Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 2036–2042
Bioorganic & Medicinal Chemistry Letters

New C-5 substituted pyrrolotriazine dual inhibitors of EGFR and HER2 protein tyrosine kinases

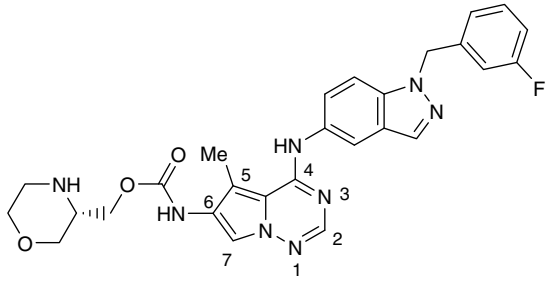
Harold Mastalerz,[a,*] Ming Chang,[b] Ping Chen,[b] Pierre Dextraze,[c] Brian E. Fink,[b] Ashvinikumar Gavai,[b] Bindu Goyal,[b] Wen-Ching Han,[b] Walter Johnson,[a] David Langley,[a] Francis Y. Lee,[b] Punit Marathe,[b] Arvind Mathur,[b] Simone Oppenheimer,[b] Edward Ruediger,[c] James Tarrant,[a] John S. Tokarski,[b] Gregory D. Vite,[b] Dolatrai M. Vyas,[a] Henry Wong,[a] Tai W. Wong,[b] Hongjian Zhang[b] and Guifen Zhang[a]

[a]*Departments of Oncology Chemistry, Discovery Biology, Pharmaceutical Candidate Optimization, Computer Aided Drug Design, and Chemical Synthesis, 5 Research Parkway, Wallingford, CT 06492-1951, USA*
[b]*Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543-4000, USA*
[c]*100 Boul. de l'Industrie, Candiac, Que., Canada J5R 1J1*

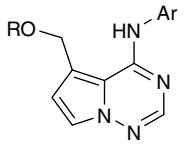
Received 29 November 2006; revised 19 December 2006; accepted 5 January 2007
Available online 12 January 2007

Abstract—Novel C-5 substituted pyrrolotriazines were optimized for dual EGFR and HER2 protein tyrosine kinase inhibition. The lead compound exhibited promising oral efficacy in both EGFR and HER2 driven human tumor xenograft models. It is hypothesized that its C-5 morpholine side chain binds in the ribose phosphate portion of the ATP binding pocket.
© 2007 Elsevier Ltd. All rights reserved.

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 and 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] There are currently several small molecule, ATP-competitive, reversible, dual EGFR, and HER2 kinase inhibitors in clinical development. These include: lapatinib (GW572016),[3] AEE-788,[4] and BMS-599626 (**1**).[5] The latter utilizes the bicyclic pyrrolo[2,1-f][1,2,4]triazine ring system as a scaffold for the construction of an ATP mimic.[6] Its lipophilic C-4 substituent provides potent and selective kinase inhibition,



1



2, R = solublizing group

Figure 1. Pyrrolotriazine dual EGFR and HER2 kinase inhibitors.

Keywords: EGFR; HER2; Receptor tyrosine kinase inhibitor; Pyrrolotriazine.
* Corresponding author. Tel.: +1 203 677 7773; e-mail: harold.mastalerz@bms.com

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.01.002

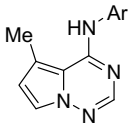
while its C-6 solubilizing side chain imparts good pharmacokinetics and further potency. We explored the SAR of analogs of **1** (Fig. 1) where the solubilizing group is tethered to C-5 via a methylene ether linkage, that is **2**, and describe our results in this report.

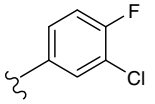
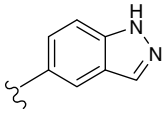
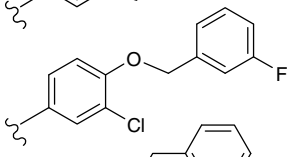
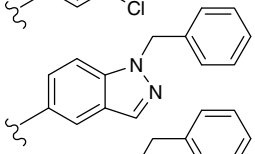
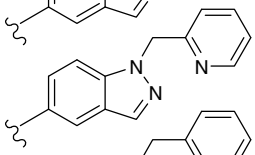
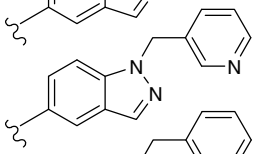
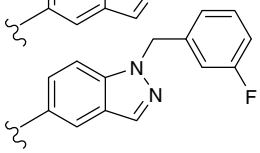
5-Methyl-pyrrolotriazines with different C-4 substituents (compounds **4**–**10** in Table 1) were prepared by reaction of 4-chloro-5-methyl-pyrrolotriazine **3**[6] with anilines in the presence of a base (Scheme 1). To prepare C-5 methylene ether analogs (compounds **12**–**27** in Table 2), the 5-methyl group of **3** was first brominated to give **11**.[7] This was treated with an excess of the alcohol of interest followed by 1-(3-fluorobenzyl)-1*H*-indazol-5-amine to give the ether analogs. A more efficient procedure was used with alcohols of limited availability. For this, **11** was converted into alcohol **28** by solvolysis in aqueous acetonitrile followed by reaction with 1-(3-fluorobenzyl)-1*H*-indazol-5-amine. Treatment of **28** with thionyl chloride gave a relatively unstable 5-chloromethyl intermediate, **29**, that was reacted with a slight excess of the alcohol of interest to give the corresponding ether analog.

The C-4 analogs of **24** (compounds **32**–**38** in Table 3) were prepared by first converting **3** to the 4-methylsulfide, **30** (Scheme 2). Bromination of the 5-methyl group followed by reaction with (*S*)-*tert*-butyl 2-(hydroxymethyl)morpholine-4-carboxylate[8] gave ether intermediate **31**. Oxidation of the sulfide group followed by reaction with different anilines and then deprotection gave the C-4 analogs.

Analogs **35**–**38** (Table 3) have chiral phenylethyl groups attached to N-1 of the indazole residue. To prepare the aminoindazole that was used to make **35**, nitroindazole **39** was coupled with (*S*)-1-phenylethanol using a Mitsunobu reaction (Scheme 3).[9] This gave a 2:1 mixture of the desired N-1 alkylation product, **40**, and its N-2 regioisomer. The isomers were separated by chromatography and their regiochemistry was established by 2D NMR (COSY). Reduction of the nitro group gave the aminoindazole, **41**, that was used to make **35** as outlined above. Analog **36** was similarly prepared from (*R*)-1-phenylethanol. Chiral HPLC analysis of **35** and **36** indicated that they were homochiral and that the Mitsunobu reaction had proceeded with complete inversion of configuration (ee > 99%). Their *m*-fluoro analogs, **37** and **38**, were similarly prepared as a racemic mixture from 1-(3-fluorophenyl)ethanol. They were separated by preparative chiral HPLC and their configuration was

Table 1. Structure–activity relationship for the C-4 position



Compound	Ar	HER2[a,b] IC_{50} (μM)	EGFR[b] IC_{50} (μM)
4		>1	0.10
5		>1	0.21
6		0.43	0.25
7		0.11	0.086
8		0.31	0.20
9		0.25	1.8
10		0.088	0.081

[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 Refs. 5 and 6 for assay conditions.
[b] IC_{50} values are reported as means of at least three determinations. Variability around the mean value was <15%.

Download English Version:

https://daneshyari.com/en/article/1377792

Download Persian Version:

https://daneshyari.com/article/1377792

Daneshyari.com