Discovery of 4-Aryl-N-arylcarbonyl-2-aminothiazoles as Hec1/Nek2 Inhibitors. Part I: Optimization of In Vitro Potencies and Pharmacokinetic Properties

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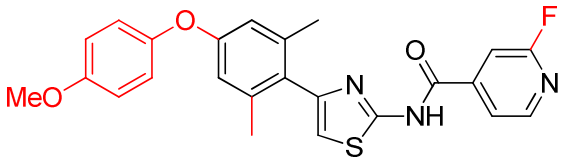
A series of 4-aryl-*N*-arylcarbonyl-2-aminothiazoles of scaffold **4** was designed and synthesized as Hec1/Nek2 inhibitors. Structural optimization of **4** led to compound **32** bearing C-4' 4-methoxyphenoxy and 4-(*o*-fluoropyridyl)carbonyl groups that showed low nanomolar in vitro antiproliferative activity (IC_{50}: 16.3–42.7 nM), high IV AUC (64.9 μM·h, 2.0 mg/Kg) in SD rat, and significant in vivo antitumor activity (T/C = 32%, 20 mg/Kg, IV) in mice bearing human MDA-MB-231 xenografts. Cell responses due to Hec1/Nek2 inhibition were observed in cells treated with **32**, including a reduced level of Hec1 co-immunoprecipitated with Nek2, degradation of Nek2, mitotic abnormalities, and apoptosis. Compound **32** showed selectivity of cancer cells over normal phenotype cells and was shown to be inactive in a [^{3}H]astemizole competitive binding assay for hERG liability screening. Therefore, **32** served as a good lead in our discovery of a preclinical candidate targeting Hec1/Nek2 interaction.



32

Hec1/Nek2 inhibitor

IC_{50}: 16.3–42.7 nM; high IV AUC

active in vivo