Zag. J. Pharm . Sci, Vol 2, No 1, June 1993

SYNTHESIS AND PRELIMINARY TESTING OF SOME ANTHRANILIC ACID DERIVATIVES AS ANTIINFLAMMATORY, ANALGESIC AND ANTIPYRETIC AGENTS

Mansour Abou Kull , Sayed Lashine , Abdulla El Shanawany, Nageh Abou Taleb and Magdy Amer *

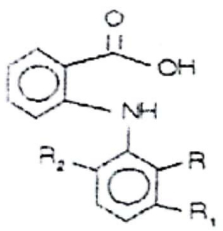
DEPARTMENT OF MEDICINAL CHEMISTRY , FACULTY OF PHARMACY, ZAGAZIG UNIVERSITY AND * FACULTY OF VETERINARY MEDICINE , SEUZ CANAL UNIVERSITY, EGYPT

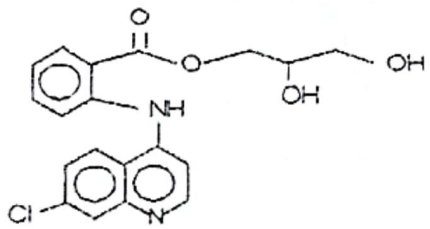
ABSTRACT

A series of N - [3 - chloro -N- substituted phenyl -2- maleimidyl] anthranilic acid and its methyl ester were prepared. The reaction of either IV or V with potassium thiocyanate afforded quinazolinone thione derivatives. four of the prepared new compounds were screened pharmacologically for their antiinflammatory , analgesic and antipyretic properties .

INTRODUCTION

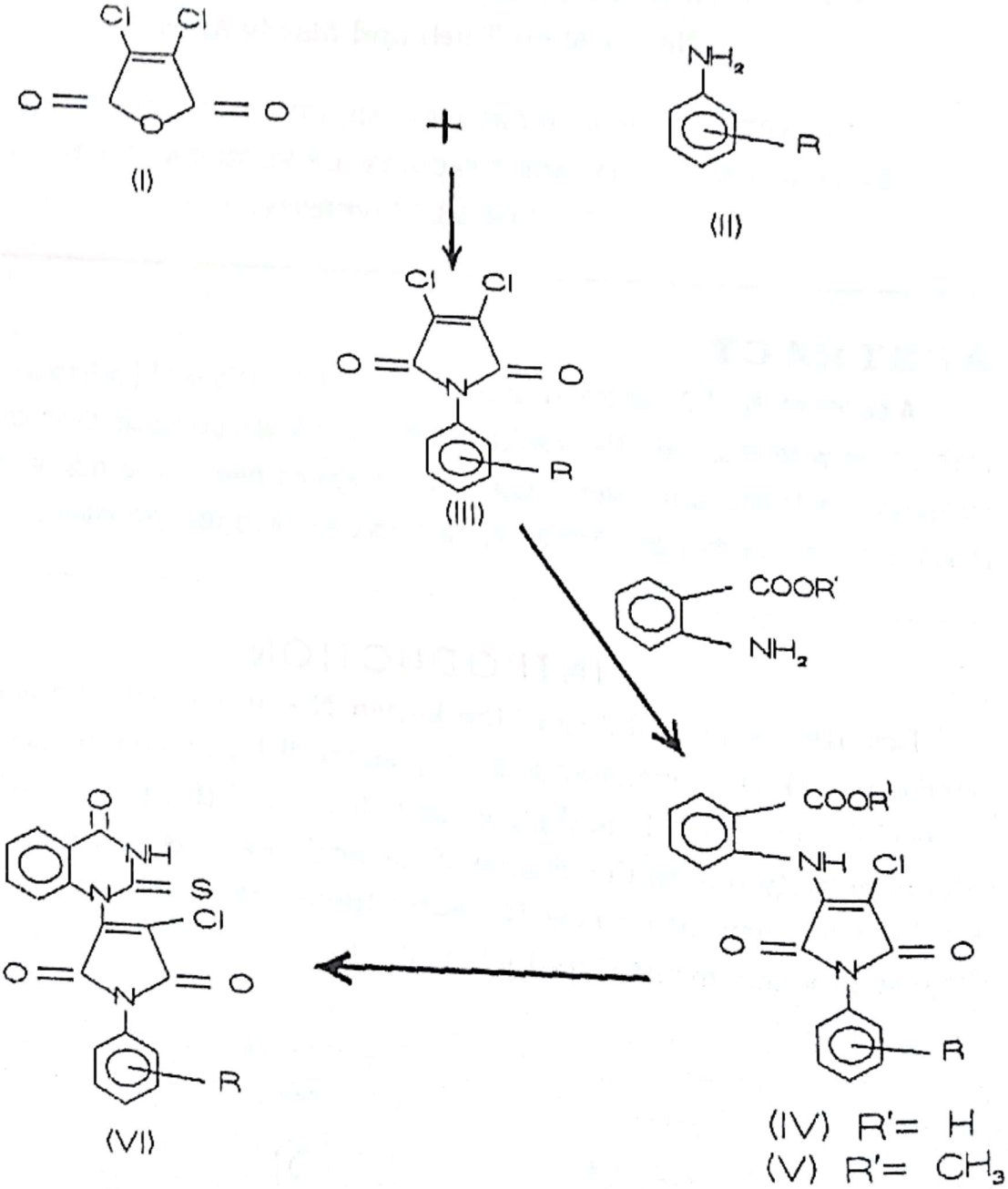
Despite the availability of the known N - arylanthranilic acid and its ester drugs (1,2) as mefenamic acid (ponstan)^{R} Ia, flufenamic acid (Arlef)^{R} Ib, meclofenamic acid Ic and glifenine (Glifenan)^{R} II , the variation in the ratio of activity due to the change of the aryl moeity is still motivating the searchers for generating new N - substituted anthranilic acid derivatives. The new products might show high activities .





	R	R_1	R_2
a	CH_3	CH_3	H
b	H	CF_3	H
c	Cl	CH_3	Cl

SCHEME I



R; a=H, b=p-Cl, c=m-Cl, d=p-CH_3, e=p-CH_3O-, and f=p-Br.

RESULTS AND DISCUSSION

The intermediates 2,3 - dichloro - N- substitutedphenyl - maleimide (III a - f) were prepared according to the reported procedure (3) through the reaction of 2,3 - dichloromaleic anhydride with the appropriate aniline derivatives . The reaction of the compound (III a - f) with either anthranilic acid or its methyl ester resulted in the formation of N - [3- chloro - N - substituted pheny1-2 - maleimidyl] anthranilic acid methyl ester (Va -f) .

In addition , 1-[3- chloro - N - substituted phenyl -2 - maleimidyl] -4 (3H) quinazolinone - 2 - thione (VIa - f) were prepared through the reaction of either IV or V with potassium thiocyanate . The yield was much higher when using the ester (V) . ^{1}H - NMR spectrum of compound (VIa -f) showed the disappearance of the singlet at δ 4.0 ppm corresponding to - OCH_3 of the ester moiety and the appearance of a singlet at δ 10.7 ppm corresponding to $\overset{N-H}{C=S}$ which is differ from the NH of compound (V) which appeared at δ 10. 2 ppm,.The cyclization of the product 1-[3-chloro - N - substituted phenyl - 2 maleimidyl] -4 (3H) quinazolinone - 2 - thione (VI) did not take place.

Pharmacological Screening :

Four of the newly prepared compounds IVa, Ve, Vf and VIe were screened for their anti inflammatory, analgesic and antipyretic properties .

1- Antiinflammatory effect

36 Mature Albino rats of both sexes weighing 190 - 210 gm , divided into six equal groups were used. Oedema in the rat paw was induced by injecting 0. 1 mL of 20 % Brewer's yeast suspended in physiological saline solution in the paw skin of the hind limb (4) . After 4 hours , the thickness of the paw was measured using a skin calibre to detect the inflammation induced by the yeast. The first group was left as control , while the second group was i.p. injected with mefenamic acid (25 mg / kg, as standard) . The remaining groups were treated with the tested compounds dissolved in ethylene glycol in a dose of 20 mg / kg . The paw thickness was measured after 3 and 6 hours post injection .

2- Antipyretic activity

Six groups of mature Albino rats (200 - 220 gm) each of 6 animals were rendered hyperthermically by the subcutaneous injection of 20 % Brewer's yeast suspension (0.1 mL / 100 gm) (5)

Fifteen hours later, the body temperature was taken rectally by a medical thermometer and recorded as the initial temperature. The first group was left as control .Whereas, the second group was injected i.p with mefenamic acid as a reference drug (25mg / kg). The tested compounds , dissolved in ethylene glycol were given in a dose of 20 mg/kg for the other groups . Then the rectal temperature was recorded every hour for a period of 3 hours .

3- Analgesic effect

The hot plate method (6) was applied. Mature Albino mice of both sexes weighing 20 - 25 gm were divided into 6 groups each of 6 animals . The first group was left as control , while the second group was i.p. injected with mefenamic acid in a dose of 25 mg/kg, the other groups were i.p. ingected with the test drugs (dissolved in ethylene glycol) in a dose of 20 mg/kg . Five minutes later, each mouse was placed in two liter beaker immersed in water bath thermostatically controlled at 56° C. The elapse time till the mouse liks or jumps was considered 10,20 ,30,60 ,90 and 120 minutes post treatment.

The results were reported as the mean ± S.E. Statistical significance was determined using student (t) test according to Snedecor (7) .

RESULTS

It was clear from table (1) that i.p. injection of the test compounds in a dose of 20 mg / kg of rats induced a significant decrease ($p < 0.01$) in the thickness of the paw skin after 3 hours from their administration. Significant decrease ($p < 0.001$) that was the some as in the case of mefenamic acid , especially with compounds IVa , Ve and VId .

The i.p. injection of the tested compounds was found to produce a significant decrease ($p < 0.01$) in body temperature in rats when given compounds IVa, Ve and VId at a dose 20 mg/kg. An effect which was superior than that induced by mefenamic acid. Compound Vf (20 mg / kg)

TABLE (1) The ant-inf lammatory activity of compounds Iva, ve, v f and VId on rats after their administratiqn I.P in a dose of 20 mg/kg body weight.

Compound (group treament)	Thickness of the paw skin (mm)			
	Before administ. Brewer's yeast	After 4hrs from. administ.(B.Y.)	3 hrs post treat.(drug)	6 hrs post treat. (drug)
Brewer's Y. 0.1 ml[20%]	1.95±0.05	7.4±0.14	5.9±0.06	5.6±0.19
Mefenamic acid 25mg/k	1.9±0.09	7.5±0.18	4.6±0.26**	3.25±0.43**
Compound IVa	1.85±0.03	6.8±0.62	4.2±0.5*	2.5±0.2**
Compound Ve	1.98±0.03	7.05±0.05	4.55±0.32	2.3±0.03**
Compound Vf	1.9±0.06	6.33±0.35	4.15±0.27*	3.38±0.38*
Compound VId	1.9±0.04	6.25±0.25	4.75±0.25*	2.75±0.48**

* p<0.01 (significant)

** p<0.001(highly significant)

TABLE (2) The antipyretic activity of Compounds Tva, Ve, Vf and VId on rats afler their administration in a dose of 20 mg/kg.

Compound group treatment)	The rectal temperature				
	Before yeast administ.	15 hrs after Y. administ.	1 hr after treatment	2 hr after treatment	3 hr after treatment
1st group (control)	36.4±0.32	38.6±0.1	38.8±0.24	37.5±0.42	37.1±0.27
2nd group Mefenamic acid	36.2±0.21	38.9±0.23	36.7±0.59*	35.1±0.38*	35.4±0.35*
3rd group Comp. IVa	36.3±0.38	39.1±0.25	37.1±0.31*	38.2±0.1*	37.3±0.26*
4th group Comp. Ve	36.2±0.05	37.7±0.3	35.6±0.38*	35.3±0.16*	35.9±0.17*
5th group Comp. Vf	36.8±0.31	38.7±0.18	35.8±0.33**	34.9±0.42**	35.4±0.2**
6th group Comp. VId	36.3±0.16	38.5±0.43	36.5± .23*	36.1±0.38*	36.2±0.21*

* P<0.01 (significant)

**p<0.001 (highly significant)

Table (3) The analgesic effect of Compounds IVa, Ve, Vf and VId (20 mg/kg) on rats after I.P administration.

Compound(group treatment)	Duration of analgesic effect in seconds						
	Before treat.	After 10 min.	After 20 min.	After 30 min.	After 60 min.	After 90 min.	After 120 min.
Control I without drug	$25.5^{\pm}0.12$	$24.0^{\pm}0.06$	$25.0^{\pm}1.02$	$32.5^{\pm}0.27$	$24.6^{\pm}0.7$	$26.1^{\pm}0.32$	$23.9^{\pm}0.83$
Control II Mefenamic acid 25 mg/kg	$24.0^{\pm}0.91$	$51.5^{\pm}0.96$	$61.3^{\pm}5.08$	$71.8^{\pm}5.38$	$74.5^{\pm}6.34$	$81.3^{\pm}8.76$	$85.0^{\pm}5.4$
Compound IVa	$24.8^{\pm}1.18$	$43.0^{\pm}3.47^{*}$	$58.0^{\pm}7.25^{*}$	$77.5^{\pm}5.63^{**}$	$78.5^{\pm}5.9^{**}$	$72.8^{\pm}6.13^{**}$	$48.8^{\pm}4.27^{*}$
Compound Ve	$22.5^{\pm}1.04$	$52.3^{\pm}6.06^{*}$	$54.0^{\pm}3.19^{**}$	$72.5^{\pm}3.23^{**}$	$85.8^{\pm}9.56^{**}$	$91.3^{\pm}6.57^{**}$	$59.5^{\pm}1.66^{**}$
Compound Vf	$25.0^{\pm}1.78$	$47.0^{\pm}5.61^{*}$	$56.0^{\pm}4.65^{**}$	$57.5^{\pm}4.33^{**}$	$62.8^{\pm}3.64^{**}$	$81.3^{\pm}3.75^{**}$	$60.5^{\pm}4.11^{**}$
Compound VId	$21.8^{\pm}2.06$	$44.8^{\pm}6.02^{*}$	$57.0^{\pm}6.57^{**}$	$75.8^{\pm}8.92^{**}$	$82.3^{\pm}6.71^{**}$	$83.8^{\pm}7.89^{**}$	$55.3^{\pm}7.47^{*}$

* Significant at $P < 0.01$

** Highly significat at $P < 0.001$

induced a significat decrease ($p < 0.001$) in body temperature 3 and 6 h post its administration .

Concerning the analgesic effect, the reaction time was significantly increased ($p < 0.01$) after 10 minutes from administration of the tested compounds i.p. in a dose of 20 mg/kg body weight of mice. A highly significant increse ($p < 0.001$) in reaction time was obtained after 20 minutes for all test compounds except IVa. On the other hand the reaction time of compounds Ve and Vf was continued for 120 minutes, while in the case of compounds VIa and VId the reactio time was continued for 90 minutes .

EXPERIMENTAL

All melting points were uncorrected. Elemental analysis was carried out at Cairo University Labs. IR spectra were determined on Perkin - Elmer PE - 298 Spectrophotometer. ^1H - -NMR was carried out on JEOL FXQ 90 MHZ spectrophotometer.

N - (3-Chloro - N - Substitutedphenyl - 2 maleimidyl) - anthranilic - acid (IVa - f) :

To a solution of III a - f [3] (10 mole) in glacial acetic acid (40 mL), anthranilic acid (1.37 g, 10 mol) in acetic acid (10 mL) was added dropwise. The mixture was heated under reflux for one hour . The reaction mixture was then concentrated under reduced pressure , cooled , diluted with ice cold water and filtered .The products were collected, dried and recrystallized from ethanol (table 4).

N - (3-Chloro -N- substituted phenyl-2 maleimidyl) - anthranilic - acid methy ester (Va -f) :

According to the described method in the synthesis of IVa - f, using anthranlic acid methyl ester (1N - (3-chloro - N - substituted phenyl - 2 maleimidyl) - anthranilic - acid (IVa - f)

5 g (10 mmol) of anthranilic acid were used. The separated products were recrystallized from ethanol / water (table 4)

Table (4)

No	R	M.F & M.wt.	Yield %	M.P°C	Microanalysis	
					Calcd	Found
IVa	H	$C_{17}H_{11}ClN_2O_4$ (342.5)	92	214-5	C 59.56	59.7
					H 3.21	3.4
					N 8.17	8.0
IVb	p-Cl	$C_{17}H_{10}Cl_2N_2O_4$ (377)	90	208-9	C 54.11	54.3
					H 2.65	2.5
					N 7.42	7.3
IVc	m-Cl	$C_{17}H_{10}Cl_2N_2O_4$ (377)	88	195-6	C 54.11	54.2
					H 2.65	2.5
					N 7.42	7.6
IVd	p-CH_3	$C_{18}H_{13}ClN_2O_4$ (356.5)	90	178-9	C 60.58	60.4
					H 3.64	3.5
					N 7.85	7.6
IVe	p-CH_3O	$C_{18}H_{13}ClN_2O_5$ (372.5)	85	185-6	C 57.98	58.1
					H 3.48	3.3
					N 7.51	7.6
IVf	p-Br	$C_{17}H_{10}BrClN_2O_4$ (421.5)	87	225-6	C 48.39	48.5
					H 2.37	2.2
					N 6.64	6.8
Va	H	$C_{18}H_{13}ClN_2O_4$ (356.5)	90	198-9	C 60.58	60.7
					H 3.64	3.6
					N 7.85	7.7
Vb	p-Cl	$C_{18}H_{12}Cl_2N_2O_4$ (389)	85	168-9	C 55.52	55.3
					H 3.08	2.9
					N 7.19	7.0
Vc	m-Cl	$C_{18}H_{12}Cl_2N_2O_4$ (389)	90	152-3	C 55.52	55.7
					H 3.08	3.2
					N 7.19	7.3
Vd*	p-CH_3	$C_{19}H_{15}ClN_2O_4$ (370.5)	87	157-8	C 62.07	62.2
					H 4.04	3.9
					N 7.55	7.7
Ve**	p-CH_3O	$C_{19}H_{15}ClN_2O_5$ (386.5)	80	165-6	C 58.99	59.1
					H 3.88	3.7
					N 7.24	7.4
Vf	p-Br	$C_{18}H_{12}BrClN_2O_4$ (435.5)	85	170-1	C 49.59	49.4
					H 2.75	2.9
					N 6.42	6.3

Cont. table (4)

VIa	H	$C_{18}H_{10}ClN_3O_3S$ (383.5)	80	187-8	C 56.32 H 2.60 N 10.95	56.5 2.4 10.8
VIb	p-Cl	$C_{18}H_9Cl_2N_3O_3S$ (418)	78	161-2	C 51.67 H 2.50 N 10.04	51.5 2.4 10.2
VIc	m-Cl	$C_{18}H_9Cl_2N_3O_3S$ (418)	82	143-4	C 51.67 H 2.50 N 10.04	51.7 2.4 9.9
VId	p-CH_3	$C_{19}H_{12}ClN_3O_3S$ (397.5)	80	145-6	C 57.35 H 3.01 N 10.56	57.5 3.2 10.4
VIe***	p-CH_3O	$C_{19}H_{12}ClN_3O_4S$ (413.5)	75	152-3	C 55.13 H 2.90 N 10.15	55.0 3.0 10.3
VIf	p-Br	$C_{18}H_9BrClN_3O_3S$ (462.5)	82	131-2	C 46.70 H 1.94 N 9.08	46.9 2.1 9.0

General IR cm^{-1} characters: NH, sharp, 3400 cm^{-1}; OH, broad, 3400-3200 cm^{-1} ; C=O, 1710, 1670 cm^{-1} .

^1H nmr of some prepared compounds :

* 2.4(s,3H,CH_3); 4(s,3H,OCH_3); 7.6-7.9(m,8H,aromatic protons); 10.2(s,1H,NH).

** 3.9(s,3H,OCH_3 of phenyl ring); 4(s,3H,OCH_3); 7.4-7.8(m,8H,aromatic protons); 10.2(s,1H,NH) .

*** 3.9(s,3H,OCH_3 of phenyl ring); 7.4-7.8(m,8H,aromatic protons); 10.7(s,1H,NH).

N - (3-Chloro - N - substituted phenyl - 2 maleimidyl) - 4 (3H) - quinazolinone - 2 - thione (VIa -f) .

To a solution of either IVa - f or Va - f (10 mmol) in glacial acetic acid (50 ml) potassium thiocyanate (1.35 g , 15 mmol) were added. The mixture was heated under reflux for two hours . The reaction mixture was concentrated under reduced pressure , cooled , diluted with ice water , filtered and recrystallized from dioxane / water (table 4) .

REFERENCES

1-Soloway , A. H. " Principles of Medicinal Chemistry " , Foye , W. O. , Ed ., Lea and Febiger , Philadelphia , pp . 270 - 273 (1974) .

2- Burka , J.F. and Eyre , P. , Can . J. Physiol . Pharmacol . , 52 (5) , 942 (1974) .

3-Howard , M. R. and Robert , W. S. J . Org . Chem ., 37 , 1742 (1972) .

4- Alpermann , H. , Berich uber Pharmakologische Untersuchungen Mit Fenbendazole Abteilung Fur Pharmakologie H. 863 : 1-9 (1972) .

5- Teotino , U. M., Faris , L. P . , Gandini , A. and Della Bella , D. , Cited in Pharmacology . Academic Press INC , New York , pp . 298 (1963).

6-Jacob , " J. and Bosovski , Cited from Tumer , R. A; " Screening Methods in Pharmacology. " Academic press, New York and London , pp 104 (1965) .

7- Snedecor , G . W, " Statistical Methods ". The Iowa State University Press , Ames, Iowa USA (1969) .

التشييد والفحص الأقرابازينى المبدئى لبعض مشتقات حامض الأنثرانيليك والتى يحتمل أن يكون لها تاثير كمضادات للإلتهابات ومسكنات ومخفضات للحرارة

منصور ابو كل - السيد لاشين - عبدالله الشنوانى - ناجح ابوطالب - ومجدى عامر *

قسم الكيمياء الصيدلية - كلية الصيدلة - جامعة الزقازيق

*و كلية الطب البيطرى - جامعة قناة السويس

لقد تم فى هذا البحث تحضير مركبات : ن - كلور - ن (مشتقات الفنيل ماليميدايل) حمض الأنثرانيليك المقابل والتى عند تفاعلها مع ثيوسيانات البوتاسيوم تم الحصول على المركبات مشتقات الكينازولينون ثيون وتم اختيار ٤ مركبات منها كمضادات للألتهابات ومسكنات ومخفضات للحرارة .