SUPPLEMENTARY INFORMATION

Zebrafish behavioral profiling identifies ligands, targets, and neurons related to sedation and paradoxical excitation

AUTHORS

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SUPPLEMENTARY NOTE 1

$GABA_AR$ ligands produce paradoxical excitation in zebrafish. Compounds with weak phenoscores ($x < 0.51$) included one $GABA_B$ receptor agonist, one PAM of δ-subunit containing $GABA_A$Rs, two non-BZ-site ligands, three structurally-related $GABA_AR$ orthosteric agonists, and seven BZ-site $GABA_AR$ PAMs (**Fig. 1g**). For these compounds, the average phenoscores were significantly less than the positive controls ($P < 0.01$, Kolmogorov-Smirnov test, **Supplementary Figure 20a**), suggesting that these compounds did not phenocopy etomidate. For example, the highest scoring ocinaplon treatment produced a behavioral profile that resembled the negative controls (**Supplementary Figure 2**). These data suggest that a variety of GABAergic compounds do not cause sedation and paradoxical excitation.

Compounds with intermediate phenoscores ($0.51 < x < 0.71$) included several types of $GABA_AR$ PAMs including thiopental, carboetomidate, THDOC, alfaxalone, diazepam, and valerenic acid. The highest scoring profiles produced by some of these compounds (including alfaxalone, thiopental, and tracazolate) showed a barely detectable statistically significant difference compared to the positive controls ($0.01 < P < 0.05$). The highest scoring profiles of animals treated with diazepam, and valerenic acid were significantly lower than the positive controls ($P < 0.01$, Kolmogorov-Smirnov test, **Supplementary Figure 20a**), however these treatments produced interesting intermediate effects on sedation and paradoxical excitation. For example, although the highest-scoring diazepam treatment was strongly sedating in most assays, it produced eASRs that were relatively weak and inconsistent (**Supplementary Figure 2**). These data suggest that a variety of PAMs have intermediate effects on sedation and paradoxical excitation.

Interestingly, although DOC and progesterone are neurosteroid precursors, they were among the most potent compounds tested (**Fig. 1g)**. As expected, progesterone's etomidate-like phenotype was suppressed by dutasteride, a 5-alpha-reductase inhibitor that blocks the metabolic conversion of progesterone to allopregnanolone, suggesting that these compounds were converted to active neurosteroids (**Supplementary Figure 5**).

SUPPLEMENTARY NOTE 2

Target prediction using SEA. We used the Similarity Ensemble Approach (SEA) to predict targets based on 'guilt-by-association' enrichment factor scores (EFs). These EFs were first developed for predicting adverse drug interactions [1], and balance the overall strength of a given target-to-compound-set association by correcting for the frequency that specific targets are predicted over random compounds sets in the screen [2]. Here, we used EFs to predict targets for the compounds that caused eASRs in the zebrafish.

SEA identified 15 compounds with enriched target predictions for mGluRs (**Supplementary Table 9**, **Supplementary Figure 12a**). We chose eight of these compounds to reorder and retest and found that four of them reproducibly caused eASRs *in vivo* (**Supplementary Figure 12b, Supplementary Table 9**). Next, we tested five of these compounds as agonists and antagonists for activity at seven human mGluRs (mGluR1-6 and mGluR8). However, none of the compounds showed strong functional effects against mGluRs *in vitro* (**Supplementary Figure 12c**), suggesting that the

compounds did not act via mGluRs *in vivo*. To further test the mGluR hypothesis, we tried to phenocopy etomidate in dose-response experiments with a panel of structurally-diverse mGluR ligands and ligand combinations (**Supplementary Table 9**). Although MPEP, a mGluR5 antagonist, reproducibly caused eASRs, MPEP-induced eASRs were substantially lower in magnitude than etomidate-induced eASRs, and MPEP-induced eASRs only occurred in a narrow concentration range (**Supplementary Figure 12b, Supplementary Table 9**). Therefore, although MPEP weakly phenocopied etomidate, we found no further evidence that hit compounds targeted mGluRs, as predicted by SEA.

SEA predicted that $GABA_AR$ was a target of four hit compounds (**Supplementary Figure 11**). We tested three of them (5658603, 5142031 and 7145248) and found that one (5658603) potentiated $GABA_AR$ *in vitro* (**Fig. 2f, red arrow)**. Curiously, we noted that SEA failed to predict $GABA_AR$ as a target for most hit compounds that tested positive in the $GABA_AR$ FLIPR assay (**Fig. 2f**), underscoring the value of behavior-based screens for identifying bioactive compounds with poorly annotated chemical structures.

SUPPLEMENTARY NOTE 3

$GABA_AR$ and HTR6 ligands likely converge on a common neural substrate

To determine if HTR6 antagonists activated the same neurons as GABAergic ligands, we took three approaches. First, we looked for overlap between 5HT immunohistochemistry and the eASR substrate neurons (**Supplementary Figure 13f**). Consistent with previous reports, we observed strong 5-HT staining in the telencephalon, pineal gland, hindbrain, and dorsal raphe nuclei [3]. In addition, we observed bilateral 5-HT staining in tracts that converged on the midline of the caudal hindbrain at the same location of the putative eASR substrate neurons in the caudal hindbrain (**Supplementary Figure 13f**). These tracts likely originated from the dorsal raphe, but we could not trace their origin definitively. Second, we visualized HTR6 mRNA expression by RNAscope but could not detect reproducible expression patterns (**Supplementary Figure 14**), suggesting that HTR6 mRNA is not abundantly expressed. Finally, we tested for pharmacological interactions between GABAergic and serotonergic ligands. As expected, pretreatment with the $GABA_AR$ antagonist PTX rescued etomidate-treated animals, increasing and decreasing the magnitude of the violet light and eASR phenotypes, respectively (**Supplementary Figure 15a)**. Similarly, PTX rescued the GABAergic compound 5658603, and partially rescued compounds 701338, and 5942595, albeit to a lesser extent than etomidate (**Supplementary Figure 15a)**. PTX also partially rescued the behavioral phenotypes of several HTR6 antagonists including BGC 20-761, 6029941, 6028165, 6030006, and 6013263 (**Supplementary Figure 15b**). By contrast, EMDT oxalate, a HTR6 agonist, did not suppress eASRs caused by HTR6 antagonists (**Supplementary Figure 15c**), suggesting that the effects of HTR6 antagonists are not easily reversed. Together, these data suggest that $GABA_AR$ agonists and HTR6 antagonists likely cause eASR behaviors via different targets that converge on a common neural substrate in the zebrafish hindbrain.

SUPPLEMENTARY DISCUSSION

Although etomidate and propofol are human anesthetics, the hit compounds identified in this study

may not be useful as human anesthetics. One reason, is that the primary screen in zebrafish did not include behavioral correlates key anesthetic effects including analgesia and amnesia. Furthermore, only a minority of the hit compounds suppressed the TrpA1-induced pain-related assay (**Fig. 6b**), suggesting that many of the compounds may not cause the analgesic effects associated with human anesthesia. Another reason is hat paradoxical excitation is an unwanted side effect of anesthetic drugs. Even if the hit compounds translated to mammals (causing both sedation and paradoxical excitation), additional studies would be necessary to determine if the paradoxical excitation phenotype could be overcome at higher concentrations or via medicinal chemistry. For example, the 21 analogs of compound 7013338 showed variable efficacies (**Fig. 6e**), suggesting that it may be possible to use medicinal chemistry to increase or decrease eASR activity. These shifts likely correspond specific effects on one or more molecular targets that would need to be identified with more sensitive functional assays, such as electrophysiological experiments, of recombinantly expressed receptor subtypes. Future studies may seek to identify different ligands that sedate zebrafish without causing eASRs, or eASRs may be used as a counter screen for other potential anesthetic lead compounds. Presumably, such compounds would work through different mechanisms than etomidate, propofol, and the other compounds identified in this study, and would further improve our understanding of GABAergic signaling, anesthesia, and paradoxical excitation.

SUPPLEMENTARY METHODS

Behavioral assays for pERK. Animals were treated with DMSO or drug for one hour then exposed to a low-volume acoustic stimulus every 10 seconds for 10 minutes. Optovin-treated animals were stimulated with violet light for one second every 10 seconds for 10 minutes. Videos were recorded to measure response to the stimulus and quantified by motion index (MI). Animals were immediately fixed in 4% PFA in PBS.

High speed imaging. Digital video was recorded at 500-1000 frames per second using an Integrated Design Tools NX5-S1 digital camera. Assay duration was 500-1000 ms. Low amplitude tap stimuli was delivered as described above. Videos and still images were assembled using Fiji (imageJ) and Photoshop (Adobe).

RNAscope. Zebrafish (6 dpf) were fixed using 10% normal buffered formaldehyde overnight at 4˚C, dehydrated in 100% methanol and stored at -20˚C until the assay was performed. Fluorescent in situ hybridization was performed using the RNAScope kit (Advanced Cell Diagnostics)[4] with the following modifications: target retrieval was performed using 150 mM Tris pH 9.5 for 15 minutes at 70˚C, washes were performed using 0.2x SSCT (0.01% Tween-20, 3mM NaCl, 0.3mM TriNa-citrate, pH7), samples were stored overnight after probe hybridization and 2x 5 minute washes in 5x SSC (75 mM NaCl, 7.5 mM TriNa-citrate, pH7) at room temperature before amplification and detection steps were performed the following day.

Viability. Animals were scored manually to determine viability after anesthetic treatments. 100 animals were scored per condition at 10 minutes, 1 hour and 5 hours post treatment. Strong heart rate was observed under a dissecting scope (Leica M-80) for our viability score.

Structural Clustering. Structural clustering was performed on the top 125 hit compounds using the rdkit function FingerprintMols package written for python. Tanimoto similarity function was used with a

threshold of 0.25 to define clusters and visualized using the scipy hierarchy dendrogram function.

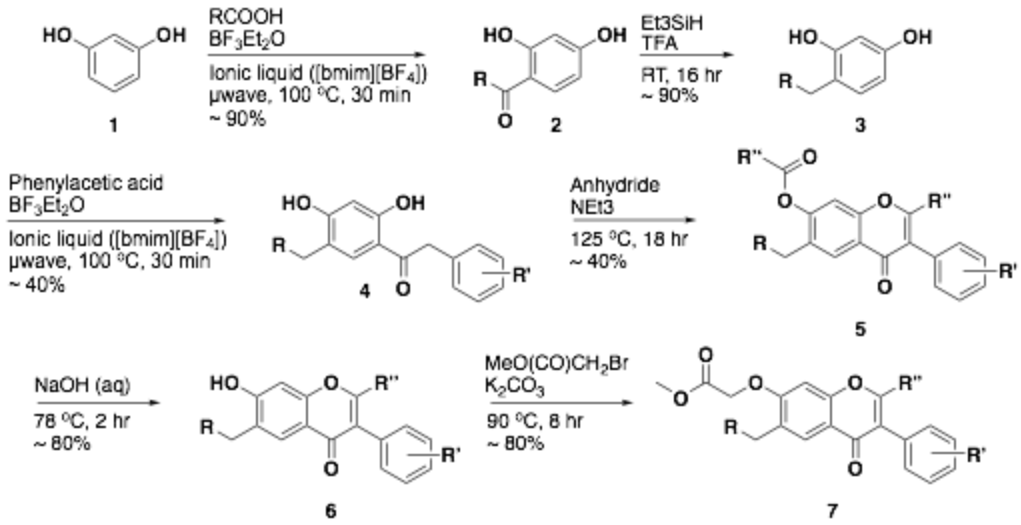
SEA and EF calculations. Here we describe our computational pipeline: 1) Use the reference trace to discover the top 125 hit compounds (most similar phenotypically related to etomidate). 2) Organize hit compounds into hierarchical supersets of increasing numbers of hit compounds. Use SEA analysis to generate target predictions for each of the compounds in the sets. Perform enrichment factor calculations on the sets, which attempt to correct the occurrence of target predictions for a set of compounds by comparing to a background distribution.[2] To do so we generated 10,000 sets of 200 random screening compounds each, and applied the following formula to calculate the enrichment of target *y* for set *x*: E_xy = n*N / (A * T), where *n* is the number of times target *y* is predicted for set *x* compounds by SEA, A is the number of times any target shows up for set *x*, T is the number of times target *y* shows up for any set, and N is a normalization factor equal to the product of all the targets and all the sets.

Determination of phenotypic thresholds and significance. For each ligand, we selected the dose that gave the highest average phenoscore, and for that dose, we performed a two-sample Kolmogorov-Smirnov (KS) test to calculate the KS statistic against the 12 positive control replicates of etomidate @ 6.25 μM using the scipy function ks_2samp from the scipy.stats package (**Supplementary Figure 20a**).

To calculate approximate thresholds of phenoscore significance, we performed a statistical simulation. For each score in the space of possible phenoscores (binned in 0.05 increments from 0 to 1), we sampled 12 replicates from a uniform distribution centered around the score ranging from -4σ to +4σ away from the mean, and calculated the KS statistic against the etomidate 6.25 μM replicates. We repeated this simulated procedure 100 times to get robust statistics, and took the average of these *P* values. However, we realized that the standard deviation of replicates across different $GABA_AR$ ligands was not a constant value. It tended to be low for extremely poor phenotypes, peaked for intermediate phenotypes, and decreased again for extremely strong phenotypes. Therefore, we fit the standard deviations for $GABA_AR$ ligands as a function of phenoscore with a 10th order polynomial using the Polynomial package in numpy (**Supplementary Figure 20b**). Using this resulting polynomial, we calculated the KS *P* values from the simulated uniform distributions as we iteratively stepped along the y-axis ; these *P* values were smoothly distributed except for a discontinuity around phenoscore 0.5 due to rapidly increasing *P* values in this range (**Supplementary Figure 20c**). We derived the threshold phenoscores associated with these *P* values by fitting another polynomial to the resulting distribution in the smooth region (above phenoscore 0.5) (**Supplementary Figure 20d**) and calculating the roots of the function at those *P* values. The resulting phenoscores corresponding to 0.01 and 0.05 *P* value thresholds were 0.51 and 0.71, respectively.

Z' and false positives and negatives calculation. To calculate the Z' (quality of screen coefficient), we use the formula Z' = $1 - 3(\sigma_p + \sigma_n)/(\mu_p - \mu_n)$, expressed in terms of the mean and SD of the positive (p) and negative (n) controls. The false positive/negative rates were determined at a threshold of 3 SD. Any positive controls with a phenoscore 3 SD away from the positive control mean (μ_p) were labeled false positives. Likewise, any negatives controls 3 SD away from the negative control mean (μ_n) were labeled false negatives.

General Synthesis Scheme of Isoflavones



General Procedure for the Synthesis of 2. To a mixture of resorcinol (1 equiv) and carboxylic acid (1 equiv), BF3·Et2O (3 equiv) and ionic liquid ([bmim][BF4]) (3.5 equiv) was added. The reaction mixture was irradiated at 100 °C for 30 min in a microwave reactor at the maximum power of 300W. The solution was allowed to cool and poured into water. The reaction mixture was extracted with ethyl acetate, and the organic layer is separated and washed with brine, dried, and concentrated. The concentrate was purified by silica gel column chromatography to get ketone 2.

General Procedure for the Synthesis of 3. 2 was dissolved in trifluoroacetic acid (20 equiv) and triethylsilane (2.5 equiv) was added at room temperature. The resulting solution was stirred overnight, and the solvent was removed by flushing nitrogen gas in mild temperature. The residue was purified by silica gel column chromatography to get diol 3.

General Procedure for the Synthesis of 4. To a mixture of 3 and a phenylacetic acid (1 equiv), BF3·Et2O (3.5 equiv) and ionic liquid ([bmim][BF4]) (3 equiv) was added. The reaction mixture was irradiated at 100 °C for 30 min in a microwave reactor at the maximum power of 300W. The solution was allowed to cool and poured into water. The reaction mixture was extracted with ethyl acetate, and the organic layer was separated and washed with brine, dried and concentrated. The concentrate was purified by silica gel column chromatography to get ketone 4.

General Procedure for the Synthesis of 5. A mixture of 4, propionic anhydride (5 equiv) and triethylamine (4 equiv) was heated at 125 °C for 12 h. Then the reaction mixture was added to cold dilute 1M HCl solution. The mixture was extracted with ethyl acetate, and the organic layer was separated and washed with brine, dried and concentrated. The concentrate was purified by silica gel column chromatography to get isoflavone 5.

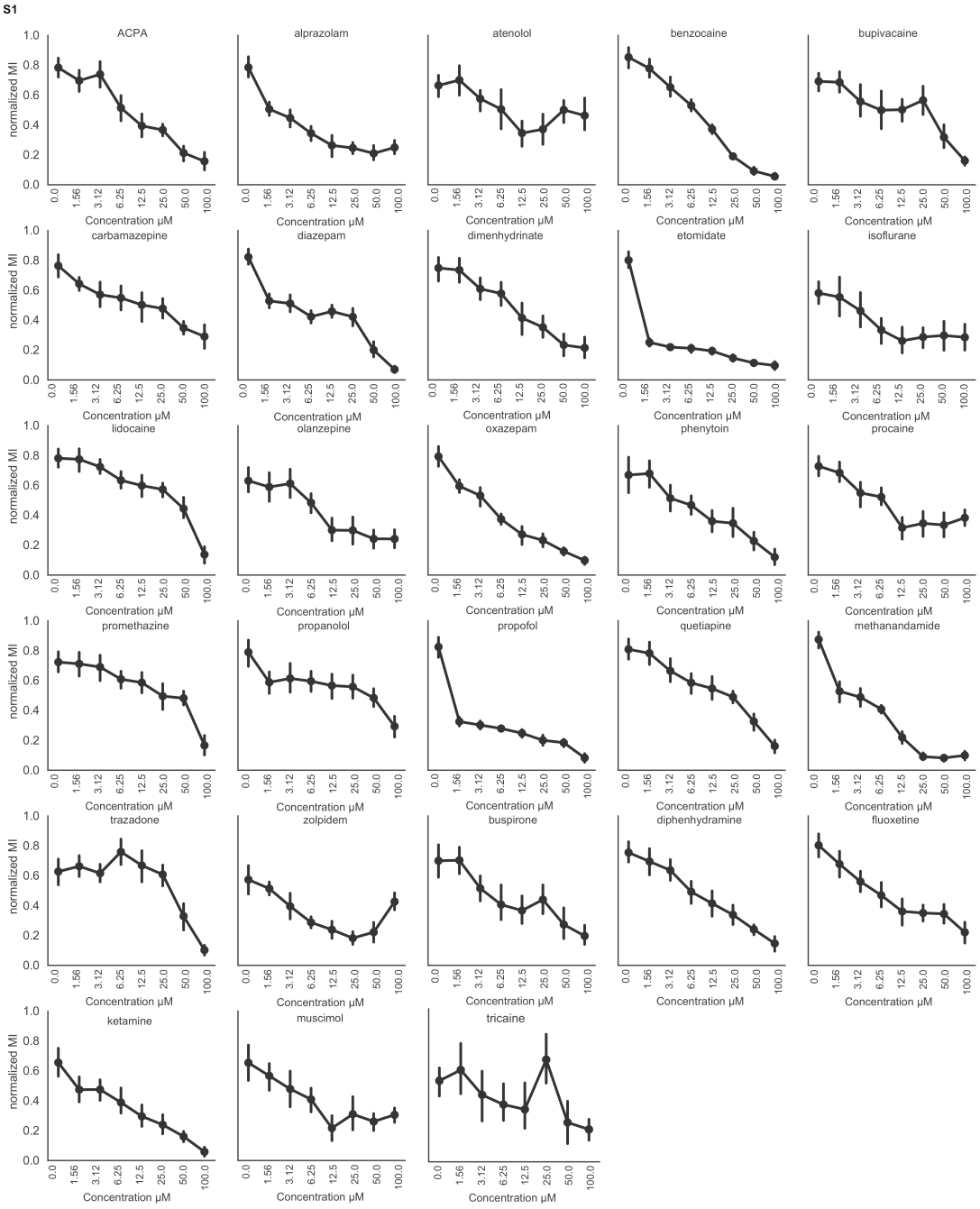
General Procedure for the Synthesis of 6. A solution of 5 in ethanol (0.2 M) containing 10% w/w NaOH was refluxed for 30 min. After 30 min, the same amount of water was added, and heating was continued for another 1.5 h. The reaction mixture was acidified with dilute hydrochloric acid and extracted with ethyl acetate, and the organic layer was separated and washed with brine, dried and concentrated. The concentrate was purified by silica gel column chromatography to get isoflavone 6.

General Procedure for the Synthesis of 7. To a solution of 6 in DMF (0.5 M), methyl bromoacetate (1.1 equiv) and K_2CO_3 (3 equiv) was added. The mixture was heated to 90 °C for 8 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate. The organic layer was

separated, washed with brine, and dried and concentrated. The concentrate was purified by silica gel column chromatography to get isoflavone 7.

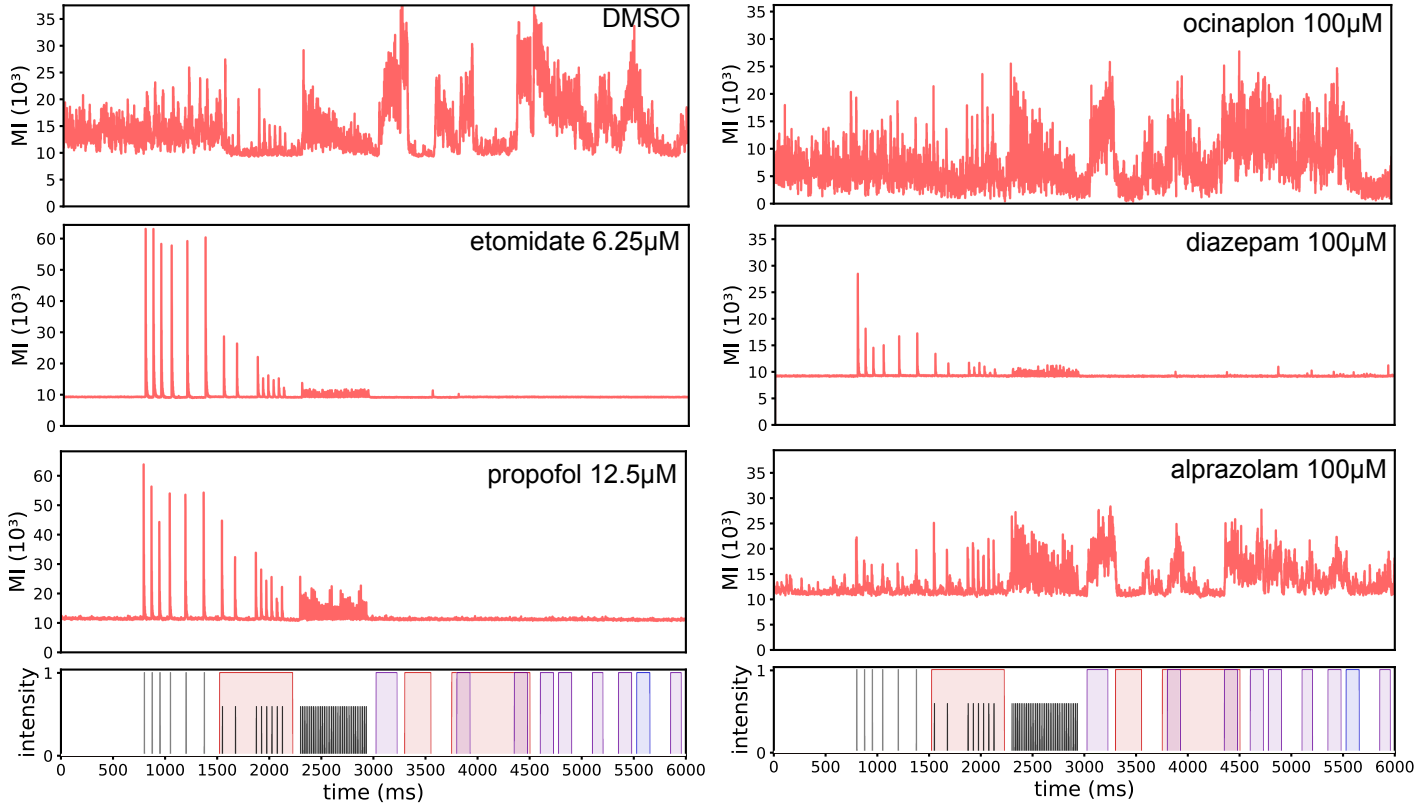
$GABA_AR$ terminology. Notation for GABA receptors conform to IUPHAR recommendations [5]. Receptor subunits are indicated by their greek symbols with subscripted numbers to indicate specific isoforms as in: “the α_1 subunit isoform”. To refer to $GABA_A$ receptor ($GABA_AR$) subtypes, the term GABA is used to indicate the receptor type, and the subscript A is used to refer to all $GABA_ARs$. Subtypes comprised of specific subunit isoforms are indicated like: “the $\alpha_1\beta_2\gamma_2$ subtype”.

SUPPLEMENTARY FIGURES

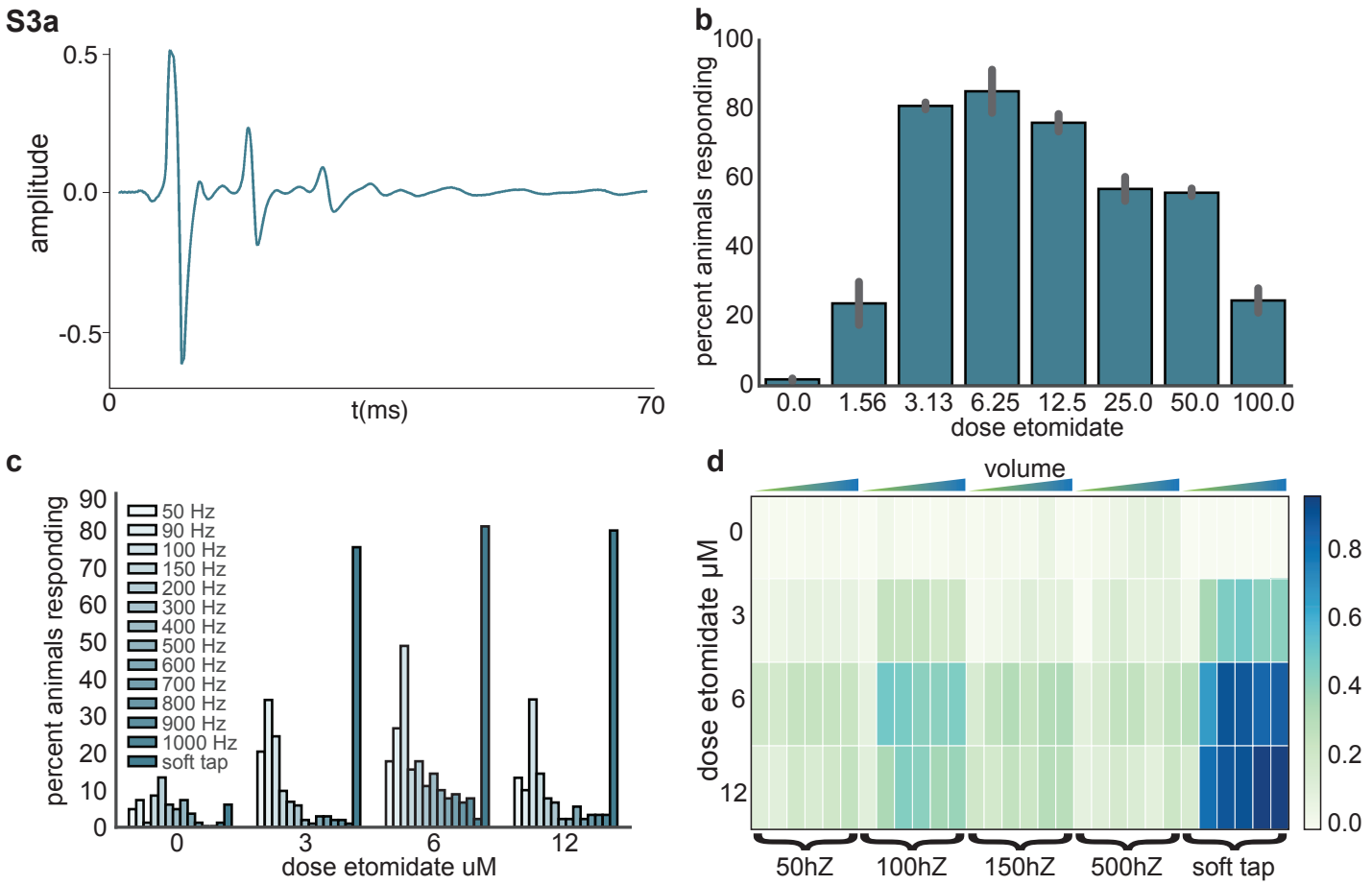


Supplementary Figure 1. Sedatives cause a dose dependent reduction in zebrafish motion. A panel of 30 known sedatives administered to 7dpf zebrafish larvae (n = 12 replicates; 96 fish/ condition) at a 2 fold dilution series. The y-axis represents motion index (MI) and the x-axis represents dose.

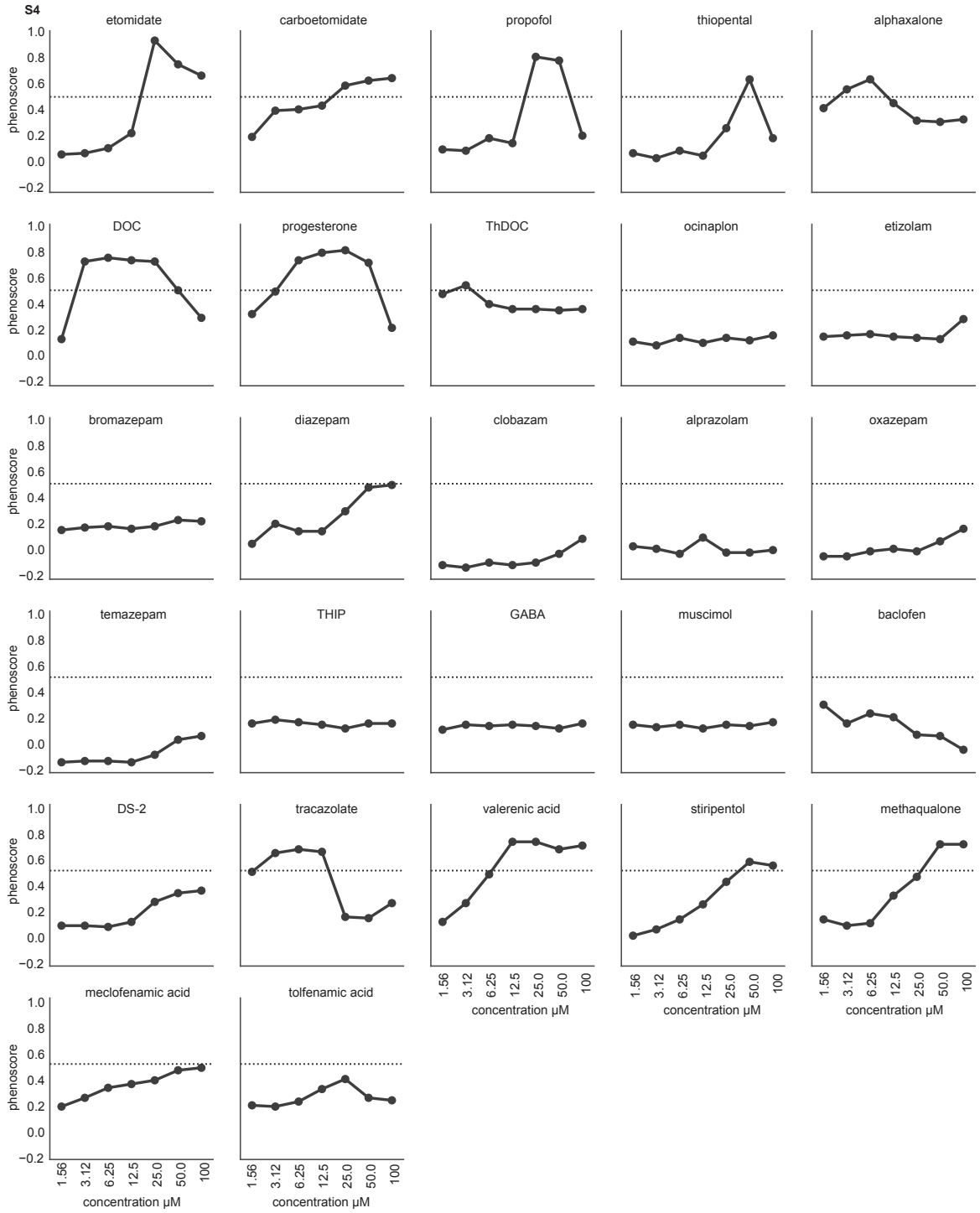
S2



Supplementary Figure 2. Propofol and etomidate block light-induced behaviors, but enhance the acoustic startle response. The plots show motor activity (*y*-axis) of zebrafish treated with the indicated compounds (n = 12 wells). Colored bars above the *x*-axis represent the timing and duration of indicated stimuli.

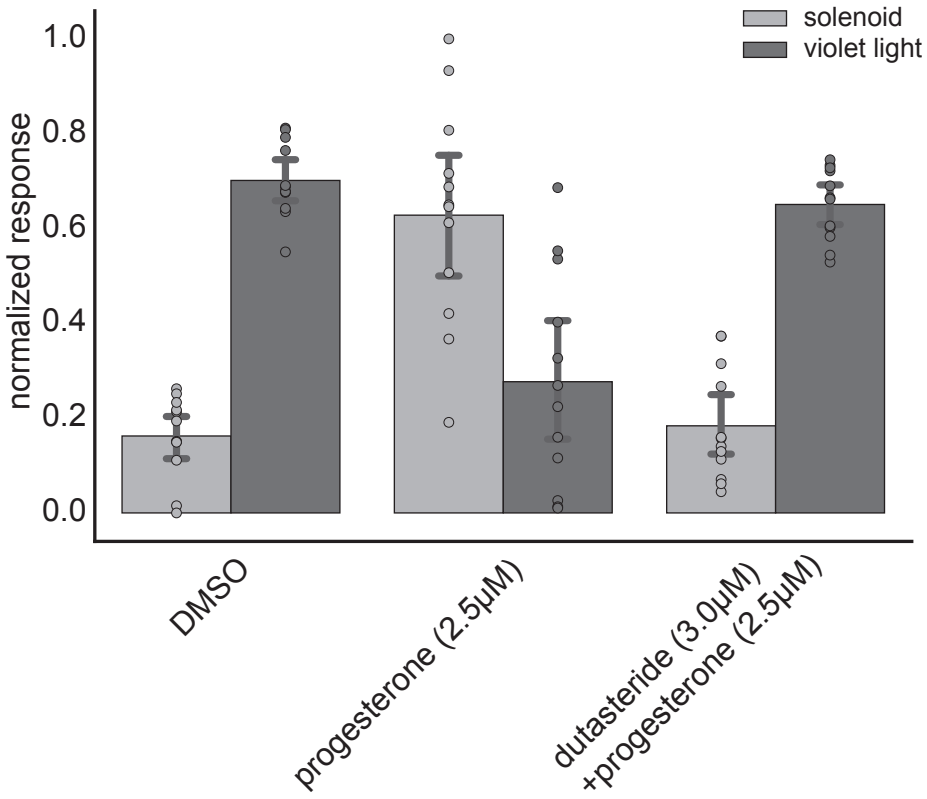


Supplementary Figure 3. eASR stimulus characterization. We explored a range of digital, acoustic stimuli to understand which parameters were important for triggering eASRs. **(a)** Recorded waveform of the dampened solenoid. The original stimulus, generated by a dampened solenoid, approximated a 100 Hz inverse fading sine wave, with a 70 dB maximum volume and 70 ms duration. **(b)** Bar graph depicting startle frequency (y-axis) of 100 animals to the dampened solenoid stimulus at increasing concentrations of etomidate (x-axis), it elicited responses in 85% of etomidate-treated animals (6.25 µM) and in 2% of controls. **(c)** Startle frequency (y-axis) of 100 animals treated with indicated concentrations of etomidate (x-axis) in response to different frequencies of synthesized and dampened solenoid acoustic stimulus (colored bars). In frequency scans from 50-1000 Hz, the highest magnitude eASRs were elicited by 100 Hz stimuli. Interestingly, the most effective synthesized stimulus (a 100 Hz inverse fading sine wave; 70ms) was only 50% as effective as the original solenoid, suggesting that some unknown feature of the original solenoid-based stimulus was not captured by the synthesized waveform and/or the surface transducers. **(d)** Heat map of the startle frequency of 100 animals (color bar) in response to increasing volume (top y-axis) of different frequency synthesized acoustic stimulus and the solenoid stimulus (x-axis). Animals were treated with increasing concentrations of etomidate (y-axis). At 100Hz, all stimuli greater than 60 dB were effective, whereas those less than 55 dB were not.



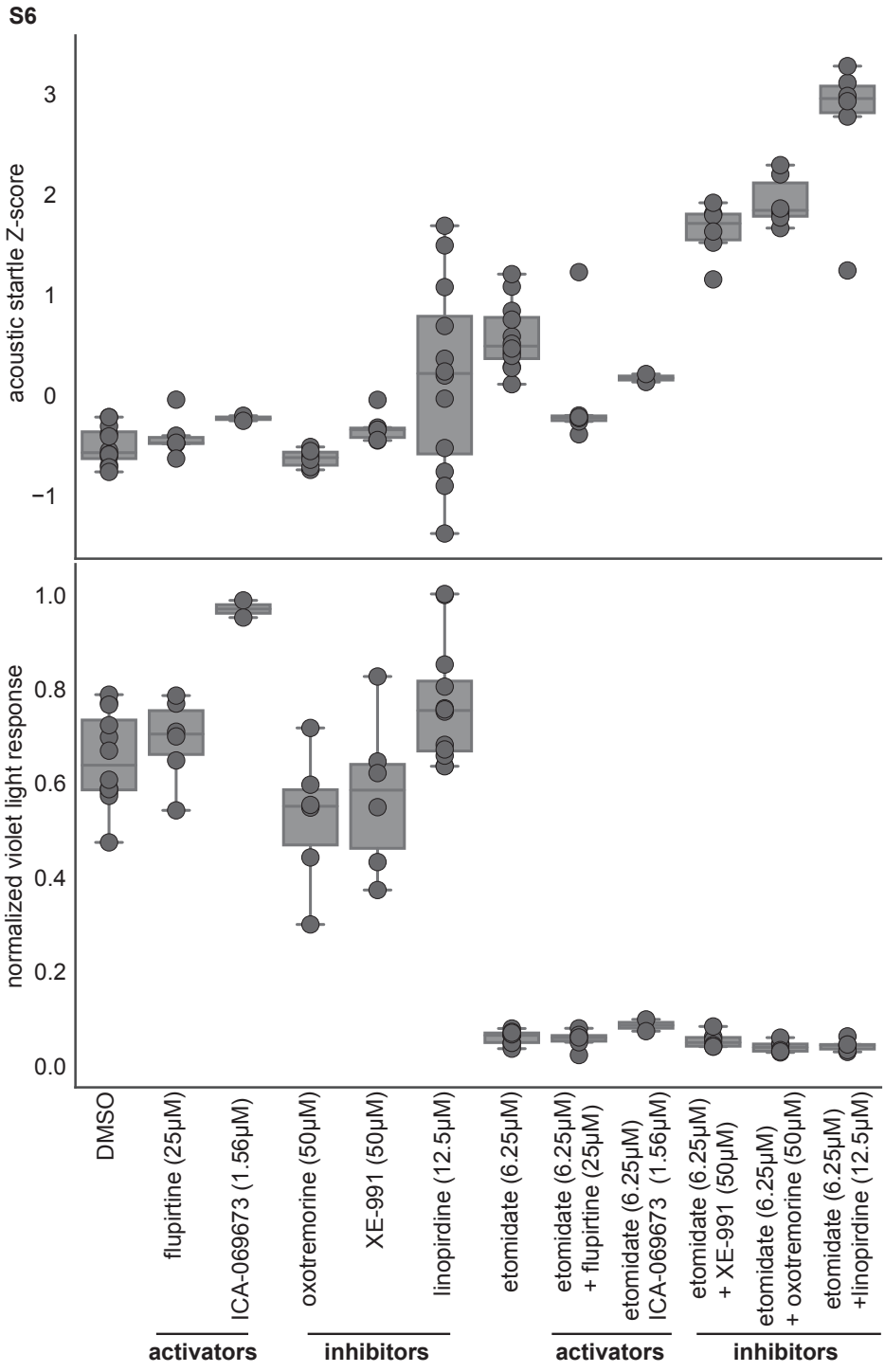
Supplementary Figure 4. Dose response analysis of GABA reference compounds. Average phenoscores (*y*-axis) of zebrafish treated with the indicated compounds (n = 12 wells) at increasing concentrations (x-axis).

S5



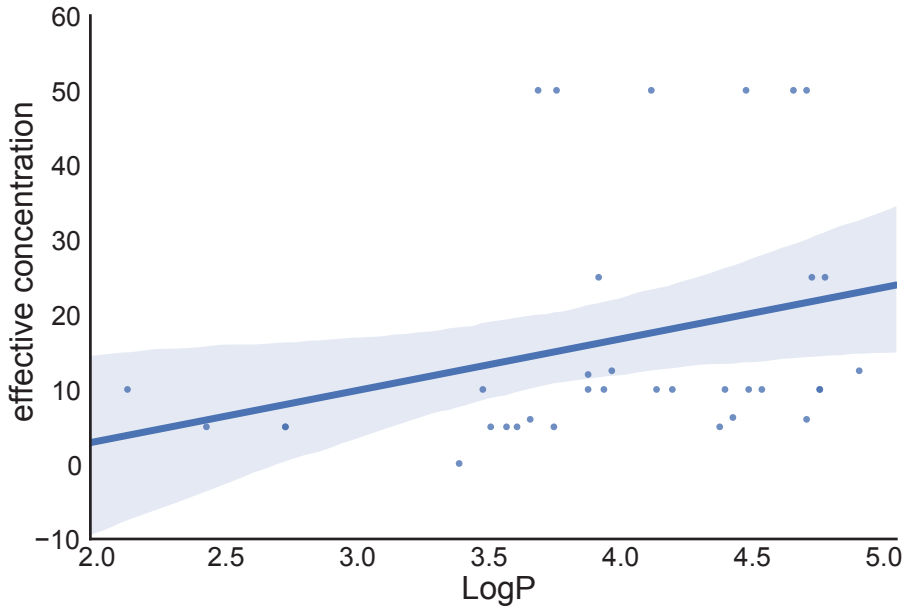
Supplementary Figure 5.

Dutasteride inhibits progesterone-induced eASRs. The plots show the normalized behavioral responses (y-axis), to acoustic (grey) or light (black) stimuli, in animals treated with the indicated compounds (x-axis).

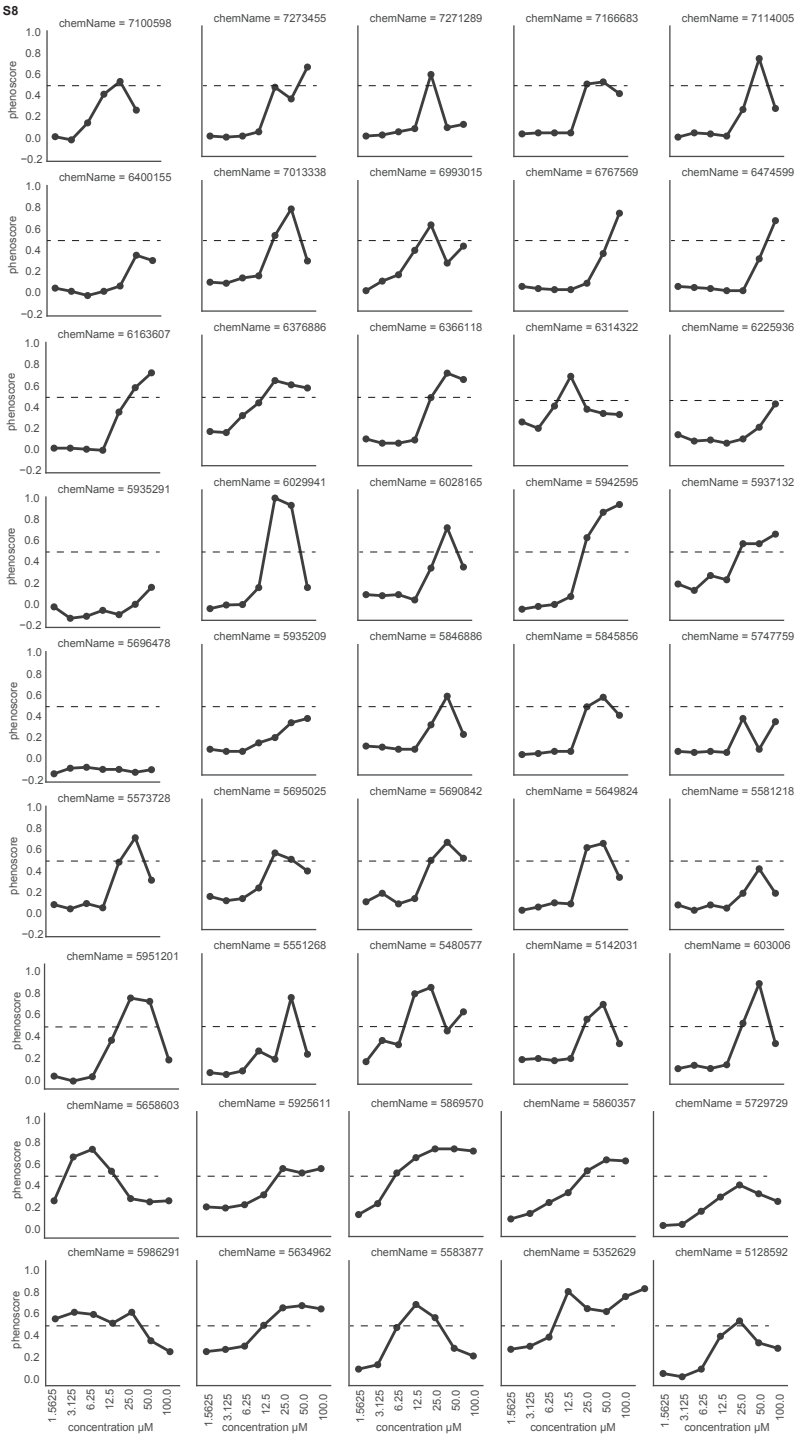


Supplementary Figure 6. M-current ligands modify eASRs. Boxplots depicting the motor activity (y-axis) of animals treated with the indicated compounds (x-axis) in response response to acoustic (top) or violet light stimuli (bottom). M-current activators and inhibitors were analyzed alone or combined with etomidate, at the indicated concentrations.

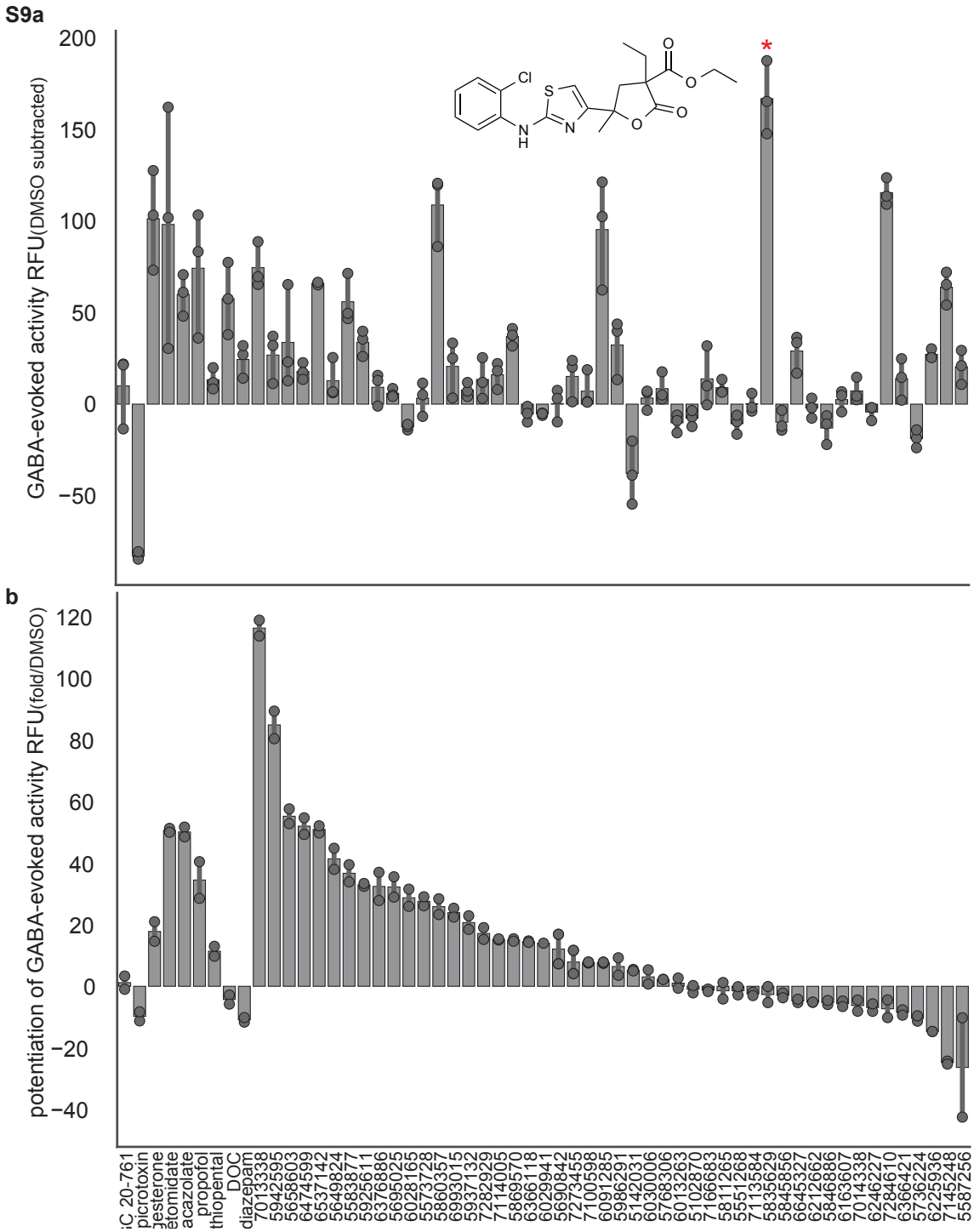
S7



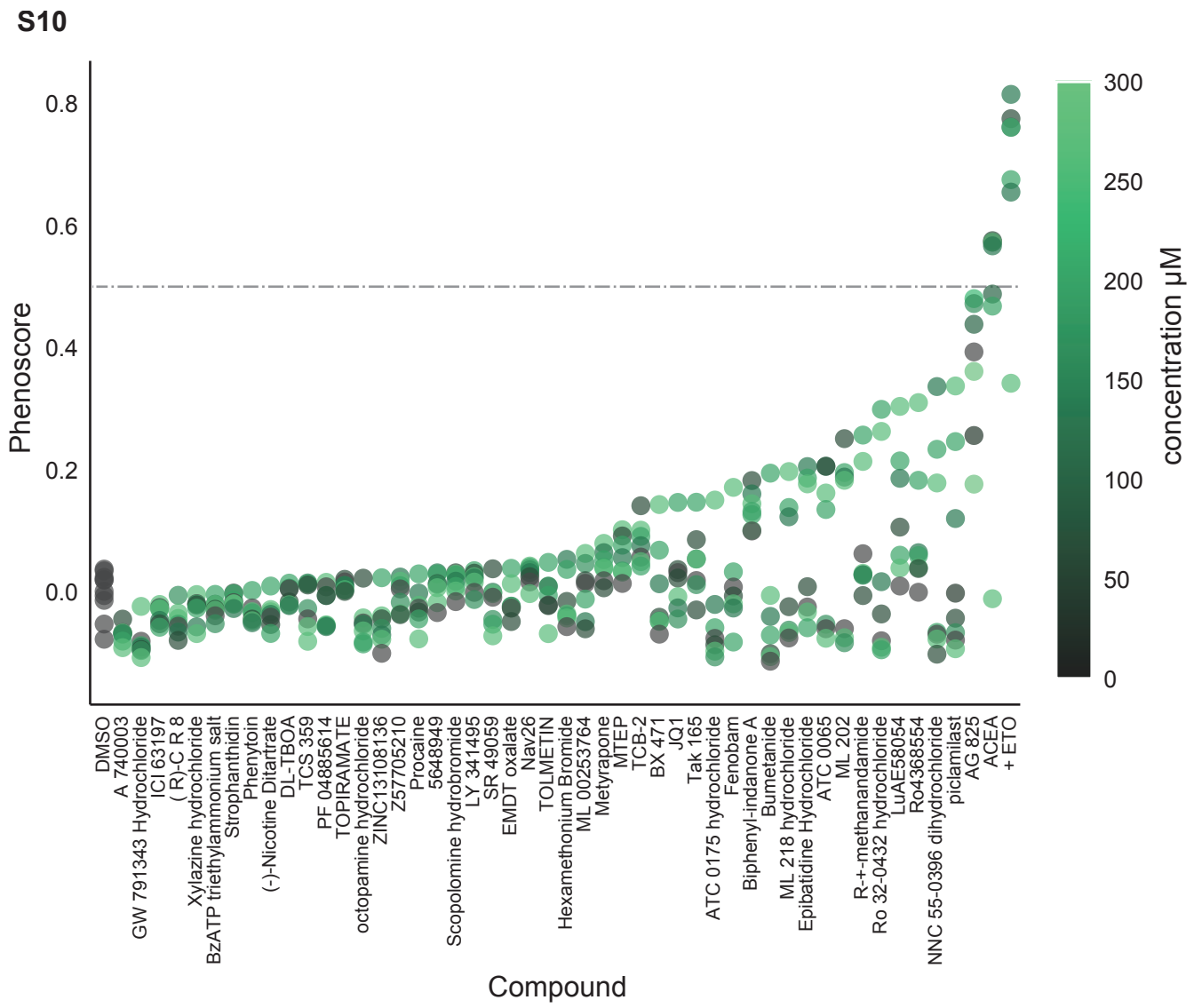
Supplementary Figure 7. Hit compound efficacy does not correlate with hydrophobicity. Animals were treated with hit compounds. For each compound, the cLogP (calculated partition coefficient) (x-axis) and minimum concentration required to cause the eASR phenotype, were plotted (y-axis). Unlike historical Myer-Overton analyses, the minimum effective concentration does not decrease with hydrophobicity. The best-fit line and shading represent the resulting regression line and a 95% confidence interval for that regression.



Supplemental Figure 8. Dose response retest of primary hit compounds. Average phenoscores (*y*-axis) of zebrafish treated with the indicated compounds (n = 12 wells) at the indicated concentrations (x-axis).

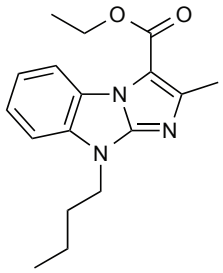


Supplementary Figure 9. Hit compounds cause direct and indirect activation of GABARs. (a,b) Human GABAAR activation (*y*-axis) was measured by FLIPR analysis in random fluorescent units (RFUs). Direct **(a)** and indirect **(b)** activation was analyzed for the indicated hit compounds (x-axis, n = 2-4).



Supplementary Figure 10. Phenoscores of ligands at targets with low value EFs. Ligands for targets with low (left of dotted line) and high (right of dotted line) EF scores. The plot shows the phenoscore (y-axis) of the indicated compounds (x-axis). Color bar represents concentration in µM.

S11



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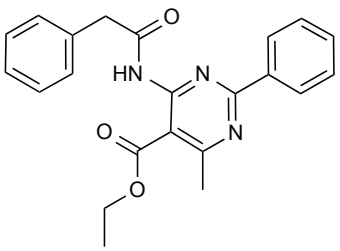

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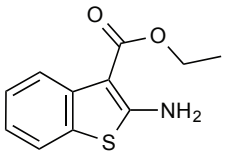

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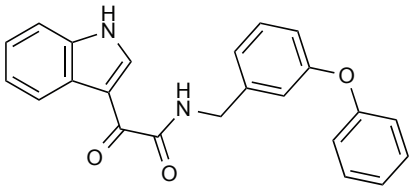

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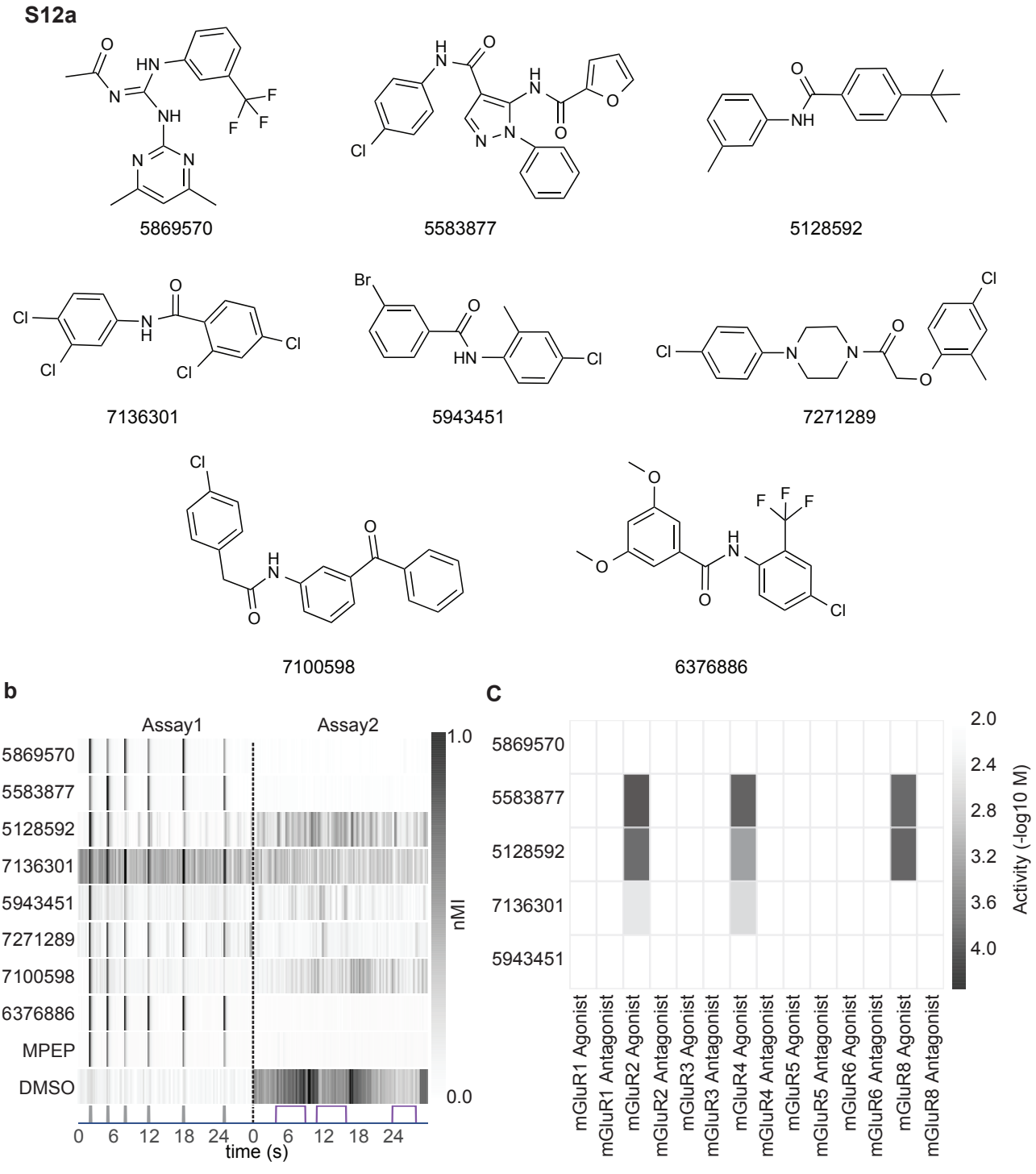
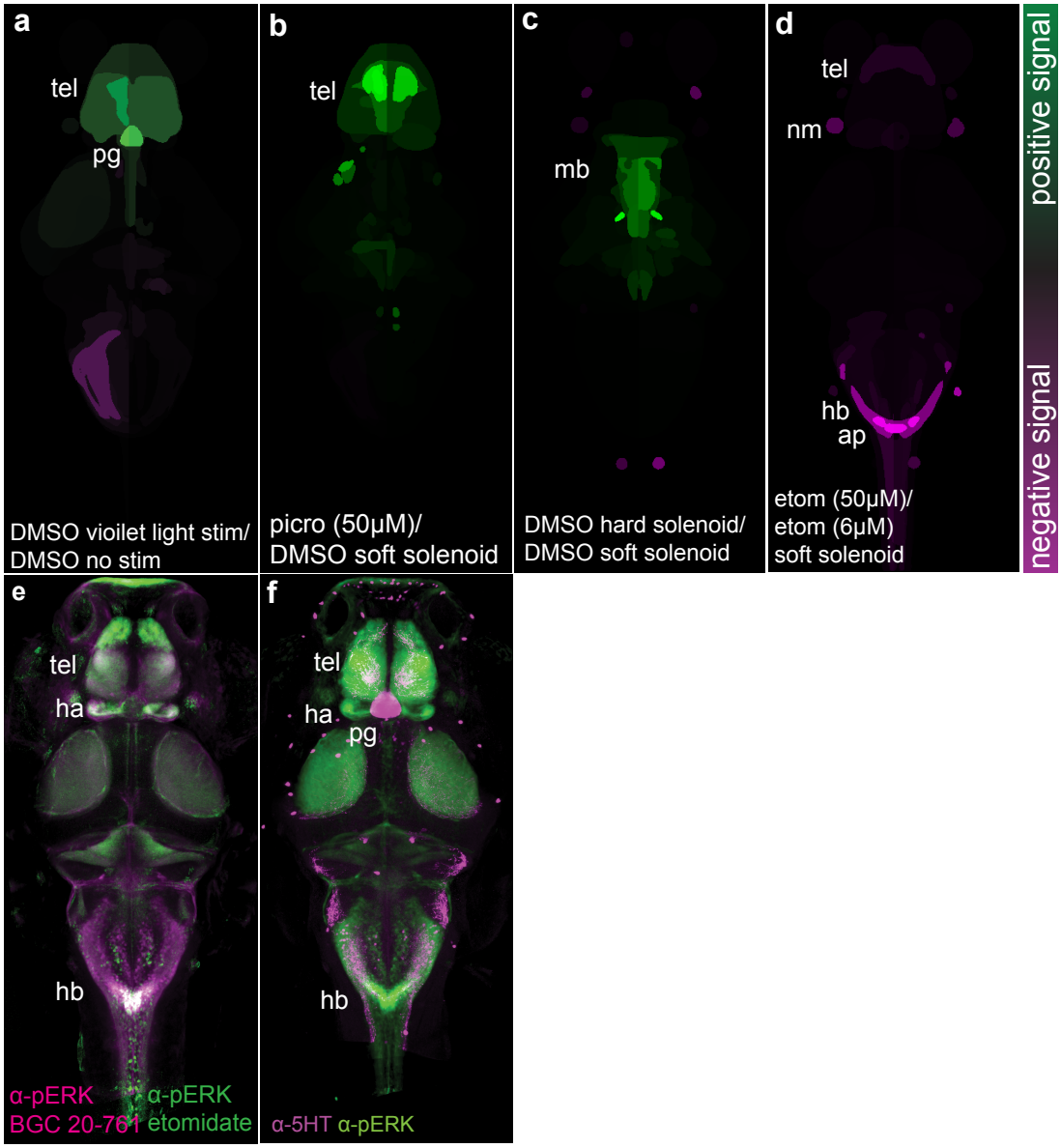
Supplementary Figure 11. Chemical structures of hit compounds predicted to target GABAARs by SEA.



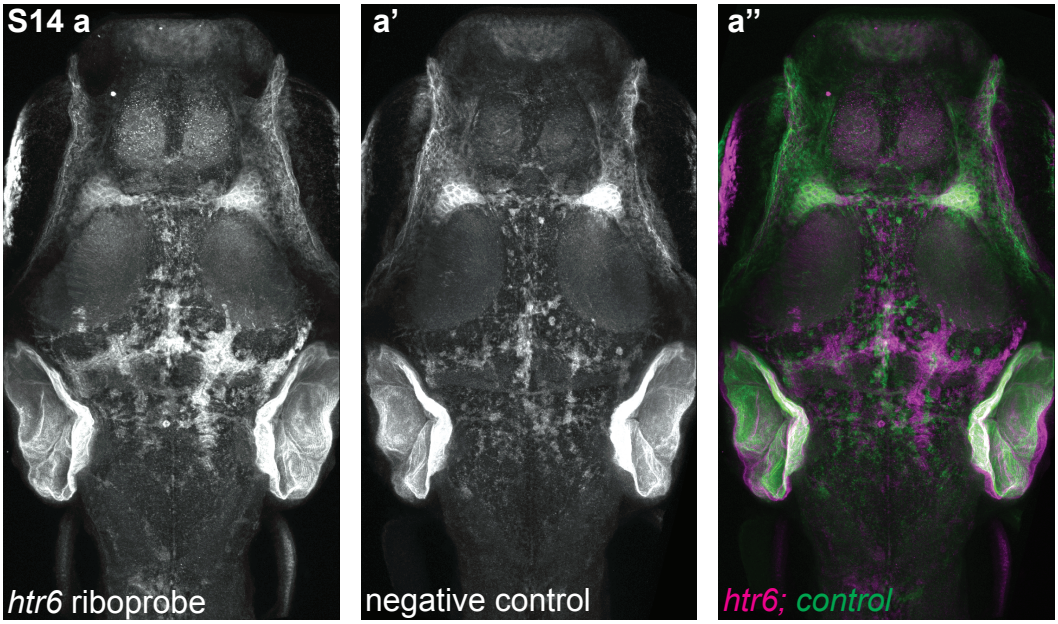
Supplementary Figure 12. Characterization of hit compounds predicted to target mGluR by SEA. (a) Chemical structures of 8 hit compounds predicted to target mGluR. **(b)** The heatmap represents the normalized motion index (nMI) of larvae treated with the indicated compounds. Assay 1 is composed of 6 low amplitude acoustic stimuli; Assay 2 is a series of 3 violet light pulses as indicated on the *x*-axis. MPEP is a known mGluR4/5 ligand. Compounds were tested for agonist and antagonist activity in Gq functional assays in-vitro. **(c)** The heat map represents the activity of 5 novel mGluR predicted compounds (y-axis) at the indicated receptor (x-axis). Low-level activation of mGlur2/4 was detected for compounds 5583877, 5128592, and 7136301 (46.13 μM to 2871 μM).

S13

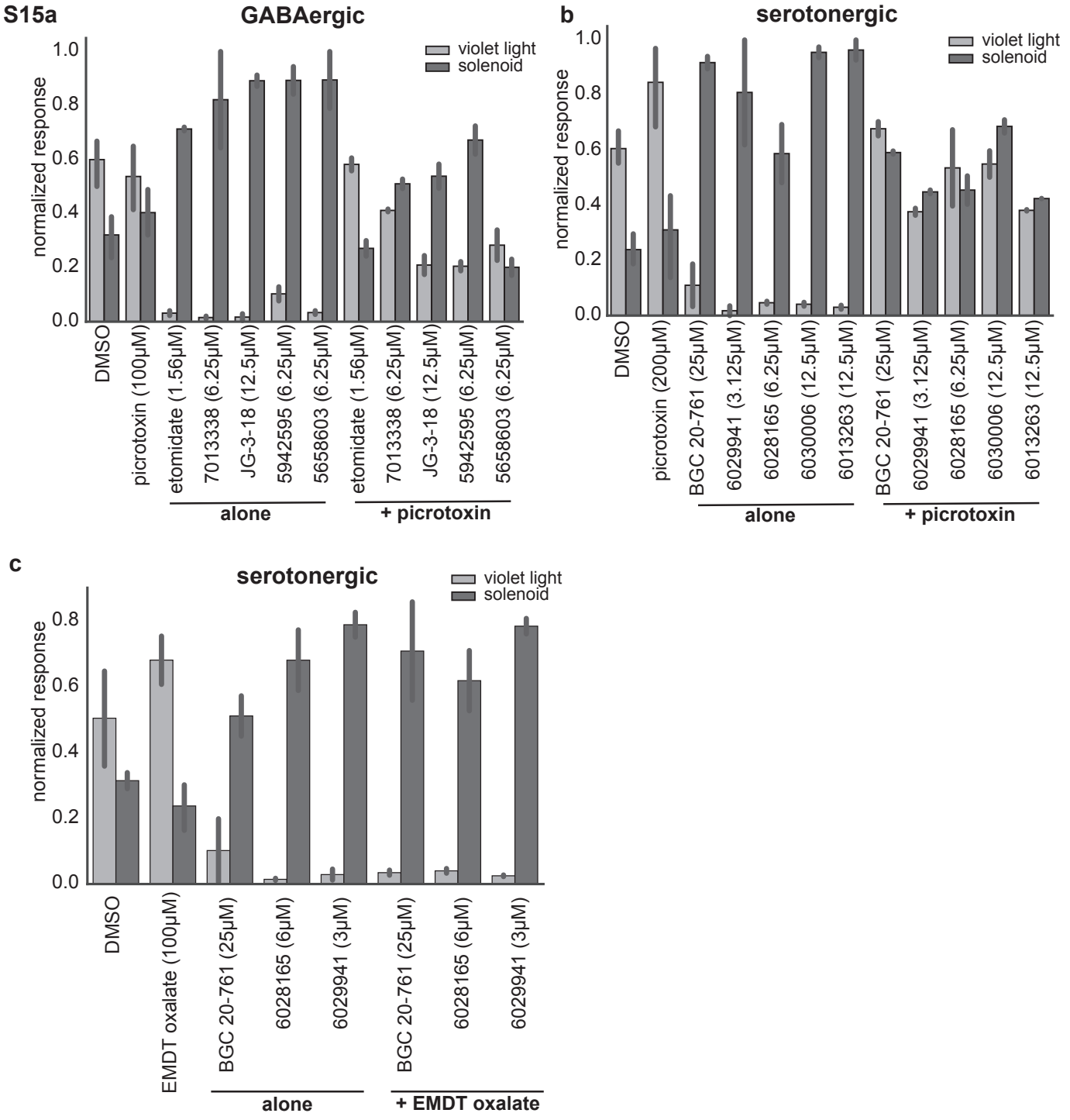


Supplementary Figure 13. pERK whole brain neural activity maps in control assays and 5-HT immunohistochemistry.

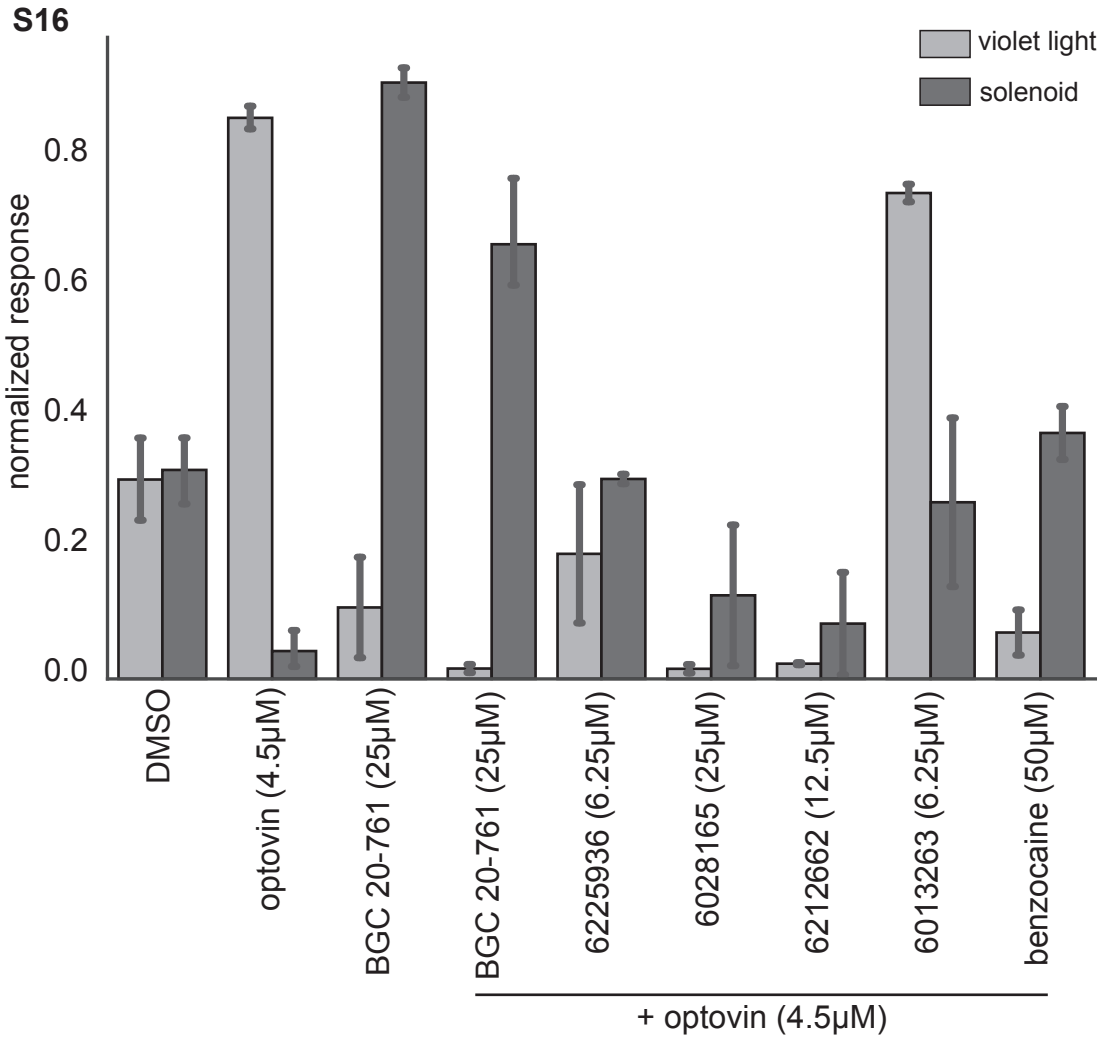
(a-d) Brain activity maps showing significant ΔpERK signals using the Z-brain online reference tool (n = 5-10 animals/condition). Heatmaps indicate positive (green), negative (purple), and nonsignificant (black) changes in pERK labeling ($p < 0.0005$, Mann-Whitney U test). All activity maps are comparisons between the indicated treatment conditions. (**e**) Overlay of average α-pERK signal for BGC 20-761(magenta), and etomidate treated animals (green). (**f**) Overlay of α-5HT staining (magenta) and the average α-pERK staining (green) for BGC 20-761 treatment. Abbreviations: tel, telencephalon; mb, midbrain; ot, optic tectum; hb, hindbrain; ha, habenula; ob, olfactory bulb; nm, neuromast; ap, area postrema; pg, pineal gland.



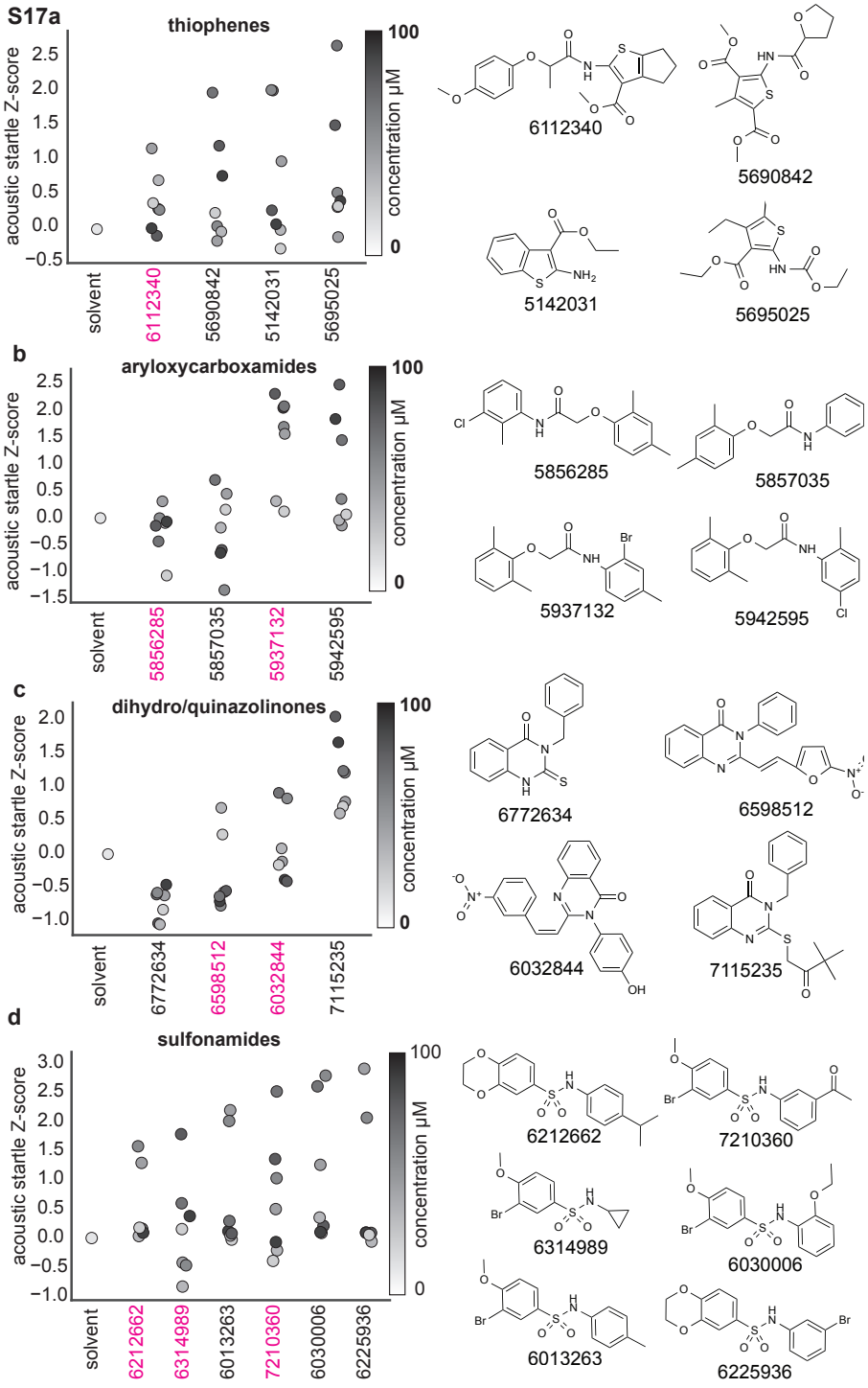
Supplementary Figure 14. Fluorescent in situ hybridization of the zebrafish *htr6* transcript shows low expression in the telencephalon. (a-a'') Confocal projections from image registered animals showing transcripts for *htr6* (a) and non specific negative control antisense probe (a'), overlay in (a'').



Supplementary Figure 15. The GABAergic antagonist picrotoxin reverses the eASRs-induced by some ligands, but the serotonergic agonist EMDT oxolate does not. (a-c) Normalized behavioral responses (y-axis) of animals treated with the indicated compounds (x-axis).

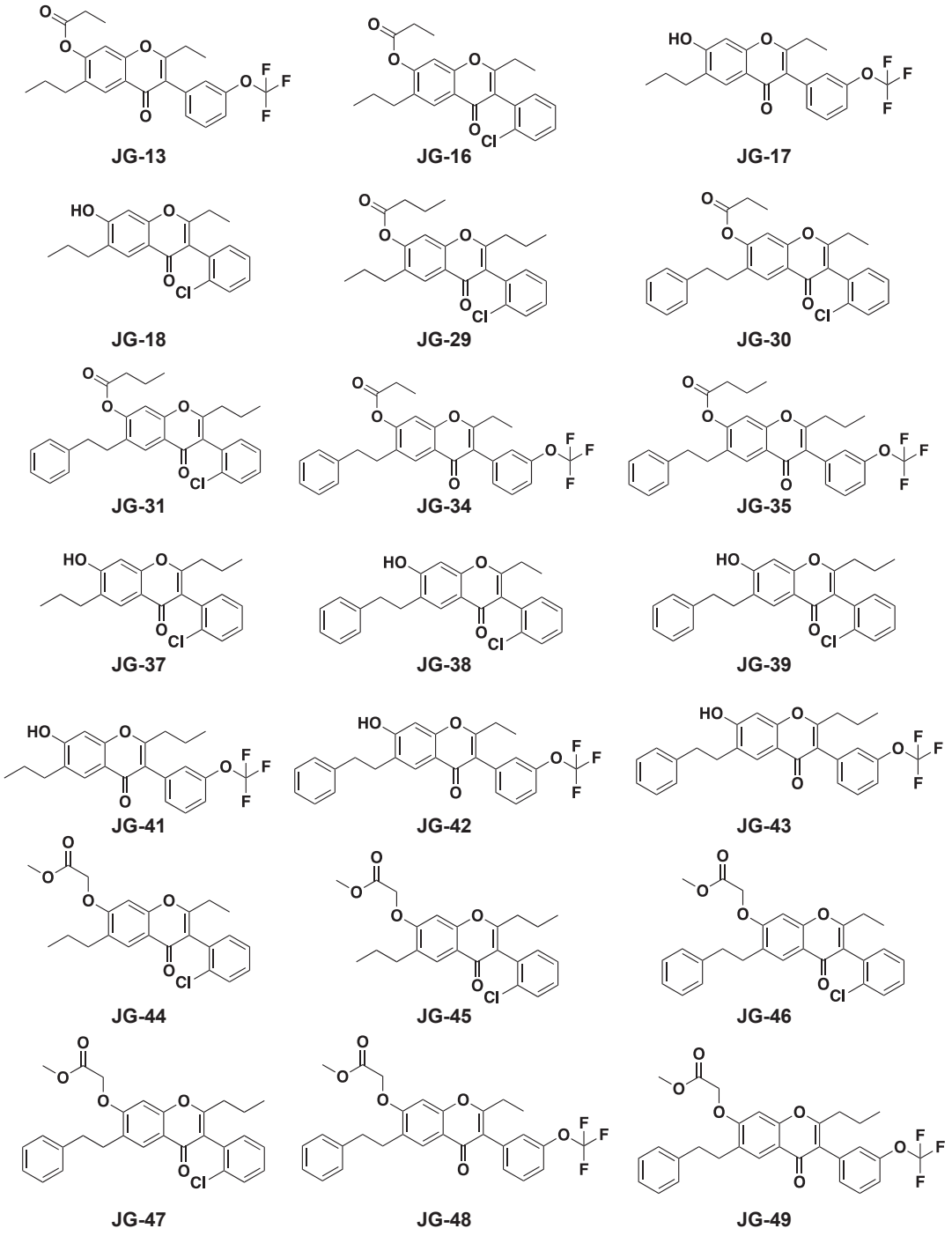


Supplementary Figure 16. Serotonergic hit compounds inhibit optovin response. Normalized behavioral response (y-axis) of animals treated with the indicated compounds (x-axis).



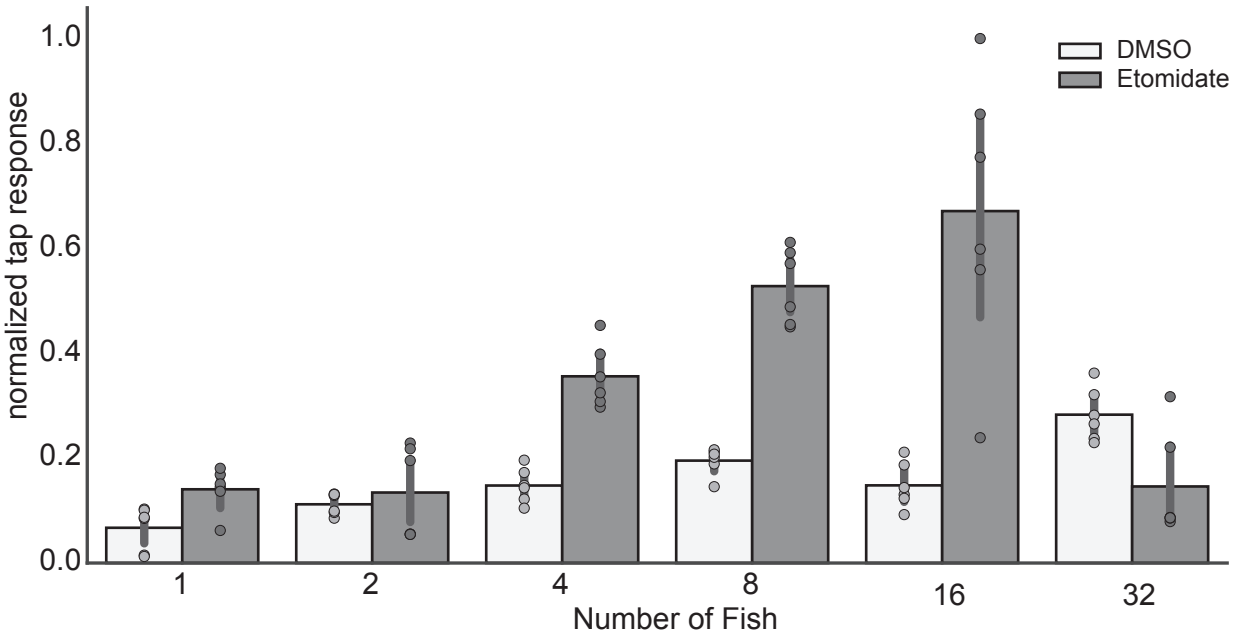
Supplementary Figure 17. Preliminary SAR of key compound classes. (a-d) The plots show the Z-score of the acoustic startle response (y-axis) in animals treated with the indicated compounds (x-axis). The compound structures in each class are shown to the right of each plot including the original hit compounds (black) and their analogs (red). Many analogs did not cause the eASR behaviors.

S18

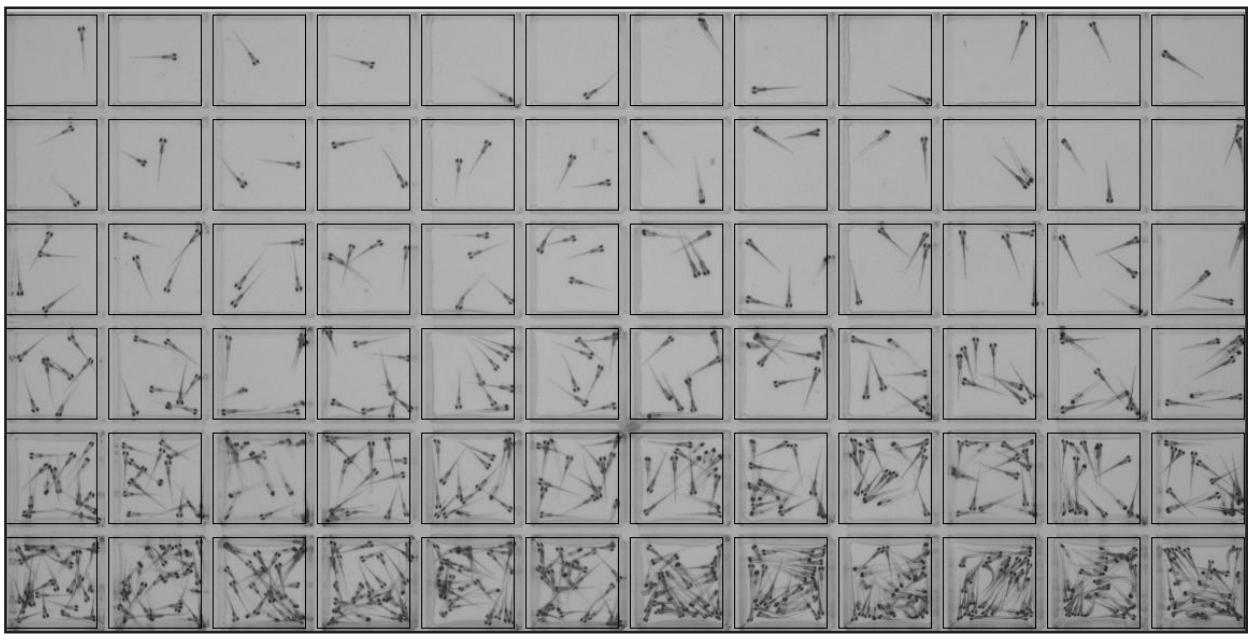


Supplementary Figure 18. Chemical structures of isoflavone analogs.

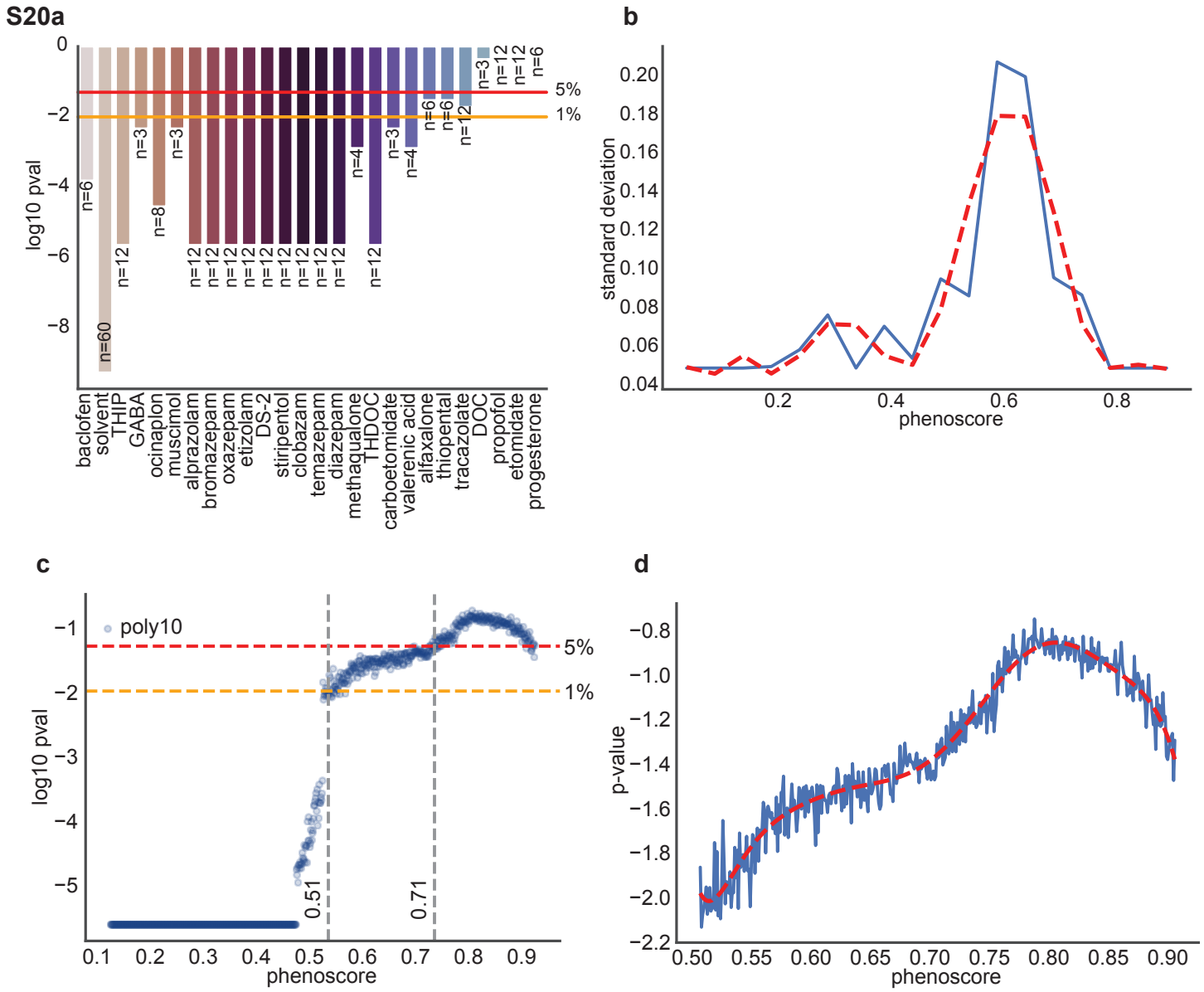
S19a



b



Supplementary Figure 19. Group size affects eASR quantification. To determine the impact of group size on this assay, we analyzed eASR behaviors from animals in different group sizes (1, 2, 4, 8, 12, 16, 32 animals per well). Groups of 8 and 16 animals generated the most robust MI values. Here, we chose to use 8 animals per group because it balanced a small group size with high signal to noise using the MI metric. **(a)** Bar graph illustrating the average tap response (*y*-axis) per tap stimulus (each marker represents one of 6 total stimuli averaged over 6 replicate wells), for wells with the indicated number of fish larvae (*x*-axis) and treated with DMSO control or 6μM etomidate, as indicated. **(b)** Representative image of wells containing increasing numbers of animals.



Supplementary Figure 20. Statistical analysis of phenotypic thresholds for $GABA_AR$ ligands. **(a)** This plot shows the Kolmogorov-Smirnov (KS Test) statistic for the highest-scoring profiles produced by the indicated treatments *(y*-axis). On the x-axis, the ligands are sorted in order of ascending average phenoscore (left to right) from lowest to highest. Horizontal lines on the *y*-axis indicate the 1%(yellow) and 5% (red) *P* value significance thresholds **(b)** Plot showing the standard deviations for GABAAR ligands as a function of phenoscore with a 10th order polynomial. **(c)** Plot showing simulated *P* values as a function of phenoscore. Horizontal dashed lines indicate 1% and 5% P value thresholds, and vertical lines indicate the phenoscores at which these thresholds are met (0.51 and 0.71, respectively). **(d)** Plot showing a 10th order polynomial fit for the smooth region of the simulation where phenoscore > 0.5 in panel (c).

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Supplementary Table 1. CNS depressants characterized on zebrafish larval behavior.

class ID	chemical name	class	citation
1	carbamazepine	anticonvulsant	19
1	phenytoin	anticonvulsant	20
2	fluoxetine	antidepressant	21
2	trazodone	antidepressant	22
3	diphenhydramine	antihistamine	23
3	dimenhydrinate	antihistamine	23
3	promethazine	antihistamine	23
4	buspirone	anxiolytic	24
4	alprazolam	anxiolytic	25
4	diazepam	anxiolytic	26
4	oxazepam	anxiolytic	27
5	quetiapine	atypical antipsychotic	28
5	olanzapine	atypical antipsychotic	29
6	atenolol	beta blocker	30
6	propranolol	beta blocker	31
7	ACPA	cannabinoid	32
7	methanandamide	cannabinoid	33
8	zolpidem	hypnotic	34
9	benzocaine	local anesthetic	35
9	lidocaine	local anesthetic	39
9	bupivacaine	local anesthetic	40
9	tricaine	local anesthetic	41
9	procaine	local anesthetic	42
10	ketamine	intravenous anesthetic	38
10	isoflurane	inhalational anesthetic	35
10	propofol	intravenous anesthetic	36
10	etomidate	intravenous anesthetic	37

Supplemental Table 2. Viability of anesthetic treated animals

treatment	concentration	alive/total 10 min	alive/total 1 hour	alive/total 5 hours
DMSO	0 μM	100/100	100/100	100/100
etomidate	3 μM	100/100	100/100	100/100
etomidate	6 μM	100/100	100/100	100/100
etomidate	12 μM	100/100	100/100	98/100
propofol	3 μM	100/100	100/100	100/100
propofol	6 μM	100/100	100/100	100/100
propofol	12 μM	100/100	100/100	99/100

Supplementary Table 3. GABAAR ligand reference set

Chemical Name	Class	Reference
dmso	vehicle control	NA
baclofen	$GABA_B$ agonist	4
GABA	orthosteric $GABA_AR$ agonist	5
muscimol	orthosteric $GABA_AR$ agonist	6
gaboxadol (THIP)	$GABA_AR$ delta subtype preferring PAM	7
DS-2	$GABA_AR$ delta subtype preferring PAM	7
ocinaplon	$GABA_AR$ BZ-site PAM	11
bromazepam	$GABA_AR$ BZ-site PAM	8
etizolam	$GABA_AR$ BZ-site PAM	12
alprazolam	$GABA_AR$ BZ-site PAM	5
oxazepam	$GABA_AR$ BZ-site PAM	8
clobazam	$GABA_AR$ BZ-site PAM	9
temazepam	$GABA_AR$ BZ-site PAM	10
diazepam	$GABA_AR$ BZ-site PAM	5
stripentol	$GABA_AR$ non BZ-site PAM	14
methaqualone	$GABA_AR$ non BZ-site PAM	15
valerinic acid	$GABA_AR$ non BZ-site PAM	16
thiopental	$GABA_AR$ non BZ-site PAM	18
tracazolate	$GABA_AR$ non BZ-site PAM	13
carboetomidate	$GABA_AR$ anesthetic PAM	18
propofol	$GABA_AR$ anesthetic PAM	18
etomidate	$GABA_AR$ anesthetic PAM	18
tetrahydrodeoxycorticosterone (THDOC)	$GABA_AR$ neurosteroid PAM	17
alphaxalone	$GABA_AR$ neurosteroid PAM	17
progesterone	$GABA_AR$ neurosteroid PAM	17
deoxycorticosterone (DOC)	$GABA_AR$ neurosteroid PAM	17

Supplementary Table 4. Chemical names and SMILES of the top 125 hit compounds from a zebrafish behavioral drug screen.

Chemical Name	SMILES	Retested
progesterone	CC(=O)C1CCC2C3CCC4=CC(=O)CCC4(C)C3CCC12C	yes
alfaxalone	CC(=O)C1CCC2C3CCC4CC(O)CCC4(C)C3C(=O)CC12C	yes
DOC	CC12CCC(=O)C=C1CCC1C2CCC2(C)C(C(=O)CO)CCC12	yes
7166683	Cc1cc(C)n2c(SCc3ccc(C(=O)c4ccccc4)cc3)nnc2n1	yes
etomidate	CCOC(=O)c1cncn1C(C)c1ccccc1	yes
6587027	CC(=O)c1cccc(NC(=O)c2ccc(-c3ccc(Cl)cc3)o2)c1	no
etomidate	CCOC(=O)c1cncn1C(C)c1ccccc1	yes
6858658	O=C(c1cc(Cl)ccc1Cl)N1CCN(c2cccc(C(F)(F)F)c2)CC1	no
5846886	Nc1ccc(Oc2ccc(Cl)c3cccnc23)c(Cl)c1	yes
6767569	Cc1nc2ccccc2n1C(=O)N(c1ccccc1)c1ccccc1	yes
6762995	Fc1ccccc1OCCn1c(S)nc2ccccc21	yes
alfaxalone	CC(=O)C1CCC2C3CCC4CC(O)CCC4(C)C3C(=O)CC12C	yes
7013338	CCc1cc2c(=O)c(-c3ccccc3Cl)c(C)oc2cc1OC	yes
7010474	CCc1cc2c(=O)c(-c3ccccc3Cl)coc2cc1OC	no
6376886	COc1cc(OC)cc(C(O)=Nc2ccc(Cl)cc2C(F)(F)F)c1	yes
7100598	O=C(c1ccccc1)c1cccc(N=C(O)Cc2ccc(Cl)cc2)c1	yes
7113584	Nc1ccc(OC(F)(F)F)cc1C(=O)c1ccccc1	yes
7114005	CCOC(=O)c1c(C)n(Cc2ccco2)c2ccc(OC)cc12	yes
6576466	O=[N+]([O-])c1cccc(C(O)=Nc2ccc(Cl)cc2C(F)(F)F)c1	no
6029941	COc1ccc(OC)c(NS(=O)(=O)c2ccc(OC)c(Br)c2)c1	yes
7285168	OC(=Nc1ccc(Cl)cc1F)c1cccc2ccccc12	no
7136301	OC(=Nc1ccc(Cl)c(Cl)c1)c1ccc(Cl)cc1Cl	yes
6890102	CCOc1ccc2c(=O)c(-c3ccccc3Cl)c(C)oc2c1	no
6225936	O=S(=O)(Nc1cccc(Br)c1)c1ccc2c(c1)OCCO2	no
6525784	O=c1c2ccccc2nc(C=Cc2ccc([N+](=O)[O-])cc2)n1-c1ccccc1Cl	no
7273455	Cc1cccc(OCCn2c(NC(=O)c3ccco3)nc3ccccc32)c1	yes
6314322	CC(C)(C)N=C(O)COc1ccc(C(C)(C)c2ccccc2)cc1	yes
6474599	CCCN(CCC)S(=O)(=O)c1ccc(Cl)c(Cl)c1OC	yes
6682129	C=CCn1c(SCC(=O)c2cccs2)nc2sc(CC)cc2c1=O	no
ivermectin	CCC(C)C1OC2(CCC1C)CC1CC(CC=C(C)C(OC3CC(OC)C(OC4CC(OC)C(O)C(C)O4)C(C)O3)C(C)C=CC=C3COC4C(O)C(C)=CC(C(=O)O1C34O)O2	yes
6028165	COc1ccc(S(=O)(=O)NC2CCCC2)cc1Br	yes
7271289	Cc1cc(Cl)ccc1OCC(=O)N1CCN(c2ccc(Cl)cc2)CC1	yes
5584178	CCc1nc2c(cnn2-c2ccccc2)c(=O)n1-c1ccc(C)cc1	no
5735460	COc1ccccc1CC(O)=Nc1ccc(Br)cc1F	no
7305598	OC(=Nc1cccc(N=C(O)c2cc(Cl)ccc2Cl)c1)c1cc(Cl)ccc1Cl	no
6993015	CC(C)CC(O)=NC(S)=NCc1ccccc1	yes
progesterone	CC(=O)C1CCC2C3CCC4=CC(=O)CCC4(C)C3CCC12C	yes
6645327	COc1ccccc1-c1coc2cc(OC(=O)c3cccs3)ccc2c1=O	yes
6772634	O=c1c2ccccc2nc(S)n1Cc1ccccc1	no
6366118	COc1ccc(S(=O)(=O)N2CCC(C)CC2)cc1Br	yes
7282929	CCOC(=O)c1c(N=C(O)C2CCCC2)sc2c1CCCC2	yes
6193422	O=S(=O)(Nc1cccc(Cl)c1)c1ccc2c(c1)OCCO2	no
5694163	Cc1csc(N=C(O)C2c3ccccc3Oc3ccccc32)n1	no
5754452	COC(=O)c1cccc(N=C(O)COc2ccc(C(C)(C)C)cc2)c1	yes
6565557	CCCCOc1ccc(C(=O)NC(C)C2COc3ccccc3O2)cc1	yes
5696478	Cc1c(C(=O)OC(C)C)sc(N=C(O)C2CCCCC2)c1C(=N)O	yes

Supplementary Table 4. Continued

Chemical Name	SMILES	Retested
5587256	O=C(Nc1c(C(=O)Nc2ccc(Cl)cc2)cnn1-c1ccccc1)c1ccccc1F	yes
5551268	Clc1ccc(CSc2nc3ccccc3[nH]2)cc1	yes
5149665	Brc1ccc(CSc2nc3ccccc3[nH]2)cc1	no
5869570	CC(O)=NC(=Nc1cccc(C(F)(F)F)c1)Nc1nc(C)cc(C)n1	yes
5729729	O=C(CC(c1ccccc1)c1ccccc1)N1CCN(c2ccc(F)cc2)CC1	yes
6877352	CC(c1ccccc1)n1c(S)nc2ccccc21	no
6595002	CCc1ccc(O)c(N=C(S)N=C(O)c2ccccc2I)c1	no
5352629	COc1ccccc1N1CCN(C(=O)c2ccc(C(=O)c3c(C)cc(C)cc3C)cc2)CC1	yes
7184284	CCc1cccc(C)c1N=C(O)COc1ccc(Cl)cc1Cl	no
7114335	Nc1ccc(SC(F)(F)F)cc1C(=O)c1ccccc1	yes
7014338	CCc1cc2c(=O)c(-c3ccccc3Cl)coc2cc1O	yes
DOC	CC12CCC(=O)C=C1CCC1C2CCC2(C)C(C(=O)CO)CCC12	yes
5142031	CCOC(=O)c1c(N)sc2ccccc12	yes
5695025	CCOC(=O)c1c(N=C(O)OCC)sc(C)c1CC	yes
5935291	Cc1ccc(N2C(=O)CC(N3CCN(c4cccc(Cl)c4)CC3)C2=O)cc1Cl	yes
6625147	CC1CC(OCC(O)CN2CCN(c3ccccc3F)CC2)CC(C)(C)C1.Cl.Cl	no
6340625	O=C(c1cc2ccccc2o1)N1CCCC(c2ccccc2)C1	no
6383686	C=C(C)Cn1c(-c2ccc(OC)c(OC)c2)nc2ccccc21	no
5813444	CCC(O)=Nc1nc(-c2ccccc2)nc(SC)c1C(C)=O	no
6570890	CCOc1ccc(NCc2ccccc2NS(=O)(=O)c2ccc(C)cc2)cc1	no
6400155	O=C(c1cc2ccccc2o1)N1CCN(c2ccc(C(F)(F)F)cc2[N+](=O)[O-])CC1	yes
5951201	CCOC(=O)c1c(C)nc(-c2ccccc2)nc1N=C(O)Cc1ccccc1	yes
riluzole	N=c1[nH]c2ccc(OC(F)(F)F)cc2s1	yes
5583877	O=C(Nc1ccc(Cl)cc1)c1cnn(-c2ccccc2)c1N=C(O)c1ccco1	yes
6642835	Cc1c(O)ccc(C(=O)Cc2ccccc2)c1O	no
5573728	CC(=O)c1c(C)nc2n(Cc3ccccc3)c3ccccc3n12	yes
5658603	CCCCn1c2ccccc2n2c(C(=O)OCC)c(C)nc12	yes
6013263	COc1ccc(S(=O)(=O)Nc2ccc(C)cc2)cc1Br	yes
riluzole	N=c1[nH]c2ccc(OC(F)(F)F)cc2s1	yes
6652383	CC(C)(C)C(=O)Oc1ccc2c(=O)c(-c3ccccc3Cl)coc2c1	no
6522346	CC(=O)Oc1ccc(OC(C)=O)c(S(=O)(=O)c2ccc(Cl)c(Cl)c2)c1	no
6271180	Cc1cccc(OCC(=O)N2CCN(c3ccc(C(F)(F)F)cc3[N+](=O)[O-])CC2)c1C	yes
5480577	CCOC(=O)c1cc2n(c1N=CN(C)C)-c1ccccc1C2=O	yes
6204912	CCC(C)c1ccc(NC(=O)CC(C)(C)C)cc1	no
6386892	Cc1cc(C)c(N=C(O)Cc2cccs2)c(C)c1	no
5846693	OC(=NCc1ccco1)c1cc2nc(-c3ccc(F)cc3)cc(C(F)(F)F)n2n1	no
6030006	CCOc1ccccc1NS(=O)(=O)c1ccc(OC)c(Br)c1	yes
6756477	COc1cccc(-n2nnnc2SCC(O)=Nc2c(C)cc(C)cc2C)c1	no
6353053	CC(C)(c1ccccc1)c1ccc(OCC(O)=Nc2ccccc2C(=N)O)cc1	no
6667020	CCCOC(O)=Nc1nc(-c2ccc(C)cc2)c(C)s1	no
5978667	OC1=Nc2c(ccc3ccccc23)C(c2ccc(C(F)(F)F)cc2)C1	no
5649824	CCC(=O)c1c(C)nc2n(Cc3ccccc3)c3ccccc3n12	yes
7211089	O=[N+]([O-])c1cccc(N=C(O)c2ccc(Cl)cc2Cl)c1	no
5577990	O=C(c1c(N=C(O)c2ccccc2Cl)sc2c1CCCCC2)N1CCCCC1	no
6805976	CCC(C)c1ccccc1N=C(O)c1ccccc1I	no
5799128	CCCCOc1nnc(-c2ccccc2)c2ccccc12	no
5795075	Clc1ccc(OCc2nc(-c3ccccn3)no2)c(Br)c1	no
7115521	O=C1CCCc2c1[nH]c1ccc(C(F)(F)F)cc21	no

Supplementary Table 4. Continued

Chemical Name	SMILES	Retested
7145248	O=C(NCc1cccc(Oc2ccccc2)c1)C(=O)c1c[nH]c2ccccc12	yes
7015047	Cc1ccc(C(C)C)c(OCCNCc2ccccc2)c1	no
5802987	Clc1ccc(OCc2nc(-c3cccnc3)no2)c(Br)c1	no
5982161	COC(=O)c1c(N=C(O)CCN2C(=O)c3ccccc3C2=O)sc2c1CCC2	no
6647373	CC(=O)Oc1ccc2c(=O)c(Oc3ccc(F)cc3)c(C(F)(F)F)oc2c1C	no
7112518	CCOC(=O)COc1ccc2c(c1)c(C(C)=O)c(C)n2Cc1ccccc1	no
6653154	CC(=O)Oc1ccc2c(=O)c(Oc3ccccc3)c(C(F)(F)F)oc2c1C	no
6689594	CCc1cc2c(=O)c(Oc3ccccc3F)c(C)oc2cc1OC(C)=O	no
6793728	Cc1cc(=Nc2cccc3ccccc23)c2cc(Cl)ccc2[nH]1.Cl	no
5846232	CC(=O)c1cc(F)c(N2CCN(C(=O)c3ccc(Cl)cc3Cl)CC2)cc1C	yes
6639477	COc1ccc2c(=O)c(-c3ccccc3Cl)c(C)oc2c1	no
5128592	Cc1cccc(NC(=O)c2ccc(C(C)(C)C)cc2)c1	yes
6216715	Cc1cccc(C)c1N=C(O)CSCc1cccc(Br)c1	no
6053334	O=C(Cc1cccc(Cl)c1)Nc1ccc(Cl)cc1	no
6646535	COc1ccc2c(=O)c(-c3ccccc3)c(C)oc2c1C	no
6367818	CCC(=O)Nc1ccc(Oc2ccc(Cl)cc2)cc1	no
7115235	CC(C)(C)C(=O)CSc1nc2ccccc2c(=O)n1Cc1ccccc1	no
promazine	CN(C)CCCN1c2ccccc2Sc2ccccc21	no
6661919	CCCCN=C(S)N=C(O)c1ccc(Cl)cc1Cl	yes
6163607	O=S(=O)(Nc1ccc(OCc2ccccc2)cc1)c1ccc2c(c1)OCCO2	yes
5690842	COC(=O)c1sc(N=C(O)C2CCCO2)c(C(=O)OC)c1C	yes
6673619	Cc1ccccc1CC(=O)c1ccc(O)c(C)c1O	no
7011253	COc1ccccc1-c1nnc(SCc2ccccc2F)n1-c1ccccc1	no
7150160	O=C(CC(CC(=O)c1ccccc1)c1ccccc1)c1ccccc1	no
5867832	COc1ccc(N=C(O)c2ccccc2Oc2ccccc2)c(OC)c1	no
5942595	Cc1ccc(Cl)cc1N=C(O)COc1c(C)cccc1C	yes
6150813	Cc1noc(C)c1CSc1nc2sc3c(c2c(=O)n1-c1ccccc1)CCC3	no
6165550	Cc1cccc(-n2c(C=Cc3cccc([N+](=O)[O-])c3)nc3ccccc3c2=O)c1	no
6678692	CCc1cc2c(=O)c(Oc3ccc(F)cc3)coc2cc1OC(C)=O	no
7237541	Cc1ccc2c3c1C(=O)C(=O)N3C(C)(C)CC2(C)c1ccccc1	yes

Supplementary Table 5. Compound names and summary of results from *in vitro* FLIPR experiments for GABAA.

Compound Name	FLIPR Results	Ave Norm FLIPR Score	SD
DMSO	Negative	1	0.992
BGC 20-761	Negative	1.188647747	3.043
picrotoxin	Negative	-9.759599332	2.087
progesterone	Positive	17.80300501	4.5
etomidate	Positive	50.67111853	0.892
tracazolate	Positive	50.13856428	2.255
propofol	Positive	34.52337229	8.439
thiopental	Positive	11.39232053	2.274
DOC	Negative	-4.308013356	2.091
diazepam	Negative	-10.89565944	1.052
7013338	Positive	116.3580968	3.651
5942595	Positive	84.9148581	6.339
5658603	Positive	55.23539232	3.39
6474599	Positive	52.02420702	3.831
6537142	Positive	50.97579299	1.64
5649824	Positive	41.41402337	4.859
5583877	Positive	36.70784641	3.964
5925611	Positive	32.94657763	0.645
6376886	Positive	32.44240401	6.486
5695025	Positive	32.2721202	4.675
6028165	Positive	28.75792989	3.955
5573728	Positive	27.62103506	2.061
5860357	Positive	25.8706177	3.621
6993015	Positive	23.92654424	2.021
5937132	Positive	20.70033389	3.122
7282929	Positive	17.15317195	2.717
7114005	Positive	15.23205343	0.272
5869570	Positive	15.03672788	0.574
6366118	Positive	14.5033389	0.336
6029941	Positive	14.00584307	NA
5690842	Positive	12.09432387	6.775
7273455	Positive	7.892320535	5.349
7100598	Positive	7.736227046	0.217
6091285	Positive	7.664440735	0.253
5986291	Positive	6.420701169	4.018
5142031	Positive	5.23706177	0.349
6030006	Negative	3.04590985	3.264
5768306	Negative	2.243739566	0.059
6013263	Negative	1.035058431	2.342

Supplementary Table 5. Continued

Compound Name	FLIPR Results	Ave Norm FLIPR Score	SD
5102870	Negative	-0.944908181	1.695
7166683	Negative	-1.302170284	0.581
5811265	Negative	-1.4557596	3.792
5551268	Negative	-1.463272121	1.876
7113584	Negative	-2.454924875	0.79
5835629	Negative	-2.682804675	3.707
5845856	Negative	-2.947412354	1.101
6645327	Negative	-4.733722872	0.776
6212662	Negative	-5.178631052	0.047
5846886	Negative	-5.25542571	0.94
6163607	Negative	-5.679465776	1.265
7014338	Negative	-6.270450752	2.581
6246227	Negative	-6.910684474	1.718
7284610	Negative	-7.29966611	4.074
6366421	Negative	-8.515859767	1.221
5736224	Negative	-10.45158598	1.238
6225936	Negative	-14.696995	0.004
7145248	Negative	-24.78631052	0.673
5587256	Negative	-26.36894825	22.82

Supplementary Table 6. SEA predictions prioritized by EF from the top 1000 hit compounds.

CHEMBL ID	EF	p-Value	q-Value	Description
CHEMBL5469	10.832	2.82E-153	9.38E-148	Protein tyrosine kinase 2 beta
CHEMBL2094122	9.2246	3.67E-20	1.22E-14	GABA-A receptor; alpha-5/beta-3/gamma-2
CHEMBL3746	8.2498	5.69E-90	1.89E-84	11-beta-hydroxysteroid dehydrogenase 2
CHEMBL3012	6.1087	6.66E-54	2.22E-48	Phosphodiesterase 7A
CHEMBL4501	5.2561	9.62E-22	3.20E-16	Ribosomal protein S6 kinase 1
CHEMBL5936	5.2175	8.15E-29	2.71E-23	Toll-like receptor 7
CHEMBL1907607	5.16	1.14E-53	3.79E-48	GABA-A receptor; anion channel
CHEMBL4409	4.6661	1.65E-09	0.000549	Phosphodiesterase 10A
CHEMBL2835	4.3081	2.33E-56	7.74E-51	Tyrosine-protein kinase JAK1
CHEMBL1787	4.3081	4.35E-30	1.45E-24	Steroid 5-alpha-reductase 1
CHEMBL2095227	4.2252	3.99E-178	1.33E-172	Vascular endothelial growth factor receptor
CHEMBL4296	4.2035	1.41E-35	4.69E-30	Sodium channel protein type IX alpha subunit
CHEMBL3055	4.1484	9.87E-10	0.000328	Cyclin-dependent kinase 7
CHEMBL4975	4.0012	8.05E-14	2.68E-08	Adenosine A1 receptor
CHEMBL2034	3.827	6.36E-34	2.12E-28	Glucocorticoid receptor
CHEMBL1856	3.5805	9.87E-79	3.28E-73	Steroid 5-alpha-reductase 2
CHEMBL4977	3.5709	8.07E-63	2.69E-57	Proto-oncogene c-JUN
CHEMBL2488	3.5637	3.50E-43	1.16E-37	Prostanoid EP2 receptor
CHEMBL4040	3.4143	7.31E-47	2.43E-41	MAP kinase ERK2
CHEMBL259	3.3269	5.86E-17	1.95E-11	Melanocortin receptor 4
CHEMBL3072	3.2333	7.50E-24	2.49E-18	Androgen Receptor
CHEMBL1907605	3.1718	1.64E-15	5.46E-10	Cyclin-dependent kinase 2/cyclin E1
CHEMBL1918	3.0062	8.12E-184	2.70E-178	Glutamate receptor ionotropic kainate 1
CHEMBL2337	2.8332	9.25E-110	3.08E-104	Glycine transporter 1
CHEMBL3687	2.7944	2.78E-49	9.26E-44	Arachidonate 12-lipoxygenase
CHEMBL4430	2.7913	4.86E-43	1.62E-37	Cytochrome P450 17A1
CHEMBL330	2.7913	3.71E-67	1.24E-61	Glutamate (NMDA) receptor subunit zeta 1
CHEMBL3514	2.7732	4.06E-30	1.35E-24	LDL-associated phospholipase A2
CHEMBL5652	2.7499	2.49E-110	8.27E-105	Glucose-dependent insulinotropic receptor
CHEMBL2569	2.7405	3.98E-110	1.32E-104	Microsomal triglyceride transfer protein large subunit
CHEMBL2971	2.6595	2.83E-47	9.41E-42	Tyrosine-protein kinase JAK2
CHEMBL5658	2.6443	6.50E-66	2.16E-60	Prostaglandin E synthase
CHEMBL1293255	2.6013	8.60E-140	2.86E-134	15-hydroxyprostaglandin dehydrogenase [NAD+]
CHEMBL1889	2.5984	4.47E-68	1.49E-62	Vasopressin V1a receptor
CHEMBL2568	2.5325	5.69E-92	1.89E-86	Liver glycogen phosphorylase
CHEMBL3230	2.4991	3.40E-103	1.13E-97	Sphingosine 1-phosphate receptor Edg-6
CHEMBL4036	2.454	2.29E-26	7.61E-21	Cyclin-dependent kinase 5
CHEMBL2903	2.4465	7.17E-17	2.39E-11	Arachidonate 15-lipoxygenase
CHEMBL3227	2.4305	6.64E-166	2.21E-160	Metabotropic glutamate receptor 5
CHEMBL1790	2.3894	1.62E-28	5.39E-23	Vasopressin V2 receptor
CHEMBL275	2.3347	2.22E-16	7.40E-11	Phosphodiesterase 4B
CHEMBL4652	2.3307	3.35E-40	1.11E-34	Somatostatin receptor 1
CHEMBL3371	2.2818	1.39E-12	4.62E-07	Serotonin 6 (5-HT6) receptor
CHEMBL5409	2.2229	7.73E-26	2.57E-20	G-protein coupled bile acid receptor 1
CHEMBL3351	2.1837	2.62E-12	8.72E-07	Acetyl-CoA carboxylase 1
CHEMBL4336	2.1425	6.56E-15	2.18E-09	Prostanoid EP3 receptor
CHEMBL235	2.1375	3.50E-48	1.16E-42	Peroxisome proliferator-activated receptor gamma
CHEMBL2095160	2.1118	2.42E-09	0.000807	Leukotriene B4 receptor
CHEMBL5071	2.0202	2.18E-57	7.25E-52	G protein-coupled receptor 44
CHEMBL1811	1.9836	1.35E-19	4.51E-14	Prostanoid EP1 receptor
CHEMBL4315	1.9642	1.48E-22	4.93E-17	Purinergic receptor P2Y1

Supplemental Table 6. Continued (2 of 3)

CHEMBL ID	EF	p-Value	q-Value	Description
CHEMBL1906	1.9542	1.78E-33	5.91E-28	Serine/threonine-protein kinase RAF
CHEMBL2001	1.9359	1.07E-72	3.55E-67	Purinergic receptor P2Y12
CHEMBL4478	1.9234	9.22E-19	3.07E-13	Voltage-gated N-type calcium channel alpha-1B subunit
CHEMBL3338	1.9062	1.44E-28	4.79E-23	Squalene synthetase
CHEMBL1966	1.8407	7.61E-12	2.53E-06	Dihydroorotate dehydrogenase
CHEMBL2993	1.8048	1.81E-19	6.01E-14	Monoamine oxidase B
CHEMBL4051	1.7585	8.50E-33	2.83E-27	Cystic fibrosis transmembrane conductance regulator
CHEMBL3974	1.7366	3.74E-29	1.24E-23	Proteinase-activated receptor 1
CHEMBL2868	1.7226	1.58E-63	5.24E-58	Vasopressin V1a receptor
CHEMBL1868	1.694	3.93E-17	1.31E-11	Vascular endothelial growth factor receptor 1
CHEMBL2736	1.6741	1.24E-32	4.14E-27	Metabotropic glutamate receptor 4
CHEMBL244	1.6674	2.31E-22	7.70E-17	Coagulation factor X
CHEMBL3553	1.6663	4.38E-44	1.46E-38	Tyrosine-protein kinase TYK2
CHEMBL285	1.6627	2.46E-10	8.20E-05	Acyl coenzyme A:cholesterol acyltransferase 1
CHEMBL1901	1.6571	2.88E-28	9.58E-23	Cholecystokinin A receptor
CHEMBL1741186	1.6522	2.90E-36	9.66E-31	Nuclear receptor ROR-gamma
CHEMBL311	1.6361	5.80E-22	1.93E-16	Glutamate [NMDA] receptor subunit epsilon 2
CHEMBL3969	1.6281	2.92E-10	9.72E-05	Carbonic anhydrase VB
CHEMBL4892	1.6142	6.42E-10	0.000213	Alpha-1a adrenergic receptor
CHEMBL3238	1.6083	4.80E-75	1.60E-69	Carnitine palmitoyltransferase 2
CHEMBL249	1.6064	1.82E-46	6.06E-41	Neurokinin 1 receptor
CHEMBL3766	1.5872	3.26E-14	1.09E-08	Vasopressin V2 receptor
CHEMBL2413	1.5732	1.63E-13	5.43E-08	C-C chemokine receptor type 1
CHEMBL2047	1.5349	1.17E-10	3.88E-05	Bile acid receptor FXR
CHEMBL3858	1.5283	7.25E-56	2.41E-50	Carnitine palmitoyltransferase 1A
CHEMBL2564	1.5215	5.48E-46	1.82E-40	Metabotropic glutamate receptor 5
CHEMBL1913	1.4884	1.72E-11	5.72E-06	Platelet-derived growth factor receptor beta
CHEMBL1293194	1.4697	1.28E-46	4.25E-41	Carnitine O-palmitoyltransferase 1 liver isoform
CHEMBL2095150	1.4663	4.96E-23	1.65E-17	Phosphodiesterase 1
CHEMBL3156	1.457	8.36E-13	2.78E-07	Thromboxane A2 receptor
CHEMBL4018	1.4434	3.32E-17	1.10E-11	Neuropeptide Y receptor type 2
CHEMBL1844	1.3767	3.24E-17	1.08E-11	Macrophage colony stimulating factor receptor
CHEMBL2216739	1.3745	2.01E-23	6.68E-18	Carnitine O-palmitoyltransferase 1 muscle isoform
CHEMBL4722	1.3586	2.22E-13	7.40E-08	Serine/threonine-protein kinase Aurora-A
CHEMBL2093869	1.3358	4.11E-15	1.37E-09	Integrin alpha-IIb/beta-3
CHEMBL2093866	1.3354	6.69E-25	2.23E-19	Estrogen receptor
CHEMBL5669	1.2425	3.27E-24	1.09E-18	Epoxide hydrolase 2
CHEMBL4140	1.2125	3.30E-37	1.10E-31	Epoxide hydratase
CHEMBL256	1.1181	3.59E-12	1.19E-06	Adenosine A3 receptor
CHEMBL3572	1.0034	8.31E-15	2.77E-09	Cholesteryl ester transfer protein
CHEMBL3105	0.89889	1.50E-20	4.99E-15	Poly [ADP-ribose] polymerase-1
CHEMBL1937	0.86861	2.11E-25	7.01E-20	Histone deacetylase 2
CHEMBL1951	0.8684	3.01E-09	0.001	Monoamine oxidase A
CHEMBL255	0.85701	2.34E-19	7.79E-14	Adenosine A2b receptor
CHEMBL2111429	0.8541	7.13E-15	2.37E-09	Histone deacetylase (HDAC1 and HDAC2)
CHEMBL3254	0.82456	9.65E-20	3.21E-14	Monoamine oxidase A
CHEMBL273	0.82284	3.24E-17	1.08E-11	Serotonin 1a (5-HT1a) receptor
CHEMBL2095189	0.78671	5.92E-11	1.97E-05	Platelet-derived growth factor receptor
CHEMBL251	0.78053	3.07E-14	1.02E-08	Adenosine A2a receptor
CHEMBL321	0.77988	1.51E-14	5.02E-09	Matrix metalloproteinase 9
CHEMBL6009	0.76082	2.88E-15	9.60E-10	Diacylglycerol O-acyltransferase 1

Supplemental Table 6. Continued (3 of 3)

CHEMBL ID	EF	p-Value	q-Value	Description
CHEMBL4191	0.74784	1.01E-11	3.36E-06	Monoglyceride lipase
CHEMBL205	0.73443	1.20E-10	3.99E-05	Carbonic anhydrase II
CHEMBL3571	0.73416	2.94E-14	9.79E-09	Cannabinoid CB1 receptor
CHEMBL3192	0.72428	1.63E-38	5.42E-33	Histone deacetylase 8
CHEMBL5393	0.71706	5.11E-59	1.70E-53	ATP-binding cassette sub-family G member 2
CHEMBL219	0.68396	5.99E-16	1.99E-10	Dopamine D4 receptor
CHEMBL3594	0.68047	7.19E-21	2.39E-15	Carbonic anhydrase IX
CHEMBL281	0.67296	3.75E-19	1.25E-13	Carbonic anhydrase IV
CHEMBL1945	0.66941	1.07E-24	3.57E-19	Melatonin receptor 1A
CHEMBL1980	0.6652	2.77E-10	9.22E-05	Sodium channel protein type V alpha subunit
CHEMBL332	0.65466	2.02E-22	6.71E-17	Matrix metalloproteinase-1
CHEMBL4302	0.65163	1.11E-12	3.71E-07	P-glycoprotein 1
CHEMBL3138	0.64379	1.19E-20	3.98E-15	Dopamine D3 receptor
CHEMBL246	0.62469	5.68E-10	0.000189	Beta-3 adrenergic receptor
CHEMBL261	0.62233	6.21E-24	2.07E-18	Carbonic anhydrase I
CHEMBL2095171	0.58411	9.03E-10	0.0003	Sodium channel alpha subunits; brain (Types I II III)
CHEMBL3180	0.58231	1.61E-12	5.36E-07	Carboxylesterase 2
CHEMBL2093865	0.57073	9.07E-25	3.02E-19	Histone deacetylase
CHEMBL4792	0.55951	8.64E-24	2.87E-18	Orexin receptor 2
CHEMBL2093870	0.55882	4.04E-20	1.34E-14	Serotonin 2 (5-HT2) receptor
CHEMBL260	0.55449	2.22E-15	7.37E-10	MAP kinase p38 alpha
CHEMBL3898	0.55037	1.05E-20	3.50E-15	Bone morphogenetic protein 1
CHEMBL1878	0.54726	1.45E-14	4.82E-09	Calcium sensing receptor
CHEMBL2096671	0.53752	1.76E-11	5.86E-06	Serotonin 2 (5-HT2) receptor
CHEMBL3229	0.53436	5.63E-21	1.87E-15	Anandamide amidohydrolase
CHEMBL3473	0.53004	2.87E-34	9.54E-29	C-C chemokine receptor type 3
CHEMBL234	0.52084	4.19E-46	1.39E-40	Dopamine D3 receptor
CHEMBL1946	0.51445	3.27E-42	1.09E-36	Melatonin receptor 1B
CHEMBL214	0.51376	1.16E-28	3.84E-23	Serotonin 1a (5-HT1a) receptor
CHEMBL3455	0.5133	1.69E-28	5.62E-23	Anandamide amidohydrolase
CHEMBL2094268	0.50345	2.06E-31	6.84E-26	Melatonin receptor
CHEMBL283	0.50011	9.33E-46	3.10E-40	Matrix metalloproteinase 3
CHEMBL3361	0.49714	4.58E-39	1.52E-33	Dopamine D4 receptor
CHEMBL3427	0.49437	2.44E-14	8.12E-09	Dopamine D2 receptor
CHEMBL264	0.49369	5.49E-16	1.83E-10	Histamine H3 receptor
CHEMBL217	0.48105	2.23E-52	7.43E-47	Dopamine D2 receptor
CHEMBL3465	0.48013	9.07E-15	3.02E-09	Sigma opioid receptor
CHEMBL220	0.47337	8.15E-17	2.71E-11	Acetylcholinesterase
CHEMBL2409	0.44961	2.31E-28	7.68E-23	Epoxide hydratase
CHEMBL4588	0.4342	2.36E-49	7.85E-44	Matrix metalloproteinase 8
CHEMBL1873	0.42696	3.40E-20	1.13E-14	Tissue-type plasminogen activator
CHEMBL325	0.42455	3.61E-39	1.20E-33	Histone deacetylase 1
CHEMBL3286	0.41945	7.47E-29	2.49E-23	Urokinase-type plasminogen activator
CHEMBL287	0.39167	2.26E-39	7.51E-34	Sigma opioid receptor
CHEMBL3223	0.37809	4.88E-32	1.62E-26	Serotonin 7 (5-HT7) receptor
CHEMBL3199	0.36708	2.07E-29	6.88E-24	Acetylcholinesterase
CHEMBL3602	0.33883	6.17E-42	2.05E-36	Sigma opioid receptor
CHEMBL3198	0.3105	2.27E-38	7.55E-33	Acetylcholinesterase

Supplementary Table 7. SEA predictions prioritized by EF from the top 30 hit compounds.

CHEMBL ID	EF	p-Value	q-Value	description
CHEMBL3746	53.234	0	0	11-beta-hydroxysteroid dehydrogenase 2
CHEMBL1787	27.799	7.30E-267	2.43E-261	Steroid 5-alpha-reductase 1
CHEMBL3072	20.864	1.26E-225	4.18E-220	Androgen Receptor
CHEMBL1856	19.253	5.42E-146	1.80E-140	Steroid 5-alpha-reductase 2
CHEMBL1907607	14.798	6.99E-127	2.33E-121	GABA-A receptor; anion channel
CHEMBL2096664	8.055	2.14E-54	7.12E-49	Steroid 5-alpha-reductase
CHEMBL230	7.6613	1.04E-24	3.47E-19	Cyclooxygenase-2
CHEMBL2903	5.92	1.39E-48	4.61E-43	Arachidonate 15-lipoxygenase
CHEMBL2095227	4.8113	2.18E-125	7.25E-120	Vascular endothelial growth factor receptor
CHEMBL1889	4.5727	3.51E-99	1.17E-93	Vasopressin V1a receptor
CHEMBL1918	4.4766	5.57E-125	1.85E-119	Glutamate receptor ionotropic kainate 1
CHEMBL3371	4.4172	2.91E-50	9.70E-45	Serotonin 6 (5-HT6) receptor
CHEMBL2564	4.0909	1.99E-49	6.60E-44	Metabotropic glutamate receptor 5
CHEMBL2337	3.6564	5.47E-147	1.82E-141	Glycine transporter 1
CHEMBL2568	3.4403	2.69E-29	8.97E-24	Liver glycogen phosphorylase
CHEMBL244	3.3105	3.62E-30	1.20E-24	Coagulation factor X
CHEMBL2993	2.9115	2.77E-20	9.22E-15	Monoamine oxidase B
CHEMBL3230	2.8458	8.52E-70	2.83E-64	Sphingosine 1-phosphate receptor Edg-6
CHEMBL1966	2.6394	3.89E-14	1.29E-08	Dihydroorotate dehydrogenase
CHEMBL2868	2.6154	1.21E-59	4.04E-54	Vasopressin V1a receptor
CHEMBL3238	2.5944	7.37E-27	2.45E-21	Carnitine palmitoyltransferase 2
CHEMBL3766	2.5604	2.80E-50	9.32E-45	Vasopressin V2 receptor
CHEMBL2216739	2.2174	5.63E-11	1.87E-05	Carnitine O-palmitoyltransferase 1 muscle isoform
CHEMBL4681	2.0292	2.43E-10	8.09E-05	Aldo-keto-reductase family 1 member C3

Supplementary Table 8. Reference compounds targeting receptors with relatively low EF scores

Compound	Target	InChiKey
SR 49059	V1 antagonist	CEBYCSRFKCEUSW-NAYZPBBASA-N
TCS 359	FLT3 RTK antagonist	FSPQCTGGIANIJZ-UHFFFAOYSA-N
Piclamilast	PDEantagonist	RRRUXBQSQLKHEL-UHFFFAOYSA-N
(R)-C R 8	CDK antagonist	ORYSYXHQFOWNDK-RGFWRHHQSA-N
DL-TBOA	EAAT antagonist	BYOBCYXURWDEDS-IUCAKERBSA-N
ML 218 hydrochloride	CAC1G antagonist	IDCVEUISZZKMKJ-ZXVFAPHLSA-N
AG 825	Erbb2 antagonist	KXDONFLNGBQLTN-WUXMJOGZSA-N
Tak 165	Erbb2 antagonist	ZTFBIUXIQYRUNT-MDWZMJQESA-N
Z57705210	PPBT antagonist	OTFKFIWLDAHEKF-UHFFFAOYSA-N
BX 471	CCR1 antagonist	XQYASZNUFDVMFH-CQSZACIVSA-N
ML 00253764	MC4R antagonist	KZUMGPQDDCBFBF-UHFFFAOYSA-N
Nav26	SCN9A antagonist	ICGMZCVSHDKQTE-UHFFFAOYSA-N
ATC 0065	MCHR1 antagonist	BPGUWYBAINNZQH-LFOVFOEYSA-N
5648949	PD2R2 antagonist	WVBVIRRWTMFJAK-AWQFTUOYSA-N
JQ1	BRD3 antagonist	DNVXATUJJDPFDM-KRWDZBQOSA-N
R-+-methanandamide	CNR1 agonist	SQKRUBZPTNJQEM-FQPARAGTSA-N
TOPIRAMATE	GluR5 antagonist	KJADKKWYZYXHBB-XBWDGYHZSA-N
ML 202	PKM2 antagonist	MORBXZMIXGYQDB-UHFFFAOYSA-N
PF 04885614	SCNAA antagonist	AGORGFNWYAUYSU-UHFFFAOYSA-N
LY 341495	Group II mGluR antagonist	VLZBRVJVCCNPRJ-KPHUOKFYSA-N
ICI 63197	PDE4 antagonist	UQDVRVNMIJAGRK-UHFFFAOYSA-N
GW 791343 Hydrochloride	P2X7 allosteric modulator	WSBRAHWNJBXXJM-UHFFFAOYSA-N
A 740003	P2X7 antagonist	PUHSRMSFDASMAE-UHFFFAOYSA-N
TOLMETIN	IL-8 antagonist	UPSPUYADGBWSHF-UHFFFAOYSA-N
EMDT oxalate	5HT6 Agonist	IFGWAHGHGDZBEH-UHFFFAOYSA-N
Metyrapone	11β-hydroxylase antagonist	FJLBFSROUSIWMA-UHFFFAOYSA-N
ACEA	CB1 receptor agonist	SCJNCDSAIRBRIA-DOFZRALJSA-N
Strophanthidin	Na+ /K+-ATPase antagonist	ODJLBQGVINUMMR-HZXDTFASSA-N
Procaine	NaV general antagonist	MFDFERRIHVXMIY-UHFFFAOYSA-N
ZINC13108136	BACE2 antagonist	SVHVIRBGQRDCIB-UHFFFAOYSA-N
ATC 0175 hydrochloride	MCH1 antagonist	FAIMGWSOSCFGRU-UHFFFAOYSA-N
Fenobam	mGlu5 agonist	DWPQODZAOSWNHB-UHFFFAOYSA-N
NNC 55-0396 dihydrochloride	NaV general antagonist	BCCQNBXHUMKLFW-HNQRYHMESA-N
Xylazine hydrochloride	α2-adronergic agonist	DIIBRMSCONGGIN-UHFFFAOYSA-N
Bumetanide	NKCC cotransporter antagonist	MAEIEVLCKWDQJH-UHFFFAOYSA-N
Epibatidine Hydrochloride	nicotinic agonist	NLPRAJRHRHZCQQ-UTLUCORTSA-N
(-)-Nicotine Ditartrate	Nicotinic acetylcholine receptor agonis	RFEJUZJILGIRHQ-UHFFFAOYSA-N
Hexamethonium Bromide	nicotinic receptor antagonist	FAPSXSAPXXJTOU-UHFFFAOYSA-L
Scopolomine hydrobromide	muscarinic antagonist	STECJAGHUSJQJN-FWXGHANASA-N
octopamine hydrochloride	β3 adrenoceptor agonist	QHGUCRYDKWKLMG-UHFFFAOYSA-N
Ro 32-0432 hydrochloride	protein kinase C antagonist	HSPRASOZRZDELU-LMOVPXPDSA-N
BzATP triethylammonium salt	P2X7 receptor agonist	HVOVBTNCGADRTH-WBLDMZOZSA-N
Phenytoin	NaV general antagonist	CXOFVDLJLONNDW-UHFFFAOYSA-N
TCB-2	5HT2AR agonist	TYMMXVZAUGQKRF-UHFFFAOYSA-N
MTEP	mGluR5 antagonist	NRBNGHCYDWUVLC-UHFFFAOYSA-N
Ro4368554	5HT6R antagonist	AOPYPEADLGTXRA-UHFFFAOYSA-N
Biphenyl-indanone A	mGluR2 allosteric modulator	KMKBEESNZAPKMP-UHFFFAOYSA-N
LuAE58054	5HT6R antagonist	YBAWYTYNMZWMMJ-UHFFFAOYSA-N

Supplementary Table 9. Compound names and descriptions for annotated and novel small molecules that interact with 3 of the primary SEA predicted targets (mGluR, GABAA, and HTR6).

mGluR Compounds tested	SMILES	Mechanism Notes	Phenoscore
Fenobam	CN1CC(=O)N=C1NC(=O)Nc2cccc(c2)Cl	mGlu5 agonist	0.3
STK234931	c1ccc(cc1)C#Cc2ccc(cc2)C(=O)N3CCC(CC3)O	MGluR antagonist	0.4
MPEP	CC1=NC(=CC=C1)C#CC2=CC=CC=C2.Cl	mGlu5 antagonist	0.73
TOPIRAMATE	CC1(O[C@@H]2CO[C@@]3([C@H]([C@@H]2O1)OC(O3)(C)C)COS(=O)(=O)N)C	mGluR5 antagonist	0.1
UBP 302	c1ccc(c(c1)Cn2c(=O)ccn(c2=O)C[C@@H](C(=O)O)N)C(=O)O	mGluR5 antagonist	0.17
VU 0361737	COc1cc(ccc1Cl)NC(=O)c2ccccn2	mGluR4 positive allosteric modulator	0.28
VU 0155041 NaSalt	c1c(cc(cc1Cl)Cl)NC(=O)[C@H]2CCCC[C@H]2C(=O)O	mGluR4 positive allosteric modulator	0.11
Cinnabarinic acid	c1cc(c2c(c1)oc-3cc(=O)c(c(c3n2)C(=O)O)N)C(=O)O	mGluR4 agonist	0.18
L-AP4	[H][C@](N)(CCP(O)(O)=O)C(O)=O	mGluR4/6/7/8 agonist	0.1
LY-354740	C1C[C@]([C@H]2[C@@H]1[C@@H]2C(=O)O)(C(=O)O)N	mGluR2/3 agonist	0.1
Biphenylindanone A	CC1=C(C=C2CC(C(=O)C2=C1C)C3CCCC3)OCC4=CC(=CC=C4)C5=CC=C(C=C5)C(=O)O	mGluR2 positive allosteric modulator	0.11
Predicted mGluR			
7285168	OC(=Nc1ccc(Cl)cc1F)c1cccc2ccccc12	predicted mGluR	0.54
7211089	O=[N+]([O-])c1cccc(N=C(O)c2ccc(Cl)cc2Cl)c1	predicted mGluR	0.5
5128592	Cc1cccc(c1)NC(=O)c2ccc(cc2)C(C)(C)C	predicted mGluR	0.52
6576466	O=[N+]([O-])c1cccc(C(O)=Nc2ccc(Cl)cc2C(F)(F)F)c1	predicted mGluR	0.57
5795075	Clc1ccc(OCc2nc(-c3ccccn3)no2)c(Br)c1	predicted mGluR	0.39
7136301	O=C(N[C@H](c1occc1)C)COC(=O)c3cc([N+]([O-])=O)ccc3N2CCCC2	predicted mGluR	0.42
6587027	CC(=O)c1cccc(NC(=O)c2ccc(-c3ccc(Cl)cc3)o2)c1	predicted mGluR	0.57
7271289	Cc1cc(Cl)ccc1OCC(=O)N1CCN(c2ccc(Cl)cc2)CC1	predicted mGluR	0.56
7305598	OC(=Nc1cccc(N=C(O)c2cc(Cl)ccc2Cl)c1)c1cc(Cl)ccc1Cl	predicted mGluR	0.51
7100598	O=C(c1ccccc1)c1cccc(N=C(O)Cc2ccc(Cl)cc2)c1	predicted mGluR	0.54
6053334	O=C(Cc1cccc(Cl)c1)Nc1ccc(Cl)cc1	predicted mGluR	0.34
6376886	COc1cc(OC)cc(C(O)=Nc2ccc(Cl)cc2C(F)(F)F)c1	predicted mGluR	0.59
5869570	Cc1cc(nc(n1)N/C(=N\C(=O)C)/Nc2cccc(c2)C(F)(F)F)C	predicted mGluR	0.68
5583877	c1ccc(cc1)n2c(c(cn2)C(=O)Nc3ccc(cc3)Cl)NC(=O)c4ccco4	predicted mGluR	0.66
5943451	CCOC(=O)c1c(C)n(Cc2ccco2)c2ccc(OC)cc21	predicted mGluR	0.37
GABA Compounds Tested			
diazepam	CN1c2ccc(cc2C(=NCC1=O)c3ccccc3)Cl	GABAA agonist	0.68
propofol	Oc1c(cccc1C(C)C)C(C)C	GABAA agonist	0.78
DMCM	CCc1c(ncc2[nH]c3cc(OC)c(OC)cc3c12)C(=O)OC	GABAA negative allosteric modulator	0.54
β-CCE	CCOC(=O)c1cc2c3ccccc3[nH]c2cn1	GABAA inverse agonist	0.37
flumazenil	CCOC(=O)c1ncn2c1CN(C)C(=O)c1cc(F)ccc1-2	GABAA antagonist	0.1
TB 21007	CC1(CC2=C(SC(=C2C(=O)C1)SCCO)C3=NC=CS3)C	GABAA inverse agonist	0.12
bicuculline (-)	CN1CCc2cc3c(cc2[C@H]1[C@H]4c5ccc6c(c5C(=O)O4)OCO6)OCO3	GABAA antagonist	0.05
picrotoxin	C[C@@]12[C@H]3[C@H]4[C@H]([C@@H]([C@@]1(C[C@@H]5[C@]2(O5)C(=O)O3)O)C(=O)O4)C(C)(C)O	GABAA antagonist	0.03
bicuculline (+)	CN1CCc2cc3c(cc2[C@H]1[C@H]4c5ccc6c(c5C(=O)O4)OCO6)OCO3	GABAA antagonist	0.23
etomidate	N1(C=NC=C1C(=O)OCC)C(C)c2ccccc2	GABAA agonist	0.81
Alphaxalone	CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC(=O)[C@H]3[C@H]2CC[C@@H]4[C@@]3(CC[C@H](C4)O)C)C	GABAA agonist	0.58
thipoental	CCCC(C)C1C(C(=O)NC(=S)NC1=O)CC	GABAA agonist	0.51
SR-95531	[H]/N=c/1\ccc(nn1CCCC(=O)O)c2ccc(cc2)OC.Br	GABAA antagonist	0.21
muscimol	NCc1cc(O)no1	GABAA agonist	0.21
GABA	NCCCC(=O)O	GABA agonist	0.21
tracazolate	CCCCNc1c2cnn(c2nc(c1C(=O)OCC)C)CC.Cl	GABAA agonist	0.8
clonazepam	c1ccc(c(c1)C2=NCC(=O)Nc3c2cc(cc3)[N+](=O)[O-])Cl	GABAA agonist	0.23
zolpidem	Cc1ccc(cc1)c2c(n3cc(ccc3n2)C)CC(=O)N(C)C	GABAA agonist	0.23
21-Hydroxyprogesterone	C[C@]12CC[C@H]3[C@H]([C@@H]1CC[C@@H]2C(=O)CO)CCC4=CC(=O)CC[C@]34C	GABAA agonist	0.79
SCS	C1=CC=C(C(=C1)/C=N/NC(=O)C2=CC=CC=C2O)O	GABAA antagonist	0.04
Isoflurane	C(C(F)(F)F)(OC(F)F)Cl	GABAA agonist	0.03
TACA	C(/C=C/C(=O)O)N	GABAA agonist	0.07
R-Baclofen	c1cc(ccc1C(CC(=O)O)CN)Cl	GABAB Agonist	0.26
Progesterone	CC(=O)[C@H]1CCC2C3CCC4=CC(=O)CC[C@]4(C)C3CC[C@]12C	GABAA agonist	0.68
Indiplon	CC(=O)N(C)C1=CC=CC(=C1)C2=CC=NC3=C(C=NN23)C(=O)C4=CC=CS4	GABA agonist	-0.06
Ocinaplon	C1=CC=NC(=C1)C(=O)C2=C3N=CC=C(N3N=C2)C4=CC=NC=C4	GABA agonist	-0.01
L-655,708	CCOC(=O)c1c2n(cn1)-c3ccc(cc3C(=O)N4[C@H]2CCC4)OC	GABAA antagonist	0.51
Gabapentin	C1CCC(CC1)(CC(=O)O)CN	increases GABA biosynthesis	0.15
Valproic Acid	CCCC(CCC)C(=O)O	GABA agonist	0.75
Predicted GABA			
5658603	CCCCn1c2ccccc2n2c(C(=O)OCC)c(C)nc12	predicted GABAA	0.74
5951201	CCOC(=O)c1c(C)nc(-c2ccccc2)nc1N=C(O)Cc1ccccc1	predicted GABAA	0.48
5142031	CCOC(=O)c1c(N)sc2ccccc12	predicted GABAA	0.54
7145248	c1ccc(cc1)Oc2cccc(c2)CNC(=O)C(=O)c3c[nH]c4c3cccc4	predicted GABAA	0.5
Serotonin-6 Compounds Tested			
BGC 20-761	CN(C)CCC1=C(NC2=C1C=C(C=C2)OC)C3=CC=CC=C3	5-HT6 antagonist	0.74
Idalopirdine	C1=CC(=CC(=C1)OCC(C(F)F)(F)F)CNCCC2=CNC3=C2C=CC(=C3)F	5-HT6 antagonist	0.55
R1485 DI HCL	c1ccc(c(c1)F)S(=O)(=O)N2CCOc3c2cccc3N4CCNCC4.Cl.Cl	5-HT6 antagonist	0.07
MS 245 OXALATE	CN(C)CCC1=CN(C2=C1C=C(C=C2)OC)S(=O)(=O)C3=CC=CC=C3.C(=O)(C(=O)O)O	5-HT6 antagonist	0.09
SB 399885 hydrochloride	COC1=C(C=C(C=C1)S(=O)(=O)NC2=C(C(=CC(=C2)Cl)Cl)OC)N3CCNCC3	5-HT6 antagonist	0.16
Ro 04-6790	CNc1cc(NS(=O)(=O)c2ccc(N)cc2)nc(NC)n1	5-HT6 antagonist	0.11
WAY 208466	CN(C)CCN1C=C(C2=C1N=CC=C2)S(=O)(=O)C3=CC=CC(=C3)F.Cl.Cl	5-HT6 agonist	0.21
ST 1936 OXALATE	Cc1c(c2cc(ccc2[nH]1)Cl)CCN(C)C.C(=O)(C(=O)O)O	5-HT6 agonist	0.09
EMD 386088 HYDROCHLORIDE	Cc1c(c2cc(ccc2[nH]1)Cl)C3=CCNCC3.Cl	5-HT6 agonist	0.15
EMDT oxalate	CCc1c(c2cc(ccc2[nH]1)OC)CCN(C)C.C(=O)(C(=O)O)O	5-HT6 agonist	-0.03
Predicted Serotonin-6			
6028165	COc1ccc(S(=O)(=O)NC2CCCC2)cc1Br	predicted 5-HT6	0.66
6366118	COc1ccc(S(=O)(=O)N2CCC(C)CC2)cc1Br	predicted 5-HT6	0.66
6029941	COc1ccc(OC)c(NS(=O)(=O)c2ccc(OC)c(Br)c2)c1	predicted 5-HT6	0.61
6030057	CCc1ccccc1NS(=O)(=O)c1ccc(OC)c(Br)c1	predicted 5-HT6	0.36
6193422	O=S(=O)(Nc1cccc(Cl)c1)c1ccc2c(c1)OCCO2	predicted 5-HT6	0.46
6030006	CCOc1ccccc1NS(=O)(=O)c1ccc(OC)c(Br)c1	predicted 5-HT6	0.52
6013263	COc1ccc(S(=O)(=O)Nc2ccc(C)cc2)cc1Br	predicted 5-HT6	0.61
5352629	COc1ccccc1N1CCN(C(=O)c2ccc(C(=O)c3c(C)cc(C)cc3C)cc2)CC1	predicted 5-HT6	0.48
Other Serotonin Compounds Tested			
ALMOTRIPTAN MALATE	CN(C)CCc1c[nH]c2c1cc(cc2)CS(=O)(=O)N3CCCC3.C(C(C(=O)O)O)C(=O)O	5-H1B/1D agonist	0.18
GR 55562 DIHYDROCHLORIDE	CN(C)CCCc1cc(ccc1O)C(=O)Nc2ccc(cc2)c3ccncc3.Cl.Cl	5-HT1B silent antagonist	0.24
LISURIDE MALEATE	CCN(CC)C(=O)N[C@@H]1CN([C@@H]2Cc3c[nH]c4c3c(ccc4)C2=C1)C.C(=C\C(=O)O)\C(=O)O	5-HT2b antagonist	0.11
MESULERGINE HYDROCHLORIDE	Cn1cc2c3c1cccc3[C@H]4C[C@@H](CN([C@@H]4C2)C)NS(=O)(=O)N(C)C.Cl	5-HT2A/2C2C antagonist	0.4
Rizatriptan Benzoate	CN(C)CCc1c[nH]c2c1cc(cc2)Cn3cncn3.c1ccc(cc1)C(=O)O	5-HT1B/1C agonist	-0.01
Duloxetine Hydrochloride	CNCCC(c1cccs1)Oc2cccc3c2cccc3.Cl	SNRI	0.27

Supplementary Table 9. Continued

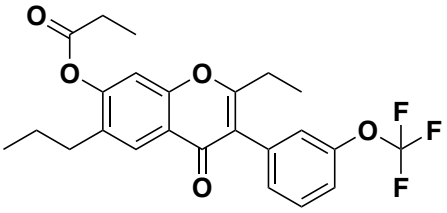
Other Serotonin Compounds Tested	SMILES	Mechanism Notes	Phenoscore
TCB-2	COc1cc(c(c2c1C(C2)CN)OC)Br.Br	5-HT2a agonist	0.1
Fluoxetine Hydrochloride	CNCCC(c1ccccc1)Oc2ccc(cc2)C(F)(F)F.Cl	SSRI	0.46
Ondansetron Hydrochloride	N2(c1c(cccc1)C3=C2CCC(C3=O)CN4C(=NC=C4)C)C	5-HT3 antagonist	0.13
SB-216641	Cc1cc(ccc1c2ccc(cc2)C(=O)Nc3ccc(c(c3)OCCN(C)C)OC)c4nc(on4)C	5-HT1B antagonist	0.11
SDZ-205557	CCN(CC)CCOC(=O)c1cc(c(cc1OC)N)Cl	5-HT3/4 antagonist	0.07
sumatriptan	CNS(=O)(=O)Cc1ccc2c(c1)c(c[nH]2)CCN(C)C	5-HT1 agonist	0.07
BW 723C86	CC(N)Cc1c[nH]c2ccc(OCc3cccs3)cc12	5-HT2B agonist	0.1
DOI HYDROCHLORIDE	CC(Cc1cc(c(cc1OC)I)OC)N.Cl	5-HT2A/2C agonist	0.1
Cisapride	Fc1ccc(cc1)OCCCN2CC(C(CC2)NC(=O)c3c(cc(c(c3)Cl)N)OC)OC	5-HT4 agonist	0.08
Sertraline	ClC1=CC=C([C@H]2C3=C([C@H](CC2)NC)C=CC=C3)C=C1Cl	SSRI	0.54
Fluvoxamine maleate	FC(F)(F)c1ccc(cc1)/C(=N/OCCN)/CCCCOC	SSRI	0.23
Paroxetine Hydrochloride	Cl.Fc1ccc(cc1)[C@@H]1CCNC[C@H]1COc1ccc2OCOc2c1	SSRI	0.2
8-HYDROXY-DPAT	CCCN(CCC)C1CCc2cccc(O)c2C1	5-HT1A agonist	0.49
alpha-METHYLSEROTONIN	CC(Cc1c[nH]c2c1cc(cc2)O)N	5-HT agonist	0.18
Trazodone hydrochloride	Cl.Clc1cccc(c1)N1CCN(CCCn2nc3ccccn3c2=O)CC1	SSRI	0.22
1-(3-CHLOROPHENYL)BIGUANIDE	c1cc(cc(c1)Cl)NC(=N)NC(=N)N.Cl	5-HT3 agonist	0.18
Quipazine maleate salt	c1ccc2c(c1)ccc(n2)N3CCNCC3.C(=C\C(=O)O)\C(=O)O	5-HT agonist	0.16
Zimelidine dihydrochloride monohydrate	Brc1ccc(cc1)/C(=C/CN(C)C)/c2cnccc2	SSRI	0.16
Chlorpheniramine maleate	Clc1ccc(cc1)C(CCN(C)C)c2ncccc2	SNRI	0.05
Buspirone hydrochloride	N1(CCN(CC1)c2ncccn2)CCCCN4C(=O)CC3(CCCC3)CC4=O	5-HT1A agonist	0.08
FENFLURAMINE	CCNC(C)Cc1cccc(c1)C(F)(F)F.Cl	SSRI and 5-HT release stimulator	0.13
57-DIHYDROXYTRYPTAMINE	c1c(cc(c2c1c(c[nH]2)CCN)O)O	5-HT neurontoxn	0.05
serotonin	NCCc1c[nH]c2ccc(O)cc12	5-HT agonist	0.19
Desipramine hydrochloride	CNCCCN1c2ccccc2CCc3c1cccc3.Cl	SNRI	0.49
clomipramine	CN(C)CCCN1c2ccccc2CCc2ccc(Cl)cc12	SNRI	0.13
Dihydroergotamine mesylate	CS(O)(=O)=O.[H][C@@]12CCCN1C(=O)[C@]([H])(Cc1cccc1)N1C(=O)[C@](C)(NC(=O)[C@@]3([H])CN(C)[C@]4([H])Cc5c[nH]c6cccc(c56)[C@@]4([H])C3)O[C@@]21O	5-HT antagonist	0.2
PROPRANOLOL	CC(NCC(O)COC1=C(C=CC=C2)C2=CC=C1)C	5-HT1/5-HT2 antagonist	0.15
clozapine	CN1CCN(CC1)C1=Nc2cc(Cl)ccc2Nc2ccccc12	5-HT2A/2C antagonist	0.23
ISAMOLTANE	CC(C)NCC(O)COc1ccccc1-n1cccc1	5-HT1B antagonist	0.15
METHIOTHEPIN	OC(=O)\C=C/C(O)=O.CSc1ccc2Sc3ccccc3CC(N3CCN(C)CC3)c2c1	5-HT2/1 antagonist	0.33

Supplementary Table 10. Isoflavone analogs of hit 7013338

Cpnd	C2	C2'	C3'	C6'	C6	C7	phenocopy
7013338	CH_3	Cl	H	H	C_2H_5	CH_3	positive
JG-17	CH_3	H	CF_3O	Cl	C_3H_7	H	negative
JG-41	C_3H_7	H	CF_3O	H	C_3H_7	H	negative
JG-30	C_2H_5	H	H	Cl	C_8H_9	C_3H_5O	negative
JG-13	C_2H_5	H	CF_3O	H	C_3H_7	C_3H_5O	negative
JG-31	C_3H_7	H	H	Cl	C_8H_9	C_4H_7O	negative
JG-48	C_2H_5	H	CF_3O	H	C_8H_9	$C_3H_5O_2$	negative
JG-47	C_3H_7	H	H	Cl	C_8H_9	$C_3H_5O_2$	negative
JG-46	C_2H_5	H	H	Cl	C_8H_9	$C_3H_5O_2$	negative
JG-34	C_2H_5	H	CF_3O	H	C_8H_9	C_3H_5O	negative
JG-49	C_3H_7	H	CF_3O	H	C_8H_9	$C_3H_5O_2$	negative
JG-35	C_3H_7	H	CF_3O	H	C_8H_9	C_4H_7O	negative
JG-39	C_3H_7	H	H	Cl	C_8H_9	H	negative
JG-43	C_3H_7	H	CF_3O	H	C_8H_9	H	negative
JG-42	C_2H_5	H	CF_3O	H	C_8H_9	H	negative
JG-38	C_2H_5	H	H	Cl	C_8H_9	H	negative
JG-37	C_3H_7	H	H	Cl	C_3H_7	H	positive
JG-29	C_3H_7	H	H	Cl	C_3H_7	C_4H_7O	positive
JG-44	C_2H_5	H	H	Cl	C_3H_7	$C_3H_5O_2$	positive
JG-16	C_2H_5	H	H	Cl	C_3H_7	C_3H_5O	positive
JG-45	C_3H_7	H	H	Cl	C_3H_7	$C_3H_5O_2$	positive
JG-18	C_2H_5	H	H	Cl	C_3H_7	H	positive

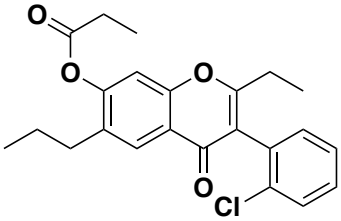
Spectral Analysis of Isoflavone Analogs

JG-13



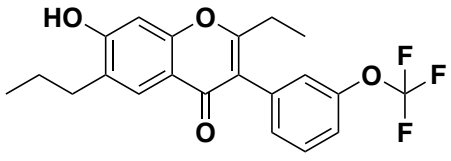
2-ethyl-4-oxo-6-propyl-3-(3-(trifluoromethoxy)phenyl)-4H-chromen-7-yl propionate: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.08 (s, 1 H), 7.47-7.45 (m, 1H), 7.27 (s, 1 H), 7.25-7.23 (d, 1 H), 7.23-7.21 (d, 1 H), 7.15 (s, 1 H), 7.27-7.27 (m, 2 H), 2.61-2.59 (m, 2 H), 2.57-2.55 (m, 2 H), 1.67-1.61 (m, 2 H), 1.35-1.32 (m, 3 H), 1.27-1.24 (m, 3 H), 0.97-0.94 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 176.31, 172.39, 167.95, 154.80, 153.18, 149.37, 135.19, 132.67, 129.91, 129.13, 127.43, 123.21, 121.87, 121.24, 120.42, 111.49, 32.09, 27.97, 26.32, 23.22, 14.00, 12.00, 9.29; HRMS (m/z): $[M+H]^{+}$ calcd., 448.1498; found, 449.1568.

JG-16



3-(2-chlorophenyl)-2-ethyl-4-oxo-6-propyl-4*H*-chromen-7-yl propionate: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.09 (s, 1 H), 7.51-7.49 (m, 1 H), 7.36-7.31 (m, 2 H), 7.26 (s, 1 H), 7.23-7.22 (m, 1 H), 2.70-2.66 (m, 2 H), 2.60-2.59 (m, 2 H), 2.53-2.40 (m, 2 H), 1.67-1.61 (m, 2 H), 1.34-1.32 (m, 3 H), 1.23-1.20 (m, 3 H), 0.96-0.94 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 175.95, 172.44, 168.20, 154.93, 153.06, 135.00, 132.54, 132.31, 129.89, 129.72, 127.53, 127.11, 121.29, 121.00, 111.50, 32.12, 27.99, 26.35, 23.25, 14.06, 11.43, 9.33; HRMS (m/z): $[M+H]^{+}$ calcd., 398.1285; found, 399.1349.

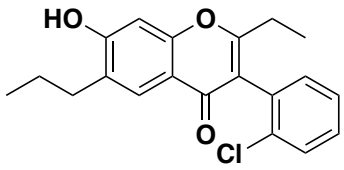
JG-17



2-ethyl-7-hydroxy-6-propyl-3-(3-(trifluoromethoxy)phenyl)-4*H*-chromen-4-one: ^{1}H-NMR (600 MHz, chloroform-d) δ = 7.94 (s, 1 H0, 7.42-7.39 (m, 1 H), 7.23-7.22 (d, 1 H), 7.17-7.11 (m, 2 H), 6.78 (m, 1 H), 3.66 (s, 1 H), 2.63-2.60 (m, 2 H), 2.56-2.52 (m, 2 H), 1.66-1.62 (m, 2 H), 1.25-1.22 (m, 3 H), 0.96-0.94 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 177.38, 167.95, 160.40, 156.44, 135.35, 130.00, 129.20, 129.01, 126.84, 123.22,

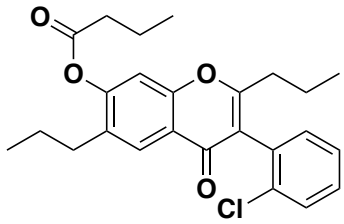
122.22, 121.35, 120.35, 119.93, 116.24, 102.25, 31.82, 26.33, 22.68, 14.05, 12.04; HRMS (m/z): $[M+H]^+$ calcd., 392.1235; found, 393.1311.

JG-18



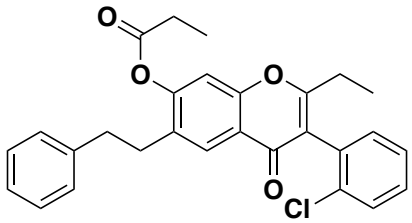
3-(2-chlorophenyl)-2-ethyl-7-hydroxy-6-propyl-4*H*-chromen-4-one: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.57 (s, 1 H), 7.94 (s, 1 H), 7.43-7.41 (d, 1 H), 7.29-7.24 (m, 3 H), 6.80 (s, 1 H), 2.62-2.59 (m, 2 H), 2.52-2.39 (m, 2 H), 1.67-1.61 (m, 2 H), 1.23-1.20 (m, 3 H), 0.96-0.94 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 177.09, 168.02, 160.08, 156.56, 135.08, 132.67, 132.39, 129.75, 129.60, 129.11, 127.04, 126.57, 120.23, 115.91, 102.28, 31.89, 26.33, 22.68, 14.12, 11.48; HRMS (m/z): $[M+H]^+$ calcd., 342.1023; found, 343.1103.

JG-29



3-(2-chlorophenyl)-4-oxo-2,6-dipropyl-4*H*-chromen-7-yl butyrate: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.09 (s, 1 H), 7.50-7.48 (m, 1 H), 7.35-7.31 (m, 2 H), 7.24 (s, 1 H), 7.23-7.21 (m, 1 H), 2.63-2.61 (m, 2 H), 2.60-2.58 (m, 2 H), 2.49-2.35 (m, 2 H), 1.86-1.81 (m, 2 H), 1.73-1.68 (m, 2 H), 1.67-1.61 (m, 2 H), 1.10-1.08 (m, 3 H), 0.97-0.94 (m, 3 H), 0.91-0.88 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 175.88, 171.64, 167.24, 154.87, 153.06, 135.03, 132.56, 132.41, 129.86, 129.70, 127.51, 127.05, 121.62, 121.25, 111.48, 36.40, 34.64, 32.13, 23.27, 20.39, 18.63, 14.07, 13.96, 13.88; HRMS (m/z): $[M+H]^+$ calcd., 426.1598; found, 427.1698.

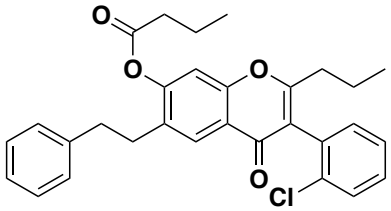
JG-30



3-(2-chlorophenyl)-2-ethyl-4-oxo-6-phenethyl-4H-chromen-7-yl propionate: 1H-NMR (600 MHz, chloroform-d) δ = 8.14 (s, 1 H), 7.52-7.50 (m, 1H), 7.36-7.34 (m, 2 H), 7.31-7.28 (m, 3 H), 7.24-7.18 (m, 4 H), 2.92 (m, 4 H), 2.68-2.64 (m, 2 H), 2.55-2.41 (m, 2 H),

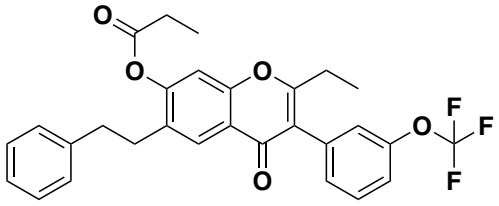
1.33-1.30 (m, 3 H), 1.24-1.21 (m, 3 H); 13C-NMR (600 MHz, chloroform-d) δ = 175.86, 172.33, 168.28, 155.06, 152.97, 141.30, 134.99, 132.48, 132.39, 131.72, 129.89, 129.76, 128.68, 128.49, 127.56, 127.13, 126.37, 121.33, 121.03, 111.56, 36.59, 32.18, 27.92, 26.36, 11.43, 9.28; HRMS (m/z): [M+H]+ calcd., 460.1441; found, 461.1531.

JG-31



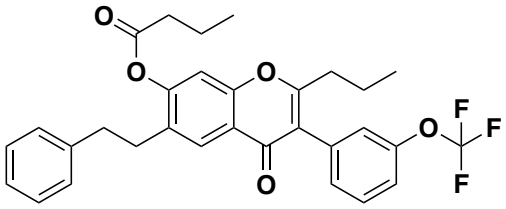
3-(2-chlorophenyl)-4-oxo-6-phenethyl-2-propyl-4*H*-chromen-7-yl butyrate: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.15 (s, 1 H), 7.52-7.50 (m, 1 H), 7.35-7.34 (m, 2 H), 7.31-7.28 (m, 3 H), 7.24-7.19 (m, 4 H), 2.92-2.91 (m, 4 H), 2.63-2.60 (m, 2 H), 2.52-2.36 (m, 2 H), 1.86-1.77 (m, 2 H), 1.76-1.65 (m, 2 H), 1.09-1.07 (m, 3 H), 0.92-0.90 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 175.79, 171.53, 167.34, 155.01, 152.98, 141.31, 135.02, 132.50, 132.39, 131.17, 129.88, 129.73, 128.48, 127.56, 127.07, 126.36, 121.66, 121.31, 111.55, 36.55, 34.65, 32.18, 20.40, 18.59, 13.98, 13.88; HRMS (m/z): $[M+H]^{+}$ calcd., 488.1754; found, 489.1849.

JG-34



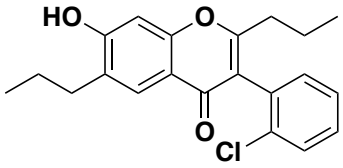
2-ethyl-4-oxo-6-phenethyl-3-(3-(trifluoromethoxy)phenyl)-4*H*-chromen-7-yl propionate: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.11 (s, 1 H), 7.48-7.46 (m, 1 H), 7.30-7.26 (m, 3 H), 7.23-7.21 (m, 3 H), 7.18-7.15 (m, 3 H), 2.92 (m, 4 H), 2.68-2.64 (m, 2 H), 2.59-2.55 (m, 2 H), 1.32-1.30 (m, 3 H), 1.27-1.24 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 176.22, 172.29, 168.02, 154.49, 153.10, 149.38, 141.21, 135.13, 131.83, 129.95, 129.13, 128.70, 128.51, 127.51, 126.40, 123.21, 121.91, 121.30, 120.47, 111.55, 36.56, 32.15, 27.93, 26.35, 12.01, 9.27; HRMS (m/z): $[M+H]^{+}$ calcd., 510.1654; found, 511.1745.

JG-35



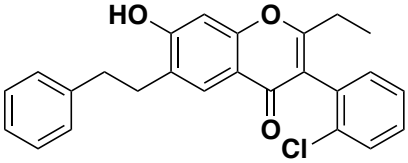
4-oxo-6-phenethyl-2-propyl-3-(3-(trifluoromethoxy)phenyl)-4*H*-chromen-7-yl butyrate: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.11 (s, 1 H), 7.48-7.46 (m, 1 H), 7.30-7.28 (m, 2 H), 7.27 (s, 1 H), 7.25-7.24 (d, 1 H), 7.22-7.21 (d, 2 H), 7.18-7.17 (d, 2 H), 7.14 (s, 1 H), 2.92 (m, 4 H), 2.62-2.60 (m, 2 H), 2.53-2.51 (m, 2 H), 1.84-1.81 (m, 2 H), 1.75-1.71 (m, 2 H), 1.09-1.06 (m, 3 H), 0.93-0.90 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 176.19, 171.49, 167.01, 154.89, 153.11, 149.36, 141.21, 131.84, 129.92, 128.68, 128.50, 127.50, 126.39, 123.31, 122.56, 121.28, 120.48, 111.55, 46.52, 36.34, 34.57, 32.15, 20.98, 18.58, 13.89, 13.85; HRMS (m/z): $[M+H]^+$ calcd., 538.1967; found, 539.2066.

JG-037



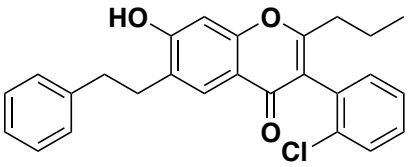
3-(2-chlorophenyl)-7-hydroxy-2,6-dipropyl-4*H*-chromen-4-one: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.76 (s, 1 H), 7.94, (s, 1 H), 7.42-7.40 (d, 1 H), 7.27-7.24 (m, 3 H), 6.80 (s, 1 H), 2.61-2.59 (m, 2 H), 2.50-2.35 (m, 2 H), 1.75-1.68 (m, 2 H), 1.68-1.60 (m, 2 H), 0.96-0.94 (m, 3 H), 0.91 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 177.16, 167.20, 160.99, 156.60, 135.17, 132.71, 132.55, 129.77, 129.61, 129.26, 127.03, 126.53, 120.89, 115.83, 102.33, 34.67, 31.96, 22.70, 20.48, 14.17, 13.98; HRMS (m/z): $[M+H]^+$ calcd., 356.1179; found, 357.1243.

JG-38



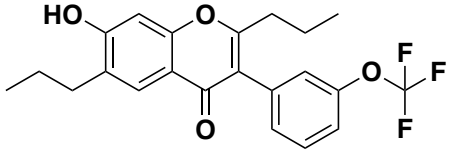
3-(2-chlorophenyl)-2-ethyl-7-hydroxy-6-phenethyl-4*H*-chromen-4-one: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.01 (s, 1 H), 7.45-7.43 (d, 1 H), 7.29-7.24 (m, 6 H), 7.22-7.19 (m, 2 H), 6.82 (s, 1 H), 2.94-2.93 (m, 4 H), 2.51-2.40 (m, 2 H), 1.25-1.20 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 176.78, 168.03, 160.12, 156.61, 141.95, 135.10, 132.64, 132.39, 129.84, 129.71, 128.67, 128.60, 127.12, 127.07, 126.24, 120.47, 116.55, 102.63, 36.17, 32.32, 26.37, 11.54; HRMS (m/z): $[M+H]^+$ calcd., 404.1179; found, 405.1255.

JG-39



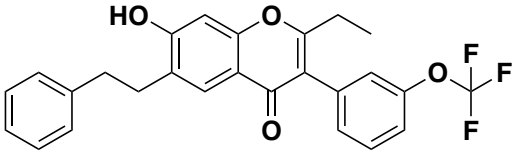
3-(2-chlorophenyl)-7-hydroxy-6-phenethyl-2-propyl-4*H*-chromen-4-one: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.80 (s, 1 H), 8.01 (s, 1 H), 7.41-7.40 (d, 1 H), 7.26-7.25 (m, 4 H), 7.22-7.21 (m, 3 H), 7.19-7.16 (m, 1 H), 6.83 (s, 1 H), 2.94-2.91 (m, 4 H), 2.50-2.35 (m, 2 H), 1.75-1.66 (m, 2 H), 0.91-0.88 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 177.14, 167.35, 161.06, 156.77,, 142.15, 135.19, 132.63, 132.53, 129.08, 129.68, 128,68, 128,59, 127.06, 126.62, 126.11, 10.92, 115.91, 102.51, 36.07, 34.69, 32.44, 20.51, 13.98; HRMS (m/z): $[M+H]^{+}$ calcd., 418.1336; found, 419.1402.

JG-41



7-hydroxy-2,6-dipropyl-3-(3-(trifluoromethoxy)phenyl)-4*H*-chromen-4-one: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.28 (s, 1 H), 7.94 (s, 1 H), 7.42-7.39 (m, 1 H), 7.23-7.22 (m, 1 H), 7.17-7.15 (m, 2 H), 6.77 (s, 1 H), 2.63-2.60 (m, 2 H), 2.51-2.48 (m, 2 H), 1.74-1.66 (m, 2 H), 1.66-1.61 (m, 2 H), 0.96-0.94 (m, 3 H), 0.91-0.90 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 177.40, 166.01, 160.67, 156.44, 149.38, 135.47, 129.91, 129.33, 129.19, 126.77, 123.34, 121.96, 120.33, 116.08, 102.20, 34.57, 31.86, 22.67, 21.04, 14.06, 13.80; HRMS (m/z): $[M+H]^{+}$ calcd., 406.1392; found, 407.1482.

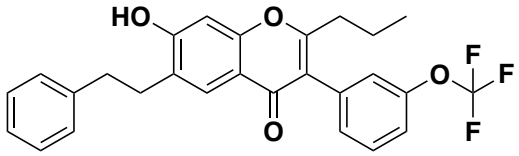
JG-42



2-ethyl-7-hydroxy-6-phenethyl-3-(3-(trifluoromethoxy)phenyl)-4*H*-chromen-4-one: ^{1}H-NMR (600 MHz, chloroform-d) δ = 7.98 (s, 1 H), 7.28-7.25 (m, 3 H), 7.23-7.22 (d, 2 H), 7.19-7.16 (m, 4 H), 6.79 (s, 1 H), 3.67 (s, 2 H), 2.95-2.91 (m, 4 H), 2.55-2.51 (m, 2 H), 1.24-1.22 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 177.24, 175.89, 170.00, 160.29, 156.53, 141.79, 130.10, 129.97, 129.73, 129.21, 128.65, 128.58, 120.01,

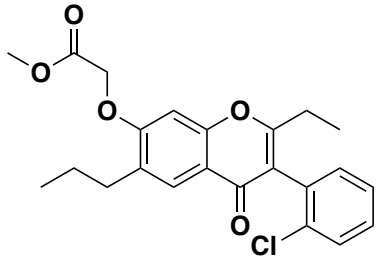
127.03, 126.26, 123.24, 122.22, 121.41, 120.40, 119.97, 102.49, 40.65, 36.06, 32.17, 26.33, 12.04; HRMS (m/z): $[M+H]^+$ calcd., 454.1392; found, 455.1460

JG-43



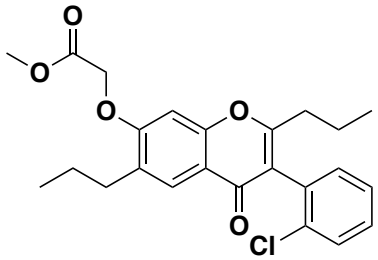
7-hydroxy-6-phenethyl-2-propyl-3-(3-(trifluoromethoxy)phenyl)-4*H*-chromen-4-one: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.00 (s, 1 H), 7.41-7.39 (m, 1 H), 7.26-7.22 (m, 3 H), 7.19-7.14 (m, 6 H), 6.79 (s, 1 H), 2.95-2.90 (m, 4 H), 2.50-2.48 (m, 2 H), 1.74-1.67 (m, 2 H), 0.91-0.89 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 177.53, 167.20, 160.95, 156.65, 149.39, 141.90, 135.46, 129.98, 129.33, 128.58, 126.72, 126.16, 123.34, 121.94, 120.41, 116.02, 102.36, 35.96, 34.59, 32.22, 21.05, 13.80; HRMS (m/z): $[M+H]^+$ calcd., 468.1458; found, 469.1593.

JG-44



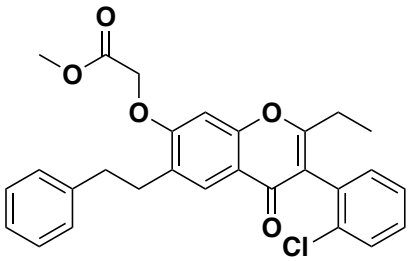
methyl 2-((3-(2-chlorophenyl)-2-ethyl-4-oxo-6-propyl-4*H*-chromen-7-yl)oxy)acetate: ^{1}H-NMR (600 MHz, chloroform-d) δ = 7.98 (s, 1 H), 7.49-7.48 (m, 1 H), 7.33-7.31 (m, 2 H), 7.23-7.21 (m, 1 H), 6.99 (s, 1 H), 4.77 (s, 1 H), 3.84 (s, 1 H), 2.73-2.71 (m, 2 H0, 2.51-2.38 (m, 2 H), 1.71-1.65 (m, 2 H), 1.23-1.20 (m, 3 H), 0.98-0.95 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 175.87, 168.72, 167.37, 160.28, 156.20, 134.99, 132.77, 132.34, 130.30, 129.81, 129.60, 127.10, 127.04, 120.91, 117.50, 98.83, 65.46, 52.63, 32.08, 29.86, 26.26, 22.87, 14.12, 11.54; HRMS (m/z): $[M+H]^+$ calcd., 414.1234; found, 415.1306.

JG-45



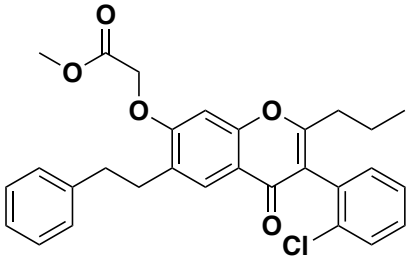
methyl 2-((3-(2-chlorophenyl)-4-oxo-2,6-dipropyl-4*H*-chromen-7-yl)oxy)acetate: ^{1}H-NMR (600 MHz, chloroform-d) δ = 7.99 (s, 1 H), 7.49-7.48 (m, 1 H), 7.33-7.31 (m, 2 H), 7.22-7.21 (m, 1 H), 6.69 (s, 1 H), 4.77 (s. 2 H), 3.85 (s, 3 H), 2.73-2.71 (m, 2 H), 2.49-2.33 (m, 2 H), 1.72-1.66 (m, 4 H), 0.98-0.95 (m, 3 H), 0.91-0.88 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 175.80, 168.74, 166.40, 160.28, 156.17, 135.04, 132.81, 132.46, 130.31, 129.83, 129.59, 127.13, 127.00, 121.58, 117.53, 98.83, 65.49, 52.65, 34.61, 32.10, 39.88, 22.91, 20.51, 14.16, 13.99; HRMS (m/z): $[M+H]^+$ calcd., 428.1392; found, 429.1467.

JG-46



methyl 2-((3-(2-chlorophenyl)-2-ethyl-4-oxo-6-phenethyl-4*H*-chromen-7-yl)oxy)acetate: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.03 (s, 1 H), 7.50-7.49 (m, 1 H), 7.34-7.33 (m, 2 H), 7.30-7.27 (m, 2 H), 7.26-7.24 (m, 3 H), 7.20-7.18 (m, 1 H), 6.72 (s, 1 H), 4.74 (s, 2 H), 3.86 (s, 3 H), 3.06-2.94 (m, 4 H), 2.53-2.39 (m, 2 H), 1.24-1.21 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 175.81, 168.61, 167.46, 160.25, 156.40, 142.09, 135.02, 132.74, 132.35, 129.87, 129.66, 128.70, 128.50, 127.27, 127.09, 126.10, 121.00, 117.66, 99.05, 65.55, 52.68, 36.31, 32.51, 26.30, 11.57; HRMS (m/z): $[M+H]^+$ calcd., 476.1392; found, 477.1470

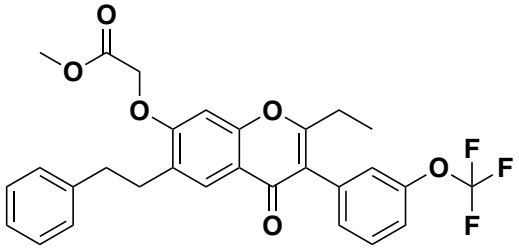
JG-047



methyl 2-((3-(2-chlorophenyl)-4-oxo-6-phenethyl-2-propyl-4*H*-chromen-7-yl)oxy)acetate: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.06 (s, 1 H0, 7.53-7.51 (d, 1 H), 7.36-7.35 (m, 2 H), 7.33-7.25 (m, 5 H), 7.23-7.20 (m, 1 H), 6.74 (s, 1 H), 4.76 (s, 2 H0, 3.89 (s, 3 H), 3.09-2.97 (m, 4 H), 2.53-2.37 (m, 2 H), 1.77-1.70 (m, 2 H), 0.94-0.92 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 175.70, 168.56, 166.46, 160.20, 156.32, 142.05, 135.01,

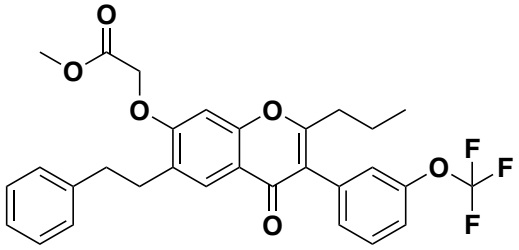
132.71, 132.41, 129.82, 129.60, 129.52, 128.66, 128.46, 127.20, 127.00, 126.06, 121.59, 117.60, 99.00, 65.50, 52.63, 36.27, 34.59, 32.49, 20.48, 13.97; HRMS (m/z): $[M+H]^+$ calcd., 490.1547; found, 491.1632.

JG-48

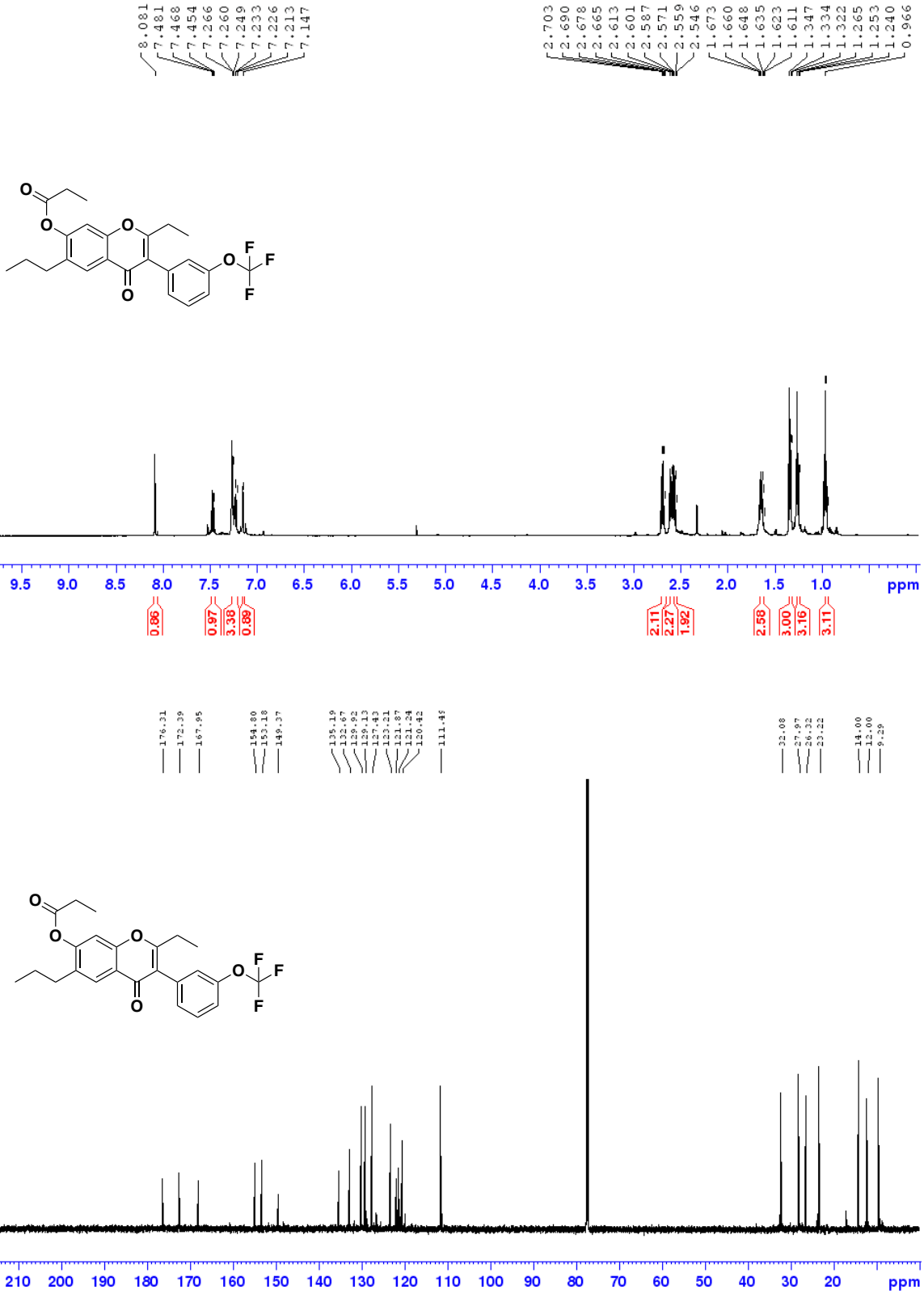


methyl 2-((2-ethyl-4-oxo-6-phenethyl-3-(3-(trifluoromethoxy)phenyl)-4*H*-chromen-7-yl)oxy)acetate: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.02 (s, 1 H), 7.50-7.47 (m, 1 H), 7.32-7.29 (m, 3 H), 7.27-7.20 (m, 4 H), 7.17 (s, 1 H), 6.72 (s, 1 H), 4.75 (s, 2 H), 3.99 (s, 3 H), 3.09-2.96 (m, 4 H), 2.60-2.56 (m, 2 H), 1.30-1.27 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 176.12, 168.55, 167.20, 160.36, 156.27, 149.36, 141.97, 135.38, 129.87, 129.68, 129.18, 128.71, 128.50, 127.21, 126.12, 123.23, 121.88, 120.36, 117.63, 98.98, 65.56, 52.68, 36.27, 32.44, 26.26, 12.14; HRMS (m/z): $[M+H]^+$ calcd., 526.1603; found, 527.1692.

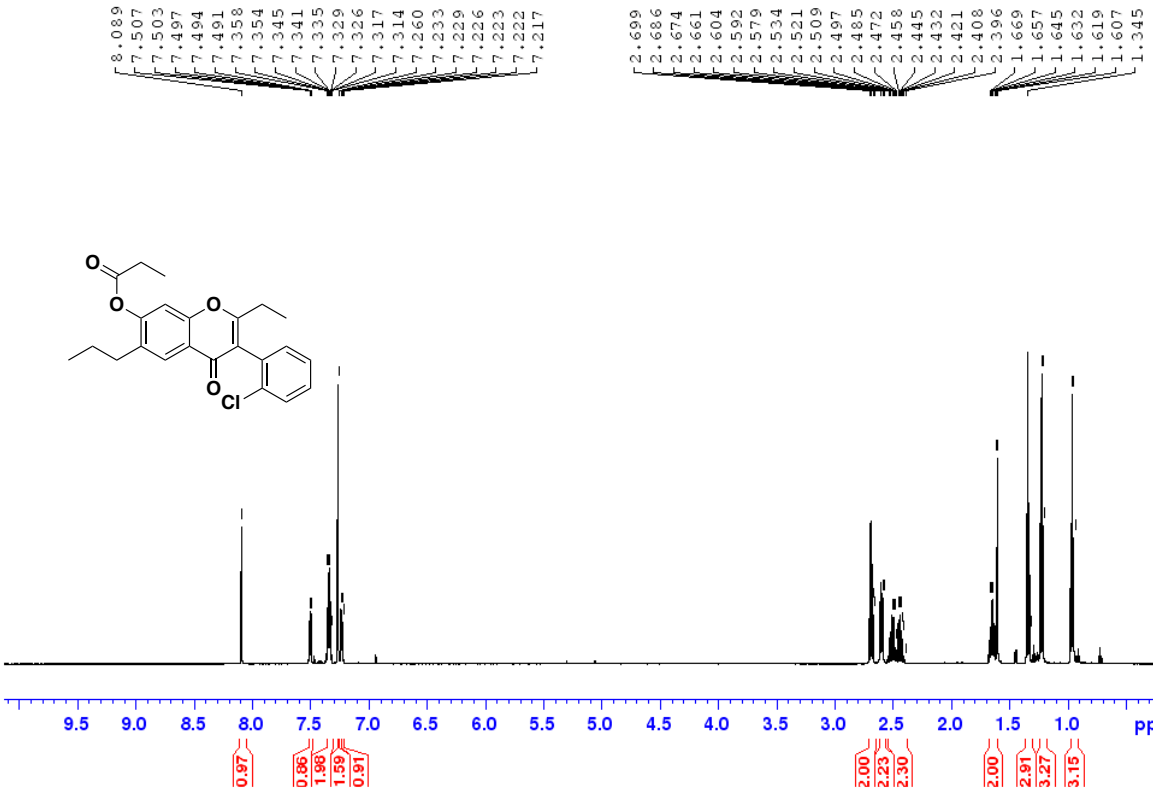
JG-49



methyl 2-((4-oxo-6-phenethyl-2-propyl-3-(3-(trifluoromethoxy)phenyl)-4*H*-chromen-7-yl)oxy)acetate: ^{1}H-NMR (600 MHz, chloroform-d) δ = 8.03 (s, 1 H), 7.50-7.47 (m, 1 H), 7.32-7.20 (m, 7 H), 7.16 (s, 1 H), 6.71 (s, 1 H), 4.75 (s, 2 H), 3.89 (s, 3 H), 3.09-3.07 (2.97 (m, 4 H), 2.54-2.52 (m, 2 H), 1.79-1.72 (m, 2 H), 0.96-0.93 (m, 3 H); ^{13}C-NMR (600 MHz, chloroform-d) δ = 176.09, 168.54, 166.16, 160.35, 156.23, 149.33, 141.98, 135.45, 129.85, 129.68, 129.30, 128.70, 128.50, 127.20, 126.11, 123.33, 122.52, 120.37, 117.63, 98.98, 65.55, 52.67, 36.27, 34.53, 32.50, 29.89, 21.09, 13.87; HRMS (m/z): $[M+H]^+$ calcd., 540.1760; found, 541.1815.


8.081
7.481
7.468
7.454
7.266
7.260
7.249
7.233
7.226
7.213
7.147
2.703
2.690
2.678
2.665
2.613
2.601
2.587
2.571
2.559
2.546
1.673
1.660
1.648
1.635
1.623
1.611
1.347
1.334
1.322
1.265
1.253
1.240
0.966
O
O
O
O
F
F
F
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.86
0.97
3.38
0.89
2.11
2.27
1.92
2.58
3.00
3.16
3.11
176.31
172.39
167.95
154.80
153.18
149.37
135.19
132.67
129.92
129.13
127.43
123.21
121.87
121.24
120.42
111.46
32.08
27.97
26.32
23.22
14.00
12.00
9.29
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

JG-16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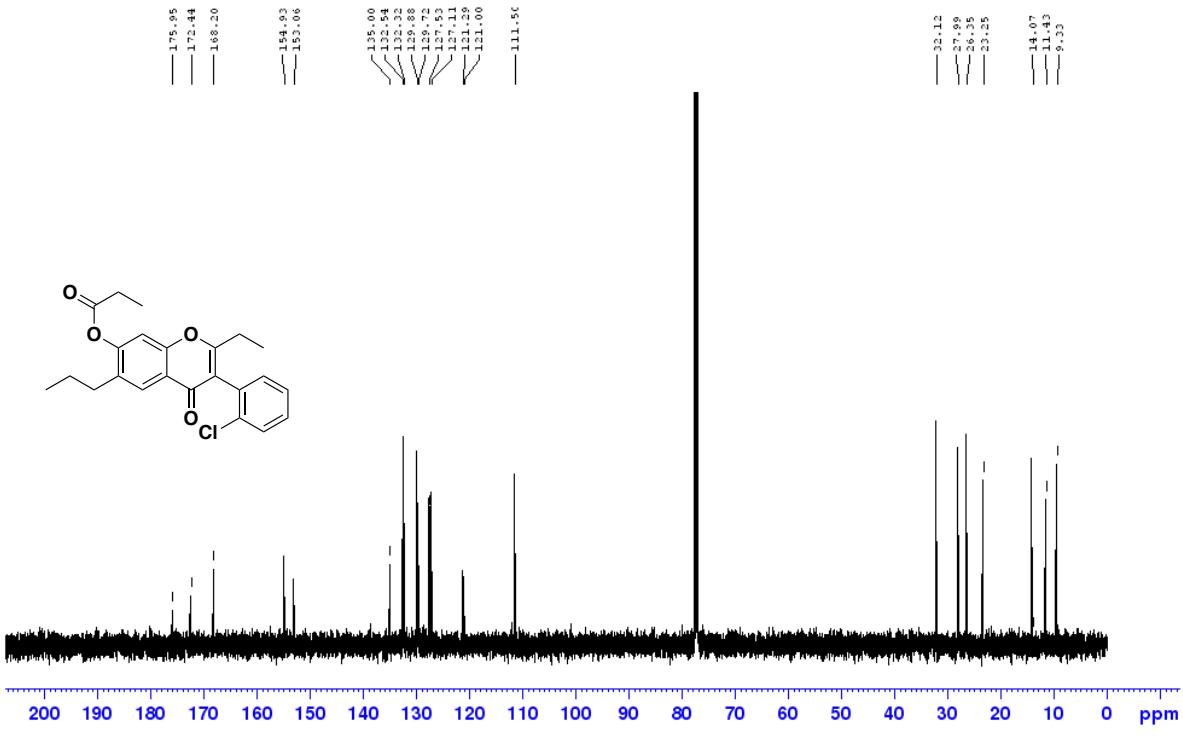
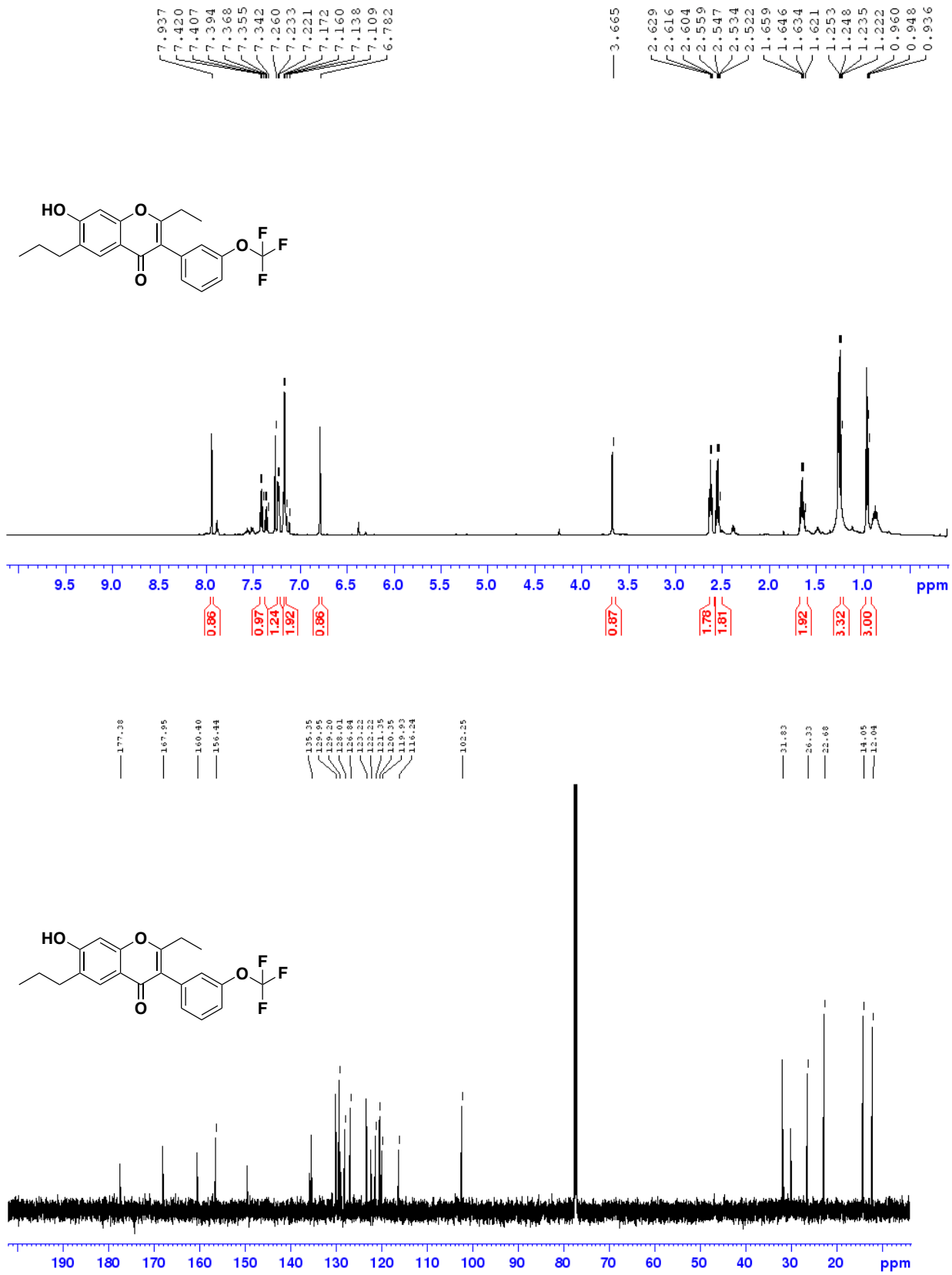
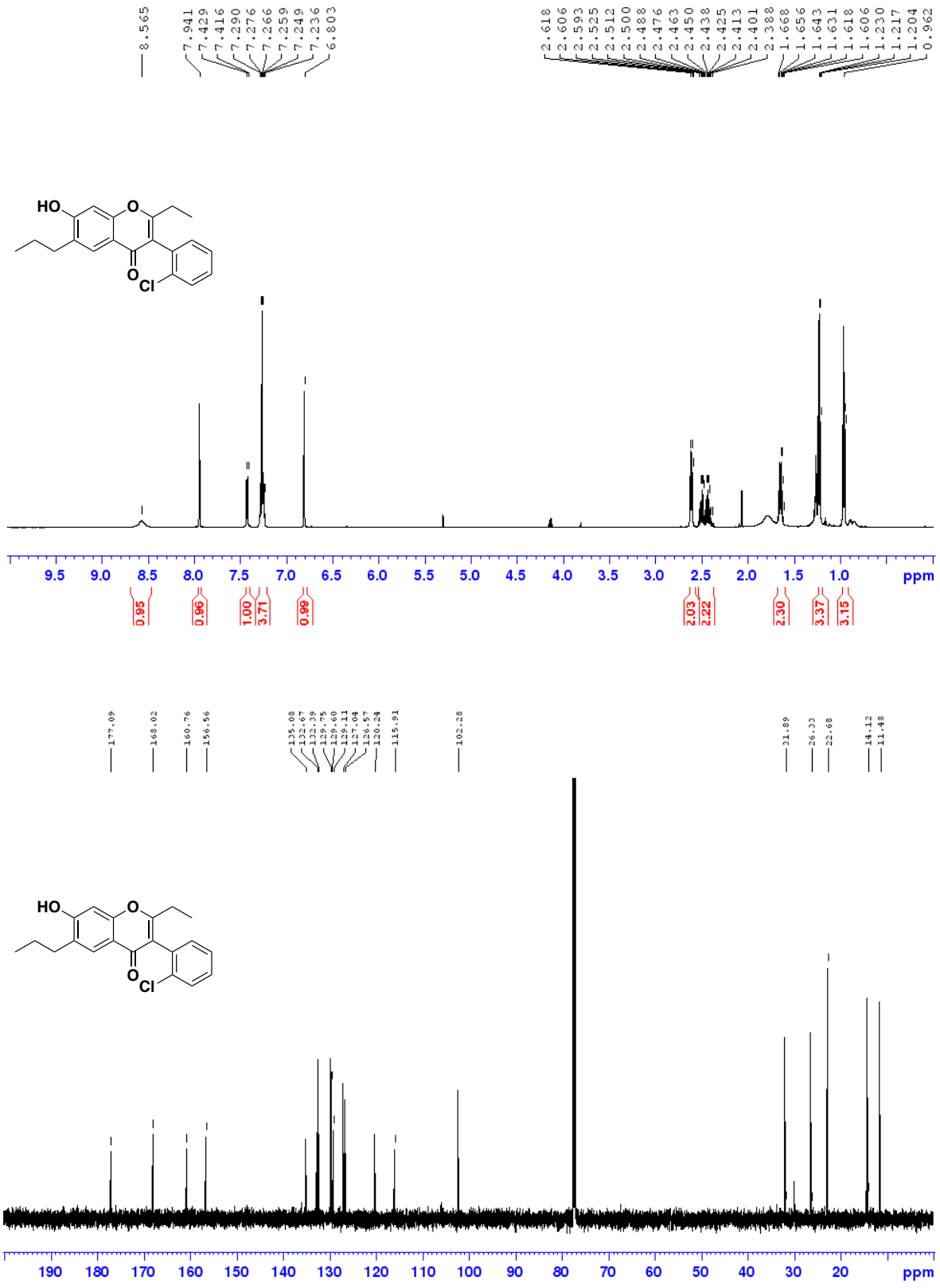
7.507
7.503
7.497
7.494
7.491
7.358
7.354
7.345
7.341
7.335
7.329
7.326
7.317
7.314
7.260
7.233
7.229
7.226
7.223
7.222
7.217
2.699
2.686
2.674
2.661
2.604
2.592
2.579
2.534
2.521
2.509
2.497
2.485
2.472
2.458
2.445
2.432
2.421
2.408
2.396
1.669
1.657
1.645
1.632
1.619
1.607
1.345
O
O
O
O
Cl
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.97
0.86
1.96
1.59
0.91
2.00
2.23
2.30
2.00
2.91
3.27
3.15


175.95
172.44
168.20
154.93
153.06
135.00
132.54
132.32
129.88
129.72
127.53
127.11
121.29
121.00
111.56
32.12
27.99
26.35
23.25
14.07
11.43
9.33
O
O
O
O
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

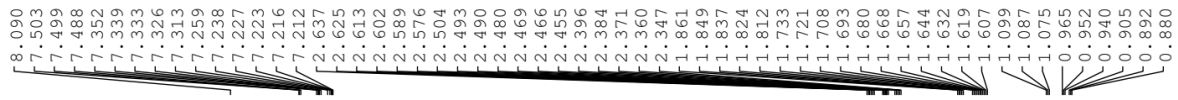
JG-17


7.937
7.420
7.407
7.394
7.368
7.355
7.342
7.260
7.233
7.221
7.172
7.160
7.138
7.109
6.782
3.665
2.629
2.616
2.604
2.559
2.547
2.534
2.522
1.659
1.646
1.634
1.621
1.253
1.248
1.235
1.222
0.960
0.948
0.936
HO
O
F
F
F
O
O
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.86
0.97
1.24
1.92
0.86
0.87
1.78
1.81
1.92
3.32
3.00
177.38
167.95
160.40
156.44
135.35
129.95
129.20
128.01
126.84
123.22
122.22
121.35
120.35
119.93
116.24
102.25
31.83
26.33
22.68
14.05
12.04
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

JG-18


8.565
7.941
7.429
7.416
7.290
7.276
7.266
7.259
7.249
7.236
6.803
2.618
2.606
2.593
2.525
2.512
2.500
2.488
2.476
2.463
2.450
2.438
2.425
2.413
2.401
2.388
1.668
1.656
1.643
1.631
1.618
1.606
1.230
1.217
1.204
0.962
HO
O
O
Cl
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
0.95
0.96
1.00
3.71
0.99
2.03
2.22
2.30
3.37
3.15
177.09
168.02
160.76
156.56
135.08
132.67
132.39
129.75
129.60
129.11
127.04
126.57
120.24
115.91
102.28
31.89
26.33
22.68
14.12
11.48
HO
O
O
Cl
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

JG-29


8.090
7.503
7.499
7.488
7.352
7.339
7.333
7.326
7.313
7.259
7.238
7.227
7.223
7.216
7.212
2.637
2.625
2.613
2.602
2.589
2.576
2.504
2.493
2.490
2.480
2.469
2.466
2.455
2.396
2.384
2.371
2.360
2.347
1.861
1.849
1.837
1.824
1.812
1.733
1.721
1.708
1.693
1.680
1.668
1.657
1.644
1.632
1.619
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1.099
1.087
1.075
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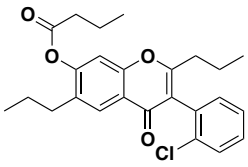
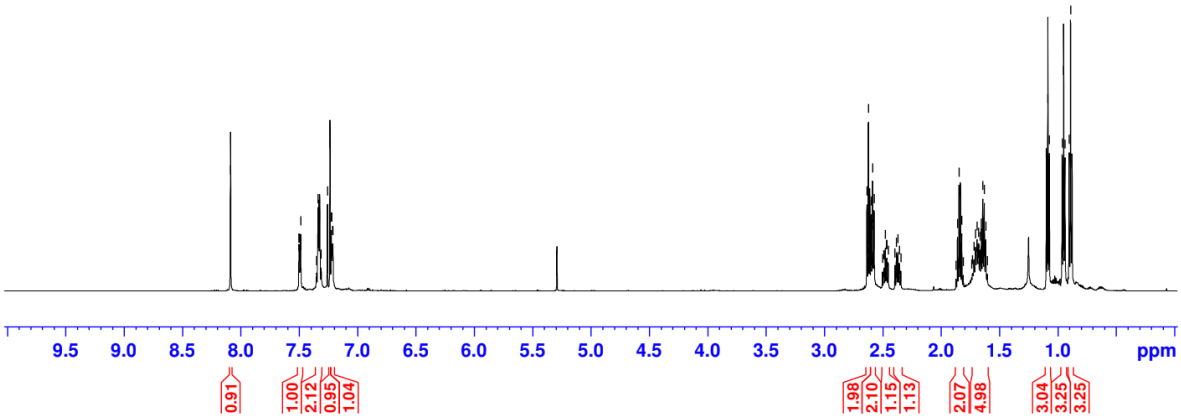
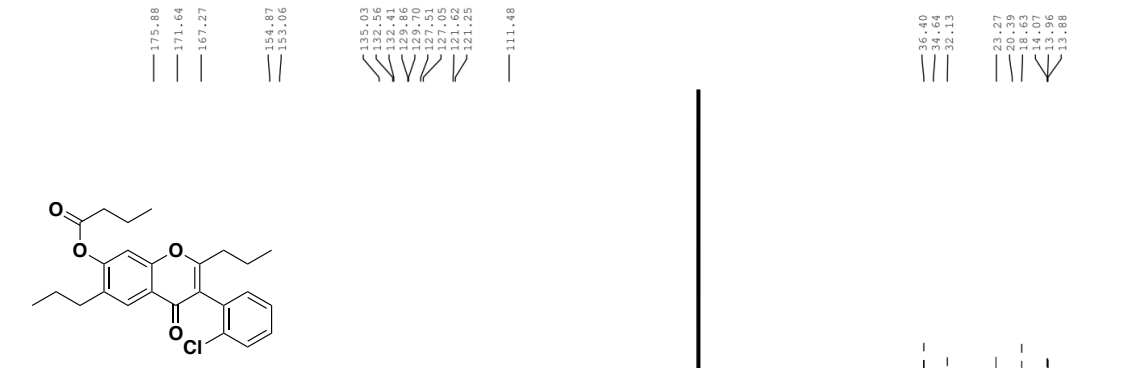
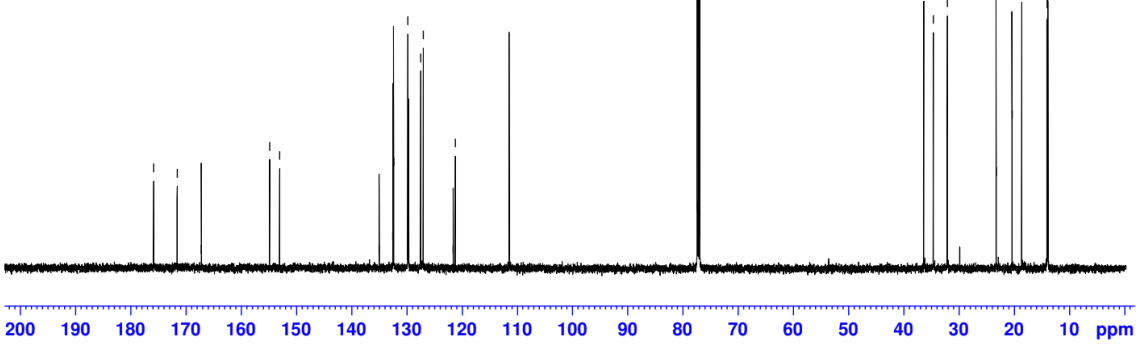
0.952
0.940
0.905
0.892
0.880


O
O
O
O
Cl


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.91
1.00
2.12
0.95
1.04
1.98
2.10
1.15
1.13
2.07
4.98
3.04
3.25
3.25

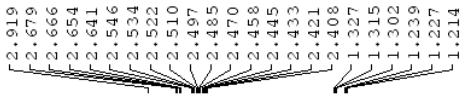

175.88
171.64
167.27
154.87
153.06
135.03
132.56
132.41
129.86
129.70
127.51
127.05
121.62
121.25
111.48
36.40
34.64
32.13
23.27
20.39
18.63
14.07
13.96
13.88

O
O
O
O
Cl


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

JG-30


8.144
7.523
7.515
7.511
7.500
7.362
7.350
7.345
7.338
7.327
7.306
7.294
7.281
7.273
7.259
7.244
7.234
7.229
7.222
7.209
7.190
7.177
7.141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2.679
2.666
2.654
2.641
2.546
2.534
2.522
2.510
2.497
2.485
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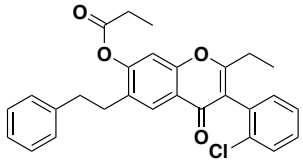
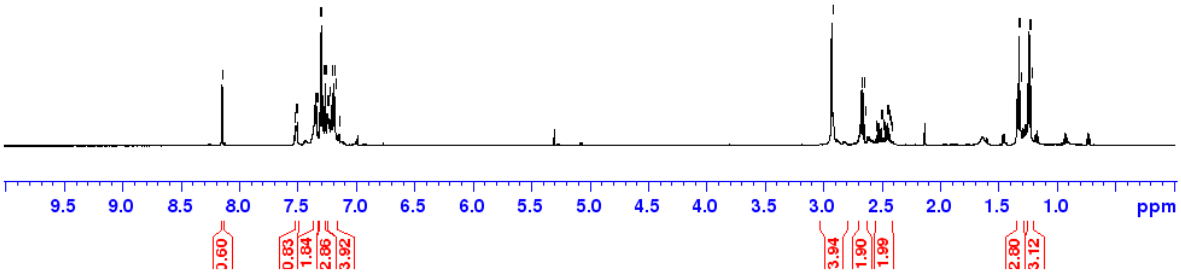
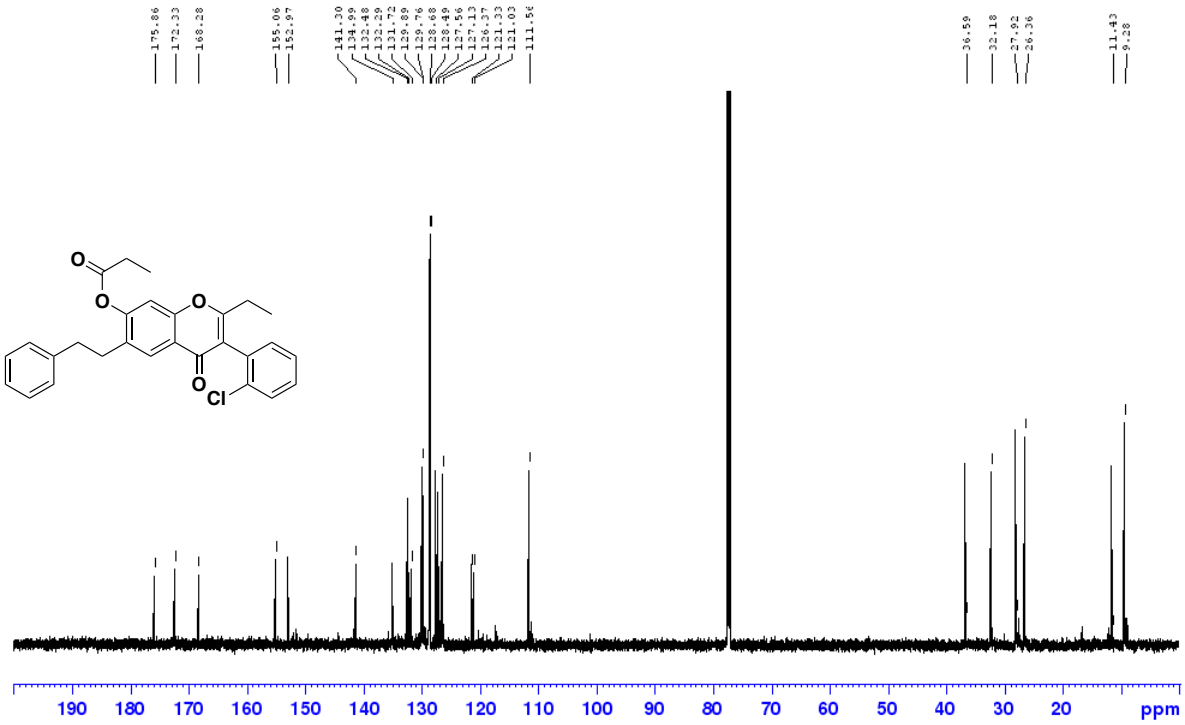
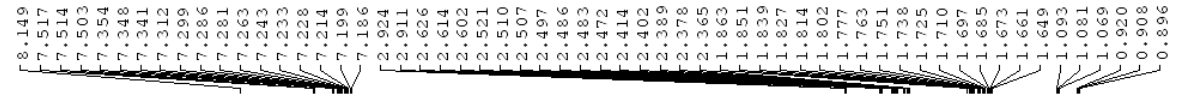
1.327
1.315
1.302
1.239
1.227
1.214

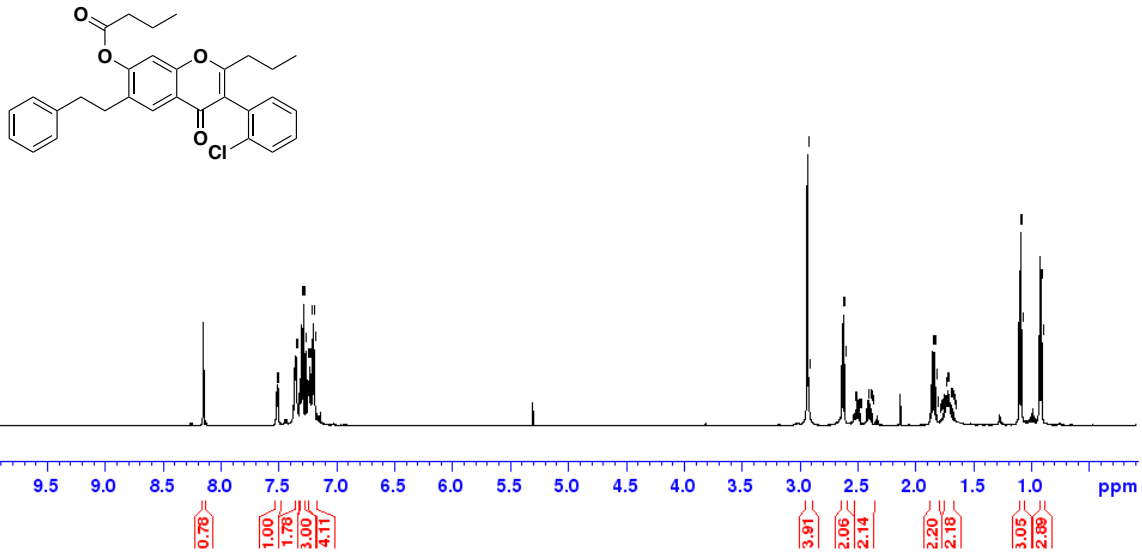

O
O
O
O
Cl

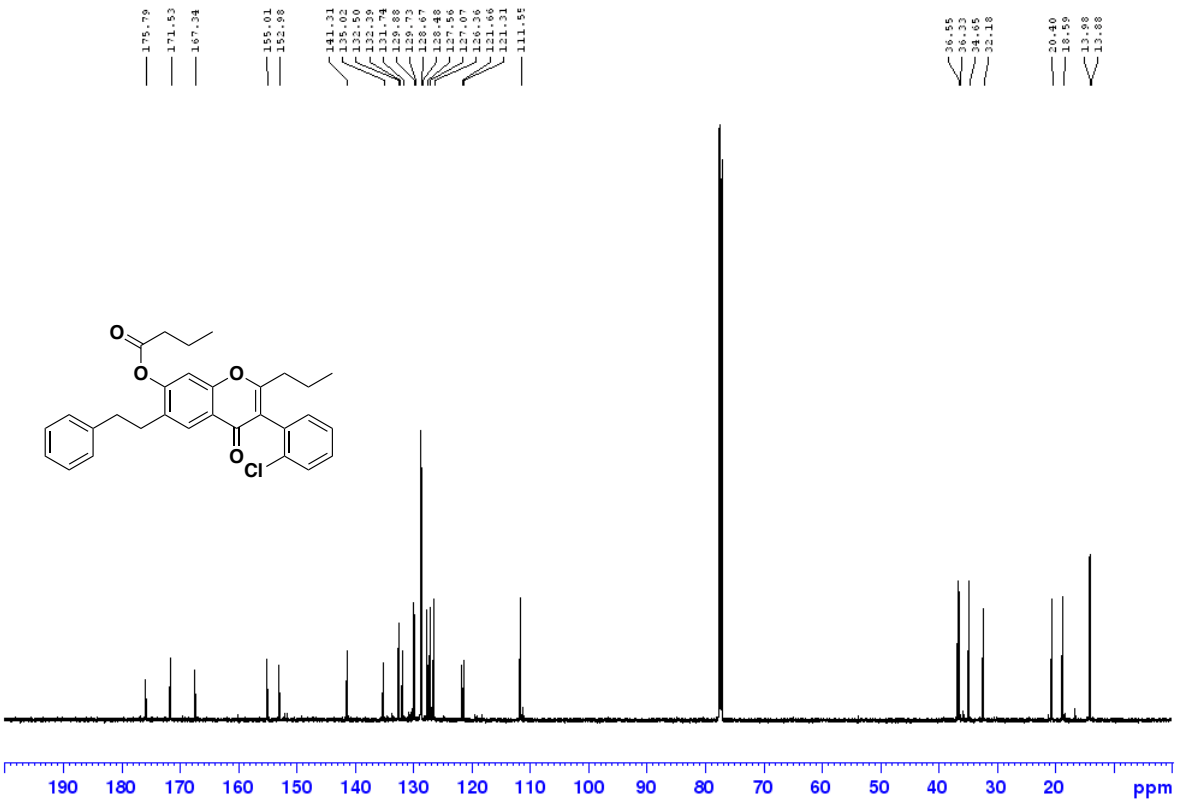

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.60
0.83
1.84
2.86
3.92
3.94
1.90
1.99
2.80
3.12


175.86
172.33
168.28
155.06
152.97
141.30
134.99
132.48
132.29
131.72
129.89
129.76
128.68
128.49
127.56
127.13
126.37
121.33
121.03
111.54
36.59
32.18
27.92
26.36
11.43
9.28
O
O
O
O
Cl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

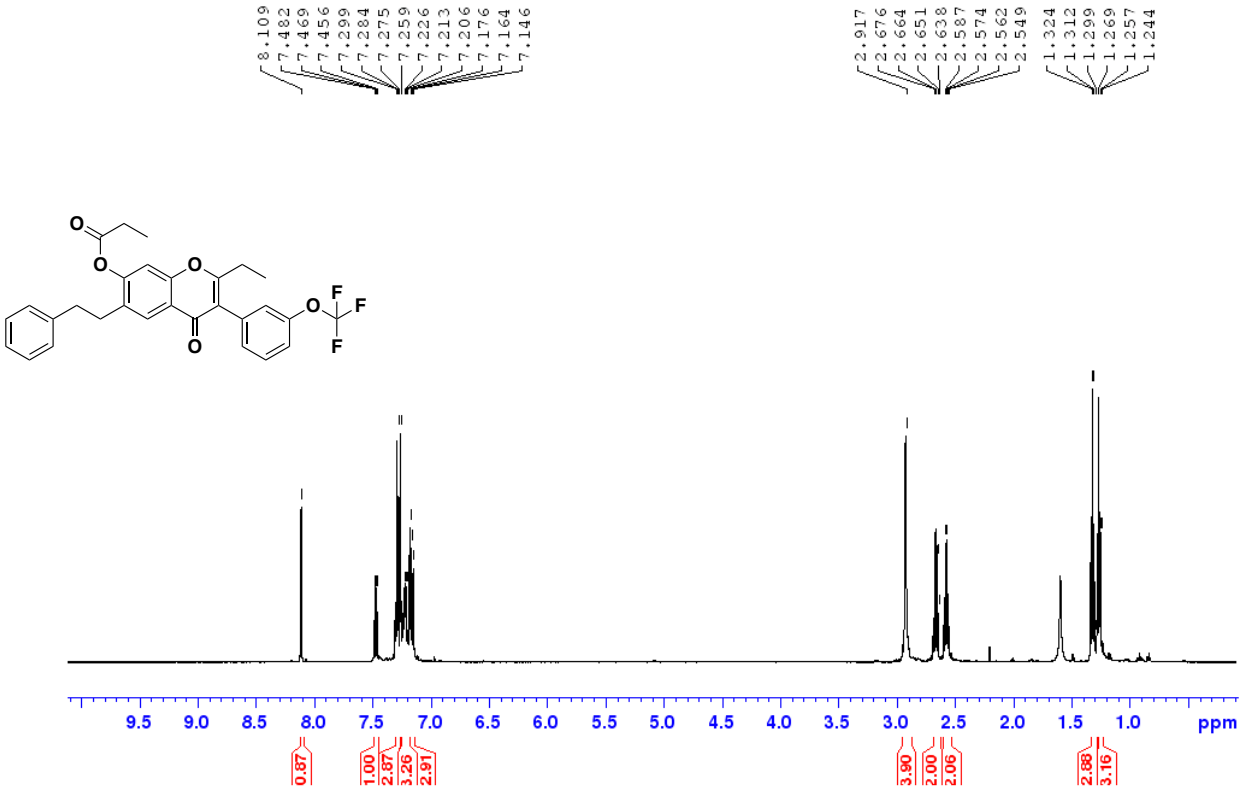
JG-31

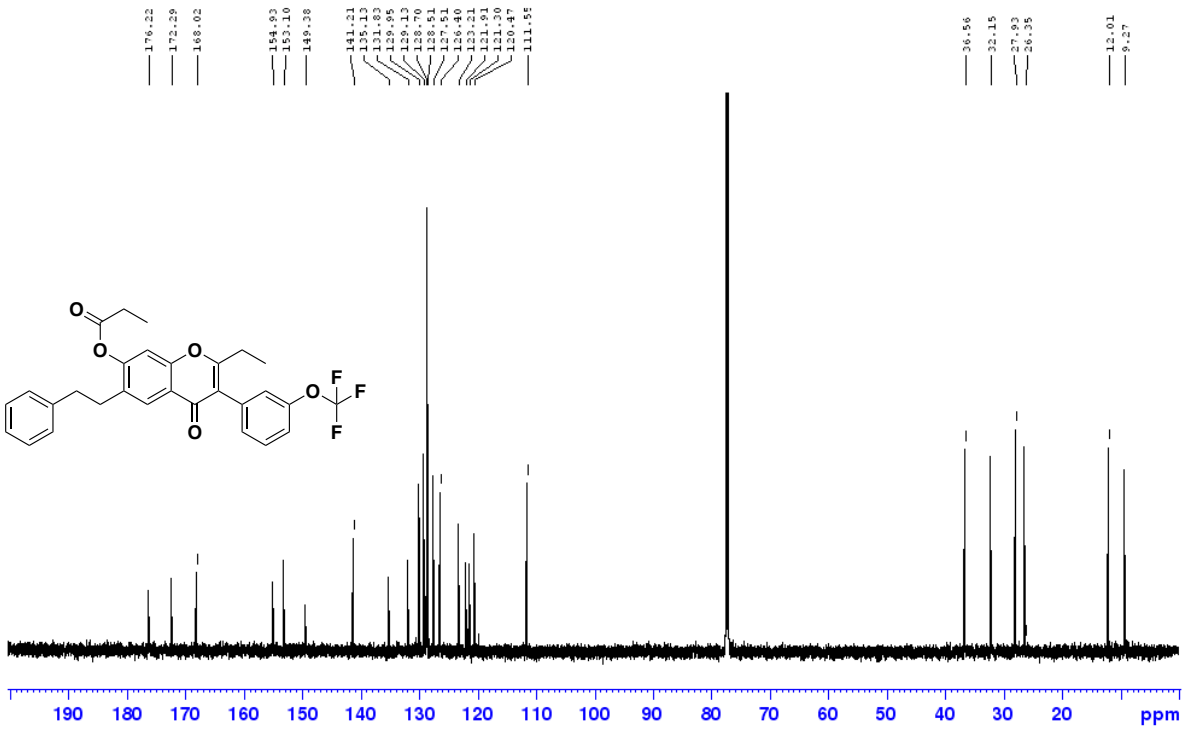

8.149
7.517
7.514
7.503
7.354
7.348
7.341
7.312
7.299
7.286
7.281
7.263
7.243
7.233
7.228
7.214
7.199
7.186
2.924
2.911
2.626
2.614
2.602
2.521
2.510
2.507
2.497
2.486
2.483
2.472
2.414
2.402
2.389
2.378
2.365
1.863
1.851
1.839
1.827
1.814
1.802
1.777
1.763
1.751
1.738
1.725
1.710
1.697
1.685
1.673
1.661
1.649
1.093
1.081
1.069
0.920
0.908
0.896


O
O
O
O
Cl
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.78
1.00
1.78
3.00
4.11
3.91
2.06
2.14
2.20
2.18
3.05
2.89

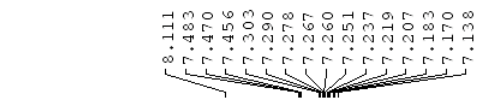

175.79
171.53
167.34
155.01
152.98
141.31
135.02
132.50
132.39
131.74
129.88
129.73
128.67
128.48
127.56
127.07
126.36
121.66
121.31
111.55
36.55
36.33
34.65
21.18
20.40
18.59
13.98
13.88
O
O
O
O
Cl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

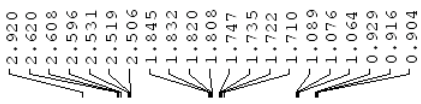
JG-34

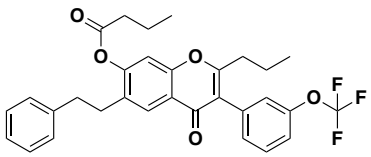

8.109
7.482
7.469
7.456
7.299
7.284
7.275
7.259
7.226
7.213
7.206
7.176
7.164
7.146
2.917
2.676
2.664
2.651
2.638
2.587
2.574
2.562
2.549
1.324
1.312
1.299
1.269
1.257
1.244
O
O
O
O
F
F
F
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.87
1.00
2.87
3.26
2.91
3.90
2.00
2.06
2.88
3.16

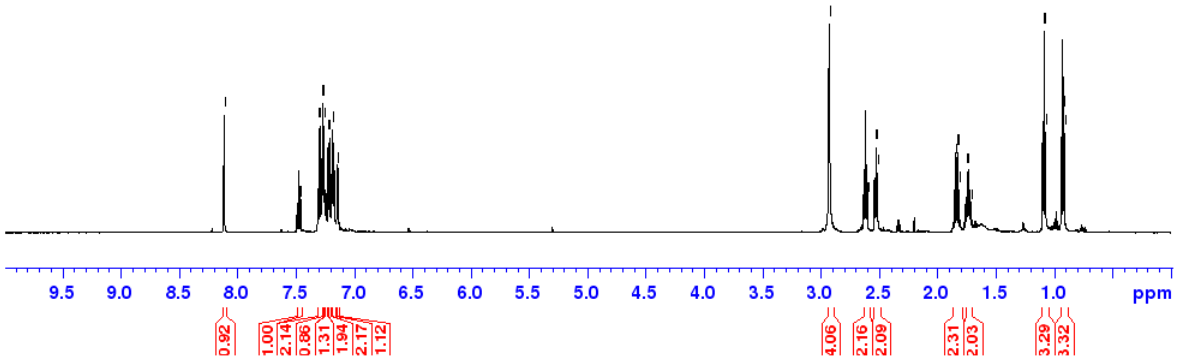

176.22
172.29
168.02
154.93
153.10
149.38
141.21
135.13
131.83
129.95
129.13
128.70
128.51
127.51
126.40
123.21
121.91
121.30
120.47
111.55
36.56
32.15
27.93
26.35
12.01
9.27
O
O
O
O
F
F
F
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

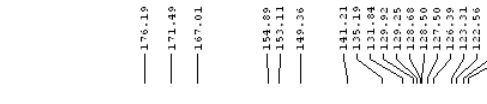
JG-35

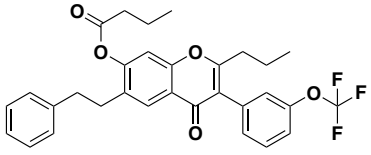

8.111
7.483
7.470
7.456
7.303
7.290
7.278
7.267
7.260
7.251
7.237
7.219
7.207
7.183
7.170
7.138


2.920
2.620
2.608
2.596
2.531
2.519
2.506
1.845
1.832
1.820
1.808
1.747
1.735
1.722
1.710
1.089
1.076
1.064
0.929
0.916
0.904


O
O
O
O
O
F
F
F

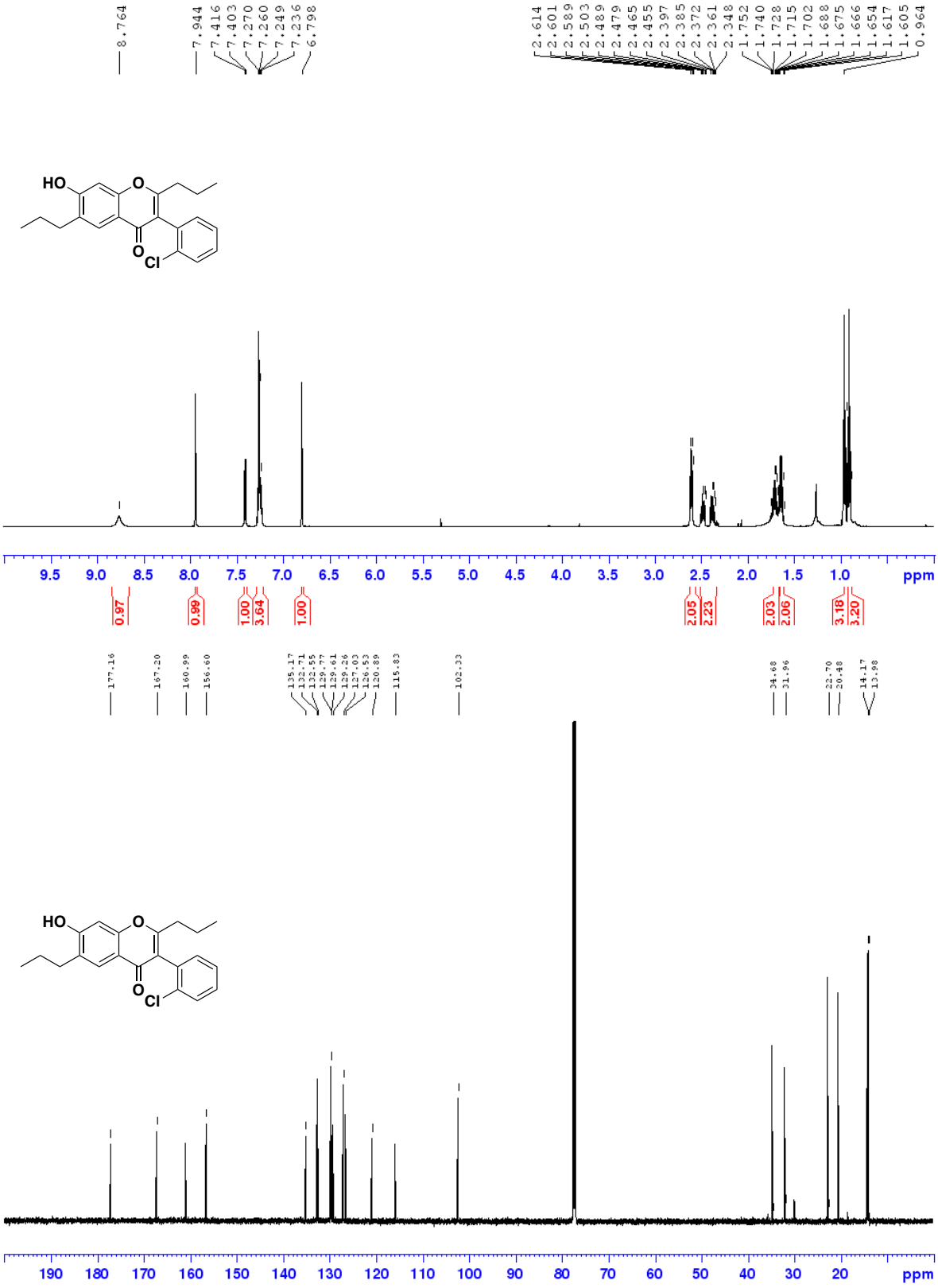

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.92
1.00
2.14
0.86
1.31
1.84
2.17
1.12
4.06
2.16
2.09
2.31
2.03
3.29
3.32


176.19
171.49
167.01
154.89
153.11
149.36
141.21
135.19
131.84
129.92
129.25
128.68
128.50
128.50
127.50
126.39
123.31
122.56
121.28
120.47
111.54
36.52
36.34
34.57
32.15
20.98
18.58
13.89
13.85

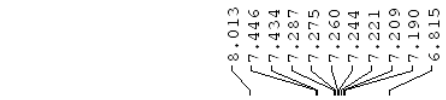

O
O
O
O
O
F
F
F

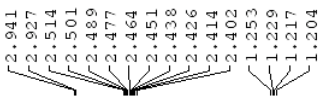
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

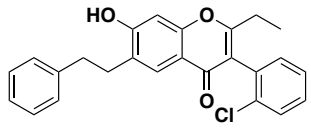
JG-37

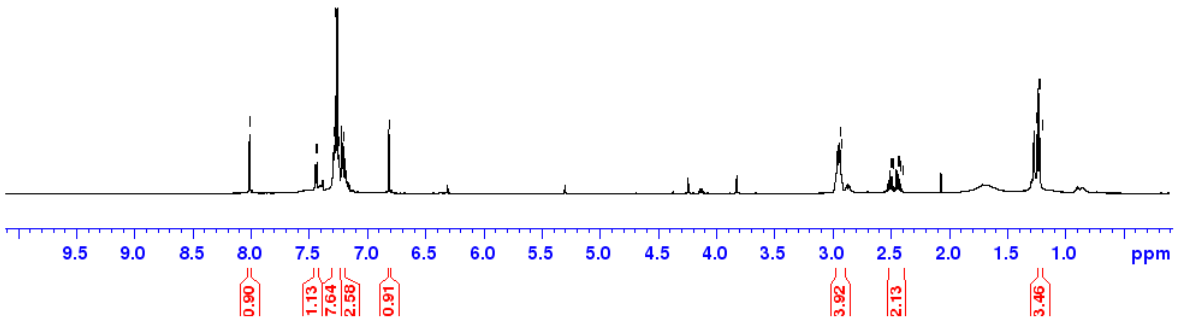

8.764
7.944
7.416
7.403
7.270
7.260
7.249
7.236
6.798
2.614
2.601
2.589
2.503
2.489
2.479
2.465
2.455
2.397
2.385
2.372
2.361
2.348
1.752
1.740
1.728
1.715
1.702
1.688
1.675
1.666
1.654
1.617
1.605
0.964
HO
O
O
Cl
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.97
0.99
1.00
3.64
1.00
2.05
2.23
2.03
2.06
3.18
3.20
177.16
167.20
160.99
156.60
135.17
132.71
132.55
129.77
129.61
129.26
127.03
126.53
120.89
115.83
102.33
34.68
31.96
22.70
20.48
14.17
13.98
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

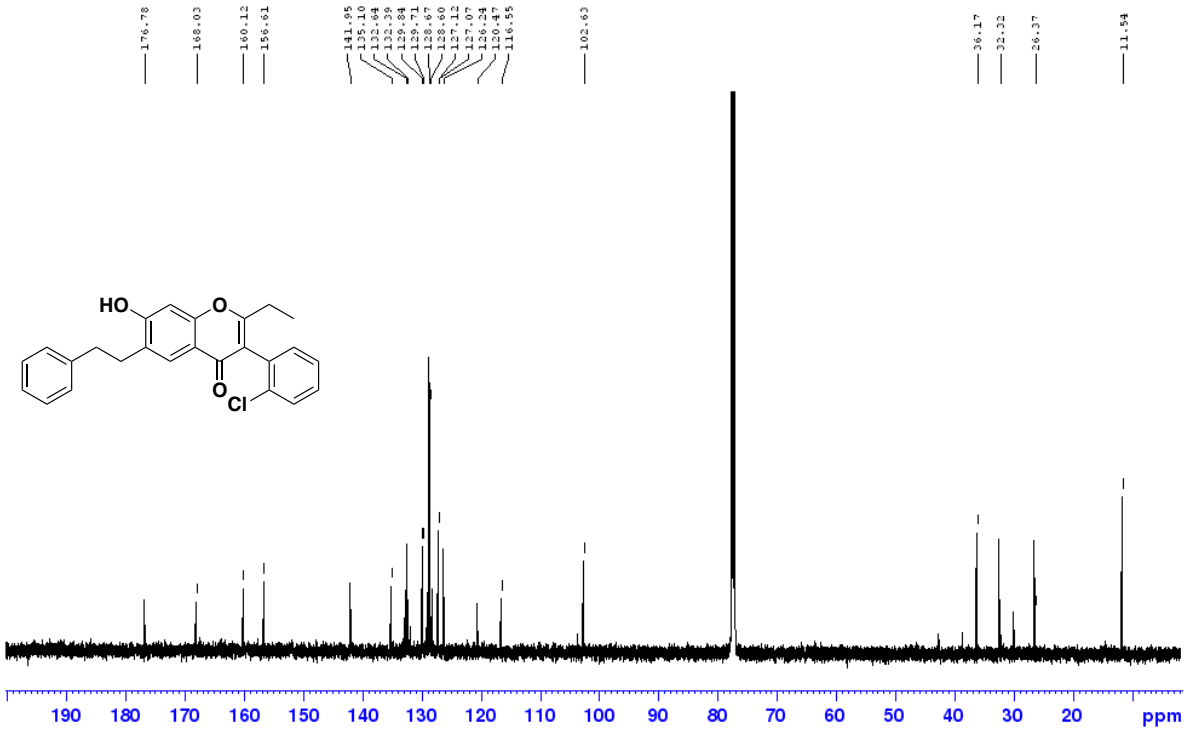
JG-38


8.013
7.446
7.434
7.287
7.275
7.260
7.244
7.221
7.209
7.190
6.815

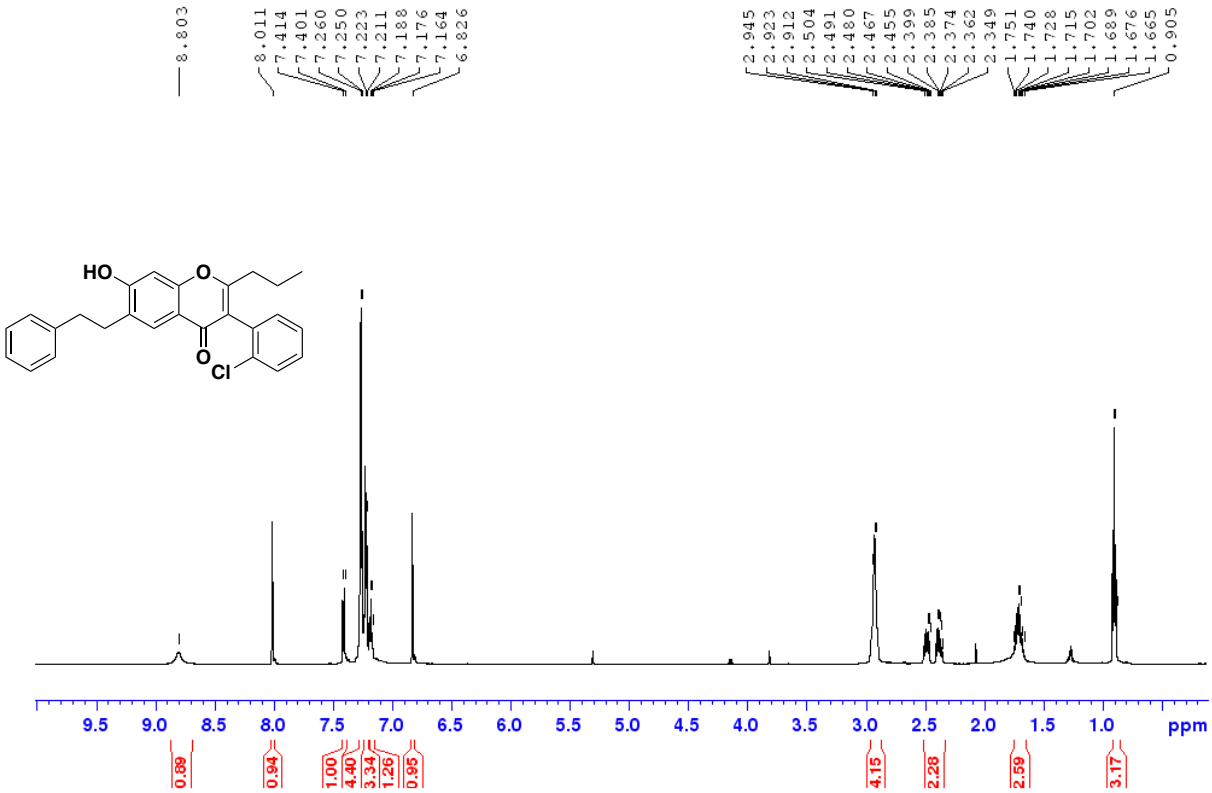

2.941
2.927
2.514
2.501
2.489
2.477
2.464
2.451
2.438
2.426
2.414
2.402
1.253
1.229
1.217
1.204

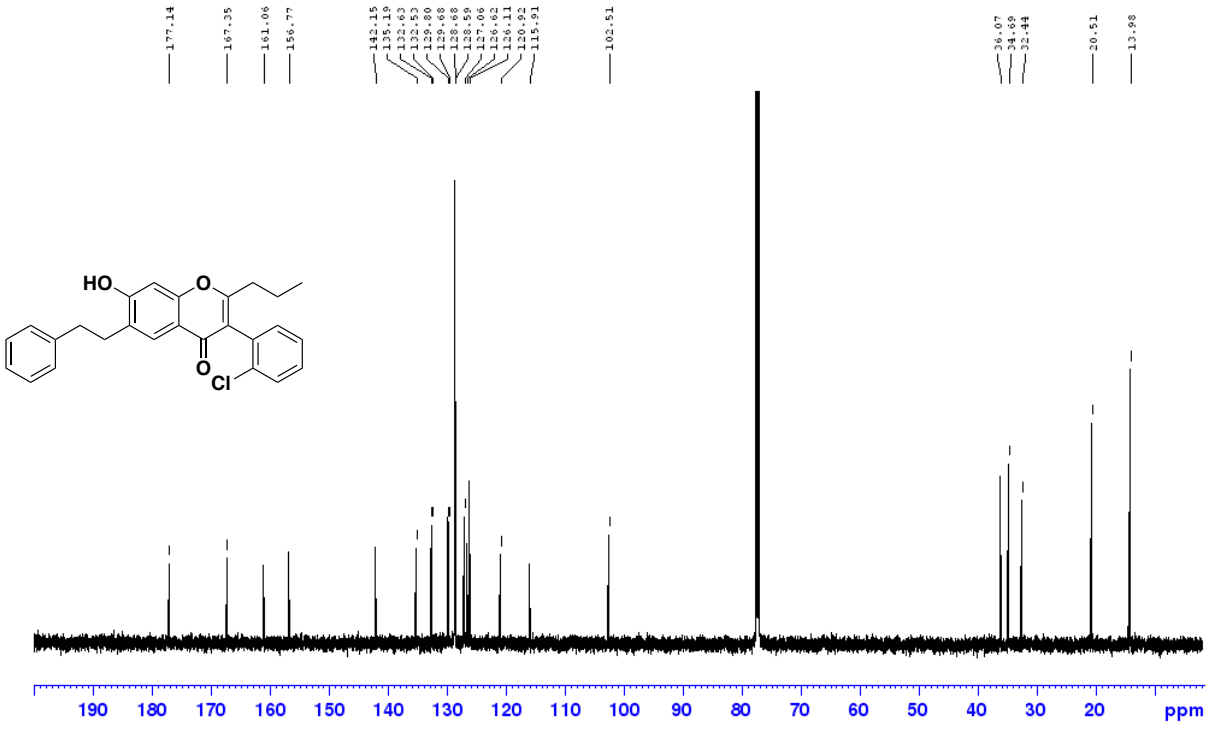

HO
O
O
Cl


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.90
1.13
7.64
2.58
0.91
3.92
2.13
3.46

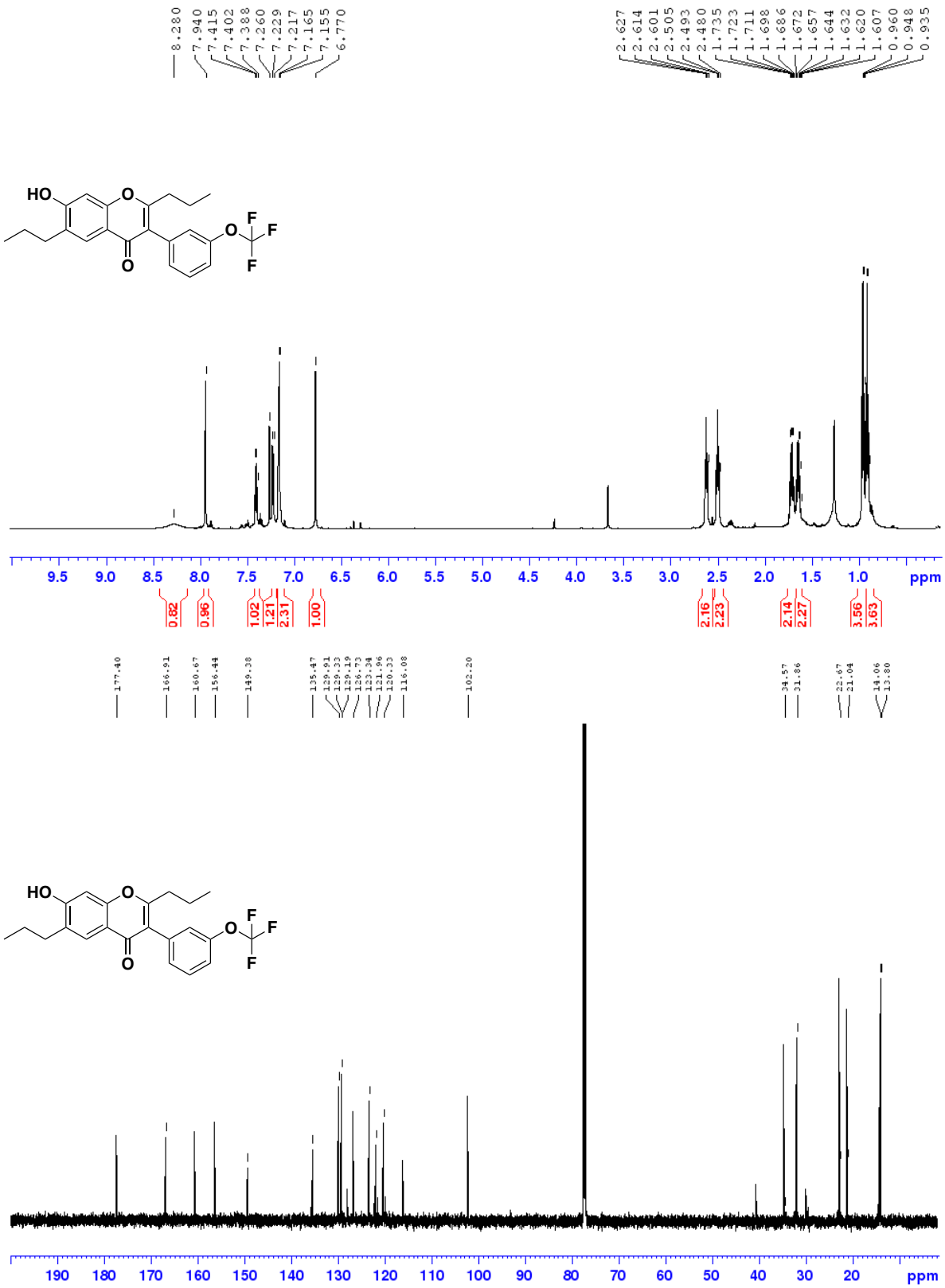

176.78
168.03
160.12
156.61
141.95
135.10
132.64
132.39
129.84
129.71
128.67
128.60
127.12
127.07
126.24
120.47
116.55
102.63
36.17
32.32
26.37
11.54
HO
O
O
Cl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

JG-39

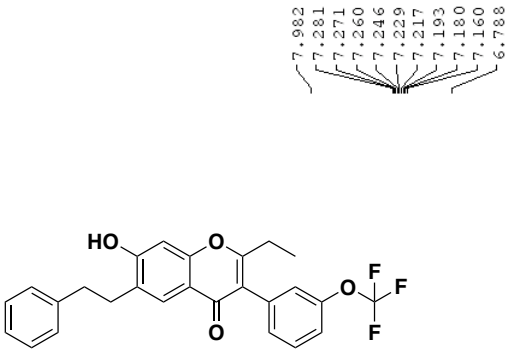

8.803
8.011
7.414
7.401
7.260
7.250
7.223
7.211
7.188
7.176
7.164
6.826
2.945
2.923
2.912
2.504
2.491
2.480
2.467
2.455
2.399
2.385
2.374
2.362
2.349
1.751
1.740
1.728
1.715
1.702
1.689
1.676
1.665
0.905
HO
O
O
Cl
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.89
0.94
1.00
4.40
3.34
1.26
0.95
4.15
2.28
2.59
3.17

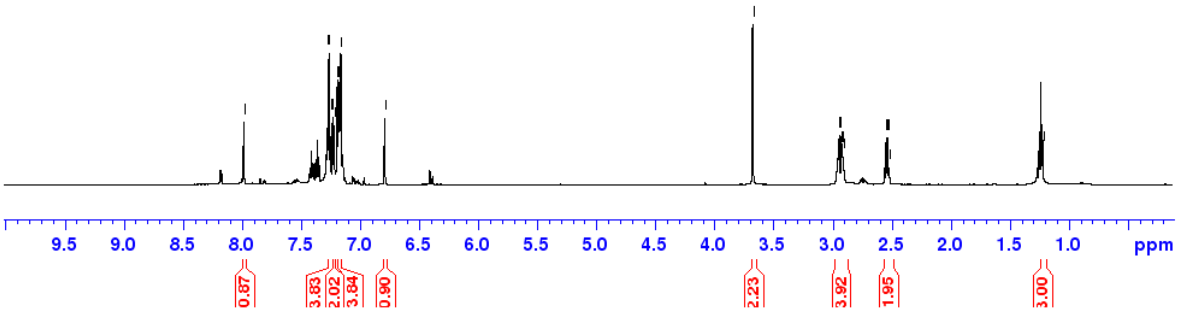

177.14
167.35
161.06
156.77
142.15
135.19
132.63
132.53
129.80
129.68
128.68
128.59
127.06
126.62
126.11
120.62
115.91
102.51
36.07
34.69
32.44
20.51
13.98
HO
O
O
Cl
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

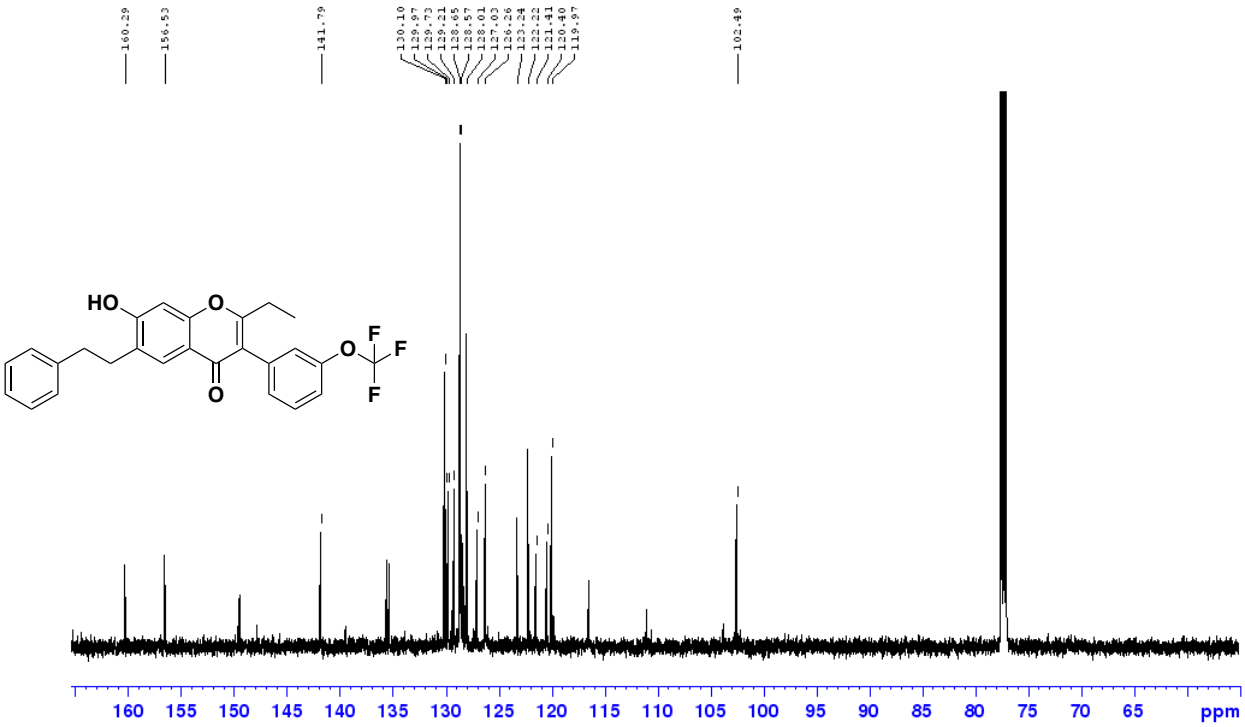
JG-41


8.280
7.940
7.415
7.402
7.388
7.260
7.229
7.217
7.165
7.155
6.770
2.627
2.614
2.601
2.505
2.493
2.480
1.735
1.723
1.711
1.698
1.686
1.672
1.657
1.644
1.632
1.620
1.607
0.960
0.948
0.935
HO
O
F
F
F
O
O
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.82
0.96
1.02
1.21
2.31
1.00
2.16
2.23
2.14
2.27
3.56
3.63
177.40
166.91
160.67
156.44
149.38
135.47
129.91
129.33
129.19
126.73
123.34
121.96
120.33
116.08
102.20
34.57
31.86
22.67
21.04
14.06
13.80
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

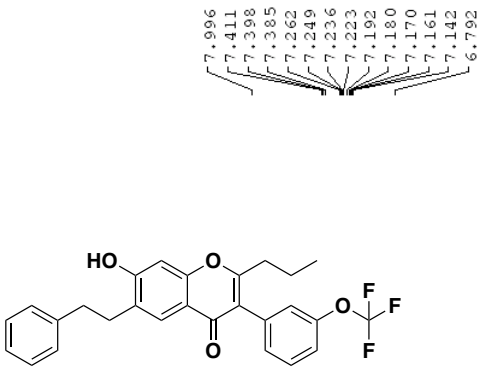
JG-42


7.982
7.281
7.271
7.260
7.246
7.229
7.217
7.193
7.180
7.160
6.788
3.671
2.949
2.943
2.936
2.920
2.913
2.907
2.550
2.538
2.525
2.513
1.241
1.228
1.216
HO
O
F
F
F
O
O

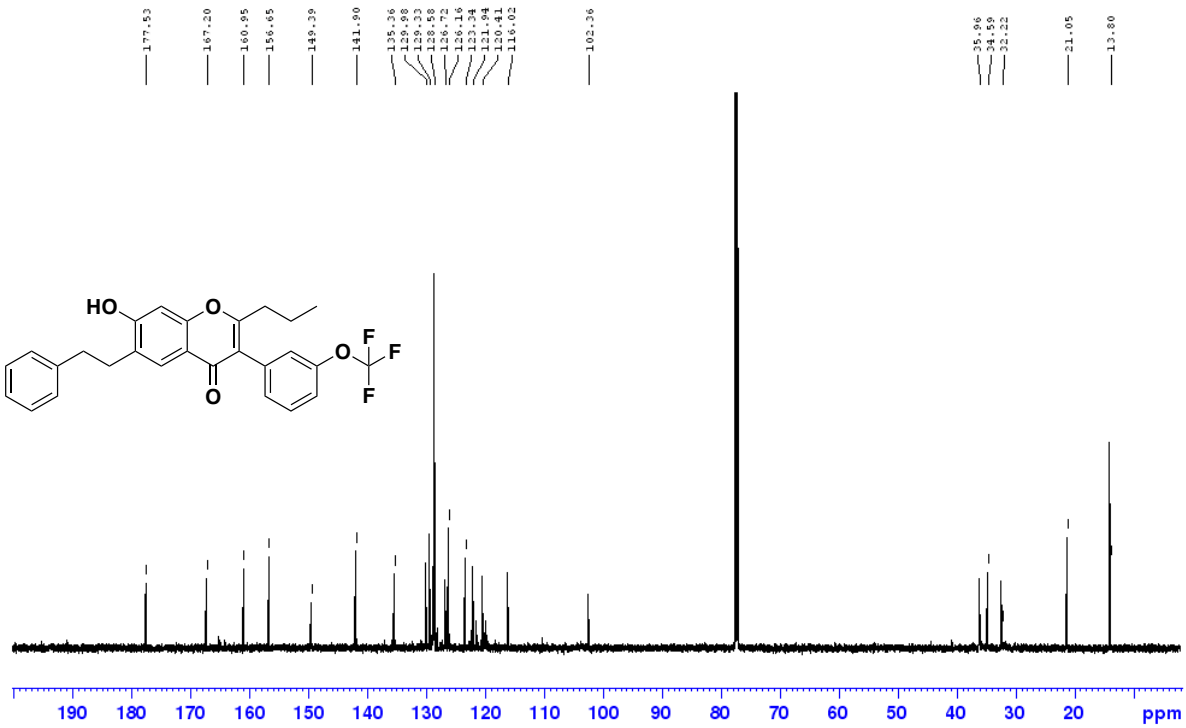

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.87
3.83
2.02
3.84
0.90
2.23
3.92
1.95
3.00


160.29
156.53
141.79
130.10
129.97
129.73
129.21
128.65
128.57
128.01
127.03
126.26
123.24
122.22
121.41
120.40
119.97
102.49
HO
O
F
F
F
O
O
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
ppm

JG-43

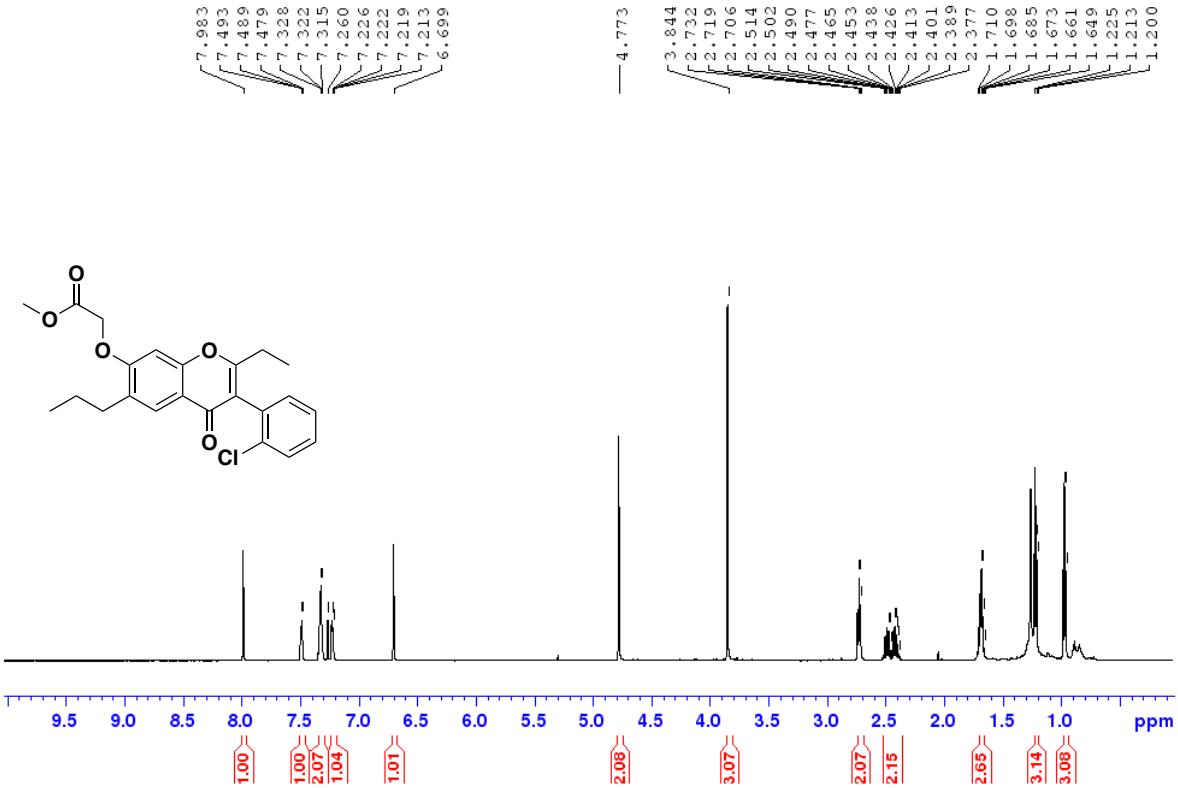

HO
O
O
F
F
F
O

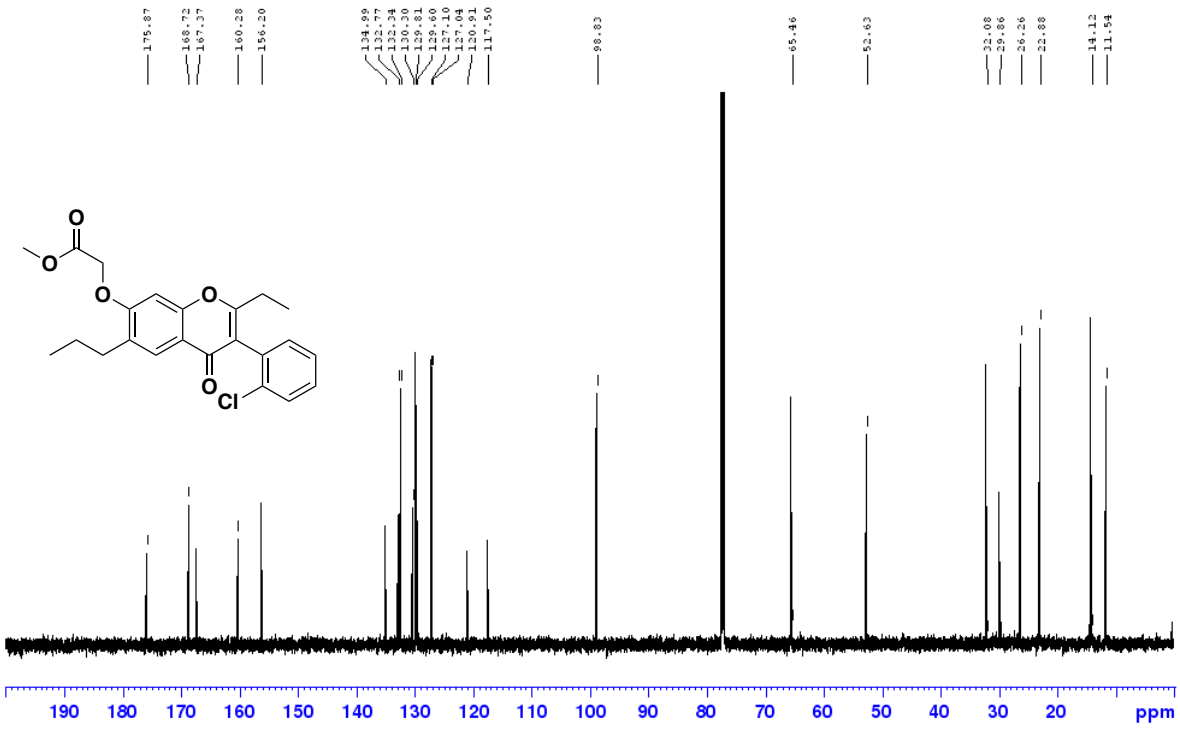
7.996
7.411
7.398
7.385
7.262
7.249
7.236
7.223
7.192
7.180
7.170
7.161
7.142
6.792
2.949
2.942
2.935
2.916
2.908
2.901
2.503
2.490
2.477
1.735
1.723
1.710
1.698
1.685
1.673
0.911
0.898
0.886
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.03
0.97
3.56
5.80
0.96
3.96
1.94
2.05
3.00


177.53
167.20
160.95
156.65
149.39
141.90
135.36
129.98
129.33
128.58
126.72
126.16
123.34
121.94
120.41
116.02
102.36
35.96
34.59
32.22
21.05
13.80
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

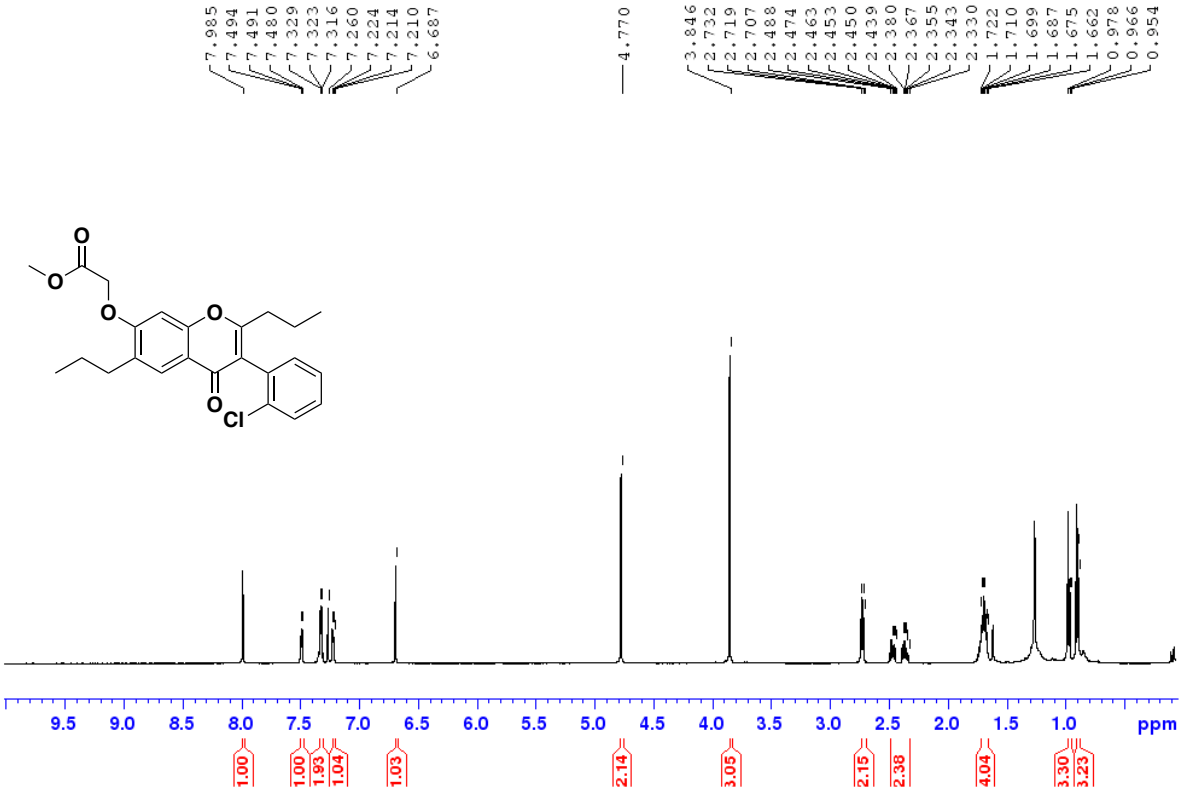
HO
O
O
F
F
F
O

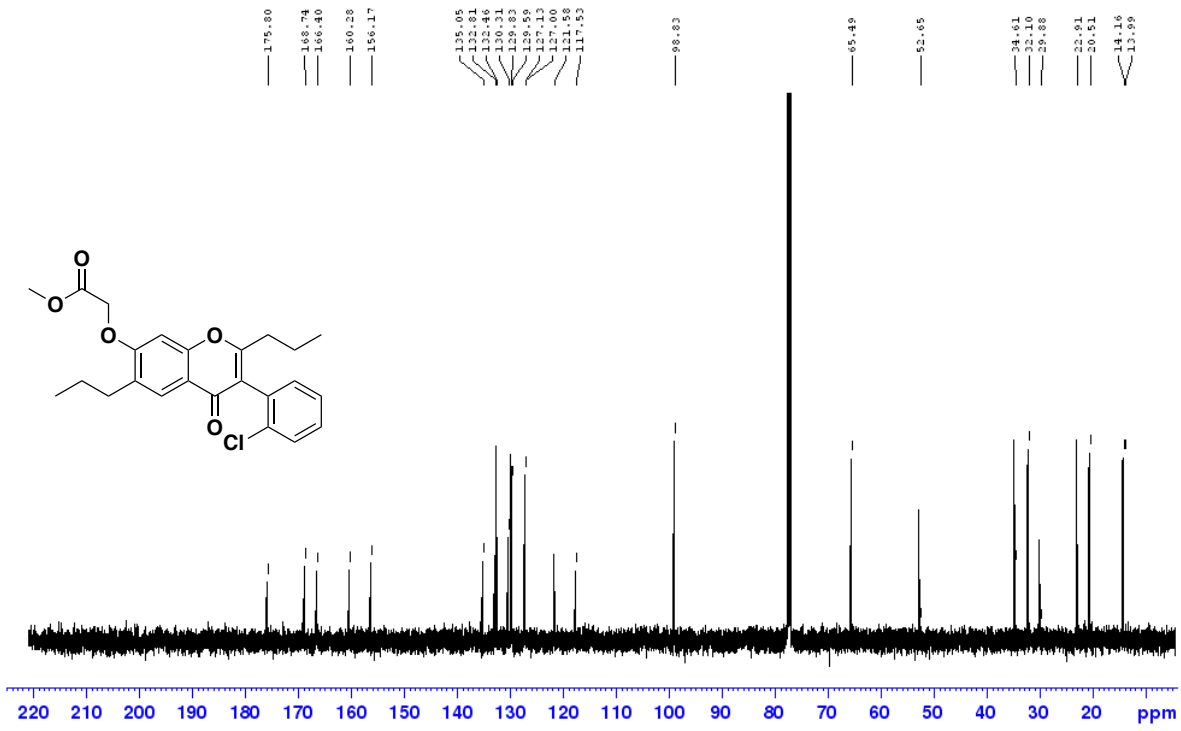
JG-44


7.983
7.493
7.489
7.479
7.328
7.322
7.315
7.260
7.226
7.222
7.219
7.213
6.699
4.773
3.844
2.732
2.719
2.706
2.514
2.502
2.490
2.477
2.465
2.453
2.438
2.426
2.413
2.401
2.389
2.377
1.710
1.698
1.685
1.673
1.661
1.649
1.225
1.213
1.200
O
O
O
O
O
Cl
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.00
2.07
1.04
1.01
2.06
3.07
2.07
2.15
2.65
3.14
3.08

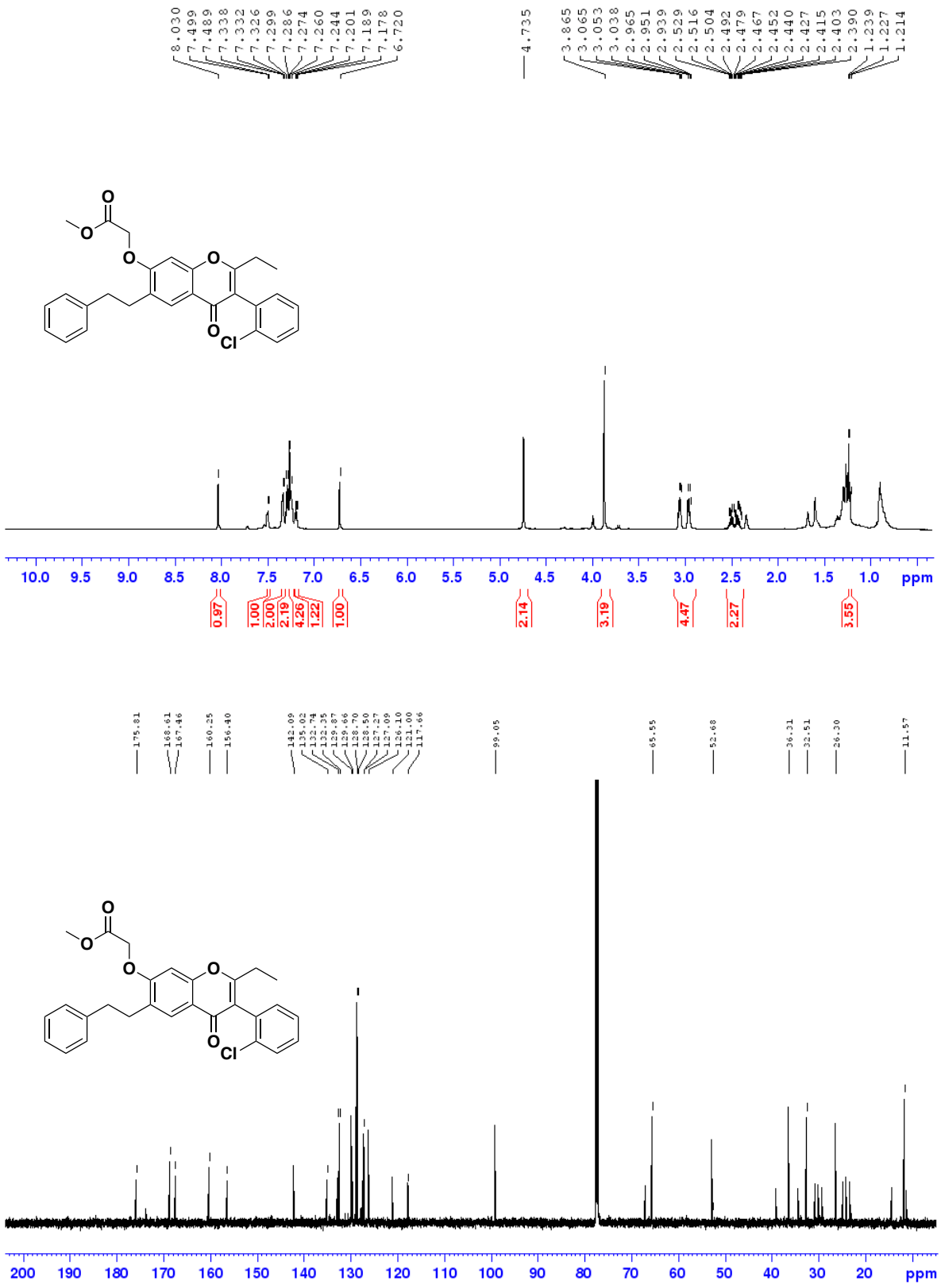

175.87
168.72
167.37
160.28
156.20
134.99
132.77
132.34
130.36
129.81
129.60
127.10
127.04
120.91
117.50
98.83
65.46
52.63
32.08
29.86
26.26
22.88
14.12
11.54
O
O
O
O
O
Cl
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

JG-45

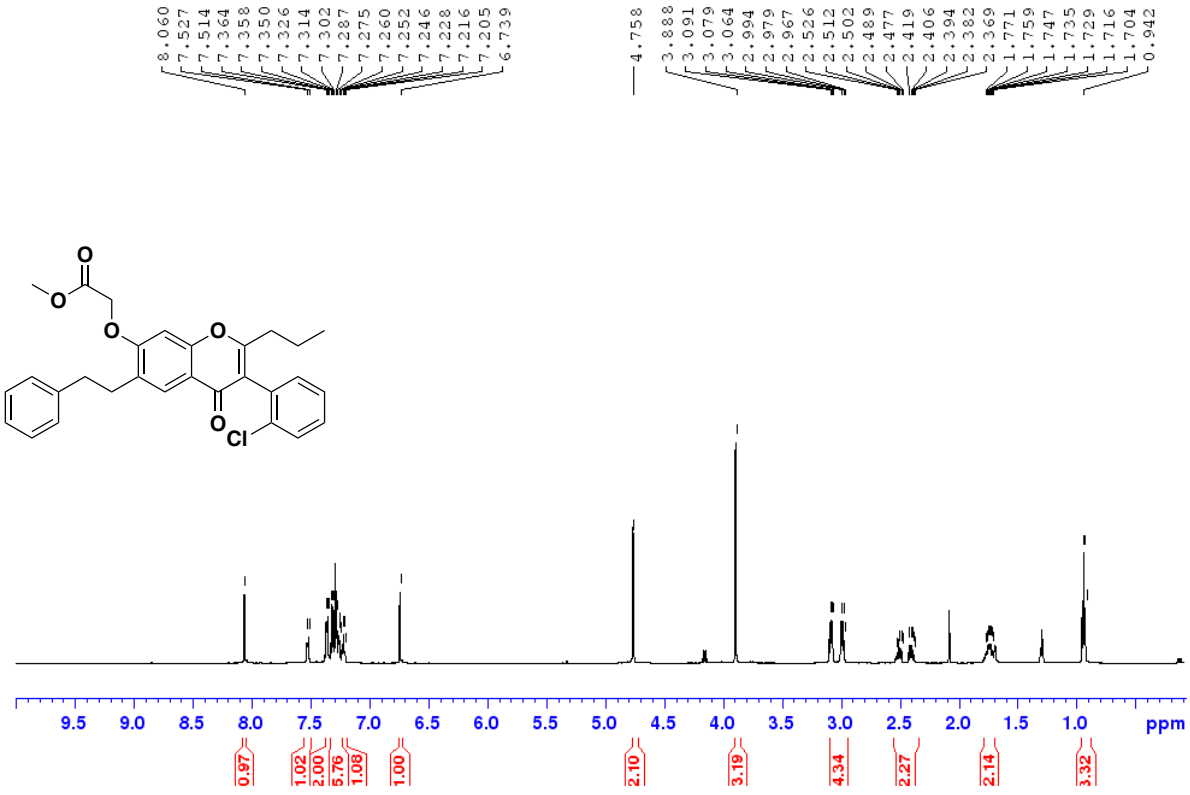

7.985
7.494
7.491
7.480
7.329
7.323
7.316
7.260
7.224
7.214
7.210
6.687
4.770
3.846
2.732
2.719
2.707
2.488
2.474
2.463
2.453
2.450
2.439
2.380
2.367
2.355
2.343
2.330
1.722
1.710
1.699
1.687
1.675
1.662
0.978
0.966
0.954
O
O
O
O
Cl
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.00
1.93
1.04
1.03
2.14
3.05
2.15
2.38
4.04
3.30
3.23

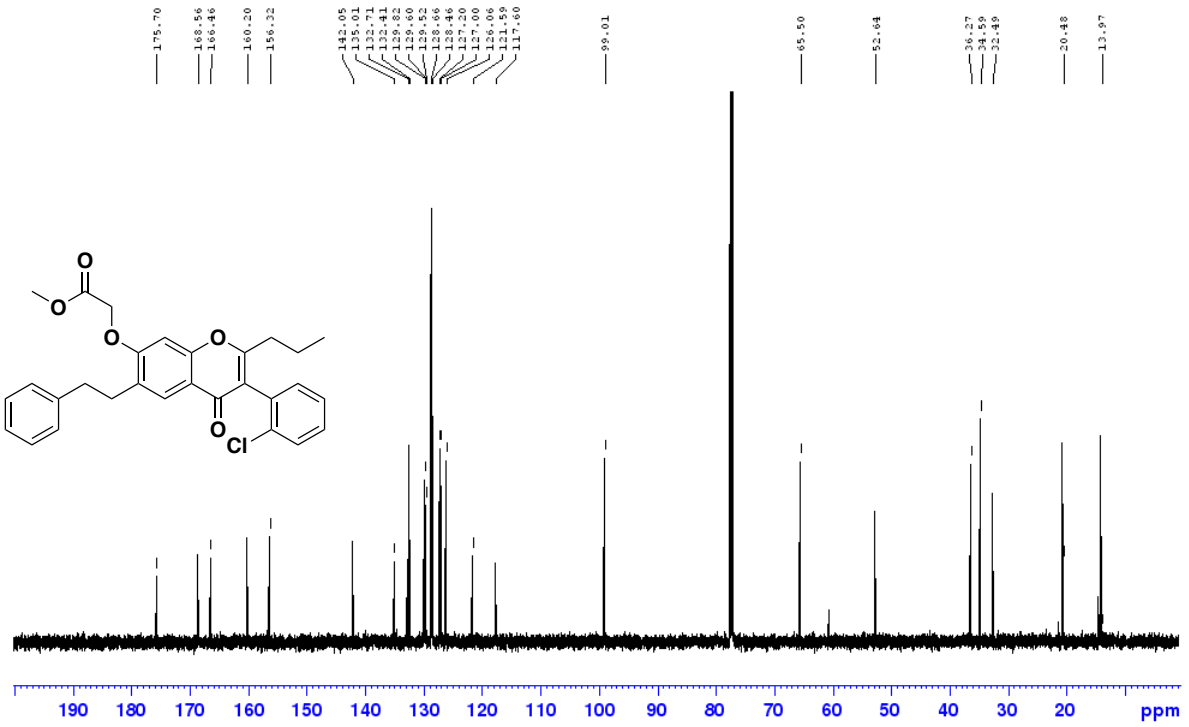

175.80
168.74
166.40
160.28
156.17
135.05
132.81
130.16
130.11
129.83
129.59
127.13
127.00
121.58
117.53
98.83
65.49
52.65
34.61
32.10
29.88
22.91
20.51
14.16
13.99
O
O
O
O
Cl
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

JG-46

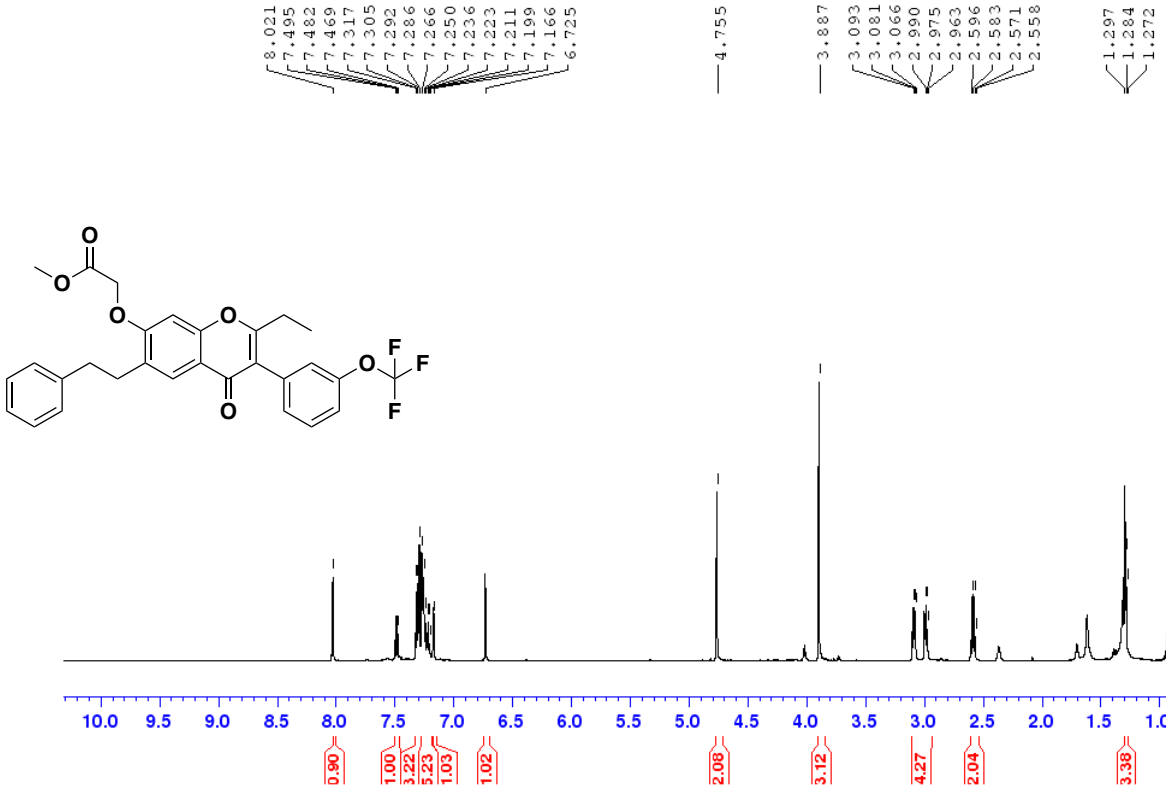

8.030
7.499
7.489
7.338
7.332
7.326
7.299
7.286
7.274
7.260
7.244
7.201
7.189
7.178
6.720
4.735
3.865
3.065
3.053
3.038
2.965
2.951
2.939
2.529
2.516
2.504
2.492
2.479
2.467
2.452
2.440
2.427
2.415
2.403
2.390
1.239
1.227
1.214
O
O
O
O
Cl
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.97
1.00
2.00
2.19
4.26
1.22
1.00
2.14
3.19
4.47
2.27
3.55
175.81
168.61
167.46
160.25
156.40
142.09
135.02
132.74
132.35
129.87
129.66
128.70
128.50
127.27
127.09
126.10
121.00
117.66
99.05
65.55
52.68
36.31
32.51
26.30
11.57
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

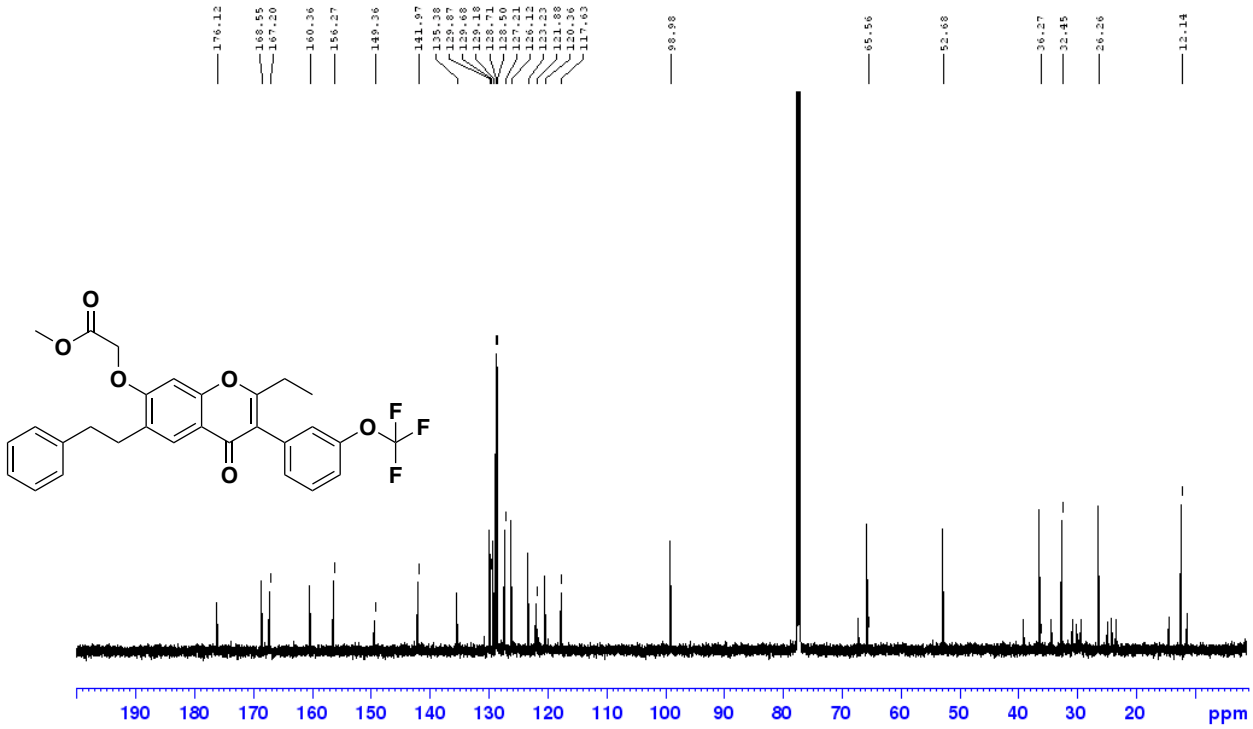
JG-47


8.060
7.527
7.514
7.364
7.358
7.350
7.326
7.314
7.302
7.287
7.275
7.260
7.252
7.246
7.228
7.216
7.205
6.739
4.758
3.888
3.091
3.079
3.064
2.994
2.979
2.967
2.526
2.512
2.502
2.489
2.477
2.419
2.406
2.394
2.382
2.369
1.771
1.759
1.747
1.735
1.729
1.716
1.704
0.942
O
O
O
O
O
Cl
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.97
1.02
2.00
5.76
1.08
1.00
2.10
3.19
4.34
2.27
2.14
3.32

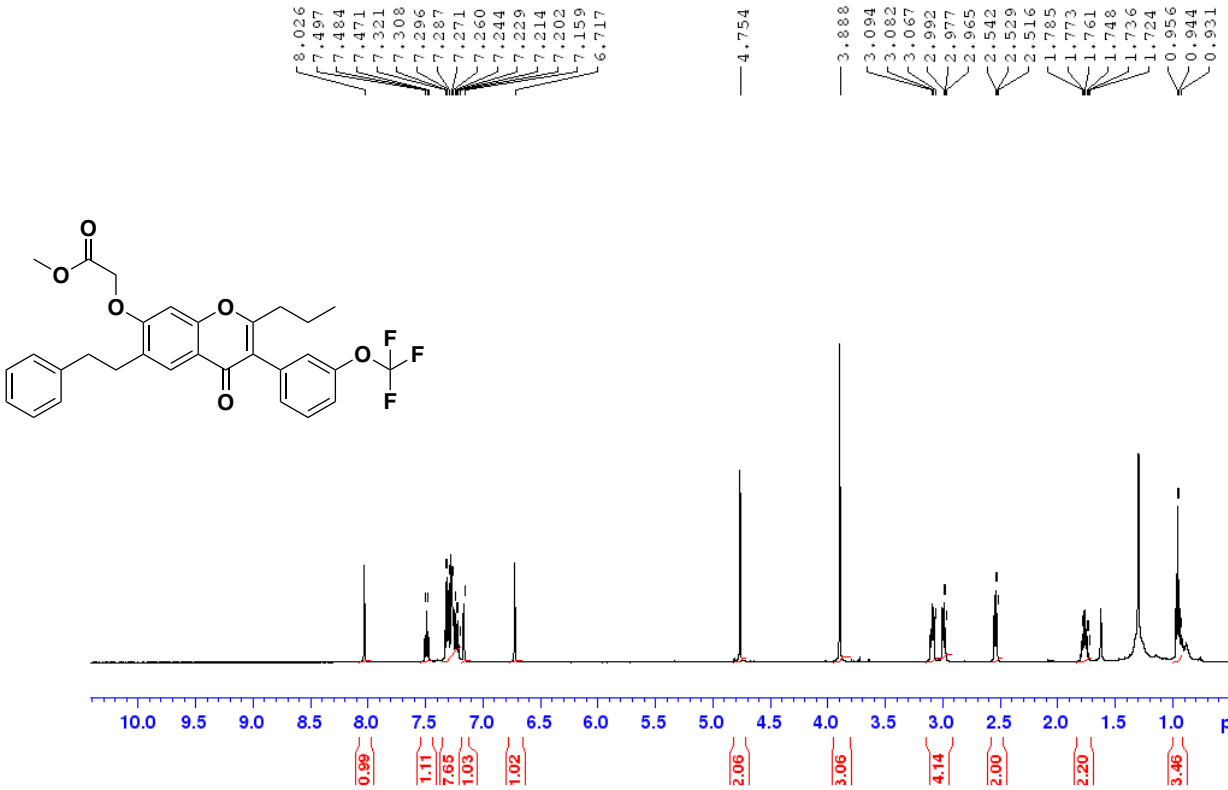

175.70
168.56
166.46
160.20
156.32
142.05
135.01
132.71
132.41
129.82
129.60
129.52
128.66
128.46
127.20
127.00
126.06
121.59
117.60
99.01
65.50
52.64
36.27
34.59
32.49
20.48
13.97
O
O
O
O
O
Cl
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

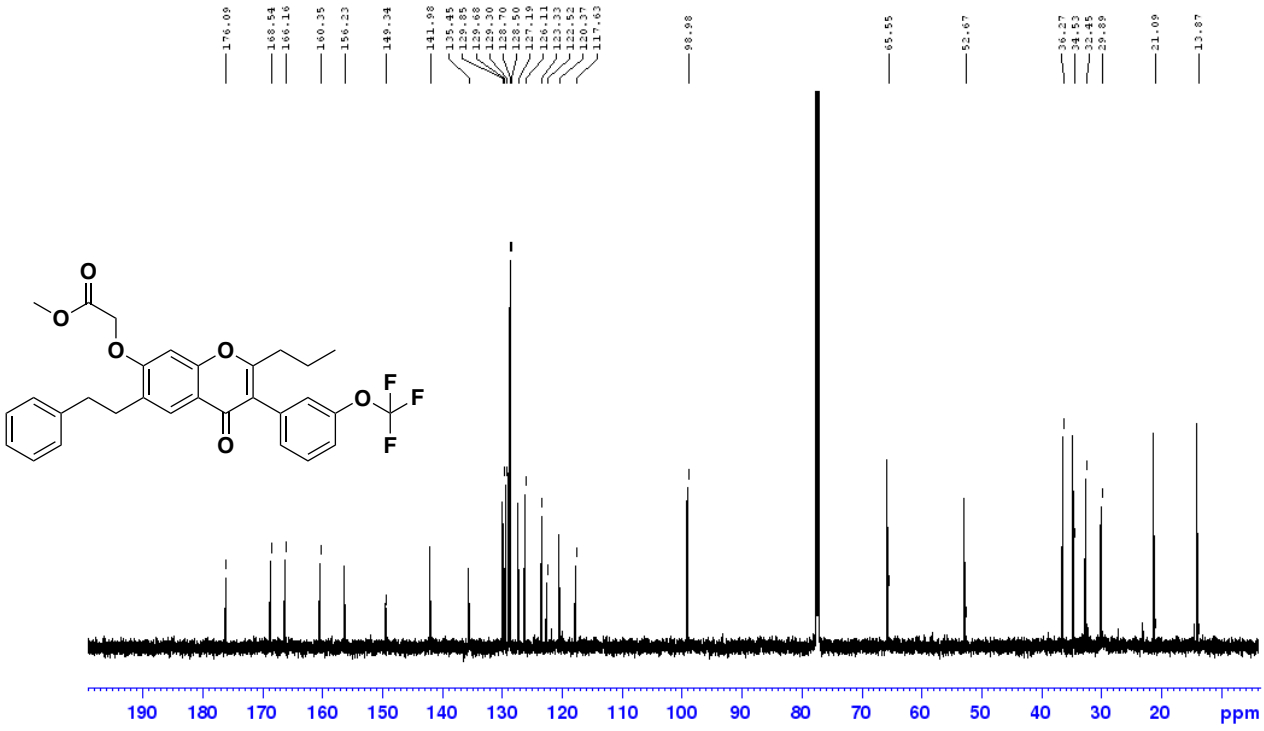
JG-48


8.021
7.495
7.482
7.469
7.317
7.305
7.292
7.286
7.266
7.250
7.236
7.223
7.211
7.199
7.166
6.725
4.755
3.887
3.093
3.081
3.066
2.990
2.975
2.963
2.596
2.583
2.571
2.558
1.297
1.284
1.272
O
O
O
O
F
F
F
O
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.90
1.00
3.22
5.23
1.03
1.02
2.08
3.12
4.27
2.04
3.38


176.12
168.55
167.20
160.36
156.27
149.36
141.97
135.38
129.87
129.68
129.18
128.71
128.50
127.11
126.12
125.33
121.88
120.36
117.63
98.98
65.56
52.68
36.27
32.45
26.26
13.14
O
O
O
O
F
F
F
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

JG-49


8.026
7.497
7.484
7.471
7.321
7.308
7.296
7.287
7.271
7.260
7.244
7.229
7.214
7.202
7.159
6.717
4.754
3.888
3.094
3.082
3.067
2.992
2.977
2.965
2.542
2.529
2.516
1.785
1.773
1.761
1.748
1.736
1.724
0.956
0.944
0.931
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.99
1.11
7.65
1.03
1.02
2.06
3.06
4.14
2.00
2.20
3.46


176.09
168.54
166.16
160.35
156.23
149.34
141.98
135.45
129.85
129.68
129.30
128.70
128.50
127.19
126.11
123.33
122.52
120.37
117.63
98.98
65.55
52.67
36.27
34.53
32.45
29.89
21.09
13.87
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm