Supplementary Material

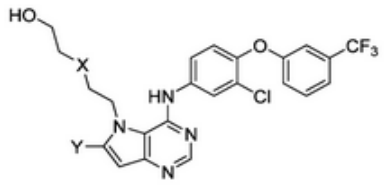
Table S1 – Prediction of absorption (A), distribution (D), metabolism (M) and excretion (E) for the new proposed compounds and some commercial available drugs.

Property	Model Name	Predicted Value					
		Lapatinib	Erlotinib	15A	15B	24A	24B
A	Water solubility (log mol/L)	-4.324	-4.403	-4.75	-4.594	-4.006	-3.746
A	Caco2 permeability (log Papp in 10^{-6} cm/s)	-0.402	1.238	0.975	0.862	0.699	0.761
A	Intestinal absorption (human) (% Absorbed)	100	95.549	93.918	93.552	81.608	80.580
A	Skin Permeability (log Kp)	-2.735	-2.738	-3.299	-2.747	-2.904	-2.884
A	P-glycoprotein substrate	Yes	No	Yes	Yes	Yes	Yes
A	P-glycoprotein I inhibitor	Yes	Yes	Yes	Yes	Yes	Yes
A	P-glycoprotein II inhibitor	Yes	Yes	No	Yes	No	No
D	VDss (human) (log L/kg)	-0.221	-0.053	0.251	0.381	0.010	0.682
D	Fraction unbound (human) (FU)	0.153	0.04	0.133	0.148	0.124	0.226
D	BBB permeability (log BB)	-0.785	-0.67	-0.682	-0.796	-1.126	-1.217
D	CNS permeability (log PS)	-3.124	-3.384	-3.062	-2.198	-3.286	-3.624
M	CYP2D6 substrate	No	No	No	No	No	No
M	CYP3A4 substrate	Yes	Yes	Yes	Yes	Yes	Yes
M	CYP1A2 inhibitor	No	Yes	No	Yes	No	No
M	CYP2C19 inhibitor	Yes	Yes	Yes	Yes	No	No
M	CYP2C9 inhibitor	Yes	Yes	Yes	Yes	No	No
M	CYP2D6 inhibitor	No	No	No	No	No	No
M	CYP3A4 inhibitor	Yes	Yes	Yes	Yes	No	Yes
E	Total Clearance (log ml/min/kg)	0.542	0.591	0.052	0.164	-0.023	0.463
E	Renal OCT2 substrate	Yes	No	No	No	No	No

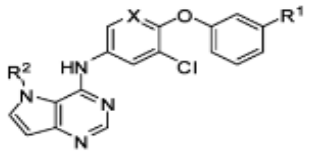
Table S2 – Prediction of toxicity for the new proposed compounds and some commercial available drugs.

Model Name	Predicted Value					
	Lapatinib	**Erlotinib**	**15A**	**15B**	**24A**	**24B**
AMES toxicity	Yes	No	No	No	No	No
Max. tolerated dose (human) (log mg/kg/day)	0.436	0.002	-0.843	0.308	-0.300	-0.331
hERG I inhibitor	No	No	No	No	No	No
hERG II inhibitor	Yes	Yes	Yes	Yes	Yes	Yes
Oral Rat Acute Toxicity (LD50) (mol/kg)	3.171	2.368	3.272	2.959	2.423	2.694
Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	0.064	0.880	0.021	0.836	1.659	1.286
Hepatotoxicity	Yes	Yes	Yes	Yes	Yes	Yes
Skin Sensitisation	No	No	No	No	No	No
T.Pyriformis toxicity (log ug/L)	0.285	0.334	0.383	0.319	0.291	0.298
Minnow toxicity (log mM)	-2.281	-0.437	0.640	0.134	0.969	2.339

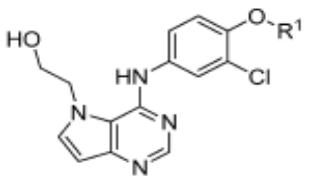
Table S3 - Structure and biological data of the compounds in the training set.

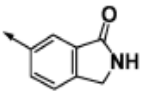
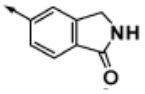
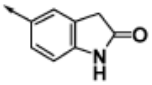
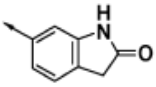
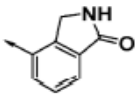
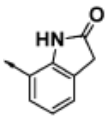
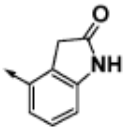
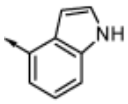
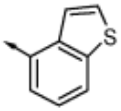
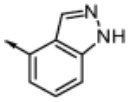
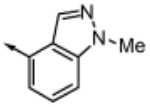
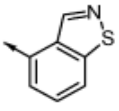


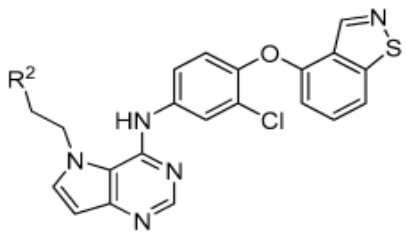
Compound	X	Y	pIC_{50} - HER2	pIC_{50} - EGFR
1	NH	H	8.114	7.657
2	S	H	8.027	7.356
3	SO_2	H	7.921	7.397
4	O	CN	7.721	6.638

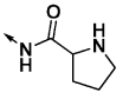


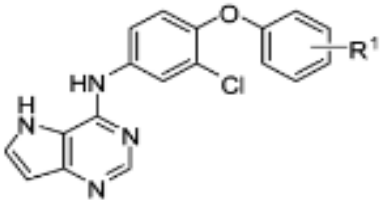
Compound	X	R^1	R^2	pIC_{50} - HER2	pIC_{50} - EGFR
5	CH	Cl	CH_3	8.481	8.036
6	CH	CF_3		7.959	7.568
7	CH	Cl	2-hydroxy ethyl	8.387	8.022
8	CH	CF_3		7.921	7.468
9	CH	OCF_3		7.538	6.958
10	CH	OCF_3		8.076	7.309
11	N	CF_3		7.959	6.376

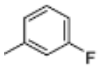


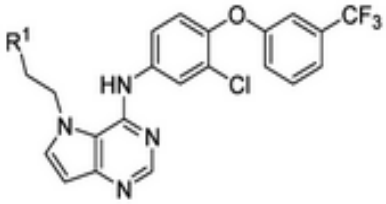
Compound	R^1	pIC_{50} - HER2	pIC_{50} - EGFR
12		8.886	8.108
13		7.745	6.292
14		7.553	6.017
15		6.886	5.638
16		6.824	6.050
17		8.824	8.552
18		8.796	8.522
19		8,602	8,508
20		8.222	8.055
21		8.770	8.721
22		8.678	7.443
23		8.678	8.387

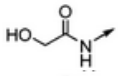
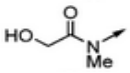
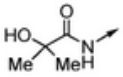


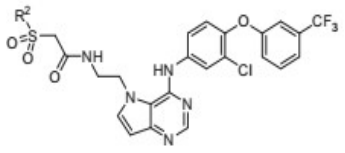
Compound	R^1	pIC_{50} - HER2	pIC_{50} - EGFR
24		9.036	8.522
25	-$NHCOC(CH_3)_2NH_2$	9.009	8.585



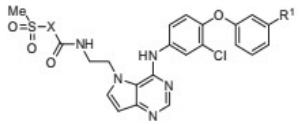
Compound	R^1	pIC_{50} - HER2	pIC_{50} - EGFR
26	H	7.796	6.958
27	2-F	8.032	7.214
28	3-F	7.699	6.823
29	2-Cl	7.959	7.568
30	3-Cl	8.081	7.455
31	2-CN	8.097	7.292
32	3-CN	8.086	6.823
33	4-CN	6.143	6.229
34	3-CF_3	7.523	7.173
35	2-OCF_3	7.260	6.677
36	3-OCF_3	7.387	6.657
37	3-CH_3	8.337	7.698
38		7.886	8.113
39		7.658	7.744



Compound	R^1	pIC_{50} - HER2	pIC_{50} - EGFR
40		8.367	8.000
41		8.244	7.823
42		7.824	7.455

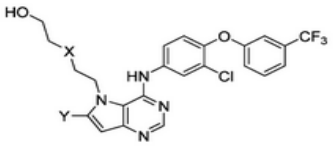


Compound	R^2	pIC_{50} - HER2	pIC_{50} - EGFR
43	Me	8.201	7.823
44	Et	8.071	7.508
45	Pr	7.959	7.275
46		7.770	7.638

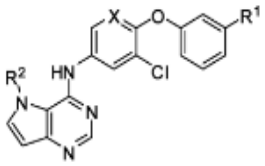


Compound	X	R^1	pIC_{50} - HER2	pIC_{50} - EGFR
47	CH(Me)	CF_3	8.149	7.744
48	$C(Me)_2$	CF_3	7.770	7.327
49	CH_2	Cl	8.538	8.173
50	CH(Me)	Cl	8.387	8.008

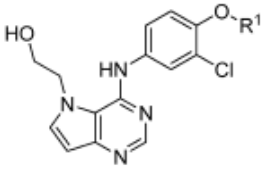
Table S4 - Structure and biological data of the compounds in the test set.

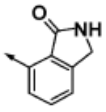


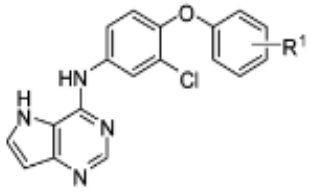
Compound	X	Y	pIC_{50} - HER2	pIC_{50} - EGFR
51	CH_2	H	15	33
52	SO	H	12	31
53	O	CH_3	12	38



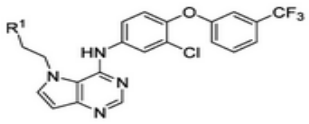
Compound	X	R1	R2	pIC_{50} - HER2	pIC_{50} - EGFR
54	CH	OCF_3		17	50
55	CH		2-(2-hydroxy ethoxy) ethyl	2,1	5,7
56	CH	CF3		5,1	15

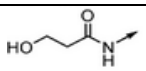
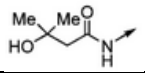


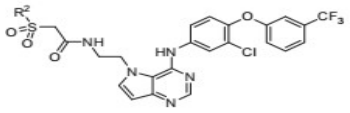
Compound	R^1	pIC_{50} - HER2	pIC_{50} - EGFR
57		2,5	21



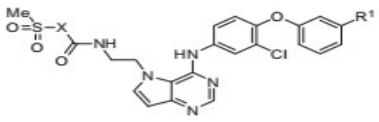
Compound	R^1	pIC_{50} - HER2	pIC_{50} - EGFR
58	2-CF3	120	150
59	3-OCH3	26	290



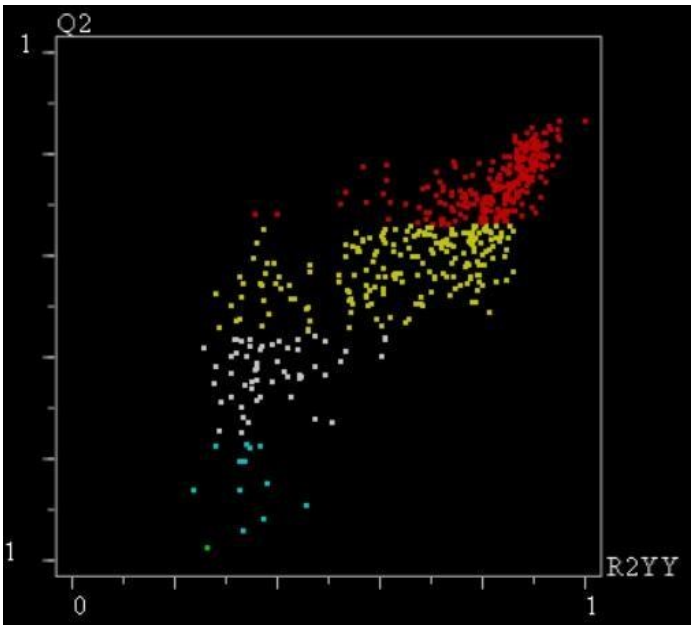
Compound	R^1	pIC_{50} - HER2	pIC_{50} - EGFR
60		8.553	8.142
61		7.770	7.638



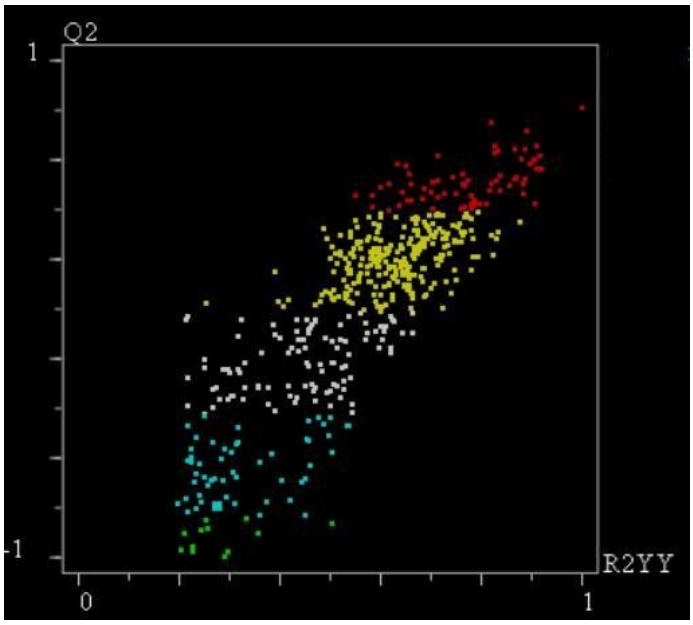
Compound	R^2	pIC_{50} - HER2	pIC_{50} - EGFR
62	Bu	7.854	7.251



Compound	X	R^1	pIC_{50} - HER2	pIC_{50} - EGFR
63	$C(Me)_2$	Cl	7.959	7.959



(A)



(B)

Figure S1. Results obtained from the scrambling tests for (A) HER-2 and (B) EGFR.