IMPROVED SYNTHESIS OF THE TYROSINE KINASE INHIBITORS CT-53518 AND GEFITINIB

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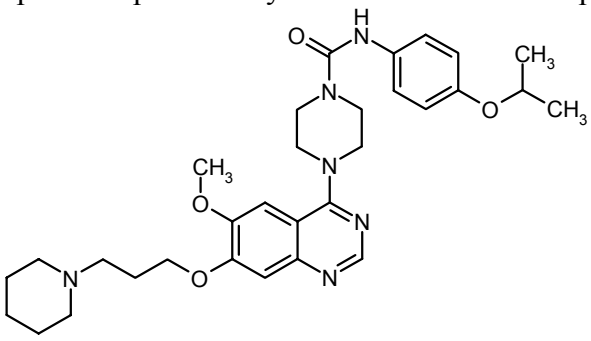
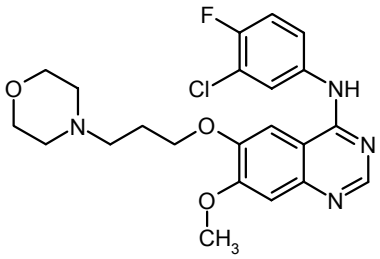
Abstract. 4-[4-(N-substituted carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazolines can function as potent and selective inhibitors of platelet-derived growth factor receptor (PDGFR) phosphorylation. A series of highly potent, specific, orally active, small mol. kinase inhibitors directed against members of PDGFR receptor have been developed recently. CT-53518 inhibits Flt-3, bPDGFR, and c-Kit receptor phosphorylation with IC50 values of 50-200 nM. Oral administration of CT-53518 promotes mice survival and significantly delayed disease progression in a Flt-3/ITD-mediated leukemia mouse model and shows efficacy in a nude mouse model of chronic myelomonocytic leukaemia [1,2].
We will report an optimized synthesis of CT-53518 that we developed in the context of the collaboration with the DrugMatrix program [3], the world's largest chemogenomics reference database and informatics system.
Gefitinib (=Iressa) has already shown its capacity as modern anticancer agent [3].

We will present optimized syntheses of the title compounds.



CT-53518



GEFITINIB

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[3] Small molecule tyrosine kinase inhibitors: clinical development of anticancer agents. Laird, A. Douglas; Cherrington, Julie M. *Expert Opinion on Investigational Drugs* **2003**, *12*, 51-64.
[4] http://www.iconixpharm.com/products/products_main.html