Zagazig J. Pharm. Sci., June 1998
Vol. , No. , pp. 94 -100

ISSN 1110 -5089

SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL HETEROCYCLIC DERIVATIVES OF FLURBIPROFEN

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ABSTRACT

The synthesis of some novel non- carboxylic heterocyclic derivatives of flurbiprofen such as pyrazole , pyrrole , oxadiazole, oxadiazines, and triazoles, is described. Structure of the new compounds was elucidated by spectroscopic data and microanalysis. Three representative compounds were tested for analgesic, antipyretic, and anti-inflammatory activities. The pyrazole derivative VIII displayed greater antipyretic activity but lower analgesic and anti-inflammatory activities compared to flurbiprofen. However, the other two compounds were , in general, less potent than flurbiprofen.

INTRODUCTION

One of the major side effects of the aryl and heteroarylalkanoic acid class of non-steroidal anti-inflammatory agents is their tendency to cause gastric ulceration. The longterm use of these drugs in case of chronic inflammation may lead finally to the development of peptic ulcer. The free carboxyl function may be the structural element responsible for this ulcerogenic effect [1,2]. It has been shown that blocking of the carboxylic function of non-steroidal anti-inflammatory agents such as aspirin, diclofenac, flufenamic acid, indomethacin, and tolmetin by converting it to the ester function results in prodrugs with almost no gastric ulcerogenic activity but with full therapeutic effectiveness [3].

In a previous work [4] , the carboxyl function of flurbiprofen was masked through conversion to the amide, alkylidene, or arylidene. In continuation of this work , we decided to direct our study toward the synthesis and evaluation of the heterocylic derivatives of flurbiprofen that have the fluorobiphenyl moiety but have no naked carboxylic function, hopefully that the new analogs may have better qualities than the parent compound. In this investigation, a pyrazole, a pyrrole, an oxadiazole, a series of oxadiazines, and a series of triazoles were synthesized and tested for analgesic, antipyretic, and anti-inflammatory activities compared to the parent acid.

The reaction sequence followed for the synthesis of the target compounds is outlined in **Scheme I** and **Scheme II.**

CHEMISTRY :

The synthesis of the key intermediate **I** was described in a previous publication [4] . Treatment of **I** with phenyl isothiocyanate in refluxing dioxane afforded the thiosemicarbazide **II** in good yield. The 5-mercapto triazole derivative **III** was obtained from **II** by the action of 2N NaOH. Condensation of **III** with formalin and the appropriate secondary amines yielded the Mannich bases **IV** (a-c) in appreciable yields. On the other hand, alkalation of **III** with methyl iodide in the presence of K_2CO_3 gave the thioether **V** in good yield. The oxadiazole derivative **VI** was obtained by treating **II** with 2N NaOH followed by 5% I_2 /KI solution **(Scheme I)** . Condensation of the hydrazide **I** with acetylacetone in refluxing EtOH afforded the alkylidene **VII** which was subsequently converted to the pyrazole **VIII** by the action of ethanolic KOH. However, the pyrrole derivative **IX** was synthesized in one step by condensation of **I** with acetonylacetone in glacial HOAc. Finally, treatment of **I** with the appropriate phenacyl halides under basic conditions gave the oxadizines **X** (a-c) in moderate yields **(Scheme II).**

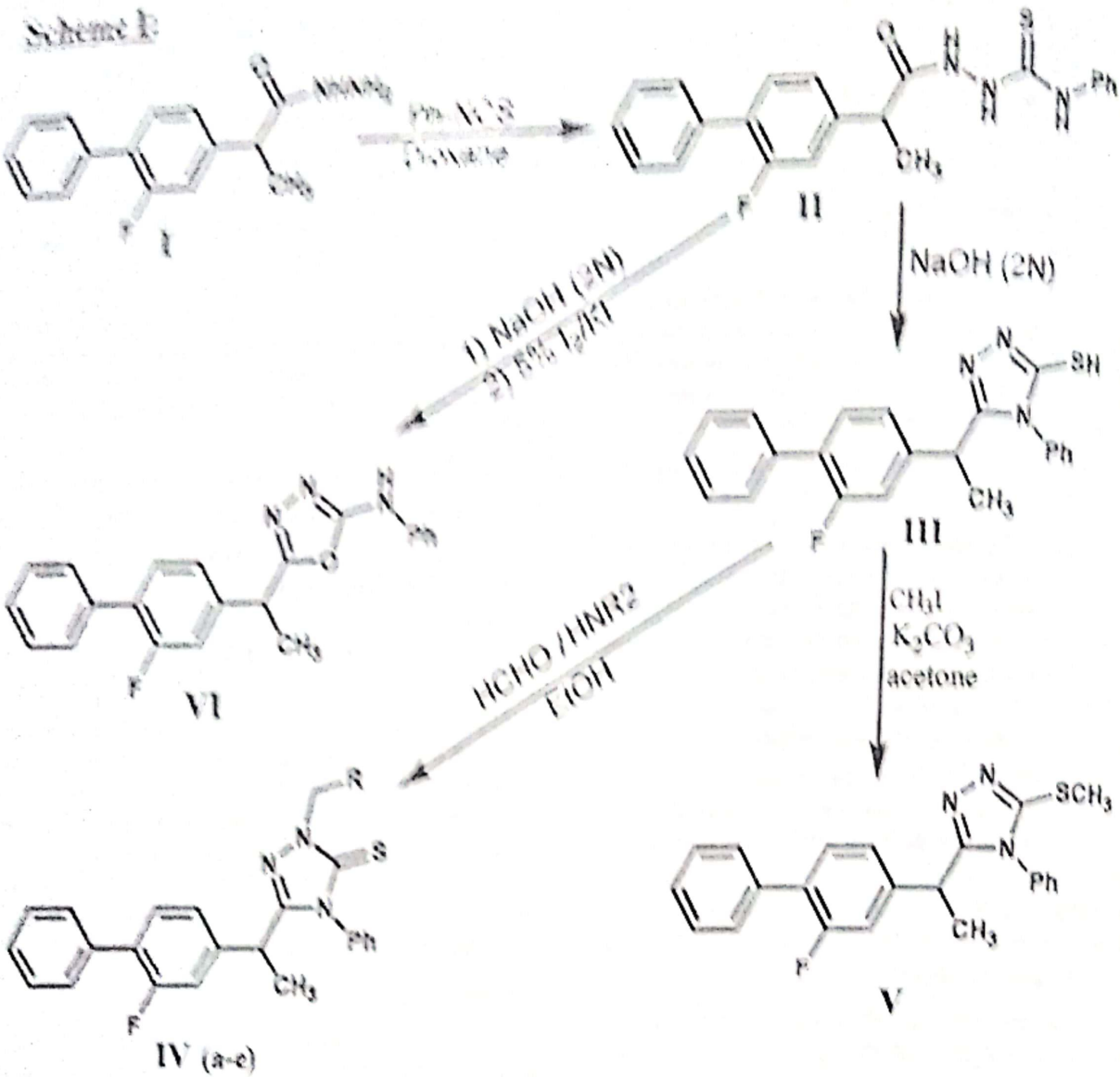
PHARMACOLOGICAL SCREENING :

Three of the new compounds **Iva, VIII , and IX** were tested for analgesic, antipyretic, and anti-inflammatory activities in comparison with flurbiprofen. Compound **VIII** showed greater antipyretic potency when compared to flurbiprofen. With respect to the analgesic and anti-inflammatory activities, however, all the tested compounds were less potent than flurbiprofen.

Analgesic activity :

The hot plate method for **Jacob and Bosoviski** [5] was applied to evaluate the analgesic activity. 25 mature albino mice of both sexes weighing 15-20 gm were divided into five groups (5 mice - each) . The first group was injected with the solvent only and was kept as control. The second one was injected (i.p) with flurbiprofen (20 mg /kg). Each group from the remaining three was injected (i.p) with the test compounds (20 mg/kg). Five minutes later, each mouse was placed in a two - litres beaker immersed in a water bath thermostatically controlled at 56.5°C. The time elapsed until the mouse licks the paw was calculated as a measure for the analgesic effect. Recording were taken (10, 20, 30, 60, 90 and 120 minutes) post treatment (Table 1).

Scheme I:



R = piperidino, morpholino, pyrrolidino, diethylamino, and N-phenyl-N'-methylamino.

Antipyretic activity :

Twenty five mature albino rats of both sexes (200-250 g) were divided into five groups (5 rats each). All animals were rendered hyperthermic using the method described by **Teotino et al.**[6] through subcutaneous injection of 20% aqueous suspension of dry yeast in a dose of 0.1 ml / 100 gm. After 18 hours, the animal temperature was taken rectally by a medical thermometer and recorded as the initial temperature. One group was saved hyperthermic as control , whereas the second group was injected (i.p) with flurbiprofen (20 mg/kg). The test compounds were given (i.p) in a dose of 20 mg / kg for the remaining three groups. One hour following treatment, the rectal temperature was recorded for a period of 3 hours. The difference between the initial body temperature and that after treatment was calculated and compared with that of the control group which received an equivalent volume of DMSO as solvent (Table 2).

Anti-inflammatory activity:

Five groups, each of five mature albino rats (200-250 g) of either sex were used. Oedema was induced by the injection of dry yeast into the skin of their hind limb paw (0.1 ml of 20% dry yeast in aqueous solution) according to the method described by **Alpermann** [7]. After 4 hours, the thickness of the paw was measured using a skin caliber to detect the inflammatory process achieved by the yeast. The first group was labelled as control and received the solvent only, while the second group was injected (i.p) with flurbiprofen in a dose of 20 mg/kg. The tested compounds were injected (i.p) to the remainder groups in a dose of 20 mg/kg. The paw thickness was measured after 3 and 6 hours post injection (Table 3).

Scheme II:

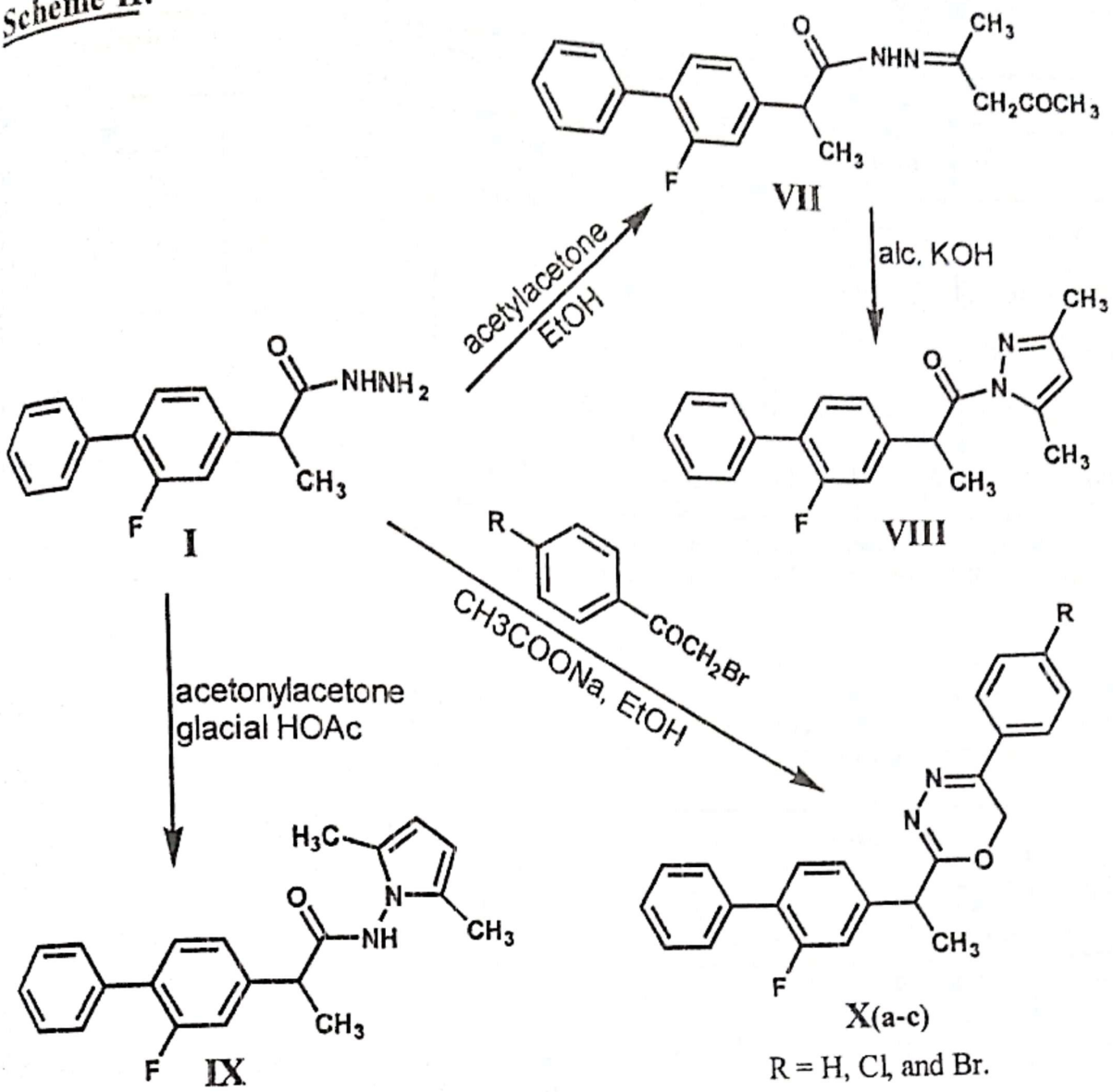


Table (1) : The analgesic activity of flurbiprofen and the tested compounds in a dose of 20 mg/kg body weight.

Groups	Reaction time before treatment	Reaction time in seconds after treatment Mean value ± S.E.					
		10 min.	20 min.	30 min.	60 min.	90 min.	120 min.
Control	9.6±1.0	10.4±2.0	10.0±1.1	10.8±1.0	10.0±2.0	9.6±1.0	11.2±1.2
Flurbiprofen	9.0±0.7	13.4*±0.5	17.8*±2.0	18.2*±1.0	22.2*±1.2	17.6*±1.6	14.8*±0.6
Compound IV	11.0±1.1	14.4*±0.8	16.6*±1.1	23.4*±2.0	24.6*±2.0	20.0*±2.0	16.4*±1.5
Compound VIII	7.0±0.7	10.6*±1.2	10.0*±0.5	12.0*±1.5	10.8*±1.4	10.6*±1.0	9.0*±1.0
Compound IX	7.4±0.9	8.6*±1.2	12.0*±1.7	13.8*±0.7	13.6*±1.3	11.8*±1.0	10.6*±0.8

* Significant at $P<0.05$

Table (2) : The antipyretic activity of the test compounds compared with flurbiprofen.

Groups	Reaction time before treatment	Reaction time after treatment	Reaction time in seconds after treatment Mean value ± S.E.		
			1 hour	2 hour	3 hour
Control	36.84±0.26	37.72*±0.2	37.76±0.22	37.70±0.21	37.74±0.22
Flurbiprofen	37.14±0.18	37.84* ±0.11	37.14**±0.23	37.24**±0.12	37.20**±0.12
Compound IVa	37.46±0.15	38.16* ±0.18	37.44**±0.26	37.48**±0.16	37.56**±1.30
Compound VIII	37.00±0.17	37.82* ±0.26	36.50**±0.45	36.10**±0.70	36.30**±0.62
Compound IX	36.70±0.28	37.60* ±0.40	37.00**±0.30	36.60**±0.48	36.96**±0.26

* Significant from normal body temperature at P<0.05
** Significant from hyperthermia induced by yeast at P<0.05

Table (3) : The anti-inflammatory activity of flurbiprofen and the tested compounds in a dose of 20 mg /kg body weight.

Groups	Thickness of paw skin in mm (Mean value ± S.E.)		
	4 h after yeast administration	3 h after treatment	6 h after treatment
Control	7.38±0.29	7.50±0.3	7.64±0.26
Flurbiprofen	*7.35±0.22	*5.75±0.12	*5.13±0.1
Compound IVa	*7.52±0.1	*5.60±0.1	*5.58±0.15
Compound VIII	*7.34±0.3	*5.70±0.2	*5.03±0.2
Compound IX	*7.57±0.2	*6.40±0.1	*5.30±0.2

** Significant at P<0.05

EXPERIMENTAL

General :

All melting points are uncorrected. Microanalyses were carried out in the microanalytical unit, Cairo University. IR spectra were carried out using Pye Unicam SP 1100 spectrophotometer. The chemical shift values were recorded in δ (parts per million) relative to tetramethylsilane (TMS) as internal standard.

N^1-[2-(2-Fluorobiphenyl-4-yl) propionyl] -N^4-phenyl thiosemicarbazide (II):

A mixture of 2-(2- fluorobiphenyl-4-yl) propionic acid hydrazide (2.58 g, 10 mmol) and phenyl isothiocyanate (1.35 g, 10 mmol) in dioxane was heated at reflux for 5h. The solvent was removed by distillation under reduced pressure and the obtained semisolid mass was triturated in cold EtOH. The crude product was filtered, washed with cold EtOH, dried, and recystallized from absolute EtOH to afford 3.20 g (81%) of the title compound; mp 210 - 212 °C; IR (KBr, cm^{-1}) : 3300, 3200 (NHs), 1660 (C-O). Analysis: Calcd for $C_{22}H_{20}FN_3OS$: C, 67.18; H, 5.09; N, 10.69 and Found: C,67.0; H,5.1; N,10.6.

3-[1-(2-Fluorobiphenyl-4-yl) ethyl]-4- phenyl-1 , 2,4-traizol-5-thiol (III):

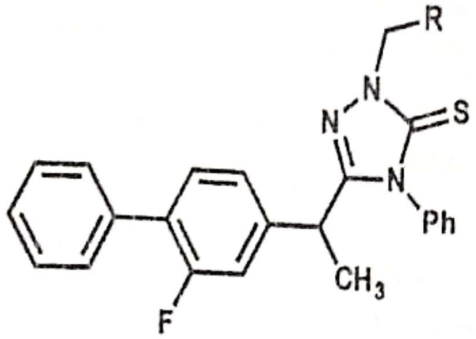
A solution of N^1 -[2- (2- Fluorobiphenyl-4-yl) propionyl]-N^4- phenylthiosemicarbazide (3.93g, 10 mmol) in NaOH (2N, 20ml) was heated at reflux for 2 h. The reaction mixture was cooled and acidified with dilute HCl. The crude product was extracted with CH_2Cl_2 (2x50ml), dried (anhydrous Na_2SO_4) ,and recrystallized from aqueous EtOH to give 3.38 g (90%) of the title compound; mp 194-197°C. Analysis: Calcd for $C_{22}H_{18}FN_3S$: C, 70.40; H, 4.80 ; N, 11.20 and Found : C, 70.6; H, 4.7; N, 110.

3-[1-(2-fluorobiphenyl-4-yl) ethyl]-4-phenyl-1- substituted methyl-Δ^2, 1,2,4,-triazoline -5-thione IV (a-e):

General procedure :

A mixture of 3-[1-(2-fluorobiphenyl-4-yl) ethyl]-4-phenyl- 1, 2, 4,-triazole-5- thiol (3.85g 10 mmol), formalin 37% (30 mmol) and the appropriate secondary amine (10 mmol) in absolute EtOH (20ml) was stirred at room temperature for 1h. The reaction mixture was then refrigerated overnight and the separated solid was filtered, washed with H_2O and

Table (4) : 3-[1-(2-fluorobipheny-4-yl) ethyl-4-phenyl-1-substituted methyl-Δ2 -1,2,4- triazoline-5 thione **IV (a-e) :**



Group	R	m.p °C	Yield %	Formula	Analysis	
					Calcd	Found
IVa	Piperidino	122-124	72	$C_{28}H_{29}FN_4S$	C =71.19 H = 6.14 N =11.86	71.2 6.0 11.7
IVb	Morpholino	146-149	76	$C_{27}H_{27}FN_4OS$	C = 68.35 H = 5.70 N =11.81	68.1 5.7 12.0
IVc	Pyrrolidino	128-130	71	$C_{27}H_{27}FN_4OS$	C = 70.74 H = 5.90 N = 12.23	70.7 6.0 12.5
IVd	Diethylamino	92-95	67	$C_{27}H_{29}FN_4S$	C = 70.43 H = 6.30 N = 12.17	70.6 6.2 12.3
IVe	N-methyl-N-phenylamino	102-104	69	$C_{30}H_{27}FN_4S$	C = 72.87 H = 5.47 N = 11.34	72.7 5.5 11.2

recrystallized from aqueous EtOH (Table 4). ^{1}H-NMR ($CDCl_3$) of compound **IVa :** δ 1.4-1.9 (br s, 9H, 3 CH_2, CH_3), 2.6 - 3.0 (br s, 4H, $2CH_2$), 3.8-4.1 (q, 1H, CH), 5.3 -5.5 (s, 2H, CH_2) 6.8 - 8.0(m, 13H, Ar-H).

3-[1-(2-fluorobiphenyl-4-yl) ethyl] -5-phenyl -5-methylthio - 1,2-4 triazole (V):

A mixture of 3-[1-(2-fluorobiphenyl -4-yl)ethyl] -4- phenyl- 1, 2, 4,-triazole-5- thiol (3.85 g, 10 mmol), CH_3I (1.42 g, 10 mmol) and anhydrous K_2CO_3 (2.80 g, 20 mmol) in dry acetone was heated at reflux for 8h. The reaction mixture was filtered while hot; the filtrate was concentrated by distillation under reduced pressure, and extracted with CH_2Cl_2 (2 x 50ml). The organic extract was washed with H_2O (100 ml), dried (Na_2SO_4), and evaporated under reduced pressure to give 3.40g (87%) of the title compound as an oil. ^{1}H-NMR ($CDCl_3$) :δ 1.6-2.0 (d, 3H, CH_3), 2.5 - 2.8 (s, 3H, SCH_3) , 3.8-4.2 (q, 1H, CH), 6.8 - 8.0 (m, 13H, Ar-H).

2-[1-(2-fluorobiphenyl-4-yl) ethyl] -5-phenylamino--1,2-4 oxadiazole (VI):

To a solution ofN^1- [2(2- fluorobipheny 1-4-yl) propionyl] -N^4-phenyl thiosemicar-bazide (3.93 g, mmol) in EtOH (30ml) , aqueous NaOH (2N, 5ml) was added with cooling and shaking . An aqueous solution of I_2 in KI (5%) was then added with cooling and stirring until the colour of iodine is persisted. Excess solvent was removed under reduced pressure. The residue was acidified with HOAc (10%) and extracted with CH_2Cl_2 (2x 50ml). The combined organic extract was washed with H_2O (100ml) , dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was recrystallized from absolute EtOH to afford 2.44

g(68%) of the title compound, mp 128 - 131°C; IR (KBr, cm^{-1}) : 3300 (NH). Analysis : Calcd for $C_{22}H_{18}FN_3O$: C, 73.54; H, 5.01; N, 11.7 and Found : C, 73.4; H, 5.0; N, 11.6.

Acetylacetone 2-(2-florobiphenyl- 4-yl) propionic acid hydrazone (VII):

A mixture of 2-(2- fluorobiphenyl-4-yl) propionic acid hydrazide (2.58 g, 10 mmol) and acetylacetone (1.0 g, 10 mmol) in absolute EtOH was heated at reflux for 4h. The reaction mixture was evaporated under reduced pressure. The residue was suspended in H_2O (10 ml) and extracted with CH_2Cl_2 (2 x 50 ml) . The combined organic extract was washed with H_2O (50ml) , dried (Na_2SO_4) , and evaporated under reduced pressure to give 2.90 g (85%) of the title compound as an oil. IR ($CHCl_3$, cm^{-1}) : 3220 (NH), 1720 (C=O ketone), 1660 (C=O hydrazone). The compound was used without further characterization in the synthesis of compound **VIII.**

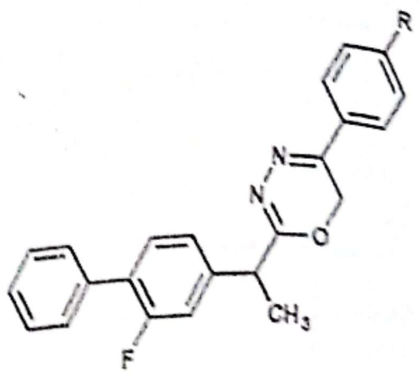
1-[2-(2-Fluorobiphenyl-4-yl) propionyl]-3, 5 dimethylpyrazole (VIII) :

A mixture of acetylacetone 2 (2- fluorobiphenyl-4-yl)propionic acid hydrazone (3.40 g, 10 mmol) and 2N ethanolic KOH (20 ml) was allowed to stand at room temperature for 1h. The separated solid was filtered , washed with cold EtOH, and recrystallized from aqueous EtOH to afford 2.87 g (89%) of the title compound as white crystals; mp 85.87°C, IR (KBr, cm^{-1}): 1660 (C=O). Anal. Calcd for $C_{20}H_{19}FN_2O$: C, 74.53; H, 5.90 ; N, 8.70. Found : C, 74.4; H, 5.9; N, 8.6.

1-[2-(2-Fluorobiphenyl-4-yl)propionamido]-2,5-dimethyl pyrrole (IX):

A mixture of 2-(2- fluorobiphenyl -4-yl) propionic acid hydrazide (2.58 g, 10 mmol) and acetonylacetone (1.14 g, 10 mmol) in glacial HOAc (25ml) was stired at room temperature for 12 h. The reaction mixture was poured onto ice water (100ml) and extracted with CH_2Cl_2 (2 x 50) . The combined organic extract was washed with H_2O (100ml) , dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was recrystallized from absolute EtOH to give 3.06 g (91%) of the title compound; mp 138-141°C ; IR (KBr, cm^{-1}) : 3250 (NH), 1660 (C=O). Anal. Calcd for $C_{21}H_{21}FN_2O$: C,75.00; H, 6.25; N, 8.33. Found : C, 75.0; H, 6.1; N,8.4.

Table 5: 2-[1-(2-Fluorobiphenyl-4-yl) ethyl] -5-substituted phenyl-1,3,4-(6H) -oxadiazines (**Xa-c**).



Group	R	m.p.°C	Yield %	Formula	Analysis	
					Calcd	Found
Xa	H	212-214	58	$C_{26}H_{20}FN_2O$	C = 77.09 H = 5.31 N = 7.82	76.08 5.3 7.7
Xb	Cl	142-145	67	$C_{26}H_{19}FCLN_2O$	C = 70.52 H = 4.59 N = 7.13	70.1 4.6 7.0
Xc	Br	131-133	60	$C_{26}H_{19}FBrN_2O$	C = 63.16 H = 4.12 N = 6.41	63.4 4.0 6.4

2-[1-(2-Fluorobiphenyl-4-yl) ethyl]-5-substituted henyl-1,3,4-(6H) - oxadiazines (Xa-c):

General procedure :

A mixture of 2-(2-fluorobiphenyl -4-yl) propionic acid hydrazide (2.58g, 10 mmol) , the appropriate phenacyl halide (10 mmol), and anhydrous CH_3COONa (1.6g, 20 mmol) in absolute EtOH was heated at reflux for 4h. The reaction mixture was filtered while hot and the filtrate was concentrated by distillation under reduced pressure and the residue was extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extract was washed with H_2O (100 ml), dried (Na_2SO_4) , and evaporated under reduced pressure. The crude product was recrystallized from absolute EtOH to afford the title compounds in 58-67% yield (Table 5).

Zagazig J. Pharm. Sci., June 1998
Vol. , No. , pp. 94 - 100

ACKNOWLEDGEMENT

The authors would like to thank Dr. Atef Saad for performing the pharmacological screening and Al Kahira Pharm. & Chem. Ind. Co. for supplying the samples of flurbiprofen.

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Received : March 14, 1998
Accepted : April 22, 1998

التشييد والفاعلية البيولوجية لبعض المشتقات الجديدة الحلقية الغير متجانسة للفلورباي بروفين

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تم فى هذا البحث تشييد بعض مشتقات جديدة حلقية غير متجانسه وغير حامضية من فلورباى بروفين ميثيل بيرازول، بيرول ، أوكسى ديازول ، أوكسى ديازين وتريازول . وقد تأكد التركيب البنائى باستخدام تحليل العناصر وكذلك الأجهزة الطيفية المختلفة .

وقد تم دراسة التأثير الأقربازينى لثلاثة من هذه المركبات وقد ثبت أن لبعضها تأثير فارماكولوجي عالى بالمقارنه بفلورباى بروفين كمسكن للألم وخافض للحرارة ومضاد للإلتهاب.