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Synthesis of Some Amino Acid and Peptide Conjugates and their Evaluation as Potential Anti-allergic and Anti-inflammatory Agents

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A NEW series of *N*-3-(2-furanyl) acryloyl, *N*-3-(5-methyl)-2-(furanyl)-acryoyl amino acids, peptide and piprazines amids, were structurally designed and synthesized. About 23 compounds (5a-w) were synthesized and their anti-allergic and anti-inflamatory activities were evaluated relative to those of Loratadine (Clorinix®) and Diclofenac®. All the obtained products showed good anti-allergic activities with the greatest activities recorded for compounds (5g, 5h, 5j, 5k, 5m, 5n, 5v and 5w). All compounds showed LD_{50} with safety margin. On the other hand most compounds have no anti-inflamatory activities except products (5d, 5e and 5p).

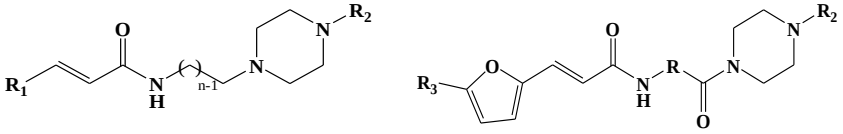
Keywords: 3-(2-Furanyl)acrylic acid, Amino acids, Piprazines and Anti-allerg and Anti-inflammatory.

The promising success of Youshinori Nishikawa *et al.* [1-3] in designing new anti-allergic drugs characterized as an antagonist of histamine as well as inhibitor for the generation of leukotrienes and prostaglandins, has stimulated a research interest. They synthesized orally active anti-allergic compounds having structure [A] with acrylamide segments responsible for inhibition of enzyme 5-lipoxygenase which catalyzed the generation of chemical mediators like (leukotrienes) from arachidonic acid and cause allergy. Tranilast®, a drug contains β–phenylacrylamide moiety. The acrylamide moiety may contribute to mediator release inhibitory activity. β-Aryl and β-heteroarylacrylamides may also show promising activity. Consequently, they designed, the acrylamide derivatives, substituted with 4-piprazinyl moieties, which, on the other hand, are expected to possess anti-histaminic activity similar to drug Oxatomide®. So the presence of piprazine moiety is responsible for this activity.

Their success led to synthesize new drug namely "Tagorizine" [*N*-[4-(4-diphenylmethyl-1-piprazinyl) butyl]-3-(3-pyridyl)acrylamide] [4-7] .

In harmony with these findings, herein, some acryloyl/ amino acids and/or peptide and piperazine amides having structure [B] have been synthesized (Fig. 1).

The addition of amino acids, peptide instead of alkyl chain was to introduce active moiety beside acrylamide and piprazine moieties. This is due to that amino acids and peptide play an outstanding role as growth factors, hormones, ionophores, immune peptides and toxins [8,9] .



[A] **[B]**

n= 1-4
R_1= aryl or heteraryl
R_2= alkyl or aryl

R= amino acid resiue
R_2= alkyl, ester or aryl
R_3= H or CH_3

Fig. 1. Structure design of the target products [B].

Amino acids and peptides, being natural and multifunctional, their conjugates with biologically active agents which are generally synthetic organics are supposed to be more potent and particularly less toxic than their parent compounds [10-13], also give better solubility, more favorable transport properties, pharmacologically adequate pattern and enzymatic degradation and general physiological compatibility.

Our previous work [14] reported that some of the β-aryl and β-heteroarylacrylamides conjugated with amino acid, peptide and piprazinyl group displayed a markedly high anti-allergic activity.

The present study focused on enhancing this activity, and new series of amino acids and peptide conjugated with *N*-3-(2-furyl)acryloyl, *N*-3-(5-methyl-2-furyl)acryloyl and piprazine derivatives were synthesized (Scheme 1). Also, the anti-allergic and anti-inflammatory activities were evaluated and promising results were obtained.

Results and Discussion

In the present study, *N*-3-(2-furanyl)acrylic acid was coupled with hydrochloride esters of glycine, L-valine, L-phenylalanine, L-tyrosinine and the dipeptide glycylglycine to afford *N*-3-(2-furanyl)acryloyl amino acid 3a-d and dipeptide 3e esters. Meanwhile, 3-(5-methyl)-2-furan acrylic acid was reacted with hydrochloride ester of glycine, L-valine and the dipeptide glycylglycine, to give the corresponding esters 3f-h, respectively (Scheme 1).

Coupling was performed *via* three methods: [i] the acid chloride method in which direct acylation is used; [ii] *in situ* active ester method (modified classical method) using 1-hydroxybenzotriazole (HOBt) and [iii] mixed anhydride method using ethyl chloroformate in the presence of *N*-methylmorpholine as a catalyst.

The corresponding acid derivatives 4a-h, have been easily obtained in 80-90% yield by the alkaline hydrolysis of their corresponding esters 3a-h under mild conditions and thin layer chromatography (TLC) control. Finally, each of the obtained acids 4a-h was coupled with 4-methylpiprazine, 4-ethoxycarbonyl-piprazine and/or 1-(4-fluorophenyl)-piperazine to afford the corresponding designed products *N*-[(4-substituted-1- piperazinyl)-oxo- (alkyl and ethylcarbamoyl)] -3-furanacrylamides 5a-w, respectively (Scheme 1).

The purity of the synthesized compounds as well as the starting materials was checked by thin layer chromatography (TLC) in an appropriate solvent system.

The structures of the synthesized compounds were confirmed by the inspection of their spectroscopic data, namely IR, ^{1}H-NMR and EI-mass spectra, as well as, their elemental analyses (Tables 1 and 2). The infrared spectra indicated the expected absorption bands of the essential functional groups, in addition to their unique fingerprints. Thus, the aromaticity, amide, C-terminal carboxylic or ester groups were traced and located.

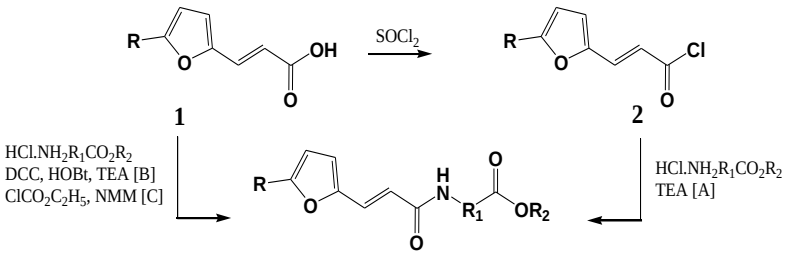
The aromaticity of the compounds was evident from their multiple absorptions ~ 3100 and 1600 cm^{-1}; the medium stretching vibration involving carbon-to-carbon skeletal aromatic ring stretching appeared at 1580-1629 cm^{-1} and finally the weak aromatic C-H stretching at 2964-3084 cm^{-1}. The secondary amide nature of the compounds was represented by amide band I absorption at 1647-1673 cm^{-1}, reflecting a resonating (N-C=O) stretching vibration.

The amide band II absorption, originating from a coupled NH bending and C-N stretching vibration appeared at 1521-1578 cm^{-1}.

The ^{1}H-NMR spectra of the synthesized conjugates confirmed their hydrogen skeleton. The two vinyl protons (H_a and H_b) split one another into two doublets centered at $\delta \approx 6.5$ and 7.62 ppm, respectively, where downfield was assigned to the aromatic resonance for H_a. The proton H_b, being attached to the carbon, bearing the heteroaromatic ring, assigned the higher chemical shift due to the deshielding effect of an isotropic field degenerated by the electrons of the aromatic ring.

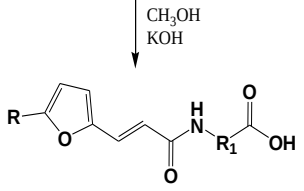
A coupling constant $J_{HH} \approx 16$ Hz, is a common value for *trans* proton-proton coupling across a double bond (*E*-configuration). Matching these absorptions from the spectra of the synthesized conjugates rendered facile the assignment of the remaining protons. Other signals at δ= 7.5–7.62 ppm for H_b, which was up-field due to the aromatic resonance for 3-(2-furanyl)acryloyl and 3-(5-methyl)-2-furanylacrylol residues, respectively. Methyl proton was assigned at δ= 1.12 ppm as a singlet.

The electron impact mass spectral data of the compounds were consistent with the proposed structures. Molecular ion peaks corresponding to the exact masses of the required formula were, generally, well represented with considerable abundances, indicating the relative stability of the compounds under electron bombardment.



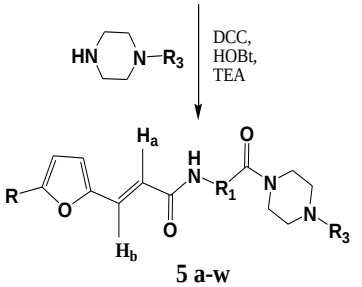
3 a-h

a, R= H, R_1= CH_2, R_2= $CO_2CH_2CH_3$,
b, R= H, R_1= $CHCH(CH_3)_2$, R_2= OCH_3
c, R= H, R_1= $CHCH_2C_6H_5$, R_2= OCH_3,
d, R= H, R_1= $CHCH_2C_6H_4OH$-*p*, R_2= OCH_3,
e, R= H, R_1= $CH_2CONHCH_2$, R_2= $CO_2CH_2CH_3$,
f, R= CH_3, R_1= CH_2, R_2= CO_2Et ,
g, R= CH_3, R_1= $CHCH(CH_3)_2$, R_2= OCH_3,
h, R= CH_3, R_1= $CH_2CONHCH_2$, R_2= CO_2Et



4 a-h

a, R= H, R_1= CH_2,
b, R= H, R_1= $CHCH(CH_3)_2$,
c, R= H, R_1= $CHCH_2C_6H_5$,
d, R= H, R_1= $CHCH_2C_6H_4OH$-4
e, R= H, R_1= $CH_2CONHCH_2$,
f, R= CH_3, R_1= CH_2,
g, R= CH_3, R_1= $CHCH(CH_3)_2$,
h, R= CH_3, R_1= $CH_2CONHCH_2$.



5 a-w

a, R= H, R_1= CH_2, R_3= CH_3,
b, R= H, R_1= CH_2, R_3= $CO_2CH_2CH_3$,
c, R= H, R_1= CH_2, R_3= C_6H_4F-4,
d, R= H, R_1= $CHCH(CH_3)_2$, R_3= CH_3
e, R= H, R_1= $CHCH(CH_3)_2$, R_3= $CO_2CH_2CH_3$,
f, R= H, R_1= $CHCH(CH_3)_2$, R_3= C_6H_4F-4,
g, R= H, R_1= $CHCH_2C_6H_5$, R_3= CH_3,
h, R= H, R_1= $CHCH_2C_6H_5$, R_3= $CO_2CH_2CH_3$,
i, R= H, R_1= $CHCH_2C_6H_5$, R_3= C_6H_4F-4,
j, R= H, R_1= $CHCH_2C_6H_4OH$-4, R_3= $CO_2CH_2CH_3$,
k, R= H, R_1= $CHCH_2C_6H_4OH$-4, R_3= C_6H_4F-4,
l, R= H, R_1= $CH_2CONHCH_2$, R_3= CH_3,
m, R= H, R_1= $CH_2CONHCH_2$, R_3= $CO_2CH_2CH_3$,
n, R= H, R_1= $CH_2CONHCH_2$, R_3= C_6H_4F-4,
o, R= CH_3, R_1= CH_2, R_3= CH_3,
p, R= CH_3, R_1= CH_2, R_3= $CO_2CH_2CH_3$,
q, R= CH_3, R_1= CH_2, R_3= $CO_2CH_2CH_3$,
r, R= CH_3, R_1= $CHCH(CH_3)_2$, R_3= CH_3,
s, R= CH_3, R_1= $CHCH(CH_3)_2$, R_3= $CO_2CH_2CH_3$,
t, R= CH_3, R_1= $CHCH(CH_3)_2$, R_3= C_6H_4F-4,
u, R= CH_3, R_1= $CH_2CONHCH_2$, R_3= CH_3,
v, R= CH_3, R_1= $CH_2CONHCH_2$, R_3= $CO_2CH_2CH_3$,
w, R= CH_3, R_1= $CH_2CONHCH_2$, R_3= C_6H_4F-4.

Scheme 1

TABLE 1. Physical data of the prepared compounds 5a-w.

Compd. No.	Yield (%)	Mp ^{0}C	Mol formula (M. Wt.)	Elemental Analysis (Calcd/Found)			R_f x 100 (Eluent)	$[\alpha]_D^{25}$ (c= 0.5, methanol)
				C	H	N		
5a	39[A] 51[C]	168-170	$C_{14}H_{19}N_3O_3$ 277.32	60.64 60.67	6.91 6.83	15.15 15.25	20 S_1	-
5b	35[A] 49[B]	170-172	$C_{16}H_{21}N_3O_5$ 335.36	57.29 57.39	6.31 6.35	12.53 12.63	59 S_2	-
5c	35[B] 52[C]	180-200	$C_{19}H_{20}FN_3O_3$ 357.15	63.84 63.22	5.64 5.60	11.75 11.85	80 S_1	-
5d	53[B]	135-140	$C_{17}H_{25}N_3O_3$ 319.75	63.93 63.89	7.89 7.91	13.16 13.23	80 S_1	-15
5e	45[B]	120-122	$C_{19}H_{27}N_3O_5$ 377.95	60.45 60.42	7.21 7.20	11.14 11.21	80 S_2	+22.5
5f	54[B] 62[C]	125-130	$C_{22}H_{26}FN_3O_3$ 399.47	66.13 66.23	6.56 6.59	10.52 10.59	74 S_2	-17.5
5g	72[B] 75[C]	183-184	$C_{21}H_{25}N_3O_3$ 367.44	68.64 68.90	6.86 6.75	11.44 11.52	80 S_2	+10
5h	63[B] 68[C]	168-170	$C_{23}H_{27}N_3O_5$ 425.48	64.93 65.11	6.40 6.26	9.88 10.97	55 S_1	-10
5i	90[B]	150-153	$C_{26}H_{26}FN_3O_3$ 447.50	69.78 69.85	5.86 5.78	9.39 9.48	43 S_2	+27.5
5j	92[B]	118-120	$C_{23}H_{27}N_3O_6$ 441.48	62.57 62.68	6.16 6.36	9.52 9.82	60 S_1	+17.5
5k	66[B]	125-130	$C_{26}H_{26}FN_3O_4$ 463.51	67.37 67.47	5.65 5.75	9.07 9.27	69 S_1	-2.5
5l	79[A]	138-140	$C_{16}H_{22}O_4N_4$ 334.38	57.47 57.51	6.63 6.75	16.76 16.80	15 S_1	-
5m	30[B]	168-170	$C_{18}H_{24}N_4O_6$ 392.42	55.08 55.12	6.16 6.25	14.28 14.33	55 S_1	-
5n	36[B]	210-215	$C_{21}H_{23}FN_4O_4$ 414.43	60.86 60.88	5.59 5.66	13.52 13.55	80 S_1	-
5o	76[B]	115-120	$C_{15}H_{21}N_3O_3$ 291.35	61.84 61.89	7.27 7.23	14.42 14.37	65 S_1	-
5p	38[A] 51[C]	149-155	$C_{17}H_{23}N_3O_5$ 349.38	58.44 58.59	6.64 6.58	12.03 11.60	60 S_2	-
5q	65[B]	220-224	$C_{20}H_{22}FN_3O_3$ 371.41	64.68 64.81	5.97 6.03	11.31 11.23	85 S_1	-
5r	84[B]	oily	$C_{18}H_{27}N_3O_3$ 333.43	64.84 64.78	8.16 8.18	12.60 12.56	80 S_1	+10
5s	72[A]	140-146	$C_{20}H_{29}N_3O_5$ 391.46	61.36 61.41	7.47 7.55	10.73 10.81	60 S_1	+20
5t	86[B]	135-140	$C_{23}H_{28}FN_3O_3$ 413.49	66.81 66.85	6.83 6.86	10.16 10.14	55 S_1	-28
5u	77[B] 76[C]	110-115	$C_{17}H_{24}O_4N_4$ 348.39	58.61 58.59	6.94 6.90	16.08 16.14	39 S_1	-
5v	65[B]	130-135	$C_{19}H_{26}N_4O_6$ 406.43	56.15 56.21	6.45 6.37	13.79 13.86	22 S_1	-
5w	31[B] 55[C]	198-200	$C_{22}H_{25}FN_4O_4$ 428.46	61.67 61.65	5.88 5.92	13.08 13.15	44 S_1	-

TABLE 2. Spectral data of the prepared compounds (5a-w).

Comp. No.	^{1}H-NMR (δ, ppm, DMSO-d_6)	Mass [m/z, (%)]	IR (KBr) [ν, cm^{-1}]
5a	2.13 (s, 3H, CH_3), 2.23-59 (m, 4H, $2CH_2$), 2.82-3.21 (m, 4H, $2CH_2$), 4.01(s, 2H, CH_2), 6.51(d, 1H, *J*= 15 Hz, CH=), 7.05 (t, 1H, *J*= 3.5 Hz, furan-4), 7.33 (d, 1H, *J*= 4.5 Hz, furan-3), 7.5 (d, 1H, *J*= 15 Hz, CH=), 7.6 (d, 1H, *J*= 5 Hz, furan-5), 8.18 (s, 1H, NH, D_2O-exchangeable).	278 [M^++1,4], 277 [M^+, 24], 276 [M^+-1, 60], 121 (100),93 (5).	3300 (NH), 1699, 1660 (CO).
5b	1.12 (t, *J*= 7.0 Hz, 3H, CH_3), 2.95-3.11 (m, 4H, $2CH_2$), 3.55-361 (m, 4H, $2CH_2$), 4.08 (s, 2H, CH_2), 4.30 (q, *J*= 7.2 Hz, 2H, CH_2), 6.4 (d, *J*= 15.6 Hz, 1H, CH=), 7.35 (t, *J*= 3.5 Hz, 1H, furan-4), 7.44 (d, *J*= 3.6 Hz, 1H, furan-3), 7.62 (d, *J*= 16 Hz, 1H, CH=), 7.65 (d, *J*= 5 Hz, 1H, furan-5), 8.12 (s, 1H, NH, D_2O-exchangeable).	338 [M^++3, 25], 335 [M^+, 30], 178 (25), 150 (43), 120 (100).	3361(NH), 1732, 1668, 1628 (CO).
5c	2.95-3.11 (m, 4H, $2CH_2$), 3.55-3.61 (m, 4H, $2CH_2$), 4.11 (s, 2H, CH_2), 6.57-6.59 (m, 2H, Ph-H), 6.55 (d, 1H, *J*= 15 Hz, CH=), 6.58 (t, 1H, *J*= 5.5 Hz, furan-4), 7.05-7.09 (m, 2H, Ph-H), 7.22 (d, 1H, *J*= 15 Hz, CH=), 7.45 (d, 1H, *J*= 5.5 Hz, furan-3), 7.58(d, 1H, *J*= 5 Hz, furan-5), 8.31 (s, 1H, NH, D_2O-exchangable).	359 [M^++2, 16], 357 (M^+, 31), 252 (32), 212 (71), 92 (100).	3330 (NH), 1698, 1614 (CO).
5d	0.89-0.90 (m, 6H, $2CH_3$), 2.13 (s, 3H, CH_3), 2.01-2.15 (m, 1H, CH), 2.32-2.95 (m, 4H, $2CH_2$), 3.19–3.39 (m, 4H, $2CH_2$), 4.97 (s, 1H, CH), 6.36 (d, 1H, *J*= 15 Hz, CH=), 6.48 (t, 1H, *J*= 5.1 Hz, furan-4), 6.83 (d, 1H, *J*= 5 Hz, furan-3), 7.35 (d, 1H, *J*= 15 Hz, CH=), 7.78 (d, 1H, *J*= 4.8 Hz, furan-5), 8.30 (s, 1H, NH, D_2O-exchangable).	320 [M^++1, 25], 319 [M^+, 18], 318 [M^+-1, 9], 121(100) 93 (25).	3320 (NH), 1667, 1637 (CO).
5e	0.93 (s, 6H, $2CH_3$), 1.18 (t, 3H, *J*= 6.0 Hz, CH_3), 2.11-2.15 (m, 1H, CH), 3.32-3.35 (m, 4H, $2CH_2$), 3.39-47 (m, 4H, $2CH_2$), 4.67 (q, 2H, *J*= 6.9 Hz, CH_2), 5.5 (s, 1H, CH), 6.63 (d, 1H, *J*= 15 Hz, CH=), 6.78 (t, 1H, *J*= 5.1 Hz, furan-4), 6.83 (d, 1H, *J*= 5 Hz, furan-3), 7.26 (d, 1H, *J*= 15 Hz, CH=), 7.78 (d, 1H, *J*= 4.8 Hz, furan-5), 8.30 (s, 1H, NH, D_2O-exchangeable)	377 [M^+, 12], 376 [M^+-1, 23], 348 (4), 304 (5), 276 (16), 256 (100).	3291 (NH), 1735, 1691, 1633 (CO).
5f	0.9 (s, 6H, $2CH_3$), 2.11-2.15 (m, 1H, CH), 3.51-3.60 (m, 4H, $2CH_2$), 3.71-3.75 (m, 4H, $2CH_2$), 4.28 (s, 1H, CH), 6.57-6.59 (m, 2H, Ph-H), 6.63 (d, 1H, *J*= 15 Hz, CH=), 6.78 (t, 1H, *J*= 4.5 Hz, furan-4), 7.05-7.09 (m, 2H, Ph-H), 7.22 (d, 1H, *J*= 15 Hz, CH=), 7.48 (d, 1H, *J*= 4.5 Hz, furan-3), 7.78 (d, 1H, *J*= 5 Hz, furan-5), 8.41 (s, 1H, NH, D_2O-exchangeable).	400 [M^++1, 8], 399 (M^+,55], 381 (100), 304 (5), 219 (25).	3290(NH), 1657, 1623 (CO).
5g	2.04 (s, 3H, CH_3), 2.20-2.40 (m, 4H, $2CH_2$), 2.97 (s, 2H, CH_2), 3.38-3.60 (m, 4H, $2CH_2$), 5.0-5.05 (m, 1H, CH), 6.40 (d, *J*= 16 Hz, 1H, CH=), 6.57-6.74 (m, 5H, Ph-H), 7.26 (t, *J*= 5 Hz, 1H, furan-4), 7.38 (d, *J*= 5.1 Hz, 1H, furan-3), 7.40 (d, *J*= 16 Hz, 1H, CH=), 7.79 (d, *J*= 5.1 Hz, 1H, furan-5), 8.70 (s, 1H, NH, D_2O-exchangeable).	368 (M^++1, 29], 367 [M^+,68], 366 [M^+-1, 16], 120 (100),92(46).	3140 (NH), 1655, 1620 (CO).
5h	1.18 (t, 3H, *J*= 6.9 Hz, CH_3), 2.79-2.90 (m, 4H, $2CH_2$), 2.97 (s, 2H, CH_2), 3.75-3.80 (m, 4H, $2CH_2$), 4.24 (q, 2H, *J*= 6.9 Hz, CH_2), 5.00-5.03 (m, 1H, CH), 6.50 (d, *J*= 16 Hz, 1H, CH=), 6.77-6.89 (m, 5H, Ph-H), 7.26 (t, *J*= 5 Hz, 1H, furan-4), 7.38 (d, *J*= 5.1 Hz, 1H, furan-3), 7.56 (d, *J*= 16 Hz, 1H, CH=), 7.79 (d, *J*= 5.1 Hz, 1H, furan-5), 8.70 (s, 1H, NH, D_2O-exchangeable).	396 (M^++4, 10], 392 [M^+, 20], 364 (45), 277 (12), 236 (100).	3278 (NH), 1701, 1619 (CO).

TABLE 2. (Continued).

Comp. No.	^{1}H-NMR (δ, ppm, DMSO-d_6)	Mass [m/z, (%)]	IR (KBr) [ν, cm^{-1}]
5i	2.79-2.90 (m, 4H, $2CH_2$), 3.20 (s, 2H, CH_2), 3.75-3.80 (m, 4H, $2CH_2$), 5.2 (t, *J*= 5.7 Hz, 1H, CH), 6.50 (d, *J*= 16 Hz, 1H, CH=), 6.70-6.74 (m, 2H, Ph-H), 7.07-7.15 (m, 5H, Ph-H), 7.13 (m, 2H, Ph-H), 7.24 (t, *J*= 5 Hz, 1H, furan-4), 7.38 (d, *J*= 5.1 Hz, 1H, furan-3), 7.60 (d, *J*= 16 Hz, 1H, CH=), 7.8 (d, *J*= 5.1 Hz, 1H, furan-5), 8.7 (s, 1H, NH, D_2O-exchangeable).	446 [M^+,35], 387 (38), 370 (11), 236 (14), 201 (39), 130 (100).	3277(NH), 1664, 1655 (CO).
5j	1.18 (t, 3H, J = 6.9Hz, CH_3), 2.79-2.90 (m, 4H, $2CH_2$), 2.97 (s, 2H, CH_2) 3.75-3.80 (m, 4H, $2CH_2$),4.24 (q, 2H, *J*= 6.9 Hz, CH_2), 5.02-5.06 (m, 1H, CH), 6.50 (d, *J*= 16 Hz, 1H, CH =), 6.77-6.91 (m, 5H, Ph-H), 7.26 (t, *J*= 5 Hz, 1H, furan-4), 7.38 (d, *J*= 5.1 Hz, 1H, furan-3), 7.56 (d, *J*= 16 Hz, 1H, CH=), 7.79 (d, *J*= 5.1 Hz, 1H furan-5), 8.70 (s, 1H, NH, D_2O-exchangeable), 9.00 (s, 1H, OH, D_2O exchangeable).	442 [M^++1, 3], 441 [M^+, 10], 364 (45), 278 (100), 236 (25), 232 (21).	3411 (NH), 1702, 1632, 1611 (CO).
5k	1.80-1.82 (m, 2H, CH_2), 3.05-3.10 (m, 4H, $2CH_2$), 3.18-3.20 (m, 4H, $2CH_2$), 3.98 (t, 1H, *J*= 5.7 Hz , CH), 6.4 (s, 1H, OH, D_2O-exchangeable), 6.65-6.72 (m, 2H, Ph-H), 6.87 (d, 1H, *J*= 15.9 Hz, CH=), 6.89-6.95 (m, 4H, Ph-H), 6.97 (t, 1H, *J*= 3.5 Hz, furan-4), 7.12-7.20 (m, 3H, Ph-H + furan-3), 7.59-7.63 (m, 3H, Ph-H + furan-5), 7.66 (d, 1H, *J*= 15.9 Hz, CH=), 7.74 (s, 1H, NH, D_2O- exchangeable).	442 [M^++1, 3], 441 [M^+, 11], 364 (45), 300 (100), 233 (25).	3422 (OH), 3130 (NH), 1650, 1629 (CO).
5l	2.13 (s, 3H, CH_3), 2.23-2.85 (m, 4H, $2CH_2$), 3.55-3.60 (m, 4H, $2CH_2$), 4.15 (s, 2H, CH_2), 4.32 (s, 2H, CH_2), 6.21 (d, 1H, *J*= 15 Hz, CH=), 6.56 (t, 1H, *J*= 5.5 Hz, furan-4), 6.70 (d, 1H, *J*= 2.5 Hz, furan-3), 7.12 (d, 1H, *J*= 16 Hz, CH=), 7.15 (d, 1H, *J*= 5 Hz, furan-5), 8.12 (s, 2H, 2NH, D_2O-exchangeable).	335 [M^++1, 9], 334 [M^+, 12], 333 [M^+-1, 14], 277 (100),137(73)	3326, 3149 (NH), 1660, 1661 (CO).
5m	1.20 (t, 3H, *J*= 7.0 Hz, CH_3), 3.55- 3.60 (m, 4H, $2CH_2$), 3.85-3.90 (m, 4H, CH_2), 4.1 (q, 2H, *J*= 7.0 Hz, CH_2) 4.20 (s, 2H, CH_2), 4.30 (s, 2H, CH_2), 6.40 (d, 1H, *J*= 15 Hz, CH=), 6.56 (t, 1H, *J*= 5.0 Hz, furan-4), 6.70 (d, 1H, *J*= 2.5 Hz, furan-3), 7.15 (d, 1H, *J*= 5 Hz, furan-5), 7.52 (d, 1H, *J*= 16 Hz, CH=), 8.32 (s, 2H, 2NH, D_2O-exchangeable).	393 [M^++1, 3], 392 (M^+, 17), 348 (21), 236 (23), 121 (100).	3348, 3149 (NH), 1689, 1653, 1626, (CO).
5n	3.06- 3.12 (m, 4H, $2CH_2$), 3.60- 3.65 (m, 4H, $2CH_2$), 4.13 (s, 2H, CH_2), 4.15 (s, 2H, CH_2), 6.58 (d, 1H, *J*= 16 Hz, CH=), 6.80-6.89 (m, 2H, Ph-H), 7.00 (d, 1H, *J*= 3.5 Hz, furan-4), 7.05-7.08 (m, 3H, Ph-H + furan-3), 7.26 (d, 1H, *J*= 15.9 Hz, CH=), 7.79 (d, 1H, *J*= 4.5 Hz, furan-5), 8.36 (s, 2H, 2NH, D_2O exchangeable).	415 [M^++1, 1], 414 [M^+, 13], 357 (28), 219 (52), 120 (100).	3278, 2099 (NH), 1656, 1635 (CO).
5o	2.01(s, 1H, CH_3), 2.30 (s, 3H, CH_3), 3.06-3.11 (m, 4H, $2CH_2$), 3.20-3.25 (m, 4H, $2CH_2$), 4.12 (t, *J*= 7.1 Hz, 2 H, CH_2), 6.08 (t, *J*= 4.5 Hz, 1H, furan-4), 6.25 (d, *J*= 15 Hz, 1H, CH=), 6.86 (d, *J*= 4.6 Hz, 1H, furan-3), 7.10 (d, *J*= 16 Hz, 1H, CH=), 8.15 (s, 1H, NH, D_2O- exchangeable).	293 [M^++1, 35), 292 [M^+, 6], 277 (25)191 (18), 133 (100).	3250 (NH), 1659, 1627 (CO).
5p	1.12 (t, *J*= 6.0 Hz, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.21-3.11 (m, 4H, $2CH_2$), 3.49-3.51 (m, 4H, $2CH_2$), 4.02 (t, *J*= 7.1 Hz, 2H, CH_2), 4.30 (q, *J*= 6.2 Hz, 2H, CH_2), 6.15 (t, *J*= 3.5 Hz, 1H, furan-4), 6.39 (d, *J*= 15.6 Hz, 1H, CH=), 6.58 (d, *J*= 3.6 Hz, 1H, furan-3), 7.10 (d, *J*= 16 Hz , 1H, CH=), 8.01 (s, 1H, NH, D_2O- exchangeable).	350 [M^+, 15], 349 [M^+-1, 6), 276 (100), 192 (19), 135 (23).	3350 (NH), 1695, 1664 (CO).

TABLE 2. (Continued).

Comp. No.	^{1}H-NMR (δ, ppm, DMSO-d_6)	Mass [m/z, (%)]	IR (KBr) [ν, cm^{-1}]
5q	2.30 (s, 3H, CH_3), 2.98-3.05 (m, 4H, $2CH_2$), 3.55- 3.70 (m, 4H, $2CH_2$), 4.14 (s, 2H, CH_2), 6.23-6.33 (m, 2H, Ph-H), 6.48 (d, 1H, *J*= 16 Hz, CH=), 6.65 (t, 1H, *J*= 4 Hz, furan-4), 6.70-6.75 (m, 2H, Ph-H), 6.98 (d, 1H, *J*= 5 Hz, furan-3), 7.09 (d, 1H, *J*= 5 Hz, furan-5), 7.12 d, 1H, *J*= 15 Hz, CH=), 8.20 (s, ,1H, NH, D_2O exchangeable).	372 [M^++1, 16], 371 [M^+, 46], 276 (9), 192 (11), 135 (100).	3330 (NH), 1698, 1651 (CO).
5r	0.97-1.0 (m, 6H, , $2CH_3$), 2.12-2.15 (m, 1H, CH), 2.14 (s, 3H, CH_3), 3.32-3.35 (m, 4H, $2CH_2$), 3.39 (m, 4H, $2CH_2$), 4.24 (s, 1H, CH) , 6.31 (d, 1H, *J*= 15 Hz, CH=), 6.14 (t, 1H, *J*= 5.1 Hz, furan-4), 6.33 (d, 1H, *J*= 5 Hz , furan-3), 7.16 (d, 1H, *J*= 15 Hz , CH=), 8.11 (s, 1H, NH, D_2O exchangeable).	320 [M^++1, 10], 319 [M^+, 35], 304 (100), 221(75).	3316 (NH), 1655, 1632 (CO).
5s	0.86-0.89 (m, 6H, $2CH_3$), 1.18 (t, 3H, *J*= 6.0 Hz, CH_3), 2.0-2.01 (m, 1H, CH), 2.38 (s, 3H, CH_3), 3.32–3.35 (m, 4H, $2CH_2$), 3.39-3.44 (m, 4H, $2CH_2$), 4.05 (q, 2H, *J*= 6.9 Hz, CH_2), 4.64 (s, 1H, CH), 6.51 (d, 1H, *J*= 15 Hz, CH=), 6.64 (t, 1H, *J*= 5.1 Hz, furan-4), 6.83 (d, 1H, *J*= 5.0 Hz, furan-3), 7.16 (d, 1H, *J*= 15 Hz, CH=), 8.32 (s, 1H, NH, D_2O exchangeable).	392 [M^++1, 4], 391 [M^+, 12], 362 (54), 134 (100).	3323 (NH), 1701, 1663, 1642 (CO).
5t	0.98-1.0 (m, 6H, 2CH3), 2.05-2.15 (m, 1H, CH), 2.42 (s, 3H, CH3), 3.32-3.35 (m, 4H, 2CH2), 3.38-3.41 (m, 4H, 2CH2), 4.54 (s, 1H, CH), 6.22 (m, 2H, Ph-H), 6.51 (d, 1H, J= 3.5 Hz, furan-4), 6.57 (d, 1H, J= 15.8 Hz, CH=), 6.87-7.04 (m, 3H, Ph-H), 7.12 (d, 1H, J= 5 Hz, furan-3), 7.17 (d, 1H, J= 15.9 Hz, CH=), 8.18 (s, 2H, 2NH, D2O exchangeable).	415 [M++1, 10],414 [M+, 14], 413 [M+-1, 35], 207 (18), 136 (100).	3369 (NH), 1642, 1610 (CO).
5u	1.91 (s, 1H, CH3), 2.31 (s, 3H, CH3), 3.36-3.41 (m, 4H, 2CH2), 3.63 (m, 4H, 2CH2), 4.09 (s, 2H, CH2), 4.27 (s, 2H, CH2), 6.21 (t, J= 3.7 Hz , 1H, furan-4), 6.59 (d, J= 15.6 Hz, 1H, CH=), 6.65 (d, J= 4.6 Hz, 1H, furan-3), 7.18 (d, J= 15.0 Hz , 1H, CH=), 8.19 (s, 2H, 2NH, D2O-exchageable).	349 [M++1, 2], 348 [M+,10), 286 (46), 190 (23), 135 (100).	3438, 3119 (NH), 1658, 1617 (CO).
5v	1.17 (t, 3H, J= 7.0 Hz, CH3), 2.30 (s, 1H, CH3), 3.56-3.60 (m, 4H, 2CH2), 3.65-3.70 (m, 4H, 2CH2), 4.07 (q, 2H, J= 7.0 Hz, CH2), 4.20 (s, 2H, CH2), 6.21 (t, 1H, J= 5.0 Hz, furan-4), 6.46 (d, 1H, J= 15 Hz, CH=), 6.66 (d, 1H, J= 2.5 Hz, furan-3), 7.15 (d, 1H, J= 16 Hz, CH=), 8.24 (s, 2H, 2NH, D2O-exchangeable).	407 [M+, 10], 378 (9), 349 (100), 191 (21), 134 (62).	3350, 3120 (NH), 1696, 1663 (CO).
5w	2.32 (s, 1H, CH3), 3.05-3.16 (m, 4H, 2CH2), 3.35-3.59 (m, 4H, 2CH2), 4.11 (s, 2H, CH2), 4.13 (s, 2H, CH2), 6.22 (m, 2H, Ph-H), 6.50 (d, 1H, J= 3.5 Hz, furan-4), 6.66 (d, 1H, J= 13.8 Hz, CH=), 6.99-7.04 (m, 2H, Ph-H), 7.10 (d, 1H, J= 5 Hz, furan-3), 7.18 (d, 1H, J= 13.9 Hz, CH=), 8.26 (s, 2H, 2NH, D2O-exchangeable).	429 [M+, 5], 317 (100), 285 (3), 191 (29), 135 (37).	3293, 3075 (NH), 1655, 1623 (CO).

Biological evaluation

All the obtained products 5a-w have been investigated for their anti-allergic and anti-inflammatory activities. All compounds showed anti-allergic effects, the highest and greatest capacities are recorded for compounds 5g, 5h, 5j, 5k, 5m, 5n, 5v and 5w relative to the anti-allergic activity of Loratadine® (Clarinix) (Table 3).

The evaluation of anti-inflammatory activity was carried out according to the method of Winter *et al.* [16,17], where the inhibitory activity of the studied compounds on carrageen an-induced rat's paw edema. Most of these compounds have no anti-inflammatory activities except 5d, 5e and 5p which showed the relative activities of 65.12, 75.12 and 69.18%, respectively. This means that derivatives comprised valinyl-residues have promised anti-inflammatory activities. Also, the presence of methyl group in *N*-3-(5-methyl)-2-furanyl acrylic acid has no valuable effect on the biological activity.

TABLE 3. Anti-allergic capacities and anti-inflammatory activities of compounds (5a-w).

Compd. No.	% Inhibition in contraction	%Protection against edema (at 2 mg/Kg)	LD_{50} mg/Kg
5a	71±0.66	NA	3145.76±4.56
5b	75±0.32	NA	1236.87±4.55
5c	78±0.64	NA	2113.67±2.39
5d	76±0.32	65.12±0.43	3456.67±3.45
5e	70±0.56	57.12±0.44	2167.66±2.11
5f	76±0.77	NA	3009±4.58
5g	86±0.32	NA	2567.8±2.44
5h	86±0.32	NA	2642.21±2.31
5i	88±0.65	NA	28765.67±4.16
5j	99±0.09	NA	2376±2.44
5k	99±0.32	NA	2468±5.44
5l	71±0.66	NA	3145.76±4.56
5m	88±0.32	NA	2556.38±5.66
5n	87±0.36	NA	2222.34±2.28
5o	73±0.64	NA	3214.67±3.56
5p	75±0.43	69.18±0.43	509.21±5.59
5q	77±0.32	40.55±0.32	456.76±4.59
5r	72±0.32	NA	987.21±2.57
5s	74±0.31	NA	3425.87±5.39
5t	79±0.34	42.121±0.23	2134.67±4.68
5u	80±0.89	NA	2698.65±2.55
5v	85±0.56	NA	2589±2.56
5w	81±0.43	NA	2564.4±4.34
Loratidine®	71±0.04	---	2250.25±2.26
Diclofenac®	---	70.14	2160.25±1.35

NA= No activity

Experimental

Melting points were determined in open glass capillaries using an Electrothermal IA 9000 SERIES digital melting point apparatus (Electrothermal, UK) and are uncorrected. Optical rotations were measured by a "Polax-D" polarimeter (ATAGO), provided by a SI-Na-1 Sodium lamp. Microanalyses were performed for all final compounds on an Elementar-Vario EL (Elementar-Vario EL, Germany) (Micro-analytical Unit, Central Services Laboratory, National Research Centre, Cairo, Egypt). The ^{1}H-NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer (Varian, USA). ^{1}H-NMR spectra were run at 300 MHz in DMSO-d_6 as solvent. Chemical shifts δ are quoted in ppm and were related to that of the solvents. Mass spectra were recorded on a Shimadzu GCMS-QP 1000EX (EI, 70 eV) (Shimadzu, Japan) and Hewlett-Packard (EI, 70 eV) (Hewlett-Packard, USA). IR spectra were obtained with a Brucker-Vector 22 (Bruker Rhein-Stetten, Germany). All the reactions were monitored using thin layer chromatography (TLC) using silica gel aluminum sheets $60F_{254}$ (Merck). While "S" stands for a chromatographic solvent system of chloroform/ methanol/ acetic acid, 85/10/5 by volume, S_1 and S_2 represent the same solvent system to which petroleum ether (40-60^{o}C) was added, in an equal or half ratio volume, respectively.

Synthesis of N-[(4-substituted-1-piperazinyl)-oxo-(alkyl and ethycarbamoyl)]-3-(2-furanyl) acrylamides (5a-n) and 3-(5-methyl-2-furanyl) acrylamides (5o-w) (General procedures)

[i] Acid Chloride method [Procedure A]

Triethylamine (2.42 g ≡ 3.4 ml, 24 mmol) was added in portions to a well stirred cold solution (0-5^{o}C) of acid derivatives 4a and 4h (12 mmol) and with the appropriate substituted piperazine (12 mmol) in THF/DCM (1:4, 150 ml). The reaction mixture was stirred for 3hr at the same temperature with simultaneous adjustment of pH≈ 8. The TEA hydrochloride was filtered off, excess solvent distilled off and residue in, mainly, ethyl acetate (EtOAc) was washed with HCl (1*N*, 3x20 ml), $NaHCO_3$ (5%, 3x20 ml), H_2O (3x20 ml) and dried over anhydrous sodium sulfate. Excess solvent was distilled off to afford 5a, b, 5l, 5p and 5s, in good yields (Table 1).

[ii] In situ active ester method [Procedure B]

A solution of DCC (3 g, 15 mmol) in THF (10 ml) was added, over 30 min, to a stirred cold solution (0-5^{o}C) of the acid product 4b-g (15 mmol) and *N*-hydroxybenzotriazole (HOBt) (1.7 g, 15 mmol) in THF (50 ml). Stirring was continued for 15 min at the same temperature, and a mixture of the appropriate substituted piperazine (15 mmol) and TEA (1.5g ≡ 2.13 ml, 15 mmol) in THF (50 ml) was then added. Stirring was continued at the same temperature for 3hr, at pH≈ 8 (Et_3N) and at 0^{o}C overnight, then at room temperature for 24hr. Drops of glacial acetic acid were added to the cold (0^{o}C) suspension and the reaction mixture was filtered off. The filtrate was evaporated and the residue was taken in acetonitrile (10 ml) and then kept in cold and the formed urea (DCHU) was

separated by filtration. Solvent was distilled off under reduced pressure and the residue was taken up in EtOAc, washed with $NaHCO_3$ (1*N*, 3x10 ml), distilled water (3 x 10 ml), $KHSO_4$ (5%, 3 x10 ml), distilled water (3x10 ml) and dried over anhydrous sodium sulfate. The dried and decolorized EtOAc solution was concentrated (5 ml) and chromatographically purified on manually prepared preparative TLC plates to get the products 5a-k, 5m-r and 5t-w (Table 1).

[iii] Mixed anhydride method [Procedure C]

Ethyl chloroformate (1.08 g ≡ 0.95 ml, 10 mmol) was added to a stirred and cold (-15^{o}C) THF solution of the acid product 4g or 4h (10 mmol) and *N*-methylmorpholine (~1 ml, 10 mmol). The reaction mixture was stirred for additional 10 min and then cold solution of appropriate substituted piperazine (10 mmol) in THF (30 ml) was added. Stirring was maintained for 3hr at (-15^{o}C) then for 12hr at room temperature. The solvent was evaporated and the residue was taken into EtOAc (30 ml) then washed with $KHSO_4$ (3%, 3×10 ml), distilled water (3×10 ml), $NaHCO_3$ (3%, 3×10 ml) and finally with water (3×10 ml) then dried over anhydrous sodium sulfate. The solvent was evaporated to dryness and the obtained residue triturated with n-hexane. The obtained solid was collected by filtration and crystallized from ethanol/n-hexane to afford 5a, 5c, 5f, 5g, 5h, 5p, 5u and 5w as identified by melting point, mixed melting point and TLC in comparison with samples prepared according to procedure B (Table 1).

Biological activities

The animal design model involved in this study is measuring the anti-anaphylactic activities due to histamine release.

Anti-allergic activity

Evaluation

The percent inhibition of spasmogen induced contraction is calculated. The percentage of inhibition in contraction (due to histamine release) is the anti-allergic potency, which is compared to that of Loratadine® (standard reference drug).

Procedure

Albino guinea pigs of either sex weighing 300-450 g are sacrificed with an overdose of ether. The chest cavity is opened and the lungs are removed. They were cut into strips of 5 cm and placed into a physiological saline solution. Thereafter, the lung strips are mounted in an organ bath containing a nutritive solution. The bath was bubbled with carbogen and maintained at 37^{o}C under a pre-load of 0.5g-3g; the tissue was left to equilibrate for 30-60 min. Prior to testing carbachol is added to the bath to test the lung strips ability of contraction. Twenty minutes later, two values are obtained by adding the spasmogen.

- Histamine dihydrochloride 10^{-6}g/ml for 5 min,
- Ca-ionophore 5x 10^{-6} g/ml for 5 min, or
- Leukotriene LTC_4 (10^{-9}-10^{-8}) g/ml for 10 min,

To the bath and recording the contractile force at its maximal level. Following

20 min, equilibration period resulted, the spasmogen is administrated again, 5min there after and the test compound is added in cumulative dose from 10^{-8}-10^{-4} g/ml at 5 or 10 min intervals. The contractile response is determined isometrically[15] (Table 3).

Evaluation of anti-inflammatory activity

The inhibitory activity of the studied compounds on carrageenin-induced rat's paw edema was carried out according to the method of Winter *et al.* [16,17].

Groups of adult male albino rats (150-180 gm), each of 8 animals were orally dosed with the test compounds at a dose level of 2.5 and 5 mg/kg an hour before carrageenin challenge.

Foot paw edema was induced by sub planter injection of 0.05ml of 1% suspension of carrageenin in saline into the planter tissue of one hind paw. An equal volume of saline was injected to the other hind paw and served as control. Four hours after drug administration the animal was decapitated, blood was collected and the paws were rapidly excised.

The average weight of edema was estimated for the treated as well as the control group and the percentage inhibition of weight of edema was also evaluated then percentage protection against edema was estimated (Table 3). Diclophenac® (2.5 and 5 mg/kg) was employed as standard reference against which the test compounds were compared.

Estimation of plasma prostaglandin E_2 (PGE_2)

Heparinized blood samples were collected from rats (n= 8), plasma was separated by centrifugation at 12000 g for 2min at 4°C and immediately stored frozen 20°C until use.

The designs correlate-EIA prostaglandin in E_2 (PGE_2) kit is a competitive immune assay for the quantitative determination of PGE_2 in biological fluids. The kit uses a monoclonal antibody to PGE_2 to bind, in a competitive manner, the PGE_2 in the sample. After a simultaneous incubation at room temperature the excess reagents were washed away and the substrate was added. After a short incubation time the enzyme reaction was stopped and the yellow color generated was read on a micro plate reader (DYNATCH, MR 5000) at 405 nm. The intensity of the bound yellow color is inversely proportional to the concentration of PGE_2 in either standard or samples. The percentage inhibition of plasma PGE_2 for each compound was estimated (Table 3).

Evaluation of acute toxicity study

The test compounds were administered orally at different dose levels in separate groups of animals. After 24 hr of drug administration percent mortality in each group was observed. From the data obtained, the lethal dose (LD_{50}) was calculated by the method of Austen *et al.* [18] (Table 3).

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تشييد بعض مشتقات الأحماض الأمينية والبيبتيدات وتقييمها كمضادات للإلتهابات والحساسية

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تم تشييد سلسلة جديدة من الأميدات 5a-w بتفاعل ن-3-(2-فيورانيل)أكريلويل، ن-3-(5-ميثيل)-2-فيورانيل) أكريلويل مع الأحماض الأمينية والبيبتيدات ثم مشتقات البيبرازين، و تقييم المركبات المشيدة (23 مركب) كمضادات للإلتهابات والحساسية مقارنة بكل من الفولتارين واللوراتيدين.

وقد أظهرت كل المركبات المشيدة فاعلية كمضادات للحساسية وخاصة المركبات (5g > 5h > 5j > 5k > 5m > 5n > 5v >5w) على التوالى فاعلية متميزة كمضادات للحساسية بينما كان لها تأثير ضعيف كمضادات للإلتهابات وأثبتت تحاليل السمية أنها أمنة وغير سامة.