2-PHENYL-PYRROLO[2,3-h]QUINOLIN-4-ONES AS NOVEL SELECTIVE ANTIMITOTIC AGENTS

Venusia Gasparotto[a,b], Gianfranco Chiarelotto[a], Vincenzo Pezzi[c], Ignazio Castagliuolo[b] and Maria Grazia Ferlin[a]

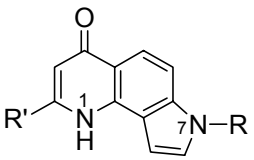
a) Department of Pharmaceutical Sciences, b) Department of Histology, Microbiology and Medical Biotechnologies, University of Padova, c) Department of Pharmaco-Biology, University of Calabria, Italy.

In our search for new potential anticancer drugs, we designed and synthesized a series of tricyclic compounds containing the antimitotic 2-phenyl-azaflavone chromophore fused [1] to a pyrrole ring in a pyrroloquinoline structure. A multi-step synthesis was performed via an amino-indole intermediate cyclized to a pyridinone structure using Conrad-Limpach or Gould-Jacobs conventional reactions.

Compounds **8**, **18**, **19**, **22**, **23**, **25** and **26**, when tested against a panel of fourteen human tumor cell lines, showed poor *in vitro* cytotoxic activity ($IC_{50} \geq 50$ μM), whereas **20, 21** and **24** showed a significant activity (IC_{50} ranging from 0.7 to 50 μM). Steroid hormones sensitive ovary, liver, breast and adrenal gland adenocarcinoma cell lines displayed highest sensitivity (IC_{50} values ranging from 0.7 to 8 μM).

Compound **24** blocked cells in the G_2/M phase of the cell cycle and induced a significant increase in apoptosis cell death, as assessed by Flow Cytometry analysis and detection of cytoplasmic histone-associated DNA fragments. Compounds **20**, **21**, **24** proved to alter the microtubule assembly and stability displaying a microtubule cytoplasmic network similar to the Vincristine caused one, as observed by Immunofluorescence Microscopy analysis.

In addition, these tree most active compounds, when subjected to the tritiated water release assay, exhibited high inhibitory effects on Aromatase activity, that can be considered the reason to explain the exerted selectivity against estrogen-sensitive tumor cell lines.



18-26

	R	R'
18	H	CH_3
19	H	tienyl
20	H	phenyl
21	CH_3	phenyl
22	H	p-NO_2-phenyl
23	H	m-NO_2-phenyl
24	H	m-OCH_3-phenyl
25	H	m-NH_2-phenyl
26	H	m-NH_2-phenyl. HCl

Finally, *in vivo* administration of compound **24** to Balb/c mice inhibited growth of a syngenic hepatocellular carcinoma by 67%.

[1] Li, L.; Wang, H.K.; Kuo, S.C.; Wu, T.S.; Lednicer, D.; Lin, C.M.; Hamel, E.; Lee, K.H. *J. Med. Chem.* **1994**, 37, 1126-35.