Supporting Information

For

Life Beyond Kinases: Structure-based Discovery of Sorafenib as Nanomolar Antagonist of 5-HT Receptors

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#MEGA
!Title beta-2 and 5-HT2A;
!Format
   DataType=Protein
   NSeqs=2 NSites=284
   Identical=. Missing=? Indel=-;


!Domain=Data;
#Beta-2_adrenoceptor DEVWVVGMGI VMSLIVLAIV FGNVLVITAI AKFERLQTVT
#5HT2A               HLQEKNWSAL LTAVVIILTI A..I...M.V SLEKK..NA.

#Beta-2_adrenoceptor NYFITSLACA DLVMGLAVVP FGAAHILM-K MWTFGNFWCE
#5HT2A               ...LM...I. .MLL.FL.M. VSMLT..YGY R.PLPSKL.A

#Beta-2_adrenoceptor FWTSIDVLCV TASIETLCVI AVDRYFAITS PFKYQSLLTK
#5HT2A               V.IYL...FS ....MH..A. SL...V..QN .IHHSRFNSR

#Beta-2_adrenoceptor NKARVIILMV WIVSGLTSFL PIQM------ ----------
#5HT2A               T..FLK.IA. .TI.VGI.MP IPVFGLQDDS KVFKEGSCLL

#Beta-2_adrenoceptor --QAYAIASS IVSFYVPLVI MVFVYSRVFQ EAKRQ-----
#5HT2A               ADDNFVLIG. F...FI..T. ..IT.FLTIK SLQKEATLCV

#Beta-2_adrenoceptor ----KEHKAL KTLGIIMGTF TLCWLPFFIV NIVHVIQDN-
#5HT2A               QSISN.Q..C .V...VFFL. VVM.C....T ..MA..CKES

#Beta-2_adrenoceptor ---LIRKEVY ILLNWIGYVN SGFNPLIYC- RSPDFRIAFQ
#5HT2A               CNEDVIGALL NVFV....LS .AV...V.TL FNKTY.S..S

#Beta-2_adrenoceptor ELLC
#5HT2A               RYIQ
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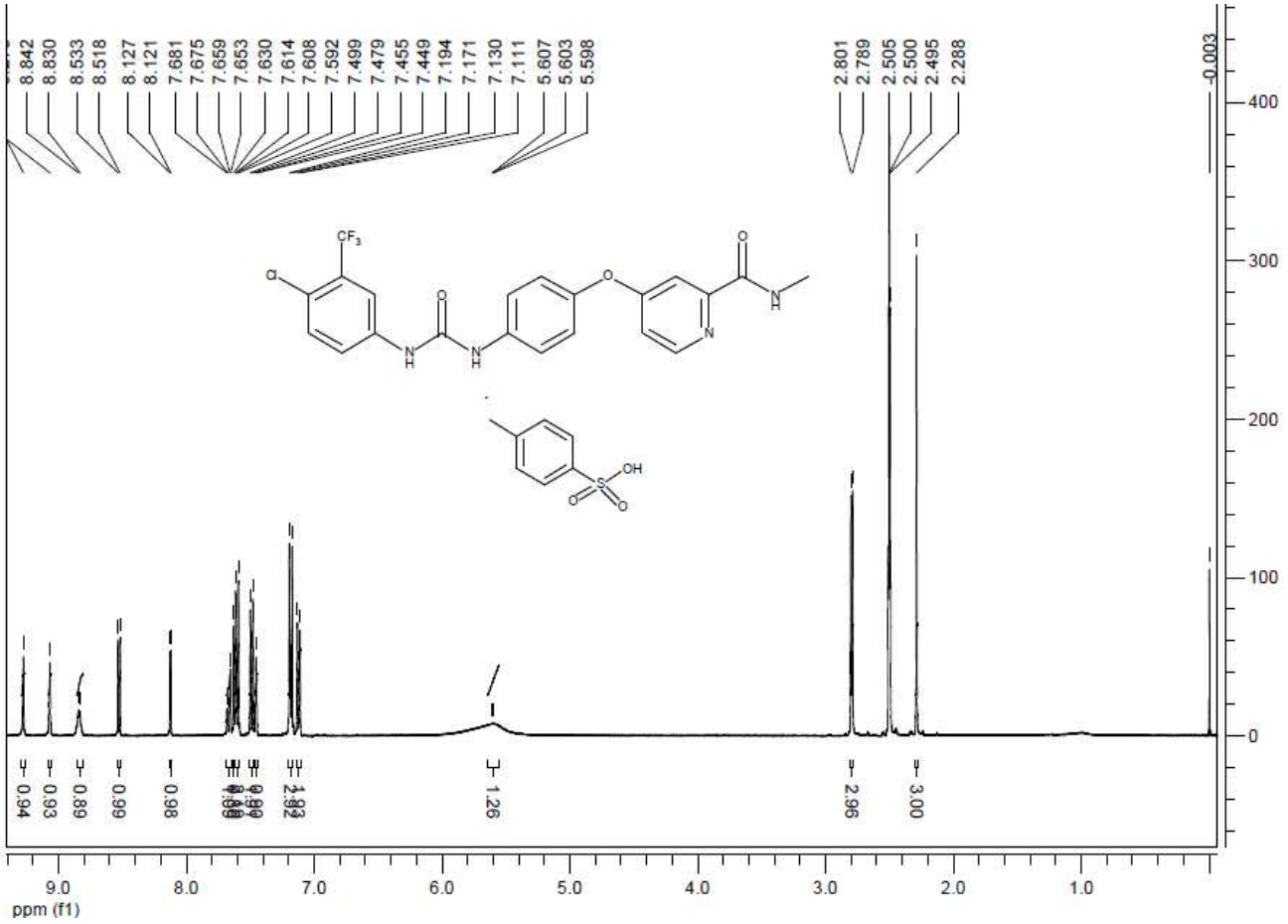
Figure S1. Sequence alignment between 5-HT_{2A} and β-2 adrenoceptor in MEGA format (only shown residues used in structure modeling).

A. 1HNMR



B. MS

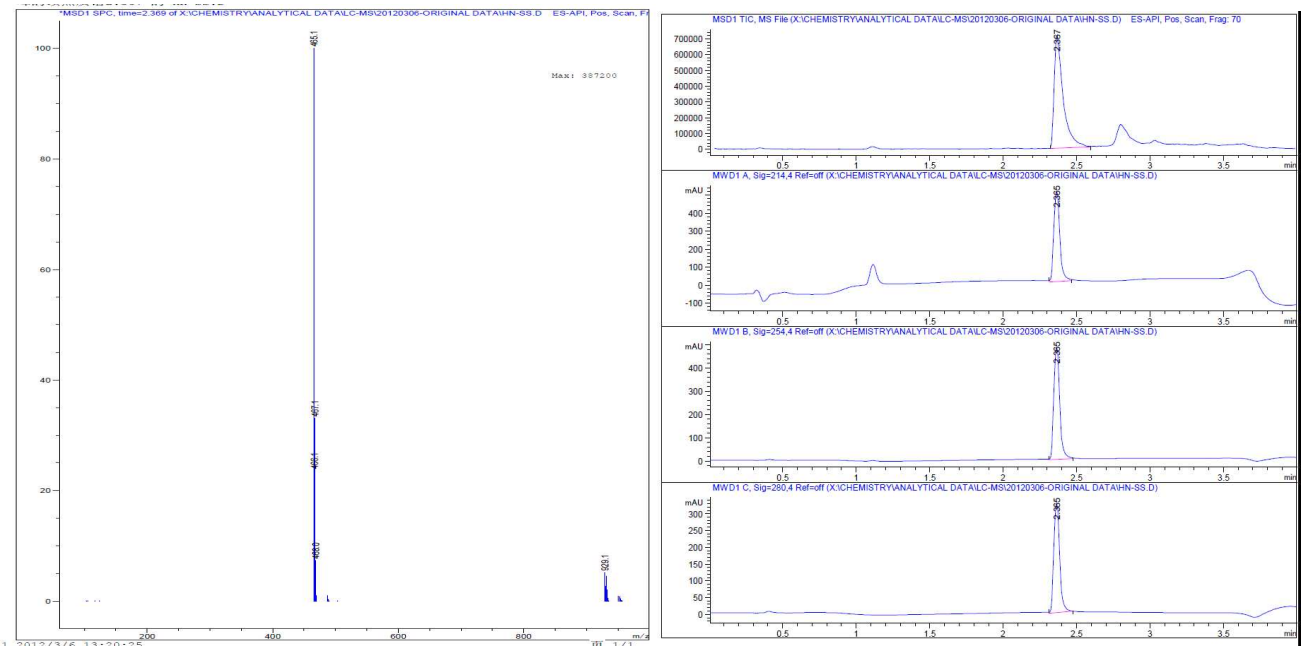


Figure S2. [1]H-NMR spectrum and MS data of sorafenib.

Table S1. The structural descriptors used to assess the simulation quality of Ketanserin complex system.

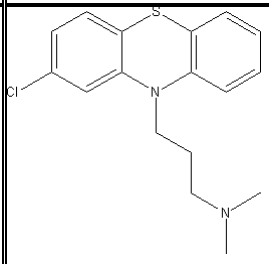
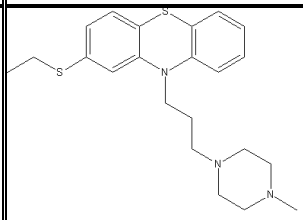
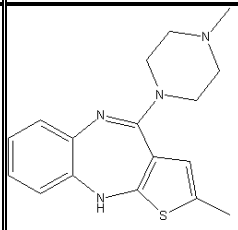
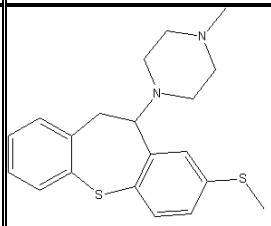
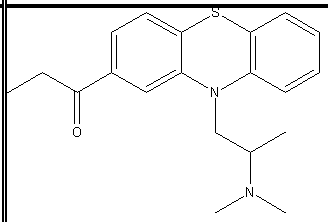
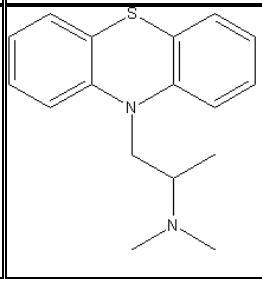
Only simulation 6 (Ket-6) satisfies all the experimental observation.

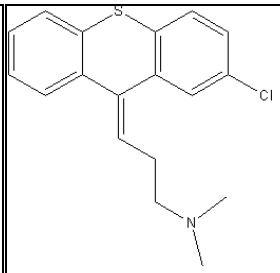
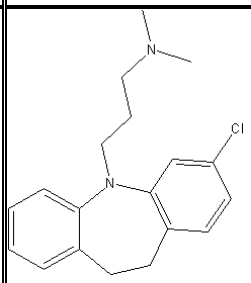
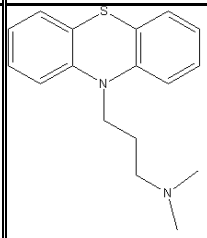
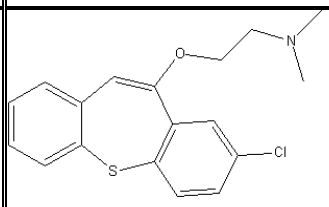
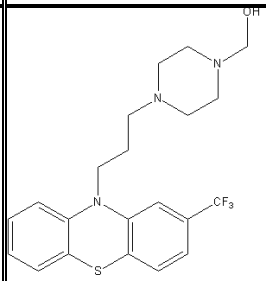
Ketanserin Simulation systems	D3.32-ligand salt bridge	S3.36-ligand H-bond	Ratio of F6.52-ligand contacts	Ratio of W6.48-ligand contacts	R3.50-E6.30 ionic lock	D3.32-Y7.43 H-bond
1	√	√	√	×	√	×
2	√	×	√	×	×	√
3	×	×	√	√	×	×
4	√	√	√	√	×	×
5	√	√	√	√	×	×
6	√	√	√	√	√	√
7	√	×	√	√	×	√
8	√	√	√	×	×	√
9	√	√	√	√	×	×
10	√	×	√	√	√	√
11	√	√	√	×	×	√
12	√	×	√	√	√	√

Note: The formation of D3.32-ligand salt bridge interaction is defined as the distance between carboxylate oxygen atom of D3.32 and the piperidine nitrogen atom of ligand less than 3.5 Å, the ratio of this interaction is defined to be larger than 70%; the hydrogen bond between ligand and hydroxyl of residue $S_{3.36}$ is defined by the distance of donor and acceptor less than 3.5 Å and angle greater than 120º (same for D3.32-Y7.43 hydrogen bond), the ratio is defined as less than 30%; the ratio of F6.52-ligand contacts is defined by the number of atom pairs within vdW contact distance between ligand and F6.52 divided by the number of atom pairs between ligand and F6.51 (same for W6.48-ligand contacts), the ratio is defined as less than 50%; and the R3.50-E6.30 ionic lock is defined by distance less than 4 Å between CZ atom of R3.50 and CD atom of E6.30, the ratio is defined to be larger than 70%.

Table S2. Docking pose assessment for ketanserin-like and cyproheptadine-like ligands.

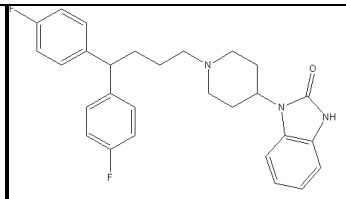
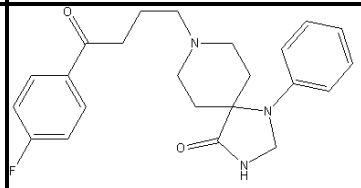
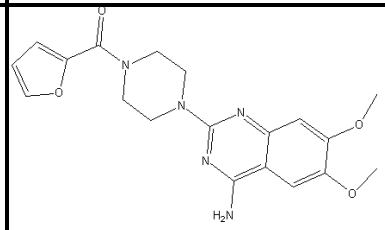
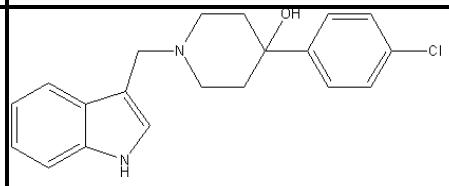
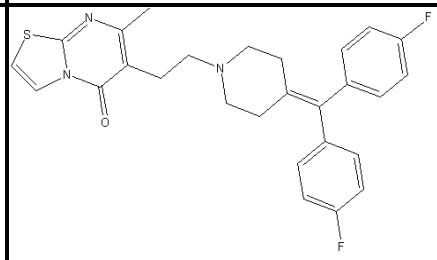
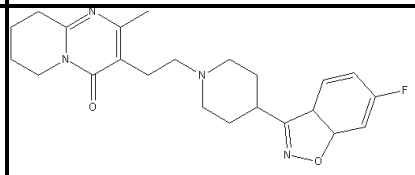
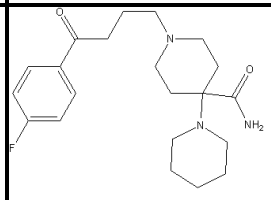
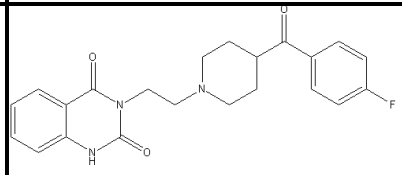
a) 12 Clozapine-like ligands

Zinc_ID	Compound Name	Chemical Structure	Docking pose from initial homology model	Docking pose from Cyp-4-4 model
C31261349	Chlorprothixene		No	Yes
C22446674	Thiethylperazine		Yes	No
C19632674	Olanzapin		No	Yes
C19362650	Methiothepin		No	Yes
C00896849	Propiomazine		Yes	Yes
C00056647	Promethazine		Yes	Yes

C00044027	Chlorpromazine		Yes	Yes
C00020248	Clomipramine		No	Yes
C00010402	Promazine		Yes	Yes
C00002264	Zotepine		No	Yes
C19203912	Fuphenazine		No	Yes
Ratio of correct pose prediction			45%	91%

b) 11 Ketanserin-like ligands

Zinc_ID	Compound Name	Chemical Structure	Initial Homology Model	Ket-6-7 model

C19796084	Pimozide		No	Yes
C00643233	Spiperone		No	Yes
C00601304	Prozasine		No	No
C00538483	Trazodone		Yes	Yes
C00538314	Ritanserin		No	No
C00538312	Risperidone		Yes	Yes
C00538184	Pipamperone		No	Yes
C00537877	Ketanserin		Yes	Yes

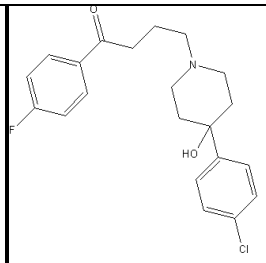
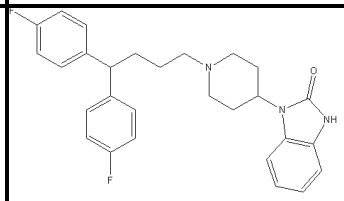
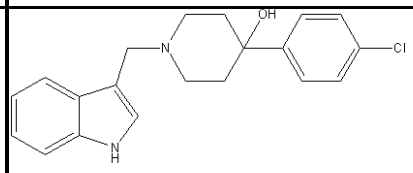
C00537822	Haloperidol		Yes	Yes
C00056646	Pindolol		No	Yes
C00006788	I-741626		No	No
Ratio of correct pose prediction			36%	73%

Table S3. The annotation of top scored molecules from docking and rescoring.

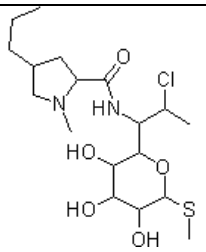
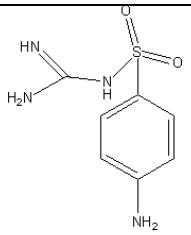
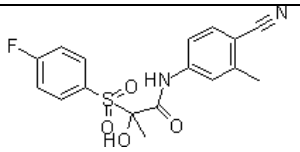
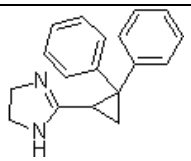
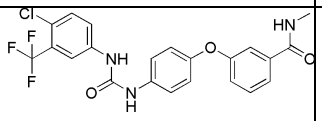
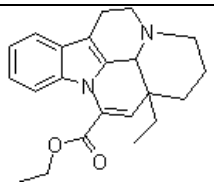
ZINC ID	annotated activity	reference	Rescore-Rank	Testing status
20251	Alpha-2A adrenergic receptor	DrugBank	10	neglect
3831042	5-hydroxytryptamine 2A receptor	DrugBank	14	neglect
3830583			18	PDSP17675
3831041	5-hydroxytryptamine 2A receptor	DrugBank	21	neglect
58791			22	PDSP17678
12503070	Alpha-2A adrenergic receptor	DrugBank	25	neglect
6157	Histamine H1 receptor	Chemble	27	neglect
18115268	Histamine H1 receptor	Chemble	29	neglect
44027	5-hydroxytryptamine 2A receptor	DrugBank	34	neglect
3831172			35	not available
1968	likely be 5-HT2A binder		36	not available
2510048	Histamine H1 receptor	Sigma-Aldrich	42	neglect
1999487	Histamine H2 receptor	DrugBank	43	neglect
968337	Histamine H1 receptor	DrugBank	44	neglect
549	Dopamine uptake inhibitor	Sigma-Aldrich	47	neglect
57321	Beta-2 adrenergic receptor	DrugBank	48	neglect
57204	Histamine H1 receptor	Chemble	50	neglect
538564	Androgen receptor	DrugBank	52	PDSP17680
3830866	likely be 5-HT2A binder		53	not available
1481714	Histamine H1 receptor	DrugBank	54	neglect
3831578			55	not available
416	Alpha-1A adrenergic receptor	DrugBank	56	neglect
57435	Alpha-2A adrenergic receptor	DrugBank	58	neglect

5626	Alpha-2A adrenergic receptor	DrugBank	59	neglect
3831238	Alpha-1A adrenergic receptor	DrugBank	63	neglect
145			66	PDSP17676
3594299	Alpha-2A adrenergic receptor	DrugBank	68	neglect
3831004	Dopamine uptake inhibitor	Chemble	70	neglect
1261	Histamine H1 receptor	DrugBank	71	neglect
2019621	Histamine H1 receptor	DrugBank	74	neglect
896849	D(1A) dopamine receptor	DrugBank	75	neglect
12503073	Alpha-2A adrenergic receptor	DrugBank	76	neglect
19156872	Histamine H1 receptor	DrugBank	77	neglect
3831110	5-hydroxytryptamine 7 receptor	DrugBank	78	neglect
669	D(1A) dopamine receptor	DrugBank	79	neglect
4351	Histamine H1 receptor	DrugBank	82	neglect
1493878	sorafenib		85	PDSP17674
20244	Histamine H1 receptor	DrugBank	87	neglect
57524	Histamine H1 receptor	DrugBank	88	neglect
122	Muscarinic acetylcholine receptor M1	DrugBank	91	neglect
57253	Histamine H1 receptor	DrugBank	94	neglect
155269	Histamine H1 receptor	DrugBank	95	neglect
2019839			96	not available
2018341			99	not available
897251	5-hydroxytryptamine 2A receptor	DrugBank	100	neglect
968306	Alpha-2A adrenergic receptor	DrugBank	102	neglect
56647	Muscarinic acetylcholine receptor M3	DrugBank	103	neglect
2266			104	PDSP17676
113410	Histamine H1 receptor	DrugBank	105	neglect

113404	Histamine H1 receptor	DrugBank	107	neglect
608117			108	not available
1087483	opioid receptor	DrugBank	111	neglect
607	Histamine H1 receptor	DrugBank	112	neglect
1530695	5-hydroxytryptamine 2A receptor	DrugBank	114	neglect
843			115	not available
403011	Alpha-1A adrenergic receptor	DrugBank	116	neglect
104	Beta-1 adrenergic receptor	Chemble	117	neglect
20250	Muscarinic acetylcholine receptor M3	DrugBank	119	neglect
3799072	Beta-2 adrenergic receptor	DrugBank	121	neglect
9073	D(1A) dopamine receptor	DrugBank	130	neglect
1482162	Histamine H1 receptor	Chemble	132	neglect
968257	Alpha-2A adrenergic receptor	DrugBank	133	neglect
57198	Dopamine receptor	DrugBank	135	neglect
3830580			136	PDSP17675
4097283			137	not available
1931	Dopamine D1 receptor	Chemble	139	neglect
1681	Kappa-type opioid receptor	DrugBank	140	neglect
10402	D(1A) dopamine receptor	DrugBank	141	neglect
242	Muscarinic acetylcholine receptor M1	DrugBank	146	neglect
608179	Mu-type opioid receptor	DrugBank	147	neglect
968338	Histamine H1 receptor	DrugBank	148	neglect
3830970			149	not available
19360739	Histamine H1 receptor	DrugBank	150	neglect
1672			151	not available
1851149	5-hydroxytryptamine 2A receptor	DrugBank	152	neglect

19632891	Histamine H1 receptor	DrugBank	153	neglect
2018342			154	not available
57206	Dopamine transporter	Chemble	155	neglect
3830995			156	PDSP17675
538065	5-hydroxytryptamine 2A receptor	DrugBank	157	neglect
637	Beta-2 adrenergic receptor	DrugBank	160	neglect
1481966	5-hydroxytryptamine 1A receptor	DrugBank	162	neglect
4319	Beta-1 adrenergic receptor	DrugBank	166	neglect
508068	Histamine H1 receptor	DrugBank	168	neglect
3831511	Histamine H1 receptor	DrugBank	169	neglect
601270	likely be 5-HT2A binder		171	not available
2032320	Beta-2 adrenergic receptor	Chemble	172	neglect
1550499	Extracellular calcium-sensing receptor	DrugBank	173	not available
1530759			174	not available
3794601	Serotonin transporter	DrugBank	176	neglect
3831236	likely be Adrenoceptor binder		177	not available
968263	5-hydroxytryptamine 2A receptor	DrugBank	184	neglect
597013	5-hydroxytryptamine 2A receptor	DrugBank	186	neglect
57623	Beta-1 adrenergic receptor	DrugBank	187	neglect
597358			189	PDSP17681
3830270			194	not available
565	Histamine H1 receptor	DrugBank	197	neglect
56651	Muscarinic acetylcholine receptor M1	DrugBank	198	neglect
480	Histamine H1 receptor	DrugBank	200	neglect

Table S4. Six FDA approved drugs selected for experimental binding assay.

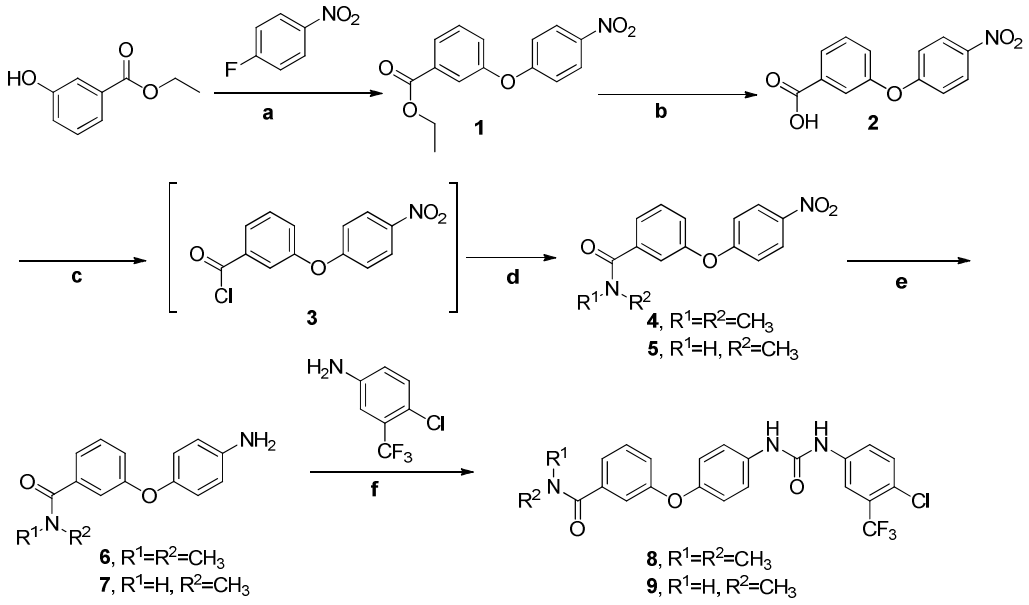
Drug Name	Vendor ID	PDSP ID	Chemical Structure	Primary screening (10 uM)	Secondary screening (Ki)	Annotated Drug Target	MM-GB/SA Ranking
Clindamycin	sigma C5269	17675		1.4%	N/A	50s ribosomal subunit	18
Sulfaguanidine	Sigma S8751	17678		-6.1%	N/A	Dihydropteroate synthetase	22
Bicalutamide	Sigma B9061	17680		8.9%	N/A	Androgen receptor antagonist	52
Cibenzoline	Sigma C1618	17676		25.4%	N/A	ATP-sensitive K channel	66
Sorafenib	LC lab S-8502	17674		88.1%	1949 nM	c-Kit VEGFR2 PDGFRb FLT3	85
Vinpocetine	Sigma V6383	17681		15%	N/A	PDE1 inhibitor	189

Detailed Experimental Assays. The experimental binding assays were performed by the National Institute of Mental Health's Psychoactive Drug Screening Program (PDSP) following the standard protocol. Briefly, the radio-labeled reference compounds ([^{3}H]8-OH-DPAT for 5-HT$_{1A}$; [^{3}H]GR127543 for 5-HT$_{1B}$ and 5-HT$_{1D}$; [^{3}H]5-HT for 5-HT$_{1E}$; [^{3}H]Ketanserin for 5-HT$_{2A}$; [^{3}H]LSD for 5-HT$_{2B}$ and 5-HT$_{2C}$, 5-HT$_{5a}$, 5-HT$_6$ and 5-HT$_7$; [^{3}H]LY278584 for 5-HT$_3$) are diluted to 5X final assay concentration (50 μM for a final assay concentration of 10 μM) in the standard binding buffer. Subsequently, 50 μl aliquots of buffer (negative control), test compound, and reference compound are added in quadruplicate to the wells of a 96-well plate, each of which contains 50 μl of 5X radioligand and 100 μl of buffer. Finally, receptor-containing, crude membrane fractions are resuspended in an appropriate volume of buffer and dispensed (50 μl per well) into the 96-well plate. Radioligand binding is allowed to equilibrate (typically for 1.5 hours at room temperature), and then bound radioactivity is isolated by filtration onto 0.3% polyethyleneimine-treated, 96-well filter mats using a 96-well Filtermate harverster. The filter mats are dried, then scintillant is melted onto the filters and the radioactivity retained on the filters is counted in a Microbeta scintillation counter. Raw dpm data from the Microbeta counter are analyzed on the PDSP DB. Total bound radioactivity is estimated from quadruplicate wells without containing test or reference compound and adjusted to 100%; non-specifically bound radioactivity is assessed from quadruplicate wells containing 10 μM of a suitable reference compound and adjusted to 0%. The average bound radioactivity in the presence of the test compound (10 μM final assay concentration, quadruplicate determinations) is expressed on the percent scale. The percent inhibition of radioligand binding is calculated as follows: $\%_{\text{inhibition}} = 100\% - \%_{\text{radioactivity-bound}}$. The PDSP on-line data entry and analysis system calculates the variance of the quadruplicate determinations (for the total, non-specific, and test compound binding values) and variances greater than 20% are flagged for further inspection and assays are repeated if necessary.

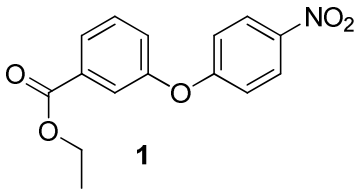
The stable cell line from GenScript Corporation, CHO-K1/5-HT$_{2A}$, was applied for the cellular screening of the compound shown significant activities in 5-HT$_{2A}$ binding assay using FLIPR method.

Briefly, the compound plate for the first addition contains the compound at concentration 5X final assay concentrations in the reading plate. The agonist plate for the second addition contains the agonist at the concentration 5X final concentrations in the reading plate. The total reading time is 420 seconds. The first addition consists of test compound after 20 seconds reading of the baseline and the fluorescence signal is captured for another 290 seconds (20 s to 310 s). Subsequently, 75 nM (5x final concentration) of 5-HT is added to the cell plate and the fluorescence signal is monitored for an additional 110 s (310 s to 420 s). In compound screening, cells stimulated with assay buffer (HBSS-HEPES) containing 0.5% DMSO are chosen as the background, cells stimulated with 15 nM (EC_{80} of the cell line) of 5-HT are chosen as the negative control, and cells treated with 10 μM of ketanserin tartrate are used as the positive control. Data acquisition and analyses are performed using ScreenWorks (version 3.1) program. The average value of 10 (300 s to 310 s) seconds reading is calculated as the baseline reading and the relative fluorescent units (ΔRFU) intensity values are calculated with the maximal fluorescent units (310 s to 420 s) subtracting the average value of baseline reading. The % inhibition of the test article is calculated from the following equation: $\%inhibition = \{1 - (\Delta RFU_{Compound} - \Delta RFU_{Background})/(\Delta RFU_{Negative\text{-}control} - \Delta RFU_{Background})\}$

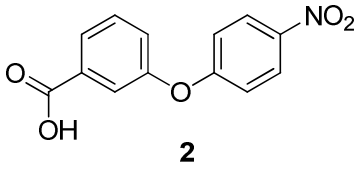
Sorafenib analogues chemical synthesis route and analysis data



(a) K_2CO_3, DMF; (b) LiOH, THF, H_2O; (c) $SOCl_2$, DCM; (d) R^1R^2NH, TEA, DCM;(e) Pd/C, H_2, MeOH; (f) Triphosgene, TEA, DCM.

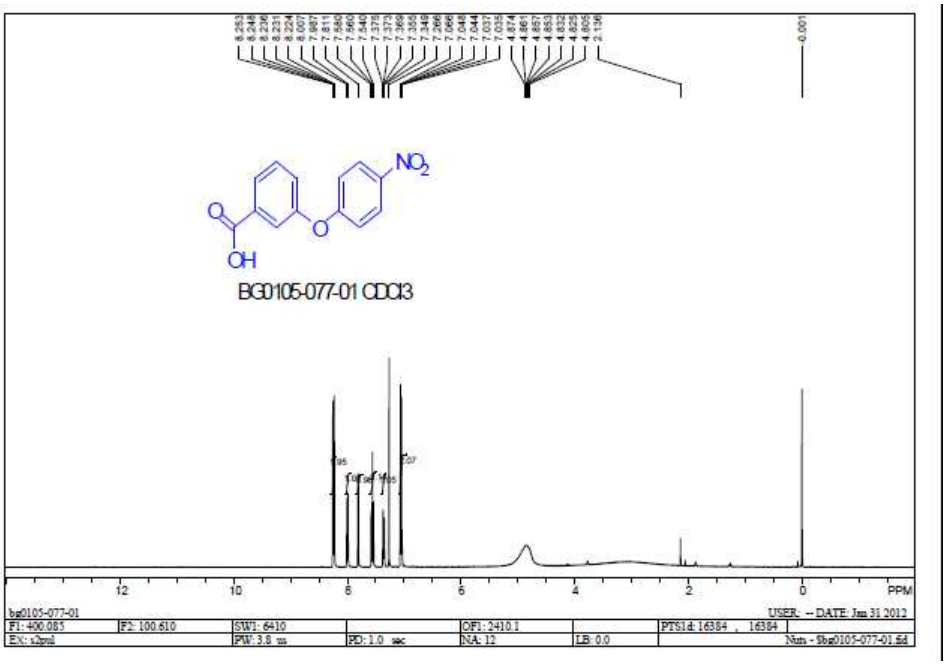


Ethyl 3-(4-nitrophenoxy)benzoate ***(1)*** To a stirred solution of 1-fluoro-4-nitrobenzene (4.23 g, 30 mmol), ethyl 3-hydroxybenzoate (4.98 g, 30 mmol) in DMF (40 mL) was added K_2CO_3 (8.28 g, 60 mmol) at 25 ^oC. The reaction was heated at 135 ^oC for 4 hours. TLC indicated the reaction was completed. The reaction was cooled to rt, diluted with water (50 mL), and extracted with ethyl acetate (3×50 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the crude title compound (8.2 g) as a yellow oil which was used directly in the next step. LCMS: (ESI) *m/z* 288 $(M+1)^+$.

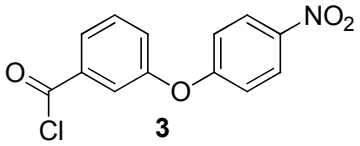


3-(4-nitrophenoxy)benzoic acid ***(2)*** To a solution of compound **1** (8.2 g, 28.5 mmol) in THF/water (75/75 mL) was added $LiOH{\cdot}H_2O$ (2.34 g, 57 mmol) in some portions. The reaction was stirred at 50 ^oC for 4 hours. The reaction was cooled to rt, diluted with water (50 mL), and extracted with ethyl acetate (30 mL). The aqueous layer was collected and adjusted to pH 2 with 2N HCl solution. The resulting pale yellow solids were filtered and washed with PE (40 mL) to give the compound **2** (4.6 g, 62% for two

steps).[(1)] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.25 - 8.22 (m, 2H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.81 (s, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.38 – 7.35 (m, 1H), 7.07 – 7.04 (m, 2H) ppm.

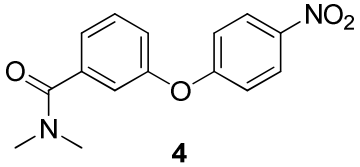


(1) Riedl, B.; Dumas, J.; Khire, U.; Lowinger, T. B.; Scott, W. J.; Smith, R. A.; Wood, J.E.; Monahan, M.-K.; Natero, R.; Renick, J.; Sibley, R. N. Omega-carboxyaryl substituted diphenyl ureas as raf kinase inhibitors. Patent Application, U.S., 7235576, (B1), 26 Jun 2007



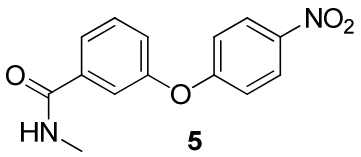
3

3-(4-nitrophenoxy)benzoyl chloride ***(3)*** To a solution of compound **2** (500 mg, 2 mmol) in DCM (5 mL) was added $SOCl_2$ (2 mL) and DMF (2 drops). The solution was stirred at 50 ^oC for 3 hours. TLC indicated the reaction was completed. The mixture was concentrated to dryness and used directly in the next step without purification.



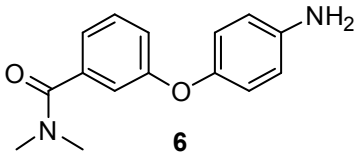
4

N,N-dimethyl-3-(4-nitrophenoxy)benzamide **(4)** To a solution of dimethylamine hydrochloride (163 mg, 2 mmol) and TEA (606 mg, 6 mmol) in DCM (3 mL) was added compound **3** in DCM (5 mL) at rt. The solution was stirred at rt for 2 hours. The solution was concentrated to dryness. The residue was dissolved in EtOAc (30 mL), washed with 1N HCl solution (15 mL) and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound (480 mg, yield 83%, two steps) as a colorless oil. LCMS: (ESI) *m/z* 287 $(M+1)^+$.



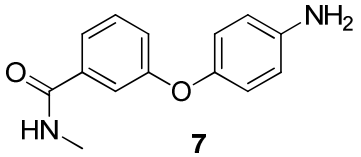
5

*N-methyl-3-(4-nitrophenoxy)benzamide **(5)*** Compound **5** was prepared from **3** as described in the preparation of **4**, providing **5** (460 mg, 84%) as a colorless oil. LCMS: (ESI) *m/z* 273 $(M+1)^+$.



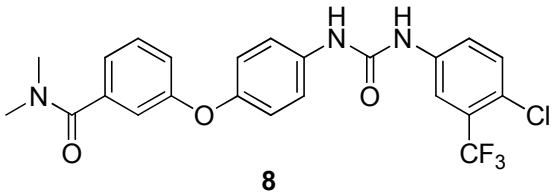
6

3-(4-aminophenoxy)-N,N-dimethylbenzamide (**6**) To a mixture of compound **4** (480 mg, 1.68 mmol) in CH_3OH (5 mL) was added Pd/C (200 mg). Then the reaction was stirred at rt under H_2 (balloon) for 5 hours. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC to give the title compound (365 mg, yield 85%) as a brown solid. LCMS: (ESI) *m/z* 257 $(M+1)^+$.



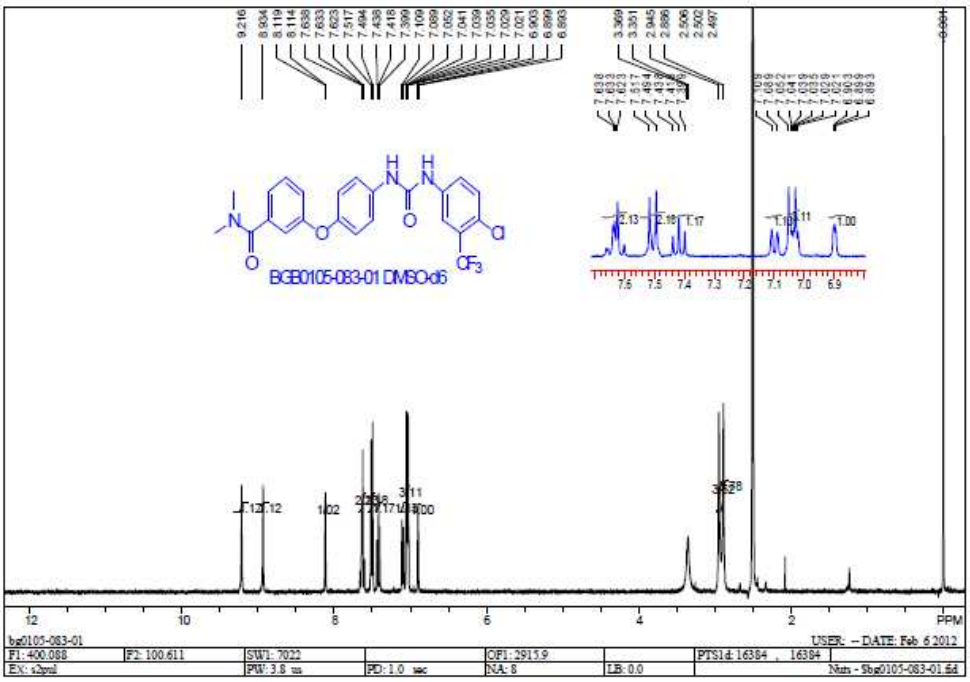
7

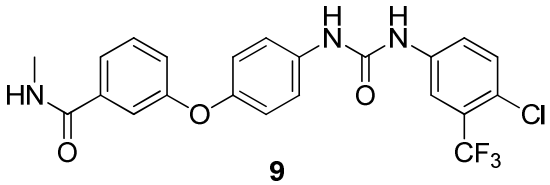
*3-(4-aminophenoxy)-N-methylbenzamide **(7)*** Compound **7** was prepared from **5** (460 mg, 1.69 mmol) as described in the preparation of **6**, providing **7**(320 mg, yield 78%) as a brown solid. LCMS: (ESI) *m/z* 243 $(M+1)^+$.



8

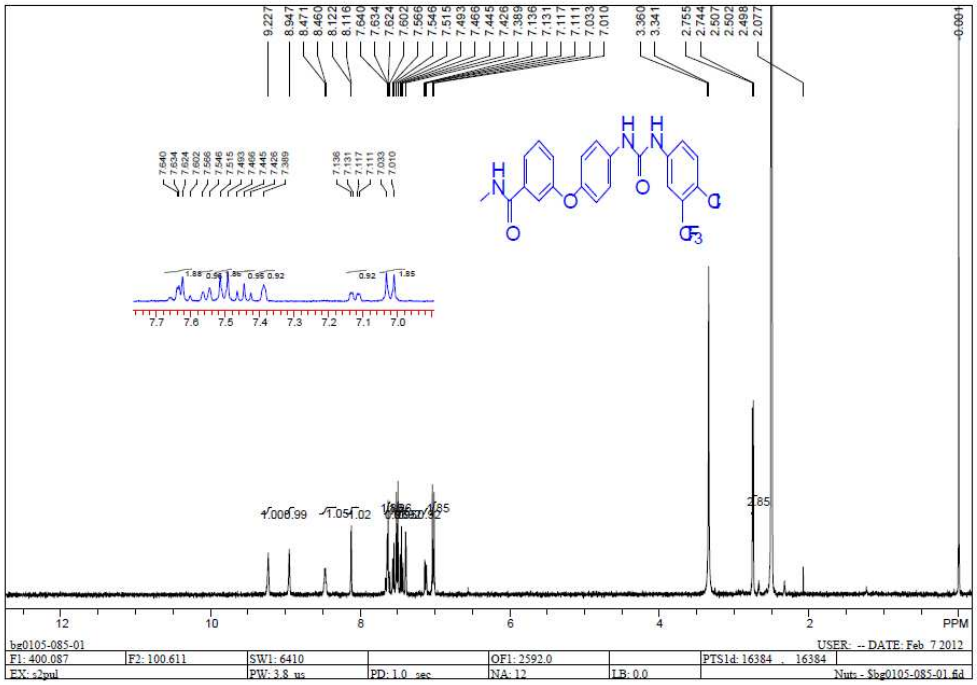
*3-(4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenoxy)-N,N-dimethyl benzamide **(8)*** To a mixture of bis(trichloromethyl) carbonate (87.4 mg, 0.3 mmol) in DCM (5 mL) at 0 ^oC was added dropwise a solution of 4-chloro-3-(trifluoromethyl) aniline (195 mg 1 mmol) and TEA (606 mg , 6 mmol). The solution was stirred at 0 ^oC for 1 hour. Compound **6** (128 mg, 0.5 mmol) was added and the reaction was stirred at rt for 4 hours. The mixture was concentrated to dryness and the residue was purified by column chromatography (DCM/MeOH=50/1) and further purified by prep-HPLC to give the title compound (8 mg, 4%) as a solid. ^{1}H-NMR (400 MHz, DMSO) δ 9.21 (s, 1H), 8.93 (s, 1H), 8.11 (d, J = 2.0 Hz, 1H), 7.64 – 7.62 (m, 2H), 7.52 – 7.49 (m, 2H), 7.42 (t, J = 8.0 Hz, 1H), 7.11 – 7.09 (m, 1H), 7.05 – 7.02 (m, 3H), 6.90 (s, 1H), 3.37 (s, 3H), 3.35 (s, 3H) ppm. LCMS: (ESI) *m/z* 478$(M+1)^+$.





9

*3-(4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenoxy)-N-methylbenzamide (**9**)* Compound **9** was prepared from **7** (120 mg, 0.5 mmol) as described in the preparation of **8**, providing **9** (10 mg, 4%) as a solid. ^{1}H-NMR (400 MHz, DMSO) δ 9.23 (s, 1H), 8.95 (s, 1H), 8.47 (d, J = 4.4 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.64 – 7.60 (m, 2H), 7.57 – 7.49 (m, 2H), 7.44 (t, J = 8.4 Hz, 1H), 7.39 (s, 1H), 7.14 – 7.11 (m, 1H), 7.03 – 7.01 (m, 2H), 3.36 (s, 3H) ppm. LCMS: (ESI) m/z 464(M+1)$^+$.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7.624
7.602
7.566
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7.493
7.466
7.445
7.426
7.389
7.136
7.131
7.117
7.111
7.033
7.010
3.360
3.341
2.755
2.744
2.507
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