BIOLOGICAL ACTIVITY:
XL228 is a multi-targeted tyrosine kinase inhibitor with IC\textsubscript{50}s of 5, 3.1, 1.6, 6.1, 2 nM for Bcr-Abl, Aurora A, IGF-1R, Src and Lyn, respectively. IC\textsubscript{50} & Target: IC\textsubscript{50}: 5 nM (Bcr-Abl), 3.1 nM (Aurora A), 1.6 nM (IGF-1R), 6.1 nM (Src), 2 nM (Lyn)\textsuperscript{[1]} In Vitro: XL228 shows a broad pattern of protein kinase inhibition, including the tyrosine kinases IGF1R, SRC, ABL, FGFR1-3, and ALK and the serine/threonine kinases Aurora A and Aurora B. A panel of kinase inhibitors including XL228 is profiled against a series of cancer cell lines with known alterations in major signaling pathways. Approximately 30% of the lines demonstrate XL228 IC\textsubscript{50} values of <100 nM in viability assays, including many lines with characterized ALK or FGFR mutations or amplifications. XL228 eliminates the phosphorylation of Aurora A and B at concentrations above 10 nM. Short-term treatment of HeLa cells leads to disruption of mitotic spindle formation, with the majority of mitotic cells exhibiting a unipolar spindle and disorganized chromosomes\textsuperscript{[2]}. It displays low nanomolar biochemical activity against wild type Abl kinase (K\textsubscript{i} \textsubscript{= 1.4 nM}). XL228 inhibits phosphorylation of BCR-ABL and its substrate STAT5 in K562 cells with IC\textsubscript{50}s of 33 and 43 nM, respectively\textsuperscript{[3]}. In Vivo: Single-dose pharmacodynamics studies demonstrate a potent effect of XL228 on BCR-ABL signaling in K562 xenograft tumors. Phosphorylation of BCR-ABL is decreased by 50% at XL228 plasma concentrations of 3.5 μM; a similar decrease in phospho-STAT5 occurred at 0.8 μM plasma concentration\textsuperscript{[3]}.

References:
\[1\]. Cortes J, et al. Preliminary Clinical Activity in a Phase I Trial of the BCR-ABL/IGF-1R/Aurora Kinase Inhibitor XL228 in Patients with Ph++ Leukemias with Either Failure to Multiple TKI Therapies or with T315I Mutation. Blood 2008 112:3232

CAIndexNames:
2,4-Pyrimidinediamine, N4-(5-cyclopropyl-1H-pyrazol-3-yl)-N2-[[3-(1-methylethyl)-5-isoxazolyl]methyl]-6-((4-methyl-1-piperazinyl)-

SMILES:
CN1CC(C2=CC(NC3=NCC(C4CC4)=C3)=NC(NCC5=CC(C(C)=NO5)=N2)=CC1
Caution: Product has not been fully validated for medical applications. For research use only.

Tel: 732-484-9848  Fax: 888-484-5008  E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA