GS04-1 **Chemoprotection and structure-activity relationships of p53 inhibiting 2-heterosubsutituted 1,3-azole derivatives**

◯Yukio MIURA[1], Yu MATSUMOTO[1], Yo YAMAGUCHI[1], Tetsuji MURASE[1], Kensuke OKUDA[1], Satoshi UEDA[1], Hideko NAGASAWA[1]

[1]Gifu Pharmaceutical University

The chemoprotection of normal cells from p53 dependent apoptosis induced by chemo- and radiotherapy could be important for cancer treatment. In order to investigate the structure-activity relationship of p53 inhibitors and to develop more potent p53 inhibitor, we designed and synthesized a series of small heterocyclic analogs including 2-heterosubstetuted 1,3-azole from PFT as a lead compound. For the biological evaluation, we examined chemoprotection ability of the analogs to abrogate cell death induced by doxorubicin and inhibition of p53 transactivation. The novel imidazothiazole derivatives GPU-100 and 62 were more potent than PFT-β. These results suggested that the presence of linear conjugated system bearing aromatic terminal group at 2-position may be important for inhibition of p53.

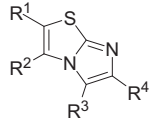

Table Structures and Chemoprotective Effects of 2-Heterosubstituted 1,3-Azole Derivatives

Compd	R^1	R^2	R^3	R^4	cLog$D_{pH=7.0}$[a]	Protection ratio[b]
PFT-β	-$(CH_2)_4$-		H	*p*-Tol	0.92	1.54
GPU-55	-$(CH_2)_3$-		H	*p*-Tol	4.21	1.27
GPU-123	H	H	H	*p*-Tol	2.88	1.18
GPU-157	-$(CH_2)_4$-		H	Cyclohexyl	1.14	1.37
GPU-62	-$(CH_2)_4$-		H		1.04	1.69
GPU-93	-$(CH_2)_4$-		H		1.49	1.53
GPU-100	-$(CH_2)_4$-		H		0.98	1.88
GPU-140	-$(CH_2)_4$-		*p*-Tol	H	0.92	1.07

[a] Caluculated by Pallas 3.0. [b] Protection ratio = Cell survival with inhibitor / Cell survival without inhibitor.