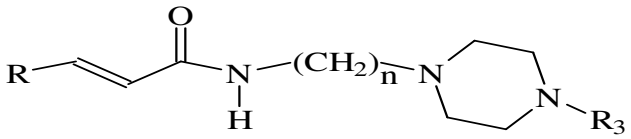
English Summary

Synthesis and reactions of some amino acid and peptide derivatives as non- steroidal anti-inflammatory and anti-allergic agents.

Substantial literature evidence indicated that, amino acids and peptides are natural and biochemically multi-functional, their conjugates with biological active agents which are; generally synthetic organics are hypothesized to be more potent and particularly less toxic than their parent compounds.

It was found that anti-allergic drugs of acrylic acid based structure (e.g. Tranilast® & Amoxanox®) are responsible for the inhibition of mediator (e.g. histamine and serotonin) release and other anti-allergic drugs of piperazine based-structure (e.g. Oxatomide® & Azelastin®) possess antagonistic activities against these mediators; Such preconception rested actually upon the work of Yoshinori Nishikawa *et al.*[120-122] as a starting concept. According to this work, the candidates were structurally designed as a hybrid structure of an acrylic acid segment and a piperazine segment [A] relating by aliphatic chains.

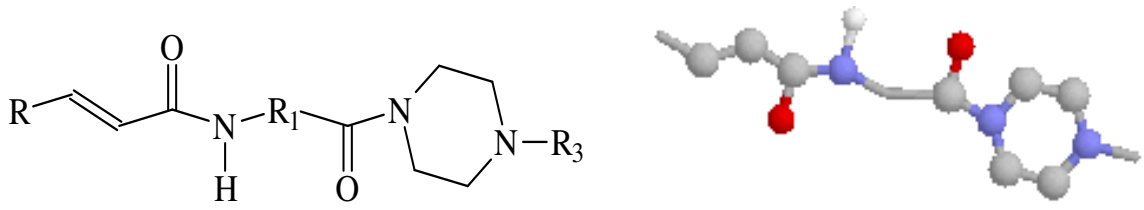


[A]

In such context, in the present thesis, it was assumed plausible to investigate the hypothetical potentiation capability of conjugating some amino acids and peptides with these active agents, in searching, meanwhile, for more potent non-steroidal anti-inflammatory and anti-allergic agents.

The synthesized conjugates, like their parent compounds are expected to interfere with the arachidonic acid metabolic cascade, as possible inhibitors at the level of its 5-lipo-oxygenase.

Herein, four acrylic acid based structures namely trans-cinnamic acid (β- phenyl acrylic acid or 3-phenyl 2-propenoic acid in IUPAC), β-thienyl acrylic acid (3- thiophene -2-propenoic acid), β- furyl acrylic acid (3- furan -2-propenoic acid) and 3-(5-methyl)-2-furyl acrylic acid were selected for an optimized chemical synthesis, structural elucidation and the subsequent biological evaluation of some new rationalized amino acid and peptide condensed conjugates, typified by the structures [C]:



[C]

Acrylic acid conjugates.

R = phenyl, thienyl, furyl and methyl furyl residue.

R_1= amino acid or peptide residue.

R_3= methyl, ethyl carboxylate and flouro phenyl.

Rationalized N- cinnamoyl, N-3-(2-thienyl), N-3-(2-furyl) and N-3-(5-methyl)-2-furyl)acryloyl amino acid and peptide derivatives and including esters, free acids and piperazine amides were synthesized (table 14) .

I. ***Acrylic acid and amino acid esters conjugate:***

I.a. *N*- cinnamoyl amino acid esters 1i(a-g) (**table 14**) have been synthesized by three methods, the modified carbodiimide coupling method using namely *N*-hydroxybenzotriazole (HOBt), the acid chloride method in which direct acylation was attained and mixed anhydride method using ethylchloroformate by which highly pure product was obtained.

I.b. *N*-3-(2-thienyl), *N*-3-(2-furyl) and *N*-3-(5-methyl)-2-furyl)acryloyl amino acid esters, [(2i(a-g)), (3i(a-e)) and (4i(a-c)), (**table 14**)] have been synthesized by both the modified carbodiimide coupling method using namely 1-hydroxybenzotriazole(HOBt) as well as active ester method using *N*-hydroxysuccinimide (HOSu) as an enhancing additives and THF as a recommended solvent medium .

II. ***Synthesis of acryloyl amino acid derivatives:***

N-cinnamoyl amino acids and *N*-3-(2-thienyl), *N*-3-(2-furyl) and *N*-3-(5-methyl)-2-furyl)acryloyl amino acids [$(1ii)_{(a-g)}$, $(2ii)_{(a-g)}$, $(3ii)_{(a-e)}$ and $(4ii)_{(a-c)}$, (**table 14**)] were obtained by the alkaline hydrolysis of the corresponding esters under mild experimental conditions and TLC monitoring in 80-95% yield.

III. ***Synthesis of acryloyl amino acid piperazine amides dervatives*****:**

N-cinnamoyl amino acid and *N*-3-(2-thienyl), *N*-3-(2-furyl) and *N*-3-(5-methyl)-2-furyl)acryloyl amino acid piperazine amides [(1iii, 1iv, 1v) $_{(a-g)}$, (2iii, 2iv, 2v) $_{(a-g)}$, (3iii, 3iv, 3v) $_{(a-e)}$ and (4iii, 4iv, 4v) $_{(a-c)}$, (**table 14**)] have

been synthesized by the coupling of the corresponding acids and *N*-piperazine derivatives by both the classical carbodiimide DCCI method using HOBt and HOSu as an enhancing agents as well as mixed anhydride method.

IV. ***Acrylic acid and peptide esters conjugate:***

IV.a. *N*-cinnamoyl glycylglycine ester (1ic) (**table 14**) has been synthesized by the modified carbodiimide coupling method using *N*-hydroxybenzotriazole (HOBt) and mixed anhydride method.

IV.b. *N*-3-(2-thienyl), *N*-3-(2-furyl) and *N*-3-(5-methyl)-2-furyl)acryloyl glycylglycine esters [(2ic), (3ic) and (4ic), (**table 14**)] have been synthesized by the modified carbodiimide coupling method using *N*-hydroxybenzotriazole (HOBt) an enhancing additive and THF as a recommended solvent medium.

V. ***Synthesis of acryloyl peptide derivatives:***

N-cinnamoyl glycylglycine and *N*-3-(2-thienyl), *N*-3-(2-furyl) and *N*-3-(5-methyl)-2-furyl)acryloyl glycylglycine [(1iic), (2iic), (3iic) and (4iic), (**table 14**)] were obtained by the alkaline hydrolysis of the corresponding esters under mild experimental conditions and TLC monitoring in 90 % yield.

VI. ***Synthesis of acryloyl peptide piperazine amides dervatives*****:**

N-cinnamoyl glycylglycine piperazine amides and *N*-3-(2-thienyl), *N*-3-(2-furyl) and *N*-3-(5-methyl)-2-furyl)acryloyl glycylglycine piperazine amides [(1iiic, 1ivc, 1vc), (2iiic, 2ivc, 2vc), (3iiic, 3ivc, 3vc) and (4iiic, 4ivc, 4vc) , (**table 14**)] have been synthesized by the coupling of the corresponding acids

and *N*-piperazine derivatives by both the classical carbodiimide DCCI method using HOBt as an enhancing agent as well as mixed anhydride method.

The purity of the synthesized compounds as well as the starting materials was checked by thin layer chromatography.
Their structures were confirmed by the inspection of their spectroscopic data, namely that of IR, ^{1}H-NMR and EI mass spectra, as well as their elemental analysis.

Biological evaluation:

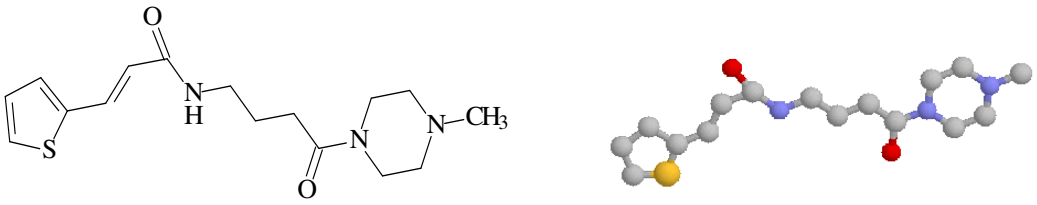
Biological evaluation of all candidates [(1iii, 1iv, 1v) $_{(a-g)}$, (2iii, 2iv, 2v) $_{(a-g)}$, (3iii, 3iv, 3v) $_{(a-e)}$ and (4iii, 4iv, 4v) $_{(a-c)}$, (**table 14**)] was realized in **Research Units, Hi-Care Pharmaceutical Co., Cairo, Egypt**.

A. Anti-allergic activity.

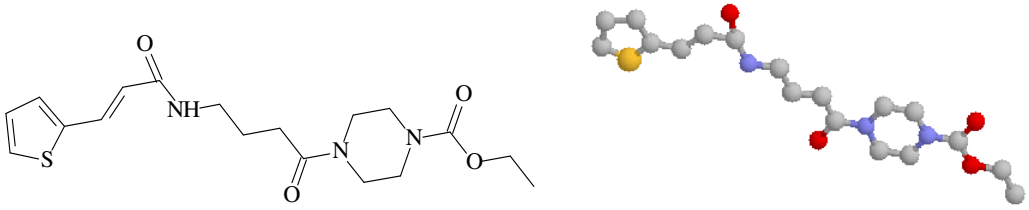
The anti-allergic activities were assayed by measuring the Spasmolytic activity in isolated guinea pig lung strips according to J.C. Foreman *et al.*[144].

The investigation of the obtained results (tables 19, 20, 21 and 22), revealed the following significant criteria:

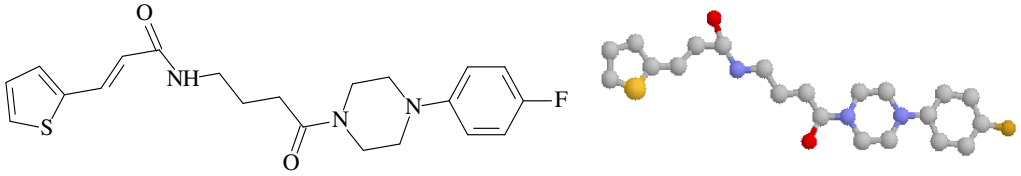
All the tested compounds showed potent activities except compounds 2iiig, 2ivg, 2vf and 2vg. This means that *N*-3-(2-thienyl)acryloyl amino butyric derivatives and *N*-3-(2-thienyl)acryloyl-β-alanyl-*N*-flourophenyl piperazine amide have no anti-allergic activities.



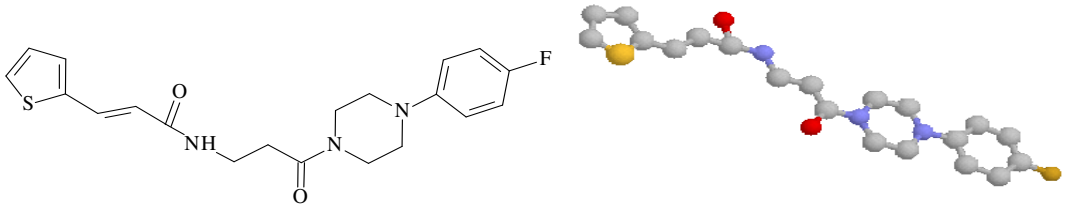
2iiig



2ivg



2vg



2vf

Furthermore, tyrosinyl derivatives show the highest anti-allergic activities that were obtained over than 90% relative to the reference drug *Loratadine*®.

Additionally, the other synthesized candidates are, prospectively, meriting further pronounced pharmacological investigations to reveal their intrinsic potency.

B. Anti-inflammatory activities:

Two types of the anti-inflammatory assay were attained:

- Protection against edema.
- Inhibition of PGE_2.

The inhibitory activity of the studied compounds on carrageenan-induced rat's paw edema was carried out according to the method of Winter *et al*.

The investigation of the obtained results (tables 23, 24, 25 and 26), revealed the following significant criteria:

1. According to, the obtained results the most of the prepared compounds have no activity except the following compounds; 1iiia, 1va, 1vb, 2iiia, 2iva, 2ivg, 2va, 2vg, 3iiib, 3ivb, 4iva, 4va and 4vb, this means that glycyl, valinyl and amino butanoyl derivatives show highly anti-inflammatory activities.
2. Compounds comprised *N*-3-(2-thienyl)acrylamide, γ-aminobutyric acid and *N*-ethyl ester or *N*-flourophenyl piperazine derivatives (2ivg and 2vg) have the highest activities.