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Design, Synthesis, and Structure–Activity Relationship, Molecular Modeling, and NMR Studies of a Series of Phenyl Alkyl Ketones as Highly Potent and Selective Phosphodiesterase-4 Inhibitors

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Abstract

Phosphodiesterase 4 catalyzes the hydrolysis of cyclic AMP and is a target for the development of anti-inflammatory agents. We have designed and synthesized a series of phenyl alkyl ketones as PDE4 inhibitors. Among them, 13 compounds were identified as having submicromolar IC₅₀ values. The most potent compounds have IC₅₀ values of in the mid- to low-nanomolar range. Compound **5v** also showed preference for PDE4 with selectivity of >2000-fold over PDE7, PDE9, PDE2, and PDE5. Docking of **5v**, **5zf**, and **5za** into the binding pocket of the PDE4 catalytic domain revealed a similar binding profile to PDE4 with rolipram except that the fluorine atoms of the difluoromethyl groups of **5v**, **5za**, and **5zf** are within a reasonable range for hydrogen bond formation with the amide hydrogen of Thr 333 and the long alkyl chain bears additional van der Waals interactions with His 160, Asp 318, and Tyr 159.

Introduction

Phosphodiesterases (PDEs) are responsible for the hydrolysis of second messengers cyclic adenosine and guanosine monophosphates (cAMP and cGMP).^{a,1} Because of the important roles that cAMP and cGMP play, PDEs are excellent targets for the development of therapeutic agents. About 100 isoforms of PDEs are coded by 21 human genes and differentially expressed in various cell types.^{2–7} Such a large number of isoforms presents a unique challenge to the design and synthesis of PDE inhibitors that are specific for PDE isoforms of interest for pharmaceutical applications. We are especially interested in developing PDE4 inhibitors because of its implication in inflammatory diseases such as asthma and chronic obstructive

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Supporting Information Available: Purity and NMR results for final compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

^aAbbreviations: PDE4, phosphodiesterase 4; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; PCC, pyridinium chlorochromate; Boc, di-*tert*-butyl dicarbonate; COPD, cardiovascular obstructive pulmonary disease; PBMCs, peripheral blood mononuclear cells; TNF, tumor necrosis factor; QSAR, quantitative structure–activity relationship; CoMSIA, comparative molecular similarity index analysis; NOE, nuclear Overhauser effect; STD, saturation transfer difference.

pulmonary disease.^{3,8–13} PDE4 specifically catalyzes the hydrolysis of cAMP¹⁴ and has been found in inflammatory^{15,16} as well in immune cells.¹⁷ Several selective PDE4 inhibitors have entered into clinical trials, the results from which have validated PDE4 as a pharmacological target for the development of therapeutic agents for the treatment of inflammatory and chronic obstructive pulmonary diseases.^{18–22} Some PDE4 inhibitors, such as rolipram (Figure 1), have been dropped from clinical studies because of side effects, which presumably arise from nonspecific inhibition of other isoforms, while others including roflumilast and cilomilast (Figure 1) are still in clinical trials.^{3,23,24} Up until now no PDE4 inhibitors have been approved for clinical use.

We are interested in the design, synthesis, and evaluation of selective PDE4 inhibitors for potential pharmaceutical applications. The design is based on published crystal structural information.²⁵ Forty-one potential PDE4 inhibitors have been designed, synthesized, and evaluated. Figure 2 shows the core structure and different substituents in general terms.

Results and Discussion

Design

The design was based on published cocrystal structures of PDE4D2 and rolipram.^{25,26} From the crystal structure, it was clear that the side chain region of rolipram still has plenty of space for structural optimization and exploration of selectivity. Therefore, three series of compounds with ketone, alcohol, and alkyl side chains as point of modification were designed with the ketone series looking especially promising because of the planar structure of the side chain moiety at the aryl attachment point. However, the other compounds also seemed like reasonable candidates (Figure 2).

Chemical Synthesis

The synthesis of the designed analogues started with catechol, which required differential alkylation of the two hydroxyl groups of the catechol core. Therefore, the synthesis started with the alkylation of **1** at either the 3- or 4-position (Scheme 1). In one series, a difluoromethyl group needed to be attached to the 4-position, which was achieved through the alkylation of 3,4-dihydroxybenzaldehyde using chlorodifluoroacetate to give 4-difluoromethoxy-3-hydroxybenzaldehyde **2a** in 45% yield and 3,4-bis(difluoromethoxy)benzaldehyde **3n** in 20% yield.^{27,28} For the series with methyl substitution at either the 3- or 4-position of the catechol core, commercially available 3-hydroxy-4-methoxybenzaldehyde **2b** or 4-hydroxy-3-methoxybenzaldehyde **2c** was used as the starting material. The second alkyl group on the catechol moiety was attached by reacting **2a–c** with racemic alcohols in THF via the Mitsunobu reaction (method A) to give racemic compounds **3a–j** or by O-alkylation with bromides (method B) to give compounds **3k–m**. Treatment of aldehydes **3a–m** with *n*-butyllithium, *tert*-butyllithium, or a Grignard reagent gave the corresponding diastereomeric mixtures of alcohols **4a–w** and **4za–zn**. Oxidation of the alcohol with pyridium chlorochromate (PCC) afforded the corresponding ketones **5a–v** and **5za–zm**. Reaction of **5g,h** with pyridinylolithium or quinolinyl-lithium gave the respective alcohols **6a,b**. Dehydration of **6a** afforded olefins **7a**. Hydrogenation of **7a** on Pd/C afforded **8**.

Compounds **4h** and **4i** were converted to their respective chlorides **9a** and **9b** upon reaction with thionyl chloride (Scheme 2). Reaction of **9a,b** with the sodium salt of methyl acetoacetate afforded a diastereomeric mixture of esters **10a,b**. Saponification followed by acidification led to spontaneous decarboxylation to give derivatives **11a,b** (Scheme 2).

SAR of Potential PDE4D Inhibitors

The enzyme inhibitory activities of the synthesized compounds were evaluated against PDE4 using human PDE4D2 (79–438) expressed in *E. coli* strain BL21 (Codonplus) as a model.²⁵ The results are summarized in Tables 1–3.

The alcohol series of compounds (entries 1–5, Table 1) only exhibited weak inhibition activities with IC₅₀ values in the range from 10 μM to over 100 μM, which were many fold less potent than the corresponding phenyl alkyl ketones (entries 9–12, 16, Table 2). Such results indicate that a planar geometry is desirable at this position for compounds with the catechol core. The inhibition results with the disubstituted alcohol (entry 6, Table 1) further suggested that the planar geometry was required. With the additional group on **6b** the inhibition potency did not improve significantly compared to the ketone series. Within the alcohol series, there are two substitution patterns: one with a bulky alkyl group on the 3-position and the other with a bulky alkyl group on the 4-position of the catechol core. It is very clear that the compound (entry 5, IC₅₀ = 10 μM) with a small methyl group on the 4-position and the bulky substitution on the 3-position has much higher potency than the analogues with a reverse substitution pattern (entries 1–4, IC₅₀ > 100 μM). The same trend is reflected in the phenyl alkyl ketone series. For example, the 4-methoxy substituted phenyl compounds (entries 14–21, Table 2) are 20- to 500-fold more potent than the corresponding 3-methoxy substituted compounds (entries 7–12, Table 2). Such results are consistent with literature reports as well.¹⁹

With the initial indication that the 4-methoxy ketones are more active, the subsequent effort was focused on optimizing this series of compounds. One approach adopted was to use a 4-difluoromethoxy group in place of the methoxy group with the idea of improved metabolic stability (entries 24–28 and 33–35, Table 2).^{27,28} It turned out that these 4-difluoromethoxy compounds were also 2- to 14-fold more potent than the corresponding 4-methoxy substituted compounds (entries 14, 16, 18–20, and 37, Table 2). Within this series, the substituent effect at the 3-position was also studied. The tetrahydrofuran-3-yloxy substituted phenyl compounds (entries 16, 17) have 3- to 8.5-fold higher potencies than the corresponding tetrahydropyran-3-yloxy substituted phenyl compounds (entries 14, 15). The replacement of the tetrahydrofuran ring by a cyclopentyl ring (entry 25) gave a compound (entry 32) with comparable potency (IC₅₀ = 28 nM). The tetrahydrofuran-3-yloxy substituted phenyl compound (entry 28) also seems to be more active than the corresponding Boc protected piperidi-4-nyl substituted compound (entry 33) by more than 20- to 30-fold, and the 3,4-bis(difluoromethoxy)phenyl compounds (entry 31) are also less active than the corresponding 4-difluoromethyl-3-tetrahydrofuran-3-yloxy substituted phenyl compounds (entries 27, 28, 34, and 35) by 2.7- to 60-fold. Similarly, replacing the tetrahydrofuran ring with a deprotected tetrahydropyrrol ring (entries 25, 28) also decreased the potency of IC₅₀ by over 100 μM (entry 22) from 26 and 61 nM.

In the series of the 4-methoxy-3-tetrahydrofuran-3-yloxy phenyl ketones (entries 16–21, 37, 38) and the series of the 4-difluoromethoxy-3-tetrahydrofuran-3-yloxy phenyl ketones (entries 25–28 and 34–36), both ketones (entries 25, 37) with an isobutyl side chain have the highest potency (IC₅₀ of 26 and 176 nM, respectively) and the ketones (entries 28 and 16) with a butyl side chain have the second highest potency (IC₅₀ of 61 and 220 nM, respectively). The ketones with the bulky cyclohexyl (entries 21 and 26) and phenylalkyl (entries 20 and 18) side chains (R₃) constantly showed the lowest potency.

We have also tested the compounds with further transformations of the ketone group into a sp³ carbon (entries 39–41, Table 3). None of these transformations led to improved potency.

Some representatives of the PDE4 inhibitors were tested for their PDE4 selectivity using human PDE7A1, 9A2, 2A3, and 5A1 subtypes, which were cloned and expressed in *E. coli* strain

BL21 (Codonplus) (Table 4).²⁵ Most of the compounds that we have synthesized showed high PDE4 selectivity. For example, **5v** showed preference for PDE4 with selectivity of at least about 2000-fold over PDE7A1, PDE9A2, PDE2A3, and PDE5A1, respectively; **5k** had selectivity at least 14-fold over PDE7A1, PDE9A2, PDE2A3, and PDE5A1.

The inhibition of TNF- α production induced by lipopolysaccharide is an essential assay for evaluation of the pharmacological effect of PDE4 inhibitors in anti-inflammation and the treatment of COPD and asthma.^{29,30} Normal and nonstimulated human blood does not contain detectable levels of TNF- α . Upon stimulation with LPS, activated monocytes express and secrete TNF- α for up to 8 h and plasma levels remain stable for 24 h. Published studies have shown that inhibition of TNF- α production by increasing intracellular cAMP via PDE4 inhibition and/or enhanced adenylyl cyclase activity occurs at the transcriptional level. Therefore, we selected the two most active compounds and studied their ability to inhibit TNF- α production. Specifically, the effect of **5v** and **5zf** for their ability to inhibit LPS-mediated TNF- α production by human peripheral blood mononuclear cells (PBMCs) was studied (Figure 3). Rolipram (IC₅₀ = 60 nM) was included as a reference. The results show that both **5v** and **5zf** were able to inhibit LPS-mediated TNF- α production with IC₅₀ values of 40 and 100 nM, respectively. IC₅₀ values for TNF- α release from the literature may not be directly comparable because of variations of assay systems and conditions. However, if rolipram is taken as a relative reference, the potency of our **5v** is higher than that of rolipram,³⁰ a compound that went into clinical trials for treatment of COPD.

Molecular Modeling

In an effort to gain an understanding of the structural basis for the empirical structure–activity relationships observed, we also studied the binding of the synthesized inhibitors with PDE4D2 through computer modeling. The crystal structure of PDE4D2–rolipram complex^{25,26} was used as the starting point.

Molecular Docking

In this investigation, the 3D structure of PDE4D was taken from a Protein Data Bank entry (PDB entry 1OYN) having the ligand rolipram in place.²⁶ The new inhibitors were built and optimized at the Hartree–Fock level with the 6-311 G basis set in the Gaussian 03 program.³¹ The optimized ligands were then embedded with Gastiger–Hückel partial charges using the SYBYL 7.1 package.³⁰ DOCK 5.2³² was employed to dock these ligands into the PDE4D active site. The resulting structures were then analyzed using HBPLUS 3.06³³ and Ligplot 4.22³⁴ programs to identify specific contacts between ligands and receptor.

Initially, we selected the most potent compounds **5v**, **5za**, and **5zf** for the docking experiments. These three compounds adopt the same alignments as rolipram in the active site. Such alignments have also been confirmed by a preliminary crystallographic study, the details of which will be published elsewhere. Figure 4 presents the docking conformations of rolipram (white), **5za** (yellow), **5v** (blue), and **5zf** (red) in the active site of PDE4. Figure 5 depicts a schematic binding profile of **5za**. Similar to the binding of rolipram (Figure 5), **5za**, **5v**, and **5zf** have a hydrogen bond with Gln 369 and hydrophobic contact with Ile 336, Met 357, Phe 340, Ser 368, Met 337, Phe 372, and Tyr 3. Different from rolipram binding are the possible interactions of the difluoromethyl group of **5za**, **5v**, and **5zf** with the Thr 333 N–H, which could engage in hydrogen bond interactions, and the additional van der Waals interactions of the long alkyl chain with His 160, Asp 318, and Tyr 159. In the case of hydrogen bond interactions, the F–O distance is 2.68 Å but with a nonideal C–F–H angle of 34.7°.

The computer modeling results are also consistent with the empirically observed structure–activity relationship. From the modeling results it is clear that the 4-methyl/difluoromethyl

group occupies a small pocket. Anything larger at this position would result in steric hindrance and therefore unfavorable interactions (Figure 6). Such a finding is consistent with earlier studies with rolipram²⁶ and the fact that 4-position substitution with a bulkier group leads to compounds with diminished potency (entries 1–6, Table 1; entries 7–12, Table 2). Figure 6 shows the unfavorable interactions of an inhibitor with large substituents at the 4-position. For **5za**, the difluoromethyl group has an additional hydrogen bond with Thr 333; meanwhile, the long alkyl chain also bears additional van der Waals interactions with His 160, Asp 318, and Tyr 159. This difference could be the reason that these difluoromethyl compounds have higher potencies than others (Figures 5 and 7). The 3-position has a fairly large hydrophobic pocket, allowing favorable interactions with bulkier groups such as tetrahydropyran and tetrahydrofuran (entries 13–28, 32–38, Table 2). At this site, there is Lys 367, which under normal physiological conditions should be positively charged. This helps to explain why the deprotected amino group in compound **5i** (entry 22, Table 2), which introduces a positively charged protonated amine, leads to reduced potency.

Within the ketone series (entries 7–38, Table 2), it seems that compounds with a four-carbon side chain have the highest potency. This is consistent with the existence of a hydrophobic binding pocket accommodating the side chain, which is somewhat narrow but deep. Bulkier groups such as the phenyl and cyclohexyl side chains protrude away from this hydrophobic pocket, resulting in unfavorable interactions (Figures 4 and 7). The planar sp²-hybridized ketone group seems to have the flexibility to put the hydrophobic side chain in the right position and orientation for favorable hydrophobic interactions. In contrast, a tetrahedral sp³ carbon would fix the side chain in a position for less favorable hydrophobic contact with PDE4, which explains why the compounds with a sp³ carbon at the benzylic position showed low potency (Figure 8).

Molecular Similarity Index Analysis (CoMSIA)

In order to achieve some semiquantitative understanding of the contribution of various parameters to binding affinity, we have also conducted a structure-based comparative molecular similarity index analysis (CoMSIA) implemented in SYBYL 7.1.³⁰ CoMSIA is an extension of the CoMFA (comparative molecular field analysis) methodology.^{35,36} Both are forms of 3D-QSAR and are based on the assumption that changes in ligand binding affinities are related to changes in molecular properties, represented by fields. They differ only in the implementation of the fields.^{35,36} In this study the docking conformations of all compounds synthesized were used as the input of molecular alignments (Figure 9).

The CoMSIA model analysis indicates that the contribution of steric, electrostatic, hydrophobic, hydrogen bond donor, and hydrogen bond acceptor of this series of PDE4 inhibitors to binding affinity is 5.8%, 26.4%, 25.4%, 23.7%, and 18.7%, respectively. In PLS analysis, the standard error of estimate of 0.312, non-cross-validated correlation coefficient r^2 of 0.939, cross-validated coefficient q^2 of 0.832, and F value of 584.051 show that our CoMSIA model has good prediction. In order to validate this CoMSIA model again, we introduced an external test set consisting of rolipram plus nine compounds (**s1–s9**) from literature (Figure 10).¹⁹ After prediction by the CoMSIA model, an r^2 of 0.803 and q^2 of 0.706 were obtained. This external validation again suggests a reliable CoMSIA model we harvested. Table 5 shows a comparison of the calculated pIC₅₀ and experimentally determined pIC₅₀ values using the CoMSIA model developed, and Figure 11 shows the schematic correlation of such data. Such results will help future optimization efforts.

NMR Studies of the Interactions of **5i** with PDE4D2 Protein

In order to achieve some experimental verification of the modeled binding modes of the inhibitors synthesized, NMR experiments were conducted in solution. We initially selected

two compounds, **5i** ($IC_{50} = 102 \mu M$) and **5zi** ($IC_{50} = 40 \mu M$), for the studies. These two compounds have moderate affinities, which allow high sensitivity detection of transferred effects through observation of spectra from ligands in 10- to 100-fold excess over protein.³⁷ Under the conditions of rapid exchange, normally associated with low to moderate binding affinities, effects such as nuclear Overhauser effects (NOEs) and saturation transfer differences (STDs) originating with ligands bound to PDE4 are carried into solution. Because of enhanced efficiencies in magnetization transfer in large complexes, the bound-state properties dominate the average effects observed through the narrow lines and high intensities of the free ligand resonances. Unfortunately, **5zi** had solubility and nonspecific binding problems that prevented the collection of meaningful data. Therefore, only **5i** was used for the NMR studies. Both STD and transferred NOEs (trNOE) experiments were performed to study the inhibitor. STD provides information on the proximity of protons on the bound ligand to protons on the protein. The relative signal intensities in an STD spectrum are interpreted to produce an epitope map with protons giving the strongest signal closest to the protein surface.³⁷ The trNOE experiment provides distance information between protons within the ligand, which can be used to determine the compound's bound state conformation.³⁷ The solubility of **5i** (up to 800 μM in D_2O) was confirmed by NMR. A reference 1H spectrum allowed assignment of resonances as indicated in Figure 12a.

The STD spectrum of **5i** in the presence of PDE4D2 is presented in Figure 12b. In an effort to map the binding epitope, the peak integrals from the reference and STD spectra were compared and normalized to give a STD percentage for each proton. The STD percentages are shown on the chemical structure in Figure 12b. The STD percentages give an indication of which protons of bound **5i** are close to the protein, i.e., an epitope map. For **5i**, peak "i" was not observed in the STD spectrum, indicating that it does not bind PDE4D2 providing evidence that it is a contaminant. The *n*-butanyl, methyl, and catechol protons show stronger STD contacts than the piperidinyl protons. While it is possible to check these intensities for consistencies with specific models when available,³⁸ it is also useful to seek a more qualitative interpretation. The results as presented are consistent with computer modeling studies indicating strong hydrophobic interactions of the alkyl chain and adjacent parts of the catechol ring. Close approach combined with the higher density of nonexchangeable protons on hydrophobic groups would lead to the observed effects.

A trNOESy spectrum of **5i** in the presence of PDE4D2 is presented in Figure 13. A short mixing time of 50 ms was used to avoid spin diffusion artifacts and provide a more accurate interpretation. The cross peaks show the same sign as the diagonal peaks indicating negative NOEs originating from the bound form of **5i**. The reference NOESY spectrum of **5i** (not shown) has positive NOEs typical of small molecules free in solution and confirms that the NOEs in the trNOESy spectrum reflect the bound state structure. The appearance of a set of cross peaks similar to those seen in the reference NOESY spectrum is indicative of some similarity in the bound form compared to the solution form of the drug. Under an initial rate assumption, the relative intensities of the NOESY cross peaks are inversely related to the sixth power of the distance between proton pairs and qualitative information on a structure can readily be determined by comparing the cross peak intensities in Figure 13. Structurally restraining NOEs include contacts between the catechol protons and the methyl, piperidinyl, and *n*-butanyl protons. The catechol proton in the 6-position (peak "a") has an NOE to the *n*-butanyl protons (peak "g"), and the catechol proton in the 5-position (peak "c") has an NOE to the methyl protons (peak "d"). This NOE would suggest a conformation different from the structure used to illustrate the NMR spectrum (Figure 12) with the keto chain rotated 180° about the chain to catechol bond. This geometry is in fact consistent with the geometries shown for **5v**, **5za**, and **5zf** (Table 2). NOEs are also seen from the catechol 2-position to the piperidinyl protons in the 4-position (peak "h") and the NMR equivalent methylene protons in the 3- and 5-positions

(peaks “j” and “k”). This NOE restrains the relative orientation of the piperidiny and catechol rings and is consistent with the docking models of **5za** in Figure 7.

Conclusions

A new series of phenyl alkyl ketones with variable side chains was investigated as potential PDE4D inhibitors. Thirteen alkyl ketones were identified to have submicromolar IC₅₀ values. Among them, the most potent compounds **5v**, **5zf**, and **5za** have IC₅₀ values of 26, 28, and 61 nM, respectively. Compound **5v** also showed a preference for PDE4D with selectivity of >2000 fold over PDE7A1, PDE9A2, PDE2A3, and PDE5A1, respectively. Docking of **5v**, **5zf**, and **5za** into the binding pocket of the PDE4 catalytic domain revealed a similar binding profile with PDE4 as rolipram. trNOEsy and STD NMR experiments on **5i** provided experimental support for many of the modeling projections. Compound **5i** appears to adopt the same overall conformation in the free and enzyme bound form and to dock in a similar manner as **5v**, **5za**, and **5zf**.

Experimental Section

General Chemistry

All reagents were purchased from Acros and Aldrich. *N*-(*tert*-Butoxycarbonyl)-4-piperidinol was synthesized according to literature procedures.¹ Microwave heating was performed in the single-mode microwave cavity of a Discover Synthesis System (CEM Co.), and all microwave reactions were conducted in a heavy-walled glass vials sealed with Teflon septa. ¹H NMR, ¹³C NMR, and DEPT spectra were recorded at 400 and 100 MHz, respectively, on a Bruker 400 NMR spectrometer. Combustion analyses and mass spectra were performed by the analytical and the mass spectrometry facilities at Georgia State University.

4-Difluoromethoxy-3-hydroxybenzaldehyde (**2a**) and 3,4-Bisdifluoromethoxybenzaldehyde (**3n**)

A mixture of 3,4-dihydroxybenzaldehyde (1.38 g, 0.01 mol), methyl chlorofluoroacetate (1.87 g, 0.013 mol), and cesium carbonate (4.24 g, 0.013 mol) in DMF (20 mL) was stirred at 65 °C for 3 h under nitrogen atmosphere. Then DMF was removed in vacuo and the residue was partitioned between aqueous 3 N HCl and ether. The aqueous layer was extracted three times with ether. The combined organic solution was washed with water and brine, dried over MgSO₄, filtered, and evaporated. The residue was purified by flash chromatography to afford **2a** as a white solid (0.85 g, 45%) and **3n** as a yellowish liquid (0.48 g, 20%).

2a

¹H NMR (CDCl₃): 9.92 (1H, s), 7.55 (1H, d, *J* = 4.0 Hz), 7.45 (1H, dd, *J* = 4.0 and 8.4 Hz), 7.28 (1H, d, *J* = 8.4 Hz), 6.67 (1H, t, *J* = 72.8 Hz), 6.17 (1H, s, br). ¹³C NMR (CDCl₃): 191.1 (d), 147.8 (s), 143.0 (s), 134.5 (s), 123.2 (d), 119.3 (d), 117.1 (d), 115.6 (triplet, *J* = 262 Hz, d). MS-EI: 188 (M⁺).

3n

¹H NMR (CDCl₃): 9.95 (1H, s), 7.79–7.77 (2H, m), 7.43 (1H, dd, *J* = 8.8 Hz), 6.68 (1H, t, *J* = 72.4 Hz), 6.63 (1H, t, *J* = 72.8 Hz). ¹³C NMR (CDCl₃): 190.1 (d), 147.1 (s), 142.3 (s), 134.1 (s), 128.7 (d), 122.1 (d), 121.4 (d), 115.5 (triplet, *J* = 263 Hz, d), 115.3 (triplet, *J* = 262 Hz, d). MS-EI: 238 (M⁺).

General Procedure for the Synthesis of 3 by Mitsunobu Reaction of 2a and 2c with R₂OH

To the mixture of compound **2** (1 mmol), R₂OH (1.1 mmol), and di-*tert*-butyl azodicarboxylate (1.2 mmol) in THF (5 mL) was added dropwise triphenylphosphine (1.2 mmol) in THF (5 mL) at 0 °C. The resulting solution was stirred until compound **2** was consumed completely (usually within 24 h). Solvent was removed in vacuo and the residue was purified by flash chromatography to afford **3**.

4-Difluoromethoxy-3-(tetrahydropyran-4-yloxy)benzaldehyde (3a)

Yield: 28%. ¹H NMR (CDCl₃): 9.93 (1H, s), 7.52 (1H, d, *J* = 2.0 Hz), 7.48 (1H, dd, *J* = 2.0 and 8.0 Hz), 7.33 (1H, d, *J* = 8.0 Hz), 6.70 (1H, t, *J* = 74.0 Hz), 4.65 (1H, m), 3.98 (2H, m), 3.61 (2H, m), 2.06 (2H, m), 1.85 (2H, m). ¹³C NMR (CDCl₃): 190.6 (d), 149.2 (s), 146.0 (s), 134.4 (s), 125.0 (d), 122.3 (d), 115.6 (triplet, *J* = 259 Hz, d), 114.1 (d), 73.3 (d), 64.7 (t), 31.4 (t). MS-EI: 272 (M⁺)

4-Difluoromethoxy-3-(tetrahydrofuran-3-yloxy)benzaldehyde (3b)

Yield: 84%. ¹H NMR (CDCl₃): 9.93 (1H, s), 7.48 (1H, dd, *J* = 1.6 and 8.4 Hz), 7.44 (1H, d, *J* = 1.6 Hz), 7.33 (1H, d, *J* = 8.4 Hz), 6.67 (1H, t, *J* = 74.4 Hz), 5.07 (1H, m), 4.06–3.91 (4H, m), 2.30 (1H, m), 2.19 (1H, m). ¹³C NMR (CDCl₃): 190.5 (d), 149.4 (s), 145.6 (s), 134.3 (s), 125.2 (d), 122.2 (d), 115.5 (triplet, *J* = 260 Hz, d), 112.9 (d), 78.8 (d), 72.5 (t), 67.0 (t), 32.7 (t). MS-EI: 258 (M⁺)

4-(2-Difluoromethoxy-5-formylphenoxy)piperidine-1-carboxylic Acid *tert*-Butyl Ester (3c)

Yield: 54%. ¹H NMR (CDCl₃): 9.93 (1H, s), 7.52 (1H, s), 7.48 (1H, dd, *J* = 1.2 and 8.4 Hz), 7.33 (1H, d, *J* = 8.4 Hz), 6.66 (1H, t, *J* = 74.0 Hz), 4.63 (1H, m), 3.69 (2H, m), 3.41 (2H, m), 1.96 (2H, m), 1.81 (2H, m), 1.48 (9H, s). ¹³C NMR (CDCl₃): 190.6 (d), 154.6 (s), 149.3 (s), 146.0 (triplet, *J* = 3 Hz, s), 134.5 (s), 125.2 (d), 122.3 (d), 115.6 (triplet, *J* = 260 Hz, d), 114.1 (d), 79.7 (s), 74.0 (d), 40.4 (multiple, t), 30.2 (t), 28.3 (q).

3-Methoxy-4-(tetrahydropyran-4-yloxy)benzaldehyde (3d)

Yield: 65%. ¹H NMR (CDCl₃): 9.85 (1H, s), 7.43–7.42 (2H, m), 7.01 (1H, d, *J* = 8.8 Hz), 4.62 (1H, m), 4.03 (2H, m), 3.93 (3H, s), 3.59 (2H, m), 2.07 (2H, m), 1.89 (2H, m). ¹³C NMR (CDCl₃): 190.7 (d), 152.2 (s), 150.7 (s), 130.4 (s), 126.1 (d), 114.0 (d), 110.0 (d), 73.2 (d), 65.1 (t), 56.0 (q), 31.7 (t). MS-EI: 236 (M⁺)

3-Methoxy-4-(tetrahydrofuran-3-yloxy)benzaldehyde (3e)

Yield: 71%. ¹H NMR (CDCl₃): 9.84 (1H, s), 7.44–7.41 (2H, m), 6.93 (1H, d, *J* = 8.4 Hz), 5.06 (1H, m), 4.02 (4H, m), 3.90 (3H, s), 2.06 (2H, m). ¹³C NMR (CDCl₃): 190.4 (d), 152.1 (s), 150.0 (s), 130.0 (s), 125.8 (d), 112.8 (d), 109.5 (d), 78.4 (d), 72.4 (t), 66.8 (t), 55.5 (q), 32.6 (t). MS-EI: 222 (M⁺)

4-(4-Formyl-2-methoxyphenoxy)piperidine-1-carboxylic Acid *tert*-Butyl Ester (3f)

Yield: 76%. ¹H NMR (CDCl₃): 9.85 (1H, s), 7.44–7.41 (2H, m), 7.03 (1H, m), 4.61 (1H, m), 3.91 (3H, s), 3.77 (2H, m), 3.32 (2H, m), 1.97 (1H, m), 1.82 (1H, m), 1.46 (9H, s). ¹³C NMR (CDCl₃): 190.7 (d), 154.6 (s), 152.1 (s), 150.7 (s), 130.3 (s), 126.1 (d), 114.1 (d), 110.0 (d), 79.5 (s), 73.7 (d), 56.0 (q), 40.5 (multiple, t), 30.3 (t), 28.3 (q).

4-Methoxy-3-(tetrahydropyran-4-yloxy)benzaldehyde (3g)

Yield: 52%. ¹H NMR (400 MHz, CDCl₃): 1.84–1.86 (2H, q, *J* = 4.4, 4.4 Hz), 2.06 (2H, d, *J* = 8.8 Hz), 3.57 (2H, t, *J* = 9.2 Hz), 3.95 (3H, s), 4.05 (2H, m), 4.51 (1H, m), 7.01 (1H, d, *J* = 8.4 Hz), 7.44 (1H, s), 7.47–7.49 (1H, q, *J* = 1.6, 6.4 Hz) 9.84 (1H, s) ppm. ¹³C NMR (100 MHz,

CDCl₃): 31.86, 56.16, 65.31, 73.49, 111.25, 113.92, 127.15, 1.99, 147.09, 156.06, 190.80 ppm.
HRMS (ESI⁺): calcd for C₁₃H₁₆O₄, 237.1127; found, 237.1121.

4-Methoxy-3-(tetrahydrofuran-3-yloxy)benzaldehyde (3h)

Yield: 40%. ¹H NMR (400 MHz, CDCl₃): 2.25 (2H, q, *J* = 6.0, 8.0 Hz), 3.94 (4H, d, *J* = 12 Hz), 4.04 (3H, d, *J* = 2.4 Hz), 5.02 (1H, s), 7.00 (1H, d, *J* = 8.0 Hz), 7.35 (1H, s), 7.48 (1H, q, *J* = 2.0, 6.4 Hz), 9.84 (1H, s) ppm. ¹³C NMR (100 MHz, CDCl₃): 32.98, 56.16, 67.72, 72.91, 78.67, 111.07, 112.18, 127.21, 1.96, 147.58, 155.56, 190.73 ppm. HRMS (ESI⁺): calcd for C₁₂H₁₄O₄, 223.0970; found, 223.0965.

4-(5-Formyl-2-methoxyphenoxy)piperidine-1-carboxylic Acid *tert*-Butyl Ester (3i)

Yield: 53%. ¹H NMR (400 MHz, CDCl₃): 1.47 (9H, s), 1.80 (2H, q, *J* = 3.2, 3.6 Hz), 1.95 (2H, q, *J* = 4.0, 4.8 Hz), 3.30 (2H, m), 3.80 (2H, s), 3.94 (3H, s), 4.52 (1H, s), 7.01 (1H, d, *J* = 8.0 Hz), 7.44 (1H, s), 7.49 (1H, d, *J* = 8.0 Hz), 9.84 (1H, s) ppm. ¹³C NMR (100 MHz, CDCl₃): 28.45, 30.61, 56.17, 74.20, 79.62, 111.26, 114.11, 127.21, 130.04, 147.16, 154.78, 156.13, 190.79 ppm. HRMS (ESI⁺): calcd for C₁₈H₂₅NO₅, 336.1811; found, 336.1814.

tert-Butyl 3-(2-(Difluoromethoxy)-5-formylphenoxy)pyrrolidine-1-carboxylate (3j)

Yield: 26%. ¹H NMR (400 MHz, CDCl₃): 1.46 (9H, s), 2.20 (2H, d, *J* = 7.6 Hz), 3.65–3.49 (4H, m), 5.01 (1H, s), 6.59 (1H, (d) t, *J* = 74 Hz), 7.32 (1H, s), 7.45 (1H, s), 7.49 (1H, d, *J* = 8.4 Hz), 9.26 (1H, s) ppm. ¹³C NMR (100 MHz, CDCl₃): 28.46, 31.53 (d), 44.00 (d), 51.47 (d), 79.72 (d), 113.54 (d), 122.53 (d), 125.64, 154.54, 190.55 ppm. HRMS (ESI⁺): calcd for C₁₃H₁₃F₂NO₅ (M⁺ – *tert*-butyl), 302.0840; found, 302.0823.

3-Cyclopentyloxy-4-difluoromethoxybenzaldehyde (3k)

A mixture of 4-difluoromethoxy-3-hydroxybenzaldehyde **2a** (0.38 g, 2.0 mmol), cyclopentyl bromide (0.45 g, 3.0 mmol), and potassium carbonate (0.41 g, 3.0 mmol) in DMF (10 mL) was stirred overnight at 65 °C. After the mixture was filtered, solvent was removed in vacuo and the residue was purified by flash chromatography to afford 3-cyclopentyloxy-4-difluoromethoxybenzaldehyde (0.18 g, 35%). ¹H NMR (CDCl₃): 9.93 (1H, s), 7.48 (1H, d, *J* = 1.6 Hz), 7.43 (1H, dd, *J* = 1.6 and 8.0 Hz), 7.00 (1H, d, *J* = 8.0 Hz), 6.65 (1H, t, *J* = 74.8 Hz), 4.90 (1H, m), 1.98–1.80 (6H, m), 1.67 (2H, m). ¹³C NMR (CDCl₃): 190.9 (d), 150.1 (s), 145.7 (s), 134.5 (s), 124.4 (d), 122.4 (d), 115.7 (triplet, *J* = 259 Hz, d), 113.3 (d), 80.9 (d), 32.7 (t), 23.9 (t).

General Procedure for the Preparation of 3- or 4-(Pyridine-2-yloxy)benzaldehydes (3l or 3m)

A mixture of 4-difluoromethoxy-3-hydroxybenzaldehyde **2a** (2.0 mmol) or **2c**, 2-bromopyridine (0.95 g, 6.0 mmol), and potassium carbonate (0.41 g, 3.0 mmol) in DMSO (1 mL) was heated under microwave irradiation for 10 min. After the solvent was removed in vacuo, the residue was purified by flash chromatography to afford the 3-(pyridine-2-yloxy)benzaldehyde **3l** or **3m**.

4-Difluoromethoxy-3-(pyridine-2-yloxy)benzaldehyde (3l)

Yield: 11%. ¹H NMR (CDCl₃): 9.94 (1H, s), 8.09 (1H, m), 7.78–7.72 (3H, m), 7.41 (1H, d, *J* = 8.8 Hz), 7.06–7.02 (2H, m), 6.52 (1H, t, *J* = 74.0 Hz). ¹³C NMR (CDCl₃): 190.1 (d), 162.6 (s), 148.3 (s), 147.2 (d), 145.5 (s), 139.8 (d), 134.5 (s), 127.7 (d), 124.4 (d), 121.3 (d), 119.2 (d), 118.3 (d), 115.7 (triplet, *J* = 260 Hz, d), 117.4 (d). MS-EI: 264 (M⁺).

3-Methoxy-4-(pyridine-2-yloxy)benzaldehyde (3m)

Yield: 85%. ¹H NMR (CDCl₃): 9.95 (1H, s), 8.13 (1H, m), 7.71 (1H, m), 7.54–7.50 (2H, m), 7.00 (1H, d, *J* = 8.0 Hz), 7.02–6.99 (2H, m), 3.83 (3H, s). ¹³C NMR (CDCl₃): 191.0 (d), 162.9 (s), 152.3 (s), 148.2 (s), 147.4 (d), 139.4 (d), 134.1 (s), 125.1 (d), 122.9 (d), 118.7 (d), 111.3 (d), 111.1 (d), 55.9 (q). MS-EI: 198 (M⁺).

General Procedure for the Synthesis of 4 by Nucleophilic Addition to Aldehydes 3

To aldehyde **3** (1 mmol) in THF (5 mL) was added dropwise *n*-butyllithium or Grignard reagent at –78 °C. The resulting mixture was stirred overnight, allowing the temperature to gradually warm from –78 °C to room temperature, and then quenched with water. The aqueous layer was extracted three times with ethyl acetate. The combined organic solution was dried over MgSO₄, filtered, and evaporated. The residue was purified by flash chromatography to afford **4**.

4-[4-(1-Hydroxypentyl)-2-methoxyphenoxy]piperidine-1-carboxylic Acid *tert*-Butyl Ester (4a)

Yield: 42%. ¹H NMR (CDCl₃): 6.91 (1H, d, *J* = 2.0 Hz), 6.87 (1H, d, *J* = 8.0 Hz), 6.81 (1H, dd, *J* = 2.0 and 8.0 Hz), 4.59 (1H, t, *J* = 6.8 Hz), 4.37 (1H, m), 3.84 (3H, s), 3.76 (2H, m), 3.23 (2H, m), 2.25 (1H, s, br), 1.89 (2H, m), 1.79–1.73 (4H, m), 1.46 (9H, s), 1.43–1.24 (4H, m), 0.89 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 154.7 (s), 150.9 (s), 145.6 (s), 139.3 (s), 118.1 (d), 117.5 (d), 109.9 (d), 79.4 (s), 74.5 (d), 74.3 (d), 55.8 (q), 40.6 (t), 38.7 (t), 30.7 (t), 28.3 (q), 27.8(t), 22.5 (t), 13.9 (q). MS-EI: 393 (M⁺).

1-[3-Methoxy-4-(tetrahydropyran-4-yloxy)phenyl]butan-1-ol (4b)

Yield: 70%. ¹H NMR (CDCl₃): 6.91 (1H, s), 6.87 (1H, d, *J* = 8.0 Hz), 6.81 (1H, d, *J* = 7.6 Hz), 4.59 (1H, m), 4.36 (1H, m), 3.98 (1H, m), 3.84 (3H, s), 3.50 (2H, m), 2.32 (1H, s, br), 1.97 (2H, m), 1.82–1.76 (3H, m), 1.64 (1H, m), 1.42 (1H, m), 1.31 (1H, m), 0.93 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 150.9 (s), 145.5 (s), 139.3 (s), 118.0 (d), 117.4 (d), 109.9 (d), 74.0 (d), 73.8 (d), 65.3 (t), 55.8 (q), 41.1 (t), 32.0 (t), 19.0 (t), 13.9 (q). MS-EI: 280 (M⁺).

1-[3-Methoxy-4-(tetrahydropyran-4-yloxy)phenyl]pentan-1-ol (4c)

Yield: 68%. ¹H NMR(CDCl₃): 6.92 (1H, s), 6.88 (1H, d, *J* = 8.0 Hz), 6.82 (1H, d, *J* = 8.0 Hz), 4.59 (1H, m), 4.38 (1H, m), 4.00 (2H, m), 3.86 (3H, s), 3.53 (2H, m), 1.99 (3H, m), 1.83–1.67 (4H, m), 1.36–1.25 (4H, m), 0.89 (3H, t, *J* = 6.8 Hz). ¹³C NMR (CDCl₃): 151.0 (s), 145.7 (s), 139.2 (s), 118.1 (d), 117.4 (d), 110.0 (d), 74.4 (d), 73.9 (d), 65.4 (t), 55.9 (q), 38.7 (t), 32.1 (t), 28.1 (t), 22.6 (t), 13.9 (q). MS-EI: 4 (M⁺).

1-[3-Methoxy-4-(tetrahydrofuran-3-yloxy)phenyl]butan-1-ol (4d)

Yield: 77%. ¹H NMR (CDCl₃): 6.90 (1H, s), 6.80 (1H, d, *J* = 8.0 Hz), 6.75 (1H, d, *J* = 8.0 Hz), 4.90 (1H, m), 4.57 (1H, m), 3.99–3.82 (7H, m), 2.66 (1H, s, br), 2.14 (2H, m), 1.74 (1H, m), 1.63 (1H, m), 1.41 (1H, m), 1.00 (1H, m), 0.92 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 150.6 (s), 145.8 (s), 139.0 (s), 117.9 (d), 115.4 (d), 109.8 (d), 78.7 (d), 73.8 (d), 72.7 (t), 66.9 (t), 55.7 (q), 41.1 (t), 32.8 (t), 18.9 (t), 13.8 (q). MS-EI: 266 (M⁺).

1-[3-Methoxy-4-(tetrahydrofuran-3-yloxy)phenyl]pentan-1-ol (4e)

Yield: 66%. ¹H NMR (CDCl₃): 6.90 (1H, s), 6.81 (1H, d, *J* = 8.0 Hz), 6.76 (1H, d, *J* = 8.0 Hz), 4.90 (1H, m), 4.56 (1H, m), 4.00–3.83 (7H, m), 2.54 (1H, s, br), 2.14 (2H, m), 1.76 (1H, m), 1.67 (1H, m), 1.35–1.23 (4H, m), 0.88 (3H, t, *J* = 6.8 Hz). ¹³C NMR (CDCl₃): 150.1 (s), 145.8 (s), 139.0 (s), 118.0 (d), 115.4 (d), 109.8 (d), 78.7 (d), 74.1 (d), 72.8 (t), 67.0 (t), 55.7 (q), 38.7 (t), 32.9 (t), 27.9 (t), 22.4 (t), 13.9 (q). MS-EI: 280 (M⁺).

1-[3-Methoxy-4-(pyridin-2-yloxy)phenyl]pentan-1-ol (4f)

Yield: 45%. ¹H NMR (CDCl₃): 8.06 (1H, dd, *J* = 1.2 and 4.8 Hz), 7.57 (1H, m), 7.03 (1H, d, *J* = 8.0 Hz), 7.01 (1H, d, *J* = 2.0 Hz), 6.90–6.85 (2H, m), 6.81 (1H, d, *J* = 8.0 Hz), 4.60 (1H, m), 3.69 (3H, s), 2.89 (1H, s, br), 1.76 (2H, m), 1.43–1.31 (4H, m), 0.88 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 163.6 (s), 151.5 (s), 147.2 (d), 143.1 (s), 141.7 (s), 138.8 (d), 122.4 (d), 118.3 (d), 117.7 (d), 110.8 (d), 110.3 (d), 73.9 (d), 55.7 (q), 38.6 (t), 27.8 (t), 22.3 (t), 13.7 (q).

1-[3-Methoxy-4-(pyridin-2-yloxy)phenyl]butan-1-ol (4g)

Yield: 80%. ¹H NMR (CDCl₃): 8.11 (1H, dd, *J* = 2.0 and 5.2 Hz), 7.63 (1H, m), 7.07 (1H, d, *J* = 8.0 Hz), 7.03 (1H, s), 6.94–6.87 (3H, m), 4.65 (1H, t, *J* = 6.0 Hz), 3.75 (3H, s), 2.40 (1H, s, br), 1.78 (1H, m), 1.69 (1H, m), 1.46 (1H, m), 1.36 (1H, m), 0.94 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 163.6 (s), 151.6 (s), 147.4 (d), 143.0 (s), 141.5 (s), 139.1 (d), 122.6 (d), 118.4 (d), 117.9 (d), 110.5 (d), 110.3 (d), 74.0 (d), 55.8 (q), 41.1 (t), 19.0 (t), 13.9 (q). HRMS-ESI (+): calcd for C₁₆H₂₀NO₃, 274.1443; found, 274.1431 [M + H]⁺.

[3-Methoxy-4-(pyridin-2-yloxy)phenyl]quinolin-3-ylmethanol (4h)

Yield: 68%. ¹H NMR (CDCl₃): 8.75 (1H, d, *J* = 1.2 Hz), 8.16 (1H, s), 8.03–8.00 (2H, m), 7.74 (1H, d, *J* = 8.0 Hz), 7.65–7.59 (2H, m), 7.48 (1H, m), 7.09 (1H, d, *J* = 1.6 Hz), 7.04 (1H, d, *J* = 8.0 Hz), 6.94–6.84 (3H, m), 5.95 (1H, s), 5.76 (1H, s, br), 3.63 (3H, s). ¹³C NMR (CDCl₃): 163.4, 151.7, 149.9, 147.2, 146.8, 141.8, 141.2, 139.3, 137.0, 133.1, 1.3, 128.5, 127.9, 127.7, 126.7, 122.7, 119.3, 118.1, 111.0, 110.6, 73.4, 55.7. MS-ESI (+): 359.58 [M + H]⁺.

[3-Methoxy-4-(pyridin-2-yloxy)phenyl]pyridin-3-ylmethanol (4i)

Yellow oil. Yield: 40%. ¹H NMR (CDCl₃): 8.51 (1H, s), 8.33 (1H, d, *J* = 3.6 Hz), 8.03 (1H, m), 7.72 (1H, m), 7.62 (1H, m), 7.22 (1H, m), 7.07–7.05 (2H, m), 6.93–6.85 (3H, m), 5.78 (1H, s), 5.26 (1H, s, br), 3.67 (3H, s). ¹³C NMR (CDCl₃): 163.4 (s), 151.7 (s), 147.9 (d), 147.8 (d), 147.1 (d), 141.7 (s), 141.4 (s), 139.9 (s), 139.2 (d), 134.5 (d), 123.4 (d), 122.6 (d), 119.0 (d), 118.0 (d), 110.9 (d), 110.6 (d), 73.1 (d), 55.7 (q).

1-[4-Methoxy-3-(tetrahydropyran-4-yloxy)phenyl]butan-1-ol (4j)

Yellow oil. Yield: 60%. ¹H NMR (400 MHz, CDCl₃): 0.92 (3H, t, *J* = 7.6 Hz), 1.44 (3H, m), 1.68 (1H, m), 1.87 (4H, m), 2.01 (2H, m), 3.56–3.51 (2H, dd, *J* = 2.4, 8.8 Hz), 3.84 (3H, s), 4.03 (2H, m), 4.44 (1H, m), 4.59 (1H, s), 6.86 (1H, d, *J* = 8.4 Hz), 6.92 (1H, d, *J* = 8.4 Hz), 6.95 (1H, s) ppm. ¹³C NMR (100 MHz, CDCl₃): 13.97, 19.10, 32.12, 41.24, 56.05, 65.38, 73.80, 73.96, 112.10, 115.34, 119.66, 137.75, 146.40, 150.28 ppm. HRMS (ESI+): calcd for C₁₆H₂₂O₃·H₂O, 263.1647; found, 263.1645.

1-[4-Methoxy-3-(tetrahydropyran-4-yloxy)phenyl]pentan-1-ol (4k)

Yellow oil. Yield: 72%. ¹H NMR (400 MHz, CDCl₃): 0.88 (3H, t, *J* = 6.8 Hz), 1.25 (1.32 (3H, m), 1.65 (1H, m), 1.85 (4H, m), 2.01 (2H, s), 3.53 (2H, t, *J* = 8.8 Hz), 3.84 (3H, s), 4.01 (2H, t, *J* = 5.6 Hz), 4.43 (1H, d, *J* = 4.0 Hz), 4.57 (1H, s), 6.86 (1H, d, *J* = 8.4 Hz), 6.92 (1H, d, *J* = 8.4 Hz), 6.95 (1H, s) ppm. ¹³C NMR (100 MHz, CDCl₃): 14.03, 22.58, 28.05, 32.10, 38.81, 56.02, 65.34, 73.76, 74.14, 112.09, 115.40, 119.69, 137.83, 146.35, 150.24 ppm. HRMS (ESI +): calcd for C₁₇H₂₇O₄ – H₂O, 277.1804; found, 277.1795.

1-[4-Methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]pentan-1-ol (4l)

Yellow oil. Yield: 41%. ¹H NMR (400 MHz, CDCl₃): 0.88 (3H, t, *J* = 6.4 Hz), 1.22–1.35 (4H, m), 1.65–1.77 (2H, m), 1.86 (1H, s), 2.18 (2H, d, *J* = 5.6 Hz), 3.84 (2H, s), 3.89–3.92 (1H, m), 4.00 (3H, s), 4.58 (1H, s), 4.96 (1H, s), 6.84–6.91 (3H, m) ppm. ¹³C NMR (100 MHz,

CDCl₃): 14.03, 22.59, 28.03, 33.04, 38.80, 56.05, 67.19, 72.98, 74.26, 78.83, 112.02, 113.65, 119.35, 137.76, 146.83, 149.62 ppm. HRMS (ESI⁺): calcd for C₁₆H₂₅O₄ – H₂O, 263.1647; found, 263.1643.

1-[4-Methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]butan-1-ol (4m)

Yield: 40%. ¹H NMR (400 MHz, CDCl₃): 0.92 (3H, t, *J* = 7.2 Hz), 1.30 (1H, dd, *J* = 6.4, 9.6 Hz), 1.42 (1H, d, *J* = 7.2 Hz), 1.63 (1H, s), 1.81 (2H, bs), 2.19 (2H, m), 3.84 (2H, s), 3.90 (2H, s), 4.00 (3H, s), 4.60 (1H, s), 4.97 (1H, s), 6.89 (3H, m) ppm. ¹³C NMR (100 MHz, CDCl₃): 13.97, 19.08, 33.07, 41.24, 56.08, 67.22, 73.01, 74.07, 78.88, 112.05, 113.66, 119.33, 137.68, 146.89, 149.70 ppm. HRMS (ESI⁺): calcd for C₁₅H₂₃O₄ – H₂O, 249.1491; found, 249.1480.

1-[4-Methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-4-phenylbutan-1-ol (4n)

Yield: 20%. ¹H NMR (400 MHz, CDCl₃): 1.60 (1H, m), 1.74 (2H, m), 1.85 (2H, m), 2.18 (2H, m), 2.64 (2H, t, *J* = 6.4 Hz), 3.83 (3H, s), 3.90 (2H, m), 4.04 (3H, s), 4.60 (1H, m), 4.95 (1H, m), 6.83 (1H, d, *J* = 2 Hz), 6.84 (1H, s), 6.87–6.89 (1H, dd, *J* = 1.6, 1.6 Hz), 7.15 (3H, m), 7.25 (2H, d, *J* = 6.8 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 27.61, 33.07, 35.72, 38.51, 56.06, 67.22, 73.02, 74.17, 78.84, 112.01, 113.49, 119.36, 125.77, 128.30, 128.42, 137.39, 142.22, 146.92, 149.73 ppm. HRMS (ESI⁺): calcd for C₂₁H₂₇O₄ – H₂O, 325.1804; found, 325.1792.

3-Cyclohexyl-1-[4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]propan-1-ol (4o)

Yield: 70%. ¹H NMR (400 MHz, CDCl₃): 0.86 (2H, t, *J* = 12 Hz), 1.09–1.30 (7H, m), 1.61–1.69 (6H, m), 1.74–1.77 (2H, m), 2.16–2.20 (2H, m), 3.84 (3H, d, *J* = 2.8 Hz), 3.88–3.91 (1H, m), 4.54 (1H, d, *J* = 6.8 Hz), 4.96 (1H, s), 6.83–6.85 (2H, dd, *J* = 2.8, 5.2 Hz), 6.70 (1H, d, *J* = 7.6 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 26.36, 26.65, 33.06, 33.35, 33.53, 36.43, 37.64, 56.06, 67.22, 73.01, 74.67, 78.84, 112.00, 113.60, 119.37, 137.67, 146.85, 149.66 ppm. HRMS (ESI⁺): calcd for C₂₀H₃₁O₄ – H₂O, 317.2117; found, 317.2112. Anal. Calcd for C₂₀H₃₀O₄: C, 71.82; H, 9.04. Found: C, 71.92; H, 9.10.

1-[4-Methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-phenylpropan-1-ol (4p)

Yield: 99%. ¹H NMR (400 MHz, CDCl₃): 1.96–2.00 (1H, m), 2.09 (1H, s), 2.11–2.18 (2H, m), 2.63–2.72 (2H, m), 3.83 (3H, s), 3.82 (3H, m), 3.85–3.90 (1H, m), 3.94–4.03 (3H, m), 4.59 (1H, t, *J* = 7.2 Hz), 4.93–4.95 (1H, m), 6.83 (1H, s), 6.85 (1H, s), 6.91 (1H, d, *J* = 8.4 Hz), 7.17 (3H, t, *J* = 4.4 Hz), 7.25–7.00 (2H, dd, *J* = 7.2, 7.6 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 32.14, 33.07, 40.49, 56.07, 67.22, 73.00, 73.49, 78.86, 112.08, 113.63, 119.41, 125.89, 128.42, 128.44, 137.35, 141.79, 146.92, 149.76 ppm. HRMS (ESI⁺): calcd for C₂₀H₂₅O₄ – H₂O, 311.1647; found, 311.1639. Anal. Calcd for C₂₀H₂₄O₄, C, 73.15; H, 7.37; found, C, 73.25; H, 7.56.

2-Cyclohexyl-1-[4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]ethanol (4q)

Yield: 55%. ¹H NMR (400 MHz, CDCl₃): 0.94 (2H, m), 1.20 (2H, m), 1.36 (1H, m), 1.48 (1H, m), 1.69 (7H, m), 2.18 (2H, m), 3.84 (3H, s), 3.90 (1H, m), 4.00 (2H, m), 4.71 (1H, s), 4.96 (1H, s), 6.83 (1H, s), 6.85 (1H, s), 6.92–6.89 (1H, q, *J* = 2.0, 6.0 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 26.17, 26., 26.56, 33.03, 33.07, 33.91, 34., 46.97, 56.07, 67.23, 71.79, 73.01, 78.86, 112.06, 113.59, 113.63, 119.27, 138.03, 146.88, 149.68 ppm. HRMS (ESI⁺): calcd for C₁₉H₂₈O₄ – H₂O, 303.1960; found, 303.1975.

1-[4-Difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-2,2-dimethylpropan-1-ol (4r)

Yield: 8.6%. ¹H NMR (400 MHz, CDCl₃): 0.92 (9H, d, *J* = 0.8 Hz), 1.95 (1H, s), 2.16–2.20 (2H, m), 3.90–3.92 (1H, m), 3.98–4.00 (3H, m), 4.36 (1H, s), 4.96 (1H, d, *J* = 2.0 Hz), 6.52 (1H, (d) t, *J* = 75.2 Hz), 6.85–6.87 (1H, dd, *J* = 2.0, 6.0 Hz), 6.89–6.91 (1H, dd, *J* = 2.0, 2.4

Hz), 7.11 (1H, d, $J = 8.0$ Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): 25.88, 0.71, 32.98, 33.02, 35.71, 67.16, 72.80, 72.83, 78.72, 81.73, 114.69 (t, $J = 160$ Hz), 120.96, 121.93, 140.05, 140.88, 148.17 ppm. MS (EI+): calcd for $\text{C}_{16}\text{H}_{22}\text{F}_2\text{O}_4$, 316; found, 316.

1-[4-Methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-3-methyl-butan-1-ol (4s)

Yield: 34%. ^1H NMR (400 MHz, CDCl_3): 0.91–0.94 (6H, q, $J = 4.4, 2.0$ Hz), 1.24 (1H, s), 1.44–1.49 (1H, m), 1.64–1.72 (2H, m), 1.92 (1H, bs, O–H), 2.16–2.19 (2H, m), 3.83 (3H, s), 3.86–3.91 (1H, m), 3.97–4.02 (3H, m), 4.64–4.67 (1H, q, $J = 5.6, 2.0$ Hz), 4.94–4.97 (1H, m), 6.84 (1H, d, $J = 8.4$ Hz), 6.86 (1H, $J = 2$ Hz), 6.91–6.89 (1H, dd, $J = 2, 6.4$ Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): 22.34, 23.09, 24.84, 33.04, 48.28, 56.06, 67.21, 72.41, 72.99, 78.85, 112.04, 113.62, 119.32, 137.96, 146.89, 149.68 ppm. HRMS (ESI+): calcd for $\text{C}_{16}\text{H}_{22}\text{O}_3 - \text{H}_2\text{O}$, 263.1647; found, 263.1648.

3-[2-Difluoromethoxy-5-(1-hydroxypentyl)phenoxy]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (4t)

Yield: 25%. ^1H NMR (400 MHz, CDCl_3): 0.89 (3H, t, $J = 6.8$ Hz), 1.36 (4H, m), 1.46 (9H, s), 1.73 (2H, m), 1.95 (1H, d, $J = 2.8$ Hz), 2.20 (2H, m), 3.67 (4H, m), 4.63 (1H, s), 4.93 (1H, s), 6.65 (1H, t, $J = 75.2$ Hz), 6.91 (1H, s), 6.96 (1H, d, $J = 1.6$ Hz), 7.12 (1H, d, $J = 6.8$ Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): 14.0, 22.55, 27.9, 28.47, 0.72, 30.82, 31.67, 39.02, 44.07, 51.08, 51.57, 74.02, 78.11, 79.61, 113.4, 119.4, 122.89 ppm. HRMS (ESI+): calcd for $\text{C}_{21}\text{H}_{31}\text{F}_2\text{NO}_5$, 416.2248; found, 416.2247.

3[2-Difluoromethoxy-5-(1-hydroxy-3-methylbutyl)phenoxy]-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (4u)

Yield: 14%. ^1H NMR (400 MHz, CDCl_3): 0.96 (6H, d, $J = 6.4$ Hz), 1.46 (9H, s), 1.69 (2H, m), 1.90 (1H, d, $J = 2.8$ Hz), 2.20 (2H, m), 3.57 (4H, m), 4.71 (1H, s), 4.94 (1H, s), 6.65 (1H, d (t), $J = 75.2$ Hz), 6.92 (1H, d, $J = 6.8$ Hz), 6.97 (1H, d, $J = 1.2$ Hz), 7.12 (1H, d, $J = 6.4$ Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): 14.1 (d), 22.6, 24.7, 28.4, 31.5, 43.6 (d), 48.5, 51.5 (d), 60.3, 72.1, 79.60, 113.5 (d, $J = 14$ Hz), 119.4, 122.9, 140.3 ppm. HRMS (ESI+): calcd for $\text{C}_{17}\text{H}_{21}\text{F}_2\text{NO}_4 - (\text{H}_2\text{O} + \text{tert-butyl})$, 342.1515; found, 342.1159.

4-[5-(1-Hydroxypentyl)-2-methoxyphenoxy]piperidine-1-carboxylic Acid *tert*-Butyl Ester (4v)

Yield: 84%. ^1H NMR (400 MHz, CDCl_3): 0.95 (3H, t, $J = 7.2$ Hz), 1.44 (2H, q, $J = 7.2, 7.6$ Hz), 1.47 (9H, s), 1.69 (4H, m), 1.73 (2H, s), 1.92–1.96 (2H, m), 2.91 (2H, t, $J = 7.2$ Hz), 3.23–3.00 (2H, m), 3.80 (2H, m), 4.63 (1H, s), 3.91 (3H, s), 4.50–4.51 (1H, m), 4.70–4.72 (1H, s), 6.92 (1H, d, $J = 8.4$ Hz), 7.57 (1H, d, $J = 2$ Hz), 7.60–7.63 (1H, dd, $J = 2, 6.4$ Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): 14.03, 22.59, 28.06, 28.45, 30.83, 38.79, 56.04, 74.28, 74.53, 79.52, 112.13, 115.49, 119.75, 137.72, 146.47, 150.37, 154.84 ppm. HRMS (ESI+): calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_4 - (\text{H}_2\text{O} + \text{tert-butyl})$: 320.1862; found, 320.1882.

1-[4-Difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-3-methylbutan-1-ol (4w)

Yield: 15%. ^1H NMR (CDCl_3): 7.13 (1H, d, $J = 8.4$ Hz), 6.95 (1H, s), 6.90 (1H, d, $J = 8.4$ Hz), 6.51 (1H, t, $J = 75.2$ Hz), 5.00 (1H, m), 4.72 (1H, m), 4.03–3.90 (4H, m), 2.20 (2H, m), 1.94 (1H, s, br), 1.70 (2H, m), 1.47 (1H, m), 0.96 (6H, d, $J = 6.0$ Hz). ^{13}C NMR (CDCl_3): 149.0, 144.3, 140.1, 122.9, 118.9, 116.3 (triplet, $J = 258$ Hz), 112.8, 78.8, 72.8, 72.2, 67.1, 48.5, 33.0, 24.8, 23.1, 22.2. MS-EI: 316 (M^+).

1-[4-Difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-pentan-1-ol (4za)

Yield: %. ^1H NMR (CDCl_3): 7.13 (1H, d, $J = 8.0$ Hz), 6.94 (1H, s), 6.90 (1H, dd, $J = 2.0$ and 8.4 Hz), 6.52 (1H, t, $J = 75.2$ Hz), 5.00 (1H, m), 4.64 (1H, m), 4.03–3.91 (4H, m), 2.18 (2H,

m), 1.98 (1H, s, br), 1.75 (1H, m), 1.67 (1H, m), 1.42–1.24 (4H, m), 0.90 (3H, t, $J = 7.2$ Hz). ^{13}C NMR (CDCl_3): 149.0 (s), 143.8 (s), 140.1 (s), 122.9 (d), 119.0 (d), 116.3 (triplet, $J = 258$ Hz, d), 112.8 (d), 78.7 (d), 74.0 (d), 72.8 (t), 67.1 (t), 39.0 (t), 33.0 (t), 27.8 (t), 22.5 (t), 14.0 (q). MS-EI: 316 (M^+).

3-Cyclohexyl-1-[4-difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]propan-1-ol (4zb)

Yield: 51%. ^1H NMR (CDCl_3): 7.11 (1H, d, $J = 8.0$ Hz), 6.94 (1H, s), 6.89 (1H, d, $J = 8.4$ Hz), 6.50 (1H, t, $J = 74.8$ Hz), 4.97 (1H, m), 4.59 (1H, m), 4.01–3.87 (4H, m), 2.18 (2H, m), 1.94 (1H, s, br), 1.80–1.67 (7H, m), 1.34–1.12 (6H, m), 0.88 (2H, m). ^{13}C NMR (CDCl_3): 149.1, 143.9, 140.4, 122.8, 119.2, 116.4 (triplet, $J = 258$ Hz), 113.4, 79.1, 74.4, 72.8, 67.1, 37.7, 36.7, 33.4, 33.3, 33.1, 26.6, 26.3.

2-Cyclohexyl-1-[4-difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]ethanol (4zc)

Yield: 35%. ^1H NMR (CDCl_3): 7.14 (1H, d, $J = 8.4$ Hz), 6.95 (1H, d, $J = 2.0$ Hz), 6.91 (1H, dd, $J = 2.0$ and 8.0 Hz), 6.53 (1H, t, $J = 75.2$ Hz), 5.01 (1H, m), 4.77 (1H, m), 4.03–3.91 (4H, m), 2.20 (2H, m), 2.00 (1H, s, br), 1.83–1.66 (6H, m), 1.52–1.39 (2H, m), 1.31–1.15 (3H, m), 0.98 (2H, m). ^{13}C NMR (CDCl_3): 149.0 (s), 144.3 (s), 140.0 (s), 122.9 (d), 118.91 (d), 118.89 (d), 116.3 (triplet, $J = 258$ Hz, d), 112.8 (d), 78.7 (d), 72.8 (t), 71.5 (d), 67.1 (t), 47.2 (t), 34.2 (d), 33.9 (t), 33.0 (t), 32.8 (t), 26.5 (t), 26.2 (t), 26.1 (t).

1-[4-Difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-3-phenylpropan-1-ol (4zd)

Yield: 46%. ^1H NMR (CDCl_3): 7.30–7.25 (2H, m), 7.20–7.11 (4H, m), 6.92–6.88 (2H, m), 6.50 (1H, t, $J = 74.8$ Hz), 4.96 (1H, m), 4.64 (1H, m), 3.99–3.89 (4H, m), 2.72 (2H, m), 2.18–1.97 (5H, m). ^{13}C NMR (CDCl_3): 149.0 (s), 143.5 (s), 141.4 (s), 140.1 (s), 128.42 (d), 128.36 (d), 126.0 (d), 122.9 (d), 119.0 (d), 116.2 (triplet, $J = 258$ Hz, d), 112.81 (d), 112.78 (d), 78.7 (d), 73.2 (d), 72.7 (t), 67.1 (t), 40.6 (t), 32.9 (t), 31.9 (t).

1-[4-Difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-4-phenylbutan-1-ol (4ze)

Yield: 56%. ^1H NMR (CDCl_3): 7.28–7.25 (2H, m), 7.19–7.10 (4H, m), 6.89–6.85 (2H, m), 6.50 (1H, t, $J = 75.2$ Hz), 4.95 (1H, m), 4.64 (1H, m), 3.99–3.89 (4H, m), 2.63 (2H, t, $J = 6.8$ Hz), 2.15 (2H, m), 2.01 (1H, s, br), 1.78–1.61 (4H, m). ^{13}C NMR (CDCl_3): 149.0 (s), 143.6 (s), 142.0 (s), 140.1 (s), 128.37 (d), 128.31 (d), 125.8 (d), 122.9 (d), 119.0 (d), 116.2 (triplet, $J = 258$ Hz, d), 112.7 (d), 78.7 (d), 73.8 (d), 72.8 (t), 67.1 (t), 38.6 (t), 35.6 (t), 33.0 (t), 27.4 (t).

1-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-3-methyl-butan-1-ol (4zf)

Yield: 34%. ^1H NMR (CDCl_3): 7.09 (1H, d, $J = 8.4$ Hz), 6.97 (1H, d, $J = 1.6$ Hz), 6.83 (1H, dd, $J = 1.6$ and 8.4 Hz), 6.51 (1H, t, $J = 75.6$ Hz), 4.82 (1H, m), 4.70 (1H, m), 1.92–1.79 (7H, m), 1.72–1.62 (4H, m), 1.46 (1H, m), 0.95 (6H, d, $J = 6.0$ Hz). ^{13}C NMR (CDCl_3): 149.6 (s), 144.0 (s), 140.0 (triplet, $J = 3.0$ Hz, s), 122.7 (d), 117.9 (d), 116.4 (triplet, $J = 257$ Hz, d), 112.6 (d), 80.5 (d), 72.4 (d), 48.4 (t), 32.74 (t), 32.73 (t), 24.8 (d), 23.8 (t), 23.1 (q), 22.2 (q).

4-[2-Difluoromethoxy-5-(1-hydroxypentyl)phenoxy]piperidine-1-carboxylic Acid *tert*-Butyl Ester (4zg)

Yield: 57%. ^1H NMR (CDCl_3): 7.12 (1H, d, $J = 8.0$ Hz), 7.02 (1H, d, $J = 1.2$ Hz), 6.90 (1H, dd, $J = 1.6$ and 8.0 Hz), 6.51 (1H, t, $J = 74.8$ Hz), 4.63 (1H, m), 4.52 (1H, m), 3.67 (2H, m), 3.41 (2H, m), 2.11 (1H, s, br), 1.90 (2H, m), 1.80–1.63 (4H, m), 1.47 (9H, s), 1.42–1.28 (4H, m), 0.88 (3H, t, $J = 7.2$ Hz).

1-[4-Difluoromethoxy-3-(tetrahydropyran-4-yloxy)phenyl]-butan-1-ol (4zh)

Yield: 35%. ¹H NMR (CDCl₃): 7.13 (1H, d, *J* = 8.4 Hz), 7.02 (1H, s), 6.90 (1H, d, *J* = 8.0 Hz), 6.54 (1H, t, *J* = 75.2 Hz), 4.64 (1H, m), 4.52 (1H, m), 3.97 (2H, m), 3.56 (2H, m), 2.02 (3H, m), 1.82–1.61 (4H, m), 1.44 (1H, m), 1.33 (1H, m), 0.94 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 148.8 (s), 143.9 (s), 140.7 (s), 122.8 (d), 119.2 (d), 116.4 (triplet, *J* = 258 Hz, d), 114.2 (d), 73.8 (d), 73.3 (d), 64.8 (t), 41.4 (t), 31.7 (t), 18.9 (t), 13.9 (q). MS-EI: 316 (M⁺).

1-[4-Difluoromethoxy-3-(pyridin-2-yloxy)phenyl]-butan-1-ol (4zi)

Yield: 52%. ¹H NMR (CDCl₃): 8.07 (1H, m), 7.70 (1H, m), 7.26–7.15 (3H, m), 7.00–6.96 (2H, m), 6.40 (1H, t, *J* = 74.4 Hz), 4.64 (1H, m), 2.33 (1H, s, br), 1.70–1.60 (2H, m), 1.48–1.26 (2H, m), 0.92 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 163.0 (s), 147.3 (d), 145.0 (s), 144.1 (s), 142.4 (s), 139.6 (d), 123.2 (d), 121.9 (d), 121.3 (d), 118.7 (d), 116.3 (triplet, *J* = 258 Hz, d), 111.2 (d), 73.3 (d), 41.1 (t), 18.9 (t), 13.9 (q).

1-(3,4-Bisdifluoromethoxyphenyl)-4-phenylbutan-1-ol (4zj)

Yield: 43%. ¹H NMR (CDCl₃): 7.00–7.14 (8H, m), 6.52 (1H, t, *J* = 73.6 Hz), 6.50 (1H, t, *J* = 73.6 Hz), 4.68 (1H, m), 2.64 (2H, t, *J* = 7.2 Hz), 2.11 (1H, s, br), 1.92–1.58 (4H, m).

1-(3,4-Bisdifluoromethoxyphenyl)pentan-1-ol (4zk)

Yield: 25%. ¹H NMR (CDCl₃): 7.24–7.18 (3H, m), 6.53 (1H, t, *J* = 73.6 Hz), 6.51 (1H, t, *J* = 73.6 Hz), 4.67 (1H, m), 1.92 (1H, s, br), 1.77–1.67 (2H, m), 1.40–1.23 (4H, m), 0.89 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 144.1 (s), 142.3 (s), 141.2 (s), 123.9 (d), 122.3 (d), 119.8 (d), 115.8 (triplet, *J* = 261 Hz, d), 73.5 (d), 38.9 (t), 27.8 (t), 22.5 (t), 13.9 (q).

1-(3,4-Bisdifluoromethoxyphenyl)butan-1-ol (4zl)

Yield: 80%. ¹H NMR (CDCl₃): 7.24–7.17 (3H, m), 6.53 (1H, t, *J* = 73.6 Hz), 6.51 (1H, t, *J* = 73.6 Hz), 4.66 (1H, t, *J* = 6.4 Hz), 2.19 (1H, s, br), 1.74–1.60 (2H, m), 1.43–1.30 (2H, m), 0.93 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 144.1 (s), 142.3 (s), 141.2 (s), 123.9 (d), 122.2 (d), 119.7 (d), 115.8 (triplet, *J* = 260 Hz, d), 73.2 (d), 41.3 (t), 18.8 (t), 13.7 (q). MS-EI: 282 (M⁺).

1-(3,4-Bisdifluoromethoxyphenyl)-3-phenylpropan-1-ol (4zm)

Yield: 73%. ¹H NMR (CDCl₃): 7.30–7.17 (8H, m), 6.51 (1H, t, *J* = 74.0 Hz), 6.50 (1H, t, *J* = 73.6 Hz), 4.67 (1H, m), 2.71 (2H, m), 2.18–1.98 (3H, m). ¹³C NMR (CDCl₃): 143.8, 142.3, 141.2, 128.9, 128.5, 128.4, 126.0, 123.9, 122.3, 119.8, 115.8 (triplet, *J* = 260 Hz), 72.6, 40.5, 31.8.

1-(3,4-Bisdifluoromethoxyphenyl)-2-cyclohexylethanol (4zn)

¹H NMR (CDCl₃): 7.24–7.17 (3H, m), 6.53 (1H, triplet, *J* = 74.0 Hz), 6.51 (1H, triplet, *J* = 74.0 Hz), 4.76 (1H, m), 2.01 (1H, s, br), 1.82–1.62 (6H, m), 1.44 (2H, m), 1.26–1.14 (3H, m), 0.94 (2H, m). ¹³C NMR (CDCl₃): 144.6, 142.3, 141.2, 123.8, 122.3, 119.7, 115.8 (triplet, *J* = 260 Hz), 71.0, 47.2, 34.1, 33.9, 32.7, 26.5, 26.2, 26.1.

General Procedure for the Synthesis of 5 by Oxidization of the Alcohols with PCC

To a solution of the alcohol **4** (1 mmol) in dichloromethane (5 mL) was added PCC in portions. The resulting mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo and the residue was purified by flash chromatography to afford **5**.

4-(2-Methoxy-4-pentanoylphenoxy)piperidine-1-carboxylic Acid *tert*-Butyl Ester (5a)

Yellow solid, mp 41–43 °C. Yield: 18%. ¹H NMR (CDCl₃): 7.55–7.53 (2H, m), 6.92 (1H, d, *J* = 8.8 Hz), 4.56 (1H, m), 3.90 (3H, s), 3.78 (2H, m), 3.30 (2H, m), 2.92 (2H, t, *J* = 7.2 Hz), 1.95 (2H, m), 1.81 (2H, m), 1.70 (2H, m), 1.47 (9H, s), 1.40 (2H, m), 0.95 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 199.2 (s), 154.7 (s), 150.8 (s), 150.4 (s), 130.9 (s), 122.2 (d), 114.4 (d), 111.2 (d), 79.6 (s), 73.9 (d), 56.0 (q), 40.6 (t), 37.8 (t), 30.5 (t), 28.4 (q), 26.8(t), 22.5 (t), 14.0 (q). MS-EI: 391 (M⁺).

4-(4-Butyryl-2-methoxyphenoxy)piperidine-1-carboxylic Acid *tert*-Butyl Ester (5b)

Yield: 40%. ¹H NMR (CDCl₃): 7.55–7.53 (2H, m), 6.93 (1H, d, *J* = 8.8 Hz), 4.56 (1H, m), 3.90 (3H, s), 3.77 (2H, m), 3.30 (2H, m), 2.92 (2H, t, *J* = 7.6 Hz), 1.94 (2H, m), 1.85–1.74 (4H, m), 1.47 (9H, s), 1.00 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 198.8 (s), 154.6 (s), 150.7 (s), 150.3 (s), 130.9 (s), 122.2 (d), 114.4 (d), 111.1 (d), 79.5 (s), 73.8 (d), 55.9 (q), 40.6 (t), 39.9 (t), 30.4 (t), 28.3 (q), 17.9 (t), 13.8 (q). MS-EI: 377 (M⁺).

1-[3-Methoxy-4-(tetrahydropyran-4-yloxy)phenyl]butan-1-one (5c)

Yellow solid, mp 60–62 °C. Yield: 93%. ¹H NMR (CDCl₃): 7.55–7.53 (2H, m), 6.93 (1H, d, *J* = 8.0 Hz), 4.57 (1H, m), 4.02 (2H, m), 3.92 (3H, s), 3.58 (2H, m), 2.90 (2H, t, *J* = 7.2 Hz), 2.04 (2H, m), 1.88 (2H, m), 1.77 (2H, m), 1.00 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 199.0 (s), 150.7 (s), 150.3 (s), 130.8 (s), 122.2 (d), 114.2 (d), 111.2 (d), 73.2 (d), 65.1 (t), 56.0 (q), 40.0 (t), 31.9 (t), 18.0 (t), 13.9 (q). MS-EI: 278 (M⁺).

1-[3-Methoxy-4-(tetrahydropyran-4-yloxy)phenyl]pentan-1-one (5d)

Yield: 99%. ¹H NMR (CDCl₃): 7.55–7.54 (2H, m), 6.93 (1H, d, *J* = 8.0 Hz), 4.58 (1H, m), 4.02 (2H, m), 3.91 (3H, s), 3.57 (2H, m), 2.92 (2H, t, *J* = 7.2 Hz), 2.05 (2H, m), 1.87 (2H, m), 1.71 (2H, m), 1.42 (2H, m), 0.95 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 199.0 (s), 150.7 (s), 150.2 (s), 130.8 (s), 122.2 (d), 114.2 (d), 111.1 (d), 73.2 (d), 65.1 (t), 55.9 (q), 37.8 (t), 31.7 (t), 26.7 (t), 22.4 (t), 13.8 (q). MS-EI: 2 (M⁺).

1-[3-Methoxy-4-(tetrahydrofuran-3-yloxy)phenyl]butan-1-one (5e)

Yield: 75%. ¹H NMR (CDCl₃): 7.56–7.54 (2H, m), 6.83 (1H, d, *J* = 8.0 Hz), 5.02 (1H, m), 4.03–3.90 (7H, m), 2.90 (2H, t, *J* = 7.2 Hz), 2.22 (2H, m), 1.76 (2H, m), 1.00 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 198.7 (s), 150.9 (s), 149.6 (s), 130.6 (s), 122.1 (d), 112.9 (d), 110.7 (d), 78.4 (d), 72.6 (t), 66.9 (t), 55.7 (q), 39.8 (t), 32.8 (t), 17.8 (t), 13.7 (q). MS-EI: 264 (M⁺).

1-[3-Methoxy-4-(tetrahydrofuran-3-yloxy)phenyl]pentan-1-one (5f)

Yield: 55%. ¹H NMR (CDCl₃): 7.56–7.54 (2H, m), 6.83 (1H, d, *J* = 8.8 Hz), 5.02 (1H, m), 4.03–3.90 (7H, m), 2.92 (2H, t, *J* = 7.2 Hz), 2.22 (2H, m), 1.71 (2H, m), 1.41 (2H, m), 0.95 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 199.1 (s), 151.0 (s), 149.8 (s), 130.7 (s), 122.2 (d), 113.0 (d), 111.0 (d), 78.5 (d), 72.8 (t), 67.1 (t), 55.9 (q), 37.8 (t), 33.0 (t), 26.7 (t), 22.4 (t), 13.8 (q). MS-EI: 278 (M⁺).

1-[3-Methoxy-4-(pyridine-2-yloxy)phenyl]pentan-1-one (5g)

Yield: 60%. ¹H NMR (CDCl₃): 8.13 (1H, dd, *J* = 2.0 and 5.2 Hz), 7.70 (1H, m), 7.66 (1H, d, *J* = 2.0 Hz), 7.61 (1H, dd, *J* = 2.0 and 8.0 Hz), 7.20 (1H, d, *J* = 8.0 Hz), 7.00–6.98 (2H, m), 3.82 (3H, s), 2.96 (2H, t, *J* = 7.2 Hz), 1.77 (2H, m), 1.42 (2H, m), 0.96 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 199.3 (s), 163.1 (s), 151.8 (s), 147.4 (d), 146.7 (s), 139.4 (d), 134.7 (s), 122.4 (d), 121.8 (d), 118.5 (d), 111.8 (d), 111.1 (d), 55.9 (q), 38.1 (t), 26.5 (t), 22.4 (t), 13.9 (q). MS-ESI (+): 286.24 [M + H]⁺.

1-[3-Methoxy-4-(pyridine-2-yloxy)phenyl]butan-1-one (5h)

Yield: 88%. ¹H NMR (CDCl₃): 8.13 (1H, dd, *J* = 2.0 and 5.2 Hz), 7.70 (1H, m), 7.66 (1H, d, *J* = 2.0 Hz), 7.61 (1H, dd, *J* = 2.0 and 8.0 Hz), 7.20 (1H, d, *J* = 8.0 Hz), 7.00–6.98 (2H, m), 3.82 (3H, s), 2.94 (2H, t, *J* = 7.2 Hz), 1.78 (2H, m), 1.01 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 199.1 (s), 163.1 (s), 151.8 (s), 147.4 (d), 146.7 (s), 139.4 (d), 134.7 (s), 122.4 (d), 121.8 (d), 118.5 (d), 111.8 (d), 111.1 (d), 55.9 (q), 40.3 (t), 17.8 (t), 13.9 (q). HRMS-ESI (+): calcd for C₁₆H₁₈NO₃, 272.1287; found, 272.1282 (M⁺).

1-[4-Methoxy-3-(piperidin-4-yloxy)phenyl]pentan-1-one (5i)

Yellow oil. Yield: 96%. ¹H NMR (400 MHz, CDCl₃): 0.93 (3H, t, *J* = 7.2 Hz), 1.36–1.43 (2H, m), 2.15 (4H, d, *J* = 3.6 Hz), 2.91 (2H, t, *J* = 7.6 Hz), 3.33 (2H, d, *J* = 12 Hz), 3.53 (2H, s), 3.91 (3H, s), 4.66 (1H, t, *J* = 3.2 Hz), 6.95 (1H, d, *J* = 8.4 Hz), 7.56 (1H, d, *J* = 2 Hz), 7.66–7.69 (1H, dd, *J* = 2, 6.4 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 13.82, 22.43, 26.97 (d), 37.96, 40.48, 55.91, 70.00, 111.28, 113.98, 116.83, 117.24, 125.08, 1.99, 145.59, 155.60, 161.00 (d), 200.65 ppm. HRMS (ESI+): calcd for C₁₇H₂₆NO₃, 2.1913; found, 2.1900.

4-Methoxy-3-(tetrahydropyran-4-yloxyphenyl)quinolin-3-ylmethanone (5j)

White solid, mp 72–74 °C. Yield: 88%. ¹H NMR (400 MHz, CDCl₃): 1.85–1.92 (2H, m), 2.04–2.10 (2H, m), 3.53–3.59 (2H, m), 3.97 (3H, s), 4.02 (2H, t, *J* = 6.0 Hz), 4.00–4.05 (2H, m), 4.56 (1H, m), 6.97 (2H, d, *J* = 8.4 Hz), 7.45–7.47 (1H, dd, *J* = 2.0, 6.4 Hz), 7.58 (1H, d, *J* = 1.6 Hz), 7.65 (1H, t, *J* = 7.2 Hz), 7.86 (1H, t, *J* = 6.8 Hz), 8.21 (1H, d, *J* = 8.4 Hz), 8.54 (1H, d, *J* = 2.0 Hz), 9.27 (1H, d, *J* = 2.0 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 0.72, 31.95, 56.19, 65.34, 73.75, 110.89, 117.15, 126.71, 127.60, 1.02, 1.51, 131.65, 138.27, 146.75, 150.27 ppm. MS (ESI+): calcd for C₂₂H₂₁NO₄, 363.1; found, 363.

1-[4-Methoxy-3-(tetrahydropyran-4-yloxy)phenyl]butan-1-one (5k)

Yellow oil. Yield: 63%. ¹H NMR (400 MHz, CDCl₃): 1.02 (3H, t, *J* = 7.2 Hz), 1.78–1.73 (2H, q, *J* = 7.6, 6.4 Hz), 1.85 (2H, m), 2.05 (2H, d, *J* = 10.8 Hz), 2.89 (2H, t, *J* = 7.2 Hz), 3.55 (2H, t, *J* = 10 Hz), 3.92 (3H, s), 4.02 (2H, t, *J* = 6.0 Hz), 4.51 (1H, s), 6.91 (1H, d, *J* = 8.0 Hz), 7.57 (1H, s), 7.62 (1H, d, *J* = 8.4 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 13.95, 18.10, 32.00, 40.08, 56.07, 65.41, 73.70, 110.87, 115.63, 123.46, 130.33, 146.44, 154.84, 199.14 ppm. HRMS (ESI+): calcd for C₁₆H₂₂O₄, 279.1596; found, 279.1606.

1-[4-Methoxy-3-(tetrahydropyran-4-yloxy)phenyl]pentan-1-one (5l)

Yield: 75%. ¹H NMR (400 MHz, CDCl₃): 0.95 (3H, t, *J* = 7.2 Hz), 1.41 (2H, q, *J* = 7.2, 7.2 Hz), 1.72 (2H, q, *J* = 7.2, 7.2 Hz), 1.84 (2H, t, *J* = 4.4 Hz), 2.05 (2H, d, *J* = 10.0 Hz), 2.90 (2H, t, *J* = 7.2 Hz), 3.55 (2H, t, *J* = 9.2 Hz), 3.92 (3H, s), 4.03 (2H, d, *J* = 11.2 Hz), 4.52 (1H, s), 6.91 (1H, d, *J* = 8.0 Hz), 7.57 (1H, s), 7.62 (1H, d, *J* = 8.4 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 13.95, 22.52, 26.83, 31.99, 37.86, 56.04, 65.37, 73.68, 110.87, 115.67, 123.48, 130.27, 146.42, 154.83, 199.14 ppm. HRMS (ESI+): calcd for C₁₇H₂₅O₄, 3.1753; found, 3.1754. Anal. Calcd for C₁₇H₂₄O₄ · ¹/₈H₂O: C, 69.24; H, 8.23. Found: C, 69.27; H, 8.61.

1-[4-Methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]pentan-1-one (5m)

Yield: 92%. ¹H NMR (400 MHz, CDCl₃): 0.95 (3H, t, *J* = 7.2 Hz), 1.43 (2H, q, *J* = 6.8, 7.2 Hz), 1.72 (2H, t, *J* = 6.8 Hz), 2.24 (2H, m), 2.91 (2H, t, *J* = 6.8 Hz), 3.92 (4H, s), 4.03 (3H, s), 5.03 (1H, s), 6.90 (1H, d, *J* = 7.6 Hz), 7.48 (1H, s), 7.61 (1H, d, *J* = 8 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 13.96, 22.54, 26.84, 33.01, 37.86, 56.07, 67.23, 72.97, 78.74, 110.72, 113.90, 123.30, 130.22, 146.90, 154.24, 199.10 ppm. HRMS (ESI+): calcd for C₁₆H₂₃O₄, 279.1596; found, 279.1598.

1-[4-Methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]butan-1-one (5n)

Yield: 64%. ¹H NMR (400 MHz, CDCl₃): 1.00 (3H, t, *J* = 7.2 Hz), 1.75 (2H, m), 2.24 (2H, m), 2.91 (2H, t, *J* = 7.2 Hz), 3.91 (4H, s), 4.06 (3H, s), 5.02 (1H, s), 6.91 (1H, d, *J* = 8.4 Hz), 7.48 (1H, s), 7.61 (1H, d, *J* = 8.4 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 13.98, 18.12, 33.03 (d), 40.08, 56.07, 67.25 (d), 72.99 (d), 78.77, 110.76 (d), 113.92, 123.31, 130.27 (d), 146.92, 154.28 (d), 198.95 ppm. HRMS (ESI+): calcd for C₁₅H₂₁O₄, 265.1440; found, 265.1436.

1-[4-Methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-4-phenyl-butan-1-one (5o)

Yield: 80%. ¹H NMR (400 MHz, CDCl₃): 2.11(2H, d, *J* = 7.6 Hz), 2.24 (2H, d, *J* = 5.2 Hz), 2.76 (2H, t, *J* = 7.6 Hz), 2.96 (2H, t, *J* = 7.6 Hz), 3.94 (4H, s), 4.06 (3H, s), 6.92 (1H, d, *J* = 8.4 Hz), 7.26 (3H, d, *J* = 7.2 Hz), 7.30–7.35 (2H, q, *J* = 7.6, 4.8 Hz), 7.50 (1H, s), 7.60 (1H, d, *J* = 8 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 26.08, 33.00, 35.27, 37.22, 56.08, 67.24, 72.97, 78.71, 110.72, 113.77, 123.27, 125.95, 128.40, 128.54, 130.11, 141.75, 146.90, 154.30, 198.63 ppm. HRMS (ESI+): calcd for C₂₁H₂₅O₄, 341.1753; found, 341.1748.

3-Cyclohexyl-1-[4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]propan-1-one (5p)

Yield: 95%. ¹H NMR (400 MHz, CDCl₃): 0.88–0.97 (2H, q, *J* = 11.6, 10 Hz), 1.31 (4H, m), 1.76 (7H, m), 2.20 (2H, m), 2.90 (2H, t, *J* = 7.6 Hz), 3.90 (4H, s), 4.02 (3H, s), 5.01 (1H, s), 6.89 (1H, d, *J* = 8.4 Hz), 7.47 (1H, s), 7.60 (1H, d, *J* = 7.6 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 26., 26.58, 32.18, 33.01, 33.23, 35.69, 37.48, 56.07, 67.24, 72.98, 78.72, 110.71, 113.89, 123., 130.16, 146.89, 154.22, 199.38 ppm. HRMS (ESI+): calcd for C₂₀H₂₈O₄, 333.2066; found, 333.2067. Anal. Calcd for C₂₀H₂₈O₄: C, 72.26; H, 8.49. Found: C, 71.95; H, 8.76.

1-[4-Methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-3-phenyl-propan-1-one (5q)

Yield: 98%. ¹H NMR (400 MHz, CDCl₃): 2.21 (2H, s), 3.06 (2H, s), 3.25 (2H, s), 3.91 (4H, s), 4.02 (3H, s), 5.01 (1H, s), 6.89 (1H, d, *J* = 7.6 Hz), 7.21–7.30 (5H, m), 7.48 (1H, s), 7.60 (1H, d, *J* = 6.8 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 30.42, 33.00, 39.99, 56.08, 67.24, 72.96, 78.73, 110.74, 113.80, 123.27, 126.14, 128.45, 128.54, 1.98, 141.41, 146.93, 154.40, 197.72 ppm. HRMS (ESI+): calcd for C₂₀H₂₃O₄, 327.1596; found, 327.1609. Anal. Calcd for C₂₀H₂₂O₄: C, 73.60; H, 6.79. Found: C, 73.57; H, 7.09.

2-Cyclohexyl-1-[4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]ethanone (5r)

Yellow oil. Yield: 78%. ¹H NMR (400 MHz, CDCl₃): 1.02 (2H, m), 1. (3H, m), 1.76 (5H, m), 1.96 (1H, m), 2.22 (2H, m), 2.76 (2H, d, *J* = 6.8 Hz), 3.91 (1H, s), 4.03 (3H, s), 5.02 (1H, s), 6.90 (1H, d, *J* = 8.4 Hz), 7.47 (1H, d, *J* = 2.0 Hz), 7.60 (1H, q, *J* = 2.0, 6.4 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 26.18, 26.27, 33.01, 33.50, 34.96, 45.73, 56.08, 67.24, 72.99, 78.72, 110.68, 113.89, 123.45, 130.62, 146.88, 154.24, 198.76 ppm. HRMS (ESI+): calcd for C₁₉H₂₆O₄, 319.1909; found, 319.1911

1-[4-Difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-2,2-dimethylpropan-1-one (5s)

Yellow oil. Yield: 81%. ¹H NMR (400 MHz, CDCl₃): 1.36 (9H, s), 2.19–2.25 (2H, m), 3.91–3.95 (1H, m), 3.99–4.03 (3H, m), 5.00 (1H, s), 6.59 (1H, t, *J* = 74.8 Hz), 7.18 (1H, d, *J* = 8.4 Hz), 7.30 (1H, d, *J* = 2.0 Hz), 7.40–7.42 (1H, dd, *J* = 2.0, 1.6 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): 28.15, 28.71, 32.96, 44.22, 67.16, 72.81, 78.94, 115.84 (d, *J* = 36 Hz), 121.77 (d), 136.04, 148.72, 206.85 ppm. MS (EI+): calcd for C₁₆H₂₀F₂O₄, 314; found, 314.

1-[4-Methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-3-methyl-butan-1-one (5t)

Yield: 93%. ¹H NMR (400 MHz, CDCl₃): 0.99 (6H, d, *J* = 6.4 Hz), 2.19–2.28 (3H, m), 2.77 (3H, d, *J* = 6.8 Hz), 3.90 (4H, d, *J* = 4.8 Hz), 4.02 (3H, t, *J* = 3.6 Hz), 5.02 (1H, d, *J* = 3.2 Hz),

6.89 (1H, d, $J = 8.4$ Hz), 7.47 (1H, d, $J = 1.6$ Hz), 7.57–7.59 (1H, dd, $J = 2.0, 1.6$ Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): 22.82, 25.48, 0.70, 33.00, 47.01, 56.05, 67.23, 72.97, 78.72, 110.67, 113.87, 123.39, 130.54, 146.90, 154.24, 198.73 ppm. MS (EI+): calcd for $\text{C}_{16}\text{H}_{22}\text{O}_4$, 278; found, 278.

1-[4-Methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-4-methyl-pentan-1-one (5u)

Yield: 93%. ^1H NMR (400 MHz, CDCl_3): 0.95 (6H, d, $J = 6.0$ Hz), 1.59–1.64 (3H, m), 2.19–2.25 (2H, m), 2.90 (2H, t, $J = 7.6$ Hz), 3.88–3.94 (4H, m), 4.02–4.06 (3H, m), 5.01–5.03 (1H, q, $J = 2.4, 2.8$ Hz), 6.91 (1H, d, $J = 8.4$ Hz), 7.48 (1H, d, $J = 1.6$ Hz), 7.59–7.62 (1H, dd, $J = 6.8, 1.6$ Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): 22.46, 27.90, 29.70, 33.00, 33.64, 36.16, 56.05, 67.22, 72.97, 78.72, 110.71, 113.88, 123., 130.15, 146.90, 154.23, 199.28 ppm. MS (EI +): calcd for $\text{C}_{17}\text{H}_{24}\text{O}_4$, 292; found, 292.

1-[4-Difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-3-methylbutan-1-one (5v)

Yield: 65%. ^1H NMR (CDCl_3): 7.56–7.53 (2H, m), 7.23 (1H, d, $J = 8.8$ Hz), 6.62 (1H, t, $J = 74.4$ Hz), 5.06 (1H, m), 4.06–3.93 (4H, m), 2.80 (2H, d, $J = 6.8$ Hz), 2.32–2.18 (3H, m), 1.01 (6H, d, $J = 6.8$ Hz). ^{13}C NMR (CDCl_3): 198.6 (s), 149.0 (s), 144.5 (s), 135.5 (s), 122.2 (d), 122.0 (d), 115.7 (triplet, $J = 259$ Hz, d), 114.0 (d), 78.9 (d), 72.8 (t), 67.1 (t), 47.3 (t), 32.9 (t), 25.2 (s), 22.7 (q). MS-EI: 314 (M^+).

1-[4-Difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-3-pentan-1-one (5za)

Yield: 43%. ^1H NMR (CDCl_3): 7.57–7.55 (2H, m), 7.23 (1H, d, $J = 8.0$ Hz), 6.62 (1H, t, $J = 74.4$ Hz), 5.06 (1H, m), 4.03–3.92 (4H, m), 2.93 (2H, t, $J = 7.2$ Hz), 2.32–2.15 (2H, m), 1.71 (2H, m), 1.41 (2H, m), 0.96 (3H, t, $J = 7.2$ Hz). ^{13}C NMR (CDCl_3): 199.0 (s), 149.0 (s), 144.5 (s), 135.2 (s), 122.08 (d), 122.05 (d), 115.7 (triplet, $J = 260$ Hz, d), 114.0 (d), 78.9 (d), 72.7 (t), 67.1 (t), 38.2 (t), 32.9 (t), 26.5 (t), 22.4 (t), 13.9 (q). MS-EI: 314 (M^+).

Cyclohexyl-1-[4-difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]propan-1-one (5zb)

Yield: 83%. ^1H NMR (CDCl_3): 7.57–7.54 (2H, m), 7.23 (1H, d, $J = 8.0$ Hz), 6.62 (1H, t, $J = 74.4$ Hz), 5.06 (1H, m), 4.03–3.92 (4H, m), 2.94 (2H, t, $J = 7.6$ Hz), 2.28–2.18 (2H, m), 1.76–1.59 (7H, m), 1.31–1.16 (4H, m), 0.97 (2H, m). ^{13}C NMR (CDCl_3): 199.3 (s), 149.0 (s), 144.5 (s), 135.2 (s), 122.1 (d), 115.7 (triplet, $J = 258$ Hz, d), 114.0 (d), 78.9 (d), 72.7 (t), 67.1 (t), 37.4 (d), 36.0 (t), 33.2 (t), 32.9 (t), 31.8 (t), 26.5 (t), 26.3 (t). MS-EI: 368 (M^+).

2-Cyclohexyl-1-[4-difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]ethanone (5zc)

Yield: 89%. ^1H NMR (CDCl_3): 7.56–7.53 (2H, m), 7.23 (1H, d, $J = 8.8$ Hz), 6.62 (1H, t, $J = 74.4$ Hz), 5.06 (1H, m), 4.06–3.90 (4H, m), 2.79 (2H, d, $J = 6.8$ Hz), 2.30–2.18 (2H, m), 1.96 (1H, m), 1.77–1.65 (5H, m), 1.31–1.15 (4H, m), 1.03 (2H, m). ^{13}C NMR (CDCl_3): 198.7 (s), 149.0 (s), 144.5 (s), 135.6 (s), 122.2 (d), 122.0 (d), 115.7 (triplet, $J = 260$ Hz, d), 114.0 (d), 78.9 (d), 72.8 (t), 67.1 (t), 46.0 (t), 34.7 (d), 33.4 (t), 32.9 (t), 26.2 (t), 26.1 (t). MS-EI: 354 (M^+).

1-[4-Difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-3-phenylpropan-1-one (5zd)

Yellow oil. Yield: 88%. ^1H NMR (CDCl_3): 7.55–7.52 (2H, m), 7.31–7.19 (6H, m), 6.61 (1H, t, $J = 74.4$ Hz), 5.03 (1H, m), 4.03–3.89 (4H, m), 3.27 (2H, t, $J = 7.6$ Hz), 3.05 (2H, t, $J = 7.6$ Hz), 2.27–2.14 (2H, m). ^{13}C NMR (CDCl_3): 197.6 (s), 149.0 (s), 144.6 (s), 141.0 (s), 134.9 (s), 128.51 (d), 128.35 (d), 126.2 (d), 122.00 (d), 121.99 (d), 115.7 (triplet, $J = 260$ Hz, d), 113.9 (d), 78.8 (d), 72.7 (t), 67.1 (t), 40.2 (t), 32.9 (t), 30.1 (t). MS-EI: 362 (M^+).

1-[4-Difluoromethoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-4-phenylbutan-1-one (5ze)

Yellow oil. Yield: 91%. ¹H NMR (CDCl₃): 7.51–7.47 (2H, m), 7.31–7.26 (2H, m), 7.21–7.19 (4H, m), 6.61 (1H, t, *J* = 74.4 Hz), 5.03 (1H, m), 4.04–3.90 (4H, m), 2.94 (2H, t, *J* = 7.2 Hz), 2.72 (2H, t, *J* = 7.2 Hz), 2.28–2.14 (2H, m), 2.08 (2H, m). ¹³C NMR (CDCl₃): 198.5 (s), 149.0 (s), 144.6 (s), 141.5 (s), 135.1 (s), 128.48 (d), 128.42 (d), 126.0 (d), 122.05 (d), 122.04 (d), 115.7 (triplet, *J* = 259 Hz, d), 113.9 (d), 78.8 (d), 72.7 (t), 67.1 (t), 37.5 (t), 35.1 (t), 32.9 (t), 25.7 (t). MS-EI: 376 (M⁺).

1-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-3-methyl-butan-1-one (5zf)

Yield: 74%. ¹H NMR (CDCl₃): 7.58 (1H, d, *J* = 4.0 Hz), 7.49 (1H, dd, *J* = 4.0 and 8.4 Hz), 7.19 (1H, d, *J* = 8.4 Hz), 6.63 (1H, t, *J* = 75.2 Hz), 4.90 (1H, m), 2.80 (2H, d, *J* = 6.8 Hz), 2.28 (1H, m), 1.97–1.79 (7H, m), 1.69–1.64 (2H, m), 1.00 (6H, d, *J* = 6.8 Hz). ¹³C NMR (CDCl₃): 198.9 (s), 149.6 (s), 144.4 (s), 135.5 (s), 122.0 (d), 121.3 (d), 115.8 (triplet, *J* = 259 Hz, d), 114.1 (d), 80.8 (d), 47.3 (t), 32.7 (t), 25.3 (d), 23.7 (t), 22.7 (q). MS-EI: 312 (M⁺).

4-(2-Difluoromethoxy-5-pentanoylphenoxy)piperidine-1-carboxylic Acid *tert*-Butyl Ester (5zg)

Yield: 10%. ¹H NMR (CDCl₃): 7.62 (1H, d, *J* = 1.6 Hz), 7.55 (1H, dd, *J* = 1.6 and 8.4 Hz), 7.23 (1H, d, *J* = 8.4 Hz), 6.61 (1H, t, *J* = 74.4 Hz), 4.60 (1H, m), 3.67 (2H, m), 3.40 (2H, m), 2.93 (2H, t, *J* = 6.8 Hz), 1.93 (2H, m), 1.80 (2H, m), 1.71 (2H, m), 1.47 (9H, s), 1.40 (2H, m), 0.96 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 199.1 (s), 154.7 (s), 148.9 (s), 145.0 (s), 135.3 (s), 122.1 (d), 122.0 (d), 115.8 (triplet, *J* = 259 Hz, d), 115.2 (d), 79.7 (s), 74.1 (d), 40.5 (t), 38.2 (t), 30.4 (t), 28.4 (q), 26.5 (t), 22.4 (t), 13.9 (q). MS-EI: 371 [M – C₄H₉ (*t*-Bu) + H]⁺, 354 [M – C₄H₉O (*t*-BuO)]⁺, 327 [M – C₅H₉O₂ (Boc) + H]⁺.

1-[4-Difluoromethoxy-3-(tetrahydropyran-4-yloxy)phenyl]-butan-1-one (5zh)

Colorless oil. Yield: 59%. ¹H NMR (CDCl₃): 7.62 (1H, s), 7.55 (1H, d, *J* = 8.4 Hz), 7.23 (1H, d, *J* = 8.4 Hz), 6.64 (1H, t, *J* = 74.4 Hz), 4.62 (1H, m), 3.98 (2H, m), 3.60 (2H, m), 2.92 (1H, t, *J* = 7.2 Hz), 2.03 (2H, m), 1.84–1.74 (4H, m), 1.01 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 198.9 (s), 148.8 (s), 145.0 (s), 135.4 (s), 122.14 (d), 122.07 (d), 115.9 (triplet, *J* = 259 Hz, d), 115.3 (d), 73.5 (d), 64.9 (t), 40.4 (t), 31.6 (t), 17.8 (t), 13.8 (q). MS-EI: 314 (M⁺).

1-[4-Difluoromethoxy-3-(pyridin-2-yloxy)phenyl]butan-1-one (5zi)

Yield: 99%. ¹H NMR (CDCl₃): 8.08 (1H, m), 7.85–7.83 (2H, m), 7.71 (1H, m), 7.32 (1H, d, *J* = 8.8 Hz), 7.03–6.99 (2H, m), 6.48 (1H, t, *J* = 73.6 Hz), 2.91 (2H, t, *J* = 7.2 Hz), 1.76 (2H, m), 0.99 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 198.1 (s), 162.7 (s), 147.2 (d), 144.8 (s), 139.7 (d), 135.3 (s), 125.9 (d), 123.7 (d), 120.8 (d), 118.9 (d), 115.8 (triplet, *J* = 260 Hz, d), 111.2 (d), 40.4 (t), 17.6 (t), 13.8 (q). HRMS-ESI (+): calcd for C₁₉H₁₅NO₂F, 308.1087; found, 308.1085.

1-(3,4-Bisdifluoromethoxyphenyl)-4-phenylbutan-1-one (5zj)

Yield: 63%. ¹H NMR (CDCl₃): 7.81 (1H, s), 7.77 (1H, dd, *J* = 2.0 and 8.4 Hz), 7.32–7.27 (3H, m), 7.22–7.19 (3H, m), 6.59 (1H, t, *J* = 72.8 Hz), 6.56 (1H, t, *J* = 73.2 Hz), 2.93 (2H, t, *J* = 7.2 Hz), 2.72 (2H, t, *J* = 7.2 Hz), 2.08 (2H, m). ¹³C NMR (CDCl₃): 197.6 (s), 145.9 (s), 141.9 (s), 141.4 (s), 135.1 (s), 128.48 (d), 128.45 (d), 126.5 (d), 126.1 (d), 121.9 (d), 121.2 (d), 115.52 (triplet, *J* = 262 Hz, d), 115.33 (triplet, *J* = 263 Hz, d), 37.5 (t), 35.0 (t), 25.5 (t). MS-EI: 356 (M⁺).

1-(3,4-Bisdifluoromethoxyphenyl)butan-1-one (5zk)

Yield: 72%. ¹H NMR (CDCl₃): 7.85–7.82 (2H, m), 7.33 (1H, d, *J* = 8.0 Hz), 6.63 (1H, t, *J* = 72.8 Hz), 6.60 (1H, t, *J* = 73.2 Hz), 2.92 (2H, t, *J* = 7.2 Hz), 1.76 (2H, m), 1.01 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 197.9 (s), 145.8 (s), 141.9 (s), 135.1 (s), 126.5 (d), 121.8 (d), 121.1 (d), 115.6 (triplet, *J* = 261 Hz, d), 115.4 (triplet, *J* = 263 Hz, d), 40.3 (t), 17.5 (t), 13.6 (q). MS-EI: 280 (M⁺).

1-(3,4-Bisdifluoromethoxyphenyl)-3-phenylpropan-1-on (5zl)

Yield: 46%. ¹H NMR (CDCl₃): 7.83–7.80 (2H, m), 7.30–7.24 (6H, m), 6.59 (1H, t, *J* = 74.4 Hz), 6.55 (1H, t, *J* = 72.8 Hz), 3.26 (2H, s), 3.06 (2H, s). ¹³C NMR (CDCl₃): 196.8, 146.0, 141.9, 140.8, 134.9, 128.6, 128.4, 126.5, 126.3, 121.3, 121.2, 115.5 (triplet, *J* = 262 Hz), 115.3 (triplet, *J* = 263 Hz), 40.3, 0.9. MS-EI: 342 (M⁺).

1-(3,4-Bisdifluoromethoxyphenyl)-2-cyclohexylethanone (5zm)

Yield: 92%. ¹H NMR (CDCl₃): 7.84–7.81 (2H, m), 7.33 (1H, d, *J* = 7.6 Hz), 6.62 (1H, triplet, *J* = 72.8 Hz), 6.60 (1H, triplet, *J* = 72.8 Hz), 2.79 (2H, d, *J* = 5.2 Hz), 1.96 (1H, m), 1.76–1.68 (5H, m), 1.31–1.15 (3H, m), 1.03 (2H, m). ¹³C NMR (CDCl₃): 197.7 (s), 145.8 (s), 141.9 (s), 135.5 (s), 126.6 (d), 121.9 (d), 121.1 (d), 115.6 (triplet, *J* = 262 Hz, d), 115.4 (triplet, *J* = 263 Hz, d), 46.0 (t), 34.4 (d), 33.3 (t), 26.1 (t), 26.0 (t). MS-EI: 334 (M⁺).

General Procedure for the Synthesis of 6 by Nucleophilic Addition to the Ketones 5

To ketones **5g** or **5h** (1 mmol) in THF (5 mL) was added dropwise 3-pyridyllithium or 3-quinollythium at -78°C . The resulting mixture was stirred overnight, during which time the mixture was allowed to gradually warm from -78°C to room temperature and quenched with water. The aqueous layer was extracted three times with ethyl acetate. The combined organic solution was dried over MgSO₄, filtered, and evaporated. The residue was purified by flash chromatography to afford **6**.

1-[3-Methoxy-4-(pyridin-2-yloxy)phenyl]-1-pyridin-3-yl-pentan-1-ol (6a)

Yield: 36%. ¹H NMR (CDCl₃): 8.61 (1H, s), 8.32 (1H, s), 8.08 (1H, dd, *J* = 1.6 and 5.2 Hz), 7.79 (1H, d, *J* = 8.0 Hz), 7.63 (1H, m), 7.21 (1H, m), 7.15 (1H, d, *J* = 1.6 Hz), 7.05 (1H, d, *J* = 8.4 Hz), 6.98–6.91 (2H, m), 6.86 (1H, d, *J* = 8.0 Hz), 4.27 (1H, s, br), 3.67 (3H, s), 2.27 (2H, t, *J* = 7.2 Hz), 1.40–1.21 (4H, m), 0.86 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 163.4 (s), 151.4 (s), 147.31 (d), 147.26 (d), 144.4 (s), 142.8 (s), 141.4 (s), 139.1 (d), 134.1 (d), 122.9 (d), 122.2 (d), 118.5 (d), 118.0 (d), 111.2 (d), 110.6 (d), 76.5 (s), 55.8 (q), 41.6 (t), 25.7 (t), 22.9 (t), 13.9 (q). MS-EI: 364 (M⁺).

1-[3-Methoxy-4-(pyridin-2-yloxy)phenyl]-1-quinolin-3-ylbutan-1-ol (6b)

Yield: 53%. ¹H NMR (CDCl₃): 8.90 (1H, d, *J* = 1.6 Hz), 8.27 (1H, d, *J* = 1.6 Hz), 8.13 (1H, dd, *J* = 1.2 and 4.4 Hz), 8.07 (1H, d, *J* = 8.0 Hz), 7.83 (1H, d, *J* = 8.0 Hz), 7.71–7.62 (2H, m), 7.55 (1H, m), 7.16 (1H, s), 7.10–7.03 (2H, m), 6.94 (1H, m), 7.89 (1H, d, *J* = 8.4 Hz), 3.70 (3H, s), 2.53 (1H, s, br), 2.38 (2H, m), 1.47 (1H, m), 1.00 (1H, m), 0.97 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 163.5 (s), 151.7 (s), 149.9 (d), 147.5 (d), 146.8 (s), 144.0 (s), 141.9 (s), 139.3 (s), 139.2 (d), 132.1 (d), 1.3 (d), 1.0 (d), 128.1 (d), 127.5 (s), 126.8 (d), 122.5 (d), 121.8 (d), 118.7 (d), 118.1 (d), 111.3 (d), 110.8 (d), 77.3 (s), 56.0 (q), 44.2 (t), 17.1 (t), 14.4 (q). HRMS-ESI (+): calcd for C₂₅H₂₅N₂O₃, 401.1865; found, 401.1853 [M + H]⁺.

Synthesis of 3-{1-[3-Methoxy-4-(pyridin-2-yloxy)phenyl]-but-1-enyl}quinoline (7a)

To a solution of **6a** (0.33 g, 0.8 mmol) in acetic acid (5 mL) was added dropwise concentrated H₂SO₄ (0.3 mL). The mixture was heated at 80 °C for 1 h and then cooled and neutralized with

saturated NaHCO₃. The aqueous solution was extracted with ethyl acetate three times. The combined organics were washed with brine, dried over MgSO₄, filtered, concentrated. The residue was purified by flash chromatography to afford 0.12 g (37%) of **7a** as a mixture of *Z*- and *E*-isomers. ¹H NMR (CDCl₃): 8.97 and 8.79 (1H, s), 8.20–7.49 (6H, m), 7.19–6.82 (5H, m), 6.00–6.25 (1H, m), 3.71 and 3.68 (3H, s), 2.30 (1H, m), 2.17 (1H, m), 1.11 (3H, m). ¹³C NMR (CDCl₃): 163.6 (s), 163.5 (s), 150.1 (d), 151.6 (s), 151.45 (s), 150.0 (d), 147.53 (d), 147.46 (d), 147.1 (s), 147.0 (s), 142.0 (s), 139.9 (s), 139.24 (d), 139.15 (d), 137.9 (s), 137.2 (s), 136.6 (s), 136.3 (d), 135.4 (s), 134.3 (d), 133.9 (d), 133.5 (d), 133.1 (s), 1.4 (d), 1.2 (d), 128.99 (d), 128.96 (d), 127.9 (d), 127.8 (d), 127.8 (s), 126.8 (d), 126.7 (d), 122.63 (d), 122.60 (d), 120.3 (d), 118.2 (d), 118.1 (d), 114.4 (d), 111.8 (d), 110.9 (d), 110.7 (d), 55.9 (q), 23.5 (t), 23.3 (t), 14.4 (q). HRMS-ESI (+): calcd for C₂₅H₂₃N₂O₂, 383.1760; found, 383.1742 [M + H]⁺.

Synthesis of 8

To a solution of **6a** (0.30 g, 0.80 mmol) in acetic acid (5 mL) was added dropwise concentrated H₂SO₄ (0.3 mL). The mixture was heated at 80 °C for 1 h. After **6a** was converted to **7a** completely, without workup the product was hydrogenated at room temperature overnight using 10% Pd/C (0.03 g) as catalyst. The reaction mixture was neutralized with saturated NaHCO₃. The aqueous solution was extracted with ethyl acetate three times. The combined organic solution was washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography to afford 0.11 g (38%) of **8** as a white solid, mp 56–58 °C. ¹H NMR (CDCl₃): 8.57 (1H, s), 8.44 (1H, d, *J* = 4.4 Hz), 8.11 (1H, dd, *J* = 2.0 and 5.2 Hz), 7.62–7.54 (2H, m), 7.20 (1H, m), 7.70 (1H, d, *J* = 8.0 Hz), 6.91–6.84 (4H, m), 3.91 (1H, t, *J* = 8.0 Hz), 3.70 (3H, s), 2.06 (2H, m), 1.38–1.24 (4H, m), 0.87 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃): 163.4 (s), 151.4 (s), 149.34 (d), 147.37 (d), 147.20 (d), 141.6 (s), 140.8 (s), 140.1 (s), 138.9 (d), 134.9 (d), 123.2 (d), 122.6 (d), 119.8 (d), 117.8 (d), 111.4 (d), 110.4 (d), 55.7 (q), 48.5 (d), 35.0 (t), 0.8 (t), 22.3 (t), 13.7 (q).

Synthesis of 4-[3-Methoxy-4-(pyridin-2-yloxy)phenyl]-4-quinolin-3-ylbutan-2-one (**11a**) and 4-(4-Hydroxy-3-methoxyphenyl)-4-pyridin-3-ylbutan-2-one (**11b**)

To compound 4h or 4i (0.50 mmol) in CH₂Cl₂ (20 mL) at room temperature was added SOCl₂ (0.75 mmol). After 45 min, the mixture was carefully poured into saturated NaHCO₃ (5 mL). The layers were separated, and the aqueous phase was extracted with CH₂Cl₂. The combined organic solution was washed with saturated NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated. The thick yellow oil (**9a** or **9b**) was used immediately in the next reaction without further purification. To a solution of ethyl acetoacetate (0.60 mmol) in THF at 0 °C was added sodium methoxide in portions. After the mixture was stirred for 30 min, a solution of **9a** or **9b** in THF was added dropwise. The mixture was stirred at room temperature overnight and then poured into saturated NH₄Cl. The layers were separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic solution was washed with 25% NH₄OAc buffer and brine, dried over MgSO₄, filtered, and concentrated to provide crude **10a** or **10b**. **10a** or **10b** was dissolved in a mixture of THF/MeOH/H₂O (3:1:1, 10 mL), and then 2 N LiOH (1 mL, 2 mmol) was added. The mixture was heated at 70 °C for 2 h. Volatile components were removed on the rotovap, and the residue was partitioned between saturated NaHCO₃ and ethyl acetate. The aqueous phase was extracted twice with ethyl acetate. The combined organic solution was washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography to afford **11a** or **11b**.

11a

Yellow oil. Yield: 28%. ¹H NMR (CDCl₃): 8.86 (1H, d, *J* = 2.0 Hz), 8.11 (1H, dd, *J* = 1.2 and 4.4 Hz), 8.06 (1H, d, *J* = 8.4 Hz), 7.96 (1H, d, *J* = 2.4 Hz), 7.76 (1H, d, *J* = 7.2 Hz), 7.68–7.59

(2H, m), 7.50 (1H, m), 7.07 (1H, d, $J = 8.0$ Hz), 6.93–6.84 (4H, m), 4.82 (1H, t, $J = 7.2$ Hz), 3.70 (3H, s), 3.31 (2H, d, $J = 7.2$ Hz), 2.14 (3H, s). ^{13}C NMR (CDCl_3): 205.5, 163.7, 152.1, 151.3, 147.6, 147.2, 142.0, 140.4, 139.1, 136.5, 133.7, 1.3, 1.1, 128.0, 127.7, 126.8, 13.2, 120.1, 118.1, 113.5, 110.8, 56.2, 49.6, 43.6, 30.5.

11b

Yellow oil. Yield: 24%. ^1H NMR (CDCl_3): 8.52 (1H, d, $J = 2.0$ Hz), 8.43 (1H, dd, $J = 1.6$ and 4.8 Hz), 7.52 (1H, d, $J = 8.0$ Hz), 7.20 (1H, m), 6.84 (1H, d, $J = 8.0$ Hz), 6.72–6.67 (2H, m), 6.15 (1H, s, br), 4.54 (1H, t, $J = 7.6$ Hz), 3.81 (3H, s), 3.17 (2H, d, $J = 7.6$ Hz), 2.11 (3H, s). ^{13}C NMR (CDCl_3): 206.1 (s), 145.0 (d), 147.7 (d), 146.8 (s), 144.6 (s), 139.7 (s), 135.3 (d), 134.5 (s), 123.5 (d), 119.8 (d), 114.6 (d), 110.7 (d), 55.9 (q), 49.4 (t), 43.2 (d), 30.6 (q).

PDE Inhibition Assays

The enzymatic activities of PDEs were assayed using ^3H -cAMP and ^3H -cGMP as substrates.^{39,40} The expression and purification of PDE has been described earlier.⁴¹ First, PDEs were incubated with the reaction mixture of 50 mM Tris-HCl, pH 7.8, 10 mM MgCl_2 , and ^3H -cAMP or ^3H -cGMP (40 000 cpm/assay) at 24 °C for 30 min. Then the reaction was terminated by addition of ZnSO_4 and $\text{Ba}(\text{OH})_2$. The reaction product ^3H -AMP or ^3H -GMP was precipitated by BaSO_4 , while unreacted ^3H -cAMP or ^3H -cGMP remained in the supernatant. Radioactivity in the supernatant was measured by liquid scintillation. The activity was measured at eight concentrations of cAMP and cGMP, and each measurement was repeated three times. V_{max} and K_m values were calculated by linear plots of Lineweaver–Burk ($1/V$ vs $1/[\text{S}]$) and Eadie–Hofstee ($V/[\text{S}]$ vs V)⁴² and also by nonlinear regression analysis as implemented in the program DynaFit.⁴³ For measurement of IC_{50} , 10 concentrations of inhibitors were used under the substrate concentration of one-tenth of K_M and the suitable enzyme concentration. For the potent inhibitors, a double or triple measurement was performed, while a single measurement was carried out for the poor inhibitors.

NMR Study of the Interaction of Inhibitors with PDE4D2 Protein

A reference ^1H spectrum and a 2D NOESY (mixing time of 500 ms) spectrum were taken on a Varian 800 MHz NMR using a 400 μM sample in 20 mM potassium phosphate (pH 7.1) D_2O buffer. A sample with a 1:80 molar ratio of the inhibitor to protein was made in 20 mM potassium phosphate (pH 7.1) D_2O buffer with concentrations of 800 μM **5i** and 10 μM PDE4D2. STD and trNOESy (mixing time of 50 ms) experiments were performed. The sample was subsequently diluted, and another STD spectrum was collected to test for nonspecific binding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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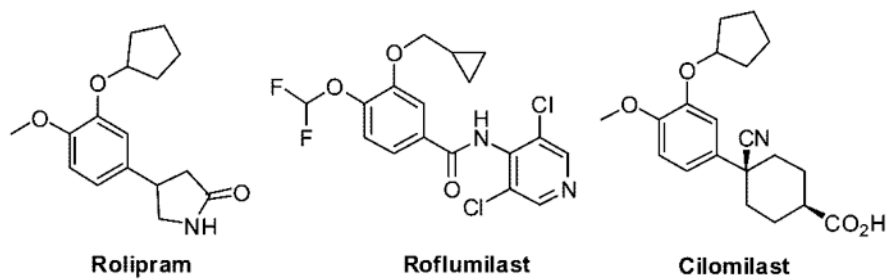


Figure 1.
Structures of selected PDE4 inhibitors.

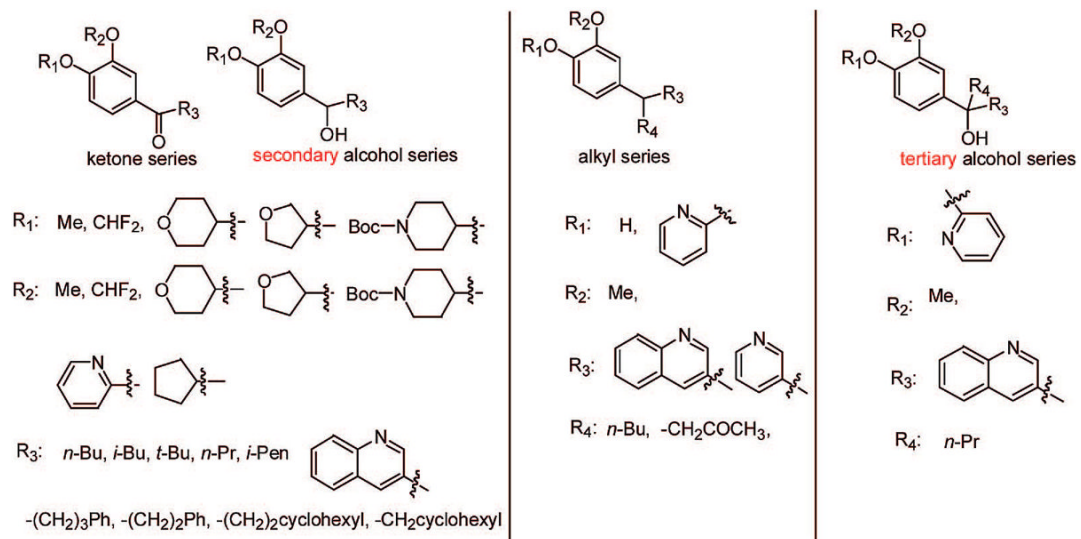


Figure 2.
General structures of potential inhibitors designed.

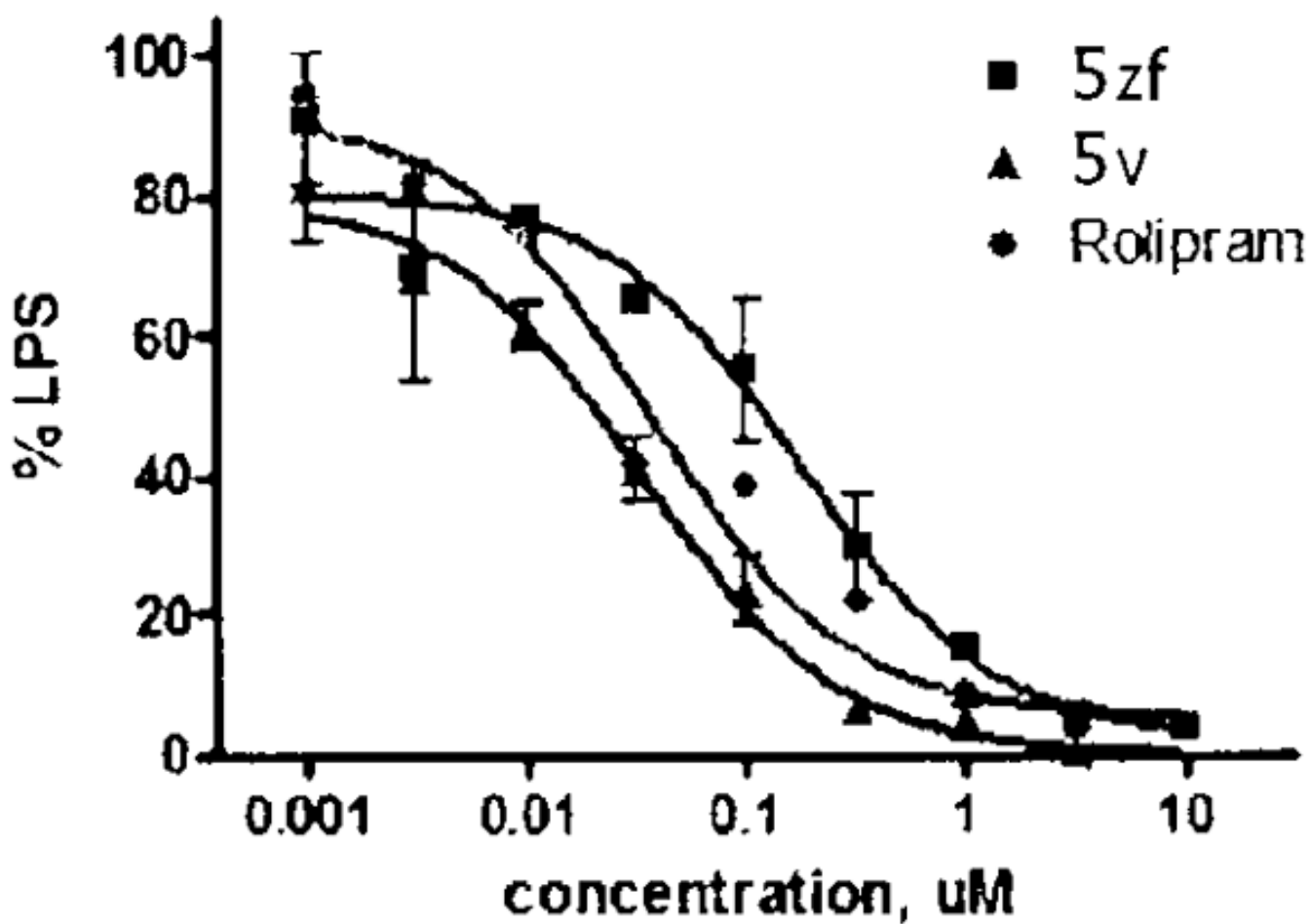


Figure 3. Inhibitory effect of 5v (▲) and 5zf (■) against LPS-mediated TNF- α production, compared with rolipram (●).

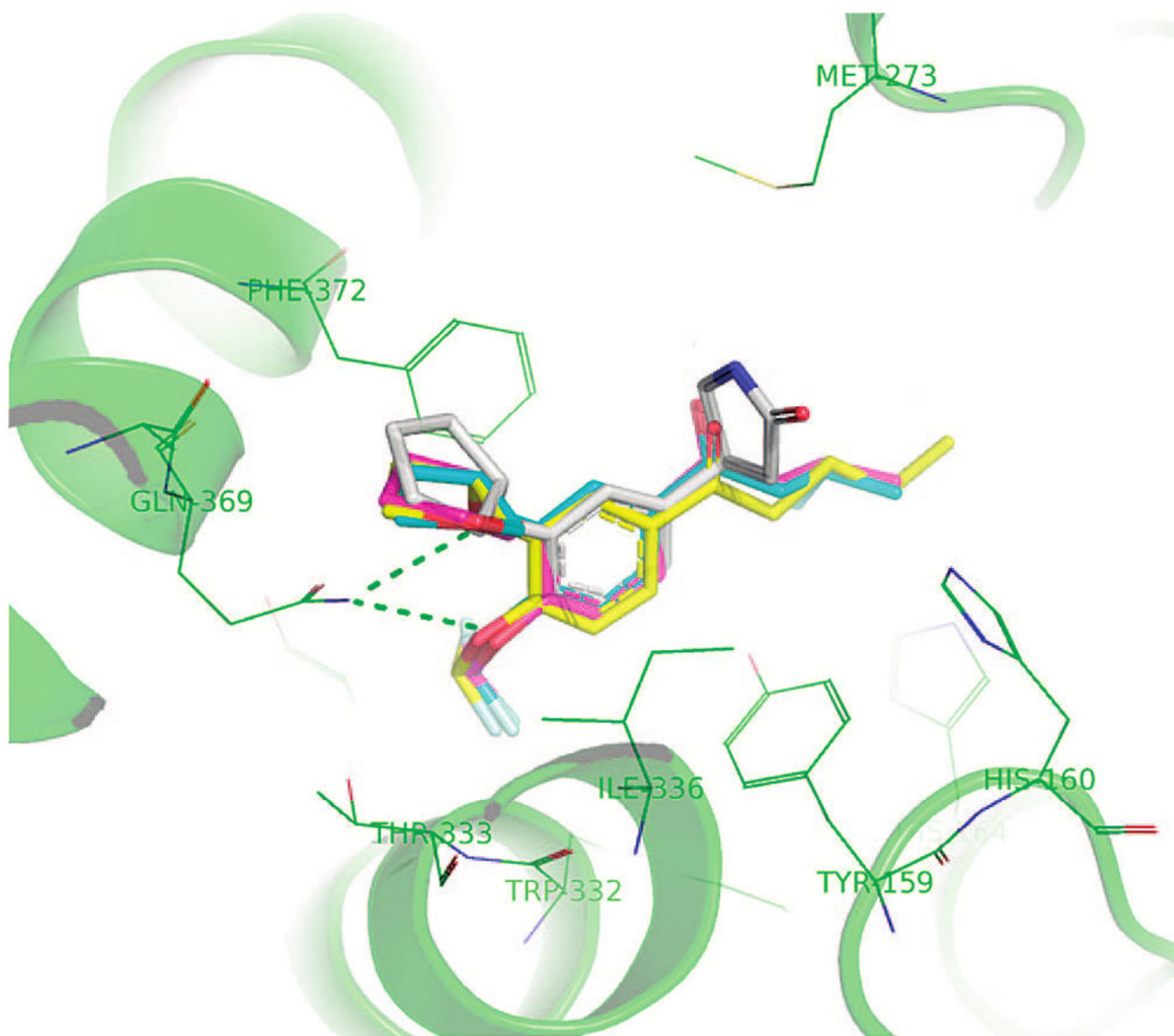


Figure 4. Key residues in the binding site of rolipram (white), **5za** (yellow), **5v** (blue), and **5zf** (red) to PDE4.

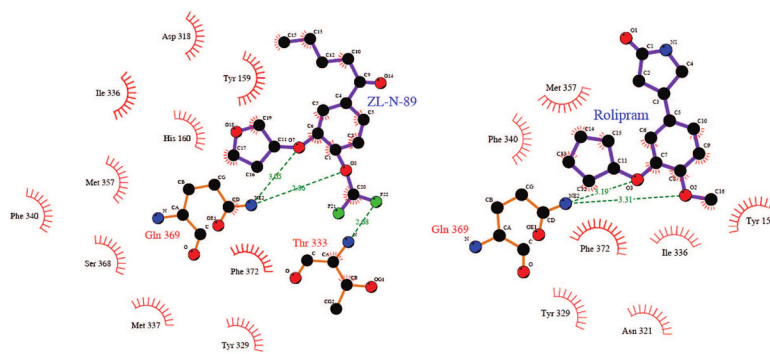


Figure 5.
Binding profile of **5za** and rolipram with PDE4D2 obtained from Ligplot analysis.

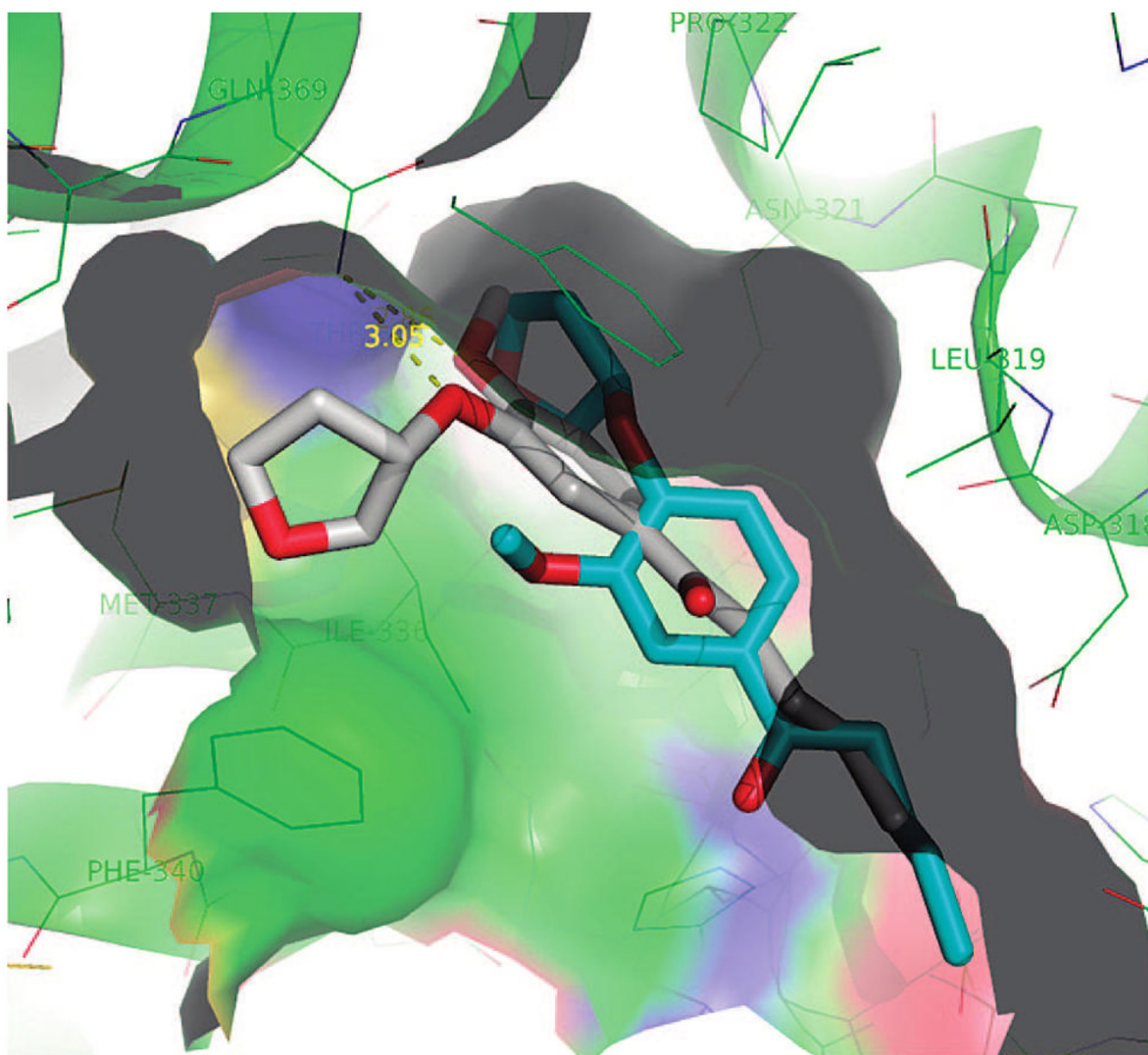


Figure 6. Negative effect observed for a bulky substitution at 4-position: blue stick, **5f**; gray stick, **5m**.

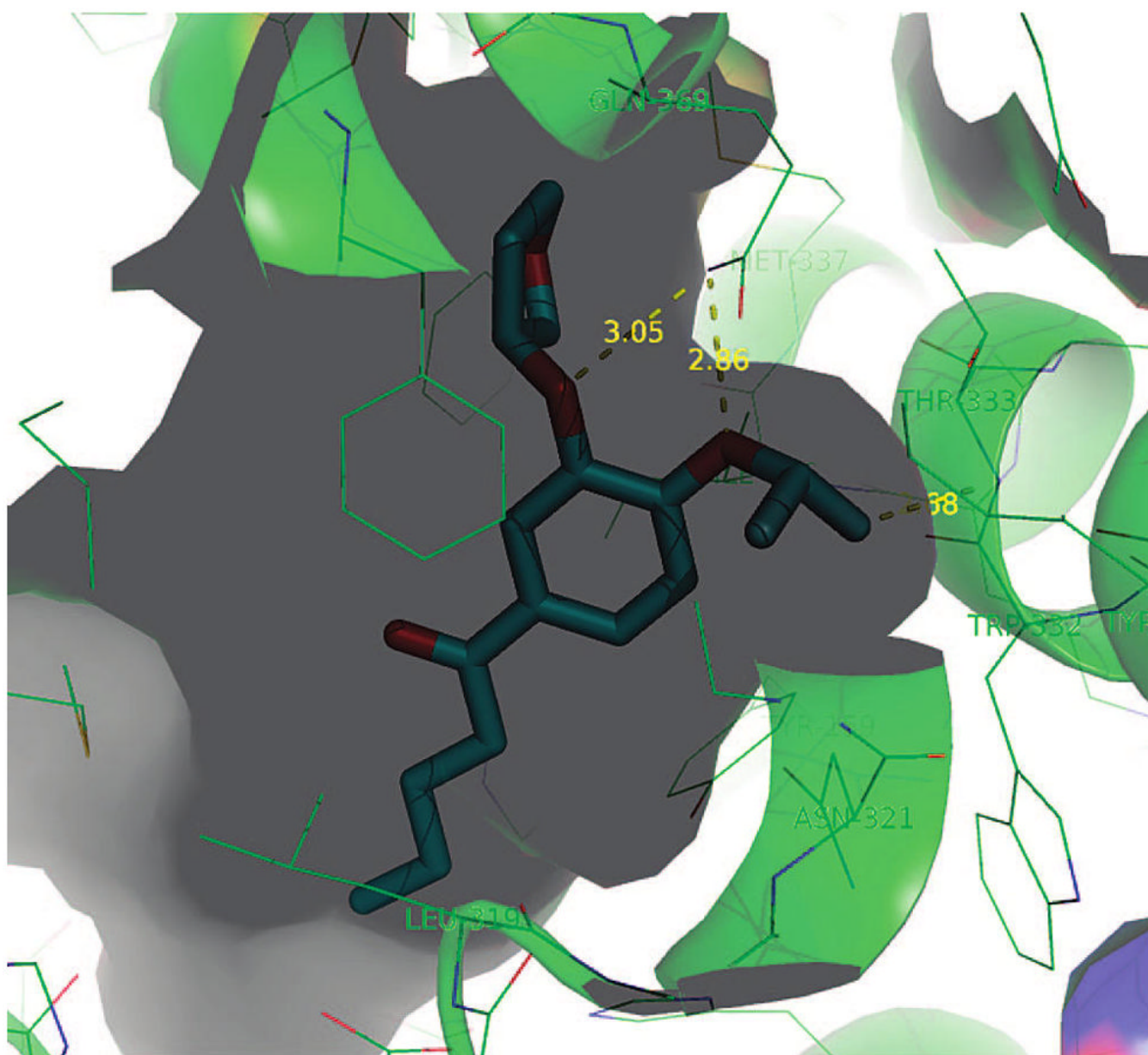


Figure 7.
Docking conformation of **5za** in the PDE4D active site.

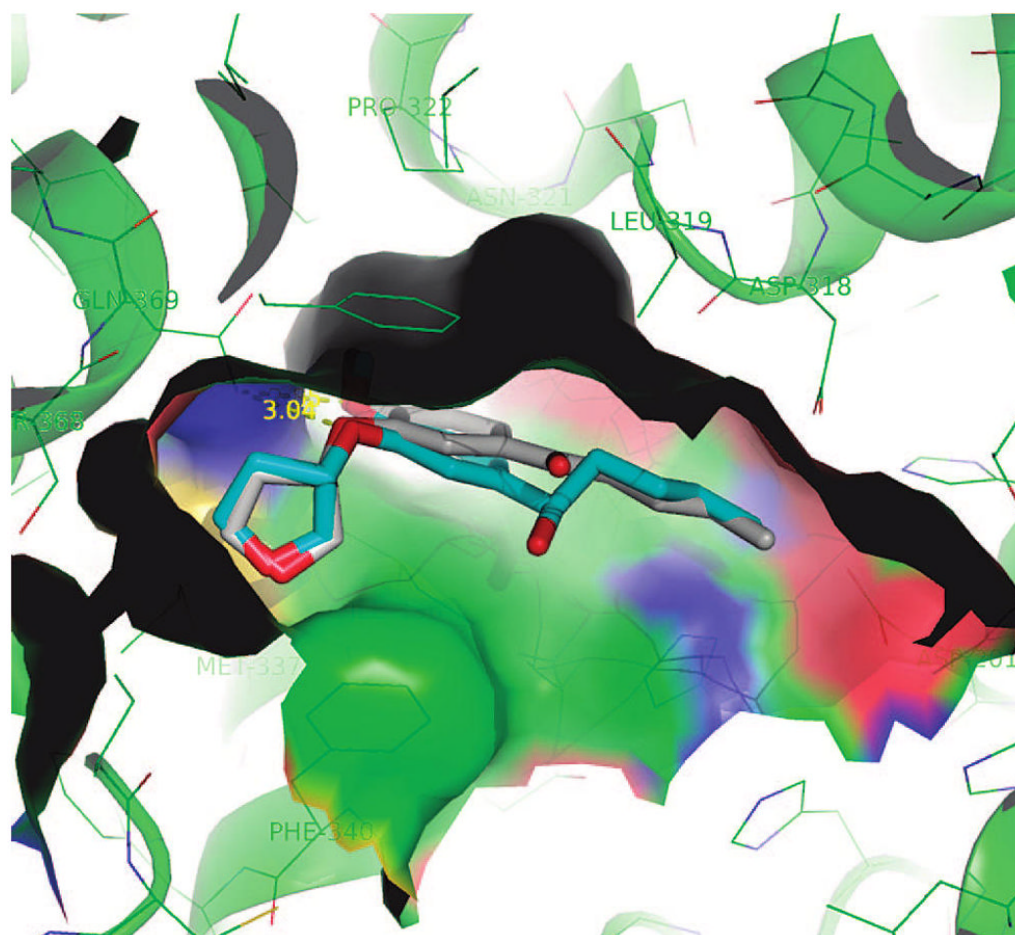


Figure 8. Comparison of sp²-hybridized ketone (blue stick, **5m**) and sp³ alcohol (gray stick, **4l**).

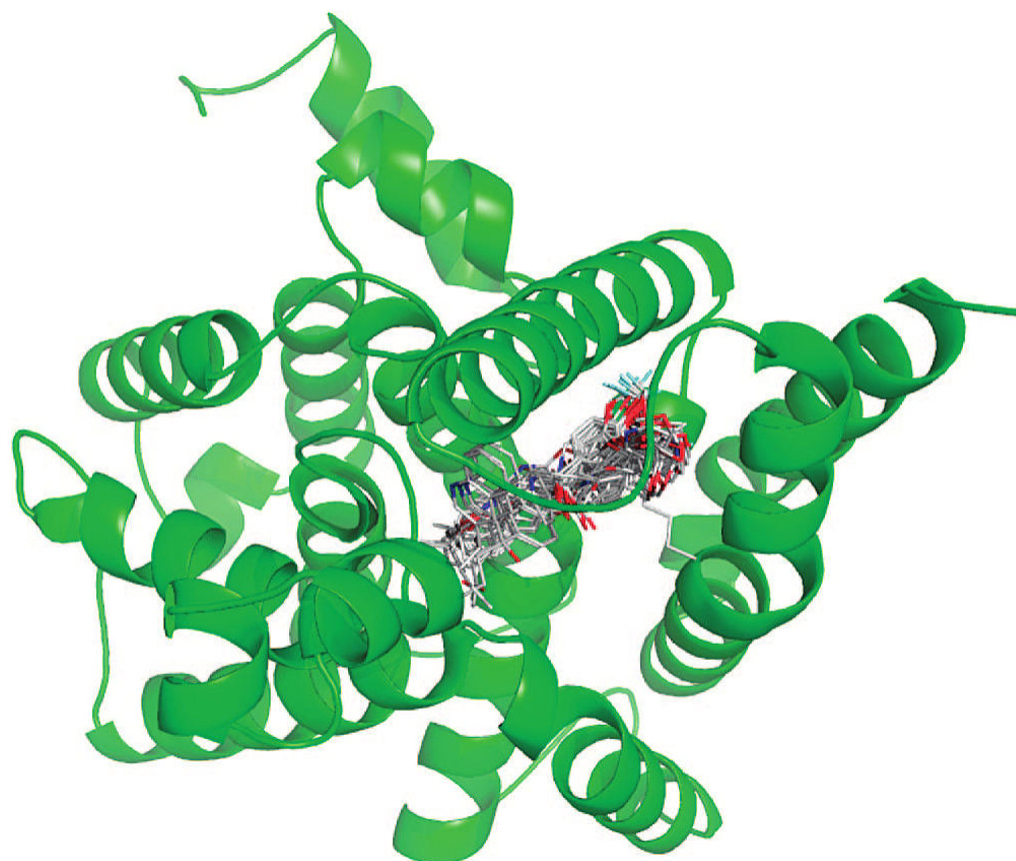


Figure 9.
Docking conformations of synthesized inhibitors in the PDE4D active site.

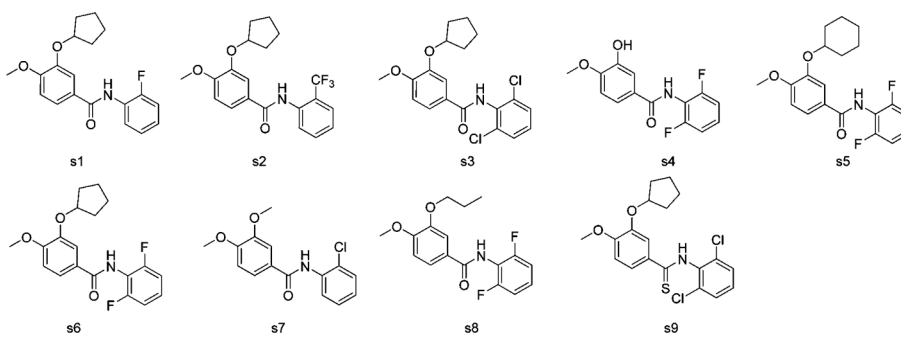


Figure 10.
Chemical structures for test set validation.

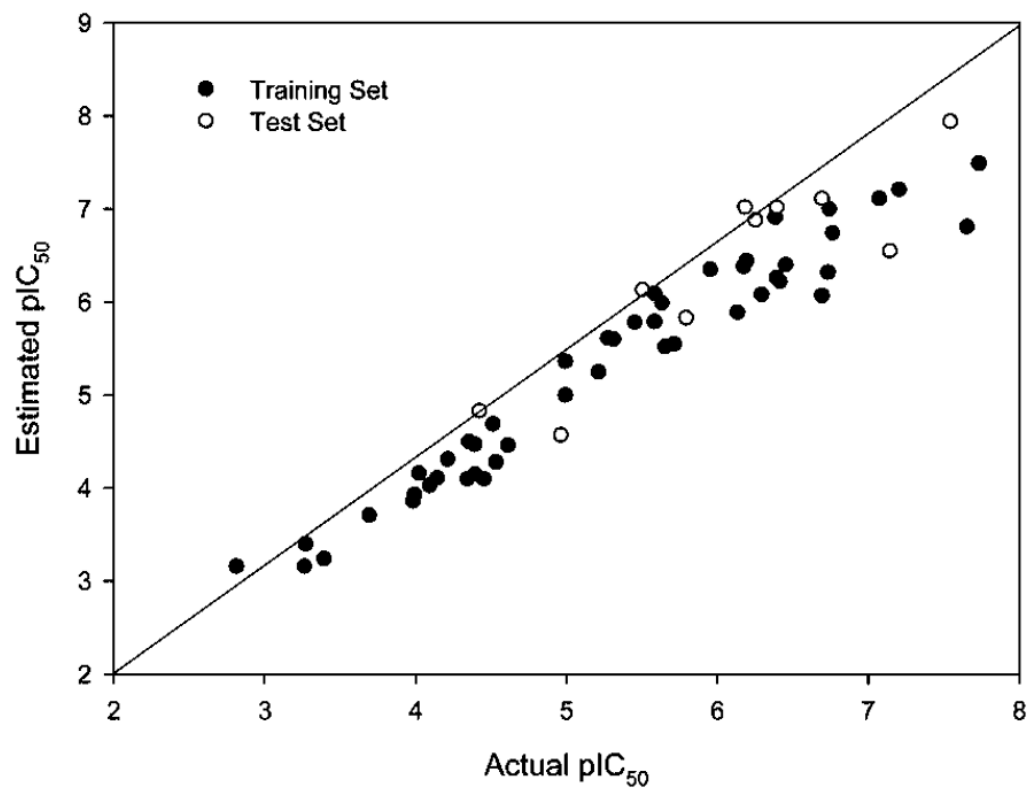


Figure 11. Actual versus predicted pIC_{50} for CoMSIA 3D-QSAR model.

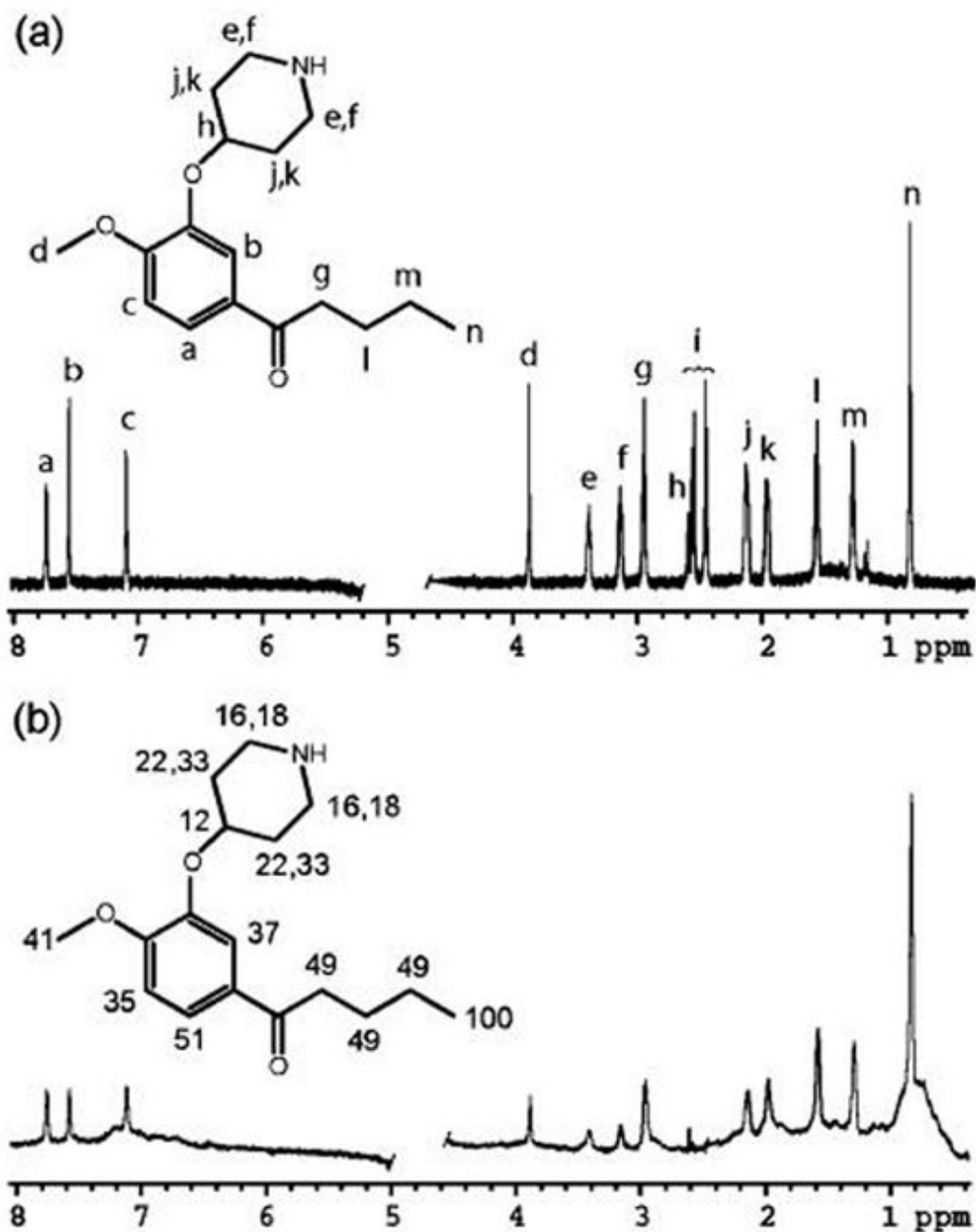


Figure 12.

(a) Reference 1D ¹H NMR spectrum of 400 μM **5i** with assignments indicated by letters on the chemical structure. The peak for the proton in the 4-position of the piperidiny group (labeled “h” on the chemical structure) is buried under the water peak. Peak “i” was not assigned and is believed to be a contaminant. (b) STD spectrum of 800 μM **5i** with 10 μM PDE4D2 using a 50 Hz Gaussian saturation pulse train of 250 ms centered at 0.5 ppm. The protein background was not subtracted or suppressed. The normalized STD percentages calculated from the STD and reference spectra of **5i** are superimposed on the chemical structure. Both spectra were collected using a Varian INOVA 800 MHz NMR instrument equipped with a cryogenic probe. The water peaks in the center of the spectra were removed for clarity.

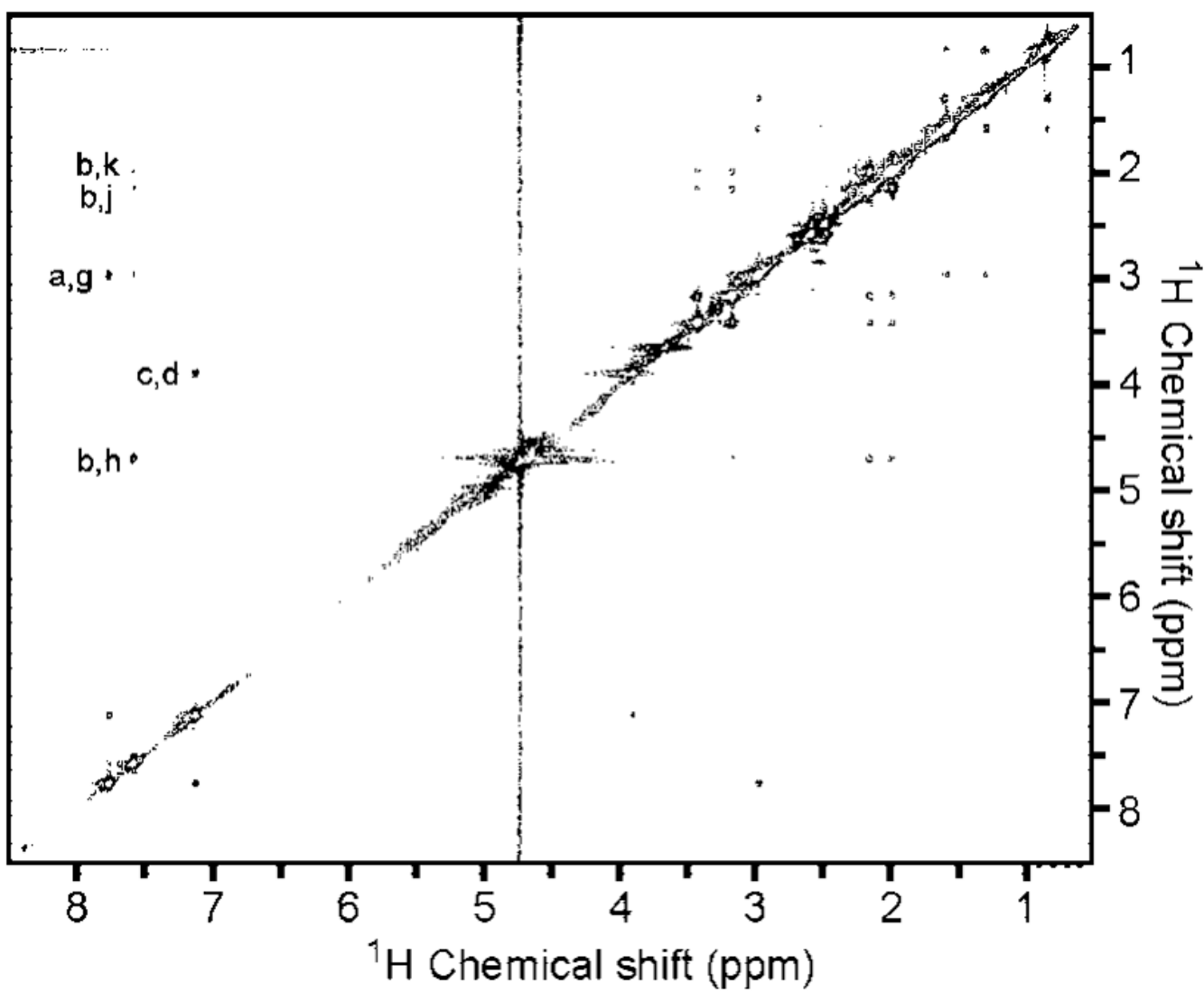
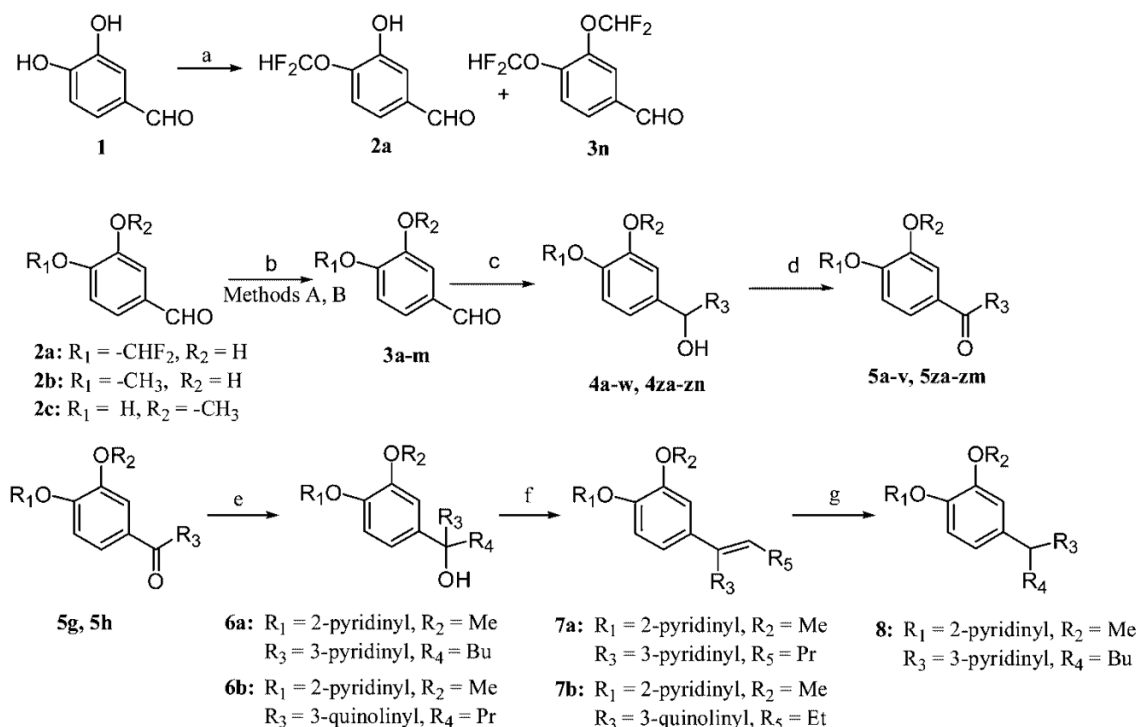
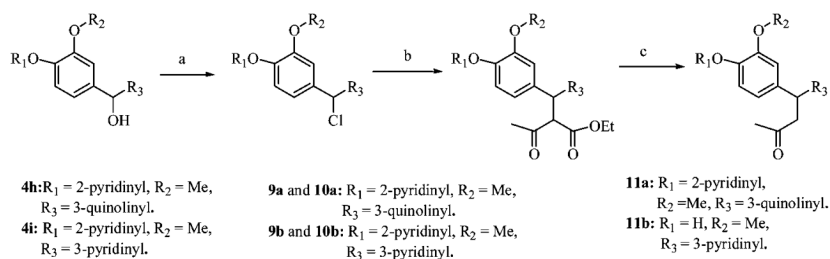


Figure 13. The 2D NOESY spectrum of 800 μM **5i** and 10 μM PDE4D2 with a 50 ms mixing time is shown. The cross peaks have positive intensities (i.e., negative NOEs), which indicate that **5i** binds PDE4D2.

**Scheme 1.**

^a (a) CClF₂COOMe, Cs₂CO₃, DMF; (b) (i) method A, R₁OH or R₂OH, PPh₃, *t*-BuO₂CN=NCO₂-*t*-Bu, THF; method B, R₁Br or R₂Br, CsCO₃, DMF; (c) R₃Li or R₃MgBr, THF, -78 °C; (d) PCC, DCM; (e) R₄Br, *n*-BuLi, THF, -78 °C; (f) AcOH, H₂SO₄, 80 °C; (g) H₂, Pd/C, room temp.

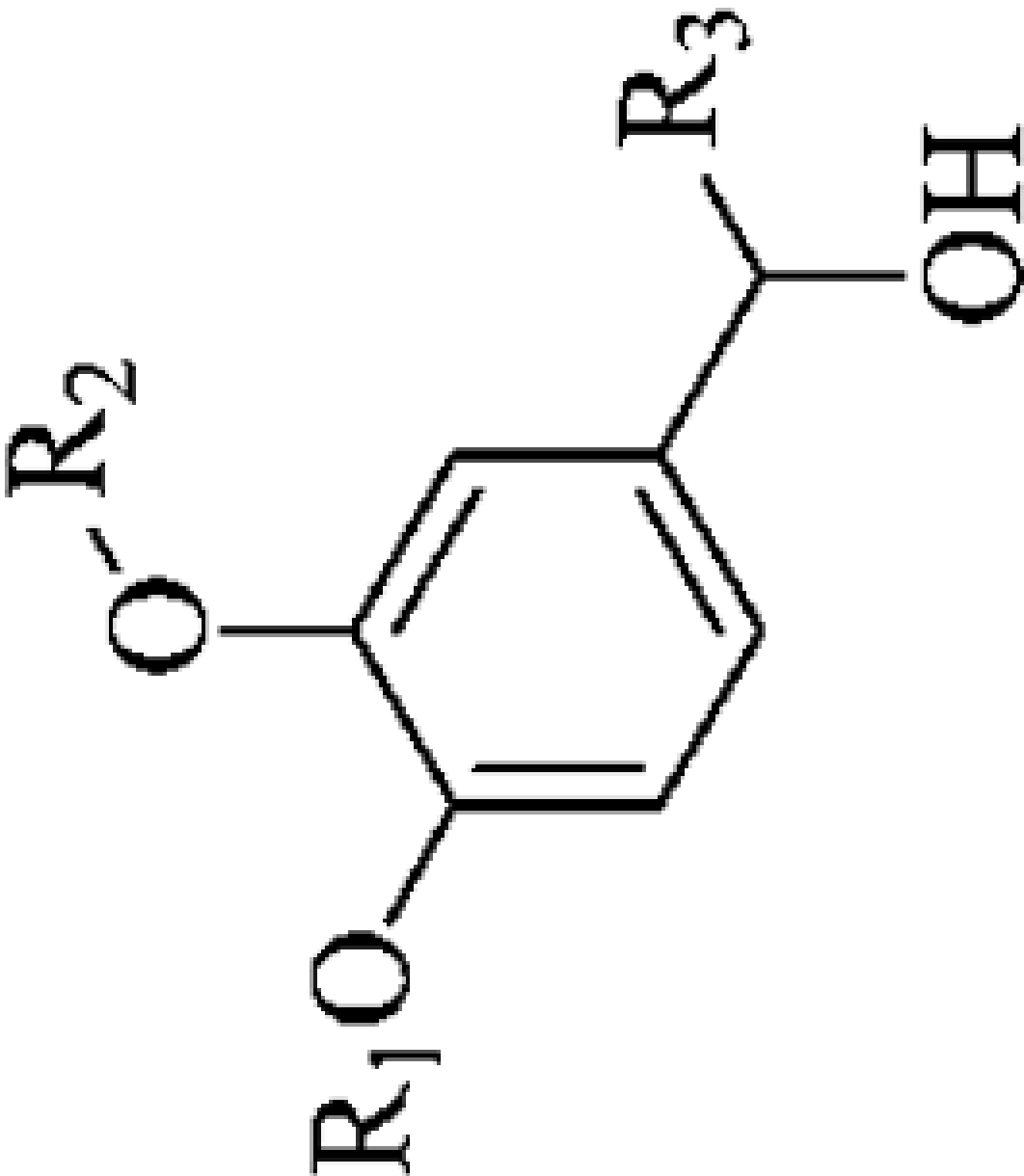
**Scheme 2.**


a

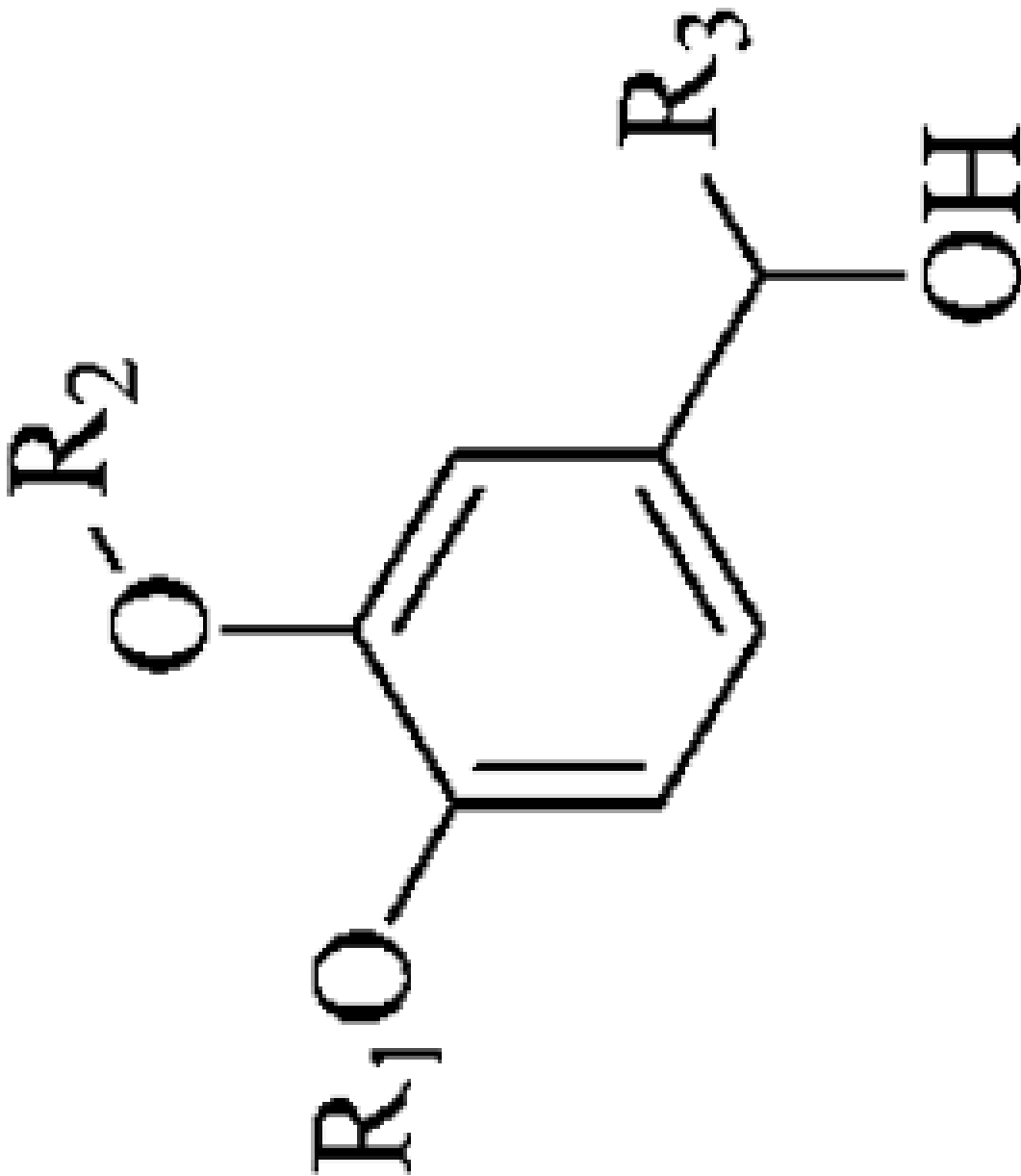
^a(a) SOCl₂, DCM; (b) ethyl acetoacetate, CH₃ONa, THF; (c) LiOH, THF/MeOH/H₂O.


Table 1

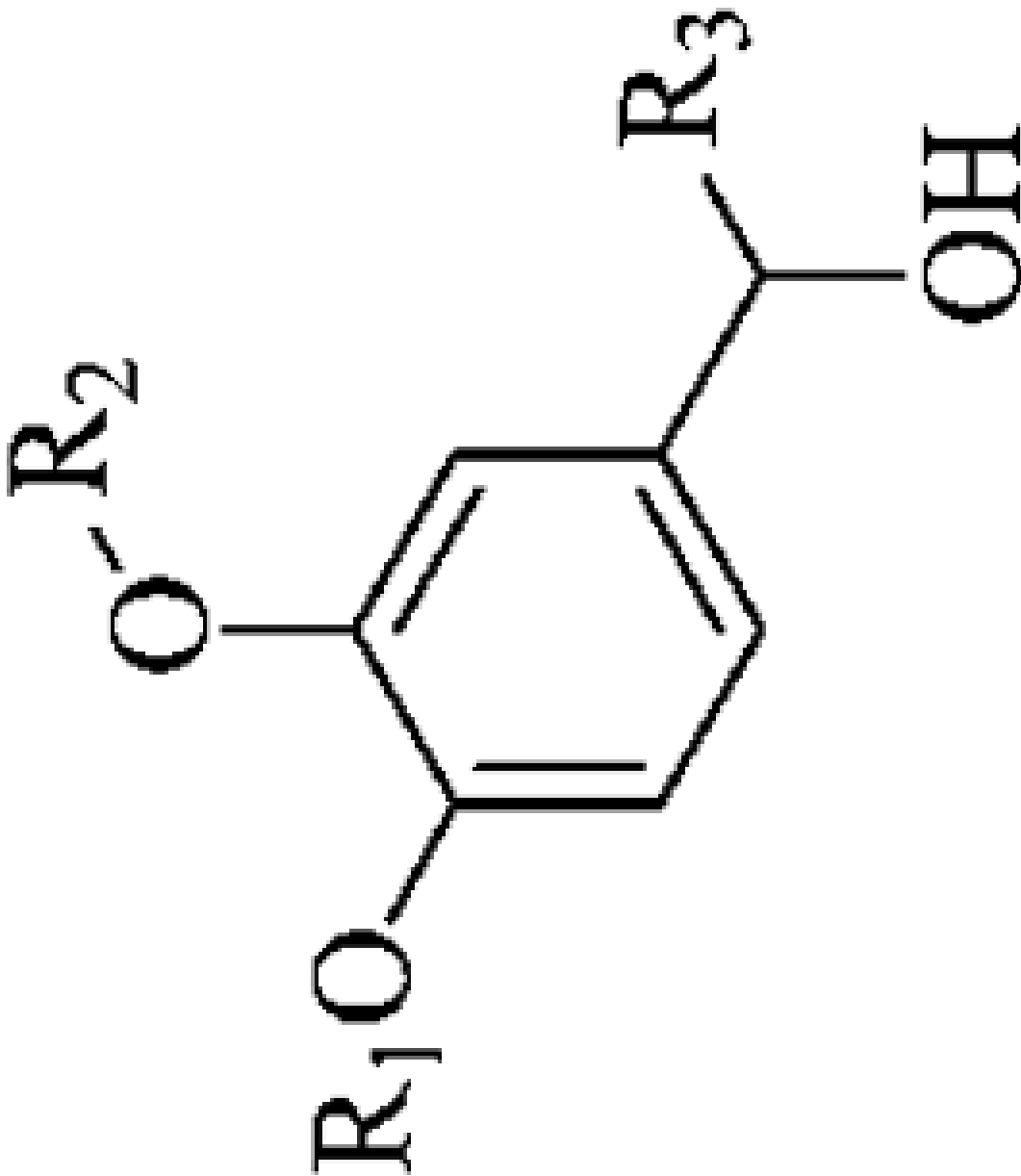
IC₅₀ (μM) Values of Phenyl Alkyl Alcohol PDE4 Inhibitors^a

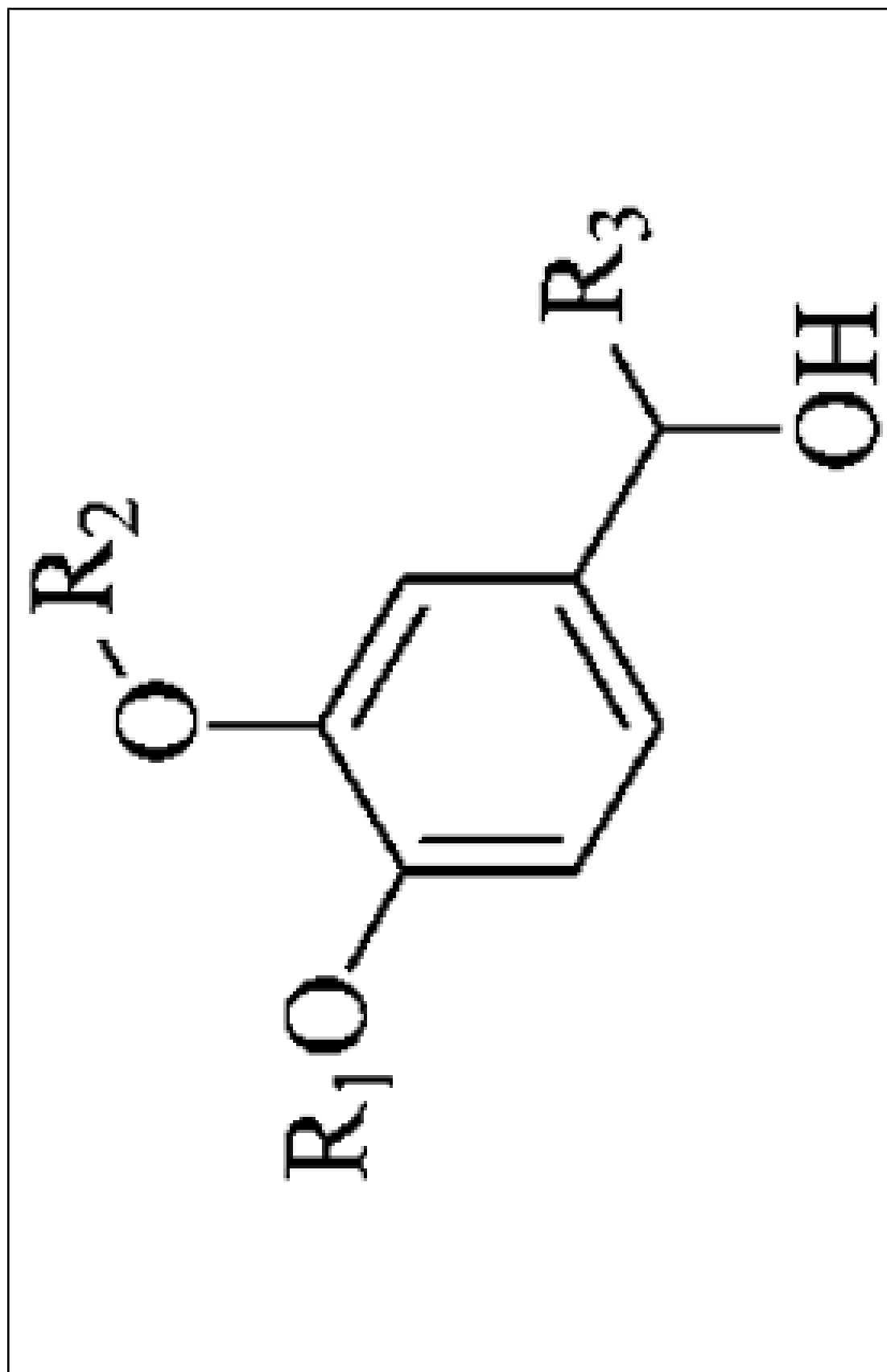
Entry	Compd	R ₁	R ₂	R ₃	IC ₅₀ (μM)
					0.55
	Rolipram				

Entry	Compd	R ₁	R ₂	R ₃	IC ₅₀ (μM)
1	4b		-CH ₃	<i>n</i> -pr	>100

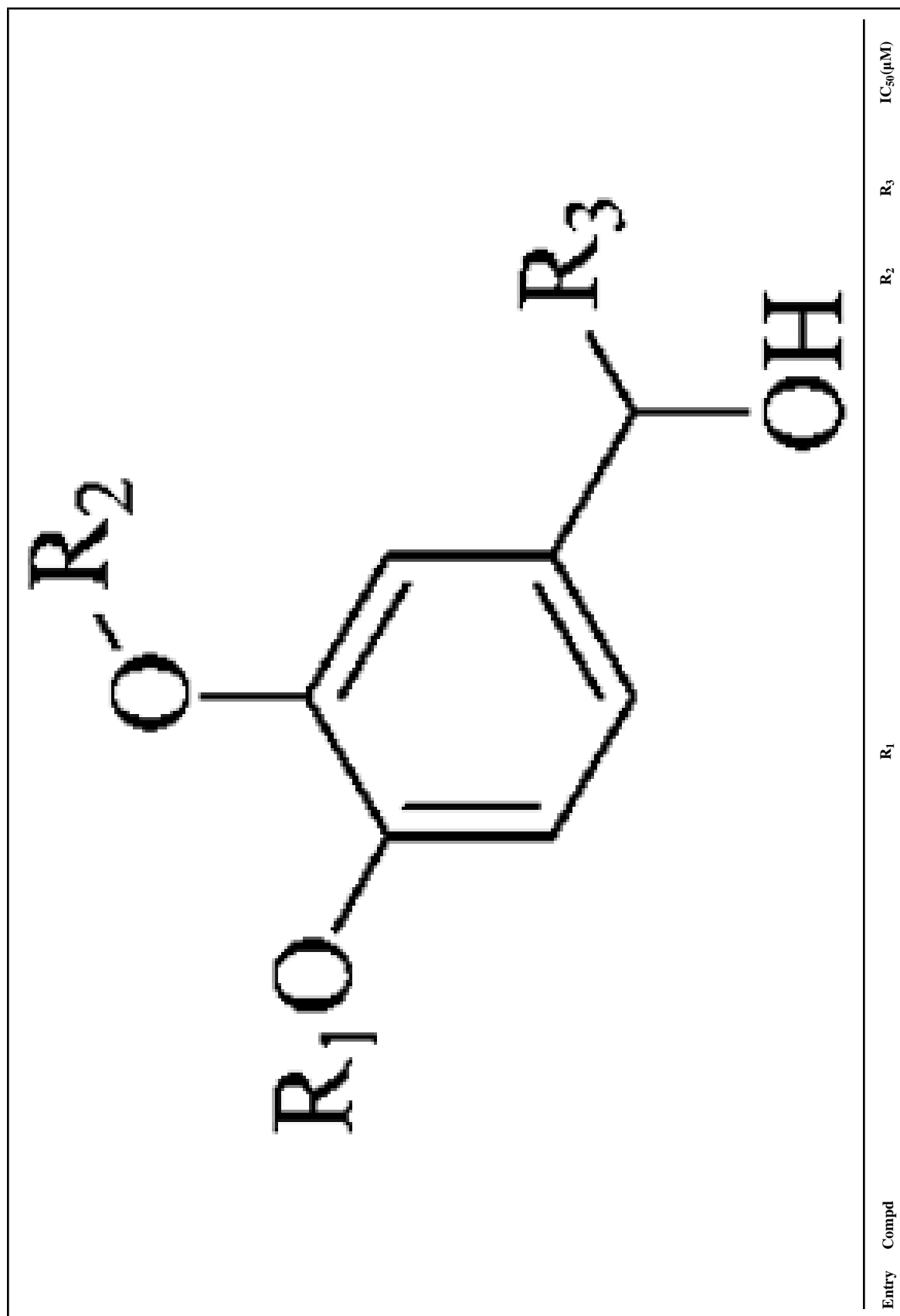


Entry	Compd	R ₁	R ₂	R ₃	IC ₅₀ (μ M)	
2	4c					>100




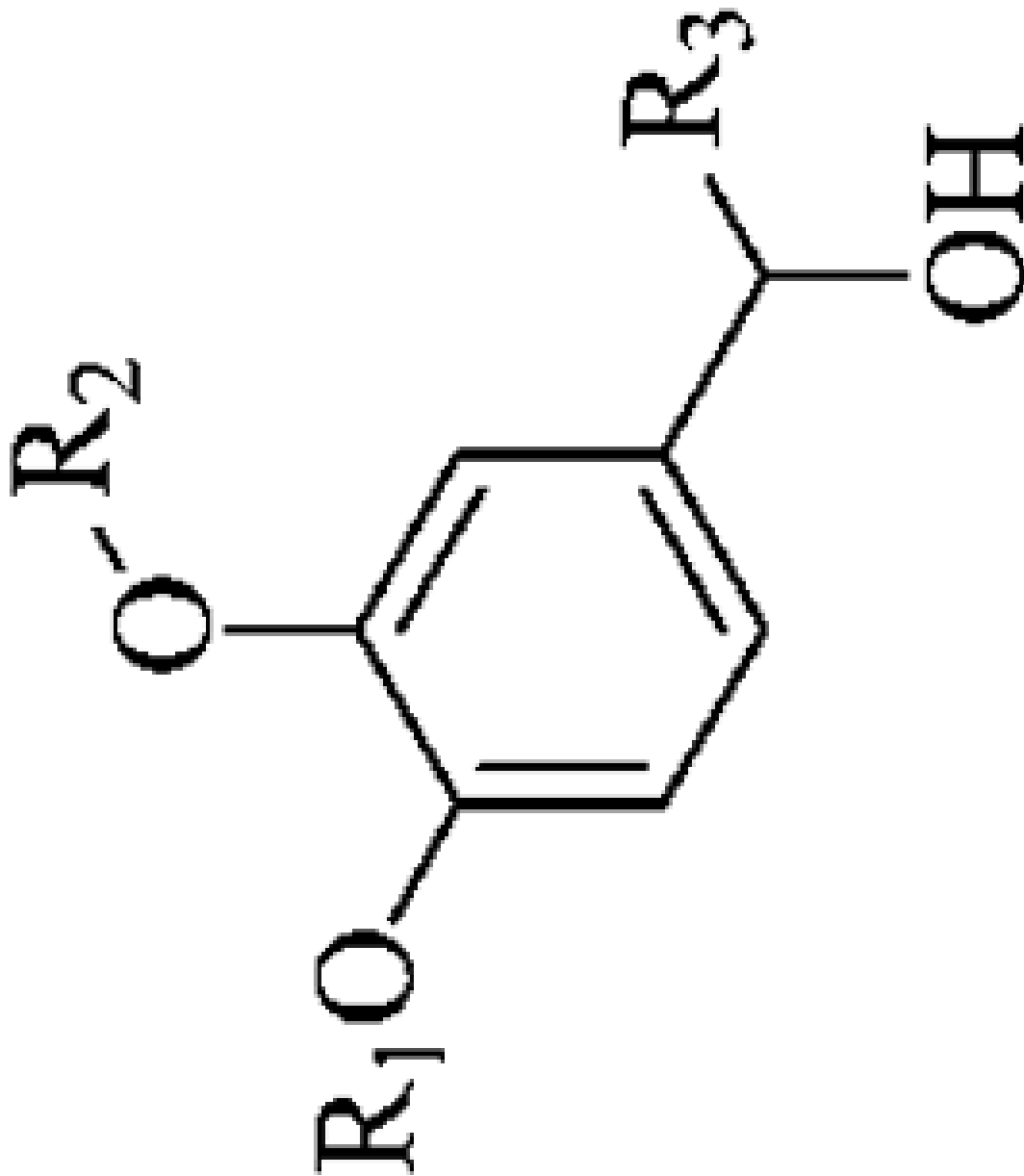


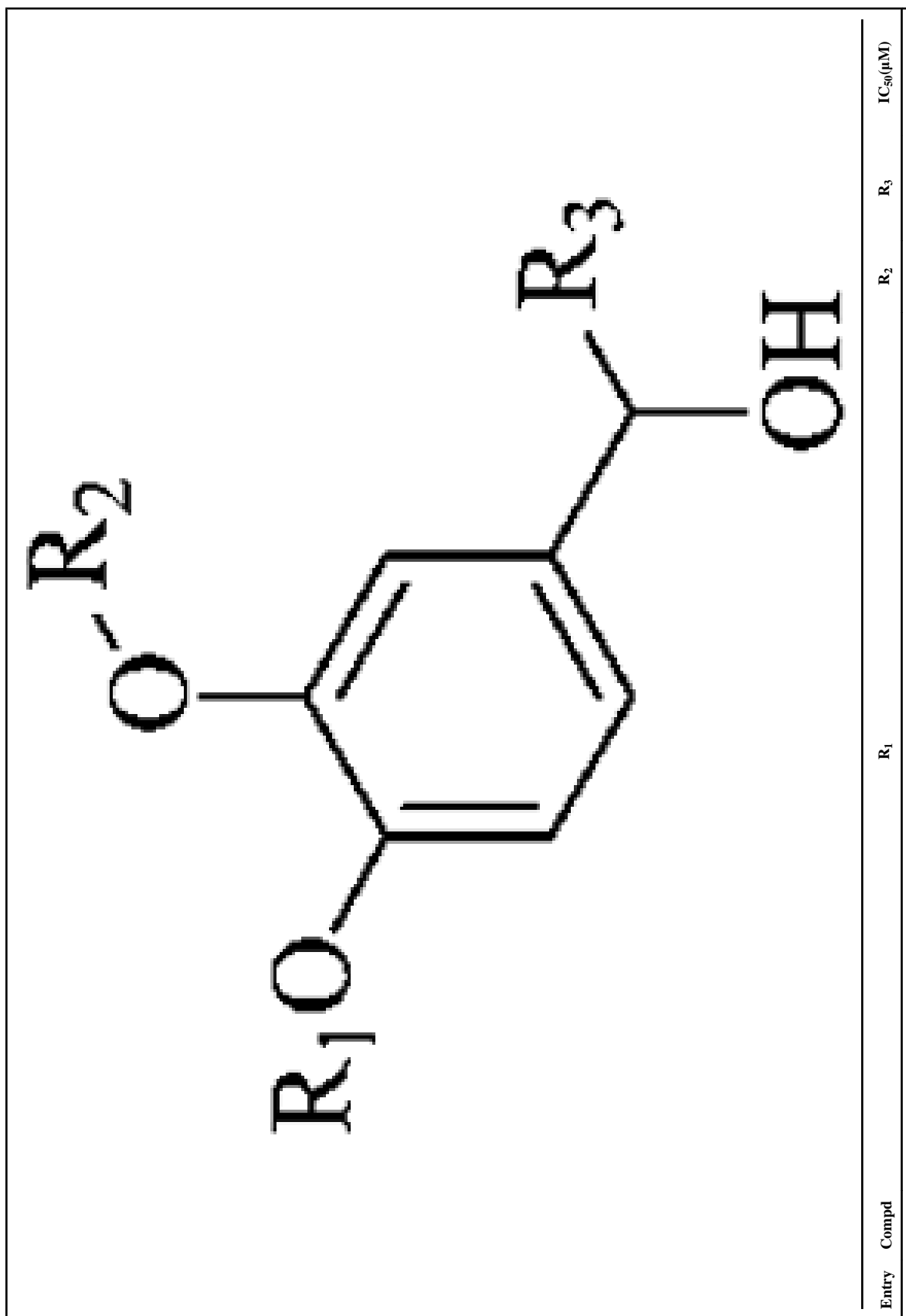
Entry	Compd	R ₁	R ₂	R ₃	IC ₅₀ (μM)
3	4d		-CH ₃	<i>n</i> -pr	>100

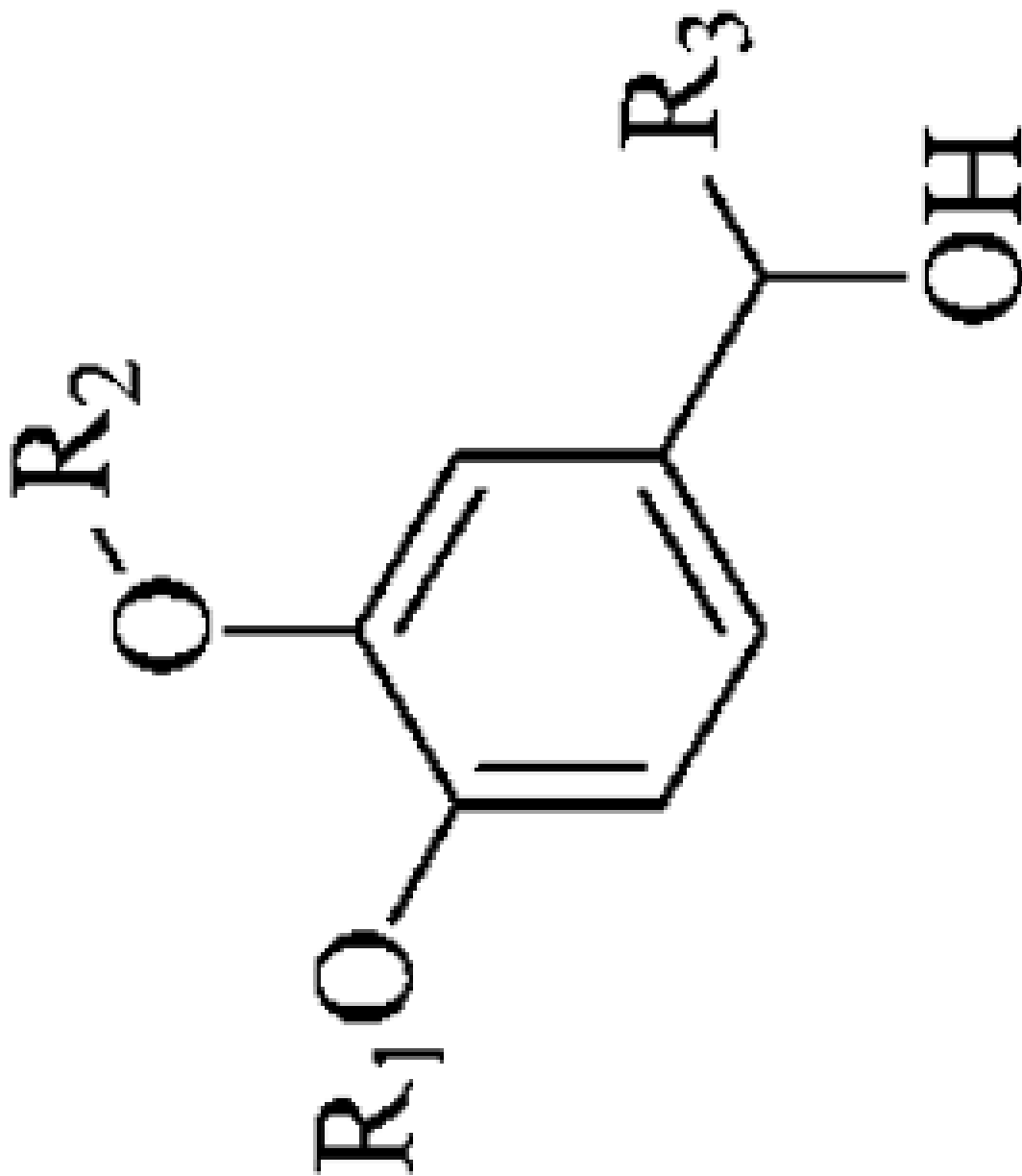


Entry	Compd	R ₁	R ₂	R ₃	IC ₅₀ (μM)
4	4e		-CH ₃	<i>n</i> -Bu	>100

Entry	Compd	R ₁	R ₂	R ₃	IC ₅₀ (μ M)
5	41	-CH ₃		<i>n</i> -Bu	10

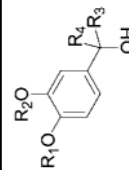


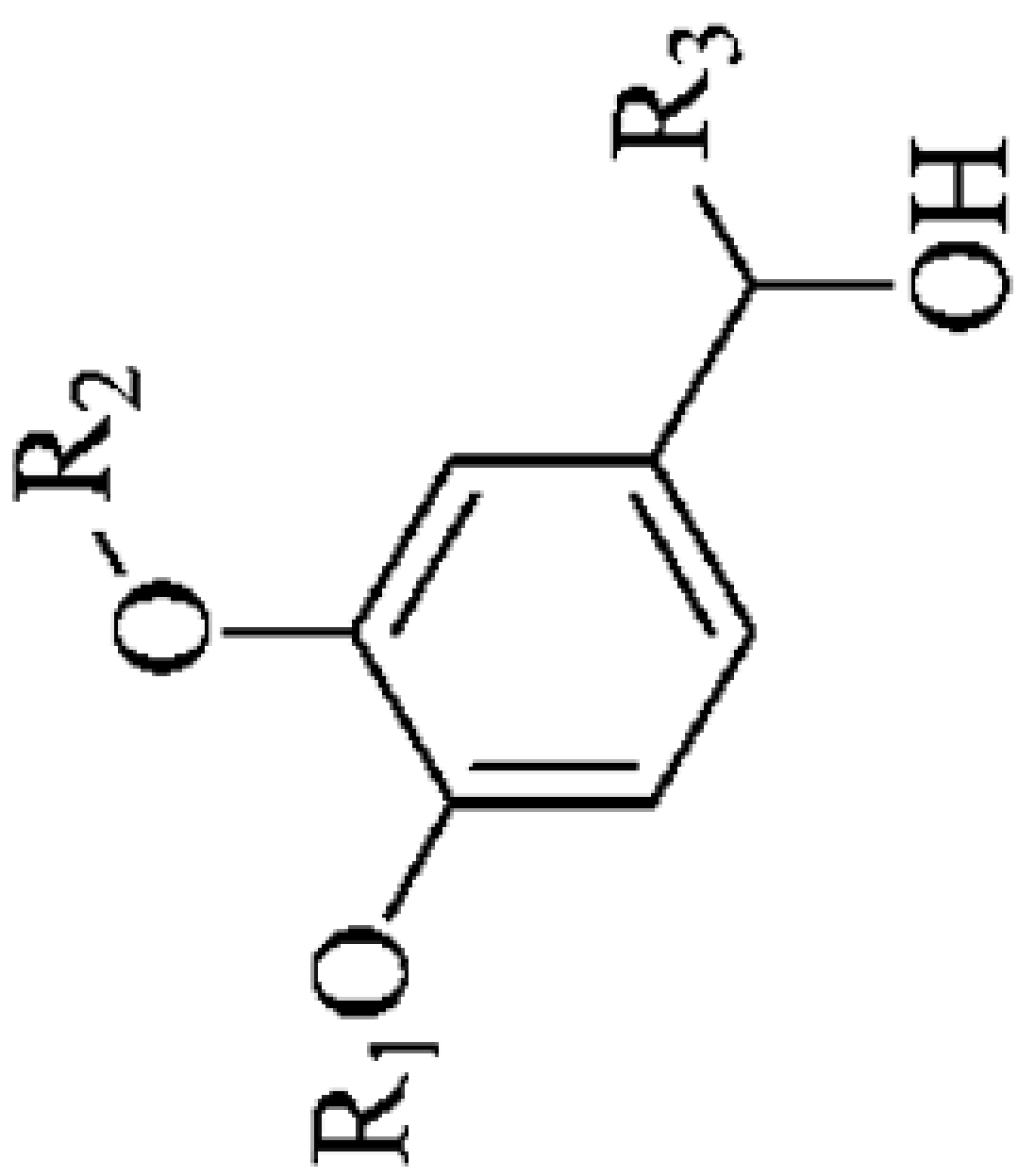




Entry

Compd

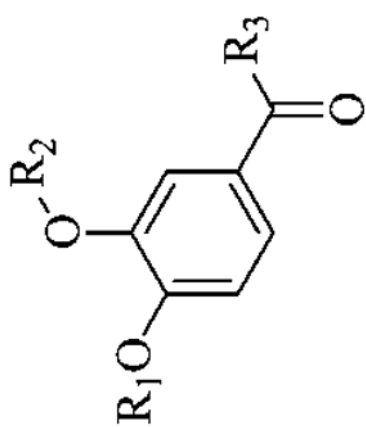
 R_1 R_2 R_3 $IC_{50}(\mu M)$ 

		R₂	R₃	IC₅₀(μM)
Entry	Compd	R₁	R₃	R₄
Entry	Compd	R ₁	R ₃	IC ₅₀ (μM)

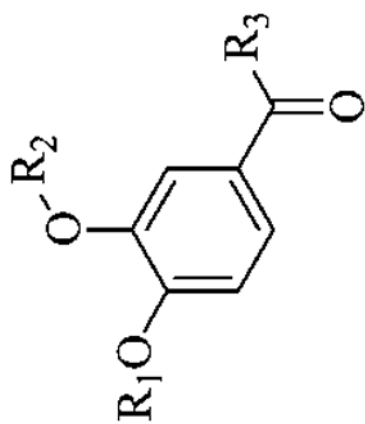
		R₁	R₂	R₃	IC₅₀(μM)
		2-py	-CH ₃	3-quinolinyl	<i>n</i> -pr
Entry	Compd				
6	6b				

^aAll potent compounds (low nanomolar) were assayed 2–3 times, and their inhibition results are expressed with standard deviations. All other results were from single runs.

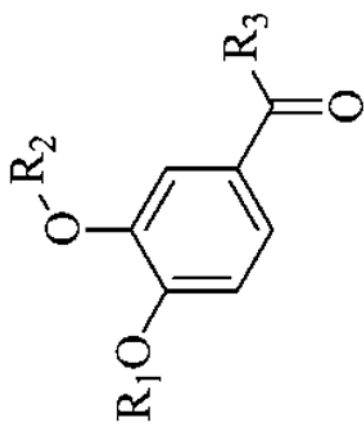
Table 2



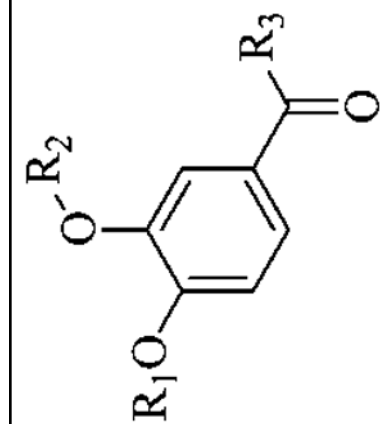
R ₂	R ₃	IC ₅₀ (μ M)
-CH ₃	<i>n</i> -Bu	93




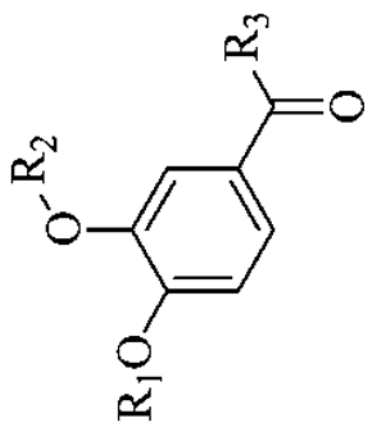
R ₂	R ₃	IC ₅₀ (μ M)
-CH ₃	<i>n</i> -Pr	29



R ₂	R ₃	IC ₅₀ (μ M)
-CH ₃	<i>n</i> -Pr	60

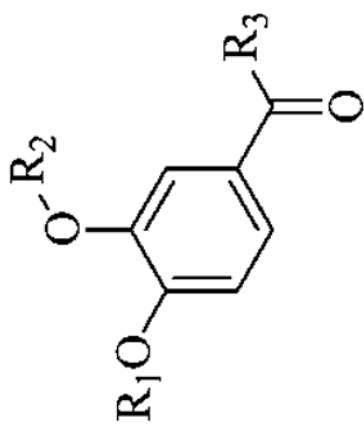


R ₂	R ₃	IC ₅₀ (μM)
-CH ₃	<i>n</i> -Bu	71
-CH ₃	<i>n</i> -Pr	24
-CH ₃	<i>n</i> -Bu	100
	3-quinolinyl	45

R₂R₃
n-PrIC₅₀(μ M)

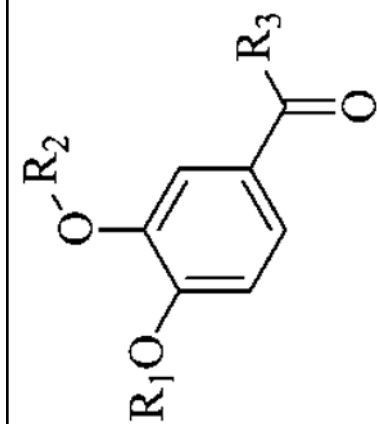
3.5




 R_2 R_3 $n\text{-Bu}$ $IC_{50}(\mu M)$

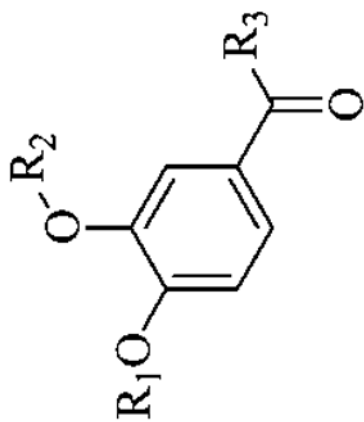
0.72

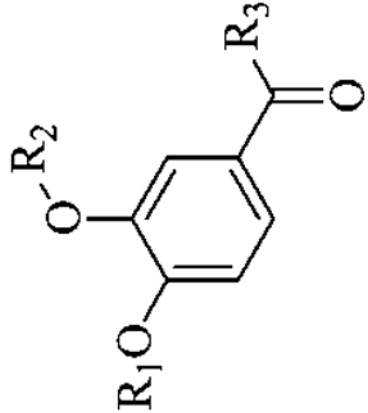
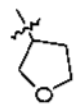
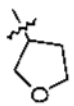
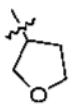



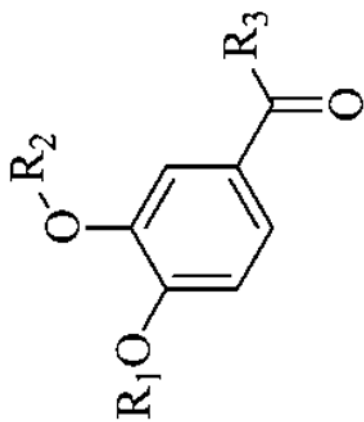


R_2	R_3	$IC_{50}(\mu M)$
	$n\text{-Bu}$	0.22

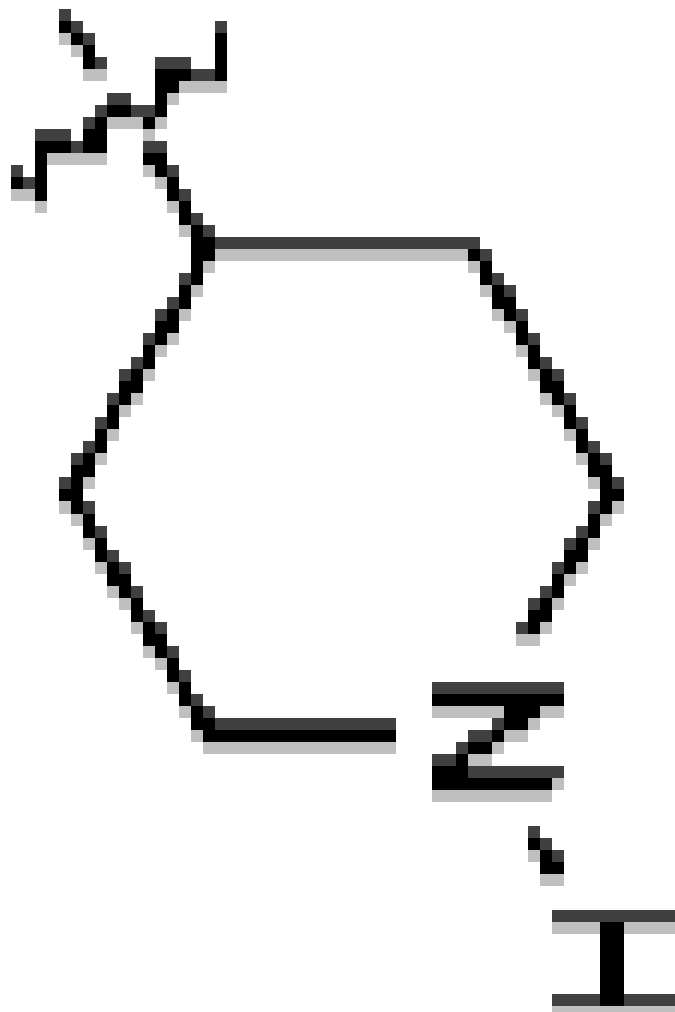


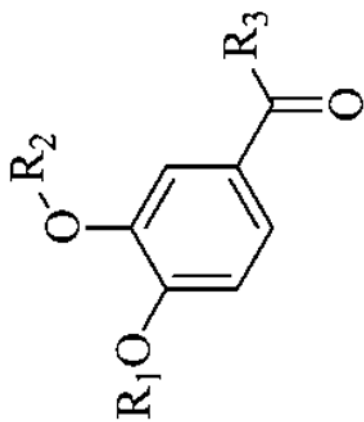
 R_2 $IC_{50}(\mu M)$ R_3 0.43 ± 0.11 *n*-Pr

	R_2	R_3	$IC_{50}(\mu M)$
		-(CH ₂) ₃ Ph	2.3
		-(CH ₂) ₂ Cyclohexyl	1.9
		-(CH ₂) ₂ Ph	2.6
		-CH ₂ cyclohexyl	2.6

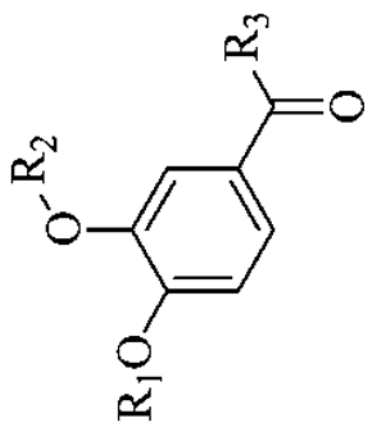
 R_2 R_3 n -Bu $IC_{50}(\mu M)$

> 100



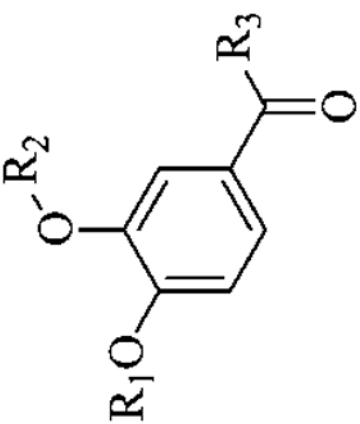
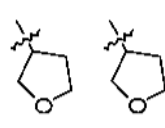


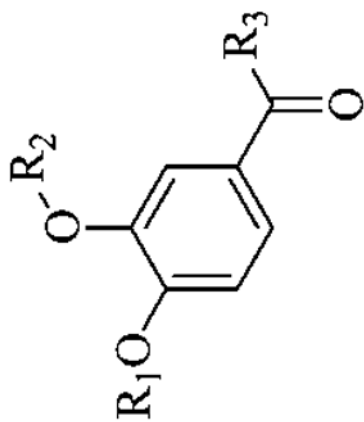
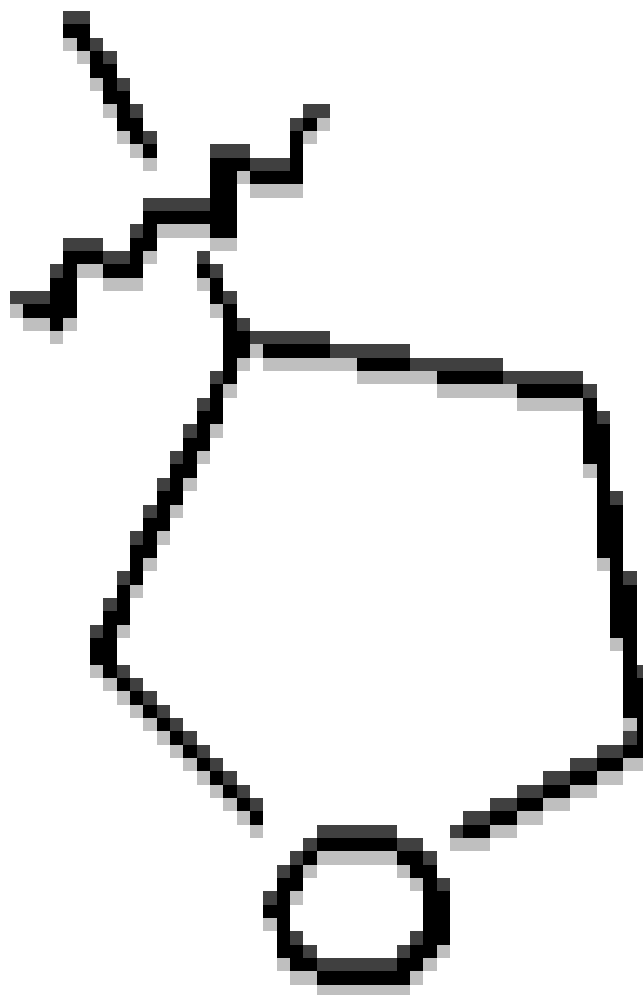
R_2	R_3	$IC_{50}(\mu M)$
2-py	<i>n</i> -Pr	40

 R_2 R_3 n -Pr $IC_{50}(\mu M)$

0.35

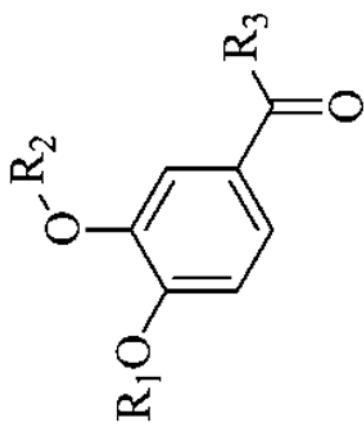
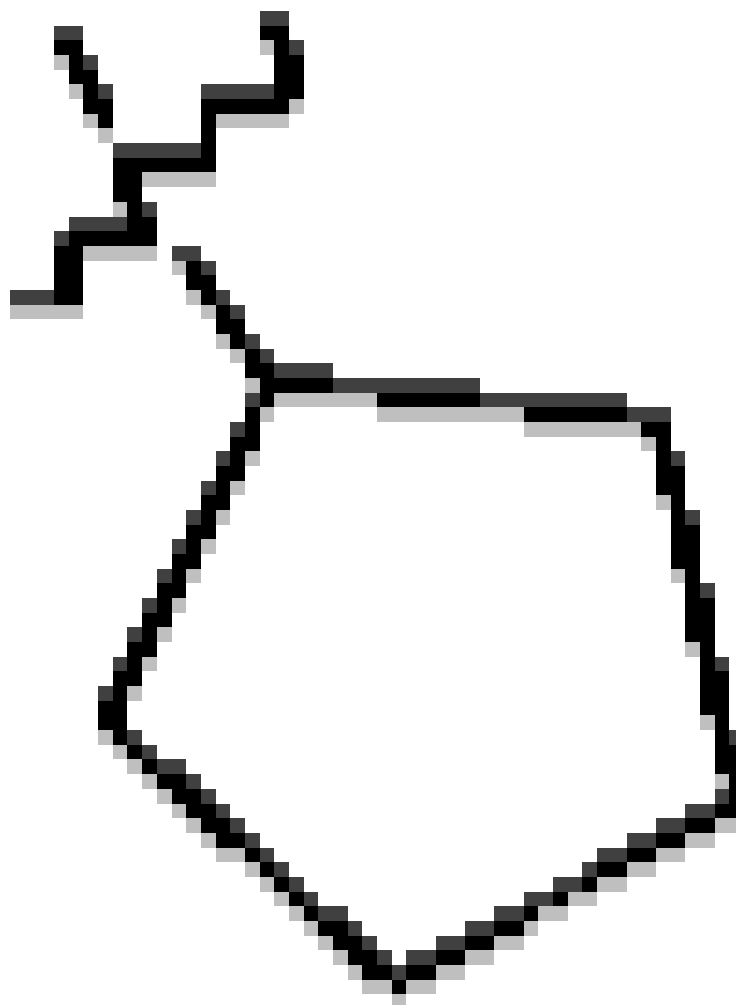


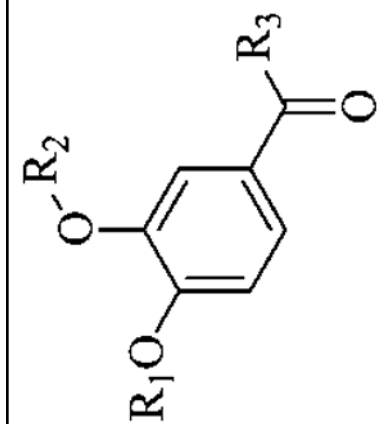
	R_2	R_3	$IC_{50}(\mu M)$
	<i>i</i> -Bu	0.026 ± 0.004	
		-(CH ₂) ₂ cyclohexyl	1.1

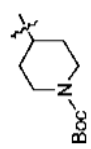
 R_2 R_3 $-(CH_2)_2Ph$ $IC_{50}(\mu M)$ 0.18 ± 0.03 

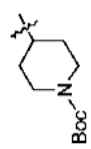
The chemical structure shows a benzene ring with three substituents: R_1O at the 3-position, R_2O at the 4-position, and $R_3C(=O)$ at the 1-position.

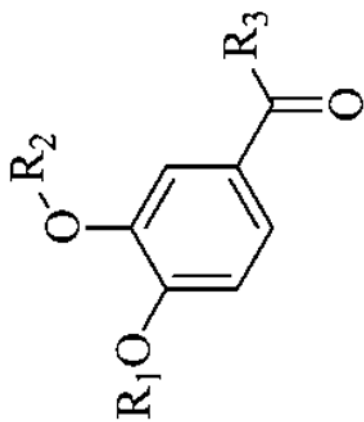
R_2	R_3	$IC_{50}(\mu M)$
	<i>n</i> -Bu	0.061 ± 0.006
-CHF ₂	-(CH ₂) ₂ Ph	0.82 ± 0.03
-CHF ₂	-CH ₂ -cyclohexyl	5.2
-CHF ₂	-(CH ₂) ₃ Ph	44

 R_2 R_3 *i*-Bu $IC_{50}(\mu M)$ 0.028 ± 0.001 

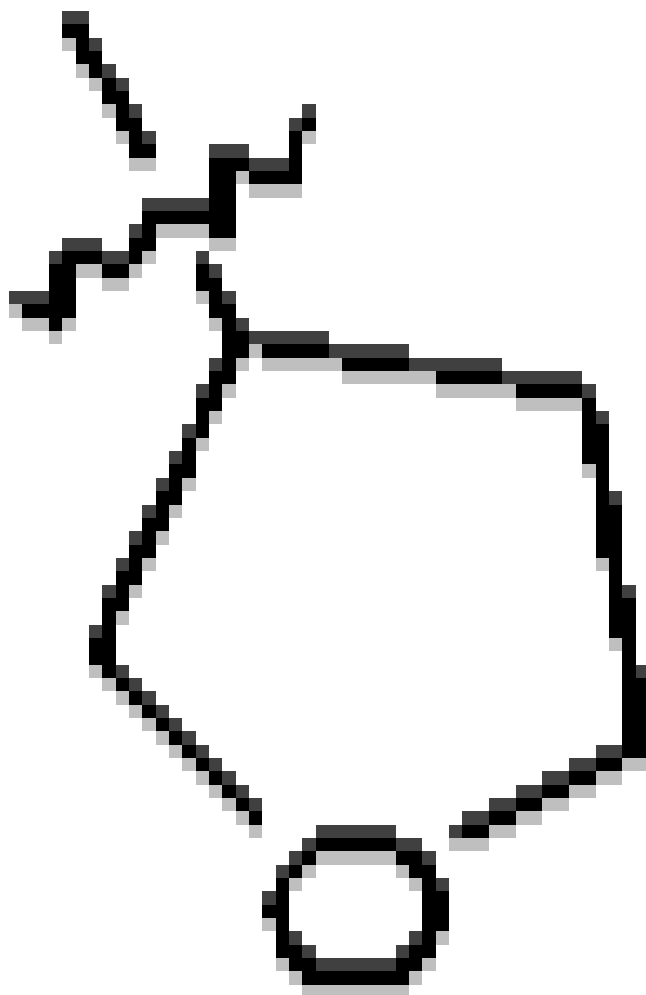


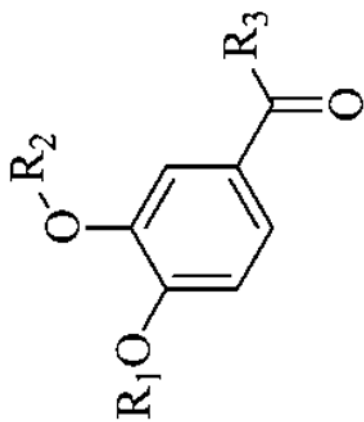
R ₂	R ₃	IC ₅₀ (μ M)
	<i>n</i> -Bu	2.2



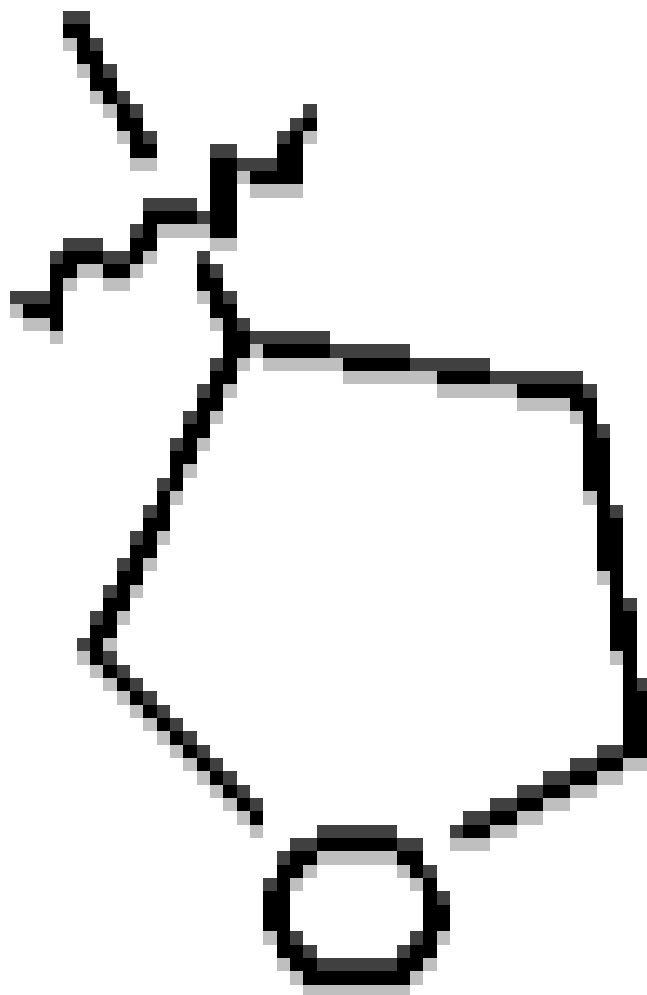
 R_2 R_3 $IC_{50}(\mu M)$ $-CH_2$ -cyclohexyl

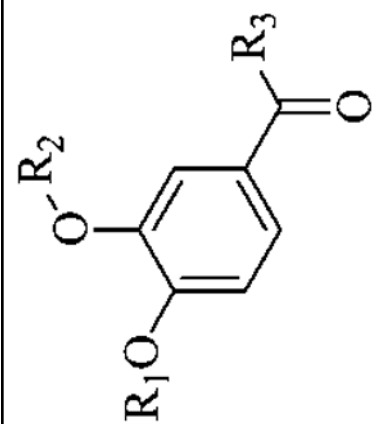

0.667

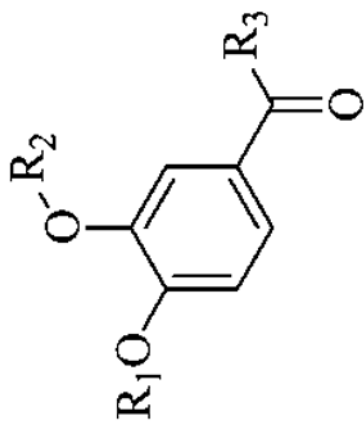
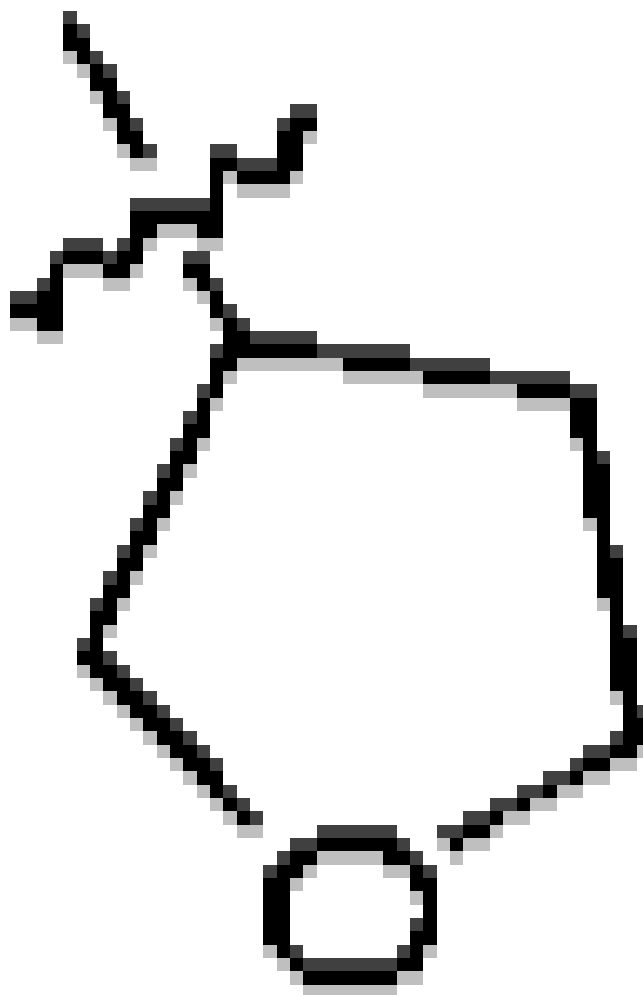


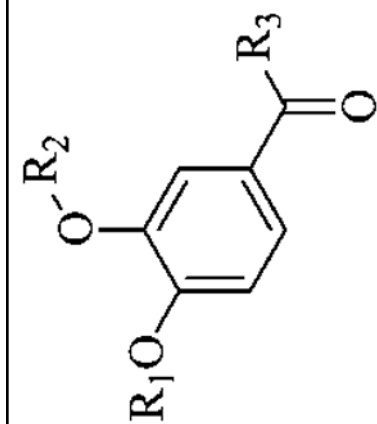
 R_2 R_3 $-(CH_2)_3Ph$ $IC_{50}(\mu M)$

0.636



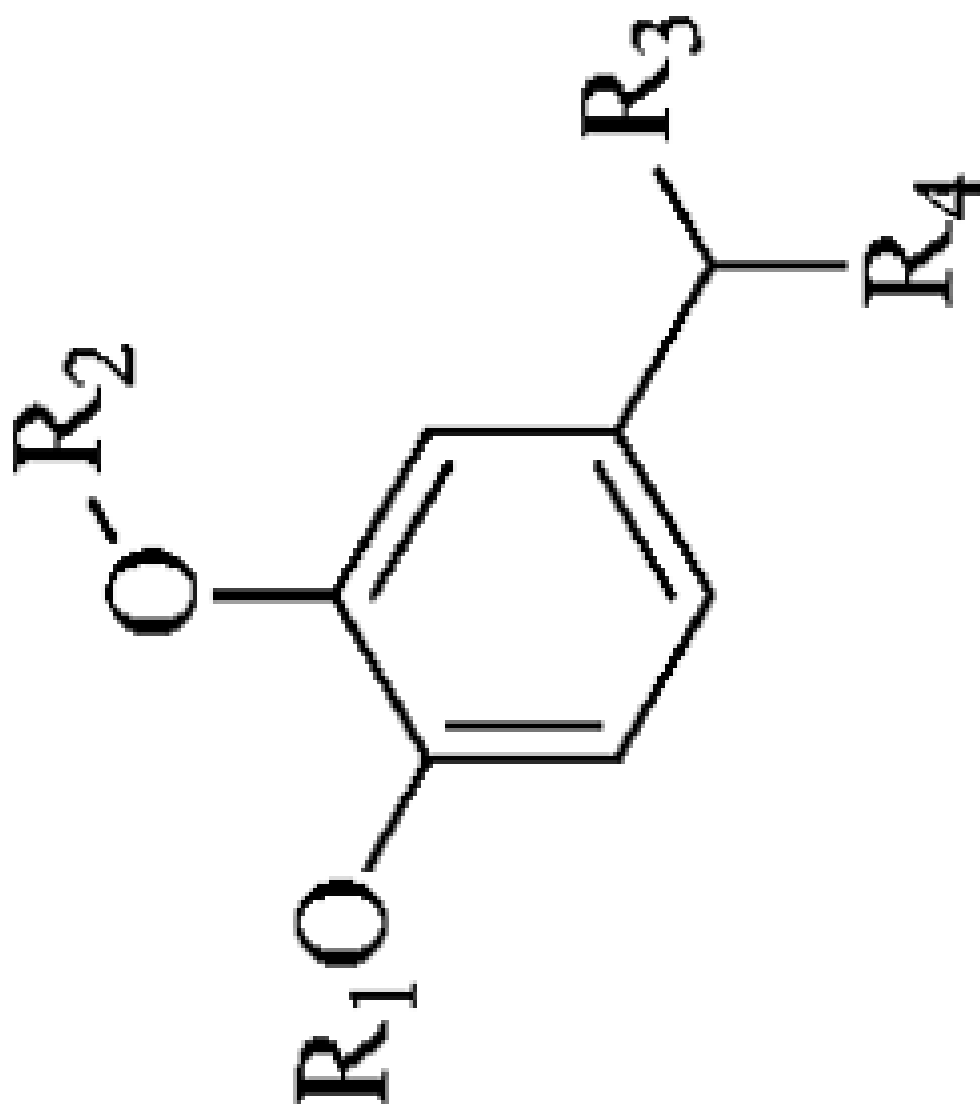
	R₂	R₃	IC₅₀(μM)
		<i>t</i> -Bu	0.41

 R_2 R_3 *i*-Bu $IC_{50}(\mu M)$ 0.19 ± 0.02 

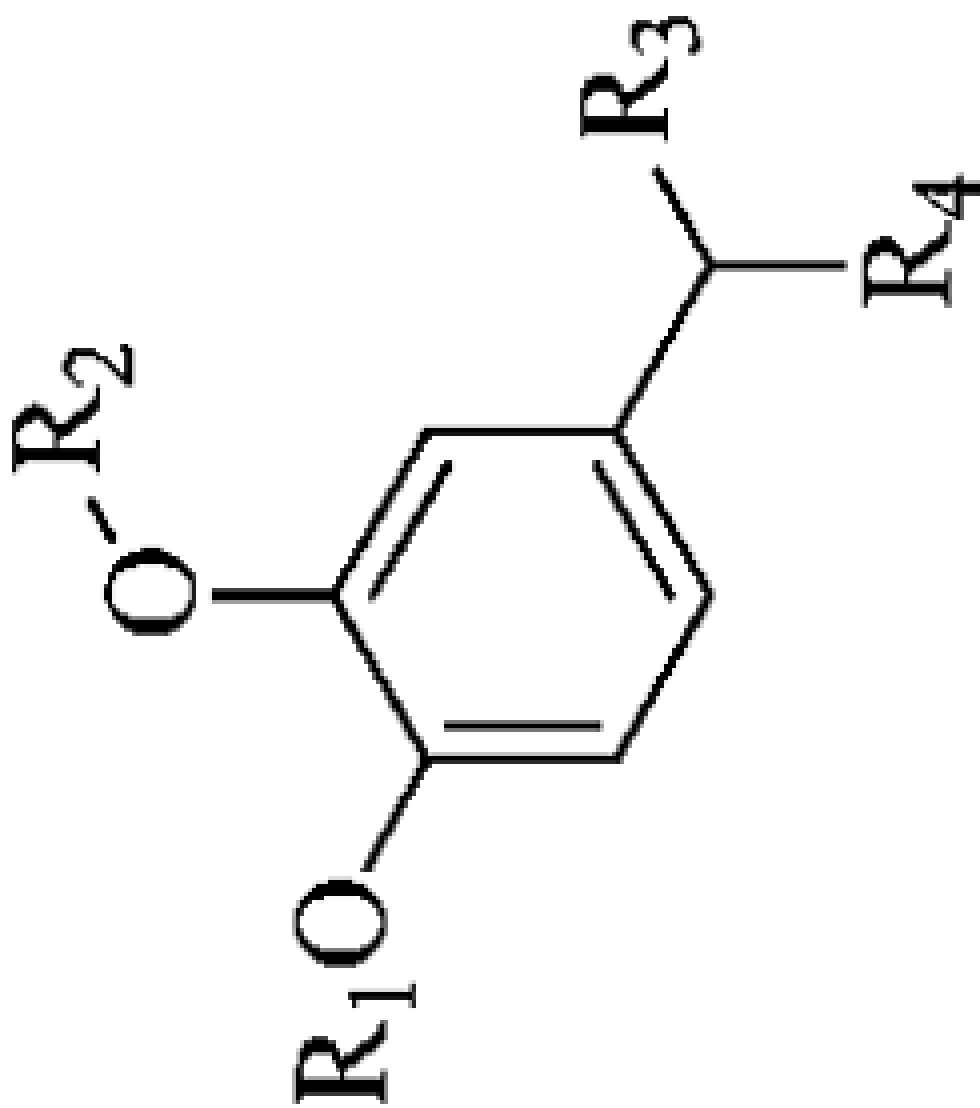
 R_2  R_3 *i*-Pen $\text{IC}_{50}(\mu\text{M})$ 0.38 ± 0.05

nd deviations. All other results were from single runs.

Table 3

IC₅₀ (μ M) Values of Phenylalkyl PDE4 Inhibitors^a

entry	compd	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (μ M)
39	11a	2-py	-CH ₃	3-quinolinyl	-CH ₂ COCH ₃	6



entry	compd	R_1	R_2	R_3	R_4	IC ₅₀ (μ M)
40	11b	H	-CH ₃	3-py	-CH ₂ COCH ₃	80
41	8	2-py	-CH ₃	3-py	<i>n</i> -Bu	10

^a All potent compounds (low nanomolar) were assayed 2–3 times, and their inhibition results are expressed with standard deviations. All other results were from single runs.

Table 4

IC₅₀ Values (μ M) of Selected Lead Inhibitors on Various PDEs

compd	PDE4D2	PDE7A1	PDE9A2	PDE2A3	PDE5A1
5v	0.026	>50	>50	>50	>50
11a	6	>50	>50	>50	>50
5k	3.5	>50	>50	>50	>50
6b	6	17	>50	>50	40

Table 5Actual pIC₅₀, Estimated pIC₅₀, and Residual Values of Molecules Used for CoMSIA

compd	actual pIC ₅₀	estimated pIC ₅₀	residual
4b	2.82	3.15	-0.33
4c	3.27	3.15	0.12
4d	3.28	3.39	-0.11
4e	3.40	3.23	0.17
5i	3.99	3.85	0.14
5f	4.00	3.92	0.08
5a	4.03	4.15	-0.12
11b	4.10	4.02	0.08
5d	4.15	4.10	0.05
5c	4.22	4.30	-0.08
5j	4.35	4.09	0.26
5zj	4.36	4.49	0.13
5zi	4.40	4.14	0.26
5b	4.54	4.27	0.27
5e	4.62	4.45	0.17
4l	5.00	5.35	-0.35
8	5.00	4.99	0.01
11a	5.22	5.24	-0.02
5zm	5.28	5.60	-0.32
5k	5.46	5.77	-0.31
5q	5.59	6.08	-0.49
5r	5.59	5.78	-0.19
5o	5.64	5.98	-0.34
5zg	5.66	5.51	0.11
5p	5.72	5.54	0.18
5zb	5.96	6.34	-0.38
5l	6.14	5.88	0.26
5zc	6.18	6.37	-0.19
5ze	6.20	6.43	-0.23
5zl	6.30	6.07	0.23
5s	6.39	6.90	-0.01
5n	6.40	6.25	0.15
5u	6.42	6.21	0.21
5zh	6.46	6.39	0.07
5m	6.7	6.06	0.14
5zd	6.74	6.31	0.43
5t	6.75	6.99	-0.24
5za	7.21	7.20	0.01
5zf	7.66	6.80	-0.25

compd	actual pIC₅₀	estimated pIC₅₀	residual
5v	7.74	7.48	0.26
Test set rolipram	6.26	6.87	-0.61
s1	4.97	4.56	0.41
s2	5.51	6.12	-0.61
s3	7.55	7.93	-0.38
s4	4.43	4.82	-0.39
s5	6.40	7.01	-0.61
s6	7.15	6.54	0.61
s7	6.19	7.01	-0.82
s8	5.80	5.82	-0.02
s9	6.70	7.1	-0.40