Bis(1H-indol-2-yl)methanones are effective inhibitors of FLT3-ITD tyrosine kinase and partially overcome resistance to PKC412A in vitro.

Inhibition of the mutated fms-like tyrosine kinase 3 (FLT3) receptor tyrosine kinase is a promising therapeutic strategy in acute myeloid leukaemia (AML). However, development of resistance to FLT3 tyrosine kinase inhibitors (TKI), such as PKC412A, has been described recently. This observation may have an increasing impact on the duration of response and relapse rates in upcoming clinical trials employing FLT3-TKI. Herein we investigated two representatives of a novel class of FLT3-TKI: Bis(1H-indol-2-yl)methanones. Both compounds effectively induced apoptosis in FLT3-internal tandem duplicate (ITD)-transfected murine myeloid cells and in primary FLT3-ITD positive blasts. Combination of both compounds with chemotherapy revealed synergistic effects in apoptosis assays. The compounds did not show significant toxicity in human bone marrow cells derived from healthy donors. Compound102 overcame resistance to PKC412 within a non-myelotoxic dose-range. Western Blotting experiments of 32D-FLT3-ITD cells showed dose-dependent dephosphorylation of FLT3-ITD and of its downstream targets STAT5, AKT and ERK upon incubation with either compound. In conclusion, bis(1H-indol-2-yl)methanones overcome resistance mediated by
FLT3-ITD mutations at position N676 and show strong efficacy in FLT3-ITD-positive cells alone as well as in combination with chemotherapy. We propose that further development of methanone compounds overcoming resistance to currently established FLT3-TKIs is an important step forward to an anticipated need within our future therapeutic algorithm in FLT3-ITD-positive AML.