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SYNTHESIS AND BIOLOGICAL ACTIVITY OF CERTAIN FLURBIPROFEN DERIVATIVES

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ABSTRACT

The synthesis of several flurbiprofen amides and hydrazones is described. Structures of the new compounds were substantiated by microanalytical and spectroscopic data. Five representative compounds were subjected to preliminary pharmacological screening which revealed that three of them exhibited superior analgesic, antipyretic and anti-inflammatory activities compared to flurbiprofen.

INTRODUCTION

Cetainly, aryl and heteroarylalkanoic acids have been one of the most widely explored groups of non-steroidal compounds for potential antiinflammatory activity[1,2]. Unfortunately, the use of this class of compounds is not quite safe, they are likely to cause gastrointestinal ulceration. This ulcerogenic effect could be ascribed to the presence of a free carboxyl function in their structures[3,4].

Literature survey revealed that blocking of the acidic function in non-steroidal anti-inflammatory agents such as aspirin, diclofenac, flufenamic acid, indomethacin and tolmetin by convertion to the ester function results in prodrugs almost devoid of gastric ulcerogenic activity with retention of full therapeutic effectivenes. This is certainly due to rapid hydrolysis following absorption[5].

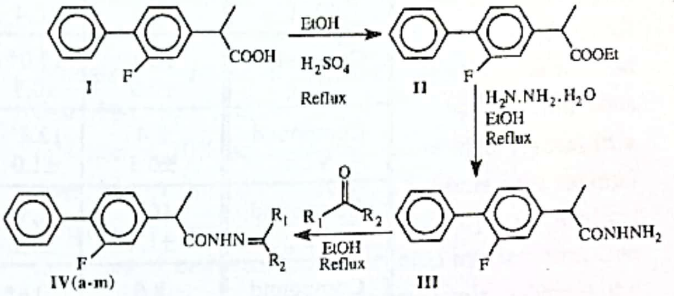
In view of the forementioned findings, our research efforts were directed towards the reduction of ulcerogenicity of these compounds through modification of the carboxylic group to other less acidic functions.

Hopefully the new derivatives might be less harmful and at the same time equipotent. Surprisingly, some of the new compounds were fund to be more potent than the starting alkanoic acid.

In this work, Flurbiprofen, being one of the arylalkanoic acids marketed in Egypt, was selected as a tool for our investigation. Two series of amides and hydrazones derived from flurbiprofen were prepared and tested for analgetic, antipyretic and anti-inflammatory activities in comparison with the parent acid.

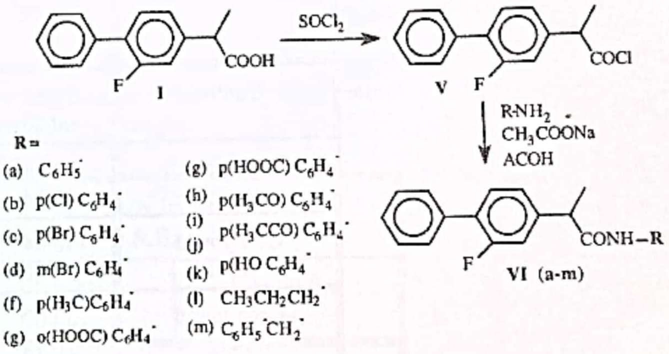
The sequence of reactions adopted for the synthesis of the designed compounds is illustrated in the following schemes:

The ethyl ester (II) was prepared classically, by refluxing flurbiprofen (I) in absolute ethanol in the presence of concentrated sulphuric acid.



	R_1	R_2
(a)	H	$C_6H_5^{\cdot}$
(b)	H	$C_6H_5^{\cdot}CH{=}CH-$
(c)	H	$P(Cl)C_6H_4^{\cdot}$
(d)	H	$P(H_3CO)C_6H_4^{\cdot}$
(e)	H	$P(HO)\,C_6H_4^{\cdot}$
(f)	H	$P(H_3C)_2NC_6H_4^{\cdot}$
(g)	CH_3	$C_6H_5^{\cdot}$
(h)	CH_3	$p(Cl)\,C_6H_4^{\cdot}$
(i)	CH_3	$p(Br)\,C_6H_4^{\cdot}$
(j)	CH_3	$p(H_3C)C_6H_4^{\cdot}$
(k)	CH_3	$p(H_2N)\,C_6H_4^{\cdot}$
(l)	CH_3	CH_3
(m)	CH_3	iso (C_4H_9)

Scheme I



R =
(a) $C_6H_5^{\cdot}$
(b) $p(Cl)\,C_6H_4^{\cdot}$
(c) $p(Br)\,C_6H_4^{\cdot}$
(d) $m(Br)\,C_6H_4^{\cdot}$
(f) $p(H_3C)C_6H_4^{\cdot}$
(g) $o(HOOC)\,C_6H_4^{\cdot}$
(g) $p(HOOC)\,C_6H_4^{\cdot}$
(h) $p(H_3CO)\,C_6H_4^{\cdot}$
(i) (j) $p(H_3CCO)\,C_6H_4^{\cdot}$
(k) $p(HO\,C_6H_4^{\cdot}$
(l) $CH_3CH_2CH_2^{\cdot}$
(m) $C_6H_5^{\cdot}CH_2^{\cdot}$

Scheme II

The hydrazide (III) was prepared in 91% yield through hydrazinolysis of the ethyl ester (II) in refluxing ethanol using hydrazine hydrate in excess to avoid formation of the bishydrazide[6]. The hydrazones $IV_{(a-m)}$ were prepared by refluxing equimolecular amounts of the hydrazide (III) and the appropriate carbonyl compounds in ethanol. It is noteworthy that aldehydes gave better yields than ketones.

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 f	7.4 ±0.5	9.2* ±0.4	10.6* ±0.7	11.4* ±1.2	10.2* ±0.5	10.6* ±0.4	10.8* ±0.5
Compound IV g	10.4 ±0.5	12.0* ±0.7	14.0* ±0.3	19.6* ±1.9	18.2* ±1.0	17.0* ±2.0	13.0* ±1.0
Compound VI b	8.4 ±0.5	12.8* ±1.0	15.2* ±1.0	22.6* ±1.5	24.4* ±2.0	18.2* ±1.5	13.4* ±1.0
Compound VI g	10.6 ±1.4	11.4* ±1.2	14.0* ±1.2	18.6* ±1.0	16.4* ±2.0	13.6* ±1.5	11.8* ±0.6
Compound VI k	8.6 ±0.1	10.8* ±1.2	11.4* ±0.8	14.2* ±0.7	15.4* ±0.7	12.0* ±0.3	11.4* ±0.6

* Significant at $P < 0.05$.

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

Groups	Rectal temp. Before yeast	Rectal temp. After yeast	Rectal temp. after treatment Mean value ± S.E		
			1 hour	2 hours	3 hours
Control	36.84 ±0.26	37.72 ±0.20	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 IV f	36.84 ±0.20	37.84 ±0.19	*36.66 ±0.36	*36.48 ±0.34	*36.44 ±0.31
Compound IV g	37.00 ±0.18	38.06 ±0.11	38.02 ±0.16	37.94 ±0.20	37.68 ±0.22
Compound VI b	37.80 ±0.15	37.83 ±0.26	*36.92 ±0.31	*36.80 ±0.34	*36.96 ±0.27
Compound VI g	36.60 ±0.19	37.62 ±0.30	*37.06 ±0.14	*36.98 ±0.17	*36.92 ±0.20
Compound VI k	36.80 ±0.16	37.48 ±0.16	*37.06 ±0.19	*37.04 ±0.21	37.12 ±0.26

* Significant at $P < 0.05$.

On the other hand, carbonyl compounds having electron withdrawing substituents gave better yeilds than those having electron-releasing substituents. This could be attributed to a combination of electronic and steric effects. The acid chloride (V) was prepared in 94% yield by refluxing the parent acid (I) with thionyl chloride neat for one hour(7).

The amides $VI_{(a-m)}$ were prepared following a reported procedure(8) by stirring a mixture of the acid chloride (V) and the appropriate amine in glacial aacetic acid in the presence of sodium acetate at room temperature. As anticipated, electrondonors raised the reactivity of the amine component while electron-attractors decreased it.

PHARMACOLOGICAL SCREENING

Five of the synthesized compounds IV_f, IV_g, VI_b, VI_g and VI_k were tested for theanalgesic, antipyretic and anti-inflammatory activities compared to flurbiprofen. Compound VI_b showed pharmacological activities superior to flurbiprofen in all aspects. It is a more potent analgetic, antipyretic and antiinflammatory as well. Compound VI_g showed greater antipyretic and antiinflammatory activities than flurbiprofen while failed to produce any significant antiinflammatory activity. Compounds IV_f and VI_k showed inferior activity compared to the parent acid.

A. Analgesic activity :

The hot plate method for Jacob and Bosoviski(9) was applied to evaluate the analgesic activity. 35 mature albino mic of both sexes weighin 15-20 gm were divided into seven groups (5 mice each). The first group was injected with the solvent only and kept as control. The second one was injected (i.p) with flurbiprofen (20 mg/kg). Five minutes later, each mouse was placed in a two-litres beaker immersed in a water bath thermostatically controlled at 65.5°C. The time elapsed until the mouse licks the paws was calculated as a measure for the analgesic effect. Recordings were taken (10, 20, 30, 60, 90 and 120 minutes) post treatment (Table 1).

B. Antipyretic activity:

35 mature albino rats of both sexes (200 - 250 gm) were divided into seven groups (5 rats each). All animals were rendered hyperthermic using the method described by Teotino et al.,(10) by subcutaneous injection of 20% aqueous suspension of dry yeast in a dose of 0.1 ml/100 g. After 15 hours, the animal temperature was taken recteally by a medical thermometer and recorded as the inital temperature. One group was saved as control hyperthermic, whereas the second group was i.p. injected with flurbiprofen (20 mg/kg).

The test compounds were given (i.p.) in a dose of 20 mg/kg for the remaining five 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 the solvent (DMSO) (Table 2).

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

Group	Thickness of paw skin in mm. (Mean value ± S.E).		
	4 hrs after yeast administration	3 hrs after treatment	6 hrs after treatment
Control	7.38±0.29	7.5±0.30	7.64±0.26
Flurbiprofen	7.35±0.22	* 5.75±0.12	* 5.13±0.10
Compound IV f	6.57±0.30	6.61±0.28	6.35±0.30
Compound IV g	7.55±0.48	* 6.74±0.36	* 6.66±0.46
Compound VI b	7.50±0.10	* 5.60±0.10	* 5.12±0.08
Compound VI g	7.29±0.30	* 4.78±0.30	* 4.67±0.20
Compound VI k	7.06±0.23	* 5.84±0.34	* 5.93±0.33

* Significant at $P< 0.05$.

Table (4) : Arylidene or alkylidene 2- (2-flurobipheny1-4-yl) propionic acid hydrazones (IV_{a-m}).

Ser. No.	R_1	R_2	Yield %	M.P. C°	Solvent of crystallization	Formula	Analysis	
							Calcd.	Found
a	H	C_6H_5-	86	202	ethanol	$C_{22}H_{19}FN_2O$	C=76.30 H=5.49 N=8.09	76.11 5.5 7.9
b	H	C_6H_5-CH=CH-	86	156	ethanol	$C_{24}H_{21}FN_2O$	C=77.41 H=5.64 N=7.52	77.3 5.7 7.4
c	H	P(Cl) C_6H_4-	88	169	aq.ethanol	$C_{22}H_{18}FClN_2O$	C=69.38 H=4.73 N=7.36	69.5 4.7 7.5
d	H	P(CH_3O)C_6H_4-	85	163	aq.ethanol	$C_{23}H_{21}FN_2O_2$	C=73.40 H=5.59 N=7.45	73.1 5.6 7.4
e	H	P(HO)C_6H_4-	83	220	chloroform/ pet.ether	$C_{22}H_{19}FN_2O_2$	C=72.93 H=5.25 N=7.73	73.2 5.0 7.6
f	H	P$(CH_3)_2NC_6H_4$-	82.5	152	aq.ethanol	$C_{24}H_{24}FN_3O$	C=74.04 H=6.17 N=10.80	73.7 6.1 11.0
g	CH_3	C_6H_5-	82	192	ethanol	$C_{23}H_{21}FN_2O$	C=76.67 H=5.83 N=7.78	76.4 5.7 7.7
h	CH_3	P(CL)C_6H_4-	84	185	aq.ethanol	$C_{23}H_{20}FCLN_2O$	C=69.96 H=5.07 N=7.10	70.2 5.0 6.9
i	CH_3	P(Br)C_6H_4-	83	188	aq.ethanol	$C_{23}H_{20}FBrN_2O$	C=62.87 H=4.56 N=6.38	62.6 4.6 6.3
j	CH_3	P(H_3C)C_6H_4-	81	176	aq.ethanol	$C_{24}H_{23}FN_2O$	C=70.01 H=6.15 N=7.49	69.7 6.3 7.5
k	CH_3	P(H_2N)C_6H_4-	80	145	aq.ethanol	$C_{23}H_{22}FN_3O$	C=73.60 H=5.87 N=11.20	73.6 6.0 11.4
l	CH_3	CH_3	78	122	aq.ethanol	$C_{18}H_{19}FN_2O$	C=72.48 H=6.38 N=9.40	72.1 6.3 9.5
m	CH_3	iso (C_4H_9)	77	134	aq.ethanol	$C_{21}H_{25}FN_2O$	C=74.12 H=7.35 N=8.24	74.0 7.2 8.5

Table (5) : 2-(2-Fluorobiphenyl-4-yl)-N-substituted propionamide (VI_{a-m}).

Ser. No.	R	M.P.C°	Yield %	Formula	Analysis	
					Calcd.	Found
a	C_6H_5-	105	92	$C_{21}H_{18}FNO$	C=78.99 H=5.64 N=4.39	78.8 5.7 4.3
b	p(Cl)C_6H_4-	118	90	$C_{21}H_{17}FCLNO$	C=71.29 H=4.80 N=3.96	71.0 4.8 3.8
c	p(Br) C_6H_4-	120	89	$C_{21}H_{17}FBrNO$	C=63.32 H=4.27 N=3.52	63.3 4.1 3.4
d	m(Br)C_6H_4-	130	87	$C_{21}H_{17}FBrNO$	C=63.32 H=4.27 N=3.52	63.2 4.2 3.6
e	o(H_3C)C_6H_4-	121	88	$C_{22}H_{20}FNO$	C=79.28 H=6.01 N=4.20	79.4 5.8 4.2
f	p(H_3C)C_6H_4-	112	90	$C_{22}H_{20}FNO$	C=79.28 H=6.01 N=4.20	79.1 5.8 3.9
g	o(HOOC)C_6H_4-	115	89	$C_{22}H_{18}FNO_3$	C=72.73 H=4.96 N=3.86	72.5 4.8 3.9
h	p(HOOC)C_6H_4-	116	91	$C_{22}H_{18}FNO_3$	C=72.73 H=4.96 N=3.86	72.6 4.9 4.0
i	p(CH_3O)C_6H_4-	126	93	$C_{22}H_{20}FNO_2$	C=75.64 H=5.73 N=4.01	75.6 5.5 4.0
j	p(CH_3CO)C_6H_4-	136	91	$C_{23}H_{20}FNO_2$	C=76.45 H=5.54 N=3.88	76.3 5.4 3.9
k	p(HO)C_6H_4-	133	94	$C_{21}H_{18}FNO_2$	C=75.22 H=5.37 N=4.18	75.0 5.3 4.1
l	$CH_3CH_2CH_2$-	109	94	$C_{18}H_{20}FNO$	C=75.79 H=7.02 N=4.91	75.6 6.9 4.9
m	C_6H_5 CH_2-	124	92	$C_{22}H_{20}FNO$	C=79.28 H=6.01 N=4.20	79.5 6.0 4.1

C. Anti-inflammatory activity:

Seven groups, each of 5 mature albino rats (200 - 250 gm) of either sex were used. Oedema was induced by the injection of dry yeast into the skin of their hind limp paw (0.1 ml of 20% dry yeast in aqueous solution) according to the method described by Alpermann(11). 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).

EXPERIMENTAL

All melting points are uncorrected. Microanalyses were carried out by the microanalytical unit, Cairo University. IR spectra were carried out using Pye Unicam SP 1100 spectrophotometer. The ^{1}H-NMR spectra were recorded on a Varian EM-390, 90 MHz spectrophotometer. The chemical shift values were recorded in δ (ppm) relative to tetramethylsilane (TMS) as internal standard.

Ethyl 2- (2-fluorobiphenyl-4-yl) propionate (II):

I (2.44 gm, 0.01 mole) was dissolved in absolute ethanol (20 ml) and few drops of concentrated sulphuric acid were added to the solution. The mixture was refluxed for 4 hours. Excess ethanol was distilled under reduced pressure. The crude oil was neutralized with aqueous sod bicarbonate, extracted twice with chloroform (2 x 100 ml) and the combined organic extract was dried over anhydrous sod. sulphate. Chloroform was then distilled under reduced pressure and a thick syrupy oil was obtained. Yield (2.54 gm, 93.4%). IR ($CHCl_3$, CM^{-1}): 3080 (C-H aromatic), 2900 (C-H aliphatic), 1730 (C=O).

2- (2-Fluorobiphenyl-4-yl) propionic acid hydrazide (III):

A mixture of **II** (2.72 gm, 0.01 mole) and hydrazine hydrate (0.55 gm, 0.011 mole) in absolute thanol (20 ml) was refluxed for 4 hours. Excess solvent was removed by distillation under reduced pressure and the obtained residue was filtered, dried and recrystallized from aqueous ethanol. the yield was (2.35 g, 91.1%) and m.p. 120°C

	C%	H%	N%
Calculated (for $C_{15}H_{15}FN_2O$)	69.76	5.81	10.85
Found	69.60	5.80	11.10

IR ($CHCl_3$, cm^{-1}) : 3280 (NH), 3080 (C-H aromatic) 2920 (C-H aliphatic), 1600 (C=O)

Arylidene or alkylidene 2-(2-fluorobiphenyl-4-yl)-propionic acid hydrazones IV(a-m). (Table 4)

General procedure:

A mixture of III (2.58 gm, 0.01 mole) and the appropriate carbonyl compound (0.01 mole) in absolute ethanol (20 ml) was heated under reflux for 3 hours. excess ethanol was distilled under reduced pressure and the remained residue was filtered, dried and recrystallized from the appropriate solvent.

IR (KBr, cm^{-1}) of compound No (**IV a**): 3250 (NH); 3100 (C-H aromatic); 2900 (C-H aliphatic); 1650 (C=O)

IR (KBr, cm^{-1}) of compound No (**IV e**): 3500 - 3200 (OH, NH overlapped); 3100 (C-H aromatic); 2880 (C-H aliphatic); 1650 (C=O)

^{1}H-NMR (DMSO-D_6, ppm) of compound No. (**IVb**):

δ 1.3-1.6 (d, 3H, CH_3), δ 3.7-4.0 (q, 1H, $CHCH_3$), δ 6.6-8.4 (m, 16H, aromatic protons + vinylic protons + azomethine proteon). δ 11.8 (s, 1H, NH)

2- (2-Fluorobiphenyl-4-yl) propionyl chloride (V)

A mixture of I (2.44 gm, 0.01 mole) and thionyl chloride (10 ml) was refluxed for one hour. Excess thionyl chloride was removed by distillation under reduced pressure and the crude praduct wa collected as an oily liquid which was used for next experiment yield 2-49 gm (94.9°6).

IR ($CHCL_3$, Cm^{-1}): 3080 (C-H aromatic), 2920 (C-H aliphatic), 1800 (C=O).

General procedure:

A mixture of V (2.63 gm, 0.01 mole) in glacial acetic acid and a saturated aqueous solution of sod. acetate were concurrently added while stiring to a solution of the appropriate amine (0.1 mole) in glacial acetic acid. Stirring was continued for one hour during which a heavy precipitate ws obtained. The reaction mixture was then poured into ice-cold sod. chloride solution and the separated solid was filtered, dried and recrystallized from aqueous ethanol.

IR (KBr, cm^{-1}) of compound No (**VI h**): 3400-2500 (hump of carboxyl overlapping NH and CH streching); 1700 (C=O of carboxyl); 1650 (C=O of amide)

IR (KBr, cm^{-1}) of compund No. (**VI j**): 3220 (NH); 3100 (C-H aromatic); 2920 (C-H aliphatic); 1715 (C=O of ketone); 1660 (C=O of amide).

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التشيد والفاعلية البيولوچية لبعض مشتقات فلوربايبروفين

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تم فى هذا البحث تشييد بعض مشتقات فلوربايبروفين مثل الأميدات والهيدرازونات وقد تأكد التركيب البنائى باستخدام تحليل العناصر وكذلك الأجهزة الطيفية المختلفة.

وقد تم دراسة التأثير الأفريازينى لخمسة من هذه المركبات وقد ثبت أن بعضها له تأثير فارماكولوجى عالى بالمقارنة بمركب فلوربيروفين كمسكن للألم وخافض للحرارة ومضاد للالتهابات.