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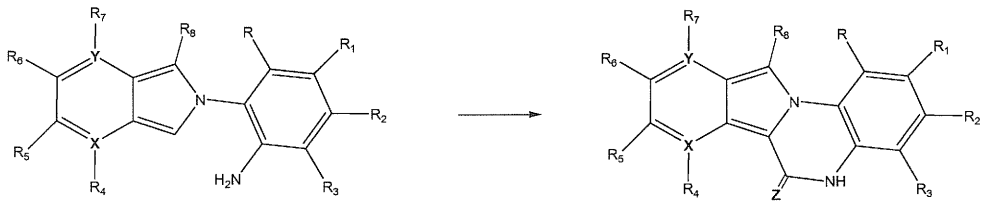
# SYNTHESIS OF AZA-ISOINDOLE QUINOXALINES WITH ANTITUMOR ACTIVITY

Barbara Parrino

Dipartimento di Scienze e Tecnologie Molecolari e Biomolecolari (STEMBIO)
Sezione di Chimica Farmaceutica e Biologica - Via Archirafi, 32 - 90123 Palermo

DNA represents one of the most important cellular targets for several antineoplastic drugs. Polycyclic nitrogen heterocycles with planar structure can be good pharmacophores for classes of antitumor drugs since they can intercalate between the base pairs of double-stranded DNA. Quinoxalines represents an important class of heterocycles that are found in a variety of biologically and medicinally useful agents such as anti-HIV and anticancer.[1] The annelation of the quinoxaline system to nitrogen heterocycles led to compounds that showed a broad spectrum antitumor activity.[2]

In our previous works we reported the synthesis of isoindolo[1,2-*a*]quinoxalines. All compounds were tested by the National Cancer Institute on a panel of 60 human tumor cell lines derived from nine different types of cancer (leukemia, melanoma, lung cancer, tumor colon, kidney cancer, ovarian cancer, breast cancer, prostate cancer and cancer of the SNC). They showed remarkable antineoplastic activity and at molecular level act through inhibition of tubulin polymerization and topoisomerase I activity.[3] These compounds showed anti-tumor efficacy and significant anti-angiogenic effects in MT-3/ADR xenografts. The strong interest in the anticancer activity associated with new classe of quinoxaline derivatives prompted us to focus our attention in the synthesis of new biologically active aza-isoindole quinoxalines.




**X**=CH, NH; **Y**=NH, CH; **Z**= O, NH

The new derivatives were obtained by treatment in acetic acid under reflux of the corresponding heteroaryl-amino derivatives. These were synthesized by reaction between heteroaryl-dicarboxaldehydes and aryl-diamines in the presence of potassium cyanide.

All new quinoxaline derivatives tested by the National Cancer Institute in Bethesda (NCI), on a total panel of 60 tumor cell lines, showed inhibitory activity against all cell lines tested from micromolar to nanomolar concentrations. In particular, the most active derivative in this series showed $pGI_{50}$ mean value of 7.20. Further studies are in progress.

**References**: 1. Lawrence D.S.; Copper J.E.; Smith C.D. Structure-activity studies of substituted quinoxalinones as multiple-drug-resistance antagonists *J. Med. Chem* 2001, *44*, 594-601; 2. Horwitz J. P.; Hazeldine S. T.; Corbett T. H.; Polin L. Preparation of quinoline derivatives and there use as antitumor agents WO Patent 03/011832, 2003; 3 Cirrincione G; Diana P.; Isoindoloquinoxaline derivatives as antitumor agents and their preparation, pharmaceutical compositions and use in the treatment of cancer *International Patent: PCT* WO 2008/041264 A1.