

Supporting Information

Computational Studies of Epidermal Growth Factor Receptor: Docking Reliability, Three-Dimensional Quantitative Structure-Activity Relationship Analysis and Virtual Screening Studies

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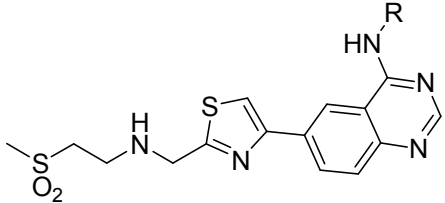
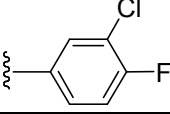
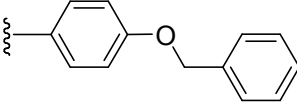
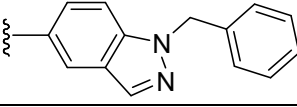
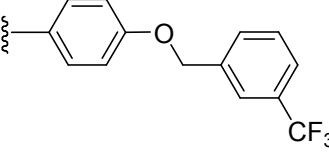
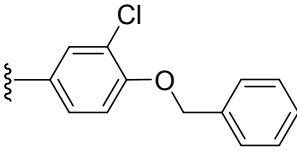
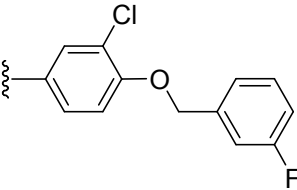
S20: Table 4: Summary of the Virtual Screening results.

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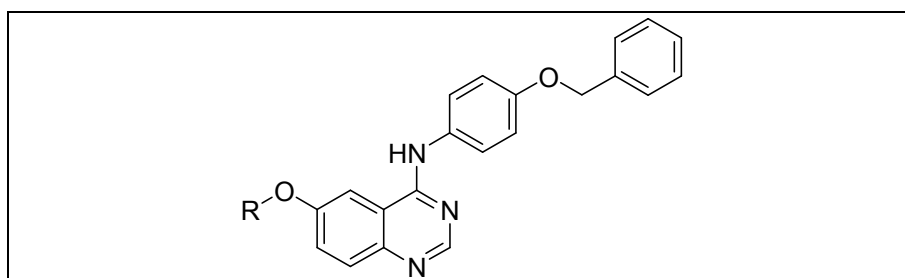
S22-S23: Table 6: ¹H-NMR Data of the Tested Compounds.

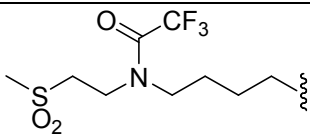
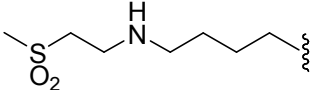
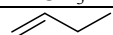
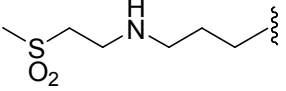
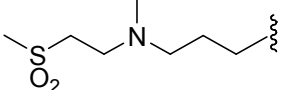
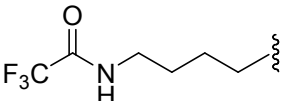
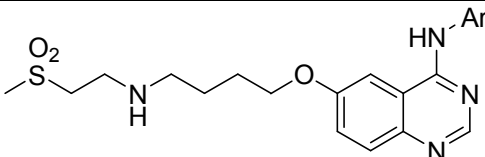
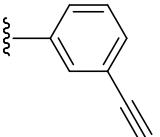
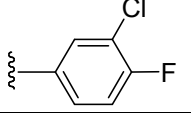
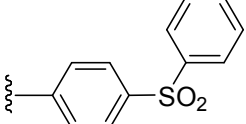
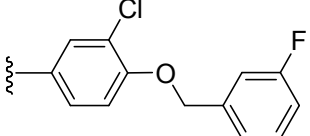
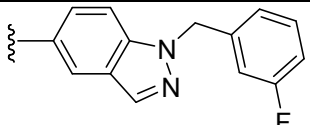
S24: Analytical Data.

Table 1. Actual *versus* predicted data of the receptor- (P_RB) and ligand-based (P_LB) 3D-QSAR models. The compounds reported in bold belong to the first external test set. pIC₅₀ values are the negative logarithms of the molar IC₅₀.

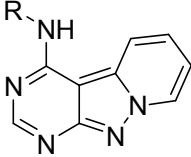
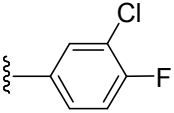
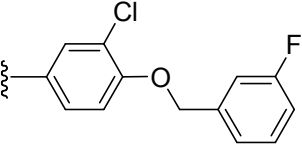
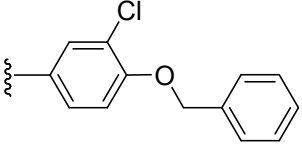
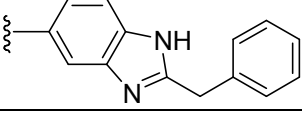
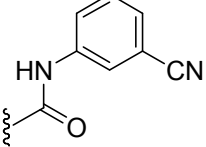
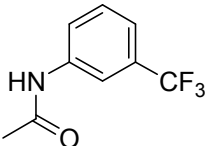
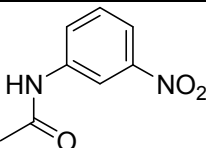
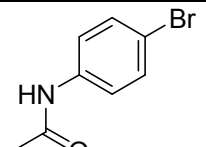
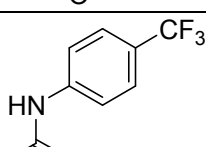
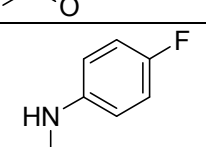
				
Cpd.	R	EGFR inhibition data (pIC ₅₀)		
		Exp ^a	P_RB	P_LB
1		7.46	8.23	8.17
2		7.09	7.31	7.04
3		7.15	7.63	7.20
4		6.27	7.19	6.91
5		8.10	7.19	7.63
6		8.00	7.61	7.63

^a Gaul, M. D.; Guo, Y.; Affleck, K.; Cockerill, G. S.; Gilmer, T. M.; Griffin, R. J.; Guntrip, S.; Keith, B. R.; Knight, W. B.; Mullin, R. J.; Murray, D. M.; Rusnak, D. W.; Smith, K.; Tadepalli, S.; Wood, E. R.; Lackey, K. Discovery and biological evaluation of potent dual ErbB-2/EGFR tyrosine kinase inhibitors: 6-thiazolylquinazolines. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 637-640.

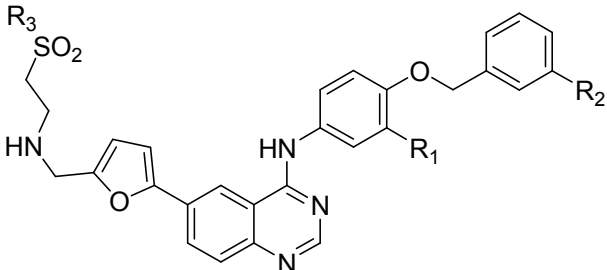
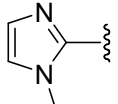
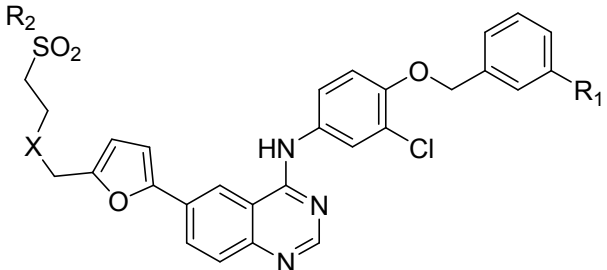
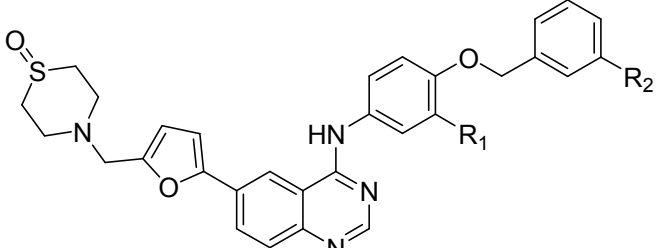


Cpd.	R	EGFR inhibition data (pIC ₅₀)		
		Exp ^b	P RB	P LB
7	H	7.01	7.16	7.53
8		6.63	7.30	6.93
9		7.13	7.26	7.09
10	CH ₃	7.17	6.91	7.93
11		7.10	7.14	7.24
12		6.98	7.43	6.93
13		6.08	7.39	7.17
14		7.13	7.38	7.12
				
Cpd.	Ar	Exp ^b	P RB	P LB
15		7.96	8.24	8.35
16		7.70	7.72	8.13
17		7.03	7.06	6.95
18		7.57	7.40	7.45
19		7.62	7.41	7.88

^b Zhang, Y. M.; Cockerill, S.; Guntrip, S. B.; Rusnak, D.; Smith, K.; Vanderwall, D.; Wood, E.; Lackey, K. Synthesis and SAR of potent EGFR/erbB2 dual inhibitors. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 111-114.

				
		EGFR inhibition data (pIC ₅₀)		
Cpd.	R	Exp ^c	P _{RB}	P _{LB}
20	H	5.00	6.06	7.88
21		6.70	8.12	7.87
22		7.50	7.33	6.88
23		7.30	7.15	7.20
24		5.30	6.23	6.83
25		5.00	5.06	5.54
26		5.00	4.76	5.85
27		5.00	5.74	7.05
28		5.00	5.31	4.74
29		5.00	4.94	5.08
30		5.00	5.55	5.35

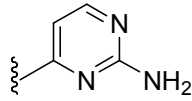
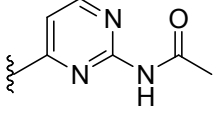
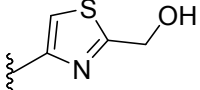
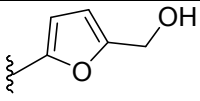
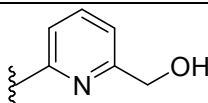
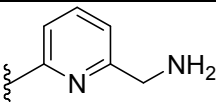
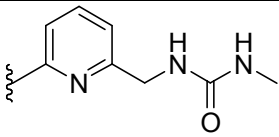
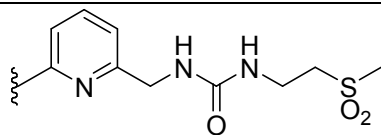
° Alberti, M. J.; Auten, E. P.; Lackey, K. E.; McDonald, O. B.; Wood, E. R.; Preugschat, F.; Cutler, G. J.; Kane-Carson, L.; Liu, W.; Jung, D. K. Discovery and in vitro evaluation of potent kinase inhibitors: Pyrido[1',2':1,5]pyrazolo[3,4-d]pyrimidines. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3778-3781.

				EGFR inhibition data (pIC ₅₀)		
Cpd.	R ₁	R ₂	R ₃	Exp ^d	P _{RB}	P _{LB}
31	H	H	CH ₃	7.57	7.07	7.23
32	H	F	CH ₃	7.62	7.58	7.50
33	H	Br	CH ₃	7.37	7.56	7.24
34	H	CF ₃	CH ₃	7.04	7.23	7.20
35	Cl	H	CH ₃	7.75	7.33	7.49
36	Br	H	CH ₃	7.60	7.70	7.48
37	MeO	F	CH ₃	7.00	7.66	7.18
38	CF ₃	H	CH ₃	6.80	7.30	7.60
39	CF ₃	F	CH ₃	7.10	7.74	7.77
40	Cl	F	<i>n</i> -Pr	7.68	7.14	7.25
41	Cl	F	<i>i</i> -Pr	7.74	7.42	7.20
42	Cl	F	-Ph	7.72	7.24	7.35
43	Cl	F	2-Pyridyl	7.72	7.47	7.43
44	Cl	F		7.77	7.45	7.34
				EGFR inhibition data (pIC ₅₀)		
Cpd.	R ₁	R ₂	X	Exp ^d	P _{RB}	P _{LB}
45	Me	F	O	7.59	7.26	7.29
46	Ph	F	O	7.60	7.81	7.42
47	Ph	H	-NCH ₂ CH ₂ -	7.30	7.39	7.02
48	Me	F	-N-(<i>n</i> -Pr)	7.07	7.62	6.95
49	Me	F	-N(CH ₂ CN)	7.57	7.48	7.62
50	Me	F	-N(Bn)	7.05	7.07	7.56
				EGFR inhibition data (pIC ₅₀)		

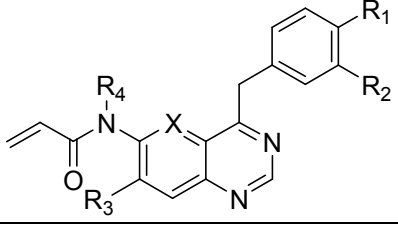
Cpd.	R ₁	R ₂	Exp ^d	P_RB	P_LB
51	CF ₃	F	7.05	7.21	7.19
52	Cl	F	7.55	8.10	7.39
53	F	H	7.80	7.51	7.72
54	Cl	H	7.92	7.45	7.04

^d Petrov, K. G.; Zhang, Y. M.; Carter, M.; Cockerill, G. S.; Dickerson, S.; Gauthier, C. A.; Guo, Y.; Mook, R. A. Jr; Rusnak, D. W.; Walker, A. L.; Wood, E. R.; Lackey, K. E. Optimization and SAR for dual ErbB-1/ErbB-2 tyrosine kinase inhibition in the 6-furanylquinazoline series. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4686-4691

Cpd.	Structure	EGFR inhibition data (pIC ₅₀)		
		Exp ^e	P_RB	P_LB
55		6.49	7.93	7.77
Cpd.	R	Exp ^e	P_RB	P_LB
56	H	7.07	7.91	7.15
57	Ph	7.10	7.84	7.75
58	2-Aminophenyl	7.20	7.34	7.23
59	3-Aminophenyl	7.38	7.00	7.47
60	4-Aminophenyl	7.52	7.73	7.24
61		7.92	7.13	7.58
62		6.96	7.62	6.95
63		7.10	7.26	7.61
64		7.22	7.22	7.31
65		7.30	7.23	6.94
66		7.51	7.20	7.24
67	3-Pyridyl	7.13	7.16	7.61
68	2-Pyridyl	7.77	7.25	7.61
69	2-Pyrimidyl	7.11	6.99	7.39

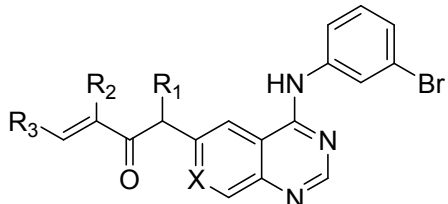
70	3-Pyrazolyl	7.38	7.30	7.35
71		7.49	7.23	7.69
72		7.04	7.04	7.56
73		7.12	7.63	7.99
74		7.48	7.29	8.06
75		7.40	7.64	7.49
76		7.68	8.00	7.25
77		7.64	7.44	7.46
78		7.82	7.39	7.37

^c Waterson, A. G.; Stevens, K. L.; Reno, M. J.; Zhang, Y. M.; Boros, E. E.; Bouvier, F.; Rastagar, A.; Uehling, D. E.; Dickerson, S. H.; Reep, B.; McDonald, O. B.; Wood, E. R.; Rusnak, D. W.; Alligood, K. J.; Rudolph, S. K. Alkynyl pyrimidines as dual EGFR/ErbB2 kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2419-2422.

						EGFR inhibition data (pIC ₅₀)		
Cpd.	X	R ₁	R ₂	R ₃	R ₄	Exp ^f	P RB	P LB
79	CH	H	Br	H	H	9.15	9.06	9.07
80	CH	CH ₂ NMe ₂	Br	H	H	7.35	8.80	7.88
81	CH	OCH ₂ CH ₂ NMe ₂	Br	H	H	7.57	8.01	7.93
82	CH	H	Br	O(CH ₂) ₃ 4-Mepip	H	8.77	8.63	8.68
83	CH	H	Br	O(CH ₂) ₃ morph	H	8.44	8.76	8.95
84	CH	H	Br	O(CH ₂) ₄ NMe ₂	H	8.41	8.87	8.70
85	CH	H	Br	O(CH ₂) ₃ imidazolyl	H	8.52	8.47	8.94
86	CH	H	Br	S(CH ₂) ₃ Net2	H	9.11	8.58	8.82
87	CH	H	CH ₃	H	H	9.38	9.21	9.08
88	CH	H	CH ₃	O(CH ₂) ₃ 4-Mepip	H	8.70	8.48	8.58
89	CH	H	CH ₃	O(CH ₂) ₃ morph	H	8.82	8.50	8.83
90	CH	F	Br	H	H	9.16	8.83	8.87
91	CH	F	Br	O(CH ₂) ₃ morph	H	8.74	8.54	8.43

92	CH	F	Cl	H	H	9.12	9.00	8.78
93	CH	F	Cl	O(CH ₂) ₃ morph	H	8.82	8.53	8.26
94	CH	F	Cl	[O(CH ₂) ₂] ₂ (CH ₂) ₂ OH	H	8.77	7.66	7.93
95	N	F	Cl	H	H	9.12	8.96	8.83
96	N	F	Cl	CH=CH(CH ₂) ₂ morph	H	9.80	7.74	8.47
97	N	F	Cl	(CH ₂) ₄ morph	H	8.57	7.97	8.45
98	N	F	Cl	OMe	H	9.02	8.40	8.19
99	N	F	Cl	O(CH ₂) ₂ OMe	H	9.01	8.11	8.70
100	N	F	Cl	O(CH ₂) ₃ morph	H	8.82	8.38	8.93
101	N	F	Cl	O(CH ₂) ₃ morph	Me	7.70	8.57	8.16
102	N	F	Cl	O(CH ₂) ₃ 4-Mepip	H	8.18	7.90	8.54

^f Smail, J. B.; Rewcastle, G. W.; Loo, J. A.; Greis, K. D.; Chan, O. H.; Reyner, E. L.; Lipka, E.; Showalter, H. D.; Vincent, P. W.; Elliott, W. L.; Denny, W. A. Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(phenylamino)quinazoline- and 4-(phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions. *J. Med. Chem.* **2000**, *43*, 1380-1397.

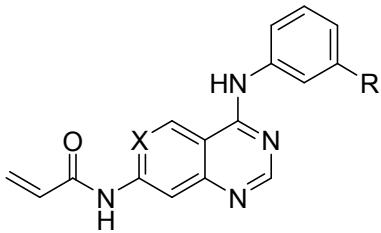
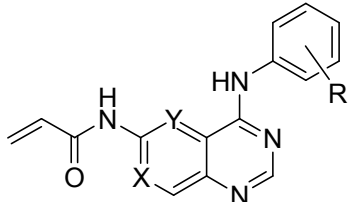
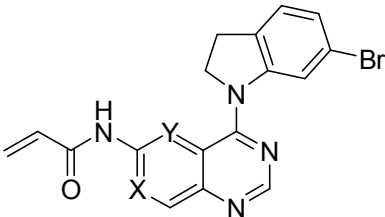
					EGFR inhibition data (pIC ₅₀)		
Cpd.	X	R ₁	R ₂	R ₃	Exp ^g	P_RB	P_LB
103	N	H	H	H	9.04	9.16	9.20
104	N	Me	H	H	9.77	8.87	9.07
105	N	H	Me	H	8.80	8.88	8.87
106	C	H	Me	H	8.92	9.08	8.81
107	N	H	H	Me	9.30	9.03	9.05
108	C	H	H	Me	9.26	9.01	9.20
109	N	H	H	<i>cis</i> -Cl	9.16	9.18	9.01
110	C	H	H	CF ₃	8.76	8.38	8.70
111	N	H	H	CH=CH ₂	8.96	8.36	8.86
112	C	H	H	=CH ₂	8.80	9.21	8.71
113	N	H	H	Ph	8.04	8.22	8.62
114	C	H	H	COMe	8.92	9.04	9.22
115	C	H	H	COOH	9.43	8.97	9.26
116	C	H	H	COOEt	8.57	9.21	8.62
117	N	H	H	COOEt	8.82	9.11	9.02
118	N	(CH ₂) ₂ NMe ₂	H	H	8.38	8.85	8.91
119	N	(CH ₂) ₃ -N-morpholinyl	H	H	8.57	8.08	8.89
120	C	(CH ₂) ₃ -N-morpholinyl	H	H	8.48	8.73	8.93
121	C	H	H	COO(CH ₂) ₃ NMe ₂	8.62	8.76	8.67
122	C	H	H	CONH(CH ₂) ₃ NMe ₂	9.36	9.03	8.59
123	N	H	H	CONH(CH ₂) ₃ NMe ₂	8.96	9.36	9.05
124	N	H	H	CONH(CH ₂) ₃ NEt ₂	9.14	9.29	8.97
125	N	H	H	CONH(CH ₂) ₃ -N-morpholinyl	9.09	9.23	8.67
126	N	H	H	CONH(CH ₂) ₃ -N-imidazolyl	9.25	9.27	8.41
127	N	Me	H	CONH(CH ₂) ₃ NMe ₂	8.84	8.76	8.97

Cpd.			Exp^g	P RB	P LB
128			9.22	8.98	8.64
			EGFR inhibition data (pIC₅₀)		
Cpd.	X	R	Exp^g	P RB	P LB
129	N	NHSO ₂ CH=CH ₂	9.12	8.91	8.90
130	C	NHSO ₂ CH=CH ₂	8.85	8.43	8.76
131	N	NHSO ₂ CH ₂ OH	7.03	8.25	8.81
132	N	SO ₂ CH=CH ₂	9.37	8.64	8.74
133	N	SOCH=CH ₂	8.34	8.94	8.46

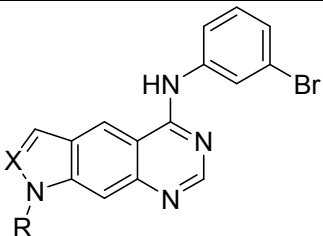
^g Smaill, J. B.; Showalter, H. D.; Zhou, H.; Bridges, A. J.; McNamara, D. J.; Fry, D. W.; Nelson, J. M.; Sherwood, V.; Vincent, P. W.; Roberts, B. J.; Elliott, W. L.; Denny, W. A. Tyrosine kinase inhibitors. 18. 6-Substituted 4-anilinoquinazolines and 4-anilinoxyrido[3,4-d]pyrimidines as soluble, irreversible inhibitors of the epidermal growth factor receptor. *J. Med. Chem.* **2001**, *44*, 429-440.

			EGFR inhibition data (pIC₅₀)		
Cpd.		R	Exp^h	P RB	P LB
134		H	9.35	8.63	8.78
135		Me	9.17	8.54	9.00
136			9.35	8.87	8.50

^h Fry, D. W.; Bridges, A. J.; Denny, W. A.; Doherty, A.; Greis, K. D.; Hicks, J. L.; Hook, K. E.; Keller, P. R.; Leopold, W. R.; Loo, J. A.; McNamara, D. J.; Nelson, J. M.; Sherwood, V.; Smaill, J. B.; Trumpp-Kallmeyer, S.; Dobrusin, E. M. Specific, irreversible inactivation of the epidermal growth factor receptor and erbB2, by a new class of tyrosine kinase inhibitor. *Proc. Natl. Acad. Sci. U S A.* **1998**, *95*, 12022-12027.

						
				EGFR inhibition data (pIC ₅₀)		
Cpd.	X	R		Exp ⁱ	P_RB	P_LB
137	CH	Br		9.60	8.89	8.97
138	N	Cl		9.27	8.83	8.63
						
Cpd.	X	Y	R	Exp ⁱ	P_RB	P_LB
139	CH	H	3'-Cl	8.80	9.18	9.15
140	CH	H	3'-Me	9.38	9.29	9.09
141	CH	H	3'-CF ₃	9.04	8.75	8.43
142	CH	H	4'-OPh	8.24	7.91	8.06
143	CH	H	4'-OBn	8.44	8.18	7.30
144	N	H	3'-Me	9.32	9.07	8.92
145	N	H	3'-Br, 4'-F	9.14	8.77	8.82
146	N	H	3'-Cl, 4'-F	9.11	8.81	8.83
147	H	N	3'-Br	8.96	8.96	9.13
148	H	N	3'-Br, 4'-F	8.92	8.96	8.84
149				9.40	9.18	8.38

ⁱ Smaill, J. B.; Palmer, B. D.; Rewcastle, G. W.; Denny, W. A.; McNamara, D. J.; Dobrusin, E. M.; Bridges, A. J.; Zhou, H.; Showalter, H. D.; Winters, R. T.; Leopold, W. R.; Fry, D. W.; Nelson, J. M.; Slintak, V.; Elliot, W. L.; Roberts, B. J.; Vincent, P. W.; Patmore, S. J. Tyrosine kinase inhibitors. 15. 4-(Phenylamino)quinazoline and 4-(phenylamino)pyrido[d]pyrimidine acrylamides as irreversible inhibitors of the ATP binding site of the epidermal growth factor receptor. *J. Med. Chem.* **1999**, *42*, 1803-1815.

						
				EGFR inhibition data (pIC ₅₀)		
Cpd.	X	R		Exp ^k	P_RB	P_LB
150	N	H		9.36	8.41	8.61
151	N	Me		9.43	8.30	8.62
152	N	CH ₂ CH(OH)CH ₂ OH		7.92	8.10	8.56

153	N	(CH ₂) ₂ NMe ₂	7.40	8.07	8.50
154	N	(CH ₂) ₂ Nmorpholide	8.43	8.18	7.93
155	N	CH ₂ COOH	7.28	7.44	8.44
156	H	H	9.36	8.69	8.75
157	H	Me	9.10	7.93	8.62
158	H	CH ₂ CH(OH)CH ₂ OH	8.80	8.53	8.75
159	H	(CH ₂) ₂ NMe ₂	7.39	7.39	8.58
160	H	(CH ₂) ₃ NMe ₂	7.68	8.31	8.42
161	H	(CH ₂) ₂ Nmorpholide	8.43	8.21	7.87
162	H	(CH ₂) ₃ Nmorpholide	8.06	8.44	8.02
163	H	CH ₂ COOH	8.29	8.09	8.54

The structure shows a pyrazoloquinazoline core. The pyrazole ring is fused to a benzene ring, which is further fused to a pyrimidine ring. A bromophenyl group (-NH-C₆H₄-Br) is attached to the pyrimidine ring at the 2-position. An R substituent is attached to the pyrazole ring at the 3-position.

Cpd.	R	Exp^k	P_{RB}	P_{LB}
164	CH ₂ N(CH ₂ CH ₂ OH) ₂	8.46	8.58	8.32
165	CH ₂ NMe ₂	8.59	8.77	8.60
166	CH ₂ Nmorpholide	8.32	8.35	8.53
167	CH ₂ N(Me)(CH ₂) ₂ NMe ₂	8.12	8.38	8.29
168	CH ₂ N(Me)CH ₂ COOMe	8.47	8.60	8.49
169	CH ₂ N(Me)CH ₂ COOH	9.14	9.21	8.54

^k Palmer, B. D.; Trumpp-Kallmeyer, S.; Fry, D. W.; Nelson, J. M.; Showalter, H. D.; Denny, W. A. Tyrosine kinase inhibitors. 11. Soluble analogues of pyrrolo- and pyrazoloquinazolines as epidermal growth factor receptor inhibitors: synthesis, biological evaluation, and modeling of the mode of binding. *J. Med. Chem.* **1997**, *40*, 1519-1529.

The structure shows a pyrazoloquinazoline core. The pyrazole ring is fused to a benzene ring, which is further fused to a pyrimidine ring. A bromophenyl group (-NH-C₆H₄-Br) is attached to the pyrimidine ring at the 2-position. An R substituent is attached to the pyrazole ring at the 3-position.

Cpd.	R	EGFR inhibition data (pIC₅₀)		
		Exp^l	P_{RB}	P_{LB}
170	NH ₂	8.00	7.78	8.81
171	NHMe	9.89	8.84	8.91
172	NMe ₂	10.05	9.07	8.66
173	NHCH ₂ CH ₂ OH	9.62	9.05	9.20
174	N(Me)CH ₂ CH ₂ OH	8.59	7.94	8.09
175	NHCH ₂ CH(OH)CH ₂ OH	9.04	9.13	8.70
176	N(Me)CH ₂ CH(OH)CH ₂ OH	8.49	8.74	8.21
177	NHCH(CH ₂ OH) ₂	7.85	8.53	8.77
178	N(CH ₂ CH ₂ OH) ₂	7.92	8.70	8.51
179	NHCH ₂ (CHOH) ₄ CH ₂ OH	8.32	8.83	8.25
180	N(Me)CH ₂ (CHOH) ₄ CH ₂ OH	8.49	8.73	8.34
181	NH(CH ₂) ₂ NMe ₂	7.35	8.81	9.06
182	NH(CH ₂) ₃ NMe ₂	8.06	8.50	8.37
183	NH(CH ₂) ₄ NMe ₂	8.13	8.29	8.42
184	NH(CH ₂) ₅ NMe ₂	8.08	7.76	8.93
185	N(Me)(CH ₂) ₂ NMe ₂	7.40	8.06	8.92
186	NH(CH ₂) ₂ Nmorpholine	8.49	8.39	9.00
187	NH(CH ₂) ₃ Nmorpholine	8.72	8.25	8.98

188	NH(CH ₂) ₄ Nmorpholine	8.27	8.73	8.22
189	NH(CH ₂) ₃ N(O)morpholine	9.13	8.51	8.88
190	NH(CH ₂) ₃ N(4-Methylpiperazin-1-yl)	8.31	8.60	8.75
191	NH(CH ₂) ₂ N(CH ₂ CH ₂ OH) ₂	8.04	7.89	8.34
192	NH(CH ₂) ₃ N(CH ₂ CH ₂ OH) ₂	8.92	8.20	8.80
193	NHNH ₂	8.15	8.53	8.66
194	NH(CH ₂) ₃ (1-imidazolyl)	9.29	8.44	8.19
195	NH(CH ₂) ₂ (4-imidazolyl)	9.04	8.80	8.54
196	NHCH ₂ COOH	8.82	8.75	8.38
197	NHCH ₂ CH ₂ COOH	9.22	9.11	8.57
198	NH(CH ₂) ₃ COOH	9.55	8.81	8.81
199	N(Me)CH ₂ COOH	7.80	8.10	8.58
200	NHCH ₂ CH ₂ SO ₃ H	8.85	8.43	9.20

Cpd.	R	Exp ¹	P _{RB}	P _{LB}
201	NHMe	8.85	8.66	8.78
202	NH(CH ₂) ₄ NMe ₂	8.27	8.14	8.36
203	NH(CH ₂) ₃ Nmorpholine	8.03	8.36	8.93
204	NH(CH ₂) ₃ N(4-Methylpiperazin-1-yl)	8.25	8.45	8.47
205	NH(CH ₂) ₃ (1-imidazolyl)	8.46	8.69	8.38
206	NH(CH ₂) ₂ (4-imidazolyl)	8.14	8.24	8.65

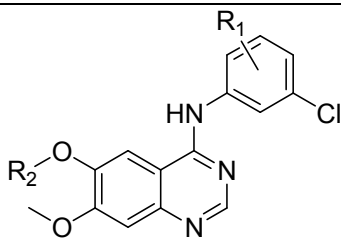
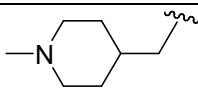
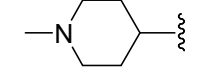
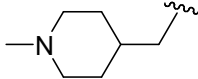
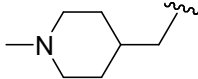
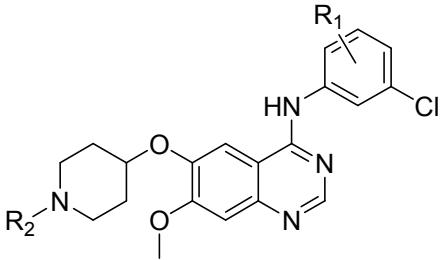
¹ Thompson, A. M.; Murray, D. K.; Elliott, W. L.; Fry, D. W.; Nelson, J. A.; Showalter, H. D.; Roberts, B. J.; Vincent, P. W.; Denny, W. A. Tyrosine kinase inhibitors. 13. Structure-activity relationships for soluble 7-substituted 4-[(3-bromophenyl)amino]pyrido[4,3-d]pyrimidines designed as inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor. *J. Med. Chem.* **1997**, *40*, 3915-3925.

Table 2. Known high affinity EGFR inhibitors used for the enrichment of the Maybridge database.

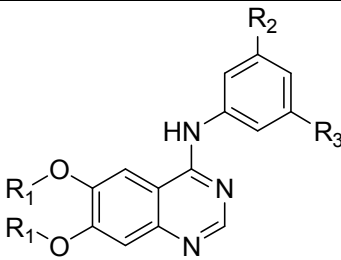
Cpd.	R ₁	R ₂	R ₃	EGFR IC ₅₀ (nM) ^a
1		H	H	3
2		H	MeO	10
3		H	MeO	<2
4		H	MeO	<2

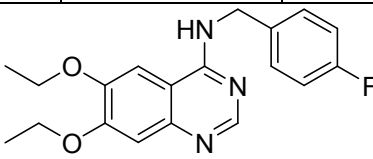
^a Ballard, P.; Bradbury, R. H.; Harris, C. S.; Hennequin, L. F.; Hickinson, M.; Johnson, P. D.; Kettle, J. G.; Klinowska, T.; Leach, A. G.; Morgentin, R.; Pass, M.; Ogilvie, D. J.; Olivier, A.; Warin, N.; Williams, E. J. Inhibitors of epidermal

growth factor receptor tyrosine kinase: Novel C-5 substituted anilinoquinazolines designed to target the ribose pocket. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1633-1637.

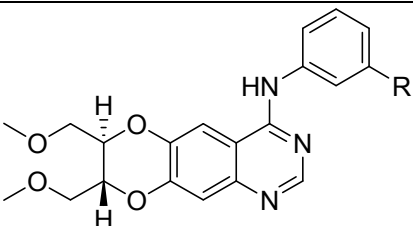
			
Cpd.	R ₁	R ₂	EGFR IC ₅₀ (nM) ^b
5	2-F		
6	2-F		
7	4-F		
8	6-F		
			
Cpd.	R ₁	R ₂	EGFR IC ₅₀ (nM) ^b
9	2-F	CH ₂ CH ₂ OMe	3
10	2-F	CH ₂ CONH ₂	2
11	2-F	SO ₂ Me	2
12	6-F	CH ₂ CONH ₂	9
13	6-F	SO ₂ Me	1

^b Ballard, P.; Bradbury, R. H.; Harris, C. S.; Hennequin, L. F.; Hickinson, M.; Kettle, J. G.; Kendrew, J.; Klinowska, T.; Ogilvie, D. J.; Pearson, S. E.; Williams, E. J.; Wilson, I. Inhibitors of epidermal growth factor receptor tyrosine kinase: optimisation of potency and in vivo pharmacokinetics. *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 4908-4912.

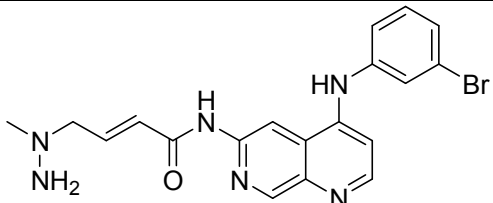
				
Cpd.	R ₁	R ₂	R ₃	EGFR IC ₅₀ (nM) ^c
14	CH ₃ CH ₂	F	H	6.5
15	CH ₃ CH ₂	Cl	H	1.2
16	CH ₃ CH ₂	Br	H	3.2

17	CH ₃ CH ₂	I	H	4.6
18	CH ₃	F	H	6.3
19	CH ₃	Cl	H	0.8
20	CH ₃	Br	H	2.6
21	CH ₃	I	H	6.4
				
Cpd.				EGFR IC₅₀ (nM)^c
22				6.6

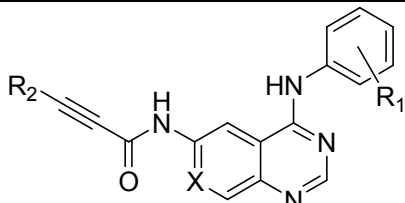
^c VanBrocklin, H. F.; Lim, J. K.; Coffing, S. L.; Hom, D. L.; Negash, K.; Ono, M. Y.; Gilmore, J. L.; Bryant, I.; Riese, D. J. 2nd. Anilindialkoxyquinazolines: screening epidermal growth factor receptor tyrosine kinase inhibitors for potential tumor imaging probes. *J. Med. Chem.* **2005**, *48*, 7445-7456.

				
Cpd.	R			EGFR IC₅₀ (nM)^d
23	Cl			10.08
24	I			1.66

^d Lee, Y. S.; Seo, S. H.; Yang, B. S.; Lee, J. Y. Synthesis and biological evaluation of bis(methoxy methyl)-7,8-dihydro-[1,4]dioxino[2,3-g]quinazolines as EGFR tyrosine kinase inhibitors. *Arch. Pharm. (Weinheim)* **2005**, *338*, 502-505.

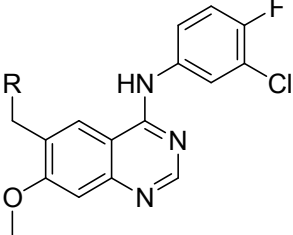
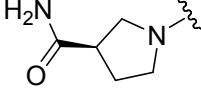
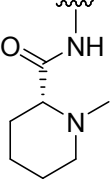
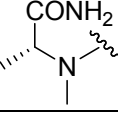
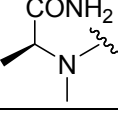
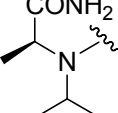
				
Cpd.				EGFR IC₅₀ (nM)^e
25				8.6

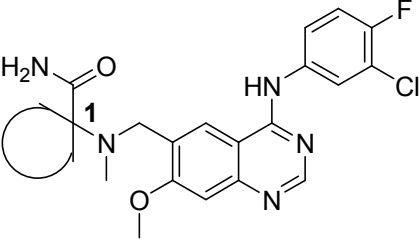

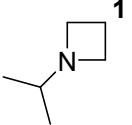
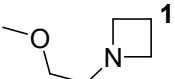
^e Wissner, A.; Hamann, P. R.; Nilakantan, R.; Greenberger, L. M.; Ye, F.; Rapuano, T. A.; Loganzo, F. Syntheses and EGFR kinase inhibitory activity of 6-substituted-4-anilino [1,7] and [1,8] naphthyridine-3-carbonitriles. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1411-1416.

				
Cpd.	X	R₁	R₂	EGFR IC₅₀

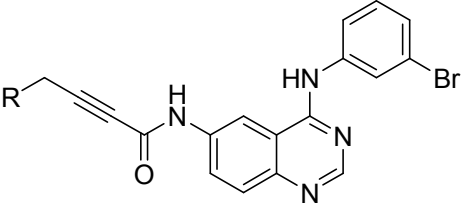
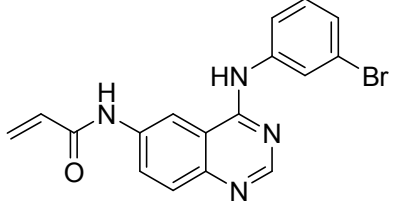
				(nM) ^f
26	CH	3-Br	H	2.7
27	CH	3-Br	Me	2.5
28	CH	3-Cl, 4-F	CH ₂ N(Et) ₂	6.8
29	CH	3-Cl, 4-F	(CH ₂) ₂ N(Et) ₂	4.5
30	N	3-Cl, 4-F	Me	2.5
31	N	3-Cl, 4-F	<i>n</i> -Pr	9.6
32	N	3-Cl, 4-F	<i>n</i> -Bu	4.5
33	N	3-Cl, 4-F	(CH ₂) ₂ Nmorpholide	1.8
34	N	3-Br, 4-F	(CH ₂) ₂ Nmorpholide	4.5
35	N	3-Cl, 4-F	(CH ₂) ₂ Npiperidine	4.3
36	N	3-Cl, 4-F	(CH ₂) ₂ N(4-Me-pz)	1.9
37	N	3-Br, 4-F	(CH ₂) ₂ N(4-Me-pz)	2.7

^f Klutchko, S. R.; Zhou, H.; Winters, R. T.; Tran, T. P.; Bridges, A. J.; Althaus, I. W.; Amato, D. M.; Elliott, W. L.; Ellis, P. A.; Meade, M. A.; Roberts, B. J.; Fry, D. W.; Gonzales, A. J.; Harvey, P. J.; Nelson, J. M.; Sherwood, V.; Han, H. K.; Pace, G.; Smail, J. B.; Denny, W. A.; Showalter, H. D. Tyrosine kinase inhibitors. 19. 6-Alkynamides of 4-anilinoquinazolines and 4-anilinopyrido[3,4-d]pyrimidines as irreversible inhibitors of the erbB family of tyrosine kinase receptors. *J. Med. Chem.* **2006**, *49*, 1475-1485.

		
Cpd.	R	EGFR IC ₅₀ (nM) ^g
38		6
39		8
40		9
41		8
42		<1

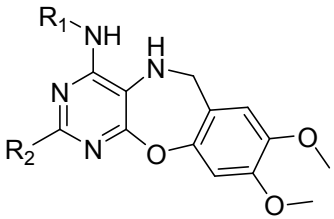
		
Cpd.	Ring	EGFR IC ₅₀ (nM) ^g
43		9
44		9
45		6

^g Hennequin, L. F.; Ballard, P.; Boyle, F. T.; Delouvrié, B.; Ellston, R. P.; Halsall, C. T.; Harris, C. S.; Hudson, K.; Kendrew, J.; Pease, J. E.; Ross, H. S.; Smith, P.; Vincent, J. L. Novel 4-anilinoquinazolines with C-6 carbon-linked side chains: synthesis and structure-activity relationship of a series of potent, orally active, EGF receptor tyrosine kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2672-2676.

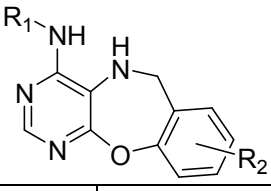
		
Cpd.	R	EGFR IC ₅₀ (nM) ^h
46	H	8
47	NMe ₂	6
		
48		2

^h Tsou, H. R.; Mamuya, N.; Johnson, B. D.; Reich, M. F.; Gruber, B. C.; Ye, F.; Nilakantan, R.; Shen, R.; Discafani, C.; DeBlanc, R.; Davis, R.; Koehn, F. E.; Greenberger, L. M.; Wang, Y. F.; Wissner, A. 6-Substituted-4-(3-bromophenylamino)quinazolines as putative irreversible inhibitors of the epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER-2) tyrosine kinases with enhanced antitumor activity. *J. Med. Chem.* **2001**, *44*, 2719-2734.

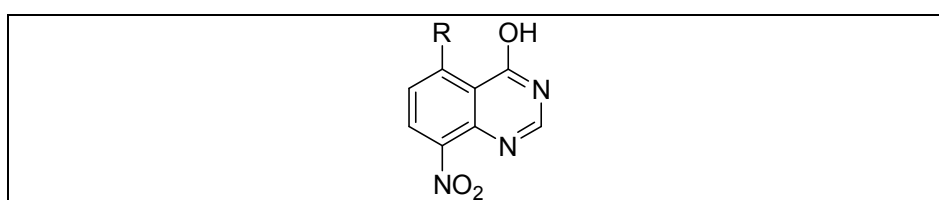
Table 3. Known low affinity EGFR inhibitors used for the enrichment the Maybridge database.

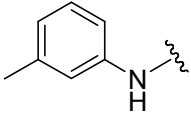
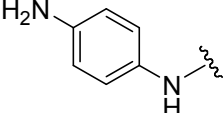
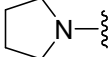
			
Cpd.	R ₁	R ₂	EGFR IC ₅₀ (nM) ^a
1	3-Me-Ph	H	7400
2	4-Br-Ph	H	8700
3	4-F-Ph	H	7100
4	3-Br-Ph	Me	>100000
5	3-Cl-2-F-Ph	Me	>100000

^a Smith, L. 2nd; Wong, W. C.; Kiselyov, A. S.; Burdzovic-Wizemann, S.; Mao, Y.; Xu, Y.; Duncton, M. A.; Kim, K.; Piatnitski, E. L.; Doody, J. F.; Wang, Y.; Rosler, R. L.; Milligan, D.; Columbus, J.; Balagtas, C.; Lee, S. P.; Kononov, A.; Hadari, Y. R. Novel tricyclic azepine derivatives: Biological evaluation of pyrimido[4,5-b]-1,4-benzoxazepines, thiazepines, and diazepines as inhibitors of the epidermal growth factor receptor tyrosine kinase. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5102-5106.

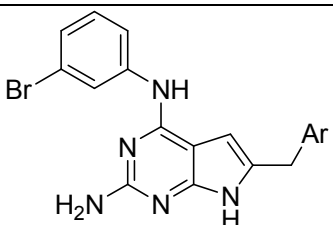
			
Cpd.	R ₁	R ₂	EGFR IC ₅₀ (nM) ^b
6	CH ₂ Ph	8-Br	6000
7	CH ₂ Ph	8-F	8900
8	Ph	8-Br	10000
9	Ph	8-F	7000
10	Ph	8-OCH ₃	7500
11	<i>p</i> -Cl-Ph	8-F	>10000
12	<i>p</i> -Cl-Ph	8-OCH ₃	5800
13	<i>m</i> -C ₆ H ₅ -Ph	8-OCH ₃	>10000
14	<i>m</i> -Br-Ph	9-OCH ₃	>10000
15	<i>m</i> -Br-Ph	8-OCF ₃	>10000
16	<i>m</i> -Cl, <i>p</i> -F-Ph	8-NHSO ₂ CH ₃	>10000
17	<i>m</i> -Br-Ph	8-NHCOCH=CH ₂	5700
18	<i>m</i> -Br-Ph	7,9-(OCH ₃) ₂	6300

^b Smith, L. 2nd; Piatnitski, E. L.; Kiselyov, A. S.; Ouyang, X.; Chen, X.; Burdzovic-Wizemann, S.; Xu, Y.; Pan, W.; Chen X, Wang Y, Rosler RL, Patel SN, Chiang HH, Milligan DL, Columbus J, Wong WC, Doody JF, Hadari YR. Tricyclic azepine derivatives: pyrimido[4,5-b]-1,4-benzoxazepines as a novel class of epidermal growth factor receptor kinase inhibitors. *Bioorg Med Chem Lett.* 2006 Mar 15;16(6):1643-6.

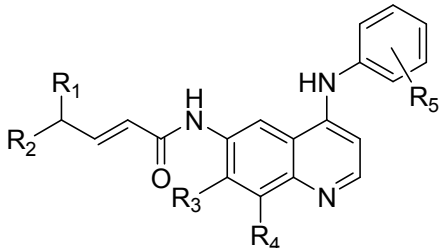
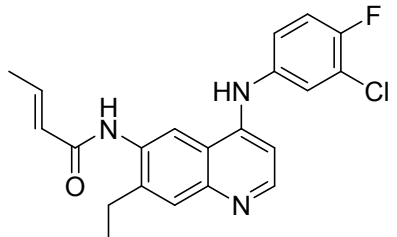


Cpd.	R	Inhib % at 10 μM^c
19		0
20	OMe	0
21		0
22		0

^c Jin, Y.; Li, H. Y.; Lin, L. P.; Tan, J.; Ding, J.; Luo, X.; Long, Y. Q. Synthesis and antitumor evaluation of novel 5-substituted-4-hydroxy-8-nitroquinazolines as EGFR signaling-targeted inhibitors. *Bioorg. Med. Chem.* **2005**, *13*, 5613-5622.

Cpd.	Ar	EGFR IC ₅₀ (nM) ^d
		
23	1-Naphthyl	>50000
24	3,4,5-triOMePh	>50000

^d Gangjee, A.; Yang, J.; Ihnat, M. A.; Kamat, S. Antiangiogenic and antitumor agents. Design, synthesis, and evaluation of novel 2-amino-4-(3-bromoanilino)-6-benzylsubstituted pyrrolo[2,3-d]pyrimidines as inhibitors of receptor tyrosine kinases. *Bioorg. Med. Chem.* **2003**, *11*, 5155-5170.

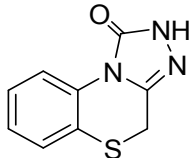
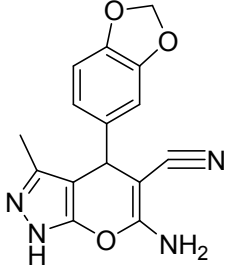
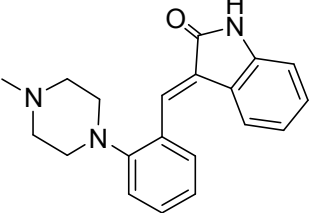
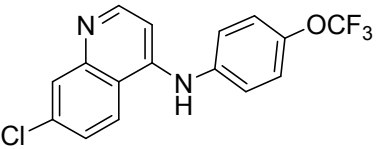
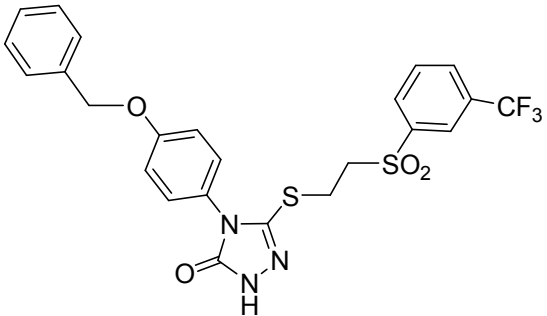
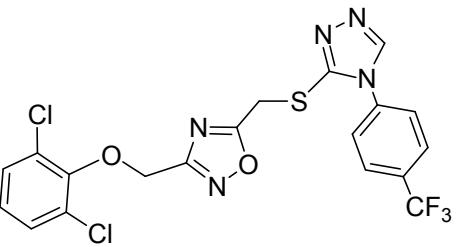
Cpd.	R ₁	R ₂	R ₃	R ₄	R ₅	EGFR IC ₅₀ (nM) ^e
						
25	H	N-morpholinyl	OC ₂ H ₅	H	3-Br	10320
26	H	N-morpholinyl	H	OCH ₃	3-Br	5390
27	H	N-morpholinyl	OCH ₃	H	3-Cl, 4-F	13570
28	CH ₃	N(CH ₃) ₂	OCH ₃	H	3-Cl, 4-F	5220
29	CH ₃	N-morpholinyl	OCH ₃	H	3-Cl, 4-F	10590
						

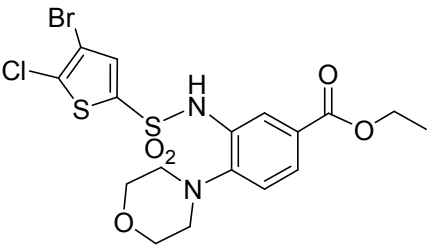
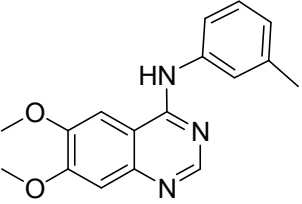
^e Wissner, A.; Overbeek, E.; Reich, M. F.; Floyd, M. B.; Johnson, B. D.; Mamuya, N.; Rosfjord, E. C.; Discafani, C.; Davis, R.; Shi, X.; Rabindran, S. K.; Gruber, B. C.; Ye, F.; Hallett, W. A.; Nilakantan, R.; Shen, R.; Wang, Y. F.; Greenberger, L. M.; Tsou, H. R. Synthesis and structure-activity relationships of 6,7-disubstituted 4-anilinoquinoline-3-carbonitriles. The design of an orally active, irreversible inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR) and the human epidermal growth factor receptor-2 (HER-2). *J. Med. Chem.* **2003**, *46*, 49-56.

Table 5. Statistical results of the receptor-based 3D-QSAR model obtained using Dock software.

Vars	PC	r²	q²	SDEP_{cv}	SDEP_{TS}
1505	2	0.63	0.46	0.78	1.06
1505	3	0.72	0.47	0.77	1.10
1505	4	0.80	0.48	0.76	1.08

Table 6. ¹H-NMR Data of the Tested Compounds.

Compd. Structure	Code	¹ H-NMR (δ, ppm)
	HTS12932	12.07 (s, 1H, NH, exc.), 8.26 (d, 1H, ArH), 7.50 (d, 1H, ArH), 7.38 (t, 1H, ArH), 7.24 (t, 1H, ArH), 4.05 (s, 2H, CH ₂)
	HTS07491	12.10 (s, 1H, NH, exc.), 6.86 (s, 2H, NH ₂ , exc.), 6.83 (s, 1H, ArH), 6.67 (d, 2H, ArH), 5.99 (s, 2H, CH ₂), 4.54 (s, 1H, CH), 1.82 (s, 3H, CH ₃)
	SEW05754	10.58 (s, 1H, NH, exc.), 7.72 (d, 1H, ArH), 7.61 (s, 1H, CH), 7.53-7.41 (m, 2H, ArH), 7.26-7.08 (m, 3H, ArH), 6.89-6.80 (m, 2H, ArH), 7.51-7.44 (m, 8H, CH ₂), 2.22 (s, 3H, CH ₃)
	KM11074	9.22 (s, 1H, NH, exc.), 8.51 (d, 1H, ArH), 8.41 (d, 1H, ArH), 7.92 (s, 1H, ArH), 7.61 (d, 1H, ArH), 7.51-7.39 (m, 4H, ArH), 7.00 (d, 1H, ArH)
	HTS02876	12.02 (s, 1H, NH, exc.), 8.20 (t, 3H, ArH), 7.92 (t, 1H, ArH), 7.45-7.34 (m, 5H, ArH), 7.21 (d, 2H, ArH), 7.08 (d, 2H, ArH), 5.15 (s, 2H, OCH ₂), 3.83 (t, 2H, SO ₂ CH ₂), 3.18 (t, 2H, SCH ₂)
	HTS00213	9.03 (s, 1H, HetH), 8.00 (d, 2H, ArH), 7.78 (d, 2H, ArH), 7.51 (d, 2H, ArH), 7.23 (t, 1H, ArH), 5.12 (s, 2H, OCH ₂), 4.78 (s, 2H, SCH ₂)

	<p>HTS02741</p>	<p>10.01 (bs, 1H, NH, exc.), 7.79 (s, 1H, HetH), 7.60 (d, 2H, ArH), 7.21 (s, 1H, ArH), 4.26 (q, 2H, CH₂), 3.64 (s, 4H, CH₂), 2.91 (s, 4H, CH₂), 1.29 (t, 3H, CH₃)</p>
	<p>GK03474</p>	<p>11.18 (bs, 1H, NH, exc.), 8.82 (s, 1H, ArH), 8.22 (s, 1H, ArH), 7.46-7.31 (m, 4H, ArH), 7.15 (s, 1H, ArH), 4.00 (s, 6H, OCH₃), 2.37 (s, 3H, CH₃)</p>

ANALYTICAL DATA

Code	formula	Calcd. %			Found %		
		C	H	N	C	H	N
HTS12932	C ₉ H ₇ N ₃ OS	52.67	3.44	20.47	52.41	3.24	20.10
HTS07491	C ₁₅ H ₁₂ N ₄ O ₃	60.81	4.08	18.91	60.42	3.75	18.61
SEW05754	C ₂₀ H ₂₁ N ₃ O	75.21	6.63	13.16	75.30	6.70	13.17
KM11074	C ₁₆ H ₁₀ ClF ₃ N ₂ O	56.74	2.98	8.27	56.73	3.01	8.29
HTS02876	C ₂₄ H ₂₀ F ₃ N ₃ O ₄ S ₂	53.82	3.76	7.85	53.80	3.73	7.79
HTS00213	C ₁₉ H ₁₂ Cl ₂ F ₃ N ₅ O ₂ S	45.43	2.41	13.94	45.45	2.48	14.03
HTS02741	C ₁₇ H ₁₈ BrClN ₂ O ₅ S ₂	40.05	3.56	5.49	40.04	3.51	5.45
GK03474	C ₁₇ H ₁₇ N ₃ O ₂	69.14	5.80	14.23	68.86	5.67	14.08