SYNTHESIS AND PRELIMINARY BIOLOGICAL EVALUATION OF NEW PARTIALLY FLUORINATED THIOL DUAL INHIBITORS OF NEUTRAL ENDOPEPTIDASE 24.11 AND ANGIOTENSIN CONVERTING ENZYME

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An interesting approach for the treatment of congestive heart failure and chronic hypertension could be to avoid the formation of Angiotensin II by inhibition of Angiotensin Converting Enzyme (ACE) and to protect atrial natriuretic factor by blocking Neutral Endopeptidase EC 3.4.24.11 (NEP). The concept of dual inhibition of the two enzymes ACE and NEP by a single molecule has shown major benefits and potential superiority versus ACE inhibitors in various experimental models of hypertension, heart failure and renal disease (1).
A structure-activity study on thiol peptide based derivatives bearing fluorinated alkyl substitutes has been recently started in our laboratories focused on the obtainment of new modified peptides able to inhibit ACE, NEP, or the others metallopeptidases Endothelin Converting Enzyme–1 (ECE-1) and Neutral Aminopeptidase (APN).
In this work we report the results on a new class of partially fluorinated thiol compounds having the following general formula:

SH-CH(R1)-CH_2C(O)NH-CH(R2)-COOH **(I)**

wherein R1 and R2 have the meaning of fluorinated alkyl substitutes and substituted or un-substituted alkyl-aryl group, respectively.
The partially fluorinated compounds obtained by a novel synthetic process have been assayed as ACE, NEP, ECE and APN inhibitors through specific continuous fluorometric procedures.
All tested compounds have shown inhibitor capability towards both NEP and ACE (inhibition, expressed as *Ki* values, in the nanomolar range), but not for ECE and APN (*Ki* >10000 nM), evidencing a potential application of this class of compounds for the treatment of congestive heart failure and chronic hypertension.
According to this study, the introduction of fluorinated alkyl groups as R1 produces a significant increase of the inhibitor capability of the thiol compounds (I) toward ACE if compared with the previously reported data on completely hydrogenated analogues (2).

References

(1) Jandeleit-Dahm K.A.M. (2006) J.Hum.Hypertens. 20: 478-481.
(2) Gomez-Monterrey I., Turcaud S., Lucas E., Bruestschy L., Roques B.P. and Fournié-Zaluski M.C. (1993) J.Med.Chem. 36: 87-94.