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5-((4-Aminopiperidin-1-yl)methyl)pyrrolotriazine dual inhibitors of EGFR and HER2 protein tyrosine kinases

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Abstract—Pyrrolotriazine dual EGFR/HER2 kinase inhibitors with a 5-((4-aminopiperidin-1-yl)methyl) solubilizing group were found to be superior to analogs with previously reported C-5 solubilizing groups. New synthetic methodology was developed for the parallel synthesis of C-4 analogs with the new solubilizing group. Interesting new leads were evaluated in tumor xenograft models and the C-4 aminofluorobenzylindazole, **1c**, was found to exhibit the best antitumor activity. It is hypothesized that this solubilizing group extends into the ribose-phosphate portion of the ATP binding pocket and enhances the binding affinity of the inhibitor.

The epidermal growth factor receptor (EGFR, ErbB1 or HER1) and the human epidermal growth factor receptor 2 (HER2, ErbB2) are members of the ErbB family of receptor tyrosine kinases that have been clinically validated as targets for cancer therapy.[1] Their frequent co-expression in a variety of tumor types and their capacity to form heterodimers with other members of the ErbB family provide a strong rationale for simultaneously targeting both of these receptors.[2] We have reported studies of pyrrolotriazine reversible dual EGFR and HER2 kinase inhibitors with C-5 solubilizing groups that identified morpholine ether **1a**[3] and homopiperazine **1b**[4] as lead compounds (Fig. 1). Both showed potent kinase inhibition, antiproliferative activity, and good oral efficacy in EGFR and HER2 driven human tumor xenograft models. It was hypothesized that their C-5 solubilizing groups extend into the ribose-phosphate portion of the ATP binding pocket where they can participate in multiple hydrogen bonding interactions. A possible limitation of these compounds was that their kinase inhibition tended to drop off when modifications were made at other sites, notably C-4. Since this could limit efforts to optimize their efficacy, we continued to explore the SAR of C-5 solubilizing groups to find those that imparted more robust kinase inhibition. This report highlights the SAR of pyrrolotriazine dual EGFR/HER2 kinase inhibitors with a C-5 aminopiperidine solubilizing group, for example, **1c**. Their in vitro performance was generally found to be superior to that of analogs with our other leading C-5 solubilizing groups. New chemistry was developed to prepare C-4 analogs of **1c** using parallel synthesis and the results of the evaluation of some of the interesting leads that emerged from this are disclosed.

Compounds **1c**–**1g** were made by heating sulfoxide **2**[4] with an excess of the mono-N-Boc protected diamine of interest and then deprotecting the product (Scheme 1).[5a] Compound **1c** could also be made by heating **2** with an excess of piperidin-4-amine. In this case, regioisomer **1d** was also formed (<10% yield) and it was removed by

Keywords: EGFR; HER2; Pyrrolotriazine; Kinase inhibitor.
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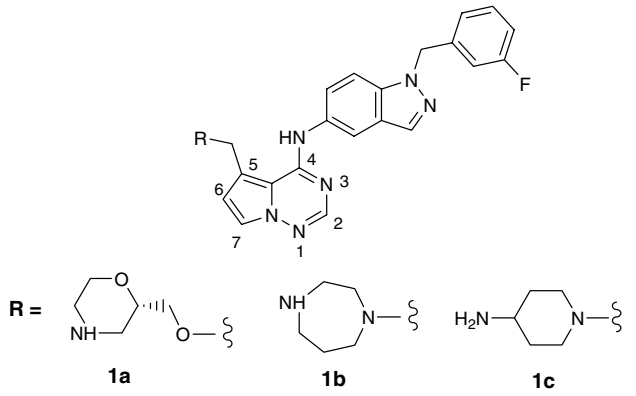
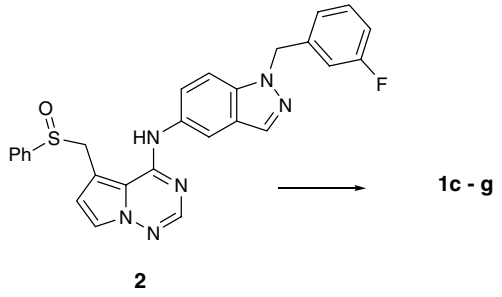


Figure 1. C-5 substituted pyrrolotriazine dual EGFR and HER2 kinase inhibitors.

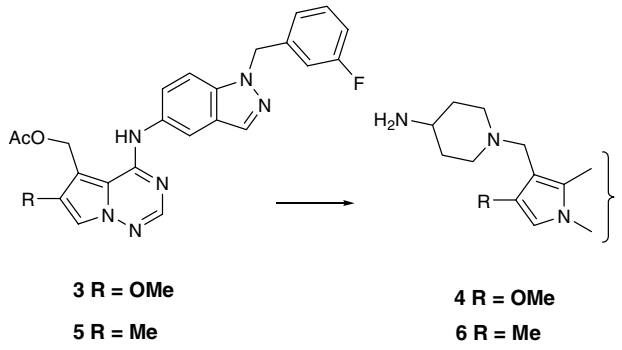


Scheme 1. Reagents and conditions: N-Boc protected diamine (10 equiv), 130 °C, 35 h, sealed tube, followed by 40% TFA/CH_2Cl_2.

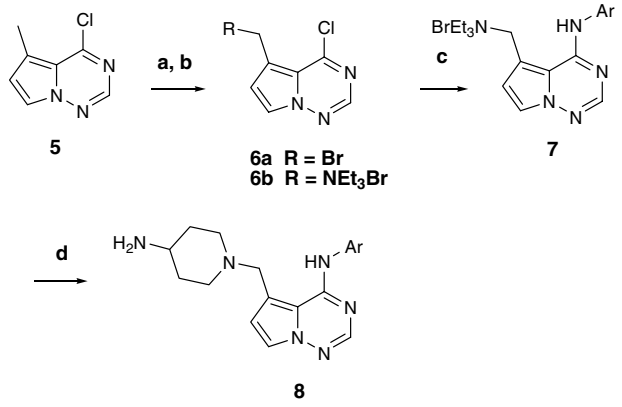
preparative HPLC. *N*-Methyl derivative **1h** was prepared by heating **1c** with ethyl formate and then reducing the resulting formamide with lithium aluminum hydride. Heating **1c** with excess 1,3-dioxolan-2-one gave hydroxyethyl derivative **1i**. Michael addition of **1c** to methyl vinyl sulfone gave **1j**. *N*,*N*-Dimethyl derivative **1k** was prepared by reductive amination of **1c** with aqueous formaldehyde in the presence of acetic acid. N-acylation of **1c** with acetic anhydride in methanol afforded **1l**. Treatment of **1c** with acetoxyacetyl chloride followed by saponification of the resulting acetoxyacetamide gave **1m**. Compound **1n** was prepared by heating **2** with excess 4-methylpiperidin-4-amine.[6]

The 6-methoxy and 6-methyl analogs, **4** and **6**, were prepared by heating acetates, **3** and **5**,[4] with excess *tert*-butylpiperidin-4-ylcarbamate and then removing the protecting group (Scheme 2).

The synthesis outlined in Scheme 1 was not suited for the rapid preparation of C-4 analogs of **1c** since the C-4 substituent is introduced early in the synthesis. Therefore a method for the parallel synthesis of C-4 analogs of **1c** was developed. We previously reported[4] that bromide **6a**, obtained by reaction of **5** with *N*-bromosuccinimide in the presence of a radical initiator, reacted with primary or secondary amines to give mixtures of products. However, triethylamine was found to react selectively with **6a** to give the triethylammonium bromide, **6b**, as a weighable solid (Scheme 3).[5b] It reacted with anilines on brief heating in *N*,*N*-dimethylacetamide



Scheme 2. Reagents and conditions: *tert*-butylpiperidin-4-ylcarbamate (10 equiv), CH_3CN, microwave, 170 °C, 30 min followed by 50% TFA/CH_2Cl_2, 0 °C, about 40% overall.

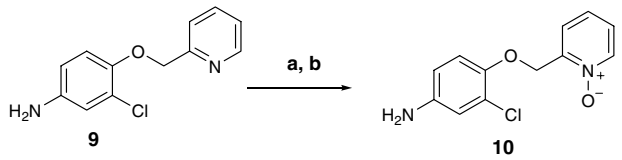


Scheme 3. Reagents and conditions: (a) NBS (1.15 equiv), AIBN (0.1 equiv), CCl_4, 80 °C, 2 h; (b) excess TEA, THF, rt, overnight, 75% overall; (c) H_2NAr (1 equiv), *N*,*N*-dimethylacetamide, 70 °C, 3–5 h then *tert*-butylpiperidin-4-ylcarbamate (1 equiv), DIPEA (1 equiv), 70 °C, overnight, then TFA/CH_2Cl_2, about 50% overall.

to give 4-anilino intermediates, **7**, which, on further heating with *tert*-butylpiperidin-4-ylcarbamate followed by deprotection, gave the C-4 analogs **8a**–**j**.

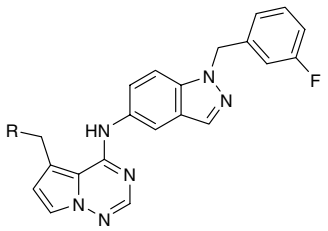
Aniline **10** was used to make the pyridine *N*-oxide **8j**. It was prepared by protection of the amino group of **9** followed by N-oxidation and deprotection (Scheme 4).

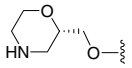
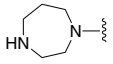
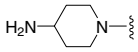
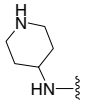
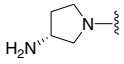
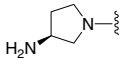
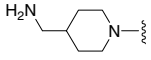
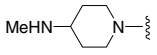
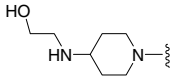
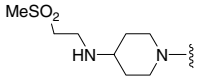
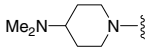
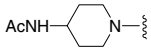
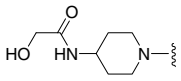
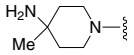
Our studies of pyrrolotriazine dual EGFR and HER2 kinase inhibitors with diamino C-5 solubilizing groups identified 4-aminopiperidine **1c** as a promising lead. It showed comparable kinase inhibition and slightly better antiproliferative potency (Table 1) against the N87 cell line, a human gastric carcinoma that overexpresses both



Scheme 4. Reagents and conditions: (a) Boc_2O (1.1 equiv), THF, 80 °C, 6 h, 92%; (b) MCPBA (1.5 equiv), CH_2Cl_2, 2 h, then TFA, rt, 2 h, 96%.

Table 1. Structure–activity relationship for C-5 analogs



Compound	R	IC_{50} (μM)			
		HER2[a]	EGFR[a]	N87[b]	HT29[c] or A2780[d]
1a		0.055	0.061	0.083	8.7[c]
1b		0.027	0.033	0.11	3.6[c]
1c		0.023	0.035	0.035	4.3[c]
1d		0.076	0.11	1.15	5[c]
1e		0.070	0.06	0.83	3.9[c]
1f		0.052	0.050	0.81	6.5[c]
1g		0.038	0.035	0.14	2.9[c]
1h		0.054	0.063	0.078	7.3[c]
1i		0.031	0.048	0.073	5.4[c]
1j		0.19	0.20	0.70	ND[e]
1k		0.11	0.10	0.45	7.6[c]
1l		0.18	0.38	0.29	>10[c]
1m		0.12	0.11	0.31	9.5[c]
1n		0.043	0.050	0.070	6.1[c]

[a] Recombinant HER2 cytoplasmic sequence is expressed in Sf9 insect cells as an untagged protein and purified by ion-exchange chromatography. HER2 kinase activity is measured under the same conditions as for EGFR. See Ref. 7 for assay conditions. IC_{50} values are reported as means of at least three determinations. Variability around the mean value was <15%.

[b] Cell line N87 is a human gastric carcinoma that overexpresses both EGFR and HER2, see Ref. 7.

[c] Cell lines HT29 (human colon carcinoma) and A2780 (human ovarian carcinoma) do not depend on EGFR or HER2 signaling.

[d] Cell lines HT29 (human colon carcenoma) and A2780 (human ovarian carcinoma) do not depend on EGFR or HER2 signaling.

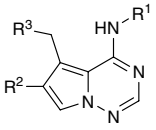
[e] ND, not determined.

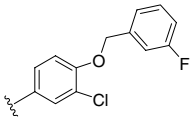
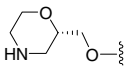
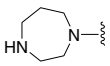
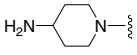
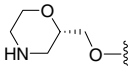
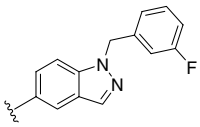
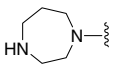
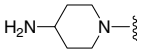
EGFR and HER2[7,8], but not against the HT29 cell line, a human colon carcinoma that does not depend on EGFR or HER2 signaling, and provided a check for off-target antiproliferative effects. The SAR of **1c** was explored to see if improvements were possible. The transposed analog, **1d**, and the pyrrolidines, **1f** and **1g**, showed slightly reduced kinase inhibition and significantly lower cellular potency. Substitution on the piperidine 4-amino group was allowed in some instances, for example, the methyl and hydroxyethyl derivatives, **1h** and **1i**, showed potency similar to that of **1c**. However disubstitution, for example, *N*,*N*-dimethyl analog **1j**, or substituents that reduced the basicity of the piperidine 4-amino group, for example, ethyl sulfone **1k** and *N*-acyl analogs, **1l** and **1m**, reduced potency.

Compounds with the leading C-5 solubilizing groups and the 4-(aminofluorobenzylindazole) side chain, **1a**, **1b**, and **1c**, showed comparable potency in the kinase and cellular assays. However, when modifications were made at other sites in the molecule, it was found that analogs with C-4 diamino solubilizing groups showed better in vitro potency than their morpholine ether counterparts. For example, when the 4-(aminofluorobenzylindazole) side chain was replaced by the fluorobenzyloxyaniline side chain[9] of the dual EGFR/HER2 kinase inhibitor, lapatinib, the aminopiperidine and homopiperazine, **8a** and **11b**, exhibited more potent kinase inhibition than the morpholine ether analog, **11a** (Table 2). One reason for this may be that analogs with the diamino solubilizing group can form an intramolecular hydrogen bond between the tertiary amine in the C-5 side chain and the C-4 aniline NH group. This would prearrange the two side chains in a conformation that is similar to that of the inhibitor when it is in the ATP binding pocket (see modeling discussion). Similar intramolecular hydrogen bonding is possible in the case of the C-5 morpholine ether analogs but it would be weaker and therefore these analogs would not benefit from the same entropic stabilization. Homopiperazine **11b** exhibited weaker antiproliferative activity than aminopiperidine **8a** and this may reflect poorer cell permeability. A striking example of differences between analogs with these solubilizing groups was seen for their 6-methoxy derivatives. Aminopiperidine **12c** was significantly more potent than morpholine ether **12a** and homopiperazine **12b**. This suggests that the aminopiperidine is functioning as more than a solubilizing group; it is also enhancing the binding affinity of the inhibitor in the ATP binding pocket to overcome the effect of less tolerated structural features such as C-6 substitution. Overall, a broader range of potent analogs were possible with the C-5 aminopiperidine solubilizing group and they became the focus of our optimization studies.

This began with a preliminary exploration of the C-4 side chain of **1c**. Analogs were generated by parallel synthesis and some of the more interesting results are summarized in Table 3. The 2-picolyl analog, **8b**, showed comparable kinase potency but reduced antiproliferative effects. The 3-picolyl analog, **8c**, was more HER2 selective while the 4-picolyl analog, **8d**, was less potent. The 5-methyl derivative of **8c**, **8e**, regained EGFR inhibition and showed a profile similar to that of **1c**. The 3-picolyl

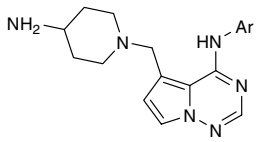
Table 2. Structure–activity relationship for modified C-5 analogs

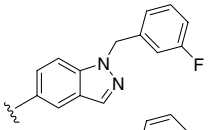
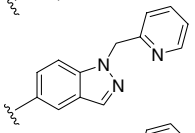
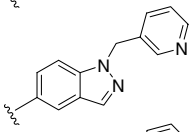
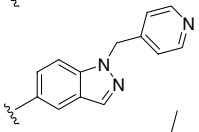
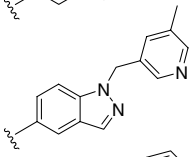
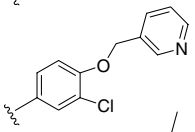
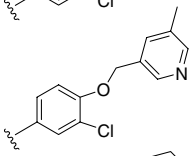
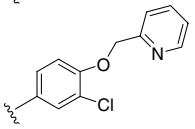


Compound	R^1	R^2	R^3	IC_{50} (μM)		
				HER2[a]	EGFR[a]	N87[b]
11a		H		0.56	0.56	0.61
11b				0.041	0.048	0.60
8a				0.032	0.038	0.083
12a				0.25	0.43	3.4
12b		OMe		0.17	0.19	3.7
12c				0.043	0.040	0.43

[a] IC_{50} values are reported as means of at least three determinations. Variability around the mean value was <15%.
[b] Data for HT29 (human colon carcinoma) or A2780 (human ovarian carcinoma) cell lines that do not depend on EGFR or HER2 signaling were comparable for these compounds with IC_{50}'s in the 3–4 μM range.

Table 3. Structure–activity relationship for C-4 analogs



Compound	Ar	IC_{50} (μM)				Metabolic stability[d]	Mouse 4 h exposure[e]			
		HER2[a]	EGFR[a]	N87	HT29[b] or A2780[c]		$AUC_{0-4\ h}$ (μM h)	4 h plasma concentrations		
								(μM)	Fold over HER2 IC_{50}	Fold over EGFR IC_{50}
1c		0.023	0.035	0.035	4.3[b]	0.05	14	2.7	120	77
8b		0.035	0.047	0.12	>10[c]	0.01	3.6	1.6	46	34
8c		0.034	0.19	0.086	>5[c]	0.01	22	4.5	130	24
8d		0.19	0.53	0.47	>5[c]	nd	nd	nd	nd	nd
8e		0.013	0.019	0.036	>5[c]	0.06	9.9	1.3	100	68
8f		0.036	0.15	0.23	2.7[c]	nd	30	7.5	210	50
8g		0.060	0.085	0.18	3.5[c]	0.00	7.8	1.8	30	21
8h		0.022	0.036	0.058	2.0[c]	0.04	13	3.7	170	100

(*continued on next page*)

Table 3 (*continued*)

Compound	Ar	IC_{50} (μM)				Metabolic stability[d]	Mouse 4 h exposure[e]			
		HER2[a]	EGFR[a]	N87	HT29[b] or A2780[c]	$AUC_{0-4\,h}$ (μM h)	4 h plasma concentrations			
							(μM)	Fold over HER2 IC_{50}	Fold over EGFR IC_{50}
8i		0.026	0.032	0.072	3.5[c]	0.12	6.3	240	200
8j		0.018	0.070	0.11	>5[c]	0.00	3.9	220	56

[a] IC_{50} values are reported as means of at least three determinations. Variability around the mean value was <15%.
[b] Cell lines HT29 (human colon carcinoma) and A2780 (human ovarian carcinoma) do not depend on EGFR or HER2 signaling.
[c] Cell lines HT29 (human colon carcenoma) and A2780 (human ovarian carcinoma) do not depend on EGFR or HER2 signaling.
[d] Rate of metabolism (nmol/min/mg protein) by mouse liver microsomes after a 10-min incubation at 3 μM in the presence of NADPH.
[e] Averaged 4 h exposure study that was obtained for compounds administered orally at 50 mg/kg in Tween 80/PEG400/water (v/v/v = 10/40/50) to three male Balb/C mice.

ether, **8f**, was more HER2 selective like its indazole analog, **8c**. The 5-methyl derivative, **8g**, showed balanced kinase inhibition but lower antiproliferative potency. The 2-picolyl ether, **8h**, and the pyrazine, **8i**, both exhibited profiles similar to that of **1c**. Surprisingly, *N*-oxide **8j** retained much of the potency of its parent, **8h**. It was not expected that its polar C-4 side chain would be tolerated in the hydrophobic selectivity pocket of the ATP binding site. Overall, the C-4 analogs exhibited good metabolic stability and 4 h exposure after oral administration to mice. Several compounds showed 4 h drug plasma levels that were more than 50-fold higher than their HER2 and EGFR IC_{50}'s.

Analogs with promising in vitro potency and 4 h oral exposure were evaluated in vivo in N87 human gastric carcinoma (HER2 and EGFR driven) and GEO human colon carcinoma (EGFR driven) athymic mouse xenograft models and these data, together with those for homopiperazine **1b**, are summarized in Table 4. Except for *N*-oxide **8j**, all of the compounds were active and produced dose-dependent antitumor effects in the N87 model. Of these, **1c** possessed the highest activity and potency. At its optimal dose (180 mg/kg), it yielded 133% TGI and remained active at dose levels as low as 60 mg/kg. This was comparable to homopiperazine **1b** but the latter had to be dosed twice a day to achieve this level of activity. Compounds **8f** and **8g** possessed robust activity in N87 at high dose levels and had similar potency at the minimum efficacious dose, 120 mg/kg. Compound **8i** only showed borderline activity at the highest tested dose. Against the GEO colon carcinoma this series suffered a considerable loss of activity. Compound **1c** demonstrated antitumor activity, 85% TGI at its maximum tolerated dose of 240 mg/kg. The homopiperazine **1b** again had to be dosed twice a day to achieve a similar level of activity. All of the other tested compounds were inactive at doses as high as 180 mg/kg. It is difficult to account for these results since the in vivo tumor models were primarily employed as screens to sort through a large number of leads and negative results were generally not followed up. Compounds like **8e** would have been expected to perform better in these models. Possibly low solubility may have resulted in a less than dose-proportional increase in exposure at higher doses. In the case of **8h**, high protein binding in mouse serum (>99.9%) may have been detrimental to in vivo efficacy. Additionally, although the oral exposure for these analogs was generally good out to 4 h, in some cases it may have subsequently dropped below efficacious levels with once a day dosing. The most active compound, **1c**, was further profiled and showed a more than dose-proportional increase in oral exposure in the rat (data not shown). If this also occurred in mice, it may have helped **1c**'s performance in these xenograft models.

Compound **1c** was screened in a small panel of kinases (Table 5) and found to be less selective than morpholine ether analog **1a**.[3] Its inhibition of VEGFR-2, the vascular endothelial growth factor receptor-2, was only 14-fold less than that of EGFR and is suggestive of AEE-788, the Novartis EGFR, HER2, and VEGF

Table 4. In vivo antitumor activity of orally administered compounds against established N87 and GEO xenografts implanted subcutaneously in athymic mice[a]

Compound	N87[b]			GEO[c]		
	Dose[e] (mg/kg)	% TGI	MED[d]	Dose[e] (mg/kg)	% TGI	MED[d]
1b	180[f] MTD	121	90	135[f] MTD	78	90
1c	180 OD	133	60	240 MTD	85	120
8e	180 HTD	89	120	180 HTD	Inactive 60–180 mg/kg	
8h	240 HTD	110	120		ND[g]	
8i	180 HTD	63	180	180 HTD	Inactive 60–180 mg/kg	
8j		ND[g]		180 HTD	Inactive 60–180 mg/kg	

[a] Tween 80–PEG400–water, 10/40/50 was the vehicle and experimental details can be found in Ref. 7.
[b] QD × 21 dosing schedule.
[c] QD × 10 dosing schedule.
[d] MED, minimum efficacious dose. Activity is defined as % TGI $\geqslant$ 50%.
[e] MTD, maximum tolerated dose; OD, optimal dose; HTD, highest test dose.
[f] BID × 14 dosing schedule.
[g] ND, not determined.

Table 5. Kinase selectivity profile for **1a** and **1c**

Kinase	IC_{50}[a] (μM)	
	1a	**1c**
EGFR	0.061	0.035
HER2	0.055	0.023
Met	6.5	3.9
LCK	>5	0.71
VEGFR2	>10	0.48
CDK2	>50	1.9
p38	>50	>50
PKA	>50	>50
PKC	ND	2.2

[a] IC_{50} values are reported as means of at least three determinations. Variability around the mean value was <15%.

receptor tyrosine kinase inhibitor that is currently in clinical trials.[10]

A potential binding mode for compound **1c** in the ATP binding site was modeled after the X-ray structure of the complex between lapatinib and EGFR kinase and is shown in Figure 2.[11] The docked poses were energy minimized in Maestro[12] using the OPLS-AA force field[13] and the GBSA continuum model,[14] an implicit solvation model. The results were similar to those previously reported for the homopiperazine **1b**[4] and quinazoline EGFR and HER2 specific kinase inhibitors with C-5 solubilizing groups.[15] The pyrrolotriazine core is oriented in the ATP binding site such that there is a hydrogen bond between N-1 and the hinge region Met769 NH. The C-4 benzyl indazole group extends back into a deep hydrophobic pocket formed partially by Met742 of helix α-C and Phe382 of the activation loop. The C-5 substituent extends out into the ribose-phosphate pocket where the protonated amino group off the piperidine ring can hydrogen bond with the side chains of Asp831 and Asn818 and also with the backbone carbonyl oxygen of Arg817. In this model there was also an intramolecular hydrogen bond between the C4 aniline NH and the piperidine tertiary N atom. However, intriguing SAR such as the HER2 selectivity of picolyl analog **8c** and the switch to potent dual EGFR/HER2 inhibition for its methyl analog, **8e**, would require a HER2 crystal structure for interpretation.

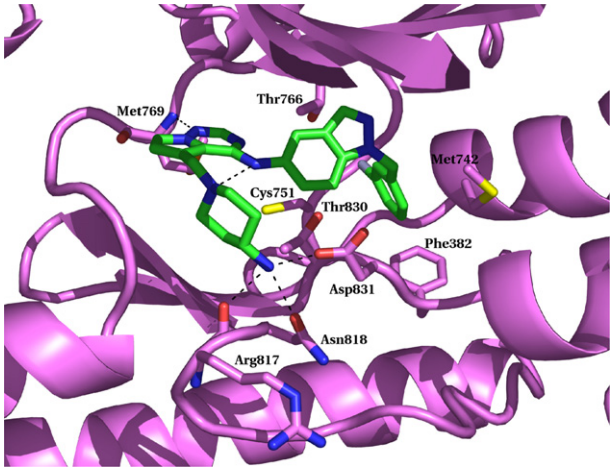


Figure 2. Predicted binding mode of compound **1c** modeled in the X-ray structure of the lapatinib/EGFR kinase complex, see Ref. 11. The C-5 side chain extends into the ribose-phosphate binding region where the protonated amino group off the piperidine ring may form hydrogen bonds with Asp831, Asn818, and/or Arg817. Image created with Pymol from DeLano Scientific LLC, San Carlos, CA, USA, http://www.pymol.org.

In summary, pyrrolotriazine dual EGFR/HER2 kinase inhibitors with a C-5 aminopiperidine solubilizing group generally exhibited an in vitro profile that was superior to that of analogs with our previously reported C-5 solubilizing groups. It is hypothesized that this solubilizing group extends into the ribose-phosphate portion of the ATP binding pocket and enhances the binding affinity of the inhibitor. New synthetic methodology was developed to permit the parallel synthesis of C-4 analogs with the new solubilizing group. Our initial efforts generated a variety of interesting leads and they were evaluated in tumor xenograft models. The 4-(aminofluorobenzylindazole) analog, **1c**, was found to exhibit the best antitumor activity. We have continued our studies of pyrrolotriazines with C-5 aminopiperidine solubilizing groups as dual EGFR/HER2 inhibitors and have

broadened the scope of our efforts, particularly with respect to the C-4 substituent. The results will be reported in future publications.

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