

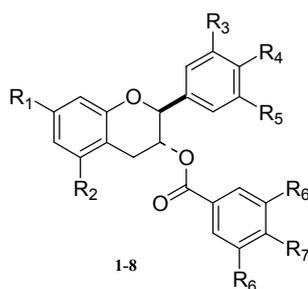
## SYNTHESIS OF ANALOGUES OF GALLOCATECHIN-3-GALLATE AS INHIBITORS OF METALLOPROTEINASE-9 ACTIVITY AND GENE EXPRESSION

Mario Dell'Agli<sup>a</sup>, Stefano Bellosta<sup>a</sup>, Luca Rizzi<sup>b</sup>, Germana Galli<sup>a</sup>, Monica Canavesi<sup>a</sup>, Filippo Rota<sup>b</sup>, Rachele Parente<sup>a</sup>, Enrica Bosisio<sup>a</sup>, Sergio Romeo<sup>b</sup>, Silvia Stefanini<sup>b</sup>

<sup>a</sup>Dipartimento di Scienze Farmacologiche, Via Balzaretti 9, 20133 Milan, Italy

<sup>b</sup>Istituto di Chimica Farmaceutica e Toss., Viale Abruzzi 42, 20131 Milan, Italy  
School of Pharmacy, University of Milan, Italy

Overexpression of metalloproteinase-9 (MMP-9) leads to an excessive breakdown of extra cellular matrix in many pathological conditions including cancer invasion and metastasis, and atherosclerotic plaque rupture. Catechins have been shown to modulate MMP-9 gelatinolytic activity and gene expression [1]; in particular, gallocatechins decreased MMP-9 secretion, following a decrease of MMP-9 promoter activity and mRNA levels [2]. For a preliminary structure-activity relationship study, 7 analogues of (±)-gallocatechin-3-gallate (GCG) selectively deprived of hydroxyl groups were synthesized by and tested on MMP-9 activity and secretion by murine peritoneal macrophages. When tested at 10 μM, the effect on MMP-9 activity was dependent on the number of hydroxyl groups on rings A and D, (±)-GCG being the most active compound (82 % inhibition). Conversely, the effect on MMP-9 promoter activity and secretion was enhanced by complete deprivation of the hydroxyl groups; compound **8**, which has no substituents, was the most active at this regard. For (±)-GCG, (±)-robidanol-3-gallate and compound **8**, the down regulation of gene expression was mirrored by decreased enzyme secretion (as shown in the table). These results supply new insight into the ability of catechin analogues to act at the transcriptional level, suggesting that the structural requirements for enzyme inhibition are different from those for gene expression.



Compound	MMP-9 secretion	MMP-9 promoter activity
(±)-gallocatechin-3-gallate	28.8 ± 2.1	38.3 ± 14.1
(±)-robidanol-3-gallate	31.6 ± 3.4	47.7 ± 14.2
<b>8</b>	68.0 ± 1.1	62.0 ± 13.7

% inhibition for the most active compounds at 10 μM

[1] Dell'Agli M., Canavesi M., Galli G., Bellosta S. *Thromb Haemost.* **2005**, *93*, in press.

[2] Bellosta S., Dell'Agli M., Canavesi M., Mitro N., Monetti M., Crestani M., Verotta L., Fuzzati N., Bernini F. and Bosisio E. *Cell. Mol. Life Sci.* **2003**, *60*, 1440.