure 3). These modifications included swapping both aromatic termini (**53**), as well as removal of these aromatic substituents (**54**). **53** was synthesised according to a literature procedure following Friedel-Crafts acylation and *N*-alkylation (Figure 3, Supplementary Scheme 6).<sup>43</sup> Compound **54** was similarly accessed through literature methods (Figure 3, Supplementary Scheme 7).<sup>41</sup>

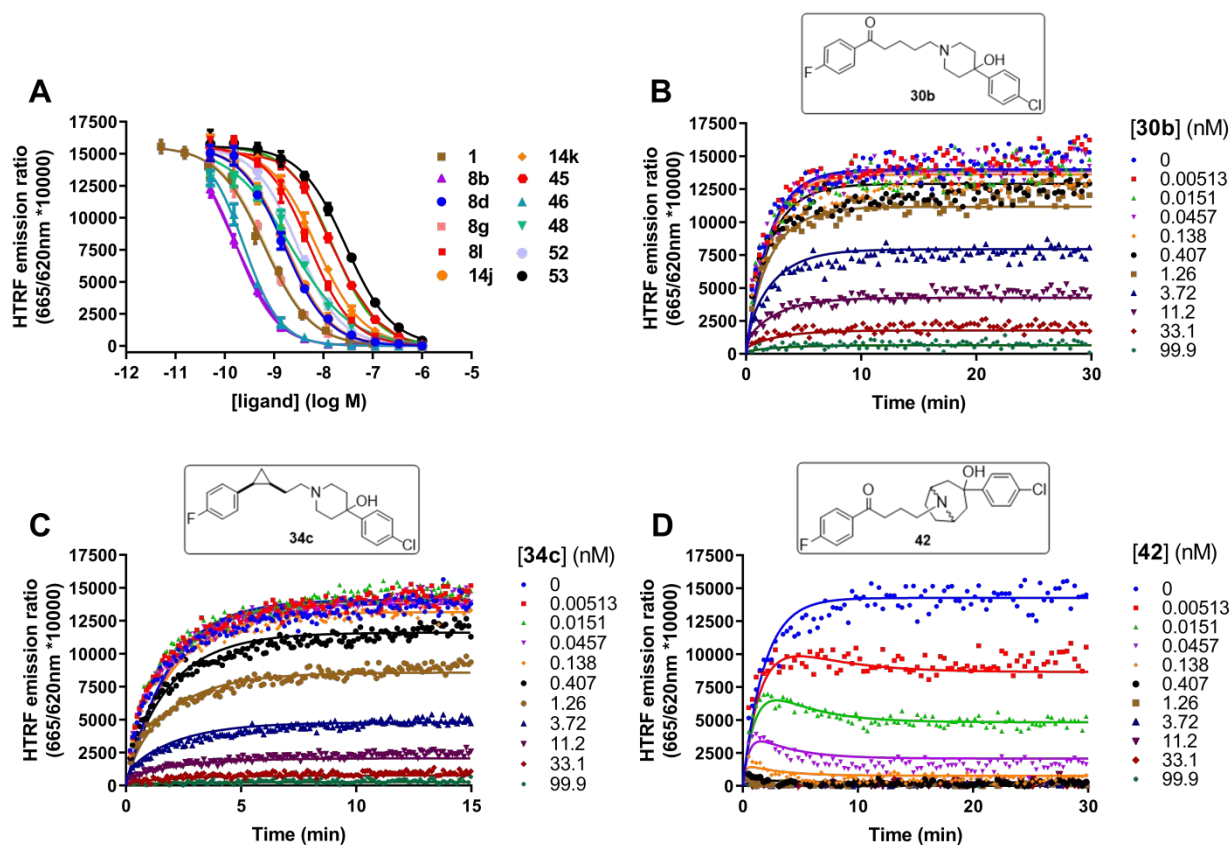
**Pharmacology.** *Characterisation of PPHT-red binding.* Specific equilibrium binding of the agonist PPHT-red (Cisbio Bioassays) to human D<sub>2L</sub> receptor (hD<sub>2L</sub>R) was saturable and best described by the interaction of PPHT-red with a single population of binding sites (Supplementary Figure 1A). From these studies, the equilibrium dissociation constant ( $K_d$ ) of the fluorescent ligand was determined to be  $43.2 \pm 0.37$  nM. The binding kinetics of PPHT-red were characterised by monitoring the observed

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3 association rates at six different ligand concentrations (Supplementary Figure 1B). The observed rate  
4 of association was related to PPHT-red concentration in a linear fashion (Supplementary Figure 1C).  
5 Kinetic rate parameters for PPHT-red were calculated by globally fitting the association time courses,  
6 resulting in a  $k_{\text{on}}$  of  $9.21 \pm 0.24 \times 10^6 \text{ M}^{-1} \text{ min}^{-1}$  and  $k_{\text{off}}$  of  $0.35 \pm 0.01 \text{ min}^{-1}$ . The resulting  $K_{\text{d}}$  ( $k_{\text{off}}/k_{\text{on}}$ )  
7 of  $46.3 \pm 0.15 \text{ nM}$  was comparable to that obtained from equilibrium studies.  
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12 *Characterisation of kinetic binding parameters of unlabelled analogues of 1 at the D<sub>2</sub>R.* The  
13 competition association binding method allows the characterisation of the kinetic rate parameters of  
14 unlabelled compounds ( $k_{\text{on}}$ ,  $k_{\text{off}}$ ) and the subsequent calculation of a kinetically derived ( $k_{\text{on}}/k_{\text{off}}$ )  
15 equilibrium dissociation constant ( $K_{\text{d}}$ ). The binding affinity of the various ligands for the hD<sub>2L</sub>R were  
16 measured at equilibrium at 37 °C in a buffer containing 5'-guanylyl imidodiphosphate (GppNHp) (0.1  
17 mM) to ensure that antagonist and tracer binding only occurred to the G protein-uncoupled form of  
18 the receptor.  $K_{\text{i}}$  values for compound **1**, and the 50 structural analogues studied are summarised in  
19 Tables 1-5, and representative competition curves are presented in Figure 4A. In these tables we have  
20 separated the analogues into five groups, those that have been modified at the *para*-chlorophenyl,  
21 *para*-fluorophenyl, piperidinol, ketone/alkyl linker, and concurrent phenyl ring moiety modification,  
22 as indicated in Figure 2. Representative kinetic competition curves for selected analogues are in  
23 Figures 4B-D. Association curves for PPHT-red alone and in the presence of competitor were globally  
24 fitted to Eq. 3 enabling the calculation of both  $k_{\text{on}}$  (k3) and  $k_{\text{off}}$  (k4) for each of the ligands, as reported  
25 in Tables 1-5. To validate the rate constants, we compared the kinetically derived dissociation  
26 constant ( $K_{\text{d}}$ ) values ( $k_{\text{on}}/k_{\text{off}}$ ) with the dissociation constant ( $K_{\text{i}}$ ) obtained from equilibrium  
27 competition binding experiments (Figure 5). There was a good correlation between these two values  
28 for all compounds tested (two-tailed Pearson's correlation  $r^2 = 0.99$ ,  $p < 0.0001$ ), indicating that the  
29 parameters determined in the kinetic assay were in agreement with those determined at equilibrium.  
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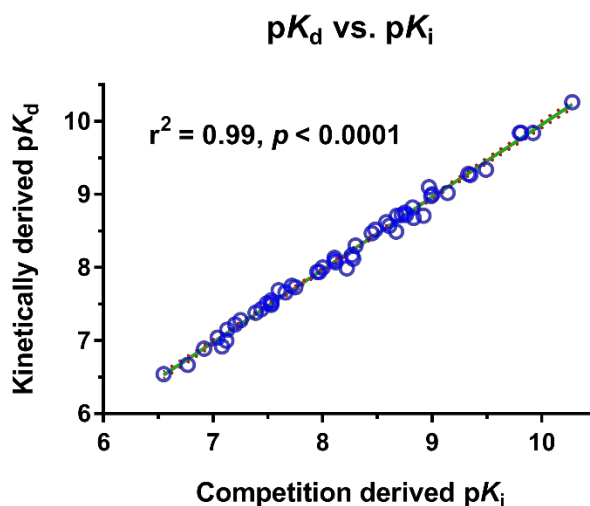
46 *Characterisation of the kinetic profile of 1 at the hD<sub>2L</sub>R.* The equilibrium affinities and kinetic rate  
47 constants of **1** and **2** have recently been determined using the aforementioned TR-FRET assay.<sup>33</sup> Prior  
48 to initiating an investigation into **1**, we also assessed its parameters and determined similar estimates  
49 in agreement with literature<sup>33</sup> ( $k_{\text{off}} = 0.61 \pm 0.04 \text{ min}^{-1}$ ,  $k_{\text{on}} = 1.29 \pm 0.21 \times 10^9 \text{ M}^{-1} \text{ min}^{-1}$ ,  $\text{p}K_{\text{d}} = 9.31$   
50  $\pm 0.05$ , Table 1), validating our experimental conditions and further demonstrating that **1** is indeed a  
51 high affinity, fast  $k_{\text{on}}$ /slow  $k_{\text{off}}$  compound at the hD<sub>2L</sub>R. Kinetic estimates for **1** are outlined in Tables  
52 1-5 and all experimental structure-kinetic data will make specific reference to these data as a  
53 comparison. Furthermore, compounds with fast  $k_{\text{off}}$  values approaching  $>1.0 \text{ min}^{-1}$  were reassessed  
54 using a modified injection protocol, whereby the hD<sub>2L</sub>R membrane homogenates were introduced  
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using an online injector whilst simultaneously measuring TR-FRET binding. This is to avoid any delay between membrane addition and initial TR-FRET measurement, improving the quality of the non-linear fit for compounds with rapid equilibration kinetics and thus increasing our confidence in the rate parameter estimate. Characterisation of **1** using this methodology returned comparable estimates to the offline injection protocol. Additional data acquired for selected compounds using this methodology are located in Tables 2 and 3.



**Figure 4. Equilibrium and competition association binding.** (A) Competition between PPHT-red (12.5 nM) and increasing concentrations of **1** and representative analogues (**8b**, **8d**, **8g**, **8l**, **14j**, **14k**, **45**, **46**, **48**, **52**, **53**) at the hD<sub>2L</sub>R. PPHT-red competition association curves in the presence of (B) **30b**; (C) **34c**; (D) **42**. All binding reactions were performed at 37 °C in the presence of GppNHp (100 μM) with non-specific binding levels determined by inclusion of haloperidol (10 μM). Kinetic and equilibrium data were fitted to the equations described in “Methods” section to calculate  $K_i$ ,  $K_d$ , and  $k_{on}$  and  $k_{off}$  values for the unlabelled ligands: these are summarised in tables 1-5. Data are presented as singlet values from a representative of four.





**Figure 5. Correlating equilibrium and kinetically derived parameters for haloperidol (**1**) and 51 structural analogues at the dopamine D<sub>2</sub> receptor.** Correlation between pK<sub>i</sub> and kinetically derived pK<sub>d</sub> for the 51 test ligands including haloperidol. pK<sub>i</sub> values were taken from PPHT-red competition binding experiments at equilibrium as exemplified in Figure 4A. The values composing the kinetically derived pK<sub>d</sub> ( $k_{\text{off}}/k_{\text{on}}$ ) were taken from competition kinetic association experiments as exemplified in Figures 4B-D. All data used in these plots are detailed in Tables 1-5. Data are presented as mean  $\pm$  S.E.M. from four separate experiments.

*Measurement of the functional activity of analogues of 1.* **1** is a hD<sub>2L</sub>R antagonist. It is possible, however, that modification of this structure may yield agonists. We measured the activity of all analogues in an assay measuring inhibition of intracellular cAMP production stimulated by forskolin using a bioluminescence resonance energy transfer (BRET) biosensor. This is a measurement of Gi/o G protein activation by the hD<sub>2L</sub>R. We performed two types of measurement. In the first, we tested the ability of a 10  $\mu$ M concentration of each analogue alone to activate the hD<sub>2L</sub>R and in the second we measured the ability of each analogue to antagonise the action of an EC<sub>80</sub> (30 nM) concentration of the agonist dopamine. The results of these experiments revealed that none of the compounds displayed agonist activity apart from **47** which displayed 20% of the maximal effect of dopamine at a concentration of 10  $\mu$ M (Supplementary Table 1). All compounds antagonised the effect of dopamine to a basal (unstimulated) level except for **47** which reduced the effect of dopamine to a level consistent with the intrinsic activity determined in the agonist assay protocol (Supplementary Table 1).

*Kinetic effects of variation of the para-chlorophenyl moiety of 1.* Initially focusing on modification of the para-chlorophenyl moiety of **1**, we sought to assess the kinetic effect of all possible mono (**8a**,

**8n**) and di-chlorophenyl substituents (**8b-g**), as well as variation of the *para*- substituent (**8h-m**) through the synthesis of 14 structural analogues (Table 1). These compounds exhibited a 17-fold variation in affinity, which was driven by interesting changes in kinetic parameters, spanning a >10-fold variation in association rate ( $k_{\text{on}} = 1.22 \pm 0.20 \times 10^8 \text{ M}^{-1} \text{ min}^{-1}$  to  $2.95 \pm 0.30 \times 10^9 \text{ M}^{-1} \text{ min}^{-1}$ ), and a ~4-fold variation in dissociation rate ( $k_{\text{off}} = 0.30 \pm 0.01 \text{ min}^{-1}$  to  $k_{\text{off}} = 1.25 \pm 0.09 \text{ min}^{-1}$ ).

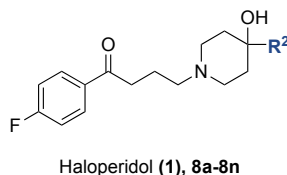
The data show that analogues lacking an electron withdrawing group (EWG) (chloro) substituent at the *meta*- and *para*-positions have reduced binding affinity, and this loss is mirrored by a decrease in  $k_{\text{on}}$  and an increase in  $k_{\text{off}}$  relative to **1**. For example, the *ortho*-Cl analogue (**8n**) displayed an ~8-fold reduction in affinity resulting from a decreased  $k_{\text{on}}$  and increased  $k_{\text{off}}$  ( $k_{\text{on}} = 3.54 \pm 0.16 \times 10^8 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 1.16 \pm 0.11 \text{ min}^{-1}$ ). This was also evident for the 2,6-diCl analogue (**8e**) losing ~6-fold affinity, also mediated by a slowed association and increased dissociation rate ( $k_{\text{on}} = 5.07 \pm 0.47 \times 10^8 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 1.05 \pm 0.05 \text{ min}^{-1}$ ). This trend continued with the *des*-Cl analogue **8h**, as it also revealed a similar change in rate constants ( $k_{\text{on}} = 1.22 \pm 0.20 \times 10^8 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 1.02 \pm 0.10 \text{ min}^{-1}$ ).

Addition of a strong electron donating group (EDG) (*N,N*-dimethylamino, **8k**) results in a >10-fold decrease in affinity ( $\text{p}K_{\text{d}} = 8.12 \pm 0.04$ ) and again appears to be driven by a decrease in  $k_{\text{on}}$  and an increase in  $k_{\text{off}}$  ( $k_{\text{on}} = 1.64 \pm 0.12 \times 10^8 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 1.25 \pm 0.09 \text{ min}^{-1}$ ). Furthermore, other analogues bearing weakly electron donating substituents (e.g. *para*-tolyl analogue **8i**) saw a smaller decrease in affinity (~3-fold), similarly mediated by a change in both rate constants towards a slow on, fast off profile ( $k_{\text{on}} = 1.00 \pm 0.06 \times 10^9 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 0.98 \pm 0.02 \text{ min}^{-1}$ ).

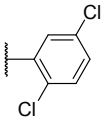
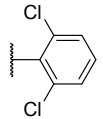
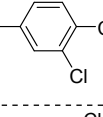
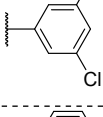

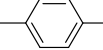
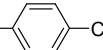

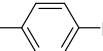
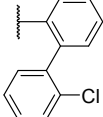
Conversely, insertion of a *meta*-Cl substituent (exemplified by **8a**), despite decreasing affinity ~8-fold, acts only to decrease the  $k_{\text{on}}$  whilst having no effect on  $k_{\text{off}}$  ( $k_{\text{on}} = 3.62 \pm 0.94 \times 10^8 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 0.64 \pm 0.10 \text{ min}^{-1}$ ), and this similarly applies to *para*-Cl substituents. The trend continued with 2,4-dichloro (**8c**) and 2,5-dichloro (**8d**) analogues, losing ~7-fold and 3-fold affinity, respectively. Again, this loss was largely mediated by a decreased association rate (**8c**:  $k_{\text{on}} = 2.87 \pm 0.56 \times 10^8 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 0.70 \pm 0.16 \text{ min}^{-1}$ ; **8d**:  $k_{\text{on}} = 5.29 \pm 0.36 \times 10^8 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 0.56 \pm 0.06 \text{ min}^{-1}$ ), relative to **1**. Interestingly, when the *ortho*- and *meta*-chloro substituents are combined (2,3-diCl analogue (**8b**)), affinity increases ~5-fold, and this is now predominantly mediated by both a ~2-fold increase in association rate and ~2-fold decrease in dissociation rate ( $\text{p}K_{\text{d}} = 9.84 \pm 0.08$ ,  $k_{\text{on}} = 2.20 \pm 0.30 \times 10^9 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 0.30 \pm 0.01 \text{ min}^{-1}$ ). Substitution with a strongly electron withdrawing *para*-CF<sub>3</sub> substituent (**8j**) maintained affinity, with no effect on the kinetic profile of the analogue relative to **1** ( $k_{\text{on}} = 1.36 \pm 0.07 \times 10^9 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 0.62 \pm 0.02 \text{ min}^{-1}$ ). Furthermore, replacing the *para*-chloro substituent for a *para*-fluoro (**8l**) predominantly decreased  $k_{\text{on}}$ .

All compounds bearing an *ortho*-substituent (**8n**, **8c**, **8d**, **8e**, **8m**), with the exception of **8b**, displayed a reduced on-rate, indicating potential sensitivity to steric bulk at this position through resulting rotation of the phenyl group relative to the piperidinol. Interestingly, the 2,3-diCl analogue (**8b**), contains the privileged 2,3-dichlorophenylpiperidine pharmacophore known to confer high affinity in other molecules at both the D<sub>2</sub>-like and 5HT receptors. This particular substitution pattern may therefore support a different binding mode. Both increased lipophilicity and steric bulk are preferred at the *meta*- and *para*-positions of the ring, with the 4-position being optimal, which is supported by **8h** (4-fluoro) and **8l** (4-H) being less favoured. For the off rate, the substituent effect is reversed in terms of increasing  $k_{\text{off}}$  ( $o > m > p$ ). This parameter appears to be less impacted by steric factors, and instead the electronics may play a greater role (**8k**, **8i**, **8h**). In summary, these initial data provide insight into how structural modifications of haloperidol (**1**) impact upon individual kinetic parameters, demonstrating the potential for differential modification of rate constants towards a slow on, fast off profile, depending on the position and nature of the aryl substituents of the 4-phenylpiperidin-4-ol moiety.

**Table 1. Kinetic binding parameters for haloperidol (**1**) and unlabelled analogues of **1** for human D<sub>2L</sub> receptors estimated using TR-FRET assay.**



	R <sup>2</sup>	$k_{\text{on}}$ (M <sup>-1</sup> min <sup>-1</sup> ) <sup>a</sup>	$k_{\text{off}}$ (min <sup>-1</sup> ) <sup>a</sup>	$t_{1/2}$ (min) <sup>a</sup>	pK <sub>d</sub> <sup>a</sup>	pK <sub>i</sub> <sup>b</sup>
<b>1</b>		1.29 ± 0.21 × 10 <sup>9</sup>	0.61 ± 0.04	1.15 ± 0.08	9.31 ± 0.05	9.33 ± 0.09
<b>8a</b>		6.32 ± 0.94 × 10 <sup>8</sup>	0.64 ± 0.10	1.19 ± 0.22	9.00 ± 0.05	9.00 ± 0.03
<b>8n</b>		3.54 ± 0.16 × 10 <sup>8</sup>	1.16 ± 0.11	0.61 ± 0.05	8.49 ± 0.03	8.67 ± 0.09
<b>8b</b>		2.20 ± 0.30 × 10 <sup>9</sup>	0.30 ± 0.01	2.28 ± 0.04	9.84 ± 0.08	9.92 ± 0.03
<b>8c</b>		2.87 ± 0.56 × 10 <sup>8</sup>	0.70 ± 0.16	1.15 ± 0.24	8.62 ± 0.02	8.58 ± 0.01

1							
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3							
4	<b>8d</b>		$5.29 \pm 0.36 \times 10^8$	$0.56 \pm 0.06$	$1.27 \pm 0.11$	$8.98 \pm 0.02$	$8.99 \pm 0.01$
5							
6							
7							
8	<b>8e</b>		$5.07 \pm 0.47 \times 10^8$	$1.05 \pm 0.05$	$0.67 \pm 0.05$	$8.68 \pm 0.04$	$8.83 \pm 0.08$
9							
10							
11							
12	<b>8f</b>		$2.95 \pm 0.30 \times 10^9$	$0.42 \pm 0.02$	$1.67 \pm 0.11$	$9.84 \pm 0.03$	$9.81 \pm 0.04$
13							
14							
15							
16	<b>8g</b>		$6.58 \pm 0.67 \times 10^8$	$0.43 \pm 0.02$	$1.94 \pm 0.30$	$9.27 \pm 0.06$	$9.35 \pm 0.04$
17							
18							
19	<b>8h</b>		$1.22 \pm 0.20 \times 10^8$	$1.02 \pm 0.10$	$0.71 \pm 0.08$	$8.07 \pm 0.04$	$8.12 \pm 0.02$
20							
21							
22	<b>8i</b>		$1.00 \pm 0.06 \times 10^9$	$0.98 \pm 0.11$	$0.73 \pm 0.07$	$9.02 \pm 0.03$	$9.14 \pm 0.08$
23							
24	<b>8j</b>		$1.36 \pm 0.07 \times 10^9$	$0.62 \pm 0.02$	$1.12 \pm 0.04$	$9.34 \pm 0.04$	$9.49 \pm 0.10$
25							
26							
27	<b>8k</b>		$1.64 \pm 0.12 \times 10^8$	$1.25 \pm 0.09$	$0.56 \pm 0.03$	$8.12 \pm 0.04$	$8.28 \pm 0.09$
28							
29							
30	<b>8l</b>		$2.61 \pm 0.24 \times 10^8$	$0.78 \pm 0.08$	$0.92 \pm 0.11$	$8.52 \pm 0.02$	$8.48 \pm 0.01$
31							
32							
33	<b>8m</b>		$3.25 \pm 0.77 \times 10^8$	$0.82 \pm 0.11$	$0.89 \pm 0.12$	$8.57 \pm 0.05$	$8.61 \pm 0.03$
34							
35							

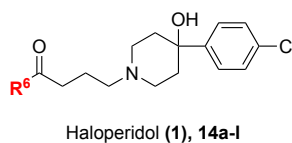
<sup>a</sup>The rate constants  $k_{\text{off}}$ ,  $k_{\text{on}}$ , the half-life ( $t_{1/2}$ ), and the kinetically derived  $pK_d$  were obtained from competition kinetic association experiments using PPHT-red. <sup>b</sup> $pK_i$  values were taken from PPHT-red competition binding experiments at equilibrium. Data are presented as mean  $\pm$  S.E.M. from four experiments performed in singlet. \*Completed using online injection protocol.

*Kinetic effects of variation of the para-fluorophenyl moiety of 1.* We examined the effect of fluoro substituents at both *ortho*-(**14a**) and *meta*-(**14b**) positions of the phenone moiety, as well as all possible di-fluorophenyl substituents (**14c-h**), together with three additional *ortho*-analogues (*o*-Cl (**14i**), *o*-CH<sub>3</sub> (**14j**), *o*-Cl (**14k**)), and an unsubstituted analogue (**14l**). Modification to this moiety caused large decreases in affinity relative to **1**, spanning over 100-fold from  $pK_d = 6.67 \pm 0.01$  (**14h**) to  $pK_d = 8.75 \pm 0.02$  (**14l**), and is associated with a wide range of association and dissociation rate constants. These losses in affinity are mediated through concurrent changes in both  $k_{\text{on}}$  and  $k_{\text{off}}$ . This applies to all but the *para*-Cl analogue (**14k**), as it lost affinity 10-fold relative to **1**, but this was largely mediated by a decreased rate of association ( $k_{\text{on}} = 1.38 \pm 0.05 \times 10^8$ ,  $k_{\text{off}} = 0.70 \pm 0.03 \text{ min}^{-1}$ ).

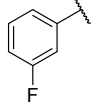
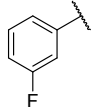
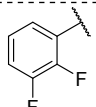
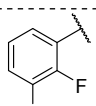
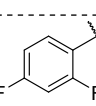
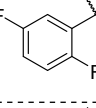
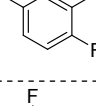
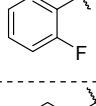
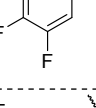
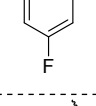
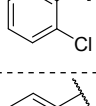
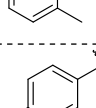

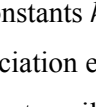
The *des*-fluoro analogue (**14l**) maintained the highest affinity, and similar to the previous series, this was facilitated by a shift in both rate constants ( $pK_d = 8.75 \pm 0.02$ ,  $k_{on} = 6.33 \pm 1.06 \times 10^8 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{off} = 1.12 \pm 0.18 \text{ min}^{-1}$ ). Of the three *ortho*-substituted analogues (**14a** (*m*-F), **14i** (*m*-Cl)), **14j** (*m*-CH<sub>3</sub>)), the fluoro substituent was the least favourable in terms of affinity, decreasing ~13-fold relative to **1**, whereas the *ortho*-tolyl substituent only reduces affinity by 6-fold. However, these changes are likewise mediated by a decreased association rate and increased rate of dissociation. Notably, the *m*-Cl (**14i**) and *m*-CH<sub>3</sub> (**14j**) substituents have similar Van der Waals radii, but very different electronic effects, thus highlighting a steric factor as being important. The *meta*-fluoro substituted analogue (**14b**) also dramatically reduced the affinity and was similarly driven by a decreased  $k_{on}$  and increased  $k_{off}$  ( $k_{on} = 2.55 \pm 0.27 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{off} = 1.08 \pm 0.21 \text{ min}^{-1}$ ).

Di-fluoro substitution of the phenyl ring revealed no clear SKR and commonly caused substantial losses in binding affinity. However, unlike the previous chloro series, greater increases in the rate of dissociation were observed. Interestingly, using our online injection protocol, we identified compounds with even slower  $k_{on}$  values relative to **2**, coupled with equal to or faster  $k_{off}$  values, despite their affinities being lower than **2**. For example, the 2,3-(**14c**), 2,4-(**14d**) and 2,5-difluoro (**14e**) analogues of **1** ( $pK_d = 7.28 \pm 0.04$ ,  $6.92 \pm 0.05$  and  $6.85 \pm 0.04$ , respectively) showed dissociation rates faster than any compound identified in the previous series ( $k_{off} = 1.70 \pm 0.09 \text{ min}^{-1}$ ,  $k_{off} = 1.36 \pm 0.21 \text{ min}^{-1}$  and  $k_{off} = 1.49 \pm 0.36 \text{ min}^{-1}$ , respectively). In conclusion, these preliminary data suggest that different fluorine substitution patterns dramatically reduce binding affinities, mediated through changes in both kinetic parameters. However, the relationship between the nature of substituents, the substitution pattern and the corresponding kinetic profile is unclear.

**Table 2. Kinetic binding parameters of unlabelled analogues of **1** with modification to the *para*-fluorophenyl moiety for human D<sub>2L</sub> receptors estimated using TR-FRET assay.**



	<b>R<sup>6</sup></b>	$k_{on} (\text{M}^{-1} \text{ min}^{-1})$	$k_{off} (\text{min}^{-1})$	$t_{1/2} (\text{min})$	$pK_d$	$pK_i$
<b>1</b>		$1.29 \pm 0.21 \times 10^9$	$0.61 \pm 0.04$	$1.15 \pm 0.08$	$9.31 \pm 0.05$	$9.33 \pm 0.09$
<b>14a</b>		$9.93 \pm 1.44 \times 10^7$	$1.04 \pm 0.11$	$0.69 \pm 0.02$	$7.99 \pm 0.05$	$8.10 \pm 0.15$

14b		$2.55 \pm 0.27 \times 10^7$	$0.96 \pm 0.13$	$0.76 \pm 0.09$	$7.43 \pm 0.03$	$7.44 \pm 0.03$
14b*		$2.64 \pm 0.49 \times 10^7$	$1.08 \pm 0.21$	$0.70 \pm 0.12$	$7.39 \pm 0.01$	$7.42 \pm 0.02$
14c		$3.01 \pm 0.47 \times 10^7$	$1.29 \pm 0.26$	$0.60 \pm 0.10$	$7.38 \pm 0.02$	$7.39 \pm 0.04$
14c*		$3.24 \pm 0.34 \times 10^7$	$1.70 \pm 0.09$	$0.41 \pm 0.10$	$7.28 \pm 0.04$	$7.33 \pm 0.04$
14d		$1.07 \pm 0.02 \times 10^7$	$1.36 \pm 0.21$	$0.51 \pm 0.07$	$6.92 \pm 0.05$	$7.08 \pm 0.10$
14e		$1.15 \pm 0.20 \times 10^7$	$1.14 \pm 0.15$	$0.63 \pm 0.08$	$7.00 \pm 0.04$	$7.12 \pm 0.12$
14e*		$1.13 \pm 0.38 \times 10^7$	$1.49 \pm 0.36$	$0.58 \pm 0.16$	$6.85 \pm 0.04$	$6.95 \pm 0.12$
14f		$1.84 \pm 0.26 \times 10^7$	$1.09 \pm 0.12$	$0.66 \pm 0.09$	$7.22 \pm 0.05$	$7.20 \pm 0.04$
14g		$1.36 \pm 0.21 \times 10^8$	$1.03 \pm 0.20$	$0.75 \pm 0.14$	$8.13 \pm 0.03$	$8.11 \pm 0.03$
14h		$4.25 \pm 0.52 \times 10^6$	$0.92 \pm 0.13$	$0.79 \pm 0.09$	$6.67 \pm 0.01$	$6.77 \pm 0.08$
14i		$3.16 \pm 0.54 \times 10^8$	$1.11 \pm 0.25$	$0.76 \pm 0.22$	$8.47 \pm 0.03$	$8.45 \pm 0.01$
14j		$3.66 \pm 0.91 \times 10^8$	$0.83 \pm 0.21$	$1.01 \pm 0.25$	$8.71 \pm 0.25$	$8.82 \pm 0.02$
14k		$1.38 \pm 0.05 \times 10^8$	$0.70 \pm 0.03$	$1.00 \pm 0.04$	$8.30 \pm 0.02$	$8.30 \pm 0.02$
14l		$6.33 \pm 1.06 \times 10^8$	$1.12 \pm 0.18$	$0.67 \pm 0.11$	$8.75 \pm 0.02$	$8.75 \pm 0.05$

<sup>a</sup>The rate constants  $k_{\text{off}}$ ,  $k_{\text{on}}$ , the half-life ( $t_{1/2}$ ), and the kinetically derived  $pK_d$  were obtained from competition kinetic association experiments using PPHT-red. <sup>b</sup> $pK_i$  values were taken from PPHT-red competition binding experiments at equilibrium. Data are presented as mean  $\pm$  S.E.M. from four experiments performed in singlet.

\*Completed using online injection protocol.

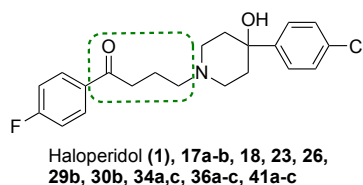
*Kinetic effects of variation of ketone and linker moieties of 1.* We next examined the effect of modification to the linker and ketone moieties of **1** through synthesis of a further 15 analogues. Specific linker-modified compounds included propiophenone (**34a**) and valerophenone (**34c**) analogues of **1**, alongside 3-5 carbon alkyl (**36a-c**) and alkyne analogues (**41a-c**). In addition, a thorough analysis of modification to the ketone moiety was undertaken *via* synthesis of geometric olefin isomers (**23**, **26**) and their corresponding cyclopropane derivatives (**29b**, **30b**), through to isosteric replacement with sulfur (**17a**) or oxygen (**17b**), as well as conversion of the ketone to the corresponding secondary alcohol (**18**).

All compounds in this series lost binding affinity relative to **1** and, for the most part, this was mediated through a decrease in  $k_{\text{on}}$  and an increase in  $k_{\text{off}}$ . Converting the ketone to its corresponding secondary alcohol (**18**) (racemic), whilst engendering a 13-fold reduction in affinity compared to **1**, was exclusively caused by a slowed  $k_{\text{on}}$  ( $\text{p}K_{\text{d}} = 7.04 \pm 0.01$ ,  $k_{\text{on}} = 6.19 \pm 0.41 \times 10^6 \text{ M}^{-1} \text{ min}^{-1}$ ). Replacement of the carbonyl moiety with sulfur (**17a**) or oxygen (**17b**) modulated both kinetic binding parameters, though their respective association rates varied ~6-fold ( $k_{\text{on}} = 4.99 \pm 0.59 \times 10^8 \text{ M}^{-1} \text{ min}^{-1}$  and  $k_{\text{on}} = 1.22 \pm 0.35 \times 10^9 \text{ M}^{-1} \text{ min}^{-1}$ , respectively). This difference may be due to a number factors, including the electronegativity and size difference between the sulfur and oxygen atoms, the relatively longer S-C bond length compared to that of the O-C bond and the orbital arrangement around each heteroatom (resulting in considerably smaller bond angles in the thioether compared to the ether). The *trans* alkene (**23**) lost ~10-fold affinity relative to **1**, and this was again predominantly due to a decreased  $k_{\text{on}}$  ( $k_{\text{on}} = 6.39 \pm 0.88 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ ). Interestingly, the *cis*- isomer (**26**) saw a further 5-fold reduction in affinity ( $\text{p}K_{\text{d}} = 7.49 \pm 0.12$ ); however, this was predominantly due to a change in association rate, displaying a  $k_{\text{on}}$  almost 20-fold slower and a  $k_{\text{off}}$  2-fold faster than **1** ( $k_{\text{on}} = 3.35 \pm 0.72 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 1.25 \pm 0.16 \text{ min}^{-1}$ ). Analysis of the racemic cycloalkane diastereomers was also interesting; introduction of the *trans*-cyclopropane (**29b**) resulted in a ~10-fold increase in affinity relative to the parent *trans*-olefin **23**, which was predominantly due to a ~10-fold increase in association rate ( $k_{\text{on}} = 6.07 \pm 0.87 \times 10^8 \text{ M}^{-1} \text{ min}^{-1}$ ). Conversely, introduction of the *cis*-cyclopropane (**30b**) had no effects on affinity relative to the parent *cis*-olefin **28**; however, this substituent marginally decreased  $k_{\text{on}}$  whilst increasing the  $k_{\text{off}}$  ( $k_{\text{on}} = 4.47 \pm 0.47 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 1.37 \pm 0.09 \text{ min}^{-1}$ ). These data indicate that *cis*-geometry is preferred as opposed to *trans*- with respect to this sub-set of compounds in reference to tuning the kinetic profile towards "slow on, fast off" characteristics, and demonstrates the importance of geometry in the corresponding pharmacological profile of APDs. Analysis of the propiophenone and valerophenone analogues of **1** returned further intriguing results. Decreasing the linker length by just one carbon (**34a**) relative to **1** resulted in

dramatic changes in both association and dissociation rate constants ( $k_{\text{on}} = 1.33 \pm 0.17 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 1.95 \pm 0.32 \text{ min}^{-1}$ ), resulting in a loss of affinity at the D<sub>2</sub>R by >20-fold ( $\text{p}K_{\text{d}} = 6.84 \pm 0.05$ ).

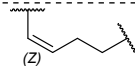
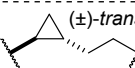
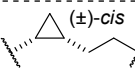
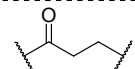
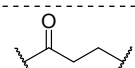
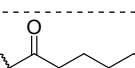
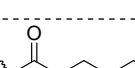
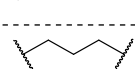
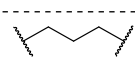
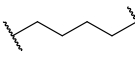
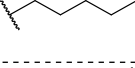
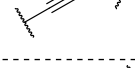

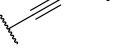
Perhaps the most exciting compound to arise from our study was the valerophenone analogue (**34c**). Despite losing affinity by >10-fold relative to **1**, this compound displayed a ~10-fold slower  $k_{\text{on}}$  and a >3.5-fold faster  $k_{\text{off}}$  than **1**. Both the kinetic profile and affinity are similar to that of **2**, which our previous studies predict would confer a low propensity to cause extrapyramidal side effects.<sup>33</sup> The alkane analogues of **1** (**36a-c**) exhibited a 10-fold variation in affinity with respect to one another, with the butylene analogue (**36b**) found to be optimal in terms of affinity conservation relative to **1** ( $\text{p}K_{\text{d}} = 8.17 \pm 0.03$ ), despite all having >10-fold losses in affinity relative to **1**. Despite having a >20-fold lower affinity compared to **1**, the propylene analogue (**36a**) was found to have a “slow on, fast off” kinetic profile ( $\text{p}K_{\text{d}} = 7.18 \pm 0.06$ ,  $k_{\text{on}} = 2.29 \pm 0.15 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 1.54 \pm 0.07 \text{ min}^{-1}$ ). Finally, analysis of the 3-5-carbon alkyne analogues (**41a-c**) saw a 10-fold variation in affinity, with the pentyne analogue (**41c**) being optimal ( $\text{p}K_{\text{d}} = 7.75 \pm 0.03$ ), as well as displaying the largest change in both rate constants towards a slow on, fast off profile ( $k_{\text{on}} = 6.41 \pm 0.80 \times 10^7$ ,  $k_{\text{off}} = 1.15 \pm 0.15 \text{ min}^{-1}$ ).

**Table 3. Kinetic binding parameters of unlabelled analogues of 1 with modifications to the ketone and linker moieties for human D<sub>2L</sub> receptors estimated using TR-FRET assay.**



	Structure	$k_{\text{on}} (\text{M}^{-1} \text{ min}^{-1})$	$k_{\text{off}} (\text{min}^{-1})$	$t_{1/2} (\text{min})$	$\text{p}K_{\text{d}}$	$\text{p}K_{\text{i}}$
<b>1</b>		$1.29 \pm 0.21 \times 10^9$	$0.61 \pm 0.04$	$1.15 \pm 0.08$	$9.31 \pm 0.05$	$9.33 \pm 0.09$
<b>17a</b>		$4.99 \pm 0.59 \times 10^8$	$0.99 \pm 0.15$	$0.74 \pm 0.10$	$8.71 \pm 0.04$	$8.68 \pm 0.04$
<b>17b</b>		$1.22 \pm 0.35 \times 10^9$	$0.91 \pm 0.12$	$0.81 \pm 0.11$	$9.10 \pm 0.08$	$8.97 \pm 0.04$
<b>18</b>		$6.19 \pm 0.41 \times 10^6$	$0.57 \pm 0.05$	$1.25 \pm 0.13$	$7.04 \pm 0.01$	$7.04 \pm 0.02$
<b>23</b>		$6.39 \pm 0.88 \times 10^7$	$0.76 \pm 0.13$	$0.74 \pm 0.10$	$7.94 \pm 0.03$	$7.95 \pm 0.03$



26		$3.35 \pm 0.72 \times 10^7$	$1.25 \pm 0.16$	$0.58 \pm 0.09$	$7.49 \pm 0.12$	$7.53 \pm 0.06$
29b		$6.07 \pm 0.87 \times 10^8$	$0.92 \pm 0.14$	$0.82 \pm 0.14$	$8.82 \pm 0.04$	$8.82 \pm 0.04$
30b		$4.47 \pm 0.47 \times 10^7$	$1.37 \pm 0.09$	$0.51 \pm 0.03$	$7.51 \pm 0.03$	$7.53 \pm 0.03$
34a		$1.03 \pm 0.18 \times 10^7$	$1.27 \pm 0.15$	$0.57 \pm 0.07$	$6.89 \pm 0.05$	$6.92 \pm 0.02$
34a*		$1.33 \pm 0.17 \times 10^7$	$1.95 \pm 0.32$	$0.43 \pm 0.04$	$6.84 \pm 0.05$	$6.88 \pm 0.02$
34c		$1.42 \pm 0.24 \times 10^8$	$1.65 \pm 0.30$	$0.48 \pm 0.10$	$7.94 \pm 0.04$	$7.97 \pm 0.02$
34c*		$1.80 \pm 0.15 \times 10^8$	$2.35 \pm 0.19$	$0.30 \pm 0.03$	$7.89 \pm 0.01$	$7.92 \pm 0.02$
36a		$2.45 \pm 0.26 \times 10^7$	$1.33 \pm 0.22$	$0.57 \pm 0.10$	$7.28 \pm 0.06$	$7.25 \pm 0.03$
36a*		$2.29 \pm 0.15 \times 10^7$	$1.54 \pm 0.07$	$0.46 \pm 0.10$	$7.18 \pm 0.06$	$7.21 \pm 0.03$
36b		$1.57 \pm 0.13 \times 10^8$	$1.11 \pm 0.05$	$0.63 \pm 0.02$	$8.17 \pm 0.03$	$8.27 \pm 0.09$
36c		$5.51 \pm 0.69 \times 10^7$	$1.22 \pm 0.15$	$0.60 \pm 0.08$	$7.66 \pm 0.03$	$7.66 \pm 0.02$
41a		$3.37 \pm 0.62 \times 10^6$	$0.96 \pm 0.14$	$0.77 \pm 0.11$	$6.54 \pm 0.01$	$6.55 \pm 0.01$
41b		$1.61 \pm 0.24 \times 10^7$	$1.10 \pm 0.21$	$0.69 \pm 0.11$	$7.15 \pm 0.05$	$7.13 \pm 0.06$
41c		$6.41 \pm 0.80 \times 10^7$	$1.15 \pm 0.15$	$0.65 \pm 0.11$	$7.75 \pm 0.03$	$7.72 \pm 0.04$

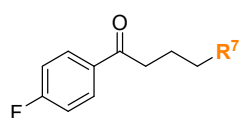
<sup>a</sup>The rate constants  $k_{\text{off}}$ ,  $k_{\text{on}}$ , the half-life ( $t_{1/2}$ ), and the kinetically derived  $\text{p}K_{\text{d}}$  were obtained from competition kinetic association experiments using PPHT-red. <sup>b</sup> $\text{p}K_{\text{i}}$  values were taken from PPHT-red competition binding experiments at equilibrium. Data are presented as mean  $\pm$  S.E.M. from four experiments performed in singlet.

\*Completed using online injection protocol.

*Kinetic effects of variation of the piperidinol moiety of 1.* The kinetic effect of structural modifications to the 4-phenylpiperidin-4-ol moiety of **1** was explored through the synthesis of eight additional analogues. We observed the effects of introducing an ethylene bridge (**42**), as well as modification primarily to the tertiary alcohol through methyl ether formation (**52**) and its subsequent removal, generating a variety of compounds containing piperazinyl (**43**), dihydropyridinyl (**45**), cyclopropyl (**46**), and piperidinyl (**47**, **48**) functionalities. We observed a wide range of affinities that spanned a  $\sim$ 30-fold difference, and unlike the previous chemical series, modification to the piperidinol moiety

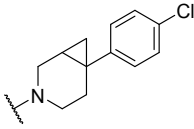
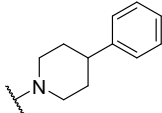
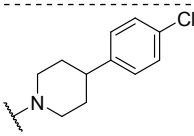
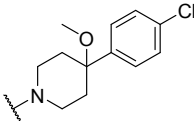
for the most part had relatively negligible effects on the  $k_{\text{off}}$ , with the majority maintaining similar values to that of **1** (Table 3). Instead, a decrease in affinity relative to **1** was largely facilitated by a decreased  $k_{\text{on}}$ . Notably, of the two analogues with higher affinities relative to **1**, these were instead largely mediated by an increase in  $k_{\text{on}}$  and decrease in  $k_{\text{off}}$ . For example, introducing the tropanyl moiety (**42**) conferred a ~10-fold increase in affinity which was equally driven by an increase in  $k_{\text{on}}$  and decrease in  $k_{\text{off}}$  ( $\text{p}K_{\text{d}} = 10.26 \pm 0.06$ ,  $k_{\text{on}} = 3.68 \pm 0.64 \times 10^9 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 0.19 \pm 0.02 \text{ min}^{-1}$ ). The cyclopropane variants (**46**) 5-fold improved affinity relative to **1** was also mediated by an increased  $k_{\text{on}}$  and decreased  $k_{\text{off}}$  ( $\text{p}K_{\text{d}} = 9.84 \pm 0.02$ ,  $k_{\text{on}} = 2.03 \pm 0.09 \times 10^9 \text{ M}^{-1} \text{ min}^{-1}$ ,  $k_{\text{off}} = 0.30 \pm 0.01 \text{ min}^{-1}$ ). The improved affinities and decreased dissociation rates of **42** and **46** (tropanyl and cyclopropane analogues, respectively) can perhaps be rationalised through a major conformational difference induced by these substituents, resulting in a more entropically favourable binding event. From these preliminary data, it appears that modification to the piperidinol moiety is not particularly amenable to significant increases in the corresponding compounds rate of dissociation.

**Table 4. Kinetic binding parameters of unlabelled analogues of 1 with modifications to the piperidinol moiety for human D<sub>2L</sub> receptors estimated using TR-FRET assay.**



Haloperidol (1), 42-43, 45-48, 52

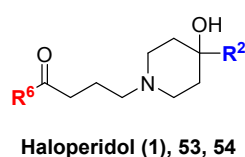
#	R <sup>7</sup>	$k_{\text{on}} (\text{M}^{-1} \text{ min}^{-1})$	$k_{\text{off}} (\text{min}^{-1})$	$t_{1/2} (\text{min})$	$\text{p}K_{\text{d}}$	$\text{p}K_{\text{i}}$
<b>1</b>		$1.29 \pm 0.21 \times 10^9$	$0.61 \pm 0.04$	$1.15 \pm 0.08$	$9.31 \pm 0.05$	$9.33 \pm 0.09$
<b>42</b>		$3.68 \pm 0.64 \times 10^9$	$0.19 \pm 0.02$	$3.59 \pm 0.39$	$10.26 \pm 0.06$	$10.28 \pm 0.08$
<b>43</b>		$2.86 \pm 0.33 \times 10^7$	$0.80 \pm 0.07$	$0.89 \pm 0.09$	$7.55 \pm 0.04$	$7.53 \pm 0.04$
<b>45</b>		$6.52 \pm 0.46 \times 10^7$	$0.65 \pm 0.05$	$1.09 \pm 0.09$	$8.00 \pm 0.02$	$8.00 \pm 0.02$

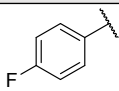
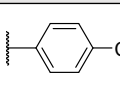
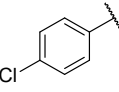
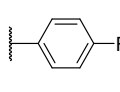
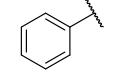
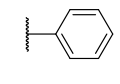
46		$2.03 \pm 0.09 \times 10^9$	$0.30 \pm 0.01$	$2.35 \pm 0.10$	$9.84 \pm 0.02$	$9.80 \pm 0.02$
47		$8.99 \pm 0.37 \times 10^7$	$0.71 \pm 0.05$	$0.99 \pm 0.07$	$8.10 \pm 0.02$	$8.11 \pm 0.03$
48		$4.31 \pm 0.37 \times 10^8$	$0.84 \pm 0.09$	$0.86 \pm 0.09$	$8.72 \pm 0.03$	$8.76 \pm 0.06$
52		$3.60 \pm 0.22 \times 10^8$	$0.68 \pm 0.03$	$1.03 \pm 0.05$	$8.72 \pm 0.01$	$8.72 \pm 0.01$

<sup>a</sup>The rate constants  $k_{\text{off}}$ ,  $k_{\text{on}}$ , the half-life ( $t_{1/2}$ ), and the kinetically derived  $\text{p}K_{\text{d}}$  were obtained from competition kinetic association experiments using PPHT-red. <sup>b</sup> $\text{p}K_{\text{i}}$  values were taken from PPHT-red competition binding experiments at equilibrium. Data are presented as mean  $\pm$  S.E.M. from four experiments performed in singlet.

*Dual modifications to both phenyl moieties of 1.* Finally, we assessed the effect of swapping the halogen substituents on each end of haloperidol (**1**) through compound (**53**), as well as their simultaneous removal as exemplified by the *des*-halo analogue **54** (Table 5). These structural changes all decreased affinity, which was reflected by decreases in the corresponding  $k_{\text{on}}$ , with only minor effects on  $k_{\text{off}}$  relative to **1**. Swapping the halogen atoms on each ring (**53**) caused a 16-fold loss in affinity ( $\text{p}K_{\text{d}} = 7.73 \pm 0.02$ ), which was predominantly driven by a 16-fold decrease in  $k_{\text{on}}$  ( $k_{\text{on}} = 4.17 \pm 0.28 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ ). Finally, removal of both halogen atoms (**54**) simultaneously caused a ~18-fold loss in affinity ( $\text{p}K_{\text{d}} = 7.51 \pm 0.01$ ), driven by a sole ~18-fold decrease in  $k_{\text{on}}$  relative to **1** ( $k_{\text{on}} = 2.28 \pm 0.13 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ ). This effect is unlike that of previous analogues bearing a *para*-halo substituent on only one of the two phenyl rings (**8h** and **14l**), whereby both  $k_{\text{on}}$  and  $k_{\text{off}}$  are altered (tables 1 and 2, respectively).

**Table 5. Kinetic binding parameters of unlabelled bi-functionalised analogues of 1 for human  $\text{D}_{2\text{L}}$  receptors estimated using TR-FRET assay.**



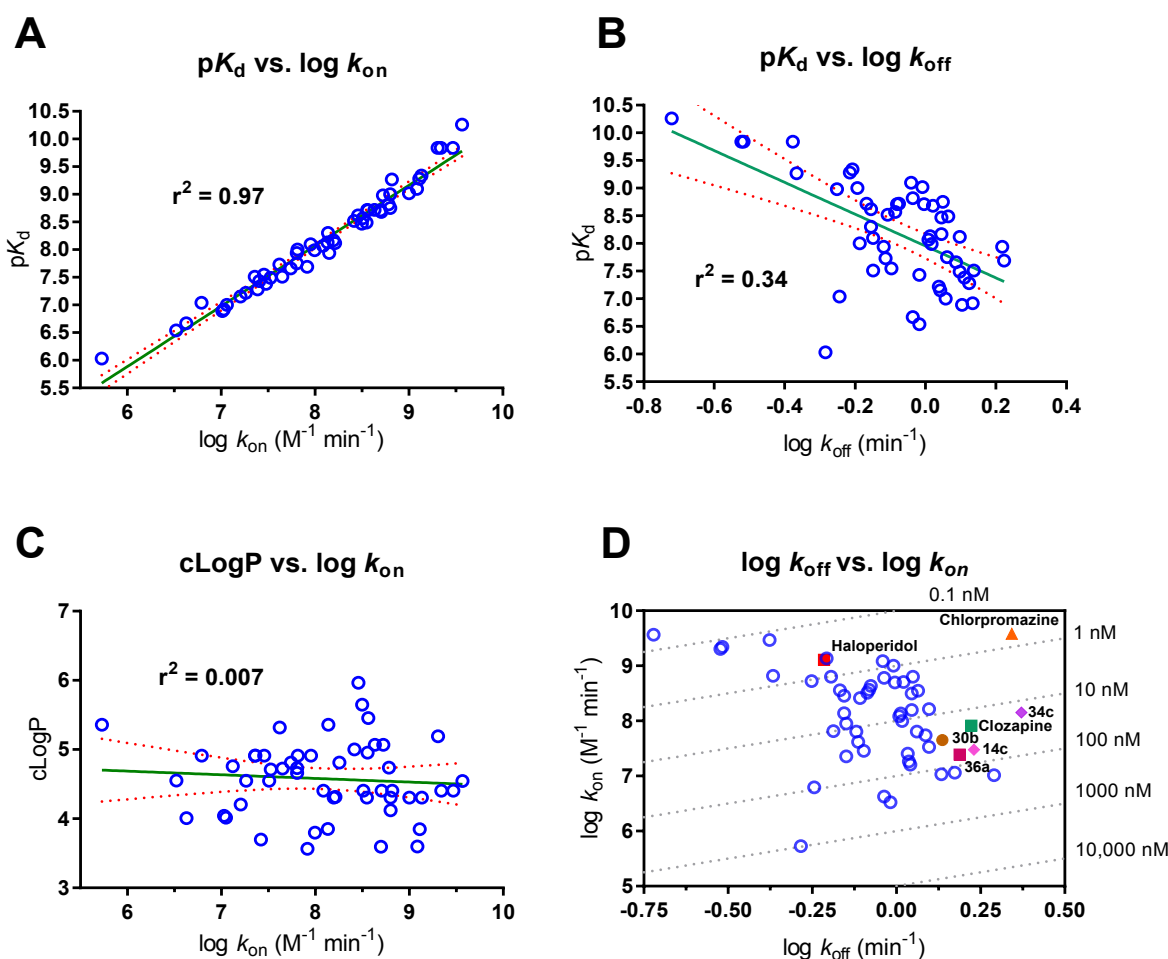
#	R <sup>6</sup>	R <sup>2</sup>	$k_{\text{on}}$ (M <sup>-1</sup> min <sup>-1</sup> )	$k_{\text{off}}$ (min <sup>-1</sup> )	$t_{1/2}$ (min)	$pK_d$	$pK_i$
1			$1.29 \pm 0.21 \times 10^9$	$0.61 \pm 0.04$	$1.15 \pm 0.08$	$9.31 \pm 0.05$	$9.33 \pm 0.09$
53			$4.17 \pm 0.28 \times 10^7$	$0.77 \pm 0.05$	$0.91 \pm 0.06$	$7.73 \pm 0.02$	$7.75 \pm 0.01$
54			$2.28 \pm 0.13 \times 10^7$	$0.71 \pm 0.05$	$0.98 \pm 0.07$	$7.51 \pm 0.01$	$7.49 \pm 0.01$

<sup>a</sup>The rate constants  $k_{\text{off}}$ ,  $k_{\text{on}}$ , the half-life ( $t_{1/2}$ ), and the kinetically derived  $pK_d$  were obtained from competition kinetic association experiments using PPHT-red. <sup>b</sup> $pK_i$  values were taken from PPHT-red competition binding experiments at equilibrium. Data are presented as mean  $\pm$  S.E.M. from four experiments performed in singlet. \*Completed using online injection protocol.

Our studies show that modifying the scaffold of **1** produces compounds with a wide range of both association rates (spanning  $\sim 3$  orders of magnitude, from  $k_{\text{on}} = 3.37 \pm 0.62 \times 10^6 \text{ M}^{-1} \text{ min}^{-1}$  to  $3.68 \pm 0.64 \times 10^9 \text{ M}^{-1} \text{ min}^{-1}$ ) and dissociation rates (spanning  $>10$ -fold, from  $k_{\text{off}} = 0.19 \pm 0.02 \text{ min}^{-1}$  to  $2.35 \pm 0.19 \text{ min}^{-1}$ ), which constituted large variations in hD<sub>2L</sub>R affinities (spanning over three orders of magnitude from  $K_d = 288 \text{ nM}$  to  $0.0549 \text{ nM}$ ). To further understand the relationship between kinetic rate constants and the affinity of D<sub>2</sub>R ligands, we have correlated the kinetic binding data of these 50 compounds ( $k_{\text{on}}$ ,  $k_{\text{off}}$ ) with the derived equilibrium affinity estimates ( $pK_d$ ) (Figure 6A). Our data confirms that  $pK_d$  is robustly correlated with association rate (see Figure 6A, Spearman's  $r^2 = 0.96$ ,  $p > 0.0001$ ), whereas  $pK_d$  is, to a much lesser extent, correlated with dissociation rate (Figure 6B). These data are in contrast to previous studies claiming the differences in APD affinities are determined entirely by how fast they dissociate from the D<sub>2</sub>R.<sup>19</sup> This is due to the fact that association rates have widely been assumed to be diffusion limited. Indeed, studies conducted at other systems, namely the M<sub>3</sub> muscarinic acetylcholine and A<sub>2A</sub> adenosine receptors, have found correlations between  $k_{\text{off}}$  values and affinity.<sup>62-64</sup> However, the association rate constants of a series of metabotropic glutamate receptor 2 positive allosteric modulators were found to be strongly correlated to affinity, whereas dissociation rate constants were not.<sup>22</sup> This correlation has also been observed at the orexin OX<sub>2</sub> receptor and  $\beta_2$ -adrenoreceptors for ligands with distinct chemotypes.<sup>65,66</sup>

It is evident that modification to the scaffold of **1** and the corresponding changes in affinity are principally mediated by a change in the rate of association (Figure 6A). Though, our study highlights that particular structural moieties of **1** are more appropriate for the modification of both kinetic parameters towards a “slow on, fast off” profile. For example, when modification to the piperidinol moiety caused a loss in binding affinity relative to **1**, this was predominantly  $k_{\text{on}}$  mediated, whilst

having negligible effects on  $k_{\text{off}}$ . However, modification of the *p*-fluorophenyl or linker moieties and subsequent losses in affinity saw greater changes in both kinetic rate constants, highlighting these areas as a focal point for future SKR investigations. In addition, we were able to derive preliminary SKR for the *p*-chlorophenyl moiety of **1**. From our kinetic data obtained from a limited amount of compound structural/chemical diversity, we determined that both the electronic nature and position of substituents on the aromatic ring dictate the corresponding kinetic profile. We found that *meta*- and *para*-EWG groups (depending on compound affinity), can either slow the  $k_{\text{on}}$  whilst having no effect on  $k_{\text{off}}$  (**8a**, **8c**, **8d**), or equally, slow the  $k_{\text{on}}$  whilst increasing  $k_{\text{off}}$  (**8b**, **8f**, **8g**). Conversely, compounds bearing *ortho*-Cl substituents and that are not *meta*- or *para*-substituted, act to slow the  $k_{\text{on}}$  but increase the  $k_{\text{off}}$  (**8e**, **8n**). This is also true for *para*-EDG substituents at these positions (**8h**, **8i**, **8k**). It may be possible to use such molecules as templates in an attempt to further increase affinity *via* decoration of the aromatic termini, whilst maintaining an ‘attractive’ or slow on, fast off kinetic profile.



**Figure 6. Correlating kinetically derived equilibrium dissociation constants vs. kinetic rate constants of haloperidol (**1**) and 51 structural analogues at the dopamine D<sub>2</sub> receptor. (A)** A plot of  $\log k_{\text{on}}$  vs.  $pK_{\text{d}}$  demonstrates a statistically significant correlation (two-tailed Pearson's

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3 correlation  $r^2 = 0.96$ ,  $p = < 0.0001$ ) between these two variables. **(B)** Conversely, a plot of  $pK_d$  vs.  $\log$   
4  $k_{off}$  demonstrates a much poorer correlation (two-tailed Pearson's correlation  $r^2 = 0.34$ ,  $p = < 0.0001$ )  
5 despite the traditional scientific consensus that APD affinity is solely driven by changes in  $k_{off}$ . **(C)**  
6 The observed association rate ( $\log k_{on}$ ) and calculated partition coefficient (cLogP) show no  
7 correlation (two-tailed Pearson's correlation  $r^2 = 0.007$ ,  $p = 0.562$ ). The central line corresponds to  
8 the linear regression of the data, the dotted lines represent the 95% confidence intervals for the  
9 regression. **(D)** Representing the diversity in affinity and corresponding kinetic profiles for analogues  
10 of **1**. A plot of  $\log k_{off}$  vs.  $\log k_{on}$  represents a spectrum of compounds with various kinetic profiles  
11 (~10-fold difference in  $k_{off}$ , ~30-fold difference in  $k_{on}$ ) identified from this study. Clozapine<sup>33</sup> (**2**) and  
12 typical APD chlorpromazine<sup>33</sup> are also included as reference points. These data identify several  
13 compounds with interesting 'slow on, fast off' kinetic profiles (**14c**, **30b**, **34c**, **36a**). Combinations of  
14  $k_{on}$  and  $k_{off}$  that result in identical affinity ( $K_d$ ) values are represented by *diagonal dotted lines*. All  
15 data used in these plots apart from chlorpromazine are detailed in Tables 1-5. Data are presented as  
16 mean from at least four separate experiments.

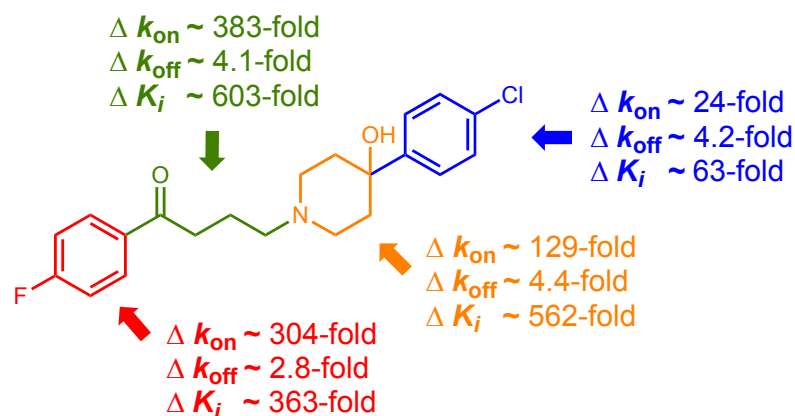
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28 The derived association rate of all compounds was further assessed for any potential correlation with  
29 physicochemical parameters such as clogP (Figure 6C) and topological polar surface area (tPSA)  
30 (Supplementary Figure 2), to which there was found to be no relationship. This is unsurprising as this  
31 study places particular emphasis on the kinetics of not only positional isomers between subsets of  
32 compounds, but close structural analogues which display very similar properties of size, lipophilicity  
33 and polarity. This further provides evidence that the observed changes to affinity and kinetic profile  
34 are not simply due to modification of physicochemical properties. These data are in contrast to  
35 previous observations at the D<sub>2</sub>R reporting that compounds with fast dissociation rates are less  
36 lipophilic and have lower molecular weights.<sup>67</sup> This is notable as additional micro-  
37 pharmacokinetic/pharmacodynamic mechanisms, such as ligand binding to the cell membrane, are  
38 known to play a role in target binding kinetics.<sup>68</sup> Although it is widely accepted that increasing  
39 lipophilicity results in increased affinity, this study shows that for this subset of compounds this is  
40 not the case, highlighting that careful analysis of kinetic parameters is essential and also likely to be  
41 context/target dependent.

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52 Our recent proposal to expand the kinetic hypothesis for APD side effects considers not only the  
53 dissociation rate (and therefore the propensity to display insurmountable antagonism), but the  
54 association rate and subsequent potential for receptor rebinding.<sup>33</sup> Based on this hypothesis, we  
55 proposed three broad classes of APDs in an attempt to explain how different kinetic characteristics  
56 have the potential to influence on-target side effects. *Class 1*: fast on/slow off compounds exemplified

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3 by haloperidol (**1**), *Class 2*: fast on/fast off compounds, namely chlorpromazine, an early typical APD  
4 and *Class 3*: slow on/fast off compounds exemplified by clozapine (**2**). A fast association rate will  
5 result in a higher D<sub>2</sub>R rebinding potential in the striatum and consequently high EPS potential. In  
6 contrast, slow dissociation from D<sub>2</sub>R<sub>s</sub> expressed on pituitary lactotrophs results in insurmountable  
7 antagonism leading to increased prolactin release (e.g. **1**). These data suggest that the profile of **1**, i.e.  
8 slow  $k_{\text{on}}$ /fast  $k_{\text{off}}$  kinetics as exhibited by **2**, is optimal for APDs targeting D<sub>2</sub>R<sub>s</sub>. Using the scaffold of  
9 **1**, we have shown that single structural modifications to one of four moieties produces structurally  
10 similar molecules with a spectrum of association and dissociation kinetic rate constants (Figure 6D),  
11 and several molecules have been identified (**14c**, **30b**, **34c**, **36a**) that display interesting profiles  
12 resembling that of **2**. Of the known literature compounds that were tested (**8f**, **8h-i**, **8l**, **14a-b**, **14g**,  
13 **14k-l**, **17a-b**, **18**, **42**, **43**, **47**, **48**, **53**, **54**), information regarding their EPS and hyperprolactinemia  
14 liabilities is absent. Our data highlights the importance of employing kinetic analyses in conjunction  
15 with other parameters toward the optimisation of APD drug leads.

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25 The identification of substituents and structural drivers that modulate kinetic profiles for the  
26 butyrophenone scaffold through a concurrent increase in  $k_{\text{on}}$  and decrease in  $k_{\text{off}}$ , such as EDGs on  
27 the *p*-chlorophenyl moiety, difluoro-substituents on the *p*-fluorophenyl moiety, replacing the ketone  
28 for a *cis*-cyclopropane, or the simple alteration of the alkyl linker length, may be used to ‘fine tune’  
29 the design of novel compounds structurally similar to **1** with optimized kinetic parameters similar to  
30 that of atypical APD **2**. Collectively, these data represent the first reported kinetic characterisation of  
31 analogues of **1** and clearly demonstrate that incorporation of kinetic binding parameter analyses into  
32 APD discovery programs may facilitate the identification of D<sub>2</sub>R antagonist APDs with an improved  
33 therapeutic window.

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42 *Structural basis for structure-kinetic relationships.* Given the focused nature of our SKR study, with  
43 modifications grouped by different moieties present on **1** (Figure 2), it is possible to conduct a global  
44 analysis of the kinetic binding parameters obtained, in relation to these modifications. Such analysis  
45 might be a useful indicator in determining whether specific regions of the haloperidol scaffold are  
46 more sensitive to structural modification in terms of  $k_{\text{on}}$ ,  $k_{\text{off}}$  and  $K_i$  (Figure 7).  
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**Figure 7. Summary of the range of kinetic binding parameters obtained for each region of structural modification to haloperidol (1).** Values describe the fold-difference between the largest and smallest value for each parameter and grouped by the moiety of **1** that was modified.

It is interesting to note that modification of the *p*-fluorophenyl and butyrophenone moieties result in a broader range of  $k_{\text{on}}$  values compared to those observed with the piperidinol and chlorophenyl moiety analogues. This may indicate that these regions play an important role in guiding ligand entry to the binding site. In contrast, the chlorophenyl moiety seems to be a relatively less important determinant of  $k_{\text{on}}$  and affinity.

The recently published structure of the  $D_2R$ <sup>69</sup> offers insight into the observed binding pose of the atypical APD risperidone at a thermostabilised  $D_2R$ . Co-crystal structures offer a wealth of structural information about the interaction between the co-crystallised ligand and receptor under specific experimental conditions and are useful in correlating pharmacologically determined measurements of affinity with such interactions. Furthermore, ligand docking studies into such structures can identify receptor-ligand interactions that in part might determine kinetic parameters (particularly,  $k_{\text{off}}$ ).

However, co-crystal structures only offer a static snapshot of a low energy ligand-bound conformation of the receptor, which may not represent the conformation stabilised by a structurally distinct ligand scaffold. In contrast, entry and egress is a complex process that involves the interaction of both a flexible receptor and the ligand, and the journey of that ligand from the extracellular milieu to the binding site. Recent MD simulations have revealed that residues in the extracellular loop regions of GPCRs play an important role in this process.<sup>58,70,71</sup> This is a highly dynamic region of the receptor and the static conformation observed in a crystal structure cannot provide the complete picture of the role of this region, thus future studies using long timescale MD simulations are needed to allow us to reconcile our present findings with this structural data.

Recently, MD simulations have been carried out, attempting to explore the ligand binding journeys of both haloperidol (**1**) and clozapine (**2**) at the  $D_2R/D_3R$ .<sup>58</sup> Interestingly, the binding of **1** at the  $D_2R$



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3 has been proposed to arise via a “handover” mechanism, whereby an initial key  $\pi$ -stacking interaction  
4 with Tyr<sup>7.35</sup> (Ballesteros-Weinstein numbering scheme)<sup>72</sup> allows this residue to act as a pivot point  
5 from which the ligand can explore the extracellular vestibule, followed by formation of a salt-bridge  
6 with Asp<sup>3.32.58</sup>. This mechanism appears to be reliant upon an optimal intramolecular distance between  
7 the *p*-fluorophenyl moiety of **1** and the protonated piperidinyl amine, thus changes in this distance  
8 through linker extension might be expected to influence orthosteric binding and the corresponding  
9 kinetic profile of the ligand (particularly  $k_{\text{on}}$ ). Our findings correlate with this observation, as  
10 homologues of **1** bearing either a propiophenone (**34a**) or valerophenone (**34c**) moiety, both exhibit  
11 relatively lower  $k_{\text{on}}$  values ( $1.03 \pm 0.18 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$  and  $1.42 \pm 0.24 \times 10^8 \text{ M}^{-1} \text{ min}^{-1}$  respectively).  
12 This is further reflected in the corresponding alkyl linker analogues (**36a-c**), whereby **36b** (bearing a  
13 butylene linker – the corresponding de-oxo analogue of **1**) retained the highest  $k_{\text{on}}$  value compared to  
14 its homologues (**36a** and **36c**, table 3).

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16 However, whilst these simulations were unbiased, only two of those reported resulted in a complete  
17 binding trajectory (determined by the presence of an ionic interaction between Asp<sup>3.32</sup> on each  
18 receptor and the protonated nitrogen atom of each ligand), which occurred at the D<sub>3</sub>R only. The D<sub>2</sub>R  
19 structure was not available at the time of this study, and a D<sub>3</sub>R crystal structure<sup>73</sup> was used as the  
20 basis for both simulations, with generation of a D<sub>2</sub>R homology model for the D<sub>2</sub>R simulations.  
21 Notably, comparison of the D<sub>2</sub>R and D<sub>3</sub>R crystal structures reveals a considerably different  
22 arrangement of the extracellular domains.<sup>69</sup>

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24 In order to further our understanding about the SKR reported in our study, our future work will focus  
25 on conducting advanced MD simulations using the recently reported D<sub>2</sub>R structure, with a view to  
26 correlating how subtle structural changes in the haloperidol analogues (imbuing distinct kinetic  
27 profiles) described above might influence interaction with specific residues which line the entry to  
28 and exit from the ligand binding site.

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### ▪ CONCLUSIONS

In this study, we report the chemical synthesis and extensive kinetic profiling of 50 analogues of haloperidol (**1**) at the hD<sub>2L</sub>R, using a TR-FRET competition association kinetic binding assay, permitting the derivation of multiple equilibrium and kinetic parameters ( $pK_i$ ,  $pK_d$ ,  $k_{\text{on}}$  and  $k_{\text{off}}$ ). All analogues retained the hD<sub>2L</sub>R antagonist action of **1** apart from **47** that gave a partial response relative to dopamine at a concentration of 10  $\mu\text{M}$ . The kinetic profile was assessed with respect to predominantly single modification of one of four structural moieties of **1**, namely the *p*-fluorophenyl, ketone and alkyl linker, piperidinol, and *p*-chlorophenyl moieties. Specifically, we observed the effect of both mono and di-halogen substituents on individual phenyl rings, as well as ketone and linker

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3 modified variants, incorporating *cis*- and *trans*-olefins and their corresponding cyclopropanes,  
4 together with numerous alkanes and alkynes. In addition, we investigated the effect of modification  
5 to the tertiary alcohol, as well as incorporation of piperazinyl, tetrahydropyridinyl and other  
6 piperidinyl moieties. Importantly, we show that there is no correlation between  $k_{\text{on}}$  and the  
7 physicochemical parameters clogP and TPSA, meaning that differences in kinetic profiles and  
8 corresponding compound affinities are not simply due to non-specific effects such as cell membrane  
9 binding. Moreover, we reveal that  $k_{\text{on}}$  is significantly correlated with  $\text{p}K_{\text{d}}$ , and is contrary to previous  
10 reports at the D<sub>2</sub>R. Thus, we found that a loss in binding affinity is generally associated with a  
11 decrease in  $k_{\text{on}}$ . However, preliminary SKR derived for the *p*-chlorophenyl moiety of **1**, demonstrates  
12 that particular substitution patterns and the nature of aromatic substituents are more likely to  
13 concurrently decrease  $k_{\text{on}}$  whilst increasing  $k_{\text{off}}$ . For example, chloro substituents at the *ortho*-position  
14 modulate the kinetic parameters toward a slow  $k_{\text{on}}$ /fast  $k_{\text{off}}$  profile, whereas *meta* and/or *para*-chloro  
15 substituents can either decrease the  $k_{\text{on}}$ , whilst having no effect on  $k_{\text{off}}$ , or, equally, they may also  
16 simultaneously decrease  $k_{\text{on}}/k_{\text{off}}$ . The *p*-fluorophenyl and ketone/alkyl linker structural moieties of **1**  
17 were found to be important for mediating changes in both kinetic rate parameters, particularly the  $k_{\text{off}}$ ,  
18 whilst the piperidinol moiety was more linked to changes in  $k_{\text{on}}$  only. For example, converting the  
19 aryl ketone to a *cis*-cyclopropane group or increasing/decreasing the linker length, significantly  
20 modulates both rate constants, whereas most modifications to the piperidinol ring simply modulate  
21 the  $k_{\text{on}}$ . We show that with minimal variation this scaffold can be converted to the slow on, fast off  
22 kinetic profile that we hypothesise is characteristic of APDs with reduced on-target side effect profiles  
23 (e.g. **14c**, **30b**, **34c**, **36a**). These compounds may be used as tools to further explore the influence of  
24 kinetic rate parameters and their role in the corresponding clinical profile of APDs toward the  
25 development of novel efficacious treatments devoid of EPS and hyperprolactinemia.  
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## 44 ■ EXPERIMENTAL SECTION

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46 **General Chemistry.** Chemicals and solvents of analytical and HPLC grade were purchased from  
47 commercial suppliers and used without further purification. Reactions were monitored by thin-layer  
48 chromatography on commercially available silica pre-coated aluminium-backed plates (Merck  
49 Kieselgel 60 F254). Visualisation was under UV light (254 nm and 366 nm), followed by staining  
50 with ninhydrin or KMnO<sub>4</sub> dips. Flash column chromatography was performed using silica gel 60,  
51 230-400 mesh particle size (Sigma Aldrich). NMR spectra were recorded on a Bruker-AV 400. <sup>1</sup>H  
52 spectra were recorded at 400.13 Hz and <sup>13</sup>C NMR spectra at 101.62 Hz. All <sup>13</sup>C NMR are <sup>1</sup>H  
53 broadband decoupled. Solvents used for NMR analysis (reference peaks listed) were CDCl<sub>3</sub> supplied  
54 by Cambridge Isotope Laboratories Inc., ( $\delta_{\text{H}} = 7.26$  ppm,  $\delta_{\text{C}} = 77.16$ ) and CD<sub>3</sub>OD supplied by VWR  
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( $\delta_{\text{H}} = 3.31$  ppm and  $\delta_{\text{C}} = 49.00$ ). Chemical shifts ( $\delta$ ) are recorded in parts per million (ppm) and coupling constants are recorded in Hz. The following abbreviations are used to describe signal shapes and multiplicities; singlet (s), doublet (d), triplet (t), quadruplet (q), broad (br), dd (doublet of doublets), ddd (double doublet of doublets), dtd (double triplet of doublets) and multiplet (m). Spectra were assigned using appropriate COSY and HSQC experiments. Processing of the NMR data was carried out using the NMR software Topspin 3.0. RP-HPLC-MS spectra were recorded on a Shimadzu UFLCXR system coupled to an Applied Biosystems API2000 and visualised at 254 nm (channel 1) and 220 nm (channel 2). RP-HPLC-MS was carried out using a Phenomenex Gemini® NX-C18 110 Å, column (50 mm × 2 mm × 3 μm) at a flow rate 0.5 mL/min over a 5-min period (Method A). The retention time ( $t_{\text{R}}$ ) of the final product is reported using a gradient method of 5-95% solvent B in solvent A over 12 minutes. (Solvent A = 0.01% trifluoroacetic acid in H<sub>2</sub>O, solvent B = 0.01% trifluoroacetic acid in CH<sub>3</sub>CN (Method B)). All screening compounds were one single peak and determined to be >95% purity at both 254 nm and 220 nm using Method B. All high-resolution mass spectra (HRMS) were recorded on a Bruker microTOF mass spectrometer using MS electrospray ionization operating in positive ion mode. Preparative RP-HPLC was performed on a Waters 515 LC system and monitored using a Waters 996 photodiode array detector at wavelengths between 190 and 800 nm. Spectra were analysed using Millennium 32 software. Preparative RP-HPLC was performed using a Gemini® NX-C18 110 Å column (250 mm × 21.2 mm × 5 μm) at a flow rate of 20.0 mL/min using a gradient method of 5-95% B over 15 minutes (Solvent A = 0.01% trifluoroacetic acid in H<sub>2</sub>O, solvent B = 0.01% trifluoroacetic acid in CH<sub>3</sub>CN (Method C)). Predicted partition coefficient (cLogP) values were calculated using Data Warrior 4.7.2, Actelion Pharmaceutical Ltd.

**General Procedure A. *n*-Butyllithium mediated addition of aryllithiums to ketones for the preparation of 5a-m.** To a stirred solution of substituted bromobenzene (**3a-l**) (1.35 equiv.) in THF at -78 °C was added *n*-butyllithium (1.30 equiv.) and the reaction maintained at -78 °C for 30 min. After this, a solution of ketone (1 equiv.) in THF was slowly introduced into the reaction and stirred at -78 °C for 2 h. The reaction was quenched with the addition of a saturated solution of NH<sub>4</sub>Cl and transferred to a separating funnel and extracted with DCM (3 × 40 mL). The organic extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>) and the residue purified by column chromatography using PE/EtOAc in a ratio as indicated to afford the desired compound.

**General procedure B. *N*-Boc deprotection for the preparation of 6a-n.** The *N*-Boc protected amine was taken up in 4 M HCl in 1,4-dioxane (20 mL) and stirred at r.t. for 2 h. The solvents were evaporated *in vacuo* to afford the corresponding amine hydrochloride. Alternatively, the residue could be taken up in H<sub>2</sub>O (20 mL) and added to a separating funnel. The aqueous solution was washed with

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3 Et<sub>2</sub>O (3 × 30 mL), and the aqueous phase made alkaline with the addition of 2 M NaOH solution.  
4 This phase was then extracted with DCM (3 × 30 mL) and the organic extracts collected, dried over  
5 anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated *in vacuo* to afford the corresponding amine free base.  
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8 **General Procedure C. N-Alkylation for the preparation of 8a-n, 14a-l, 17a-b, 18, 23, 26, 29b,**  
9 **30b, 34a, 34c, 36a-c, 41a-c, 42-43, 45-48, 52, 53, 54.** To a round-bottom flask or sealed microwave  
10 vessel was added the amine (1.1 equiv.), alkyl halide or mesylate (1 equiv.), KI (0.1 equiv.) and  
11 NaHCO<sub>3</sub> (2 equiv.) followed by toluene. This suspension was then heated at reflux temperature for  
12 24 h. The reaction was filtered and evaporated to dryness followed by direct chromatographic  
13 purification using an appropriate eluent as indicated.  
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18 **General Procedure D. Sonogashira cross-coupling of aryl iodides for the preparation of 12a-j,**  
19 **40b.** PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (1 mol %) and copper(I) iodide (2 mol %) were placed in a 50 mL round-bottomed  
20 flask equipped with a magnetic bar and then non-dried 1,4-dioxane (10 mL), the corresponding iodide  
21 (1.0 equiv.), 4-chloro-1-butyne (1.2 equiv.), and triethylamine (5.0 equiv.) were added. The flask was  
22 capped with a rubber septum, and the resulting mixture was magnetically stirred at 50 °C for 2-6 h.  
23 The reaction was diluted with Et<sub>2</sub>O (100 mL) after cooling, removing the solids by filtration. The  
24 resulting solution was purified by column chromatography (petroleum ether) to yield the  
25 corresponding alkyne product.  
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32 **General Procedure E. Sonogashira cross-coupling of aryl iodides for the preparation of 39a,**  
33 **39c.** To a N<sub>2</sub>-degassed solution of CH<sub>3</sub>CN and triethylamine (2.0 equiv.) were added alkyne (1.1  
34 equiv.), the appropriate iodobenzene (1.0 equiv.), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2% mol) and CuI (2% mol), and the  
35 mixture was stirred at room temperature for 5 hr. The reaction was diluted with Et<sub>2</sub>O, filtered,  
36 concentrated, and purified on silica gel (*n*-hexanes).  
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41 **General Procedure F. Triflic acid-catalysed Markovnikov-type hydration of internal alkynes**  
42 **for the preparation of 13a-j.** The purified alkyne was treated with triflic acid (0.5 equiv.) and H<sub>2</sub>O  
43 (2 equiv) in 2,2,2-trifluoroethanol in a sealed vial equipped with a magnetic stirring bar, and stirred  
44 at 60 °C for 6 h. The reaction mixture was concentrated under reduced pressure and the corresponding  
45 ketone directly purified by FCC with an appropriate eluent as indicated.  
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50 **General procedure G. Alcohol mesylation for the preparation of 22, 27, 29a, 30a, 40a, 40c).** To  
51 a solution of alcohol (1 equiv.), Et<sub>3</sub>N (2.5 equiv.), in DCM was added at room temperature MsCl (1.3  
52 equiv.). The mixture was stirred at room temperature for 1.5-24 h until complete consumption of  
53 starting material was evident. The mixture was diluted with EtOAc, washed with H<sub>2</sub>O, brine, and the  
54 organic fraction dried (Na<sub>2</sub>SO<sub>4</sub>). The solvents were removed *in vacuo* and the residue  
55 chromatographed on silica eluting with the appropriate solvent as indicated. Similarly, and in many  
56 cases, the residue could be used for the next reaction without the need for purification.  
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***tert*-Butyl 4-(4-chlorophenyl)-4-hydroxypiperidine-1-carboxylate (5a).** General procedure A. Purification by FCC (eluent: EtOAc/hexane 0-40%) gave 7.64 g of a white foam (74%). LCMS (*m/z*): 312.1 [M+H]<sup>+</sup>, *t*<sub>R</sub> 2.95 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.43 – 7.38 (m, 2H), 7.34 – 7.30 (m, 2H), 4.08 – 3.91 (m, 2H), 3.21 (td, *J* = 13.0, 2.7 Hz, 2H), 1.94 (td, *J* = 13.3, 4.9 Hz, 2H), 1.75 (s, 1H), 1.69 (dq, *J* = 14.2, 2.8 Hz, 2H), 1.47 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 154.9, 146.7, 133.2, 128.7, 126.2, 79.8, 71.5, 39.9, 38.2, 28.6.

***tert*-Butyl 4-(3-chlorophenyl)-4-hydroxypiperidine-1-carboxylate (5b).** General procedure A. Purification by FCC (eluent: EtOAc/hexane 0-40%) gave 1.25 g of a white solid (69.1%). LCMS (*m/z*): 312.1 [M+H]<sup>+</sup>, *t*<sub>R</sub> 2.95 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.51 (t, *J* = 1.8 Hz, 1H), 7.35 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.25 (dt, *J* = 7.7, 1.7 Hz, 1H), 4.03 (ddt, *J* = 13.4, 4.2, 1.7 Hz, 2H), 3.23 (td, *J* = 13.0, 2.7 Hz, 2H), 2.03 (s, 1H), 1.96 (td, *J* = 13.3, 4.9 Hz, 2H), 1.77 – 1.66 (m, 2H), 1.49 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 154.9, 150.4, 134.5, 129.8, 127.4, 125.2, 122.9, 79.8, 71.5, 39.9, 38.1, 28.6.

***tert*-Butyl 4-(2,3-dichlorophenyl)-4-hydroxypiperidine-1-carboxylate (5c).** General procedure A. Purification by FCC (eluent: EtOAc/hexane 0-40%) gave 1.87 g of a white solid (65.9%). LCMS (*m/z*): 346.1 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.05 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.55 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.35 – 7.26 (m, 1H), 4.15 – 4.05 (m, 2H), 3.33 (td, *J* = 13.0, 2.7 Hz, 2H), 2.38 – 2.27 (m, 2H), 2.07 – 1.98 (m, 2H), 1.54 (s, 9H), 1.51 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 155.0, 145.7, 135.2, 130.2, 129.9, 127.7, 125.4, 79.7, 72.9, 39.9, 35.3, 28.6.

***tert*-Butyl 4-(2,4-dichlorophenyl)-4-hydroxypiperidine-1-carboxylate (5d).** General procedure A. Purification by FCC (eluent: EtOAc/hexane 0-40%) gave 1.30 g of a transparent oil (71%). LCMS (*m/z*): 346.1 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.02 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.27 (d, *J* = 8.0 Hz, 2H), 7.03 (t, *J* = 8.0 Hz, 1H), 4.01 (s, 2H), 3.42 (s, 1H), 3.23 (s, 2H), 2.76 (td, *J* = 13.2, 5.0 Hz, 2H), 1.90 (d, *J* = 12.9 Hz, 2H), 1.44 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 155.0, 145.2, 133.4, 133.0, 129.9, 128.7, 127.7, 79.8, 72.4, 35.0, 28.6.

***tert*-Butyl 4-(2,5-dichlorophenyl)-4-hydroxypiperidine-1-carboxylate (5e).** General procedure A. Purification by FCC (eluent: EtOAc/hexane 0-40%) gave 1.48 g of a white solid (68%). LCMS (*m/z*): 346.3 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.02 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.59 (d, *J* = 2.5 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.18 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.09 – 4.00 (m, 2H), 3.28 – 3.21 (m, 2H), 2.83 (d, *J* = 1.0 Hz, 1H), 2.32 (td, *J* = 13.3, 4.9 Hz, 2H), 1.84 (d, *J* = 13.4 Hz, 2H), 1.47 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 155.0, 145.2, 133.4, 133.0, 129.9, 128.7, 127.7, 79.8, 72.4, 35.0, 28.6.

***tert*-Butyl 4-(2,6-dichlorophenyl)-4-hydroxypiperidine-1-carboxylate (5f).** General procedure A. Purification by FCC (eluent: EtOAc/hexane 0-40%) gave 1.72 g of a transparent oil (76%). LCMS (*m/z*): 346.1 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.03 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.12 – 7.03 (m, 1H),

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3 4.02 (dd,  $J = 13.2, 4.8$  Hz, 2H), 3.26 (td,  $J = 12.9, 2.8$  Hz, 2H), 2.81 (td,  $J = 13.2, 5.0$  Hz, 2H), 2.01  
4 – 1.89 (m, 2H), 1.48 (s, 9H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  155.1, 140.1, 133.8, 132.1, 128.4, 79.6, 76.1, 39.9,  
5 35.7, 28.6.

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8 ***tert*-Butyl 4-(3,4-dichlorophenyl)-4-hydroxypiperidine-1-carboxylate (5g)**. General procedure A.  
9 Purification by FCC (eluent: EtOAc/hexane 0-40%) gave 1.25 g of a white foam (73.4%). LCMS  
10 ( $m/z$ ): 346.2  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.06 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.59 (d,  $J = 2.2$  Hz, 1H), 7.38 (d,  $J = 8.4$  Hz,  
11 1H), 7.26 (dd,  $J = 8.4, 2.2$  Hz, 1H), 3.97 (dt,  $J = 12.9, 3.3$  Hz, 2H), 3.19 (t,  $J = 12.9$  Hz, 2H), 1.86 (td,  
12  $J = 13.2, 4.8$  Hz, 2H), 1.71 – 1.65 (m, 2H), 1.46 (s, 1H), 1.44 (s, 9H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  154.9,  
13 148.9, 132.4, 130.9, 130.3, 127.2, 124.3, 79.8, 70.9, 42.9, 36.6, 28.5.

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18 ***tert*-Butyl 4-(3,5-dichlorophenyl)-4-hydroxypiperidine-1-carboxylate (5h)**. General procedure A.  
19 Purification by FCC (eluent: EtOAc/hexane 0-40%) gave 2.22 g of a white solid (78.2%). LCMS  
20 ( $m/z$ ): 345.9  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.09 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.35 (d,  $J = 1.9$  Hz, 2H), 7.24 (t,  $J = 1.9$  Hz,  
21 1H), 4.01 (ddt,  $J = 13.5, 4.7, 1.8$  Hz, 2H), 3.18 (td,  $J = 13.1, 2.7$  Hz, 2H), 2.22 (s, 1H), 1.90 (td,  $J =$   
22 13.3, 4.9 Hz, 2H), 1.71 – 1.62 (m, 2H), 1.45 (s, 9H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  154.9, 151.9, 135.2, 127.3,  
23 123.7, 79.9, 71.5, 39.8, 38.1, 28.6.

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28 ***tert*-Butyl 4-hydroxy-4-phenylpiperidine-1-carboxylate (5i)**. General procedure A. Purification by  
29 FCC (eluent: EtOAc/hexane 0-40%) gave 1.49 g of a white foam (76%). LCMS ( $m/z$ ): 278.1  $[\text{M}+\text{H}]^+$ ,  
30  $t_{\text{R}}$  2.83 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.53 – 7.45 (m, 2H), 7.43 – 7.33 (m, 2H), 7.34 – 7.24 (m, 1H), 4.03  
31 (ddt,  $J = 13.3, 4.4, 1.8$  Hz, 2H), 3.26 (td,  $J = 13.1, 2.7$  Hz, 2H), 2.01 (td,  $J = 13.4, 4.9$  Hz, 2H), 1.84  
32 (s, 1H), 1.50 (s, 9H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  154.9, 148.1, 128.5, 127.2, 124.5, 79.5, 71.5, 39.9, 38.1,  
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38 ***tert*-Butyl 4-hydroxy-4-(*p*-tolyl)piperidine-1-carboxylate (5j)**. General procedure A. Purification  
39 by FCC (eluent: EtOAc/hexane 0-40%) gave 1.29 g of white foam (68%). LCMS ( $m/z$ ): 292.2  
40  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  2.93 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.37 – 7.33 (m, 2H), 7.17 (dt,  $J = 7.9, 0.7$  Hz, 2H), 3.99  
41 (dt,  $J = 13.1, 2.6$  Hz, 2H), 3.23 (td,  $J = 13.1, 2.7$  Hz, 2H), 2.34 (s, 3H), 1.96 (td,  $J = 13.4, 4.9$  Hz, 2H),  
42 1.84 – 1.78 (m, 1H), 1.76 – 1.66 (m, 2H), 1.47 (s, 9H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  155.0, 145.3, 136.9,  
43 129.2, 124.5, 79.6, 71.4, 40.0, 38.3, 28.6, 21.1.

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49 ***tert*-Butyl 4-hydroxy-4-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (5k)**. General  
50 procedure A. Purification by FCC (eluent: EtOAc/hexane 0-40%) gave 1.43 g of a white foam (84%).  
51 LCMS ( $m/z$ ): 346.2  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.00 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.60 (m, 4H), 4.04 (ddt,  $J = 13.7, 4.6,$   
52 1.8 Hz, 2H), 3.22 (td,  $J = 13.0, 2.6$  Hz, 2H), 1.98 (td,  $J = 13.3, 4.9$  Hz, 2H), 1.75 – 1.66 (m, 2H), 1.47  
53 (s, 9H), 1.35 – 1.27 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  154.9, 152.2 (d,  $J = 1.5$  Hz), 129.6 (q,  $J = 32.5$  Hz),  
54 125.5 (q,  $J = 3.8$  Hz), 125.1, 124.2 (q,  $J = 272.1$  Hz), 79.9, 71.7, 39.8, 38.1, 28.6.

**tert-Butyl 4-(4-(dimethylamino)phenyl)-4-hydroxypiperidine-1-carboxylate (5l).** General procedure A. Purification by FCC (eluent: EtOAc/hexane 0-40%) gave 1.22 g of white solid (69%). LCMS (*m/z*): 321.0 [M+H]<sup>+</sup>, *t*<sub>R</sub> 2.51 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.34 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.5 Hz, 2H), 3.96 (s, 2H), 3.25 (t, *J* = 11.6 Hz, 2H), 2.94 (s, 6H), 2.03 – 1.88 (m, 2H), 1.79 – 1.71 (m, 2H), 1.47 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 155.1, 129.2, 128.3, 125.7, 112.6, 79.5, 71.1, 40.8, 28.6, 28.6.

**tert-Butyl 4-(4-fluorophenyl)-4-hydroxypiperidine-1-carboxylate (5m).** General procedure A. Purification by FCC (eluent: EtOAc/hexane 0-40%) gave 1.24 g of transparent oil (71%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.42 – 7.35 (m, 2H), 6.94 (t, *J* = 8.7 Hz, 2H), 3.88 (dd, *J* = 12.8, 4.4 Hz, 2H), 3.22 – 3.09 (m, 2H), 3.07 (s, 1H), 1.83 (td, *J* = 13.2, 4.7 Hz, 2H), 1.64 (dd, *J* = 14.1, 2.5 Hz, 2H), 1.39 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 161.8 (d, *J* = 245.3 Hz), 154.9, 144.3 (d, *J* = 3.1 Hz), 126.4 (d, *J* = 7.9 Hz), 114.9 (d, *J* = 21.2 Hz), 79.6, 70.9, 38.1, 28.4.

**tert-Butyl 4-(2'-chloro-[1,1'-biphenyl]-2-yl)-4-hydroxypiperidine-1-carboxylate (5n).** General procedure A. Purification by FCC (eluent: EtOAc/hexane 0-40%) gave 700 mg of a white solid (55%). Reaction by-product from the attempted synthesis of TF-01-62. LCMS (*m/z*): 388.1 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.12 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.51 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.49 – 7.41 (m, 1H), 7.40 (td, *J* = 7.7, 1.6 Hz, 1H), 7.29 (dtd, *J* = 10.5, 6.2, 5.6, 2.9 Hz, 4H), 7.01 (dd, *J* = 7.5, 1.5 Hz, 1H), 3.89 (dddd, *J* = 15.5, 13.2, 5.0, 2.6 Hz, 2H), 3.06 (qd, *J* = 12.4, 2.7 Hz, 2H), 2.09 – 1.98 (m, 1H), 1.96 – 1.85 (m, 1H), 1.74 (ddd, *J* = 13.8, 11.4, 2.7 Hz, 2H), 1.44 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 154.9, 145.0, 142.9, 137.3, 133.5, 132.3, 131.0, 129.5, 128.8, 128.2, 126.9, 126.4, 126.3, 79.5, 73.6, 38.6, 38.2, 28.6.

**tert-Butyl 4-(2-chlorophenyl)-4-hydroxypiperidine-1-carboxylate (5n).** To a stirred solution of 1-bromo-2-chloro-benzene (609 μL, 5.22 mmol) in Et<sub>2</sub>O was added magnesium turnings (150 mg, 6.17 mmol), followed by catalytic iodide and the reaction stirred at room temperature for 2 h. This mixture was then cooled to 0°C, and treated with 4-oxopiperidine-1-carboxylic acid tert-butyl ester (946 mg, 4.75 mmol) dissolved in Et<sub>2</sub>O (10 mL) and added to the reaction mixture slowly. The reaction was heated at reflux temperature for 3 h. The reaction was quenched with a saturated solution NH<sub>4</sub>Cl and the aqueous phase extracted with EtOAc. The organic extracts were combined and dried over MgSO<sub>4</sub>, filtered and evaporated *in vacuo*. The residue was purified by FCC (eluent: EtOAc/*n*-hexanes 0-40%) and gave 800 mg of a white foam (54%). LCMS (*m/z*): 312.2 [M+H]<sup>+</sup>, *t*<sub>R</sub> 2.97 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.56 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.30 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.21 (td, *J* = 7.6, 1.5 Hz, 1H), 7.15 (td, *J* = 7.5, 1.7 Hz, 1H), 3.96 (dd, *J* = 13.4, 4.8 Hz, 2H), 3.22 (t, *J* = 12.9 Hz, 2H), 3.05 (s, 1H), 2.29 (td, *J* = 13.2, 4.9 Hz, 2H), 1.87 – 1.78 (m, 2H), 1.43 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 154.9, 143.5, 131.7, 131.5, 128.6, 127.2, 127.1, 79.5, 72.2, 39.8, 34.9, 28.5.

**4-(3-Chlorophenyl)piperidin-4-ol (6a).** General procedure B. Alkaline work-up afforded 660 mg of a white solid (97%). LCMS (*m/z*): 212.0 [M+H]<sup>+</sup>, *t*<sub>R</sub> 0.74 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.52 (t, *J* = 1.9

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3 Hz, 1H), 7.37 (dt,  $J = 7.7, 1.5$  Hz, 1H), 7.29 (t,  $J = 7.8$  Hz, 1H), 7.24 (dt,  $J = 7.9, 1.7$  Hz, 1H), 3.10  
4 (td,  $J = 12.3, 2.6$  Hz, 2H), 2.99 – 2.90 (m, 2H), 2.42 (d,  $J = 9.1$  Hz, 2H), 1.97 (td,  $J = 13.2, 4.6$  Hz,  
5 2H), 1.70 (dd,  $J = 14.1, 2.5$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  151.2, 134.4, 129.8, 127.1, 125.2, 122.9,  
6 71.4, 42.2, 39.1.

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9 **4-(2,3-Dichlorophenyl)-4-hydroxypiperidin-1-ium chloride (6b).** General procedure B.  
10 Concentration in vacuo gave 685 mg of a beige solid (94%). LCMS ( $m/z$ ): 246.0  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  2.53  
11 min.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  9.19 (d,  $J = 55.0$  Hz, 2H), 7.75 (dd,  $J = 8.1, 1.7$  Hz, 1H), 7.60 (dd,  $J =$   
12 8.0, 1.6 Hz, 1H), 7.40 (t,  $J = 8.0$  Hz, 1H), 5.88 (s, 1H), 3.20 (s, 4H), 2.74 (dt,  $J = 14.1, 8.9$  Hz, 2H),  
13 1.80 (dd,  $J = 14.3, 2.4$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  146.4, 133.4, 129.7, 128.8, 128.0, 126.8,  
14 69.8, 30.5.

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17 **4-(2,4-Dichlorophenyl)piperidin-4-ol (6c).** General procedure B. Alkaline work-up afforded 325  
18 mg of a white solid (65 %). LCMS ( $m/z$ ): 246.0  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  2.65 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.27 (dd,  
19  $J = 8.0, 1.9$  Hz, 2H), 7.01 (td,  $J = 8.0, 2.1$  Hz, 1H), 3.20 – 3.09 (m, 2H), 2.96 – 2.84 (m, 2H), 2.80 –  
20 2.66 (m, 3H), 1.91 (dt,  $J = 14.0, 2.4$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  140.9, 133.9, 131.9, 131.9, 127.9,  
21 76.0, 42.1, 36.6.

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24 **4-(2,5-Dichlorophenyl)-4-hydroxypiperidin-1-ium chloride (6d).** General procedure B.  
25 Concentration in vacuo gave 180 mg of a white solid (98%). LCMS ( $m/z$ ): 246.2  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  1.34  
26 min.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  9.42 – 8.91 (m, 2H), 7.79 (d,  $J = 2.6$  Hz, 1H), 7.45 (d,  $J = 8.4$  Hz, 1H),  
27 7.39 (dd,  $J = 8.5, 2.6$  Hz, 1H), 5.98 (s, 1H), 3.23 – 3.11 (m, 4H), 2.77 (dt,  $J = 14.1, 9.0$  Hz, 2H), 1.70  
28 (d,  $J = 13.9$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  146.1, 133.2, 132.1, 129.1, 128.8, 128.0, 69.4, 39.2,  
29 30.3.

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32 **4-(2,6-Dichlorophenyl)piperidin-4-ol (6e).** General procedure B. Alkaline work-up afforded 682  
33 mg of a white solid (96%). LCMS ( $m/z$ ): 246.0  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  0.88 min.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  8.93 (d,  
34  $J = 60.3$  Hz, 2H), 7.45 (d,  $J = 7.9$  Hz, 2H), 7.28 (dd,  $J = 8.4, 7.5$  Hz, 1H), 5.67 (s, 1H), 3.21 (s, 4H),  
35 2.90 – 2.76 (m, 2H), 2.16 (d,  $J = 13.7$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  139.9, 133.6, 132.0, 129.2,  
36 72.0, 32.1.

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39 **4-(3,4-Dichlorophenyl)piperidin-4-ol (6f).** General procedure B. Alkaline work-up afforded 702 mg  
40 of a white solid (98%). LCMS ( $m/z$ ): 246.0  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  1.86 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.61 (d,  $J = 2.2$   
41 Hz, 1H), 7.40 (d,  $J = 8.4$  Hz, 1H), 7.30 (dd,  $J = 8.4, 2.2$  Hz, 1H), 3.07 (td,  $J = 12.3, 2.7$  Hz, 2H), 2.97  
42 – 2.90 (m, 2H), 2.21 (s, 2H), 1.94 (ddd,  $J = 13.6, 12.2, 4.8$  Hz, 2H), 1.70 – 1.63 (m, 2H).  $^{13}\text{C}$  NMR  
43 ( $\text{CDCl}_3$ )  $\delta$  149.3, 132.4, 130.8, 127.1, 124.2, 71.2, 42.1, 38.9.

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46 **4-(3,5-Dichlorophenyl)-4-hydroxypiperidin-1-ium chloride (6g).** General procedure B.  
47 Concentration in vacuo gave 755 mg of a white solid (93%). LCMS ( $m/z$ ): 246.0  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  2.62  
48 min.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  9.03 (s, 2H), 7.52 (t,  $J = 1.9$  Hz, 1H), 7.45 (d,  $J = 1.9$  Hz, 2H), 5.79 (s,  
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3 1H), 3.17 (dtd,  $J = 22.5, 12.8, 11.9, 7.0$  Hz, 4H), 2.26 (td,  $J = 13.5, 5.0$  Hz, 2H), 1.74 (dd,  $J = 13.9,$   
4 2.3 Hz, 2H).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  152.7, 134.0, 126.5, 123.7, 68.5, 33.9.

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6 **4-Phenylpiperidin-4-ol (6h).** General procedure B. Alkaline work-up afforded 622 mg of a white  
7 solid (97%). LCMS ( $m/z$ ): 178.2  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  0.42 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.55 – 7.48 (m, 2H), 7.41  
8 – 7.32 (m, 2H), 7.31 – 7.22 (m, 1H), 3.10 (dd,  $J = 12.2, 2.6$  Hz, 2H), 2.98 – 2.89 (m, 2H), 2.22 (s,  
9 2H), 2.00 (ddd,  $J = 13.5, 12.2, 4.6$  Hz, 2H), 1.75 – 1.69 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  149.1, 128.4,  
10 126.9, 124.6, 71.5, 42.4, 39.3.

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13 **4-(*p*-Tolyl)piperidin-4-ol (6i).** General procedure B. Alkaline work-up afforded 621 mg of a white  
14 solid (95%). LCMS ( $m/z$ ): 192.1  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  0.62 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.37 (d,  $J = 8.3$  Hz, 2H),  
15 7.15 (d,  $J = 8.0$  Hz, 2H), 3.07 (dd,  $J = 12.2, 2.7$  Hz, 2H), 2.92 – 2.86 (m, 2H), 2.42 – 2.26 (m, 5H),  
16 1.96 (td,  $J = 13.0, 4.6$  Hz, 2H), 1.69 (dd,  $J = 14.1, 2.6$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  146.2, 136.5,  
17 129.1, 124.6, 71.2, 42.4, 39.3, 21.0.

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22 **4-(4-(Trifluoromethyl)phenyl)piperidin-4-ol (6j).** General procedure B. Alkaline work-up afforded  
23 702 mg of a light yellow solid (92%). LCMS ( $m/z$ ): 246.1  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  1.41-1.82 min.  $^1\text{H}$  NMR  
24 ( $\text{CDCl}_3$ )  $\delta$  7.66 – 7.56 (m, 4H), 3.11 (td,  $J = 12.3, 2.6$  Hz, 2H), 3.01 – 2.92 (m, 2H), 2.20 – 2.07 (m,  
25 2H), 2.01 (ddd,  $J = 13.5, 12.3, 4.8$  Hz, 2H), 1.74 – 1.65 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  152.9, 129.3  
26 (q,  $J = 32.4$  Hz), 125.4 (q,  $J = 3.7$  Hz), 125.1, 71.7, 42.3, 39.2.

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31 **4-(4-(Dimethylamino)phenyl)piperidin-4-ol (6k).** General procedure B. Alkaline work-up afforded  
32 675 mg of a light orange solid (98%). LCMS ( $m/z$ ): 221.2  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  0.31 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$   
33 7.40 – 7.31 (m, 2H), 6.76 – 6.68 (m, 2H), 3.09 (td,  $J = 12.1, 2.7$  Hz, 2H), 2.93 (s, 6H), 2.90 (dt,  $J =$   
34 11.9, 3.5 Hz, 2H), 2.07 (s, 2H), 1.96 (ddd,  $J = 13.3, 11.9, 4.5$  Hz, 2H), 1.77 – 1.68 (m, 2H).  $^{13}\text{C}$  NMR  
35 ( $\text{CDCl}_3$ )  $\delta$  149.6, 136.9, 125.4, 112.4, 70.9, 42.5, 40.7, 39.3.

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41 **4-(4-Fluorophenyl)piperidin-4-ol (6l).** General procedure B. Alkaline work-up afforded 600 mg of  
42 a light yellow solid (92%). LCMS ( $m/z$ ): 196.2  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  0.42 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.47 – 7.42  
43 (m, 2H), 7.01 (t,  $J = 8.7$  Hz, 2H), 3.07 (td,  $J = 12.2, 2.6$  Hz, 2H), 2.91 (ddd,  $J = 12.6, 4.2, 2.1$  Hz,  
44 2H), 1.95 (td,  $J = 13.0, 4.7$  Hz, 2H), 1.69 (dd,  $J = 14.1, 2.6$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  161.9 (d,  $J =$   
45 245.2 Hz), 144.9 (d,  $J = 3.0$  Hz), 126.4 (d,  $J = 8.0$  Hz), 115.1 (d,  $J = 21.1$  Hz), 71.4, 42.5, 39.5.

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51 **4-(2'-Chloro-[1,1'-biphenyl]-2-yl)piperidin-4-ol (6m).** General procedure B. Alkaline work-up  
52 afforded 200 mg of a white solid (95%). LCMS ( $m/z$ ): 288.0  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  2.06 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  
53  $\delta$  7.61 (dd,  $J = 8.1, 1.3$  Hz, 1H), 7.49 – 7.41 (m, 1H), 7.44 – 7.37 (m, 1H), 7.35 – 7.25 (m, 4H), 7.02  
54 (dd,  $J = 7.6, 1.5$  Hz, 1H), 3.05 – 2.95 (m, 2H), 2.90 – 2.81 (m, 2H), 2.37 (s, 2H), 2.09 (ddd,  $J = 13.9,$   
55 12.2, 4.6 Hz, 1H), 1.98 (ddd,  $J = 13.7, 12.2, 4.7$  Hz, 1H), 1.78 (ddt,  $J = 13.5, 10.5, 2.7$  Hz, 2H).  $^{13}\text{C}$   
56 NMR ( $\text{CDCl}_3$ )  $\delta$  145.6, 143.1, 137.2, 133.4, 132.2, 131.1, 129.4, 128.6, 128.2, 126.7, 126.5, 126.2,  
57 73.5, 39.2, 38.8.

**4-(2-Chlorophenyl)piperidin-4-ol (6n).** General procedure B. Alkaline work-up afforded 285 mg of a white solid (72 %). LCMS (*m/z*): 2121 [M+H]<sup>+</sup>, *t*<sub>R</sub> 0.48 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.57 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.34 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.6, 1.5 Hz, 1H), 7.18 (td, *J* = 7.6, 1.8 Hz, 1H), 3.15 (td, *J* = 12.4, 2.7 Hz, 2H), 2.99 – 2.89 (m, 2H), 2.63 (s, 1H), 2.29 (ddd, *J* = 13.4, 12.3, 4.7 Hz, 2H), 1.96 – 1.86 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 144.2, 131.9, 131.8, 128.5, 127.3, 127.2, 72.4, 42.2, 36.3.

**4-(4-Chlorophenyl)piperidin-4-ol (7b).** General procedure B. Alkaline work-up afforded 1.62 g of a beige solid (96%). LCMS (*m/z*): 311.1 [M+H]<sup>+</sup>, *t*<sub>R</sub> 0.76 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.43 – 7.38 (m, 2H), 7.32 – 7.27 (m, 2H), 3.05 (td, *J* = 12.3, 2.7 Hz, 2H), 2.91 – 2.84 (m, 2H), 2.18 (s, 2H, broad), 1.91 (ddd, *J* = 13.4, 12.2, 4.7 Hz, 2H), 1.71 – 1.60 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 147.7, 132.7, 128.5, 126.2, 71.3, 42.3, 39.3.

**4-(4-(3-Chlorophenyl)-4-hydroxypiperidin-1-yl)-1-(4-fluorophenyl)butan-1-one (8a).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 91 mg of the title compound as a white solid (68%). LCMS (*m/z*): 376.2 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.37 min. HRMS (*m/z*): C<sub>21</sub>H<sub>23</sub>ClFNO<sub>2</sub>: requires 376.1505 [M+H]<sup>+</sup>; found 376.1546. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.02 (t, *J* = 6.7 Hz, 2H), 7.44 (s, 1H), 7.35 – 7.18 (m, 3H), 7.14 (t, *J* = 8.4 Hz, 2H), 2.98 (t, *J* = 7.0 Hz, 2H), 2.78 (d, *J* = 11.4 Hz, 2H), 2.55 – 2.35 (m, 4H), 2.06 – 1.90 (m, 5H), 1.67 (d, *J* = 13.6 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 198.5, 165.7 (d, *J* = 254.5 Hz), 150.7, 134.4, 133.8 (d, *J* = 3.1 Hz), 130.8 (d, *J* = 9.2 Hz), 129.7, 127.2, 125.2, 122.9, 115.8 (d, *J* = 21.7 Hz), 71.3, 57.9, 49.4, 38.5, 36.4, 22.1.

**4-(4-(2,3-Dichlorophenyl)-4-hydroxypiperidin-1-yl)-1-(4-fluorophenyl)butan-1-one (8b).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 82 mg of the title compound as a white solid (68%). LCMS (*m/z*): 410.3 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.58 min. HRMS (*m/z*): C<sub>21</sub>H<sub>22</sub>Cl<sub>2</sub>FNO<sub>2</sub>: requires 410.1118 [M+H]<sup>+</sup>; found 410.1151. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.99 (dd, *J* = 8.6, 5.6 Hz, 2H), 7.41 (ddd, *J* = 16.5, 8.0, 1.5 Hz, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.6 Hz, 2H), 2.98 (t, *J* = 7.1 Hz, 3H), 2.94 (s, 1H), 2.81 (dt, *J* = 11.9, 3.2 Hz, 2H), 2.58 – 2.45 (m, 4H), 2.26 (td, *J* = 13.0, 4.4 Hz, 2H), 2.04 – 1.93 (m, 4H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 198.5, 165.7 (d, *J* = 254.4 Hz), 145.9, 134.9, 133.7 (d, *J* = 3.0 Hz), 130.8 (d, *J* = 9.2 Hz), 129.7, 127.5, 125.5, 115.7 (d, *J* = 21.8 Hz), 72.4, 57.7, 49.1, 36.3, 35.4, 21.8.

**4-(2,4-Dichlorophenyl)-1-(4-(4-fluorophenyl)-4-oxobutyl)-4-hydroxypiperidin-1-ium 2,2,2-trifluoroacetate (8c).** General procedure C. Purification by preparative HPLC (Method C) afforded the title compound as a white solid (44 mg, 60%). LCMS (*m/z*): 410.3 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.47 min. HRMS (*m/z*): C<sub>21</sub>H<sub>22</sub>Cl<sub>2</sub>FNO<sub>2</sub>: requires 410.1012 [M+H]<sup>+</sup>; found 410.1094. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.05 (s, 1H), 8.00 – 7.92 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.12 (td, *J* = 8.2, 4.1 Hz, 2H), 5.59 (s, 1H), 3.58 (d, *J* = 11.3 Hz, 2H), 3.36 (q, *J* = 11.2 Hz, 2H), 3.28 – 3.10 (m, 6H), 2.35 (d, *J* = 14.1 Hz, 2H), 2.22

(p,  $J = 6.8$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  196.78, 166.1 (d,  $J = 255.6$  Hz), 137.8, 133.8, 132.7 (d,  $J = 3.1$  Hz), 132.2, 130.8 (d,  $J = 9.5$  Hz), 129.2, 116.0 (d,  $J = 21.9$  Hz), 73.3, 56.7, 48.5, 35.1, 33.7, 18.2.

**4-(4-(2,5-Dichlorophenyl)-4-hydroxypiperidin-1-yl)-1-(4-fluorophenyl)butan-1-one (8d).**

General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/ $\text{NH}_4\text{OH}$ ) gave 91 mg of the title compound as a white solid (70%). LCMS ( $m/z$ ): 410.3  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.65 min. HRMS ( $m/z$ ):  $\text{C}_{21}\text{H}_{22}\text{Cl}_2\text{FNO}_2$ : requires 410.1012  $[\text{M}+\text{H}]^+$ ; found 410.1093.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.04 – 7.94 (m, 2H), 7.53 (d,  $J = 2.5$  Hz, 1H), 7.25 (d,  $J = 8.5$  Hz, 1H), 7.17 – 7.07 (m, 3H), 2.97 (t,  $J = 7.0$  Hz, 2H), 2.77 (dt,  $J = 10.8, 2.8$  Hz, 3H), 2.51 – 2.42 (m, 4H), 2.28 (td,  $J = 13.0, 4.4$  Hz, 2H), 1.96 (p,  $J = 7.1$  Hz, 2H), 1.86 (dd,  $J = 13.7, 2.6$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  198.7, 165.7 (d,  $J = 254.4$  Hz), 145.6, 133.8 (d,  $J = 3.1$  Hz), 133.2, 132.8, 130.8 (d,  $J = 9.1$  Hz), 130.1, 128.4, 127.7, 115.7 (d,  $J = 21.8$  Hz), 72.0, 57.7, 49.1, 36.3, 35.2, 21.9.

**4-(4-(2,6-Dichlorophenyl)-4-hydroxypiperidin-1-yl)-1-(4-fluorophenyl)butan-1-one (8e).**

General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/ $\text{NH}_4\text{OH}$ ) gave 69 mg of the title compound as a white solid (73%). LCMS ( $m/z$ ): 410.72  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.50 min. HRMS ( $m/z$ ):  $\text{C}_{21}\text{H}_{22}\text{Cl}_2\text{FNO}_2$ : requires 410.1111  $[\text{M}+\text{H}]^+$ ; found 410.1066.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.01 (dd,  $J = 8.7, 5.6$  Hz, 2H), 7.29 (d,  $J = 7.9$  Hz, 2H), 7.12 (t,  $J = 8.6$  Hz, 2H), 7.04 (t,  $J = 8.0$  Hz, 1H), 3.24 (s, 1H), 2.98 (t,  $J = 7.1$  Hz, 2H), 2.81 – 2.69 (m, 4H), 2.54 – 2.48 (m, 2H), 2.45 (t,  $J = 7.1$  Hz, 2H), 2.06 (d,  $J = 13.6$  Hz, 2H), 1.97 (p,  $J = 7.1$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  198.8, 165.7 (d,  $J = 254.1$  Hz), 140.7, 134.0, 133.8 (d,  $J = 3.0$  Hz), 132.0, 130.8 (d,  $J = 9.2$  Hz), 128.2, 115.7 (d,  $J = 21.7$  Hz), 75.8, 57.8, 49.2, 36.4, 36.2, 22.1.

**4-(4-(3,4-Dichlorophenyl)-4-hydroxypiperidin-1-yl)-1-(4-fluorophenyl)butan-1-one (8f).**

General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/ $\text{NH}_4\text{OH}$ ) gave 84 mg of the title compound as a white solid (70%). LCMS ( $m/z$ ): 410.2  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.69 min. HRMS ( $m/z$ ):  $\text{C}_{21}\text{H}_{22}\text{Cl}_2\text{FNO}_2$ : requires 410.1111  $[\text{M}+\text{H}]^+$ ; found 410.1066.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.03 (dd,  $J = 8.7, 5.5$  Hz, 2H), 7.55 (d,  $J = 2.1$  Hz, 1H), 7.40 (d,  $J = 8.5$  Hz, 1H), 7.31 – 7.23 (m, 1H), 7.16 (t,  $J = 8.6$  Hz, 2H), 2.99 (t,  $J = 7.0$  Hz, 2H), 2.80 (dt,  $J = 11.4, 2.9$  Hz, 2H), 2.54 – 2.37 (m, 4H), 2.08 – 1.91 (m, 4H), 1.66 (dd,  $J = 14.1, 2.6$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  198.4, 167.0, 164.5, 148.9, 133.8, 133.8, 132.5, 130.9, 130.8, 130.7, 130.3, 127.2, 124.3, 115.9, 115.7, 77.5, 77.2, 76.8, 71.1, 57.9, 49.3, 38.4, 36.3, 22.0.

**4-(4-(3,5-Dichlorophenyl)-4-hydroxypiperidin-1-yl)-1-(4-fluorophenyl)butan-1-one (8g).**

General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/ $\text{NH}_4\text{OH}$ ) gave 92 mg of the title compound as a white solid (62%). LCMS ( $m/z$ ): 410.7  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.59 min. HRMS ( $m/z$ ):  $\text{C}_{21}\text{H}_{22}\text{Cl}_2\text{FNO}_2$ : requires 410.1084  $[\text{M}+\text{H}]^+$ ; found 410.1097.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  8.08 (dd,  $J = 8.5, 5.6$  Hz, 2H), 7.41 (t,  $J = 1.9$  Hz, 1H), 7.35 (t,  $J = 8.7$  Hz, 2H), 7.28 (d,  $J = 1.9$  Hz, 2H), 5.04 (s,

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3 1H), 2.95 (t,  $J = 6.6$  Hz, 2H), 2.57 (d,  $J = 10.9$  Hz, 2H), 2.35 (t,  $J = 6.8$  Hz, 2H), 2.29 (t,  $J = 11.4$  Hz,  
4 2H), 1.85 (t,  $J = 6.7$  Hz, 2H), 1.58 (dt,  $J = 12.9, 6.4$  Hz, 2H), 1.42 (d,  $J = 12.9$  Hz, 2H).  $^{13}\text{C}$  NMR  
5 (DMSO- $d_6$ )  $\delta$  198.2, 164.7 (d,  $J = 251.1$  Hz), 154.7, 134.1 (d,  $J = 2.9$  Hz), 133.7, 130.8 (d,  $J = 9.4$   
6 Hz), 125.8, 123.8, 115.6 (d,  $J = 21.7$  Hz), 69.9, 57.2, 48.7, 37.5, 35.6, 22.2.

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10 **1-(4-Fluorophenyl)-4-(4-hydroxy-4-phenylpiperidin-1-yl)butan-1-one (8h)**. General procedure  
11 C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 101 mg of the title  
12 compound as a white solid (88%). LCMS ( $m/z$ ): 342.3 [M+H]<sup>+</sup>,  $t_R$  2.92 min. HRMS ( $m/z$ ):  
13 C<sub>21</sub>H<sub>24</sub>FNO<sub>2</sub>: requires 342.1864 [M+H]<sup>+</sup>; found 342.1873.  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  8.08 – 7.99 (m, 2H),  
14 7.48 (dd,  $J = 7.6, 1.7$  Hz, 2H), 7.36 (t,  $J = 7.7$  Hz, 2H), 7.31 – 7.22 (m, 1H), 7.15 (t,  $J = 8.6$  Hz, 2H),  
15 3.00 (t,  $J = 7.1$  Hz, 2H), 2.81 (dt,  $J = 11.7, 3.1$  Hz, 2H), 2.56 – 2.42 (m, 4H), 2.05 (ddd,  $J = 28.3,$   
16 13.9, 5.8 Hz, 4H), 1.89 (s, 1H), 1.73 (dd,  $J = 14.2, 2.6$  Hz, 2H).  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>)  $\delta$  198.5, 165.7 (d,  
17  $J = 254.3$  Hz), 148.5, 133.8 (d,  $J = 3.0$  Hz), 130.8 (d,  $J = 9.3$  Hz), 128.4, 127.1, 124.6, 115.7 (d,  $J =$   
18 21.7 Hz), 71.4, 57.9, 49.5, 38.5, 36.4, 22.0.

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25 **1-(4-Fluorophenyl)-4-(4-hydroxy-4-(*p*-tolyl)piperidin-1-yl)butan-1-one (8i)**. General procedure  
26 C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 84 mg of the title compound  
27 as a white solid (80%). LCMS ( $m/z$ ): 356.2 [M+H]<sup>+</sup>,  $t_R$  3.22 min. HRMS ( $m/z$ ): C<sub>22</sub>H<sub>26</sub>FNO<sub>2</sub>: requires  
28 356.2067 [M+H]<sup>+</sup>; found 356.2068.  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  8.01 (dd,  $J = 8.7, 5.6$  Hz, 2H), 7.34 (d,  $J =$   
29 8.0 Hz, 2H), 7.18 – 7.08 (m, 4H), 2.98 (t,  $J = 7.1$  Hz, 2H), 2.78 (dt,  $J = 12.1, 3.3$  Hz, 2H), 2.52 – 2.40  
30 (m, 4H), 2.33 (s, 3H), 2.09 – 1.94 (m, 5H), 1.70 (dd,  $J = 14.2, 2.6$  Hz, 2H).  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>)  $\delta$  198.5,  
31 165.7 (d,  $J = 254.3$  Hz), 145.6, 136.7, 133.8 (d,  $J = 3.1$  Hz), 130.8 (d,  $J = 9.3$  Hz), 129.1, 124.6, 115.7  
32 (d,  $J = 21.8$  Hz), 71.1, 57.9, 49.6, 38.5, 36.4, 21.9, 21.1. CDCl<sub>3</sub>

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38 **1-(4-Fluorophenyl)-4-(4-hydroxy-4-(4-(trifluoromethyl)phenyl)piperidin-1-yl)butan-1-one**  
39 **(8j)**. General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 65  
40 mg of the title compound as a white solid (69%). LCMS ( $m/z$ ): 410.2 [M+H]<sup>+</sup>,  $t_R$  3.59 min. HRMS  
41 ( $m/z$ ): C<sub>22</sub>H<sub>23</sub>F<sub>4</sub>NO<sub>2</sub>: requires 410.1756 [M+H]<sup>+</sup>; found 410.1778.  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  8.00 (dd,  $J =$   
42 8.6, 5.5 Hz, 2H), 7.57 (s, 4H), 7.13 (t,  $J = 8.6$  Hz, 2H), 2.99 (t,  $J = 7.0$  Hz, 2H), 2.85 (d,  $J = 11.2$  Hz,  
43 2H), 2.57 – 2.45 (m, 4H), 2.17 – 1.90 (m, 5H), 1.79 – 1.63 (m, 2H).  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>)  $\delta$  198.4, 165.8  
44 (d,  $J = 254.7$  Hz), 152.3, 133.7 (d,  $J = 3.1$  Hz), 129.4 (d,  $J = 32.4$  Hz), 125.4 (q,  $J = 3.7$  Hz), 125.2,  
45 124.3 (q,  $J = 272.9$  Hz), 115.8 (d,  $J = 21.9$  Hz), 71.3, 57.9, 49.3, 38.2, 36.3, 21.7.

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52 **4-(4-(4-(Dimethylamino)phenyl)-4-hydroxypiperidin-1-yl)-1-(4-fluorophenyl)butan-1-one (8k)**.  
53 General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 60 mg of  
54 the title compound as a light orange solid (62%). LCMS ( $m/z$ ): 385.4 [M+H]<sup>+</sup>,  $t_R$  1.41 min. HRMS  
55 ( $m/z$ ): C<sub>23</sub>H<sub>29</sub>FN<sub>2</sub>O<sub>2</sub>: requires 385.2310 [M+H]<sup>+</sup>; found 385.2274.  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  7.99 (dd,  $J =$   
56 8.7, 5.6 Hz, 2H), 7.32 (d,  $J = 8.8$  Hz, 2H), 7.12 (t,  $J = 8.6$  Hz, 2H), 6.70 (d,  $J = 8.9$  Hz, 2H), 3.01 (t,  
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$J = 7.0$  Hz, 2H), 2.92 (s, 6H), 2.93 – 2.86 (m, 2H), 2.60 (dt,  $J = 14.8$ , 8.4 Hz, 4H), 2.14 (td,  $J = 13.3$ , 4.3 Hz, 2H), 2.02 (p,  $J = 7.3$  Hz, 2H), 1.94 (s, 1H), 1.77 (dd,  $J = 14.3$ , 2.7 Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  198.2, 165.8 (d,  $J = 254.4$  Hz), 149.8, 135.8, 133. (d,  $J = 3.0$  Hz), 130.8 (d,  $J = 9.2$  Hz), 125.5, 115.7 (d,  $J = 21.8$  Hz), 112.5, 70.4, 57.5, 49.4, 40.7, 37.7, 36.3, 21.2.

**1-(4-Fluorophenyl)-4-(4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl)butan-1-one (8l).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/ $\text{NH}_4\text{OH}$ ) gave 80 mg of the title compound as a white solid (74%). LCMS ( $m/z$ ): 360.3  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.09 min. HRMS ( $m/z$ ):  $\text{C}_{21}\text{H}_{23}\text{F}_2\text{NO}_2$ : requires 360.1697  $[\text{M}+\text{H}]^+$ ; found 360.1777.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.12 – 7.96 (m, 2H), 7.44 – 7.36 (m, 2H), 7.13 (t,  $J = 8.6$  Hz, 2H), 7.00 (t,  $J = 8.7$  Hz, 2H), 2.98 (t,  $J = 7.0$  Hz, 2H), 2.80 (dt,  $J = 11.7$ , 3.0 Hz, 2H), 2.55 – 2.41 (m, 4H), 2.02 (dt,  $J = 14.3$ , 10.2 Hz, 5H), 1.70 (dd,  $J = 14.2$ , 2.6 Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  198.5, 165.8 (d,  $J = 254.4$  Hz), 161.9 (d,  $J = 245.3$  Hz), 144.2 (d,  $J = 2.6$  Hz), 133.8 (d,  $J = 3.3$  Hz), 130.8 (d,  $J = 9.2$  Hz), 126.4 (d,  $J = 8.0$  Hz), 115.7 (d,  $J = 21.8$  Hz), 115.1 (d,  $J = 21.1$  Hz), 71.1, 57.9, 49.5, 38.5, 36.4, 21.9.

**4-(2'-Chloro-[1,1'-biphenyl]-2-yl)-1-(4-(4-fluorophenyl)-4-oxobutyl)-4-hydroxypiperidin-1-ium 2,2,2-trifluoroacetate (8m).** General procedure C. Purification by preparative HPLC (Method C) afforded 95 mg of the title compound as a transparent oil (76%). LCMS ( $m/z$ ): 452.2  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  4.00 min. HRMS ( $m/z$ ):  $\text{C}_{27}\text{H}_{27}\text{ClFNO}_2$ : requires 452.1787  $[\text{M}+\text{H}]^+$ ; found 452.1811.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  12.19 (s, 1H), 7.94 (dd,  $J = 8.6$ , 5.3 Hz, 2H), 7.53 (d,  $J = 8.0$  Hz, 1H), 7.49 – 7.38 (m, 2H), 7.33 (ddd,  $J = 7.5$ , 5.1, 2.7 Hz, 2H), 7.25 (d,  $J = 7.6$  Hz, 2H), 7.12 (t,  $J = 8.5$  Hz, 2H), 7.02 (d,  $J = 7.5$  Hz, 1H), 3.44 (dd,  $J = 26.7$ , 11.6 Hz, 2H), 3.22 – 2.99 (m, 6H), 2.71 – 2.58 (m, 1H), 2.46 (td,  $J = 14.0$ , 4.1 Hz, 1H), 2.35 (s, 1H), 2.15 (t,  $J = 7.2$  Hz, 2H), 2.01 (dd,  $J = 30.5$ , 14.6 Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  196.7, 166.1 (d,  $J = 255.6$  Hz), 142.3, 142.1, 137.1, 133.4, 132.8 (d,  $J = 3.0$  Hz), 132.4, 130.9, 130.8 (d,  $J = 9.5$  Hz), 129.6, 129.2, 128.8, 127.8, 126.7, 126.4, 116.0 (d,  $J = 21.9$  Hz), 71.4, 56.6, 48.6, 35.9, 35.6, 35.1, 18.2.

**4-(2-Chlorophenyl)-1-(4-(4-fluorophenyl)-4-oxobutyl)-4-hydroxypiperidin-1-ium 2,2,2-trifluoroacetate (8n).** General procedure C. Purification by preparative HPLC (Method C) afforded 88 mg of the title compound as a white solid (62%). LCMS ( $m/z$ ): 376.2  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.37 min. HRMS ( $m/z$ ):  $\text{C}_{21}\text{H}_{23}\text{ClFNO}$ : requires 376.1474  $[\text{M}+\text{H}]^+$ ; found 376.1479.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  12.14 (s, 1H), 8.01 – 7.92 (m, 2H), 7.46 (dd,  $J = 7.7$ , 1.9 Hz, 1H), 7.37 (dd,  $J = 7.5$ , 1.8 Hz, 1H), 7.32 – 7.19 (m, 2H), 7.13 (t,  $J = 8.5$  Hz, 2H), 4.05 (s, 1H), 3.58 (d,  $J = 11.5$  Hz, 2H), 3.36 (q,  $J = 11.2$  Hz, 2H), 3.15 (q,  $J = 6.5$ , 5.2 Hz, 4H), 2.67 (td,  $J = 13.9$ , 4.1 Hz, 2H), 2.31 (d,  $J = 14.1$  Hz, 2H), 2.22 (p,  $J = 6.6$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  196.6, 166.0 (d,  $J = 255.5$  Hz), 140.6, 132.6 (d,  $J = 3.0$  Hz), 131.9, 131.5, 130.7 (d,  $J = 9.4$  Hz), 129.5, 127.7, 127.1, 115.9 (d,  $J = 22.0$  Hz), 69.8, 56.6, 48.4, 35.0, 32.9, 18.1.

**4-Chlorobut-1-yne (9).** 3-Butynol (25.0 mL, 330 mmol) and pyridine (2.66 mL, 33 mmol) were placed in a 100 mL roundbottomed flask, and the mixture was cooled in an ice bath. Then, thionyl chloride (24.4 mL, 334 mmol) was added dropwise for 10 min. The flask was shaken occasionally during the addition, and after the thionyl chloride was added, the mixture was heated under reflux for 30 min. Fractional distillation of the products gave 4-chloro-1-butyne as a light-yellow liquid (24 mL, 82%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.58 (t, *J* = 7.1 Hz, 2H), 2.63 (td, *J* = 7.1, 2.6 Hz, 2H), 2.07 (t, *J* = 2.7 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 80.2, 70.5, 41.9, 22.8.

**1-(4-Chlorobut-1-yn-1-yl)-2-fluorobenzene (12a).** General procedure D. Purification by FCC (*n*-hexanes) gave 1.24 g of a yellow oil (72%). LCMS (*m/z*): 183.1 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.05 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.47 – 7.40 (m, 1H), 7.34 – 7.26 (m, 1H), 7.15 – 7.03 (m, 2H), 3.73 (t, *J* = 7.2 Hz, 2H), 2.95 (t, *J* = 7.2 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 162.9 (d, *J* = 251.0 Hz), 133.8 (d, *J* = 1.5 Hz), 129.9 (d, *J* = 7.9 Hz), 124.0 (d, *J* = 3.8 Hz), 115.6 (d, *J* = 21.0 Hz), 111.7 (d, *J* = 15.7 Hz), 91.2 (d, *J* = 3.3 Hz), 75.9 (d, *J* = 1.1 Hz), 42.1, 24.1.

**1-(4-Chlorobut-1-yn-1-yl)-3-fluorobenzene (12b).** General procedure D. Purification by FCC (*n*-hexanes) gave 1.55 g of a yellow oil (90%). LCMS (*m/z*): 183.0 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.02 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.32 – 7.25 (m, 1H), 7.22 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.14 (ddd, *J* = 9.5, 2.6, 1.4 Hz, 1H), 7.03 (tdd, *J* = 8.4, 2.7, 1.2 Hz, 1H), 3.71 (t, *J* = 7.2 Hz, 2H), 2.91 (t, *J* = 7.2 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 162.6 (d, *J* = 246.3 Hz), 129.9 (d, *J* = 8.5 Hz), 127.7 (d, *J* = 3.1 Hz), 125.1 (d, *J* = 9.5 Hz), 118.6 (d, *J* = 22.7 Hz), 115.6 (d, *J* = 21.2 Hz), 86.9, 81.5 (d, *J* = 3.4 Hz), 42.1, 23.9.

**1-(4-Chlorobut-1-yn-1-yl)-2,3-difluorobenzene (12c).** General procedure D. Purification by FCC (*n*-hexanes) gave 1.65 g of a yellow oil (87%). LCMS (*m/z*): 201.1 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.02 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.20 – 7.11 (m, 1H), 7.15 – 7.05 (m, 1H), 7.00 (dddd, *J* = 8.3, 7.8, 4.9, 1.6 Hz, 1H), 3.70 (t, *J* = 7.2 Hz, 2H), 2.93 (td, *J* = 7.2, 0.7 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 151.3 (dd, *J* = 252.7, 13.4 Hz), 150.7 (dd, *J* = 248.3, 12.2 Hz), 128.5 (d, *J* = 3.4 Hz), 123.9 (dd, *J* = 7.3, 4.9 Hz), 117.4 (d, *J* = 17.5 Hz), 113.9 (dd, *J* = 12.3, 1.8 Hz), 92.6 (d, *J* = 3.8 Hz), 74.9 (dd, *J* = 4.6, 1.3 Hz), 41.9, 24.1.

**1-(4-Chlorobut-1-yn-1-yl)-2,4-difluorobenzene (12d).** General procedure D. Purification by FCC (*n*-hexanes) gave 1.72 g of a yellow oil (82.3%). LCMS (*m/z*): 201.1 [M+H]<sup>+</sup>, *t*<sub>R</sub> 2.99 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.42 – 7.35 (m, 1H), 6.86 – 6.78 (m, 2H), 3.69 (t, *J* = 7.2 Hz, 2H), 2.91 (t, *J* = 7.2 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 163.3 (dd, *J* = 253.7, 12.2 Hz), 162.6 (dd, *J* = 251.7, 11.3 Hz), 134.6 (dd, *J* = 9.7, 2.8 Hz), 111.6 (dd, *J* = 21.9, 3.8 Hz), 108.1 (dd, *J* = 16.0, 4.1 Hz), 104.3 (dd, *J* = 24.9, 0.2 Hz), 90.9 (dd, *J* = 3.4, 1.8 Hz), 75.0 (d, *J* = 1.4 Hz), 42.04, 24.1.

**2-(4-Chlorobut-1-yn-1-yl)-1,4-difluorobenzene (12e).** General procedure D. Purification by FCC (*n*-hexanes) gave 1.45 g of a yellow oil (70%). LCMS (*m/z*): 201.1 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.00 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.10 (ddd, *J* = 8.5, 5.4, 2.9 Hz, 1H), 7.04 – 6.93 (m, 2H), 3.69 (t, *J* = 7.2 Hz, 2H), 2.92 (t,

$J = 7.2$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  159.3 (d,  $J = 249.6$  Hz), 158.2 (d,  $J = 242.8$  Hz), 128.8 (d,  $J = 81.5$  Hz), 119.8 (dd,  $J = 25.2, 1.9$  Hz), 116.7 (dd,  $J = 10.6, 8.6$  Hz), 116.5 (dd,  $J = 10.5, 8.5$  Hz), 92.3 (d,  $J = 3.4$  Hz), 75.1 (d,  $J = 2.6$  Hz), 41.9, 24.1.

**2-(4-Chlorobut-1-yn-1-yl)-1,3-difluorobenzene (12f).** General procedure D. Purification by FCC (*n*-hexanes) gave 992 mg of a pink oil (53%). LCMS ( $m/z$ ): 200.9  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  2.97 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.32 – 7.20 (m, 1H), 6.96 – 6.86 (m, 2H), 3.74 (t,  $J = 7.3$  Hz, 2H), 2.99 (t,  $J = 7.3$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  163.5 (d,  $J = 253.2$  Hz), 163.4 (d,  $J = 253.3$  Hz), 129.6 (t,  $J = 10.0$  Hz), 111.4 (dd,  $J = 4.5, 0.3$  Hz), 111.2 (dd,  $J = 4.5, 1.2$  Hz), 102.2 (t,  $J = 19.8$  Hz), 96.2 (t,  $J = 3.1$  Hz), 69.6 (t,  $J = 1.4$  Hz), 41.8, 24.3.

**4-(4-Chlorobut-1-yn-1-yl)-1,2-difluorobenzene (12g).** General procedure D. Purification by FCC (*n*-hexanes) gave 1.53g of a yellow oil (81%). LCMS ( $m/z$ ): 200.9  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.03 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.21 (ddd,  $J = 10.9, 7.5, 2.0$  Hz, 1H), 7.13 (dd,  $J = 4.6, 1.6$  Hz, 1H), 7.08 (dt,  $J = 10.2, 8.2$  Hz, 1H), 3.67 (t,  $J = 7.1$  Hz, 2H), 2.86 (t,  $J = 7.1$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  150.6 (dd,  $J = 250.9, 12.5$  Hz), 150.0 (dd,  $J = 248.7, 13.0$  Hz), 128.4 (dd,  $J = 6.4, 3.6$  Hz), 120.8 (d,  $J = 18.3$  Hz), 117.5 (d,  $J = 17.8$  Hz), 86.5 (d,  $J = 1.9$  Hz), 80.6 (t,  $J = 2.3$  Hz), 42.1, 23.8.

**1-(4-Chlorobut-1-yn-1-yl)-3,5-difluorobenzene (12h).** General procedure D. Purification by FCC (*n*-hexanes) gave 1.61 g of a yellow oil (85%). LCMS ( $m/z$ ): 200.9  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.03 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.98 – 6.91 (m, 2H), 6.79 (tt,  $J = 9.0, 2.4$  Hz, 1H), 3.70 (t,  $J = 7.1$  Hz, 2H), 2.90 (t,  $J = 7.1$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  162.8 (d,  $J = 248.5$  Hz), 162.7 (d,  $J = 248.6$  Hz), 125.9 (t,  $J = 11.8$  Hz), 114.9 (d,  $J = 7.4$  Hz), 114.7 (d,  $J = 7.4$  Hz), 104.5 (t,  $J = 25.4$  Hz), 88.2, 80.6 (t,  $J = 3.9$  Hz), 41.94, 23.8.

**1-Chloro-2-(4-chlorobut-1-yn-1-yl)benzene (12i).** General procedure E. Purification by FCC (*n*-hexanes) gave 1.12 g of a light-yellow liquid (88%). LCMS ( $m/z$ ): 200.4  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.02 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.45 (dd,  $J = 7.5, 1.9$  Hz, 1H), 7.38 (dd,  $J = 7.9, 1.5$  Hz, 1H), 7.21 (dtd,  $J = 16.1, 7.4, 1.6$  Hz, 2H), 3.72 (t,  $J = 7.3$  Hz, 2H), 2.95 (t,  $J = 7.3$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  136.0, 133.5, 129.3, 129.2, 126.5, 123.1, 91.3, 79.5, 42.1, 24.1.

**1-(4-Chlorobut-1-yn-1-yl)-2-methylbenzene (12j).** General procedure E. Purification by FCC (*n*-hexanes) gave 1.32 g of a transparent liquid (92%). LCMS ( $m/z$ ): 179.1  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.03 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.39 (dd,  $J = 7.4, 1.3$  Hz, 1H), 7.23 – 7.17 (m, 2H), 7.17 – 7.07 (m, 1H), 3.71 (t,  $J = 7.2$  Hz, 2H), 2.93 (t,  $J = 7.2$  Hz, 2H), 2.44 (s, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  140.4, 132.0, 129.5, 128.2, 125.6, 123.0, 89.7, 81.5, 42.5, 24.1, 20.8.

**4-Chloro-1-(2-fluorophenyl)butan-1-one (13a).** General procedure F. Purification by FCC (*n*-hexanes/EtOAc 10:0.1) gave 1.12 g of a yellow oil (82%). LCMS:  $t_{\text{R}}$  2.91 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.87 (td,  $J = 7.6, 1.9$  Hz, 1H), 7.52 (dddd,  $J = 8.3, 7.1, 5.0, 1.9$  Hz, 1H), 7.23 (ddd,  $J = 7.8, 7.3, 1.1$

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3 Hz, 1H), 7.14 (ddd,  $J = 11.3, 8.3, 1.1$  Hz, 1H), 3.66 (t,  $J = 6.4$  Hz, 2H), 3.18 (td,  $J = 6.9, 3.1$  Hz, 2H),  
4 2.27 – 2.17 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  197.4 (d,  $J = 4.0$  Hz), 162.2 (d,  $J = 254.6$  Hz), 134.8 (d,  $J$   
5 = 9.1 Hz), 130.7 (d,  $J = 2.7$  Hz), 125.6 (d,  $J = 13.0$  Hz), 124.6 (d,  $J = 3.4$  Hz), 116.9 (d,  $J = 24.0$  Hz),  
6 44.6, 40.5 (d,  $J = 7.8$  Hz), 26.8 (d,  $J = 2.1$  Hz).

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9 **4-Chloro-1-(3-fluorophenyl)butan-1-one (13b)**. General procedure F. Purification by FCC (*n*-  
10 hexanes/EtOAc 10:0.1) gave 449 mg of a dark red oil (41%). LCMS ( $m/z$ ): 201.1  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  2.91  
11 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.77 (ddd,  $J = 7.8, 1.6, 1.0$  Hz, 1H), 7.66 (ddd,  $J = 9.5, 2.6, 1.5$  Hz, 1H),  
12 7.46 (td,  $J = 8.0, 5.5$  Hz, 1H), 7.28 (tdd,  $J = 8.3, 2.7, 1.0$  Hz, 1H), 3.69 (t,  $J = 6.2$  Hz, 2H), 3.17 (t,  $J$   
13 = 6.9 Hz, 2H), 2.27 – 2.20 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  197.7 (d,  $J = 2.0$  Hz), 162.9 (d,  $J = 248.0$   
14 Hz), 138.9 (d,  $J = 6.0$  Hz), 130.4 (d,  $J = 7.6$  Hz), 123.9 (d,  $J = 3.0$  Hz), 120.3 (d,  $J = 21.4$  Hz), 114.8  
15 (d,  $J = 22.3$  Hz), 44.6, 35.5, 26.7.

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18 **4-Chloro-1-(2,3-difluorophenyl)butan-1-one (13c)**. General procedure F. Purification by FCC (*n*-  
19 hexanes/EtOAc 10:0.1) gave 745 mg of a yellow oil (81%). LCMS:  $t_{\text{R}}$  2.94 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  
20  $\delta$  7.61 (ddt,  $J = 7.8, 6.0, 1.7$  Hz, 1H), 7.36 (dddd,  $J = 9.8, 8.2, 7.4, 1.8$  Hz, 1H), 7.17 (tdd,  $J = 8.1, 4.6,$   
21 1.5 Hz, 1H), 3.66 (t,  $J = 6.3$  Hz, 2H), 3.18 (td,  $J = 6.9, 3.1$  Hz, 2H), 2.22 (dddd,  $J = 13.3, 6.9, 6.2, 0.8$   
22 Hz, 32H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  196.2 (dd,  $J = 3.8, 2.6$  Hz), 151.1 (dd,  $J = 250.1, 14.0$  Hz), 150.5 (dd,  
23  $J = 256.7, 13.7$  Hz), 127.5 (d,  $J = 9.9$  Hz), 125.1 (dd,  $J = 3.6, 1.6$  Hz), 124.5 (dd,  $J = 6.6, 4.5$  Hz),  
24 121.6 (dd,  $J = 17.5, 1.4$  Hz), 44.4, 40.5 (d,  $J = 7.0$  Hz), 26.6 (d,  $J = 2.0$  Hz).

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27 **4-Chloro-1-(2,4-difluorophenyl)butan-1-one (13d)**. General procedure F. Purification by FCC (*n*-  
28 hexanes/EtOAc 10:0.1) gave 294 mg of a yellow oil (58%). LCMS:  $t_{\text{R}}$  2.91 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$   
29 7.94 (td,  $J = 8.6, 6.6$  Hz, 1H), 7.01 – 6.91 (m, 1H), 6.87 (ddd,  $J = 11.1, 8.6, 2.4$  Hz, 1H), 3.65 (t,  $J =$   
30 6.3 Hz, 2H), 3.14 (td,  $J = 6.9, 3.3$  Hz, 2H), 2.20 (dddd,  $J = 13.3, 6.9, 6.2, 0.8$  Hz, 2H).  $^{13}\text{C}$  NMR (101  
31 MHz,  $\text{CDCl}_3$ )  $\delta$  195.7 (d,  $J = 4.8$  Hz), 165.9 (dd,  $J = 257.2, 12.4$  Hz), 162.9 (dd,  $J = 257.5, 12.6$  Hz),  
32 132.7 (dd,  $J = 10.5, 4.3$  Hz), 122.0 (dd,  $J = 13.2, 3.6$  Hz), 112.4 (dd,  $J = 21.4, 3.4$  Hz), 104.9 (dd,  $J =$   
33 27.9, 25.4 Hz), 44.5 (s), 40.3 (d,  $J = 7.8$  Hz), 26.7 (d,  $J = 2.2$  Hz).

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36 **4-Chloro-1-(2,5-difluorophenyl)butan-1-one (13e)**. General procedure F. Purification by FCC (*n*-  
37 hexanes/EtOAc 10:0.1) gave 384 mg of a clear oil (82%). LCMS:  $t_{\text{R}}$  2.90 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$   
38 7.50 (ddd,  $J = 8.7, 5.5, 3.3$  Hz, 1H), 7.18 (ddt,  $J = 9.0, 7.0, 3.6$  Hz, 1H), 7.10 (ddd,  $J = 10.1, 9.0, 4.2$   
39 Hz, 1H), 3.62 (t,  $J = 6.3$  Hz, 2H), 3.13 (td,  $J = 6.9, 3.2$  Hz, 2H), 2.17 (pd,  $J = 6.6, 0.8$  Hz, 2H).  $^{13}\text{C}$   
40 NMR ( $\text{CDCl}_3$ )  $\delta$  195.8 (dd,  $J = 4.8, 1.3$  Hz), 158.7 (dd,  $J = 244.6, 2.2$  Hz), 158.1 (dd,  $J = 250.8, 2.4$   
41 Hz), 126.4 (dd,  $J = 15.8, 6.2$  Hz), 121.4 (dd,  $J = 24.6, 9.4$  Hz), 118.3 (dd,  $J = 27.4, 7.9$  Hz), 116.4  
42 (dd,  $J = 25.0, 3.3$  Hz), 44.4, 40.3 (d,  $J = 8.2$  Hz), 26.6 (d,  $J = 2.3$  Hz).

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45 **4-Chloro-1-(2,6-difluorophenyl)butan-1-one (13f)**. General procedure F. Purification by FCC (*n*-  
46 hexanes/EtOAc 10:0.1) gave 408 mg of a clear oil (79%). LCMS ( $m/z$ ): 219.1  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  2.90 min.  
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<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.39 (tt, *J* = 8.4, 6.3 Hz, 1H), 6.94 (t, *J* = 8.2 Hz, 2H), 3.63 (t, *J* = 6.3 Hz, 2H), 3.06 (t, *J* = 7.0 Hz, 2H), 2.20 (p, *J* = 6.7 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 196.6, 159.9 (d, *J* = 253.5 Hz), 159.9 (d, *J* = 253.7 Hz), 132.6 (t, *J* = 10.5 Hz), 112.4 – 112.3 (m), 112.21 – 112.06 (m), 44.2, 41.9 (t, *J* = 2.3 Hz), 26.5.

**4-Chloro-1-(3,4-difluorophenyl)butan-1-one (13g).** General procedure F. Purification by FCC (*n*-hexanes/EtOAc 10:0.1) gave 1.27 g of a yellow oil (78%). LCMS (*m/z*): 219.5 [M+H]<sup>+</sup>, *t<sub>R</sub>* 2.94 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.87 – 7.78 (m, 1H), 7.78 (dtd, *J* = 6.5, 2.1, 1.0 Hz, 1H), 7.34 – 7.22 (m, 1H), 3.71 – 3.67 (m, 2H), 3.16 (t, *J* = 6.9 Hz, 2H), 2.30 – 2.20 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 196.5, 153.8 (dd, *J* = 257.1, 13.0 Hz), 150.6 (dd, *J* = 251.0, 13.0 Hz), 133.9 (t, *J* = 3.8 Hz), 125.1 (dd, *J* = 7.5, 3.6 Hz), 117.7 (d, *J* = 17.8 Hz), 117.4 (dd, *J* = 17.9, 1.9 Hz), 44.6, 35.3, 26.7.

**4-Chloro-1-(3,5-difluorophenyl)butan-1-one (13h).** General procedure F. Purification by FCC (*n*-hexanes/EtOAc 10:0.1) gave 309 mg of a red oil (72%). LCMS: *t<sub>R</sub>* 2.96 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.53 – 7.42 (m, 2H), 7.02 (tt, *J* = 8.4, 2.4 Hz, 1H), 3.67 (t, *J* = 6.2 Hz, 2H), 3.13 (t, *J* = 6.9 Hz, 2H), 2.22 (tt, *J* = 6.8, 6.0 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 196.47 (t, *J* = 2.4 Hz), 163.20 (dd, *J* = 251.1, 11.7 Hz), 139.71 (t, *J* = 7.4 Hz), 111.07 (dd, *J* = 18.9, 7.3 Hz), 108.63 (t, *J* = 25.4 Hz), 44.46, 35.61, 26.57.

**4-Chloro-1-(2-chlorophenyl)butan-1-one (13i).** General procedure F. Purification by FCC (*n*-hexanes/EtOAc 10:0.1) gave 1.12 g of a yellow oil (80%). LCMS (*m/z*): 217.1 [M+H]<sup>+</sup>, *t<sub>R</sub>* 2.90 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.48 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.32 (td, *J* = 7.2, 1.8 Hz, 1H), 3.65 (t, *J* = 6.3 Hz, 2H), 3.14 (t, *J* = 7.0 Hz, 2H), 2.21 (p, *J* = 6.7 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 202.2, 139.3, 131.9, 130.9, 130.7, 128.9, 127.1, 44.4, 39.9, 26.9.

**4-Chloro-1-(*o*-tolyl)butan-1-one (13j).** General procedure F. Purification by FCC (*n*-hexanes/EtOAc 10:0.1) gave 900 mg of a yellow oil (74%). LCMS (*m/z*): 197.3 [M+H]<sup>+</sup>, *t<sub>R</sub>* 2.90 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.68 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1H), 7.30 – 7.23 (m, 2H), 3.67 (t, *J* = 6.3 Hz, 2H), 3.10 (t, *J* = 6.9 Hz, 2H), 2.50 (s, 3H), 2.20 (p, *J* = 6.6 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 203.1, 138.2, 137.8, 132.1, 131.5, 128.6, 125.9, 44.7, 38.3, 27.0, 21.5.

**4-(4-Chlorophenyl)-1-(4-(2-fluorophenyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-1-ium 2,2,2-trifluoroacetateone (14a).** General procedure C. Purification by preparative HPLC (Method C) afforded 49 mg of white solid (45%). LCMS (*m/z*): 376.3 [M+H]<sup>+</sup>, *t<sub>R</sub>* 3.34 min. HRMS (*m/z*): C<sub>21</sub>H<sub>23</sub>ClFNO<sub>2</sub>: requires 376.1401 [M+H]<sup>+</sup>; found 376.1483. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.71 (s, 1H), 7.87 (td, *J* = 7.6, 1.8 Hz, 1H), 7.57 (tdd, *J* = 7.3, 5.0, 1.8 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.29 – 7.22 (m, 1H), 7.17 (dd, *J* = 11.4, 8.3 Hz, 1H), 3.88 (s, 1H), 3.55 (d, *J* = 11.6 Hz, 2H), 3.34 (q, *J* = 11.2 Hz, 2H), 3.14 (tt, *J* = 6.6, 3.3 Hz, 4H), 2.53 (td, *J* = 14.1, 4.1 Hz, 2H), 2.26 – 2.14 (m, 2H), 1.94 (d, *J* = 14.4 Hz, 2H).

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3 **4-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-1-(3-fluorophenyl)butan-1-one (14b).** General  
4 procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 55 mg of a white  
5 solid (39%). LCMS (*m/z*): 376.1 [M+H]<sup>+</sup>, *t<sub>R</sub>* 3.21 min. HRMS (*m/z*): C<sub>21</sub>H<sub>23</sub>ClFNO<sub>2</sub>: requires  
6 376.1474 [M+H]<sup>+</sup>; found 376.1480. <sup>1</sup>H NMR (Methanol-*d*<sub>4</sub>) δ 7.89 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.75  
7 (ddd, *J* = 9.7, 2.7, 1.6 Hz, 1H), 7.63 – 7.51 (m, 3H), 7.45 – 7.35 (m, 3H), 3.61 (d, *J* = 11.9 Hz, 2H),  
8 3.49 (td, *J* = 12.7, 2.8 Hz, 2H), 3.34 – 3.24 (m, 4H), 2.43 (td, *J* = 14.5, 4.4 Hz, 2H), 2.31 – 2.18 (m,  
9 2H), 2.01 (dq, *J* = 15.3, 2.9 Hz, 2H). <sup>13</sup>C NMR (Methanol-*d*<sub>4</sub>) δ 198.9 (d, *J* = 2.3 Hz), 164.3 (d, *J* =  
10 246.3 Hz), 147.0, 140.1 (d, *J* = 6.2 Hz), 134.23, 131.8 (d, *J* = 7.7 Hz), 129.5, 127.5, 125.2 (d, *J* = 3.0  
11 Hz), 121.3 (d, *J* = 21.7 Hz), 115.5 (d, *J* = 22.8 Hz), 69.3, 50.3, 49.6, 36.4, 36.3, 19.6.

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18 **4-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-1-(2,3-difluorophenyl)butan-1-one (14c).** A  
19 solution of 4-(4-chlorophenyl)-1-(4-(2,3-difluorophenyl)-4,4-dimethoxybutyl)piperidin-4-ol (110  
20 mg, 250 μmol) in 15 mL of 15:1 acetone:H<sub>2</sub>O was treated with pTsOH (61.8 mg, 326 μmol), and the  
21 mixture was heated at reflux for 48 h. The mixture was concentrated under reduced pressure. The  
22 residue was dissolved in EtOAc (20 mL) and poured into saturated NaHCO<sub>3</sub> (20 mL). The aqueous  
23 phase was extracted with EtOAc (2 × 20 mL) and the combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), and  
24 concentrated under reduced pressure. The residue was purified by FCC (SiO<sub>2</sub>, 98:1 EtOAc:MeOH),  
25 affording the title compound as a beige solid (75 mg, 76%). LCMS (*m/z*): 394.2 [M+H]<sup>+</sup>, *t<sub>R</sub>* 3.37 min.  
26 HRMS (*m/z*): C<sub>21</sub>H<sub>22</sub>ClF<sub>2</sub>NO<sub>2</sub>: requires 394.1380 [M+H]<sup>+</sup>; found 394.1390. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.62  
27 (ddt, *J* = 7.9, 6.1, 1.8 Hz, 1H), 7.38 – 7.32 (m, 3H), 7.32 – 7.25 (m, 2H), 7.16 (tdd, *J* = 8.1, 4.5, 1.5  
28 Hz, 1H), 3.01 (td, *J* = 7.0, 2.8 Hz, 2H), 2.82 – 2.76 (m, 2H), 2.51 – 2.38 (m, 4H), 2.05 – 1.79 (m, 5H),  
29 1.66 (dd, *J* = 14.0, 2.7 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 197.0 (dd, *J* = 6.3, 2.6 Hz), 151.1 (dd, *J* = 250.4,  
30 14.8 Hz), 150.4 (dd, *J* = 256.2, 13.6 Hz), 147.0, 132.8, 128.5, 128.1 (d, *J* = 9.9 Hz), 126.2, 125.2 (dd,  
31 *J* = 3.5, 1.3 Hz), 124.3 (dd, *J* = 6.6, 4.5 Hz), 121.2 (d, *J* = 17.4 Hz), 71.2, 57.8, 49.4, 41.4 (d, *J* = 6.8  
32 Hz), 38.5, 21.9.

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44 **4-(4-Chlorophenyl)-1-(4-(2,4-difluorophenyl)-4-oxobutyl)-4-hydroxypiperidin-1-ium 2,2,2-**  
45 **trifluoroacetate (14d).** General procedure C. Purification by preparative HPLC (Method C) afforded  
46 68 mg of a white solid (66%). LCMS (*m/z*): 394.3 [M+H]<sup>+</sup>, *t<sub>R</sub>* 3.35 min. HRMS (*m/z*):  
47 C<sub>21</sub>H<sub>22</sub>ClF<sub>2</sub>NO<sub>2</sub>: requires 394.1380 [M+H]<sup>+</sup>; found 394.1387. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.54 (s, 1H), 7.53  
48 (ddd, *J* = 8.6, 5.4, 3.3 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.31 – 7.20 (m, 3H), 7.15 (td, *J* = 9.5, 4.1  
49 Hz, 1H), 4.83 (s, 1H), 3.47 (d, *J* = 10.2 Hz, 2H), 3.33 (q, *J* = 11.3 Hz, 2H), 3.11 (td, *J* = 6.4, 3.2 Hz,  
50 4H), 2.45 (td, *J* = 14.0, 4.2 Hz, 2H), 2.18 (dq, *J* = 13.7, 6.7 Hz, 2H), 1.93 (d, *J* = 14.4 Hz, 2H). <sup>13</sup>C  
51 NMR (CDCl<sub>3</sub>) δ 195.1, 158.7 (dd, *J* = 245.1, 1.9 Hz), 158.3 (dd, *J* = 251.3, 2.2 Hz), 144.8, 133.6,  
52 128.8, 126.1, 125.6 (dd, *J* = 15.4, 6.4 Hz), 122.1 (dd, *J* = 24.5, 9.6 Hz), 118.6 (dd, *J* = 27.2, 7.8 Hz),  
53 116.4 (d, *J* = 27.9 Hz), 68.8, 56.5, 48.9, 39.9 (d, *J* = 9.0 Hz), 35.4, 18.1.

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3 **4-(4-Chlorophenyl)-1-(4-(2,5-difluorophenyl)-4-oxobutyl)-4-hydroxypiperidin-1-ium 2,2,2-**  
4 **trifluoroacetate (14e).** General procedure C. Purification by preparative HPLC (Method C) afforded  
5 60 mg of a white solid (66%). LCMS (*m/z*): 394.3 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.35 min. HRMS (*m/z*):  
6 C<sub>21</sub>H<sub>22</sub>ClF<sub>2</sub>NO<sub>2</sub>: requires 394.1380 [M+H]<sup>+</sup>; found 394.1385. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.15 (s, 1H), 7.53  
7 (ddd, *J* = 8.7, 5.4, 3.3 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.23 (dq, *J* = 6.9,  
8 3.1 Hz, 1H), 7.14 (td, *J* = 9.6, 4.1 Hz, 1H), 3.55 (d, *J* = 11.4 Hz, 2H), 3.33 (q, *J* = 11.3 Hz, 2H), 3.21  
9 – 3.05 (m, 4H), 2.53 – 2.42 (m, 2H), 2.19 (t, *J* = 7.9 Hz, 2H), 1.9 (d, *J* = 14.5 Hz, 2H). <sup>13</sup>C NMR  
10 (CDCl<sub>3</sub>) δ 195.1, 158.6 (dd, *J* = 245.1, 1.9 Hz), 158.2 (dd, *J* = 251.0, 2.3 Hz), 144.2, 133.8, 128.9,  
11 125.8, 122.0 (dd, *J* = 24.5, 9.8 Hz), 118.5 (dd, *J* = 27.5, 8.0 Hz), 116.4 (d, *J* = 3.1 Hz), 116.2 (d, *J* =  
12 2.8 Hz), 69.0, 56.5, 48.9, 39.8 (d, *J* = 8.9 Hz), 35.3, 18.1.

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20 **4-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-1-(2,6-difluorophenyl)butan-1-one (14f).** A  
21 solution of 4-(4-chlorophenyl)-1-(3-(2-(2,6-difluorophenyl)-1,3-dioxolan-2-yl)propyl)piperidin-4-ol  
22 (150 mg, 342 μmol) in 15 mL of 15:1 acetone:H<sub>2</sub>O was treated with pTsOH (84.7 mg, 445 μmol),  
23 and the mixture was heated at reflux for 48 h. The mixture was concentrated under reduced pressure.  
24 The residue was dissolved in EtOAc (20 mL) and poured into saturated NaHCO<sub>3</sub> (20 mL). The  
25 aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined extracts were dried  
26 (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by FCC (eluent, 98:1  
27 EtOAc/MeOH), affording the title compound as a beige solid (110 mg, 82%). LCMS (*m/z*): 394.2  
28 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.27 min. HRMS (*m/z*): C<sub>21</sub>H<sub>22</sub>ClF<sub>2</sub>NO<sub>2</sub>: requires 394.1418 [M+H]<sup>+</sup>; found 394.1465. <sup>1</sup>H  
29 NMR (CDCl<sub>3</sub>) δ 7.45 – 7.37 (m, 2H), 7.36 (td, *J* = 8.4, 7.3, 5.3 Hz, 1H), 7.32 – 7.25 (m, 2H), 6.94 (t,  
30 *J* = 8.1 Hz, 2H), 2.92 (t, *J* = 7.1 Hz, 2H), 2.79 (dt, *J* = 11.7, 3.1 Hz, 2H), 2.50 – 2.37 (m, 4H), 2.07  
31 (td, *J* = 13.2, 4.5 Hz, 2H), 1.94 (p, *J* = 7.2 Hz, 3H), 1.69 (dd, *J* = 14.0, 2.7 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  
32 δ 197.6, 159.9 (dd, *J* = 253.1, 7.5 Hz), 147.1, 132.8, 132.3 (t, *J* = 10.4 Hz), 128.5, 126.2, 118.5 (t, *J* =  
33 19.6 Hz), 112.4 – 112.2 (m), 112.2 – 111.9 (m), 71.12, 57.6, 49.4, 42.9, 38.5, 21.3.

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44 **4-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-1-(3,4-difluorophenyl)butan-1-one (14g).**  
45 General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 48 mg of  
46 a white solid (74%). LCMS (*m/z*): 364.2 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.51 min. HRMS (*m/z*): C<sub>21</sub>H<sub>22</sub>ClF<sub>2</sub>NO<sub>2</sub>: requires  
47 394.1380 [M+H]<sup>+</sup>; found 394.1388. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.82 (ddd, *J* = 10.5, 7.7, 2.1 Hz, 1H), 7.76  
48 (ddd, *J* = 8.8, 4.1, 1.8 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.28 – 7.18 (m, 1H),  
49 2.95 (t, *J* = 7.0 Hz, 2H), 2.76 (d, *J* = 12.2 Hz, 2H), 2.49 – 2.34 (m, 4H), 2.03 – 1.90 (m, 4H), 1.80 (s,  
50 1H), 1.66 (dd, *J* = 14.2, 2.6 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 197.5, 153.6 (dd, *J* = 256.7, 13.0 Hz), 150.5  
51 (dd, *J* = 250.7, 12.9 Hz), 147.0, 134.5 (t, *J* = 3.8 Hz), 132.9, 128.5, 126.2, 125.1 (dd, *J* = 7.3, 3.6 Hz),  
52 117.7 – 117.6 (m), 117.5 – 117.4 (m), 71.1, 57.8, 49.4, 38.4, 36.3, 21.9.

**4-(4-Chlorophenyl)-1-(4-(3,5-difluorophenyl)-4-oxobutyl)-4-hydroxypiperidin-1-ium 2,2,2-trifluoroacetate (14h).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 42 mg of a white solid (44%). LCMS (*m/z*): 394.3 [M+H]<sup>+</sup>, *t<sub>R</sub>* 3.44 min. HRMS (*m/z*): C<sub>21</sub>H<sub>22</sub>ClF<sub>2</sub>NO<sub>2</sub>: requires 394.1307 [M+H]<sup>+</sup>; found 394.1371. <sup>1</sup>H NMR (Methanol-*d*<sub>4</sub>) δ 7.64 – 7.53 (m, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.17 (m, 1H), 3.71 – 3.54 (m, 2H), 3.44 (td, *J* = 12.8, 2.8 Hz, 2H), 2.34 (td, *J* = 14.1, 4.3 Hz, 2H), 2.27 – 2.15 (m, 2H), 2.04 – 1.94 (m, 2H). <sup>13</sup>C NMR (Methanol-*d*<sub>4</sub>) δ 197.6, 164.6 (d, *J* = 249.3 Hz), 164.5 (d, *J* = 249.3 Hz), 147.0, 141.1 (t, *J* = 7.5 Hz), 134.2, 129.5, 127.4, 112.1 (d, *J* = 7.2 Hz), 111.9 (d, *J* = 7.4 Hz), 109.3 (t, *J* = 26.0 Hz), 69.2, 57.5, 36.6, 36.3, 19.4.

**1-(2-Chlorophenyl)-4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)butan-1-one (14i).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 89 mg of a white solid (70%). LCMS (*m/z*): 392.2 [M+H]<sup>+</sup>, *t<sub>R</sub>* 3.40 min. HRMS (*m/z*): C<sub>21</sub>H<sub>23</sub>Cl<sub>2</sub>NO<sub>2</sub>: requires 392.1106 [M+H]<sup>+</sup>; found 392.1184. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.47 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.42 – 7.34 (m, 4H), 7.33 – 7.25 (m, 3H), 2.97 (t, *J* = 7.1 Hz, 2H), 2.77 (dt, *J* = 11.9, 3.0 Hz, 2H), 2.47 – 2.36 (m, 4H), 2.10 – 1.98 (m, 3H), 1.93 (p, *J* = 7.2 Hz, 2H), 1.68 (dd, *J* = 14.2, 2.6 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 203.4, 147.1, 139.7, 132.8, 131.7, 130.9, 130.6, 128.9, 128.4, 126.9, 126.2, 71.1, 57.7, 49.4, 40.9, 38.5, 21.7.

**4-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-1-(*o*-tolyl)butan-1-one (14j).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 90 mg as a white solid (70%). LCMS (*m/z*): 372.3 [M+H]<sup>+</sup>, *t<sub>R</sub>* 3.47 min. HRMS (*m/z*): C<sub>22</sub>H<sub>26</sub>ClNO<sub>2</sub>: requires 372.1652 [M+H]<sup>+</sup>; found 372.1626. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.66 (d, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 2H), 2.92 (t, *J* = 7.1 Hz, 2H), 2.78 (dt, *J* = 12.0, 3.1 Hz, 2H), 2.49 (s, 3H), 2.50 – 2.36 (m, 4H), 2.04 (td, *J* = 13.3, 4.5 Hz, 2H), 1.93 (p, *J* = 7.2 Hz, 3H), 1.68 (dd, *J* = 14.1, 2.6 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 204.4, 147.1, 138.3, 138.0, 132.8, 132.0, 131.2, 128.6, 128.4, 126.2, 125.7, 71.2, 57.9, 49.5, 39.5, 38.6, 21.9, 21.4.

**4-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-1-phenylbutan-1-one (14k).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 75mg of a white solid (75 mg, 79%). LCMS (*m/z*): 358.1 [M+H]<sup>+</sup>, *t<sub>R</sub>* 3.21 min. HRMS (*m/z*): C<sub>21</sub>H<sub>24</sub>ClNO<sub>2</sub>: requires 358.1558 [M+H]<sup>+</sup>; found 358.1579. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.60 – 7.51 (m, 1H), 7.51 – 7.42 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.32 – 7.22 (m, 2H), 3.00 (t, *J* = 7.0 Hz, 2H), 2.79 (dt, *J* = 12.0, 3.0 Hz, 2H), 2.51 – 2.37 (m, 4H), 2.07 – 1.92 (m, 5H), 1.65 (dd, *J* = 14.1, 2.6 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 200.1, 147.1, 137.4, 132.9, 132.8, 128.7, 128.5, 128.2, 126.2, 71.2, 58.0, 49.4, 38.5, 36.4, 22.1.

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3 **1-(4-Chlorophenyl)-4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)butan-1-one (14l)**. General  
4 procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 68 mg of the title  
5 compound as a yellow solid (80%). LCMS (*m/z*): 392.4 [M+H]<sup>+</sup>, *t<sub>R</sub>* 3.68 min. HRMS (*m/z*):  
6 C<sub>21</sub>H<sub>23</sub>Cl<sub>2</sub>NO<sub>2</sub>: requires 392.1106 [M+H]<sup>+</sup>; found 392.1174. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.92 (d, *J* = 8.6 Hz,  
7 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 2.96 (t, *J* = 7.0 Hz,  
8 2H), 2.75 (dt, *J* = 12.2, 3.2 Hz, 2H), 2.50 – 2.35 (m, 4H), 2.06 – 1.90 (m, 4H), 1.73 (s, 1H), 1.65 (dd,  
9 *J* = 14.1, 2.6 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 198.8, 147.1, 139.4, 135.7, 132.8, 129.7, 128.9, 128.5,  
10 126.2, 71.2, 57.9, 49.4, 38.5, 36.4, 22.1.

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18 **1-(4-Chloro-1,1-dimethoxybutyl)-2,3-difluorobenzene (15c)**. 4-Chloro-1-(2,3-  
19 difluorophenyl)butan-1-one (450 mg, 2.06 mmol), was taken up in MeOH (15 mL) and treated with  
20 trimethyl orthoformate (450 mL, 4.12 mmol), *p*-toluenesulphonic acid monohydrate (7.83 mg, 41.2  
21 mmol) and stirred for 3 hr at r.t. This was diluted with sat. aq. NaHCO<sub>3</sub> (20 mL), H<sub>2</sub>O (20 mL) and  
22 extracted with EtOAc (3 x 15 mL). The organic extracts were combined, washed with brine (20 mL),  
23 dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford 425 mg of the title compound as a  
24 light green oil (77%). LCMS (*m/z*): 265.8 [M+H]<sup>+</sup>, *t<sub>R</sub>* 3.08 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.35 (ddt, *J* =  
25 8.1, 6.4, 1.7 Hz, 1H), 7.14 (dddd, *J* = 9.9, 8.7, 7.1, 1.8 Hz, 1H), 7.06 (tdd, *J* = 8.1, 5.0, 1.6 Hz, 1H),  
26 3.42 (t, *J* = 6.6 Hz, 2H), 3.19 (s, 6H), 2.22 – 2.13 (m, 2H), 1.54 – 1.42 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ  
27 151.1 (dd, *J* = 247.4, 13.6 Hz), 147.9 (dd, *J* = 253.0, 13.5 Hz), 129.8 (d, *J* = 7.3 Hz), 125.1 (dd, *J* =  
28 3.7, 2.2 Hz), 123.5 (dd, *J* = 6.8, 4.8 Hz), 117.3 (d, *J* = 17.2 Hz), 101.8 (d, *J* = 3.2 Hz), 48.8, 44.8, 32.4  
29 (d, *J* = 3.1 Hz), 27.3.

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39 **2-(3-Chloropropyl)-2-(2,6-difluorophenyl)-1,3-dioxolane (15f)**. A solution of 4-chloro-1-(2,6-  
40 difluorophenyl)butan-1-one (250 mg, 1.14 mmol), ethylene glycol (320 μL, 5.72 mmol), and *p*-  
41 TsOH.H<sub>2</sub>O (10.9 mg, 57.2 μmol) in toluene (15 mL) was heated at reflux temperature with use of a  
42 Dean-Stark water trap for 16 h. The cooled reaction mixture was washed with NaOH (3 × 20 mL),  
43 followed by H<sub>2</sub>O (2 × 20 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The organic layer was removed *in vacuo* and the  
44 residue purified by FCC (5:95 EtOAc/PE) to afford 249 mg of a clear oil (83%). LCMS (*m/z*): 263.3  
45 [M+H]<sup>+</sup>, *t<sub>R</sub>* 2.91 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.23 (tt, *J* = 8.2, 5.3 Hz, 1H), 6.85 (t, *J* = 8.7 Hz, 2H), 4.12  
46 – 4.03 (m, 2H), 3.93 – 3.84 (m, 2H), 3.56 (t, *J* = 6.8 Hz, 2H), 2.25 – 2.19 (m, 2H), 1.93 (dt, *J* = 14.1,  
47 6.9 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 160.6 (dd, *J* = 252.0, 7.6 Hz), 129.9 (t, *J* = 11.1 Hz), 117.7 (t, *J* =  
48 14.7 Hz), 112.7 – 112.6 (m), 112.5 – 112.4 (m), 109.1 (t, *J* = 3.5 Hz), 64.9, 45.1, 36.5 (t, *J* = 1.8 Hz),  
49 26.8.

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58 **4-(4-Chlorophenyl)-1-(4-(2,3-difluorophenyl)-4,4-dimethoxybutyl)piperidin-4-ol (16c)**. General  
59 procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 130 mg as a  
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transparent oil (71%). LCMS ( $m/z$ ): 440.1  $[M+H]^+$ ,  $t_R$  2.39 min.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.40 (d,  $J = 8.7$  Hz, 2H), 7.38 – 7.33 (m, 1H), 7.29 (d,  $J = 8.6$  Hz, 2H), 7.12 (dtd,  $J = 9.6, 7.9, 1.8$  Hz, 1H), 7.04 (tdd,  $J = 8.1, 5.0, 1.4$  Hz, 1H), 3.18 (s, 6H), 2.66 (d,  $J = 11.4$  Hz, 2H), 2.38 – 2.19 (m, 4H), 2.11 – 1.97 (m, 4H), 1.76 (s, 1H), 1.65 (dd,  $J = 14.1, 2.6$  Hz, 2H), 1.29 – 1.16 (m, 2H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  151.1 (dd,  $J = 246.8, 13.8$  Hz), 147.9 (dd,  $J = 252.8, 13.3$  Hz), 146.9, 132.9, 130.1 (d,  $J = 7.1$  Hz), 128.5, 126.2, 125.2 (t,  $J = 4.9, 2.3$  Hz), 123.4 (dd,  $J = 12.0, 5.1$  Hz), 117.1 (d,  $J = 17.2$  Hz), 102.2 (t,  $J = 3.1$  Hz), 71.1, 58.2, 49.4, 48.8, 38.4, 32.7 (d,  $J = 2.9$  Hz), 21.4.

**4-(4-Chlorophenyl)-1-(3-(2-(2,6-difluorophenyl)-1,3-dioxolan-2-yl)propyl)piperidin-4-ol (16f).**

General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/ $NH_4OH$ ) gave 325 mg as a transparent oil (77%). LCMS ( $m/z$ ): 438.1  $[M+H]^+$ ,  $t_R$  2.39 min.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.42 (d,  $J = 8.6$  Hz, 2H), 7.29 (d,  $J = 8.6$  Hz, 2H), 7.25 – 7.17 (m, 1H), 6.89 – 6.79 (m, 2H), 4.12 – 4.02 (m, 2H), 3.93 – 3.86 (m, 2H), 2.78 (d,  $J = 11.3$  Hz, 2H), 2.44 – 2.34 (m, 4H), 2.15 – 2.01 (m, 4H), 1.85 (s, 1H), 1.68 (d,  $J = 11.5$  Hz, 4H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  160.7 (d,  $J = 251.7$  Hz), 160.7 (d,  $J = 251.9$  Hz), 147.1, 132.8, 129.7 (t,  $J = 11.0$  Hz), 128.5, 126.2, 117.9 (t,  $J = 14.8$  Hz), 112.6 (d,  $J = 7.2$  Hz), 112.4 (d,  $J = 7.2$  Hz), 109.5 (t,  $J = 3.5$  Hz), 71.2, 64.9, 58.5, 49.4, 38.5, 37.2, 20.9.

**4-(4-Chlorophenyl)-1-(3-((4-fluorophenyl)thio)propyl)piperidin-4-ol (17a).** General procedure

C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/ $NH_4OH$ ) gave 67 mg of a white solid (77%). LCMS ( $m/z$ ): 380.1  $[M+H]^+$ ,  $t_R$  3.73 min. HRMS ( $m/z$ ):  $C_{20}H_{23}ClFNOS$ : requires 380.1276  $[M+H]^+$ ; found 380.1308.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.43 (d,  $J = 8.6$  Hz, 2H), 7.39 – 7.31 (m, 2H), 7.34 – 7.24 (m, 2H), 6.99 (t,  $J = 8.6$  Hz, 2H), 2.92 (t,  $J = 7.3$  Hz, 2H), 2.75 (dt,  $J = 11.8, 3.0$  Hz, 2H), 2.50 (t,  $J = 7.3$  Hz, 2H), 2.40 (td,  $J = 12.0, 2.4$  Hz, 2H), 2.08 (td,  $J = 13.2, 4.5$  Hz, 2H), 1.82 (p,  $J = 7.3$  Hz, 2H), 1.70 (dd,  $J = 14.2, 2.6$  Hz, 3H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  161.8 (d,  $J = 246.1$  Hz), 146.9, 132.9, 132.3 (d,  $J = 8.0$  Hz), 131.5 (d,  $J = 3.4$  Hz), 128.5, 126.2, 116.1 (d,  $J = 21.8$  Hz), 71.2, 57.4, 49.6, 38.6, 33.2, 26.8.

**4-(4-Chlorophenyl)-1-(3-(4-fluorophenoxy)propyl)piperidin-4-ol (17b).** General procedure C.

Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/ $NH_4OH$ ) gave 77 mg of a white solid (80%). LCMS ( $m/z$ ): 364.2  $[M+H]^+$ ,  $t_R$  3.51 min. HRMS ( $m/z$ ):  $C_{20}H_{23}ClFNO_2$ : requires 380.1474  $[M+H]^+$ ; found 364.1492.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.44 (d,  $J = 8.7$  Hz, 2H), 7.31 (d,  $J = 8.6$  Hz, 2H), 6.96 (dd,  $J = 9.6, 7.7$  Hz, 2H), 6.84 (dd,  $J = 9.1, 4.3$  Hz, 2H), 3.98 (t,  $J = 6.3$  Hz, 2H), 2.88 – 2.76 (m, 2H), 2.58 (t,  $J = 7.5$  Hz, 2H), 2.51 – 2.39 (m, 2H), 2.11 (td,  $J = 13.2, 4.5$  Hz, 2H), 2.03 – 1.93 (m, 2H), 1.73 (dd,  $J = 14.2, 2.7$  Hz, 3H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  157.3 (d,  $J = 238.0$  Hz), 155.2 (d,  $J = 2.1$  Hz), 147.0, 132.9, 128.5, 126.3, 115.9 (d,  $J = 23.0$  Hz), 115.6 (d,  $J = 7.8$  Hz), 71.2, 67.1, 55.4, 49.6, 38.6, 27.1.

**4-(4-Chlorophenyl)-1-(4-(4-fluorophenyl)-4-hydroxybutyl)piperidin-4-ol (18).** General

procedure C. Purification by FCC (20:1:0.1, EtOAc/MeOH/ $NH_4OH$ ) gave 60 mg of the title

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3 compound as a white solid (67%). LCMS ( $m/z$ ): 378.3  $[M+H]^+$ ,  $t_R$  3.05 min. HRMS ( $m/z$ ):  
4  $C_{21}H_{25}ClFNO_2$ : requires 378.1558  $[M+H]^+$ ; found 378.1643.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.48 – 7.38 (m,  
5 2H), 7.36 – 7.23 (m, 4H), 6.99 (t,  $J$  = 8.7 Hz, 2H), 4.67 – 4.61 (m, 1H), 3.07 – 2.99 (m, 1H), 2.89 –  
6 2.79 (m, 1H), 2.64 (td,  $J$  = 12.1, 2.7 Hz, 1H), 2.58 – 2.47 (m, 3H), 2.22 (ddt,  $J$  = 18.7, 12.9, 4.7 Hz,  
7 2H), 2.00 – 1.88 (m, 1H), 1.81 – 1.65 (m, 6H), 1.25 (s, 1H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  161.9 (d,  $J$  = 244.1  
8 Hz), 146.4, 141.6 (d,  $J$  = 3.1 Hz), 133.2, 128.6, 127.4 (d,  $J$  = 8.0 Hz), 126.3, 115.1 (d,  $J$  = 21.2 Hz),  
9 73.3, 70.9, 58.9, 50.2, 48.6, 40.2, 37.9, 37.7, 24.1.

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14 **Cyclopropyl(4-fluorophenyl)methanone (19)**. To a stirred solution of NaOH (1.82 g, 45.6 mmol)  
15 in  $H_2O$  (30 mL) at room temperature was added a solution of 4-chloro-1-(4-fluorophenyl)butan-1-  
16 one (5.00 mL, 30.4 mmol) in THF (10 mL). After addition, the reaction temperature was increased  
17 to 60 °C and stirred for a further 5 hours. EtOAc and  $H_2O$  were added and the organic phase was  
18 washed with additional  $H_2O$ , brine, and dried ( $Na_2SO_4$ ) followed by concentration *in vacuo* to yield  
19 the product as a light-yellow oil (5.00 g, quantitative). LCMS:  $t_R$  2.73 min.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.08  
20 – 7.99 (m, 2H), 7.19 – 7.09 (m, 2H), 2.62 (tt,  $J$  = 7.8, 4.6 Hz, 1H), 1.23 (ddt,  $J$  = 6.8, 4.6, 2.2 Hz, 2H),  
21 1.04 (dq,  $J$  = 7.3, 3.6 Hz, 2H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  199.1, 165.7 (d,  $J$  = 254.0 Hz), 134.5 (d,  $J$  = 3.0  
22 Hz), 130.7 (d,  $J$  = 9.2 Hz), 115.7 (d,  $J$  = 21.8 Hz), 17.2, 11.8.

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30 **Cyclopropyl(4-fluorophenyl)methanol (20)**. To a stirred solution of cyclopropyl(4-  
31 fluorophenyl)methanone (5.00 g, 30.5 mmol) in MeOH (40 mL) at 0° C was added  $NaBH_4$  (1.50 g,  
32 39.6 mmol) portion-wise. The reaction mixture was allowed to come to room temperature and stirred  
33 for a further 4 hours. To the reaction mixture was added to sat. aqueous  $NH_4Cl$  solution and EtOAc,  
34 the phases were separated, the aqueous phase was extracted twice with EtOAc, the combined organic  
35 phases were dried ( $Na_2SO_4$ ), filtered, and concentrated *in vacuo* to afford 5.01 g of a gold oil (99%).  
36 LCMS ( $m/z$ ):  $t_R$  2.73 min.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.08 – 7.99 (m, 1H), 7.19 – 7.09 (m, 1H), 2.62 (tt,  $J$  =  
37 7.8, 4.6 Hz, 1H), 1.23 (ddt,  $J$  = 6.8, 4.6, 2.2 Hz, 2H), 1.04 (dq,  $J$  = 7.3, 3.6 Hz, 2H).  $^{13}C$  NMR ( $CDCl_3$ )  
38  $\delta$  199.1, 165.7 (d,  $J$  = 254.0 Hz), 134.5 (d,  $J$  = 3.0 Hz), 130.7 (d,  $J$  = 9.2 Hz), 115.7 (d,  $J$  = 21.8 Hz),  
39 17.2, 11.8.

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47 **(E)-4-(4-Fluorophenyl)but-3-en-1-ol (21)**. To a mixture of vanadyl acetylacetonate (639 mg, 2.41  
48 mmol), 2,6-di-*tert*-butyl-*p*-cresol (265 mg, 1.20 mmol), and chlorobenzene (40 mL) in a round-  
49 bottom flask was added solution of cyclopropyl(4-fluorophenyl)methanol (4.00 g, 24.1 mmol) in  
50 chlorobenzene (5.00 mL) and the resulting mixture was stirred at 80 °C. After 48 h, the reaction  
51 mixture was cooled to r.t. and filtered through a pad of Florisil. The solvent was evaporated and the  
52 residue was purified by FCC (eluent, 4:1 *n*-hexanes/EtOAc) to yield 1.41 g of a transparent oil (35%).  
53 LCMS:  $t_R$  2.73 min.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.35 – 7.26 (m, 2H), 6.98 (t,  $J$  = 8.7 Hz, 2H), 6.45 (d,  $J$  =  
54 15.9 Hz, 1H), 6.11 (dt,  $J$  = 15.8, 7.1 Hz, 1H), 3.74 (t,  $J$  = 6.3 Hz, 2H), 2.46 (qd,  $J$  = 6.4, 1.4 Hz, 2H),  
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2.04 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 162.2 (d, *J* = 246.2 Hz), 133.5 (d, *J* = 3.2 Hz), 131.6, 127.6 (d, *J* = 8.0 Hz), 126.3 (d, *J* = 2.3 Hz), 115.5 (d, *J* = 21.5 Hz), 62.1, 36.4.

**(*E*)-4-(4-Fluorophenyl)but-3-en-1-yl methanesulfonate (22).** General procedure G. Purification by FCC (eluent 4:1, PE/EtOAc) gave 152 mg of a transparent oil (83%). LCMS (*m/z*): *t<sub>R</sub>* 2.79 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.35 – 7.28 (m, 2H), 6.99 (t, *J* = 8.7 Hz, 2H), 6.48 (dt, *J* = 15.8, 1.5 Hz, 1H), 6.07 (dt, *J* = 15.8, 7.0 Hz, 1H), 4.33 (t, *J* = 6.6 Hz, 2H), 3.01 (s, 3H), 2.65 (qd, *J* = 6.7, 1.4 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 162.4 (d, *J* = 246.7 Hz), 133.1 (d, *J* = 3.2 Hz), 132.5, 127.8 (d, *J* = 7.9 Hz), 123.7 (d, *J* = 2.3 Hz), 115.6 (d, *J* = 21.6 Hz), 69.1, 37.7, 32.9.

**(*E*)-4-(4-Chlorophenyl)-1-(4-(4-fluorophenyl)but-3-en-1-yl)piperidin-4-ol (23).** General procedure C. Purification by FCC (20:1:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 80 mg of a white solid (82%). LCMS (*m/z*): 360.3 [M+H]<sup>+</sup>, *t<sub>R</sub>* 3.62 min. HRMS (*m/z*): C<sub>21</sub>H<sub>23</sub>ClFNO: requires 360.1452 [M+H]<sup>+</sup>; found 360.1541. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.48 – 7.40 (m, 2H), 7.35 – 7.26 (m, 4H), 6.98 (t, *J* = 8.7 Hz, 2H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.12 (dt, *J* = 15.7, 6.9 Hz, 1H), 2.85 (dt, *J* = 11.9, 3.0 Hz, 2H), 2.59 – 2.51 (m, 2H), 2.49 – 2.39 (m, 4H), 2.13 (td, *J* = 13.2, 4.5 Hz, 2H), 1.91 (s, 1H), 1.73 (dd, *J* = 14.2, 2.6 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 162.1 (d, *J* = 245.8 Hz), 147.1, 133.9 (d, *J* = 3.2 Hz), 132.9, 129.9, 128.5, 128.2 (d, *J* = 2.3 Hz), 127.5 (d, *J* = 7.8 Hz), 126.2, 115.5 (d, *J* = 21.5 Hz), 71.1, 58.5, 49.5, 38.6, 30.9.

**(*Z*)-4-(4-Fluorophenyl)but-3-en-1-ol (26).** An oven-dried round-bottom flask containing a stirring bar was charged with Ni(COD)<sub>2</sub> (319 mg, 10 mol%), 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (492 mg, 10 mol%) and LiCl (491 mg, 11.6 mmol). The flask was fitted with a rubber septum, evacuated and back-filled with argon (this sequence was repeated an additional two times). 2,3-Dihydrofuran (875 μL, 11.6 mmol) was added to the flask along with THF (15 mL). The reaction mixture was then cooled to -30 °C and stirred for 2 minutes. Then, (4-fluorophenyl)magnesium bromide (0.8 M solution in THF; 28.9 mL, 23.1 mmol) was added via syringe. The mixture was stirred at this temperature for 6 hours and then diluted with EtOAc (30 mL) and a solution of aqueous sat. NH<sub>4</sub>Cl (20 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude material was purified by FCC (eluent 4:1 *n*-hexanes/EtOAc) to afford 600 mg of a transparent oil (31%). LCMS: *t<sub>R</sub>* 2.73 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.35 – 7.26 (m, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 6.45 (d, *J* = 15.9 Hz, 1H), 6.11 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.74 (t, *J* = 6.3 Hz, 2H), 2.46 (qd, *J* = 6.4, 1.4 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 161.8 (d, *J* = 246.1 Hz), 133.3 (d, *J* = 3.4 Hz), 130.6, 130.4 (d, *J* = 7.8 Hz), 128.3 (d, *J* = 1.5 Hz), 115.2 (d, *J* = 21.1 Hz), 62.5, 31.9.

**(*Z*)-4-(4-Fluorophenyl)but-3-en-1-yl methanesulfonate (27).** General procedure G. Compound degraded after attempted FCC purification (eluent 4:1 EtOAc/PE). Therefore, the compound was used for the next reaction without purification.



**(Z)-4-(4-Chlorophenyl)-1-(4-(4-fluorophenyl)but-3-en-1-yl)-4-hydroxypiperidin-1-ium 2,2,2-trifluoroacetate (28).** General procedure C. Purification by preparative HPLC (Method C) gave 65 mg of a white solid (75%). LCMS ( $m/z$ ): 360.3  $[M+H]^+$ ,  $t_R$  3.65 min. HRMS ( $m/z$ ):  $C_{21}H_{23}ClFNO$ : requires 360.1452  $[M+H]^+$ ; found 360.1533.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  11.28 (s, 1H), 7.36 (d,  $J = 8.5$  Hz, 2H), 7.29 (d,  $J = 8.5$  Hz, 2H), 7.20 (dd,  $J = 8.5, 5.4$  Hz, 2H), 7.05 (t,  $J = 8.6$  Hz, 2H), 6.59 (d,  $J = 11.5$  Hz, 1H), 5.89 (s, 1H), 5.50 (dt,  $J = 11.5, 7.1$  Hz, 1H), 3.37 (d,  $J = 11.4$  Hz, 2H), 3.23 (q,  $J = 11.2$  Hz, 2H), 3.05 (dq,  $J = 9.2, 4.4$  Hz, 2H), 2.75 (q,  $J = 7.7$  Hz, 2H), 2.41 (td,  $J = 14.0, 4.2$  Hz, 2H), 1.87 (d,  $J = 14.4$  Hz, 2H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  161.9 (d,  $J = 247.4$  Hz), 144.4, 133.6, 132.2, 132.1 (d,  $J = 3.6$  Hz), 130.2 (d,  $J = 8.0$  Hz), 128.8, 125.9, 124.4, 115.5 (d,  $J = 21.5$  Hz), 68.7, 56.5, 48.9, 35.2, 23.1.

**trans-2-(2-(4-Fluorophenyl)cyclopropyl)ethan-1-ol (29).** A solution of (*E*)-4-(4-fluorophenyl)but-3-en-1-ol (250 mg, 1.50 mmol) in DCM (30 mL), was treated with  $Et_2Zn$  (0.9 M in hexanes; 8.36 mL, 7.52 mmol). After 10 minutes, the reaction mixture was cooled to 0 °C, and treated with a solution of  $CH_2I_2$  (607  $\mu$ L, 7.52 mmol) in DCM (10 mL) drop-wise over 10 minutes and allowed to warm to ambient temperature. After 24 h, the reaction mixture was quenched slowly with sat. aqueous  $NH_4Cl$  and stirred for 10 minutes. The reaction mixture was extracted with DCM (3 x 20 mL), and the combined organic phases were washed with sat. aqueous  $NaHCO_3$ , dried ( $Na_2SO_4$ ), filtered, and concentrated *in vacuo* to yield the desired cyclopropane as a transparent oil (265 mg, 98%). LCMS:  $t_R$  2.67 min.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.00 (dd,  $J = 8.6, 5.5$  Hz, 2H), 6.93 (dd,  $J = 9.8, 7.6$  Hz, 2H), 3.76 (t,  $J = 6.5$  Hz, 2H), 1.72 – 1.57 (m, 4H), 1.09 – 1.00 (m, 1H), 0.87 (dt,  $J = 8.5, 5.0$  Hz, 1H), 0.80 (dt,  $J = 8.7, 5.2$  Hz, 1H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  161.1 (d,  $J = 243.0$  Hz), 139.0 (d,  $J = 3.0$  Hz), 127.2 (d,  $J = 7.9$  Hz), 115.1 (d,  $J = 21.3$  Hz), 62.9, 37.3, 22.2, 20.1, 15.5.

**trans-2-(2-(4-Fluorophenyl)cyclopropyl)ethyl methanesulfonate (29a).** General procedure G. No purification required post work-up, giving 366 mg of a transparent oil (95%). LCMS ( $m/z$ ): 259.4  $[M+H]^+$ ,  $t_R$  2.83 min.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.04 – 6.98 (m, 2H), 6.93 (dd,  $J = 9.9, 7.6$  Hz, 2H), 4.32 (td,  $J = 6.5, 1.5$  Hz, 2H), 2.96 (s, 3H), 1.83 (qd,  $J = 6.7, 3.3$  Hz, 2H), 1.71 (dt,  $J = 9.2, 4.9$  Hz, 1H), 1.10 – 1.00 (m, 1H), 0.92 (dt,  $J = 8.5, 5.1$  Hz, 1H), 0.83 (dt,  $J = 8.7, 5.3$  Hz, 1H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  161.2 (d,  $J = 243.4$  Hz), 138.3 (d,  $J = 3.1$  Hz), 127.3 (d,  $J = 7.7$  Hz), 115.2 (d,  $J = 21.3$  Hz), 69.8, 37.4, 33.8, 22.3, 19.4, 15.2.

**trans-4-(4-Chlorophenyl)-1-(2-(2-(4-fluorophenyl)cyclopropyl)ethyl)piperidin-4-ol (29b).** General procedure C. Purification by FCC (20:1:0.1, EtOAc/MeOH/ $NH_4OH$ ) gave 72 mg of a white solid (80%). LCMS ( $m/z$ ): 374.3  $[M+H]^+$ ,  $t_R$  3.73 min. HRMS ( $m/z$ ):  $C_{22}H_{25}ClFNO$ : requires 374.1609  $[M+H]^+$ ; found 374.1690.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.46 – 7.39 (m, 2H), 7.33 – 7.26 (m, 2H), 7.00 (dd,  $J = 8.6, 5.5$  Hz, 2H), 6.97 – 6.88 (m, 2H), 2.81 (dt,  $J = 11.5, 3.3$  Hz, 2H), 2.54 (dd,  $J = 8.9, 6.9$  Hz, 2H), 2.43 (ddd,  $J = 11.8, 9.7, 2.0$  Hz, 2H), 2.10 (td,  $J = 13.3, 4.4$  Hz, 3H), 1.71 (dd,  $J = 14.2,$

2.7 Hz, 2H), 1.66 – 1.55 (m, 3H), 1.01 – 0.91 (m, 1H), 0.85 (dt,  $J = 8.4, 5.0$  Hz, 1H), 0.77 (dt,  $J = 8.6, 5.2$  Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  161.1 (d,  $J = 243.0$  Hz), 147.1, 139.2 (d,  $J = 3.1$  Hz), 132.8, 128.5, 127.2 (d,  $J = 7.7$  Hz), 126.2, 115.1 (d,  $J = 21.3$  Hz), 71.1, 58.5, 49.7, 49.6, 38.5 (d,  $J = 1.5$  Hz), 32.1, 22.6, 21.6, 15.8.

**cis-2-(2-(4-Fluorophenyl)cyclopropyl)ethan-1-ol (30).** A solution of (*Z*)-4-(4-fluorophenyl)but-3-en-1-ol (250 mg, 1.50 mmol) in DCM (30 mL), was treated with  $\text{Et}_2\text{Zn}$  (0.9 M in hexanes; 8.36 mL, 7.52 mmol). After 10 minutes, the reaction mixture was cooled to 0 °C, and treated with a solution of  $\text{CH}_2\text{I}_2$  (607  $\mu\text{L}$ , 7.52 mmol) in DCM (10 mL) drop-wise over 10 minutes and allowed to warm to ambient temperature. After 24 h, the reaction mixture was quenched slowly with sat. aqueous  $\text{NH}_4\text{Cl}$  and stirred for 10 minutes. The reaction mixture was extracted with DCM (3 x 20 mL), and the combined organic phases were washed with sat. aqueous  $\text{NaHCO}_3$ , dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated *in vacuo* to yield the desired cyclopropane as a yellow oil (271 mg, quantitative). LCMS ( $m/z$ ): 181.3  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  2.65 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.16 – 7.11 (m, 2H), 6.95 (t,  $J = 8.7$  Hz, 2H), 3.56 (td,  $J = 6.3, 2.5$  Hz, 2H), 2.11 (td,  $J = 8.3, 5.8$  Hz, 1H), 1.58 (s, 1H), 1.43 – 1.31 (m, 1H), 1.19 – 1.05 (m, 2H), 1.01 (td,  $J = 8.2, 4.9$  Hz, 1H), 0.65 (q,  $J = 5.3$  Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  161.4 (d,  $J = 243.7$  Hz), 134.8 (d,  $J = 3.2$  Hz), 130.5 (d,  $J = 7.8$  Hz), 114.8 (d,  $J = 21.1$  Hz), 62.8, 31.9, 19.8, 15.4, 9.6.

**cis-2-(2-(4-Fluorophenyl)cyclopropyl)ethyl methanesulfonate (30a).** General procedure G. Purification by FCC (eluent 4:1, PE/EtOAc) gave 274 mg of a transparent oil (83%). LCMS:  $t_{\text{R}}$  2.83 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.19 – 7.10 (m, 2H), 6.96 (t,  $J = 8.7$  Hz, 2H), 4.20 – 4.04 (m, 2H), 2.92 (s, 3H), 2.18 (td,  $J = 8.6, 6.0$  Hz, 1H), 1.56 (dq,  $J = 13.2, 6.6$  Hz, 1H), 1.31 (dt,  $J = 14.4, 7.2$  Hz, 1H), 1.22 – 1.15 (m, 1H), 1.05 (td,  $J = 8.4, 5.3$  Hz, 1H), 0.69 (q,  $J = 5.6$  Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  161.5 (d,  $J = 244.2$  Hz), 134.1 (d,  $J = 3.1$  Hz), 130.5 (d,  $J = 7.9$  Hz), 115.1 (d,  $J = 21.2$  Hz), 69.8, 37.3, 28.6, 19.9, 14.7, 9.5.

**cis-4-(4-Chlorophenyl)-1-(2-(2-(4-fluorophenyl)cyclopropyl)ethyl)piperidin-4-ol (30b).** General procedure C. Purification by FCC (20:1:0.1, EtOAc/MeOH/ $\text{NH}_4\text{OH}$ ) gave 49 mg of a white solid (66%). LCMS ( $m/z$ ): 374.3  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.73 min. HRMS ( $m/z$ ):  $\text{C}_{22}\text{H}_{25}\text{ClFNO}$ : requires 374.1609  $[\text{M}+\text{H}]^+$ ; found 374.1687.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.44 – 7.37 (m, 2H), 7.33 – 7.26 (m, 2H), 7.21 – 7.12 (m, 2H), 6.97 (t,  $J = 8.7$  Hz, 2H), 2.70 – 2.59 (m, 2H), 2.51 – 2.40 (m, 1H), 2.42 – 2.29 (m, 2H), 2.25 (td,  $J = 13.3, 11.7, 3.8$  Hz, 1H), 2.16 – 1.98 (m, 3H), 1.86 (s, 1H), 1.65 (dq,  $J = 14.2, 2.8$  Hz, 2H), 1.34 (td,  $J = 11.9, 11.2, 5.4$  Hz, 1H), 1.20 – 0.97 (m, 3H), 0.64 (q,  $J = 5.3$  Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  161.2 (d,  $J = 243.5$  Hz), 146.9, 134.8 (d,  $J = 3.0$  Hz), 132.7, 130.4 (d,  $J = 7.7$  Hz), 128.4, 126.1, 114.7 (d,  $J = 21.2$  Hz), 70.9, 58.3, 49.6, 48.9, 38.2, 26.0, 20.1, 16.9, 9.7.

**3-Chloro-1-(4-fluorophenyl)propan-1-one (33a).** To a stirred suspension of  $\text{AlCl}_3$  (3.40 g, 25.5 mmol) in DCM (100 mL) at 0 °C was added fluorobenzene (2.00 mL, 21.2 mmol) drop-wise. After

30 minutes, 3-chloropropionyl chloride (2.81 mL, 25.5 mmol) was added drop-wise. The reaction was brought to room temperature and stirred for a further 6 hours, poured out on ice and extracted with DCM (2 x 30 mL). The organic fractions were collected and washed with sat. aqueous NaHCO<sub>3</sub> and H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and the solvent removed *in vacuo*. The residue was purified by FCC (eluent, 99:1 PE/EtOAc) to afford 3.68 g of beige crystals (93%). LCMS (*m/z*): 187.3 [M+H]<sup>+</sup>, *t*<sub>R</sub> 2.75 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.07 – 7.90 (m, 2H), 7.19 – 7.09 (m, 2H), 3.91 (t, *J* = 6.8 Hz, 2H), 3.43 (t, *J* = 6.8 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 195.2, 166.1 (d, *J* = 255.6 Hz), 132.9 (d, *J* = 3.1 Hz), 130.9 (d, *J* = 9.4 Hz), 116.0 (d, *J* = 21.9 Hz), 41.3, 38.7.

**5-Chloro-1-(4-fluorophenyl)pentan-1-one (33c).** To a stirred suspension of AlCl<sub>3</sub> (2.12 g, 15.9 mmol) in DCM (75 mL) at 0 °C was added fluorobenzene (1.25 mL, 13.3 mmol) drop-wise. After 30 minutes, 5-chloropentanoyl chloride (2.06 mL, 15.9 mmol) was added drop-wise. The reaction was brought to room temperature and stirred overnight, poured out on ice and extracted with DCM (2 x 30 mL). The organic fractions were collected and washed with sat. aqueous NaHCO<sub>3</sub> and H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and the solvent removed *in vacuo*. The residue was purified by FCC (eluent, 1:99 PE/EtOAc) to afford 2.55 g of a light brown oil (90%). LCMS (*m/z*): 215.3 [M+H]<sup>+</sup>, *t*<sub>R</sub> 2.91 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.01 – 7.92 (m, 2H), 7.12 (t, *J* = 8.6 Hz, 2H), 3.57 (t, *J* = 6.0 Hz, 2H), 2.98 (t, *J* = 6.5 Hz, 2H), 1.91 – 1.79 (m, 4H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 198.0, 165.8 (d, *J* = 254.7 Hz), 133.4 (d, *J* = 3.1 Hz), 130.7 (d, *J* = 9.4 Hz), 115.8 (d, *J* = 21.9 Hz), 44.8, 37.6, 32.1, 21.6.

**3-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-1-(4-fluorophenyl)propan-1-one (34a).**

General procedure C. Purification by FCC (20:1:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 110 mg of a white solid (77%). LCMS (*m/z*): 362.4 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.42 min. HRMS (*m/z*): C<sub>20</sub>H<sub>21</sub>ClFNO<sub>2</sub>: requires 362.1245 [M+H]<sup>+</sup>; found 362.1357. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.01 – 7.95 (m, 2H), 7.46 – 7.39 (m, 2H), 7.34 – 7.26 (m, 2H), 7.13 (t, *J* = 8.6 Hz, 2H), 3.18 (dd, *J* = 7.9, 6.7 Hz, 2H), 2.89 (dd, *J* = 8.0, 6.7 Hz, 2H), 2.82 (dt, *J* = 11.6, 3.2 Hz, 2H), 2.54 (td, *J* = 12.0, 2.5 Hz, 2H), 2.09 (td, *J* = 13.2, 4.5 Hz, 2H), 1.89 – 1.83 (s, 1H), 1.73 (dt, *J* = 14.0, 2.8 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 197.7, 165.9 (d, *J* = 254.8 Hz), 146.9, 133.5 (d, *J* = 3.0 Hz), 132.9, 130.8 (d, *J* = 9.2 Hz), 128.6, 126.2, 115.9 (d, *J* = 21.9 Hz), 70.9, 53.3, 49.6, 38.5, 36.4.

**5-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-1-(4-fluorophenyl)pentan-1-one (34c).** General procedure C. Purification by FCC (20:1:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 115 mg of a white solid (75%). LCMS (*m/z*): 390.3 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.42 min. HRMS (*m/z*): C<sub>22</sub>H<sub>25</sub>ClFNO<sub>2</sub>: requires 390.1558 [M+H]<sup>+</sup>; found 390.1640. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.02 – 7.92 (m, 2H), 7.45 – 7.37 (m, 2H), 7.31 – 7.24 (m, 2H), 7.11 (t, *J* = 8.6 Hz, 2H), 2.96 (t, *J* = 7.2 Hz, 2H), 2.79 (dt, *J* = 11.9, 3.0 Hz, 2H), 2.50 – 2.35 (m, 4H), 2.26 (s, 1H), 2.08 (td, *J* = 13.1, 4.4 Hz, 2H), 1.80 – 1.65 (m, 4H), 1.66 – 1.53 (m, 2H). <sup>13</sup>C

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3 NMR (CDCl<sub>3</sub>) δ 198.6, 165.8 (d, *J* = 254.6 Hz), 147.1, 133.5 (d, *J* = 3.0 Hz), 132.8, 130.8 (d, *J* = 9.3  
4 Hz), 128.5, 126.2, 115.8 (d, *J* = 21.8 Hz), 71.1, 58.5, 49.5, 38.5, 38.4, 26.6, 22.4.

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6 **1-(3-Chloropropyl)-4-fluorobenzene (35a)**. 3-Chloro-1-(4-fluorophenyl)propan-1-one (600 mg,  
7 3.22 mmol) was taken up in trifluoroacetic acid (5 mL) and the solution cooled to 0 °C. To this  
8 solution was added dropwise triethylsilane (1.44 mL, 9.00 mmol) and the reaction stirred at 0 °C for  
9 5 h. The solvents were removed *in vacuo* and the crude product was purified by FCC (eluent, *n*-  
10 hexanes) to afford 437 mg of a transparent oil (79%). LCMS: *t*<sub>R</sub> 3.00 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.20  
11 – 7.12 (m, 2H), 7.03 – 6.94 (m, 2H), 3.52 (t, *J* = 6.4 Hz, 2H), 2.77 (t, *J* = 7.4 Hz, 2H), 2.13 – 2.01 (m,  
12 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 161.6 (d, *J* = 243.8 Hz), 136.4 (d, *J* = 3.1 Hz), 130.0 (d, *J* = 7.9 Hz), 115.4  
13 (d, *J* = 21.1 Hz), 44.2, 34.2, 32.0.

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20 **1-(4-Chlorobutyl)-4-fluorobenzene (35b)**. 4-Chloro-1-(4-fluorophenyl)butan-1-one (1.25 mL, 7.66  
21 mmol) was taken up in trifluoroacetic acid (10 mL) and the solution cooled to 0 °C. To this solution  
22 was added dropwise triethylsilane (3.42 mL, 21.5 mmol) and the reaction stirred at 0 °C for 2 h. The  
23 solvents were removed *in vacuo* and the crude product was purified by FCC (eluent, *n*-hexanes) to  
24 afford 1.27 g of a transparent oil (89%). LCMS (*m/z*): 187.2 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.10 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  
25 δ 7.19 – 7.09 (m, 1H), 7.03 – 6.92 (m, 1H), 3.55 (t, *J* = 6.3 Hz, 1H), 2.63 (t, *J* = 7.1 Hz, 1H), 1.87 –  
26 1.70 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 161.41 (d, *J* = 243.4 Hz), 137.55 (d, *J* = 3.1 Hz), 129.80 (d, *J* =  
27 7.8 Hz), 115.21 (d, *J* = 21.2 Hz), 44.95, 34.41, 32.10, 28.81.

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34 **1-(5-Chloropentyl)-4-fluorobenzene (35c)**. 5-Chloro-1-(4-fluorophenyl)pentan-1-one (600 mg,  
35 2.80 mmol) was taken up in trifluoroacetic acid (5 mL) and the solution cooled to 0 °C. To this  
36 solution was added dropwise triethylsilane (1.25 mL, 7.83 mmol) and the reaction stirred at 0 °C for  
37 5 h. The solvents were removed *in vacuo* and the crude product was purified by FCC (eluent, *n*-  
38 hexanes) to afford 472 mg of a transparent oil (84%). LCMS: *t*<sub>R</sub> 3.15 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.13  
39 (dd, *J* = 8.4, 5.6 Hz, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 3.53 (t, *J* = 6.7 Hz, 2H), 2.60 (t, *J* = 7.7 Hz, 2H),  
40 1.81 (dd, *J* = 8.0, 6.7 Hz, 2H), 1.67 – 1.58 (m, 2H), 1.54 – 1.43 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 161.3  
41 (d, *J* = 243.0 Hz), 138.0 (d, *J* = 3.2 Hz), 129.8 (d, *J* = 7.9 Hz), 115.1 (d, *J* = 21.0 Hz), 45.1, 35.1, 32.6,  
42 30.9, 26.6.

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50 **4-(4-Chlorophenyl)-1-(3-(4-fluorophenyl)propyl)piperidin-4-ol (36a)**. General procedure C.  
51 Purification by FCC (20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 105 mg of a white solid (72 mg, 70%).  
52 LCMS (*m/z*): 348.3 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.52 min. HRMS (*m/z*): C<sub>20</sub>H<sub>23</sub>ClFNO: requires 348.1452 [M+H]<sup>+</sup>;  
53 found 348.1532. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.47 – 7.40 (m, 2H), 7.35 – 7.27 (m, 2H), 7.18 – 7.10 (m, 2H),  
54 7.01 – 6.91 (m, 2H), 2.82 (dd, *J* = 9.1, 3.2 Hz, 2H), 2.62 (t, *J* = 7.7 Hz, 2H), 2.49 – 2.37 (m, 4H), 2.13  
55 (td, *J* = 13.2, 4.5 Hz, 3H), 1.84 (dq, *J* = 9.6, 7.7 Hz, 2H), 1.77 – 1.67 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ  
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3 161.2 (d,  $J = 243.1$  Hz), 146.8, 137.6 (d,  $J = 3.2$  Hz), 132.8, 129.7 (d,  $J = 7.8$  Hz), 128.4, 126.1, 115.1  
4 (d,  $J = 21.1$  Hz), 71.0, 57.9, 49.4, 38.4, 32.9, 28.7.

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6 **4-(4-Chlorophenyl)-1-(4-(4-fluorophenyl)butyl)piperidin-4-ol (36b)**. General procedure C.  
7 Purification by FCC (20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 150 of a white solid (77%). LCMS  
8 ( $m/z$ ): 362.2 [M+H]<sup>+</sup>,  $t_R$  3.72 min. HRMS ( $m/z$ ): C<sub>21</sub>H<sub>25</sub>ClFNO: requires 362.1712 [M+H]<sup>+</sup>; found  
9 362.1743. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.43 (d,  $J = 8.6$  Hz, 2H), 7.30 (d,  $J = 8.6$  Hz, 2H), 7.12 (dd,  $J = 8.4$ ,  
10 5.6 Hz, 2H), 6.95 (t,  $J = 8.7$  Hz, 2H), 2.80 (dd,  $J = 9.1$ , 3.1 Hz, 2H), 2.61 (t,  $J = 7.3$  Hz, 2H), 2.47 –  
11 2.35 (m, 4H), 2.12 (td,  $J = 13.2$ , 4.4 Hz, 2H), 1.81 (s, 1H), 1.71 (dd,  $J = 14.1$ , 2.7 Hz, 2H), 1.58 (dtd,  
12  $J = 23.0$ , 8.4, 3.3 Hz, 4H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  161.3 (d,  $J = 243.1$  Hz), 147.0, 138.1 (d,  $J = 3.3$  Hz),  
13 132.9, 129.8 (d,  $J = 7.7$  Hz), 128.5, 126.2, 115.1 (d,  $J = 21.0$  Hz), 71.2, 58.8, 49.6, 38.5, 35.1, 29.7,  
14 26.6.

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22 **4-(4-Chlorophenyl)-1-(5-(4-fluorophenyl)pentyl)piperidin-4-ol (36c)**. General procedure C.  
23 Purification by FCC (20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 116 mg of a white solid (80%).

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25 LCMS ( $m/z$ ): 376.3 [M+H]<sup>+</sup>,  $t_R$  3.88 min. HRMS ( $m/z$ ): C<sub>22</sub>H<sub>27</sub>ClFNO: requires 376.1765  
26 [M+H]<sup>+</sup>; found 376.1846. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.43 (d,  $J = 8.6$  Hz, 2H), 7.30 (d,  $J = 8.6$  Hz, 2H), 7.12  
27 (dd,  $J = 8.4$ , 5.6 Hz, 2H), 6.95 (t,  $J = 8.7$  Hz, 2H), 2.82 (dt,  $J = 11.6$ , 3.2 Hz, 2H), 2.58 (t,  $J = 7.7$  Hz,  
28 2H), 2.45 – 2.35 (m, 4H), 2.13 (td,  $J = 13.3$ , 4.5 Hz, 3H), 1.76 – 1.67 (m, 2H), 1.67 – 1.57 (m, 2H),  
29 1.55 (ddt,  $J = 10.9$ , 7.8, 3.7 Hz, 2H), 1.40 – 1.29 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  161.3 (d,  $J = 243.0$   
30 Hz), 147.0, 138.3 (d,  $J = 3.1$  Hz), 132.9, 129.8 (d,  $J = 7.7$  Hz), 128.5, 126.2, 115.1 (d,  $J = 21.0$  Hz),  
31 71.2, 58.9, 49.6, 38.5, 35.2, 31.6, 27.3, 26.9.

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37 **3-(4-Fluorophenyl)prop-2-yn-1-ol (39a)**. General procedure E. Purification by FCC (eluent, 1:5  
38 EtOAc/*n*-hexanes) gave 2.45 g of a brown oil (94%). LCMS ( $m/z$ ): 151.1 [M+H]<sup>+</sup>,  $t_R$  2.47 min. <sup>1</sup>H  
39 NMR (CDCl<sub>3</sub>)  $\delta$  7.44 – 7.37 (m, 2H), 7.03 – 6.93 (m, 2H), 4.48 (s, 2H), 2.29 (s, 1H). <sup>13</sup>C NMR  
40 (CDCl<sub>3</sub>)  $\delta$  162.7 (d,  $J = 249.6$  Hz), 133.7 (d,  $J = 8.4$  Hz), 118.7 (d,  $J = 3.5$  Hz), 115.7 (d,  $J = 22.1$   
41 Hz), 87.1 (d,  $J = 1.5$  Hz), 84.7, 51.6.

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47 **4-(4-Fluorophenyl)but-3-yn-1-ol (39b)**. General procedure E. Purification by FCC (eluent, 1:5  
48 EtOAc/*n*-hexanes) gave 3.41 g of a brown oil that solidified upon standing (96%). LCMS ( $m/z$ ): 165.3  
49 [M+H]<sup>+</sup>,  $t_R$  2.56 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.43 – 7.36 (m, 2H), 6.99 (t,  $J = 8.7$  Hz, 2H), 3.82 (t,  $J =$   
50 6.3 Hz, 2H), 2.68 (t,  $J = 6.3$  Hz, 2H), 2.14 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  162.4 (d,  $J = 248.8$  Hz), 133.6  
51 (d,  $J = 8.3$  Hz), 119.5 (d,  $J = 3.5$  Hz), 115.56 (d,  $J = 22.0$  Hz), 86.2 (d,  $J = 1.4$  Hz), 81.4, 61.2, 23.8.

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57 **5-(4-Fluorophenyl)pent-4-yn-1-ol (39c)**. General procedure E. Purification by FCC (eluent, 1:5  
58 EtOAc/*n*-hexanes) gave 2.05 g of a brown oil (94%). LCMS ( $m/z$ ): 179.3 [M+H]<sup>+</sup>,  $t_R$  2.65 min. <sup>1</sup>H  
59 NMR (CDCl<sub>3</sub>)  $\delta$  7.40 – 7.31 (m, 2H), 7.01 – 6.92 (m, 2H), 3.81 (t,  $J = 6.1$  Hz, 2H), 2.52 (t,  $J = 7.0$   
60 Hz, 1H), 1.85 (p,  $J = 6.6$  Hz, 2H), 1.72 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  162.2 (d,  $J = 248.3$  Hz), 133.5

(d,  $J = 8.3$  Hz), 119.91 (d,  $J = 3.5$  Hz), 115.55 (d,  $J = 22.1$  Hz), 89.1 (d,  $J = 1.5$  Hz), 80.2, 61.9, 31.5, 16.1.

**3-(4-Fluorophenyl)prop-2-yn-1-yl methanesulfonate (40a).** General procedure G. Compound degraded after attempted FCC purification (eluent 4:1, PE/EtOAc). Therefore, the compound was used for the next reaction without purification.

**1-(4-Chlorobut-1-yn-1-yl)-4-fluorobenzene (40b).** General procedure D. Purification by FCC (eluent, *n*-hexanes) gave 2.56 g of a yellow oil (75%). LCMS ( $m/z$ ): 183.0  $[M+H]^+$ ,  $t_R$  3.00 min.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.44 – 7.34 (m, 1H), 7.04 – 6.93 (m, 1H), 3.67 (t,  $J = 7.2$  Hz, 1H), 2.87 (t,  $J = 7.2$  Hz, 1H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  162.5 (d,  $J = 249.1$  Hz), 133.7 (d,  $J = 8.4$  Hz), 119.3 (d,  $J = 3.5$  Hz), 115.6 (d,  $J = 22.0$  Hz), 85.5 (d,  $J = 1.5$  Hz), 81.6, 42.3, 23.9.

**5-(4-Fluorophenyl)pent-4-yn-1-yl methanesulfonate (40c).** General procedure G. Purification by FCC (eluent 4:1, PE/EtOAc) gave 333 mg of a transparent oil (93%). LCMS ( $m/z$ ): 257.2  $[M+H]^+$ ,  $t_R$  2.83 min.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.40 – 7.33 (m, 2H), 6.97 (t,  $J = 8.7$  Hz, 2H), 4.40 (t,  $J = 6.1$  Hz, 2H), 3.03 (s, 3H), 2.56 (t,  $J = 6.8$  Hz, 2H), 2.03 (p,  $J = 6.5$  Hz, 2H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  162.3 (d,  $J = 248.7$  Hz), 133.5 (d,  $J = 8.4$  Hz), 119.5 (d,  $J = 3.6$  Hz), 115.6 (d,  $J = 22.1$  Hz), 87.32, 80.9, 37.4, 28.2, 15.8.

**4-(4-Chlorophenyl)-1-(3-(4-fluorophenyl)prop-2-yn-1-yl)piperidin-4-ol (41a).** General procedure C. Purification by FCC (20:0.5:0.1, EtOAc/MeOH/ $NH_4OH$ ) gave 84 mg of a yellow solid (74%). LCMS ( $m/z$ ): 344.2  $[M+H]^+$ ,  $t_R$  3.46 min. HRMS ( $m/z$ ):  $C_{20}H_{19}ClFNO$ : requires 344.1139  $[M+H]^+$ ; found 344.1214.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.47 – 7.37 (m, 4H), 7.31 (d,  $J = 8.3$  Hz, 2H), 6.98 (t,  $J = 8.5$  Hz, 2H), 3.52 (s, 1H), 2.90 (dt,  $J = 11.6, 3.0$  Hz, 2H), 2.71 (td,  $J = 12.0, 2.5$  Hz, 2H), 2.18 (td,  $J = 13.2, 4.6$  Hz, 2H), 1.84 (s, 1H), 1.77 (dd,  $J = 14.2, 2.6$  Hz, 2H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  162.5 (d,  $J = 249.1$  Hz), 146.9, 133.7 (d,  $J = 8.3$  Hz), 132.9, 128.6, 126.2, 119.2 (d,  $J = 3.5$  Hz), 115.6 (d,  $J = 22.1$  Hz), 84.4 (d,  $J = 6.1$  Hz), 70.8, 48.7, 48.0, 38.5.

**4-(4-Chlorophenyl)-1-(4-(4-fluorophenyl)but-3-yn-1-yl)piperidin-4-ol (41b).** General procedure C. Purification by FCC (20:0.5:0.1, EtOAc/MeOH/ $NH_4OH$ ) gave 45 mg of a light brown solid (45 mg, 80%). LCMS ( $m/z$ ): 358.2  $[M+H]^+$ ,  $t_R$  3.60 min. HRMS ( $m/z$ ):  $C_{21}H_{21}ClFNO$ : requires 358.1400  $[M+H]^+$ ; found 358.1440.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.44 (d,  $J = 8.3$  Hz, 2H), 7.37 (dd,  $J = 8.4, 5.5$  Hz, 2H), 7.31 (d,  $J = 8.3$  Hz, 2H), 6.97 (t,  $J = 8.5$  Hz, 2H), 2.89 – 2.80 (m, 2H), 2.75 (t,  $J = 7.6$  Hz, 2H), 2.66 – 2.57 (m, 2H), 2.55 (d,  $J = 11.9$  Hz, 2H), 2.12 (td,  $J = 13.2, 4.5$  Hz, 2H), 1.81 (s, 1H), 1.79 – 1.68 (m, 2H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  162.3 (d,  $J = 248.5$  Hz), 146.9, 133.5 (d,  $J = 8.3$  Hz), 132.9, 128.6, 126.2, 119.9, 115.5 (d,  $J = 21.9$  Hz), 88.1, 80.5, 71.1, 57.5, 49.2, 38.6, 17.9.

**4-(4-Chlorophenyl)-1-(5-(4-fluorophenyl)pent-4-yn-1-yl)piperidin-4-ol (41c).** General procedure C. Purification by FCC (20:0.5:0.1, EtOAc/MeOH/ $NH_4OH$ ) gave 74 mg of a gold oil (68%). LCMS

(*m/z*): 372.3 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.78 min. HRMS (*m/z*): C<sub>22</sub>H<sub>23</sub>ClFNO: requires 372.1452 [M+H]<sup>+</sup>; found 372.1532. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.45 – 7.38 (m, 2H), 7.39 – 7.31 (m, 2H), 7.32 – 7.25 (m, 2H), 6.96 (t, *J* = 8.7 Hz, 2H), 2.80 (dt, *J* = 11.9, 3.1 Hz, 2H), 2.57 – 2.48 (m, 2H), 2.49 – 2.38 (m, 4H), 2.25 (s, 1H), 2.10 (td, *J* = 13.2, 4.5 Hz, 2H), 1.80 (p, *J* = 7.2 Hz, 2H), 1.70 (dd, *J* = 14.1, 2.7 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 162.1 (d, *J* = 248.3 Hz), 147.1, 120.0 (d, *J* = 3.5 Hz), 115.5 (d, *J* = 22.0 Hz), 89.45 (d, *J* = 1.5 Hz), 79.9, 71.1, 57.8, 49.5, 38.5, 26.2, 17.6.

**3-(4-Chlorophenyl)-8-(4-(4-fluorophenyl)-4-oxobutyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-ium 2,2,2-trifluoroacetate (42).** General procedure C. Purification by preparative HPLC (Method C) afforded 45 mg of the title compound as a white solid (68%). LCMS (*m/z*): 402.3 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.58 min. HRMS (*m/z*): C<sub>23</sub>H<sub>25</sub>ClFNO<sub>2</sub>: requires 402.1631 [M+H]<sup>+</sup>; found 402.1633. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.34 (s, 1H), 7.99 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.25 (m, 2H), 7.17 (t, *J* = 8.5 Hz, 2H), 4.71 (s, 1H), 4.00 (t, *J* = 4.1 Hz, 2H), 3.13 (t, *J* = 6.1 Hz, 2H), 3.06 (dt, *J* = 10.5, 5.8 Hz, 4H), 2.84 – 2.69 (m, 4H), 2.26 – 2.12 (m, 4H), 2.05 (d, *J* = 15.4 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 197.1, 166.2 (d, *J* = 256.0 Hz), 145.8, 133.5, 132.7 (d, *J* = 3.0 Hz), 130.8 (d, *J* = 9.4 Hz), 128.7, 126.3, 116.1 (d, *J* = 22.0 Hz), 71.9, 61.6, 50.9, 43.6, 34.9, 24.4, 18.8.

**4-(4-(4-Chlorophenyl)piperazin-1-yl)-1-(4-fluorophenyl)butan-1-one (43).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 115 mg of the title compound as a white solid (69%). LCMS (*m/z*): 361.3 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.41 min. HRMS (*m/z*): C<sub>20</sub>H<sub>22</sub>ClFN<sub>2</sub>O: requires 361.1405 [M+H]<sup>+</sup>; found 361.1487. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.05 – 7.93 (m, 2H), 7.20 – 7.14 (m, 2H), 7.11 (t, *J* = 8.6 Hz, 2H), 6.84 – 6.79 (m, 2H), 3.09 (dd, *J* = 6.2, 3.8 Hz, 4H), 2.99 (t, *J* = 7.0 Hz, 2H), 2.57 (t, *J* = 5.0 Hz, 4H), 2.45 (t, *J* = 7.0 Hz, 2H), 1.97 (p, *J* = 7.1 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 198.4, 165.7 (d, *J* = 254.4 Hz), 150.0, 133.7 (d, *J* = 3.0 Hz), 130.7 (d, *J* = 9.2 Hz), 128.9, 124.4, 117.2, 115.7 (d, *J* = 21.8 Hz), 57.7, 53.0, 49.1, 36.2, 21.6.

**4-(4-Chlorophenyl)-1,2,3,6-tetrahydropyridine (44).** To concentrated hydrochloric acid (10 mL) in a 25 mL round-bottom flask was added 4-(4-chlorophenyl)piperidin-4-ol (500 mg, 2.36 mmol), and the suspension was stirred at reflux for 5 h. The solution was allowed to cool, then slowly added to 5 M NaOH (20 mL), and extracted with DCM (3 × 20 mL). The organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to afford the 457 mg of a white solid (quantitative yield). LCMS (*m/z*): 194.3 [M+H]<sup>+</sup>, *t*<sub>R</sub> 1.87 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.34 – 7.23 (m, 4H), 6.11 (dt, *J* = 3.5, 1.8 Hz, 1H), 3.51 (q, *J* = 3.0 Hz, 2H), 3.09 (t, *J* = 5.7 Hz, 2H), 2.41 (dddd, *J* = 6.9, 4.0, 2.7, 1.2 Hz, 2H), 1.65 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 139.9, 134.4, 132.7, 128.5, 126.2, 124.3, 45.7, 43.4, 27.9.

**4-(4-(4-Chlorophenyl)-3,6-dihydropyridin-1(2H)-yl)-1-(4-fluorophenyl)butan-1-one (45).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/NH<sub>4</sub>OH) gave 49 mg of the title compound as a white solid (80%). LCMS (*m/z*): 358.2 [M+H]<sup>+</sup>, *t*<sub>R</sub> 3.64 min. HRMS (*m/z*):

$C_{21}H_{21}ClFNO$ : requires 358.1296  $[M+H]^+$ ; found 358.1379.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.04 – 7.94 (m, 2H), 7.33 – 7.23 (m, 4H), 7.11 (t,  $J = 8.6$  Hz, 2H), 6.04 (t,  $J = 1.7$  Hz, 1H), 3.14 (q,  $J = 3.0$  Hz, 2H), 3.02 (t,  $J = 7.1$  Hz, 2H), 2.69 (t,  $J = 5.7$  Hz, 2H), 2.54 (t,  $J = 7.1$  Hz, 2H), 2.49 (tt,  $J = 5.8, 2.5$  Hz, 2H), 2.01 (p,  $J = 7.1$  Hz, 2H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  198.6, 165.8 (d,  $J = 254.4$  Hz), 139.4, 134.1, 133.7 (d,  $J = 3.0$  Hz), 132.8, 130.8 (d,  $J = 9.3$  Hz), 126.3, 122.6, 115.7 (d,  $J = 21.8$  Hz), 57.5, 53.3, 50.3, 36.3, 28.1, 21.9.

**4-(6-(4-Chlorophenyl)-3-azabicyclo[4.1.0]heptan-3-yl)-1-(4-fluorophenyl)butan-1-one (46).** A solution of 4-(4-(4-chlorophenyl)-3,6-dihydropyridin-1(2*H*)-yl)-1-(4-fluorophenyl)butan-1-one (110 mg, 307  $\mu$ mol) in DCM (20 mL), was treated with  $Et_2Zn$  (0.9 M in hexanes; 1.71 mL, 1.54 mmol). After 10 minutes, the reaction mixture was cooled to 0  $^\circ C$ , and treated with a solution of  $CH_2I_2$  (124  $\mu$ L, 1.54 mmol) in DCM (2 mL) drop-wise over and allowed to warm to ambient temperature. After 24 h, the reaction mixture was quenched slowly with sat. aqueous  $NH_4Cl$  and stirred for 10 minutes. The reaction mixture was extracted with DCM (3 x 20 mL), and the combined organic phases were washed with sat. aqueous  $NaHCO_3$ , dried ( $Na_2SO_4$ ), and concentrated *in vacuo*. The resulting residue was purified by FCC (eluent, 5% MeOH/EtOAc) to yield 82 mg of the title compound as a white solid (72%). LCMS ( $m/z$ ): 372.2  $[M+H]^+$ ,  $t_R$  3.94 min. HRMS ( $m/z$ ):  $C_{22}H_{23}FNO$ : requires 372.1452  $[M+H]^+$ ; found 372.1517.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.05 – 7.95 (m, 2H), 7.24 – 7.17 (m, 2H), 7.18 – 7.07 (m, 4H), 2.97 (t,  $J = 7.1$  Hz, 2H), 2.81 (dd,  $J = 11.3, 5.8$  Hz, 1H), 2.69 (dd,  $J = 11.3, 1.7$  Hz, 1H), 2.36 (t,  $J = 6.9$  Hz, 2H), 2.26 – 2.20 (m, 2H), 2.03 (dq,  $J = 14.0, 7.4, 6.9$  Hz, 2H), 1.92 (p,  $J = 7.1$  Hz, 2H), 1.37 – 1.28 (m, 1H), 0.87 (dd,  $J = 9.2, 4.2$  Hz, 1H), 0.79 (dd,  $J = 5.7, 4.3$  Hz, 1H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  196.7, 166.1 (d,  $J = 256.1$  Hz), 142.7, 132.9, 132.7 (d,  $J = 3.0$  Hz), 130.8 (d,  $J = 9.3$  Hz), 129.9, 128.9, 116.0 (d,  $J = 22.2$  Hz), 56.3, 52.7, 48.1, 34.9, 28.7, 23.6, 18.1, 17.7, 15.1.

**1-(4-Fluorophenyl)-4-(4-phenylpiperidin-1-yl)butan-1-one (47).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/ $NH_4OH$ ) gave 89 mg of the title compound as a white solid (75%). LCMS ( $m/z$ ): 326.4  $[M+H]^+$ ,  $t_R$  3.35 min. HRMS ( $m/z$ ):  $C_{21}H_{24}FNO$ : requires 326.1842  $[M+H]^+$ ; found 326.1930.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.08 – 7.97 (m, 2H), 7.33 – 7.25 (m, 2H), 7.20 (d,  $J = 7.3$  Hz, 3H), 7.14 (t,  $J = 8.6$  Hz, 2H), 3.07 – 2.95 (m, 4H), 2.51 – 2.41 (m, 3H), 2.10 – 2.02 (m, 2H), 2.01 – 1.94 (m, 2H), 1.84 – 1.77 (m, 2H), 1.71 (qd,  $J = 12.4, 3.7$  Hz, 2H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  198.6, 165.8 (d,  $J = 254.4$  Hz), 146.5, 133.8 (d,  $J = 3.0$  Hz), 130.8 (d,  $J = 9.2$  Hz), 128.5, 126.9, 126.2, 115.7 (d,  $J = 21.8$  Hz), 58.2, 54.4, 42.8, 36.5, 33.5, 22.1.

**4-(4-(4-Chlorophenyl)piperidin-1-yl)-1-(4-fluorophenyl)butan-1-one (48).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/ $NH_4OH$ ) gave 59 mg of the title compound as a beige solid (68%). LCMS ( $m/z$ ): 360.2  $[M+H]^+$ ,  $t_R$  3.72 min. HRMS ( $m/z$ ):  $C_{21}H_{23}ClFNO$ : requires 360.1452  $[M+H]^+$ ; found 360.1539.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.01 (dd,  $J = 8.7, 5.5$  Hz, 2H), 7.26 – 7.22



(m, 2H), 7.16 – 7.08 (m, 4H), 3.05 – 2.94 (m, 4H), 2.52 – 2.38 (m, 3H), 2.09 – 1.90 (m, 4H), 1.76 (dq,  $J = 12.6, 2.2$  Hz, 2H), 1.63 (qd,  $J = 12.4, 3.8$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  198.5, 165.7 (d,  $J = 254.2$  Hz), 144.9, 133.8 (d,  $J = 3.0$  Hz), 131.8, 130.8 (d,  $J = 9.2$  Hz), 128.6, 128.3, 115.7 (d,  $J = 21.7$  Hz), 58.2, 54.3, 42.2, 36.4, 33.5, 22.0.

***tert*-Butyl 4-(4-chlorophenyl)-4-hydroxypiperidine-1-carboxylate (49).** To a suspension of 4-(4-chlorophenyl)piperidin-4-ol (500 mg, 2.36 mmol) and  $\text{Et}_3\text{N}$  (823  $\mu\text{L}$ , 5.90 mmol) in DCM (20 mL), was added di-*tert*-butyl dicarbonate (2.06 g, 9.45 mmol) and the reaction stirred at rt for 4 h. The solvent was evaporated under reduced pressure and the residue was purified by FCC (eluent, 10:1 *n*-hexanes/EtOAc) to afford 715 mg of a clear oil (97%). LCMS ( $m/z$ ): 312.3  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.09 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.38 (d,  $J = 7.2$  Hz, 2H), 7.15 (d,  $J = 7.3$  Hz, 2H), 3.94 (br s, 2H), 3.18 (br s, 2H), 1.89 (br s, 2H), 1.46 (s, 11H).

***tert*-Butyl 4-(4-chlorophenyl)-4-methoxypiperidine-1-carboxylate (50).** To a stirred suspension of sodium hydride (64.7 mg, 2.69 mmol) in dry DMF (15 mL) at rt was added *tert*-butyl 4-(4-chlorophenyl)-4-hydroxypiperidine-1-carboxylate (700 mg, 2.24 mmol). After 30 minutes, methyl iodide (168  $\mu\text{L}$ , 2.69 mmol) was added and the mixture was stirred overnight. The mixture was poured into an equal volume of  $\text{H}_2\text{O}$  and extracted with EtOAc ( $2 \times 30$  mL). The EtOAc extracts were collected and washed with additional  $\text{H}_2\text{O}$  ( $3 \times 30$  mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo* to give an orange oil. The crude oil was purified by FCC (eluent, 10:1 *n*-hexanes/EtOAc) to afford 645 mg of a clear oil (88%). LCMS ( $m/z$ ): 326.3  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.18 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.00 (dd,  $J = 8.7, 5.5$  Hz, 2H), 7.33 – 7.25 (m, 4H), 7.16 – 7.06 (m, 2H), 2.97 (t,  $J = 7.1$  Hz, 2H), 2.93 (s, 3H), 2.75 – 2.65 (m, 2H), 2.45 (t,  $J = 7.2$  Hz, 2H), 2.38 (td,  $J = 11.7, 2.5$  Hz, 2H), 2.03 – 1.90 (m, 4H), 1.84 (dt,  $J = 13.1, 6.7$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  198.5, 165.7 (d,  $J = 254.4$  Hz), 143.6, 133.8 (d,  $J = 3.0$  Hz), 133.0, 130.8 (d,  $J = 9.3$  Hz), 128.6, 127.6, 115.7 (d,  $J = 21.8$  Hz), 75.4, 49.2, 36.4, 34.7, 22.1.

**4-(4-Chlorophenyl)-4-methoxypiperidin-1-ium chloride (51).** General procedure B. Concentration *in vacuo* gave 296 mg of a white solid (95%).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  9.30 (s, 2H), 7.53 – 7.45 (m, 2H), 7.45 – 7.36 (m, 2H), 3.18 (d,  $J = 12.5$  Hz, 12H), 3.11 – 2.96 (m, 2H), 2.89 (s, 3H), 2.20 – 2.08 (m, 4H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  141.9, 132.4, 128.6, 127.8, 73.4, 49.6, 39.3, 30.5.

**4-(4-(4-Chlorophenyl)-4-methoxypiperidin-1-yl)-1-(4-fluorophenyl)butan-1-one (52).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/ $\text{NH}_4\text{OH}$ ) gave 88 mg of the title compound as a white solid (81%). LCMS ( $m/z$ ): 390.3  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.82 min. HRMS ( $m/z$ ):  $\text{C}_{22}\text{H}_{25}\text{ClFNO}_2$ : requires 390.1558  $[\text{M}+\text{H}]^+$ ; found 390.1639.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.00 (dd,  $J = 8.7, 5.5$  Hz, 2H), 7.33 – 7.25 (m, 4H), 7.16 – 7.06 (m, 2H), 2.97 (t,  $J = 7.1$  Hz, 2H), 2.93 (s, 3H), 2.75 – 2.65 (m, 2H), 2.45 (t,  $J = 7.2$  Hz, 2H), 2.38 (td,  $J = 11.7, 2.5$  Hz, 2H), 2.03 – 1.90 (m, 4H), 1.84 (dt,

$J = 13.1, 6.7$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  198.5, 165.7 (d,  $J = 254.4$  Hz), 143.6, 133.8 (d,  $J = 3.0$  Hz), 133.0, 130.8 (d,  $J = 9.3$  Hz), 128.6, 127.6, 115.7 (d,  $J = 21.8$  Hz), 75.4, 49.2, 36.4, 34.7, 22.1.

**1-(4-Chlorophenyl)-4-(4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl)butan-1-one (53).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/ $\text{NH}_4\text{OH}$ ) gave 75 mg of the title compound as a light yellow solid (71%). LCMS ( $m/z$ ): 376.3  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  3.39 min. HRMS ( $m/z$ ):  $\text{C}_{21}\text{H}_{23}\text{ClFNO}_2$ : requires 376.1401  $[\text{M}+\text{H}]^+$ ; found 376.1488.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.99 – 7.88 (m, 2H), 7.48 – 7.36 (m, 4H), 7.01 (t,  $J = 8.7$  Hz, 2H), 2.98 (t,  $J = 7.0$  Hz, 2H), 2.76 (dd,  $J = 9.1, 6.1$  Hz, 2H), 2.51 – 2.38 (m, 4H), 2.03 – 1.92 (m, 5H), 1.69 (dd,  $J = 14.2, 2.6$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  198.9, 161.9 (d,  $J = 245.2$  Hz), 144.3 (d,  $J = 3.1$  Hz), 139.4, 135.7, 129.6, 128.9, 126.4 (d,  $J = 7.9$  Hz), 115.0 (d,  $J = 21.2$  Hz), 71.1, 57.9, 49.5, 38.6, 36.4, 22.1.

**4-(4-Hydroxy-4-phenylpiperidin-1-yl)-1-phenylbutan-1-one (54).** General procedure C. Purification by FCC (eluent 20:0.5:0.1, EtOAc/MeOH/ $\text{NH}_4\text{OH}$ ) gave 125 mg of the title compound as a white solid (88%). LCMS ( $m/z$ ): 324.3  $[\text{M}+\text{H}]^+$ ,  $t_{\text{R}}$  2.72 min. HRMS ( $m/z$ ):  $\text{C}_{21}\text{H}_{25}\text{NO}_2$ : requires 324.1865  $[\text{M}+\text{H}]^+$ ; found 324.1965.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.03 – 7.94 (m, 2H), 7.59 – 7.51 (m, 1H), 7.46 (dd,  $J = 8.4, 6.9$  Hz, 4H), 7.33 (dd,  $J = 8.4, 6.8$  Hz, 2H), 7.27 – 7.21 (m, 1H), 3.01 (t,  $J = 7.0$  Hz, 2H), 2.82 (dt,  $J = 11.9, 3.2$  Hz, 2H), 2.55 – 2.44 (m, 4H), 2.14 – 1.94 (m, 5H), 1.71 (dd,  $J = 14.1, 2.7$  Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  200.1, 148.4, 137.3, 132.9, 128.7, 128.4, 128.2, 127.1, 124.6, 71.3, 57.9, 49.5, 38.3, 36.5, 21.9.

**Pharmacological Characterisation.** *Materials.* Tag-lite labeling medium (LABMED), SNAP-Lumi4-Tb, and the PPHT (( $\pm$ )-2-(*N*-phenethyl-*N*-propyl)amino-5-hydroxytetralin hydrochloride; 1-Naphthalenol,5,6,7,8-tetrahydro-6-[(2-phenylethyl)propylamino]) derivative labelled with a red fluorescent probe (PPHT-red) was obtained from Cisbio Bioassays (Bagnolssur-Cèze, France). Ninety-six-well polypropylene plates (Corning) were purchased from Fisher Scientific UK (Loughborough, UK) and 384-well optiplate plates were purchased from PerkinElmer (Beaconsfield, UK). GppNHp used in competition assays were obtained from Sigma-Aldrich (Poole, UK).

*Cell culture.* The host Chinese hamster ovary (CHO) K1 cell line was transfected with the cDNA encoding a SNAP-tagged human dopamine  $\text{D}_{2\text{L}}$  receptor (Genbank ref.: NM\_000795), and a stable dilution-cloned cell line (CHO-h $\text{D}_{2\text{L}}$ ) was established by zeocin resistance encoded by the plasmid vector (pcDNA3.1zeo<sup>+</sup>, Invitrogen, Paisley UK). Cells were maintained in Dulbecco's modified Eagle's medium: Ham F12 (DMEM:F12) containing 2 mM glutamine (Sigma-Aldrich, Poole, UK) and supplemented with 10% fetal calf serum (Life Technologies, Paisley UK).

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3 *Terbium labelling of SNAP-tagged D<sub>2L</sub> cells.* Cell culture medium was removed from the t175 cm<sup>2</sup>  
4 flasks containing confluent adherent CHO–D<sub>2L</sub> cells. Twelve mL of Tag-lite labelling medium  
5 containing 100 nM of SNAP-Lumi4-Tb was added to the flask and incubated for 1 h at 37 °C under  
6 5% CO<sub>2</sub>. Cells were washed 2× in PBS (GIBCO Carlsbad, CA) to remove the excess of SNAP-  
7 Lumi4-Tb then detached using 5 mL of GIBCO enzyme-free Hank's-based cell dissociation buffer  
8 (GIBCO, Carlsbad, CA) and collected in a vial containing 5 mL of DMEM:F12 containing 2mM  
9 glutamine (Sigma-Aldrich) and supplemented with 10% fetal calf serum. Cells were pelleted by  
10 centrifugation (5 min at 1500 rpm) and the pellets were frozen to –80 °C. To prepare membranes,  
11 homogenisation steps were conducted at 4 °C (to avoid receptor degradation). Specifically 20 mL per  
12 t175-cm<sup>2</sup> flask of wash buffer (10 mM HEPES and 10 mM EDTA, pH 7.4) was added to the pellet.  
13 This was homogenised using an electrical homogenizer Ultra-Turrax (Ika-Werk GmbH & Co. KG,  
14 Staufen, Germany) (position 6, 4 × 5-s bursts) and subsequently centrifuged at 48,000×g at 4 °C  
15 (Beckman Avanti J-251 Ultracentrifuge; Beckman Coulter, Fullerton, CA) for 30 min. The  
16 supernatant was discarded, and the pellet was re-homogenised and centrifuged as described above in  
17 wash buffer. The final pellet was suspended in ice-cold 10mM HEPES and 0.1mM EDTA, pH 7.4,  
18 at a concentration of 5–10 mg mL<sup>-1</sup>. Protein concentration was determined using the bicinchoninic  
19 acid assay kit (Sigma-Aldrich), using BSA as a standard and aliquots maintained at –80 °C until  
20 required. Prior to their use, the frozen membranes were thawed and the membranes suspended in the  
21 assay buffer at a membranes concentration of 0.2 mg mL<sup>-1</sup>.

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36 *Fluorescent ligand-binding assays.* All fluorescent binding experiments using PPHT-red were  
37 conducted in white 384-well Optiplate plates, in assay binding buffer, 20 mM HEPES, 138 mM NaCl,  
38 6 mM MgCl<sub>2</sub>, 1 mM EGTA, 1 mM EDTA, and 0.02% pluronic acid pH 7.4, 100 μM GppNHp, and  
39 0.1% ascorbic acid. GppNHp was included to remove the G protein-coupled population of receptors  
40 that can result in two distinct populations of binding sites in membrane preparations, since the  
41 Motulsky-Mahan model<sup>30</sup> is only appropriate for ligands competing at a single site. In all cases,  
42 nonspecific binding was determined in the presence of 10 μM haloperidol.

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49 *Determination of PPHT-red binding kinetics.* To accurately determine association rate ( $k_{on}$ ) and  
50 dissociation rate ( $k_{off}$ ) values, the observed rate of association ( $k_{ob}$ ) was calculated using at least four  
51 different concentrations of PPHT-red (50-1.56 nM). The appropriate concentration of PPHT-red was  
52 incubated with human D<sub>2L</sub> CHO cell membranes (2 μg per well) in assay binding buffer (final assay  
53 volume, 40 μL). The degree of PPHT-red bound to the receptor was assessed at multiple time points  
54 by HTRF detection to allow construction of association kinetic curves. The kinetic parameters of  
55 PPHT-red and plus those of unlabelled compounds were determined using a start time of ~1sec and  
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an interval time of 20sec. The resulting data were globally fitted to the association kinetic model Eq. 2 to derive a single best-fit estimate for  $k_{\text{on}}$  and  $k_{\text{off}}$  as described under data analysis. The expression level of the hD<sub>2L</sub>R recombinantly expressed in CHO cells was assessed, using [<sup>3</sup>H]-spiperone saturation binding and determined to be  $1.13 \pm 0.11$  pmol mg<sup>-1</sup> protein.<sup>33</sup>

*Competition binding kinetics.* To determine the association and dissociation rates of D<sub>2</sub>R ligands, we used a competition kinetic binding assay recently described to profile the kinetics of a series of D<sub>2</sub>R agonists<sup>31</sup> and antipsychotic drugs.<sup>33</sup> This approach involves the simultaneous addition of both fluorescent ligand and competitor to the receptor preparation, so that at  $t = 0$  all receptors are unoccupied. 12.5 nM PPHT-red (a concentration which avoids ligand depletion in this assay volume), was added simultaneously with the unlabelled compound of varying concentrations (at  $t = \sim 1$  sec) to CHO cell membranes derived from cells stably expressing the human D<sub>2L</sub>R (2 μg per well) in 40 μL of assay buffer. The degree of PPHT-red bound to the receptor was assessed at multiple time points by HTRF detection.

Non-specific binding was determined as the amount of HTRF signal detected in the presence of haloperidol (10 μM) and was subtracted from each time point, meaning that  $t = 0$  was always equal to zero. Each time point was conducted on the same 384-well plate incubated at 37 °C with orbital mixing (1 s of 100 RPM per cycle). Multiple concentrations of unlabelled competitor were tested for determination of rate parameters. Data were globally fitted using Eq. 3 to simultaneously calculate  $k_{\text{on}}$  and  $k_{\text{off}}$ .

*Signal detection and data analysis.* Signal detection was performed on a Pherastar FS (BMG Labtech, Offenburg, Germany) using standard HTRF settings. The terbium donor was always excited with three laser flashes at a wavelength of 337 nm. A kinetic TR-FRET signal was collected at 20 s intervals both at 665 and 620 nm, when using red acceptor. HTRF ratios were obtained by dividing the acceptor signal (665 nm) by the donor signal (620 nm) and multiplying this value by 10,000. All experiments were analysed by non-linear regression using Prism 6.0 (Graphpad Software, San Diego, USA). Competition displacement data were fitted to sigmoidal (variable slope) curves using a “four parameter logistic equation”:

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{\log EC_{50} - X} \text{Hillcoefficient}). \quad (1)$$

IC<sub>50</sub> values obtained from the inhibition curves were converted to  $K_i$  values using the method of Cheng and Prusoff.<sup>74</sup> PPHT-red association data were fitted as follows to a global fitting model using

Graphpad Prism 6.0 to simultaneously calculate  $k_{on}$  and  $k_{off}$  using the following equation, where  $k_{ob}$  equals the observed rate of association:

$$k_{ob} = [PPHT - red] \cdot k_{on} + k_{off}. \quad (2)$$

Association and dissociation rates for unlabelled compounds were calculated using the equations described by Motulsky and Mahan.<sup>30</sup>

$$K_A = k_1[L] + k_2 \quad K_B = k_2[I] + k_4 \quad S = \sqrt{(K_A - K_B)^2 + 4 \cdot k_1 \cdot k_3 \cdot L \cdot I \cdot 10^{-18}} \quad K_F$$

$$= 0.5 \cdot (K_A + K_B + S) \quad (3) \quad K_S = 0.5 \cdot (K_A + K_B - S) \quad DIFF = K_F - K_S \quad Q =$$

$$\frac{B_{max} \cdot k_1 \cdot L \cdot 10^{-9}}{DIFF} \quad Y = Q \times \left( \frac{k_4 \cdot DIFF}{K_F \times K_S} + \frac{k_4 - K_F}{K_F} \cdot \exp(-K_F \cdot X) - \frac{k_4 - K_S}{K_S} \cdot \exp(-K_S \cdot X) \right).$$

Where:  $X$  = Time (min),  $Y$  = Specific binding (HTRF ratio 665 nm/620 nm $\times$ 10,000),  $k_1 = k_{on}$  PPHT-red,  $k_2 = k_{off}$  PPHT-red,  $L$  = Concentration of PPHT-red used (nM),  $B_{max}$  = Total binding (HTRF ratio 665 nm/620 nm $\times$ 10,000),  $I$  = Concentration of unlabelled antagonist (nM). Fixing the above parameters allowed the following to be calculated:  $k_3$  = Association rate of unlabelled ligand ( $M^{-1} \text{ min}^{-1}$ ),  $k_4$  = Dissociation rate of unlabelled ligand ( $\text{min}^{-1}$ ). Dissociation of PPHT-red was fitted to a one phase mono-exponential decay function to estimate the dissociation rate of PPHT-red directly. Specific binding was determined by subtracting the nonspecific HTRF ratio from the total HTRF ratio.

*cAMP assay.* FlpIn CHO cells stably expressing the SNAP-tagged hD<sub>2L</sub>R and the CAMYEL BRET biosensor were plated into 96-well white-walled plates (Greiner, Kremsmünster, Austria) at a density of 40,000 cells per well and grown overnight. The cells were equilibrated in Dulbecco's phosphate buffered saline with 5 mM glucose at 37°C for 30 minutes before starting the experiment. Coelenterazine (Nanolight, Pinetop, Arizona, USA) was added at a final concentration of 5  $\mu$ M at 5 min prior to addition of agonist. For the agonist mode experiments the cells were co-stimulated with the analogues and 3  $\mu$ M forskolin for 10 minutes before BRET readings were taken. For the antagonist mode experiments, a 10  $\mu$ M concentration of each analogue was added prior to cells being co-stimulated with 3  $\mu$ M forskolin and an EC<sub>80</sub> concentration (30 nM) dopamine for 10 minutes before BRET readings were taken. The signals were detected at 445-505 and 505-565 nm using a Pherastar FS instrument (BMG LabTech, Offenburg, Germany). Net BRET was determined by subtraction of the vehicle control co-added with 3  $\mu$ M forskolin.

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## ■ ASSOCIATED CONTENT

**Supporting Information.** Synthetic schemes and characterisation data for literature analogues of **1**.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra and reverse-phase analytical chromatograms for representative screening compounds. Plot of determined PPHT-red equilibrium and kinetic binding parameters. Plot of observed association rate ( $k_{\text{on}}$ ) with calculated topological polar surface area. Molecular formula strings for all screening compounds.

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## ■ ABBREVIATIONS USED

D<sub>2</sub>R, dopamine D<sub>2</sub> receptor; DA, dopamine; APD, antipsychotic drug; EPS, extrapyramidal symptoms; FGA, first generation antipsychotic; SGA, second generation antipsychotic; TR-FRET, time-resolved fluorescence resonance energy transfer;  $k_{\text{off}}$ , dissociation rate constant;  $k_{\text{on}}$ , association rate constant; SAR, structure-activity relationship; SKR, structure-kinetic relationship; FCC, flash column chromatography; HPLC, high-performance liquid chromatography; S<sub>N</sub>Ar, nucleophilic aromatic substitution; HBSS, Hank's balanced salt solution; FBS, foetal bovine serum.

## ■ REFERENCES

1. Seeman, P.; Lee, T.; Chau-Wong, M.; Wong, K. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* **1976**, *261*, 717-719.

- 1  
2  
3 2. Ginovart, N.; Kapur, S. Role of dopamine D(2) receptors for antipsychotic activity. *Handb.*  
4  
5 *Exp. Pharmacol.* **2012**, *212*, 27-52.
- 6  
7 3. Miyamoto, S.; Miyake, N.; Jarskog, L. F.; Fleischhacker, W. W.; Lieberman, J. A.  
8  
9 Pharmacological treatment of schizophrenia: a critical review of the pharmacology and clinical  
10  
11 effects of current and future therapeutic agents. *Mol. Psychiatr.* **2012**, *17*, 1206-1227.
- 12  
13 4. Meltzer, H. Y. Update on typical and atypical antipsychotic drugs. *Annu. Rev. Med.* **2013**,  
14  
15 *64*, 393-406.
- 16  
17 5. Leucht, S.; Corves, C.; Arbter, D.; Engel, R. R.; Li, C.; Davis, J. M. Second-generation  
18  
19 versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* **2009**, *373*,  
20  
21 31-41.
- 22  
23 6. Farde, L.; Nordstrom, A. L.; Wiesel, F. A.; Pauli, S.; Halldin, C.; Sedvall, G. Positron  
24  
25 emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients  
26  
27 treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. *Arch. Gen.*  
28  
29 *Psychiat.* **1992**, *49*, 538-544.
- 30  
31 7. Caron, M. G.; Beaulieu, M.; Raymond, V.; Gagne, B.; Drouin, J.; Lefkowitz, R. J.; Labrie,  
32  
33 F. Dopaminergic receptors in the anterior pituitary gland. Correlation of [3H]dihydroergocryptine  
34  
35 binding with the dopaminergic control of prolactin release. *J. Biol. Chem.* **1978**, *253*, 2244-2253.
- 36  
37 8. Casey, D. E. Neuroleptic drug-induced extrapyramidal syndromes and tardive dyskinesia.  
38  
39 *Schizophr. Res.* **1991**, *4*, 109-120.
- 40  
41 9. Leucht, S.; Pitschel-Walz, G.; Abraham, D.; Kissling, W. Efficacy and extrapyramidal side-  
42  
43 effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to  
44  
45 conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials.  
46  
47 *Schizophr. Res.* **1999**, *35*, 51-68.
- 48  
49 10. Halbreich, U.; Kinon, B. J.; Gilmore, J. A.; Kahn, L. S. Elevated prolactin levels in patients  
50  
51 with schizophrenia: mechanisms and related adverse effects. *Psychoneuroendocrinology* **2003**, *28*,  
52  
53 53-67.
- 54  
55  
56  
57  
58  
59  
60

11. Mauri, M. C.; Paletta, S.; Maffini, M.; Colasanti, A.; Dragogna, F.; Di Pace, C.; Altamura, A. C. Clinical pharmacology of atypical antipsychotics: an update. *EXCLI J.* **2014**, *13*, 1163-1191.
12. Roth, B. L.; Sheffler, D. J.; Kroeze, W. K. Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. *Nat. Rev. Drug Discov.* **2004**, *3*, 353.
13. Kapur, S.; Remington, G. Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biol. Psychiat.* **2001**, *50*, 873-883.
14. Meltzer, H. Y.; Matsubara, S.; Lee, J. C. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin<sub>2</sub> pKi values. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 238-246.
15. Marcus, M.; Wiker, C.; Frånberg, O.; Konradsson-Geuken, A.; Langlois, X.; Jardemark, K.; Svensson, T. Adjunctive alpha(2)-adrenoceptor blockade enhances the antipsychotic-like effect of risperidone and facilitates cortical dopaminergic and glutamatergic, NMDA receptor-mediated transmission. *Int. J. Neuropsychopharmacol.* **2009**, *13*, 891-903.
16. Horacek, J.; Bubenikova-Valesova, V.; Kopecek, M.; Palenicek, T.; Dockery, C.; Mohr, P.; Hoschl, C. Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. *CNS Drugs* **2006**, *20*, 389-409.
17. Kapur, S.; Seeman, P. Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: A new hypothesis. *Am. J. Psychiat.* **2001**, *158*, 360-369.
18. Raja, M. Clozapine safety, 35 years later. *Curr. Drug. Saf.* **2011**, *6*, 164-184.
19. Kapur, S.; Seeman, P. Antipsychotic agents differ in how fast they come off the dopamine D2 receptors. Implications for atypical antipsychotic action. *J. Psychiatr. Neurosci.* **2000**, *25*, 161-166.
20. Copeland, R. A.; Pompliano, D. L.; Meek, T. D. Drug-target residence time and its implications for lead optimization. *Nat. Rev. Drug Discov.* **2006**, *5*, 730-739.
21. Guo, D.; Heitman, L. H.; AP, I. J. The role of target binding kinetics in drug discovery. *ChemMedChem* **2015**, *10*, 1793-1796.



- 1  
2  
3 22. Doornbos, M. L. J.; Cid, J. M.; Haubrich, J.; Nunes, A.; van de Sande, J. W.; Vermond, S.  
4  
5 C.; Mulder-Krieger, T.; Trabanco, A. A.; Ahnaou, A.; Drinkenburg, W. H.; Lavreysen, H.;  
6  
7 Heitman, L. H.; AP, I. J.; Tresadern, G. Discovery and kinetic profiling of 7-aryl-1,2,4-triazolo[4,3-  
8  
9 a]pyridines: positive allosteric modulators of the metabotropic glutamate receptor 2. *J. Med. Chem.*  
10  
11 **2017**, *60*, 6704-6720.  
12  
13  
14 23. Xia, L.; Burger, W. A. C.; van Veldhoven, J. P. D.; Kuiper, B. J.; van Duijl, T. T.;  
15  
16 Lenselink, E. B.; Paasman, E.; Heitman, L. H.; Ijzerman, A. P. Structure–affinity relationships and  
17  
18 structure–kinetics relationships of pyrido[2,1-*f*]purine-2,4-dione derivatives as human adenosine A3  
19  
20 receptor antagonists. *J. Med. Chem.* **2017**, *60*, 7555-7568.  
21  
22  
23 24. Vilums, M.; Zweemer, A. J. M.; Yu, Z.; de Vries, H.; Hillger, J. M.; Wapenaar, H.; Bollen,  
24  
25 I. A. E.; Barmare, F.; Gross, R.; Clemens, J.; Krenitsky, P.; Brussee, J.; Stamos, D.; Saunders, J.;  
26  
27 Heitman, L. H.; Ijzerman, A. P. Structure–kinetic relationships—An overlooked parameter in hit-to-  
28  
29 lead optimization: a case of cyclopentylamines as chemokine receptor 2 antagonists. *J. Med. Chem.*  
30  
31 **2013**, *56*, 7706-7714.  
32  
33  
34 25. Tautermann, C. S. Impact, determination and prediction of drug–receptor residence times  
35  
36 for GPCRs. *Curr. Opin. Pharmacol.* **2016**, *30*, 22-26.  
37  
38  
39 26. de Witte, W. E. A.; Danhof, M.; van der Graaf, P. H.; de Lange, E. C. M. In vivo target  
40  
41 residence time and kinetic selectivity: The association rate constant as determinant. *Trends.*  
42  
43 *Pharmacol. Sci.* **2016**, *37*, 831-842.  
44  
45  
46 27. Schuetz, D. A.; de Witte, W. E. A.; Wong, Y. C.; Knasmueller, B.; Richter, L.; Kokh, D. B.;  
47  
48 Sadiq, S. K.; Bosma, R.; Nederpelt, I.; Heitman, L. H.; Segala, E.; Amaral, M.; Guo, D.; Andres,  
49  
50 D.; Georgi, V.; Stoddart, L. A.; Hill, S.; Cooke, R. M.; De Graaf, C.; Leurs, R.; Frech, M.; Wade,  
51  
52 R. C.; de Lange, E. C. M.; AP, I. J.; Muller-Farnow, A.; Ecker, G. F. Kinetics for drug discovery:  
53  
54 an industry-driven effort to target drug residence time. *Drug. Discov. Today* **2017**, *22*, 896-911.  
55  
56  
57 28. Sykes, D. A.; Stoddart, L. A.; Kilpatrick, L. E.; Hill, S. J. Binding kinetics of ligands acting  
58  
59 at GPCRs. *Mol. Cell. Endocrinol.* **2019**.  
60

- 1  
2  
3 29. Seeman, P.; Tallerico, T. Rapid release of antipsychotic drugs from dopamine D2 receptors:  
4 an explanation for low receptor occupancy and early clinical relapse upon withdrawal of clozapine  
5 or quetiapine. *Am. J. Psychiat.* **1999**, *156*, 876-884.  
6  
7  
8  
9 30. Motulsky, H. J.; Mahan, L. C. The kinetics of competitive radioligand binding predicted by  
10 the law of mass action. *Mol. Pharmacol.* **1984**, *25*, 1-9.  
11  
12  
13 31. Klein Herenbrink, C.; Sykes, D. A.; Donthamsetti, P.; Canals, M.; Coudrat, T.; Shonberg, J.;  
14 Scammells, P. J.; Capuano, B.; Sexton, P. M.; Charlton, S. J.; Javitch, J. A.; Christopoulos, A.;  
15 Lane, J. R. The role of kinetic context in apparent biased agonism at GPCRs. *Nat. Commun.* **2016**,  
16 *7*, 10842.  
17  
18  
19 32. Albizu, L.; Cottet, M.; Kralikova, M.; Stoev, S.; Seyer, R.; Brabet, I.; Roux, T.; Bazin, H.;  
20 Bourrier, E.; Lamarque, L.; Breton, C.; Rives, M.-L.; Newman, A.; Javitch, J.; Trinquet, E.;  
21 Manning, M.; Pin, J.-P.; Mouillac, B.; Durroux, T. Time-resolved FRET between GPCR ligands  
22 reveals oligomers in native tissues. *Nat. Chem. Biol.* **2010**, *6*, 587-594.  
23  
24  
25 33. Sykes, D. A.; Moore, H.; Stott, L.; Holliday, N.; Javitch, J. A.; Lane, J. R.; Charlton, S. J.  
26 Extrapiramidal side effects of antipsychotics are linked to their association kinetics at dopamine D2  
27 receptors. *Nat. Commun.* **2017**, *8*, 763.  
28  
29  
30 34. Sikazwe, D. M.; Li, S.; Mardenborough, L.; Cody, V.; Roth, B. L.; Ablordeppey, S. Y.  
31 Haloperidol: towards further understanding of the structural contributions of its pharmacophoric  
32 elements at D2-like receptors. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5739-5742.  
33  
34  
35 35. Ablordeppey, S. Y.; Altundas, R.; Bricker, B.; Zhu, X. Y.; Eyunni, S. E. V. K.; Jackson, T.;  
36 Khan, A.; Roth, B. L. Identification of a butyrophenone analog as a potential atypical antipsychotic  
37 agent: 4-[4-(4-chlorophenyl)-1,4-diazepan-1-yl]-1-(4-fluorophenyl)butan-1-one. *Bioorg. Med.*  
38 *Chem.* **2008**, *16*, 7291-7301.  
39  
40  
41 36. Sikazwe, D. M.; Nkansah, N. T.; Altundas, R.; Zhu, X. Y.; Roth, B. L.; Setola, V.;  
42 Ablordeppey, S. Y. Synthesis and evaluation of ligands for D2-like receptors: the role of common  
43 pharmacophoric groups. *Bioorg. Med. Chem.* **2009**, *17*, 1716-1723.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 37. Sampson, D.; Bricker, B.; Zhu, X. Y.; Peprah, K.; Lamango, N. S.; Setola, V.; Roth, B. L.;  
4  
5 Ablordeppey, S. Y. Further evaluation of the tropane analogs of haloperidol. *Bioorg. Med. Chem.*  
6  
7 *Lett.* **2014**, *24*, 4294-4297.
- 8  
9 38. Lyles-Eggleston, M.; Altundas, R.; Xia, J.; Sikazwe, D. M.; Fan, P.; Yang, Q.; Li, S.;  
10  
11 Zhang, W.; Zhu, X.; Schmidt, A. W.; Vanase-Frawley, M.; Shrihkande, A.; Villalobos, A.; Borne,  
12  
13 R. F.; Ablordeppey, S. Y. Design, synthesis, and evaluation of metabolism-based analogues of  
14  
15 haloperidol incapable of forming MPP<sup>+</sup>-like species. *J. Med. Chem.* **2004**, *47*, 497-508.
- 16  
17 39. Ravina, E.; Casariego, I.; Masaguer, C. F.; Fontenla, J. A.; Montenegro, G. Y.; Rivas, M. E.;  
18  
19 Loza, M. I.; Enguix, M. J.; Villazon, M.; Cadavid, M. I.; Demontis, G. C. Conformationally  
20  
21 constrained butyrophenones with affinity for dopamine (D(1), D(2), D(4)) and serotonin (5-  
22  
23 HT(2A), 5-HT(2B), 5-HT(2C)) receptors: synthesis of aminomethylbenzo[*b*]furanones and their  
24  
25 evaluation as antipsychotics. *J. Med. Chem.* **2000**, *43*, 4678-4693.
- 26  
27 40. Nishinomiya, H. Y.; Ashiya, T. O.; Sasajima, K.; Mino, S. K. Butyrophenone Derivatives.  
28  
29 US003907812, 1973.
- 30  
31 41. Janssen, P. A. J.; Van De Westeringh, C.; Jageneau, A. H. M.; Demoen, P. J. A.; Hermans,  
32  
33 B. K. F.; Van Daele, G. H. P.; Schellekens, K. H. L.; Van Der Eycken, C. A. M.; Niemegeers, C. J.  
34  
35 E. Chemistry and pharmacology of CNS depressants related to 4-(4-Hydroxy-4-  
36  
37 phenylpiperidino)butyrophenone. Part I--Synthesis and screening data in mice. *J. Med. Pharm.*  
38  
39 *Chem.* **1959**, *1*, 281-297.
- 40  
41 42. Leyva-Pérez, A.; Cabrero-Antonino, J. R.; Rubio-Marqués, P.; Al-Resayes, S. I.; Corma, A.  
42  
43 Synthesis of the ortho/meta/para isomers of relevant pharmaceutical compounds by coupling a  
44  
45 sonogashira reaction with a regioselective hydration. *ACS Catal.* **2014**, *4*, 722-731.
- 46  
47 43. Farrokhzad, S.; Diksic, M. The syntheses of no-carrier-added and carrier-added <sup>18</sup>F-labelled  
48  
49 haloperidol. *J. Labelled Compd. Rad.* **1985**, *22*, 721-733.
- 50  
51 44. Liu, W.; Wang, H.; Li, C.-J. Metal-free Markovnikov-type alkyne hydration under mild  
52  
53 conditions. *Org. Lett.* **2016**, *18*, 2184-2187.
- 54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 45. Peprah, K.; Zhu, X. Y.; Eyunni, S. V. K.; Setola, V.; Roth, B. L.; Ablordeppey, S. Y. Multi-  
4  
5 receptor drug design: Haloperidol as a scaffold for the design and synthesis of atypical  
6  
7 antipsychotic agents. *Bioorg. Med. Chem.* **2012**, *20*, 1291-1297.  
8  
9  
10 46. Olivieri, M.; Amata, E.; Vinciguerra, S.; Fiorito, J.; Giurdanella, G.; Drago, F.; Caporarello,  
11  
12 N.; Prezzavento, O.; Arena, E.; Salerno, L.; Rescifina, A.; Lupo, G.; Anfuso, C. D.; Marrazzo, A.  
13  
14 Antiangiogenic effect of (±)-haloperidol metabolite II valproate ester [(±)-MRJF22] in human  
15  
16 microvascular retinal endothelial cells. *J. Med. Chem.* **2016**, *59*, 9960-9966.  
17  
18  
19 47. Iorio, M. A.; Reymer, T. P.; Frigeni, V. Combined analgesic/neuroleptic activity in *N*-  
20  
21 butyrophenone prodine-like compounds. *J. Med. Chem.* **1987**, *30*, 1906-1910.  
22  
23  
24 48. Iversen, L. L.; Rogawski, M. A.; Miller, R. J. Comparison of the effects of neuroleptic drugs  
25  
26 on pre- and postsynaptic dopaminergic mechanisms in the rat striatum. *Mol. Pharmacol.* **1976**, *12*,  
27  
28 251-262.  
29  
30  
31 49. Cornella, J.; Martin, R. Ni-catalyzed stereoselective arylation of inert C-O bonds at low  
32  
33 temperatures. *Org. Lett.* **2013**, *15*, 6298-6301.  
34  
35  
36 50. Simmons, H. E.; Smith, R. D. A new synthesis of cyclopropanes from olefins. *J. Am. Chem.*  
37  
38 *Soc.* **1958**, *80*, 5323-5324.  
39  
40  
41 51. Khan, H. A.; Kou, K. G. M.; Dong, V. M. Nitrogen-directed ketone hydroacylation:  
42  
43 Enantioselective synthesis of benzoxazecinones. *Chem. Sci.* **2011**, *2*, 407-410.  
44  
45  
46 52. Komissarov, V. V.; Knyazhanskaya, E. S.; Atrokhova, A. V.; Gottikh, M. B.; Kritzyn, A. M.  
47  
48 The search of novel inhibitors of HIV-1 integrase among 5-(4-halogenophenyl)-5-oxopentyl  
49  
50 derivatives of nucleic bases. *Russ. J. Bioorg. Chem.* **2014**, *40*, 532-540.  
51  
52  
53 53. Wang, D.; Mao, J.; Zhu, C. Visible light-promoted ring-opening functionalization of  
54  
55 unstrained cycloalkanols via inert C-C bond scission. *Chem. Sci.* **2018**, *9*, 5805-5809.  
56  
57  
58 54. Jumreang, T.; Somsak, R.; Poonsakdi, P. A convergent general strategy for the  
59  
60 functionalized 2-aryl cycloalkyl-fused chromans: intramolecular hetero-Diels-Alder reactions of  
*ortho*-quinone methides. *Chem. Eur. J.* **2010**, *16*, 1445-1448.

- 1  
2  
3 55. Chen, Z.; Liang, P.; Ma, X.; Luo, H.; Xu, G.; Liu, T.; Wen, X.; Zheng, J.; Ye, H. Catalyst-  
4 free annulation of 2-pyridylacetates and ynals with molecular oxygen: an access to 3-acylated  
5 indolizines. *J. Org. Chem.* **2019**, *84*, 1630-1639.  
6  
7  
8  
9 56. Kristianslund, R.; Aursnes, M.; Tungen, J. E.; Hansen, T. V. Squaramide catalyzed  
10 enantioselective iodolactonization of allenic acids. *Tetrahedron Lett.* **2016**, *57*, 5232-5236.  
11  
12  
13 57. Subramanyam, B.; Woolf, T.; Castagnoli, N., Jr. Studies on the in vitro conversion of  
14 haloperidol to a potentially neurotoxic pyridinium metabolite. *Chem. Res. Toxicol.* **1991**, *4*, 123-  
15 128.  
16  
17  
18  
19  
20 58. Thomas, T.; Fang, Y.; Yuriev, E.; Chalmers, D. K. Ligand binding pathways of clozapine  
21 and haloperidol in the dopamine D2 and D3 receptors. *J. Chem. Inf. Model.* **2016**, *56*, 308-321.  
22  
23  
24 59. Kalani, M. Y.; Vaidehi, N.; Hall, S. E.; Trabanino, R. J.; Freddolino, P. L.; Kalani, M. A.;  
25 Floriano, W. B.; Kam, V. W.; Goddard, W. A., 3rd. The predicted 3D structure of the human D2  
26 dopamine receptor and the binding site and binding affinities for agonists and antagonists. *Proc.*  
27 *Natl. Acad. Sci.* **2004**, *101*, 3815-3820.  
28  
29  
30  
31  
32  
33 60. Luedtke, R. R.; Mishra, Y.; Wang, Q.; Griffin, S. A.; Bell-Horner, C.; Taylor, M.;  
34 Vangveravong, S.; Dillon, G. H.; Huang, R.-Q.; Reichert, D. E.; Mach, R. H. Comparison of the  
35 binding and functional properties of two structurally different D2 dopamine receptor subtype  
36 selective compounds. *ACS Chem. Neurosci.* **2012**, *3*, 1050-1062.  
37  
38  
39  
40  
41  
42 61. Wang, Q.; Mach, R. H.; Luedtke, R. R.; Reichert, D. E. Subtype selectivity of dopamine  
43 receptor ligands: insights from structure and ligand-based methods. *J. Chem. Inf. Model.* **2010**, *50*,  
44 1970-1985.  
45  
46  
47  
48  
49  
50 62. Sykes, D. A.; Dowling, M. R.; Charlton, S. J. Exploring the mechanism of agonist efficacy:  
51 a relationship between efficacy and agonist dissociation rate at the muscarinic M3 receptor. *Mol.*  
52 *Pharmacol.* **2009**, *76*, 543-551.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 63. Deyrup, M. D.; Nowicki, S. T.; Richards, N. G.; Otero, D. H.; Harrison, J. K.; Baker, S. P.  
4  
5 Structure-affinity profile of 8-hydroxycarbostyryl-based agonists that dissociate slowly from the  
6  
7 beta2-adrenoceptor. *Naunyn-Schmiedebergs Arch. Pharmacol.* **1999**, *359*, 168-177.  
8  
9  
10 64. Guo, D.; Mulder-Krieger, T.; Ijzerman, A. P.; Heitman, L. H. Functional efficacy of  
11  
12 adenosine A(2A) receptor agonists is positively correlated to their receptor residence time. *Br. J.*  
13  
14 *Pharmacol.* **2012**, *166*, 1846-1859.  
15  
16  
17 65. Mould, R.; Brown, J.; Marshall, F. H.; Langmead, C. J. Binding kinetics differentiates  
18  
19 functional antagonism of orexin-2 receptor ligands. *Br. J. Pharmacol.* **2014**, *171*, 351-363.  
20  
21  
22 66. Sykes, D. A.; Charlton, S. J. Slow receptor dissociation is not a key factor in the duration of  
23  
24 action of inhaled long-acting beta2-adrenoceptor agonists. *Br. J. Pharmacol.* **2012**, *165*, 2672-2683.  
25  
26  
27 67. Tresadern, G.; Bartolome, J. M.; Macdonald, G. J.; Langlois, X. Molecular properties  
28  
29 affecting fast dissociation from the D2 receptor. *Bioorg. Med. Chem.* **2011**, *19*, 2231-2241.  
30  
31  
32 68. Vauquelin, G. Cell membranes... and how long drugs may exert beneficial pharmacological  
33  
34 activity in vivo. *Br. J. Clin. Pharmacol.* **2016**, *82*, 673-682.  
35  
36  
37 69. Wang, S.; Che, T.; Levit, A.; Shoichet, B. K.; Wacker, D.; Roth, B. L. Structure of the D2  
38  
39 dopamine receptor bound to the atypical antipsychotic drug risperidone. *Nature* **2018**, *555*, 269-  
40  
41 273.  
42  
43 70. Guo, D.; Pan, A. C.; Dror, R. O.; Mocking, T.; Liu, R.; Heitman, L. H.; Shaw, D. E.; AP, I.  
44  
45 J. Molecular Basis of Ligand Dissociation from the Adenosine A2A Receptor. *Mol. Pharmacol.*  
46  
47 **2016**, *89*, 485-491.  
48  
49  
50 71. Dror, R. O.; Pan, A. C.; Arlow, D. H.; Borhani, D. W.; Maragakis, P.; Shan, Y.; Xu, H.;  
51  
52 Shaw, D. E. Pathway and mechanism of drug binding to G-protein-coupled receptors. *Proc. Natl.*  
53  
54 *Acad. Sci. U. S. A.* **2011**, *108*, 13118-13123.  
55  
56  
57 72. Ballesteros, J. A.; Weinstein, H. Integrated methods for the construction of three-  
58  
59 dimensional models and computational probing of structure-function relations in G protein-coupled  
60  
receptors. In *Methods Neurosci.*, Sealfon, S. C., Ed. Academic Press: 1995; Vol. 25, pp 366-428.

73. Chien, E. Y.; Liu, W.; Zhao, Q.; Katritch, V.; Han, G. W.; Hanson, M. A.; Shi, L.; Newman, A. H.; Javitch, J. A.; Cherezov, V.; Stevens, R. C. Structure of the human dopamine D3 receptor in complex with a D2/D3 selective antagonist. *Science* **2010**, *330*, 1091-1095.

74. Cheng, Y.; Prusoff, W. H. Relationship between the inhibition constant ( $K_1$ ) and the concentration of inhibitor which causes 50 per cent inhibition ( $I_{50}$ ) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099-3108.

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