Supporting Information

Interacting with GPCRs; on the use of Interaction Fingerprints for Virtual Screening.

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Docking

Crystal structure(s)
A_{2A}:4EIY (ensemble; 4EIY, 3EML, 3UZA, 3UZC, 3RFM, 3PWH and 3REY). H_1:3RZE. M_2:3UON. β_2:2RH1 (ensemble; 2RH1, 3D4S, 3NY8, 3NY9, 3YNA, and 4GBR). **CCR5**: 4MBS

Ligands
100 ligands, decoys retrieved from the DUD-e web service, prepared using Ligprep.

1-50 poses generated using Glide-SP docking

Interaction Fingerprint

Deng (Schrödinger script) Credo, Elements, SYBYL (Python script) SPLIF (Pipeline Pilot)

SPLIF
Atom type abstraction: Functional class (F), Atom type (E), ALogPcode (L), and Sybyl (S). Radius:2,4,6

Enrichment Calculation

Similarity with respect to the crystal structure ligand.

SPLIF
Tanimoto, Tversky and SPLIF

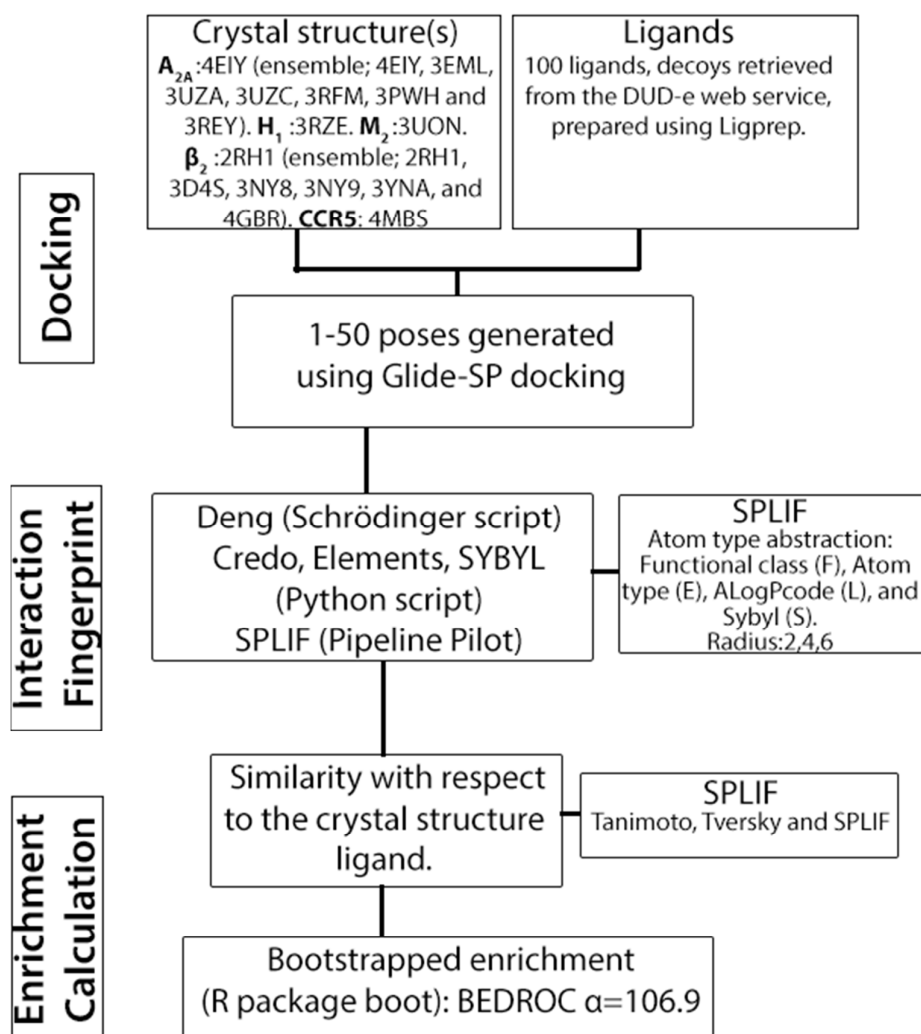Bootstrapped enrichment (R package boot): BEDROC α=106.9

Figure S1. Workflow used in this study; in general the three steps included docking, generation of the interaction fingerprint and calculation of the enrichment. Additional settings explored for SPLIF are shown on the right hand side.

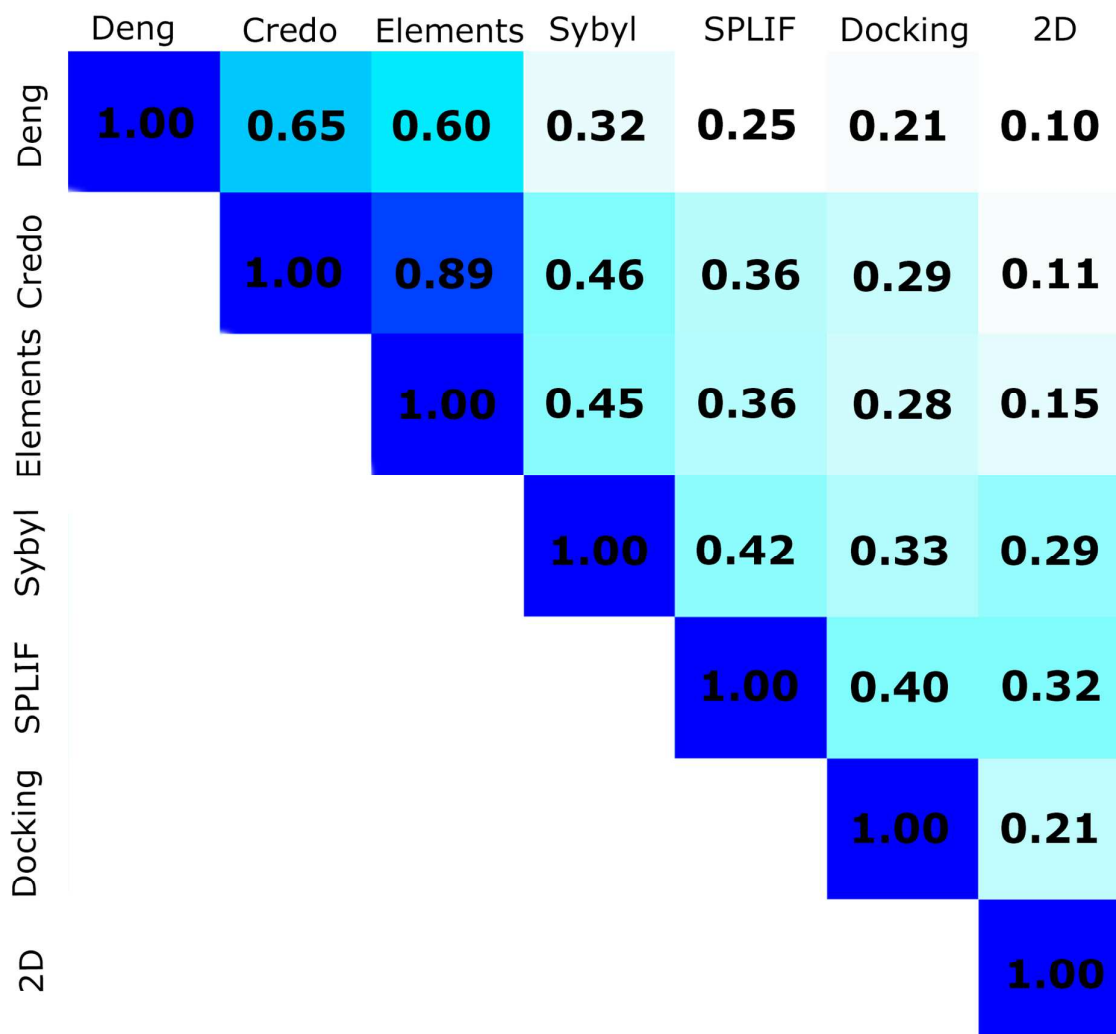|	Deng	Credo	Elements	Sybyl	SPLIF	Docking	2D
Deng	1.00	0.65	0.60	0.32	0.25	0.21	0.10
Credo		1.00	0.89	0.46	0.36	0.29	0.11
Elements			1.00	0.45	0.36	0.28	0.15
Sybyl				1.00	0.42	0.33	0.29
SPLIF					1.00	0.40	0.32
Docking						1.00	0.21
2D							1.00

Figure S2. Average correlation coefficient between the different methods tested in table 1. Correlations are colored based on a color gradient, white represents no correlation and dark blue represents a correlation of 1.

Table S1. Overview of the enrichment (AUC) for the different IFPs on the five different receptors

	Interaction Fingerprints					Other	
Receptor (PDB ID)	Deng	Credo	Elements	SYBYL	SPLIF	Docking	2D
Adenosine A_{2A} (4EIY)	0.76 (0.72-0.81)	0.82 (0.78-0.86)	0.81 (0.77-0.86)	0.87 (0.83-0.91)	0.83 (0.78-0.88)	0.81 (0.77-0.85)	0.88 (0.85-0.92)
Histamine H_1 (3RZE)	0.57 (0.50-0.63)	0.64 (0.56-0.72)	0.65 (0.57-0.72)	0.76 (0.71 -0.82)	0.79 (0.74-0.85)	0.87 (0.82-0.92)	0.78 (0.70-0.81)
Muscarinic M_2 (3UON)	0.77 (0.71-0.82)	0.77 (0.71-0.83)	0.81 (0.75-0.87)	0.81 (0.76-0.86)	0.84 (0.79-0.89)	0.86 (0.82-0.91)	0.90 (0.86-0.94)
β_2-adrenergic (2RH1)	0.68 (0.62-0.73)	0.70 (0.65-0.75)	0.71 (0.65-0.76)	0.83 (0.79-0.88)	0.81 (0.77-0.86)	0.86 (0.83-0.90)	0.94 (0.91-0.97)
Chemokine CCR5 (4MBS)	0.72 (0.67-0.77)	0.83 (0.79-0.87)	0.87 (0.83-0.91)	0.94 (0.91-0.97)	0.81 (0.75-0.88)	0.85 (0.81-0.90)	0.95 (0.93-0.98)
Average	0.70	0.75	0.77	0.84	0.82	0.85	0.89

Table S2. Enrichments using different SPLIF fingerprints

Fingerprint	A2A	H1	M2	β2	CCR5	Average
ECFC2	0.553	0.510	0.761	0.644	0.806	0.655
ECFC4	0.566	0.533	0.749	0.724	0.816	0.678
ECFC6	0.568	0.544	0.759	0.719	0.836	0.685
FCFC2	0.495	0.507	0.748	0.648	0.818	0.643
FCFC4	0.498	0.441	0.731	0.725	0.821	0.643
FCFC6	0.511	0.458	0.772	0.752	0.846	0.668
LCFC2	0.571	0.475	0.753	0.732	0.842	0.675
LCFC4	0.568	0.437	0.746	0.738	0.847	0.667
LCFC6	0.565	0.453	0.758	0.731	0.854	0.672
SCFC2	0.471	0.485	0.762	0.654	0.824	0.639
SCFC4	0.464	0.445	0.748	0.713	0.838	0.642
SCFC6	0.467	0.412	0.777	0.721	0.861	0.648

Overview of the enrichment of the different Fingerprints (atom abstraction and radius) tested in this study. The number represents the radius that is used in the generation of the fingerprint. The first letter represents the atom type abstraction: Atom type (E), Functional class (F), ALogPcode (L), and Sybyl (S).

Table S3. Enrichments using Tanimoto SPLIF similarity

Fingerprint	A_{2A}	H_1	M_2	$β_2$	CCR5	Average
ECFC2	0.535	0.607	0.777	0.657	0.830	0.681
ECFC4	0.555	0.605	0.768	0.720	0.835	0.697
ECFC6	0.558	0.608	0.776	0.721	0.856	0.704
FCFC2	0.468	0.639	0.782	0.674	0.838	0.680
FCFC4	0.479	0.537	0.761	0.736	0.845	0.672
FCFC6	0.501	0.527	0.786	0.762	0.865	0.688
LCFC2	0.561	0.527	0.767	0.732	0.866	0.691
LCFC4	0.565	0.463	0.764	0.740	0.870	0.680
LCFC6	0.561	0.474	0.773	0.734	0.875	0.683
SCFC2	0.452	0.615	0.797	0.693	0.849	0.681
SCFC4	0.441	0.561	0.779	0.746	0.859	0.677
SCFC6	0.443	0.477	0.793	0.747	0.877	0.667

Overview of the enrichment of the different Fingerprints (atom abstraction and radius) tested in this study. The number represents the radius that is used in the generation of the fingerprint. The first letter represents the atom type abstraction: Atom type (E), Functional class (F), ALogPcode (L), and Sybyl (S).

Table S4. Enrichments using Tversky SPLIF similarity

Fingerprint	A2A	H1	M2	β2	CCR5	Average
ECFC2	0.570	0.640	0.777	0.665	0.839	0.698
ECFC4	0.571	0.593	0.773	0.717	0.848	0.701
ECFC6	0.576	0.584	0.780	0.727	0.871	0.707
FCFC2	0.501	0.667	0.786	0.674	0.843	0.694
FCFC4	0.510	0.565	0.764	0.726	0.855	0.684
FCFC6	0.515	0.497	0.788	0.758	0.874	0.687
LCFC2	0.558	0.548	0.775	0.733	0.877	0.698
LCFC4	0.562	0.469	0.771	0.741	0.884	0.685
LCFC6	0.561	0.476	0.778	0.737	0.883	0.687
SCFC2	0.477	0.707	0.802	0.690	0.856	0.706
SCFC4	0.478	0.640	0.783	0.735	0.870	0.701
SCFC6	0.478	0.472	0.777	0.743	0.888	0.671

Overview of the enrichment of the different Fingerprints (atom abstraction and radius) tested in this study. The number represents the radius that is used in the generation of the fingerprint. The first letter represents the atom type abstraction: Atom type (E), Functional class (F), ALogPcode (L), and Sybyl (S).

Table S5. Enrichments using Fingerprints instead of matching atoms.

Fingerprint	A2A	H1	M2	β2	CCR5	Average
ECFC2	0.618	0.475	0.775	0.727	0.806	0.680
ECFC4	0.613	0.425	0.771	0.760	0.796	0.673
ECFC6	0.611	0.498	0.777	0.749	0.800	0.687
FCFC2	0.576	0.450	0.782	0.728	0.822	0.671
FCFC4	0.530	0.411	0.768	0.761	0.821	0.658
FCFC6	0.521	0.414	0.785	0.768	0.831	0.664
LCFC2	0.591	0.449	0.774	0.767	0.819	0.680
LCFC4	0.582	0.399	0.778	0.757	0.807	0.664
LCFC6	0.578	0.398	0.775	0.749	0.791	0.658
SCFC2	0.529	0.449	0.790	0.737	0.829	0.667
SCFC4	0.501	0.397	0.774	0.766	0.838	0.655
SCFC6	0.499	0.378	0.782	0.754	0.844	0.651

Overview of the enrichment of the different Fingerprints (atom abstraction and radius) tested in this study. The number represents the radius that is used in the generation of the fingerprint. The first letter represents the atom type abstraction: Atom type (E), Functional class (F), ALogPcode (L), and Sybyl (S).

Table S6. Similarities were calculated using Tanimoto similarity. Fingerprints instead of matching atoms were used.

Fingerprint	A2A	H1	M2	β2	CCR5	Average
ECFC2	0.613	0.514	0.787	0.731	0.828	0.695
ECFC4	0.609	0.457	0.776	0.763	0.825	0.686
ECFC6	0.605	0.498	0.782	0.754	0.830	0.694
FCFC2	0.552	0.553	0.795	0.737	0.842	0.696
FCFC4	0.519	0.461	0.777	0.757	0.846	0.672
FCFC6	0.513	0.439	0.786	0.771	0.858	0.673
LCFC2	0.592	0.472	0.780	0.771	0.845	0.692
LCFC4	0.585	0.414	0.781	0.760	0.848	0.677
LCFC6	0.583	0.419	0.780	0.752	0.841	0.675
SCFC2	0.507	0.571	0.801	0.758	0.848	0.697
SCFC4	0.477	0.445	0.784	0.774	0.854	0.667
SCFC6	0.475	0.410	0.783	0.761	0.868	0.659

Overview of the enrichment of the different Fingerprints (atom abstraction and radius) tested in this study. The number represents the radius that is used in the generation of the fingerprint. The first letter represents the atom type abstraction: Atom type (E), Functional class (F), ALogPcode (L), and Sybyl (S).

Table S7. Similarities were calculated using Tversky similarity. Fingerprints instead of matching atoms were used.

Fingerprint	A2A	H1	M2	β2	CCR5	Average
ECFC2	0.633	0.528	0.790	0.737	0.842	0.706
ECFC4	0.629	0.456	0.782	0.763	0.847	0.695
ECFC6	0.623	0.494	0.788	0.757	0.850	0.702
FCFC2	0.580	0.588	0.796	0.744	0.853	0.712
FCFC4	0.553	0.495	0.782	0.761	0.861	0.690
FCFC6	0.544	0.447	0.790	0.773	0.869	0.685
LCFC2	0.569	0.483	0.788	0.772	0.859	0.694
LCFC4	0.566	0.412	0.787	0.760	0.865	0.678
LCFC6	0.567	0.428	0.786	0.753	0.858	0.678
SCFC2	0.532	0.671	0.803	0.761	0.859	0.725
SCFC4	0.513	0.485	0.786	0.774	0.870	0.686
SCFC6	0.428	0.407	0.777	0.764	0.878	0.651

Overview of the enrichment of the different Fingerprints (atom abstraction and radius) tested in this study. The number represents the radius that is used in the generation of the fingerprint. The first letter represents the atom type abstraction: Atom type (E), Functional class (F), ALogPcode (L), and Sybyl (S).

Table S8. Overview of the enrichment of the different crystal structures of the β_2-adrenergic receptor, for both the Interaction Fingerprint and docking.

Receptor/PDB id	BEDROC IFP	BEDROC Docking
β2 adrenergic (2RH1)	0.72 (0.64-0.82)	0.29 (0.19-0.39)
β2 adrenergic (3NY9)	0.79 (0.72-0.89)	0.17 (0.08)
β2 adrenergic (3NYA)	0.70 (0.60-0.82)	0.16 (0.05-0.25)
β2 adrenergic (3NY8)	0.51 (0.39-0.63)	0.41 (0.29-0.52)
β2 adrenergic (3D4S)	0.73 (0.64-0.84)	0.40 (0.28-0.53)
β2 adrenergic (4GBR)	0.66 (0.56-0.78)	0.29 (0.18-0.40)
Average	0.69	0.29

Table S9. Overview of the enrichment of the different crystal structures of the adenosine A_{2A} receptor, for both the Interaction Fingerprint and docking.

Receptor/PDB id	BEDROC IFP	BEDROC Docking
Adenosine A2A (4EIY)	0.56 (0.45-0.69)	0.21 (0.11-0.31)
Adenosine A2A (3EML)	0.62 (0.52-0.76)	0.07 (0.01-0.12)
Adenosine A2A (3UZA)	0.31 (0.19-0.43)	0.16 (0.05-0.25)
Adenosine A2A (3UZC)	0.32 (0.20-0.44)	0.16 (0.06-0.24)
Adenosine A2A (3PWH)	0.49 (0.37-0.62)	0.06 (0.01-0.10)
Adenosine A2A (3RFM)	0.08 (0.00-0.14)	0.04 (0.00-0.07)
Adenosine A2A (3REY)	0.16 (0.06-0.27)	0.18 (0.08-0.28)
Average	0.36	0.13