Bull. Pharm. Sci., Assiut University
Vol. 7, Part: 1, pp. 224-236

SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NEW SALICYLIC ACID DERIVATIVES CONTAINING A QUINAZOLIN-4-ONE MOIETY

M.A. Abd-Alla, A.S. Yanni, Sh. H. Ahmed* and M.H. Abdel-Raheam**
Department of Chemistry, Faculty of Science, Assiut University, Assiut, Egypt.

ABSTRACT

A new series of salicylic acid derivatives of the general formula (IV) was prepared through the interaction of substituted 2-aryl-3-(haloformylalkyl)-3,4-dihydroquinazolin-4-one(III) with salicylic acid, methyl salicylate and sodium salicylate. The biological activities of these compounds such as antibacterial, analgesic and antipyretic were determined.

INTRODUCTION

Salicylic and homosalicylic acid derivatives are reported to possess hypoglyceamic activity whereas aspirin potentiates the action of chlorpropamide in diabetic patients[1-3]. Moreover, salicylic acid, sodium salicylate, salicylamide and acetylsalicylic acid are long known to have a therapeutic action mainly as antimicrobial, antipyretic and analgesic agents[4,5]. Quinazolones are known to be CNS depressants[6-8], anticonvulsants[9,10], hypnotics, muscle relaxants[11] and possess

* Microbiology Dept. Faculty of Medicine, Assiut Univ.
** Pharmacology Dept. Faculty of Medicine, Assiut Univ.

a monoamine oxidase inhibitor activity[12]. Also some amino acid derivatives are reported to be used in treating high blood pressure[13]. In view of the biological importance of the forgoing fragments, it was thought of interest to prepare a molecule with a modified biological activity from the combination of these moieties.

EXPERIMENTAL

Completion of the reaction and the purity of compounds prepared were checked by thin layer chromatography (t.l.c.) using plates covered with silica gel (25-40 mesh)and elution with benzene. Melting points were uncorrected. The infrared (i.r.) spectra were recorded on a Perkin Elmer 599 B using a KBr disc.

1- 2-Aryl-3,1-benzoxazin-4-ones (I)

These compounds were prepared according to the literature[14].

2- Substituted 2-aryl-3-(carboxyalkyl)-3,4-dihydroquinazolin-4-ones (II)

A mixture of 2-aryl-3,1-benzoxazin-4-ones (I) (0.05 mol) and the amino acid (0.06 mol) was dissolved in a 2:1 pyridine-water mixture (30 ml)and refluxed for 5-6 h. The major portion of pyridine was distilled off under reduced pressure; the residue was digested with 4N HCl (100 ml) on a steam bath for 2-3 h and the solid which separated was collected and recrystallised from ethanol (see Table 1).

3- Salicylic esters of type (IV)

A sample of the acid (II) (0.07 mol) was converted into the corresponding acyl chloride, the latter was refluxed with salicylic acid, methyl salicylate or sodium salicylate

(0.01 mol) respectively in dry benzene (50 ml) and anhydrous sodium carbonate (0.01 mol)for 4-5 h. The reaction mixture was filtered while hot, the filtrate concentrated and cooled. The separated solid product was collected and recrystallised from benezene (see Table 2).

4- Hydrolysis of Salicylic esters (IV).

A sample of compound (IV) was refluxed with alcoholic solution of 10% sodium hydroxide (20 ml) for 30 min. The hydrolysate solution was cooled, neutralized and tested with neutral $FeCl_3$ solution where a violet blue colour appeared indicating the presence of the salicylate anion.

5- Bacteriological evaluation of the prepared compounds.

Preliminary evaluation of antibacterial activities of compounds (IVa-h) against both gram-positive and gram-negative bacteria were determined using filter paper-disc method[15].

The results obtained showed that most of these compounds have valuable effects against Staphylococcus aureus, Escherichia coli and Klebsilla pneumoniae. The minimum inhibitory concentration (M.I.C.) of each compound against the above mentioned organisms was estimated using the agar-cup-diffusion method[16] (see Table 3).

6- Analgesic activity of compounds (IVa-h).

Analgesic activity was determined by following the procedure of Beecher[17].

The appropriate compound was administered intraperitoneally in graded doses in groups of 6 male mice, weighing between 16-20 g. Propylene glycol was used as a solvent and injected alone in another group of animals as a control. To measure the analgesic activity, hot plate analgesometry

was used (see Table 4).

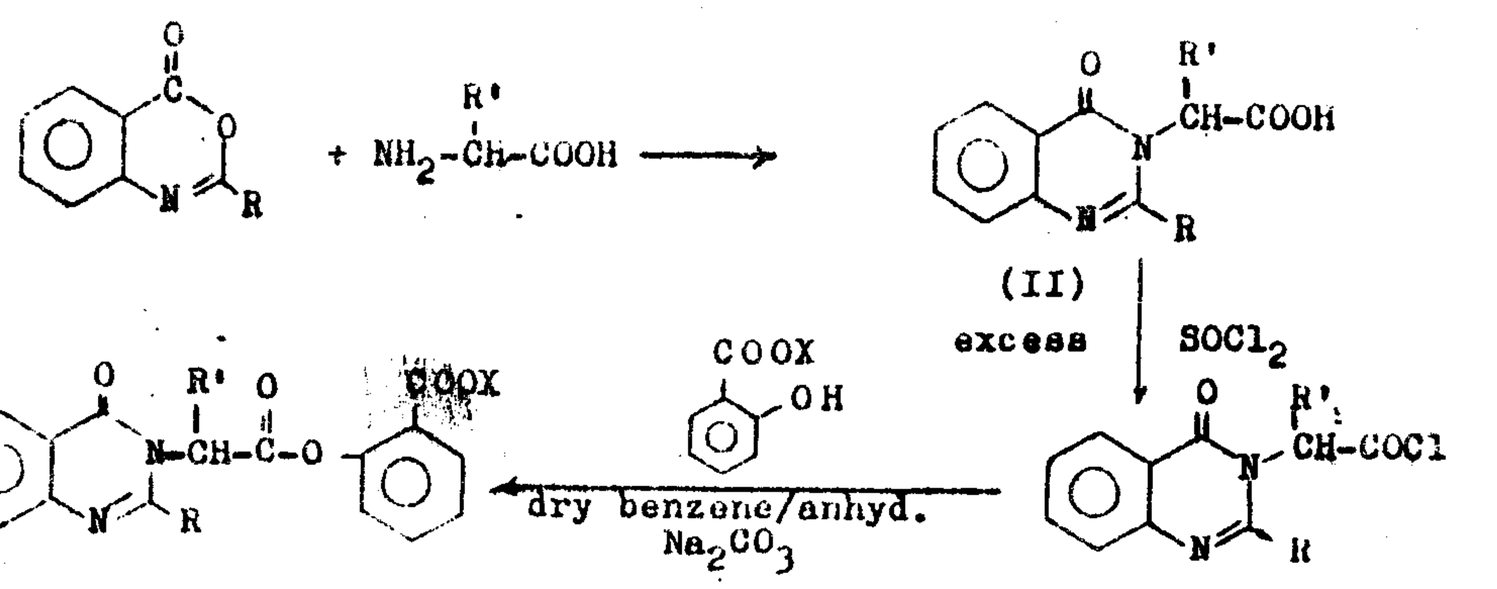
7- Antipyretic activity of compounds (IVa-h).

The method of Krane[18] was followed for this study. Hyperthermia was induced by yeast extract (12%). The appropriate compound was administered intraperitoneally in graded doses in groups of 6 male rats, weighing between 150-180 g. The body temperature was recorded using a thermistor probe connected to a thermistor coupler (Biosience 400 Series Washington Oscillographs). Control was carried out using propylene glycol (see Table 4).

RESULTS AND DISCUSSION

Interaction of substituted 2-aryl-3,1-benzoxazin -4-ones (I) with glycine, DL-alanine, L-methionine and DL-valine in a 2:1 pyridine-water mixture gave the corresponding substituted 2-aryl-3-(carboxyalkyl)-3,4-dihydroquinazolin-4-ones (II). Interaction of II with excess thionyl chloride afforded the substituted 2-aryl-3-(haloformylalkyl)-3,4-dihydroquinazolin-4-ones (III).

Salicylic acid, methyl salicylate and sodium salicylate were reacted with the acid chlorides(III) in dry benzene and in presence of anhydrous sodium carbonate and gave the new compounds of type (IV) according to the following scheme:



(IV)
R= C_6H_5; o-ClC_6H_4
X= H; CH_3; Na

(III)
R'= H; CH_3; $CH_3S(CH_2)_2$; $(CH_3)_2CH$

The structures of the synthesised compounds were confirmed by elemental analysis and i.r.spectra which showed well defined bands characterising the quinazolone ring, phenolic ester and the aromatic carboxyl at 1620 cm^{-1}(-C=N), 1660 cm^{-1}(-H-C=O), 1759 cm^{-1} (-$\overset{O}{\overset{\|}{C}}$-OPh) and at 1690 cm^{-1}(-COOH) respectively. However, involvement of salicylic acid residue in IV was clarified chemically by hydrolysis, wherein the hydrolysate gave a positive $FeCl_3$ color test of the salicylate anion.

The minimum inhibitory concentrations of the prepared compounds (IVa-h,see Table 3)revealed that gram-positive Staphylococcii were more sensitive than the gram-negative Escherichia coli and Klebsiella pneumoniae organisms. However, Escherichi coli was slightly more sensitive than Klebsiella pneumoniae. The values of M.I.C. reflected the structure-activity relationship between the different substitutions and their antibacterial activities, wherein compounds IV_{f_1} ,IV_{f_2} and IV_{f_3} in which R'=$CH_3S(CH_2)_2$-and R=o-ClC_6H_4exhibited the greatest effect . Replacement of R by a phenyl group in compounds ($IV_{f_{1-3}}$ i.e. ($IV_{e_{1-3}}$)respectively slightly decreased the antibacterial activities which reflected the importance of the presence of an o-chloro substituent in the phenyl ring. On the other hand, a comparison of compounds ($IV_{h_{1-3}}$) with compounds($IV_{d_{1-3}}$) and ($IV_{g_{1-3}}$) to compounds ($IV_{c_{1-3}}$) showed the superior effect of an isopropyl substituent over the methyl in the R' position

The evaluation of analgesic and antipyretic activities of the synthesised compounds (IV_{a-h}) showed that most of these compounds have analgesic and antipyretic activities and the effective minimum doses were recorded (see Table 4).

Table 1: Physical data of compounds II.

Comp. II	*R*	*R'*	*Melting point (°C)*	*Molecular formula*	*Microanalysis, % Calculated/Found*		
					C	*H*	*N*
IIa	C_6H_5	H	174	$C_{16}H_{12}N_2O_3$	68.57 68.40	4.28 4.08	10.00 9.89
IIb	o-Cl-C_6H_4	H	188	$C_{16}H_{11}ClN_2O_3$	61.04 60.98	3.49 3.28	8.90 8.72
IIc	C_6H_5	CH_3	167	$C_{17}H_{14}N_2O_3$	68.38 [illegible]	4.76 4.80	9.52 [illegible]
IId	o-Cl-C_6H_4	CH_3	184	$C_{17}H_{13}ClN_2O_3$	[illegible].10 62.45	3.95 4.08	8.52 8.42
IIe	C_6H_5	$CH_3S(CH_2)_2$-	210	$C_{19}H_{18}N_2O_3S$	64.40 64.52	5.08 5.18	7.90 7.82
IIf	o-Cl-C_6H_4	$CH_3S(CH_2)_2$-	179	$C_{19}H_{17}ClN_2O_3S$	58.68 58.82	4.37 4.30	7.20 7.42
IIg	C_6H_5	$(CH_3)_2CH$-	172	$C_{19}H_{18}N_2O_3$	70.80 70.99	5.59 5.42	8.69 8.72
IIh	o-Cl-C_6H_4	$(CH_3)_2CH$	192	$C_{19}H_{17}ClN_2O_3$	63.95 64.08	4.76 4.80	7.85 8.01

Table 2: Physical data of Compounds IV

Comp.	R	R'	X	Melting point (°C)	Molecular formula	Microanalysis, % Calculated/found		
						C	H	N
IVa$_1$	C_6H_5	H	H	118	$C_{23}H_{16}O_5N_2$	69.00 69.08	4.00 3.99	7.00 7.08
IVa$_2$	C_6H_5	H	CH_3	129	$C_{24}H_{18}O_5N_2$	69.56 69,62	4.34 4.38	6.76 6.70
IVa$_3$	C_6H_5	H	Na	125	$C_{23}H_{15}O_5N_2Na$	65.40 65.48	3.55 3.47	6.35 6.42
IVb$_1$	o-ClC_6H_4	H	H	127	$C_{23}H_{15}ClO_5N_2$	63.52 63.60	3.45 3.50	6.44 6.56
IVb$_2$	o-ClC_6H_4	H	CH_3	205	$C_{24}H_{17}ClO_5N_2$	64.50 64.62	3.35 3.40	6.27 6.32
IVb$_3$	o-ClC_6H_4	H	Na	139	$C_{23}H_{14}ClO_5N_2Na$	60.46 60.52	3.06 3.11	6.13 6.25
IVc$_1$	C_6H_5	CH_3	H	123	$C_{24}H_{18}O_5N_2$	69.56 69.68	4.34 4.42	6.76 6.80
IVc$_2$	C_6H_5	CH_3	CH_3	118	$C_{25}H_{20}O_5N_2$	70.09 70.15	4.67 4.72	6.54 6.62
IVc$_3$	C_6H_5	CH_3	Na	132	$C_{24}H_{17}O_5N_2Na$	66.05 66.18	3.89 3.92	6.42 6.58

Table 2: (Contained)

Comp.	R	R'	X	Melting point (°C)	Molecular formula	Microanalysis, % Calculated/found		
						C	H	N
IVd_1	o-ClC_6H_4	CH_3	H	140	$C_{24}H_{17}ClO_5N_2$	64.21 64.38	3.79 3.82	6.24 6.32
IVd_2	o-ClC_6H_4	CH_3	CH_3	150	$C_{25}H_{19}ClO_5N_2$	64.86 64.92	4.10 4.01	6.05 6.18
IVd_3	o-ClC_6H_4	CH_3	Na	143	$C_{24}H_{16}ClO_5N_2Na$	61.21 61.32	3.40 3.49	5.95 6.03
IVe_1	C_6H_5	$CH_3S(CH_2)_2$	H	251	$C_{26}H_{22}O_5N_2S$	65.82 65.[illegible]	4.64 [illegible]	5.90 5.82
IVe_2	C_6H_5	$CH_3S(CH_2)_2$	CH_3	126	$C_{27}H_{22}O_5N_2S$	66.66 66.72	4.52 4.40	5.76 5.82
IVe_3	C_6H_5	$CH_3S(CH_2)_2$	Na	112	$C_{26}H_{21}O_5N_2SNa$	62.90 63.03	4.23 4.25	5.64 5.72
IVf_1	o-ClC_6H_4	$CH_3S(CH_2)_2$	H	136	$C_{26}H_{21}ClO_5N_2S$	61.35 61.42	4.12 4.20	5.50 5.62
IVf_2	o-ClC_6H_4	$CH_3S(CH_2)_2$	CH_3	141	$C_{27}H_{23}ClO_5N_2S$	62.00 62.11	4.10 4.15	5.35 5.42
IVf_3	o-ClC_6H_4	$CH_3S(CH_2)_2$	Na	144	$C_{26}H_{20}ClO_5N_2SNa$	61.47 61.52	3.94 3.92	5.51 5.66

Table 2: (Contained)

Comp.	R	R'	X	Melting point (°C)	Molecular formula	Microanalysis, % Calculated/Found		
						C	H	N
IVg_1	C_6H_5	$(CH_3)_2CH$	H	116	$C_{26}H_{22}O_5N_2$	73,93 74.08	4.97 5.03	6.33 6.42
IVg_2	C_6H_5	$(CH_3)_2CH$	CH_3	128	$C_{27}H_{24}O_5N_2$	71.05 71.18	5.26 5.33	6.14 6.22
IVg_3	C_6H_5	$(CH_3)_2CH$	Na	121	$C_{26}H_{21}O_5N_2Na$	67.24 67.35	4.52 4.60	6.03 6.08
IVh_1	o-ClC_6H_4	$(CH_3)_2CH$	H	147	$C_{26}H_{21}ClO_5N_2$	65.47 65.50	4.40 4.32	5.87 5.95
IVh_2	o-ClC_6H_4	$(CH_3)_2CH$	CH_3	132	$C_{27}H_{23}ClO_5N_2$	66.05 66.18	4.68 4.70	5.70 5.82
IVh_3	o-ClC_6H_4	$(CH_3)_2CH$	Na	148	$C_{26}H_{20}ClO_5N_2Na$	62.58 62.50	4.01 4.08	5.61 5.76

Table 3: Minimum Inhibitory Concentrations(M.I.C.) of Compounds IVa-h against Different Organisms.

Comp..	R	R'	X	M.I.C.(ug/ml)		
				Staphylococcus aureus	*Escherichia coli*	*Klebsilla pneumoniae*
IVa_1	C_6H_5	H	H	239	219	198
IVa_2	C_6H_5	H	CH_3	209	257	277
IVa_3	C_6H_5	H	Na	222	253	274
IVb_1	o-ClC_6H_4	H	H	150	243	239
IVb_2	o-ClC_6H_4	H	CH_3	239	284	272
IVb_3	o-ClC_6H_4	H	Na	219	258	244
IVc_1	C_6H_5	CH_3	H	220	247	257
IVc_2	C_6H_5	CH_3	CH_3	239	258	273
IVc_3	C_6H_5	CH_3	Na	202	230	185
IVd_1	o-ClC_6H_4	CH_3	H	89	250	198
IVd_2	o-ClC_6H_4	CH_3	CH_3	95	177	151
IVd_3	o-ClC_6H_4	CH_3	Na	142	156	241
IVe_1	C_6H_5	$CH_3S(CH_2)_2$	H	96	199	180
IVe_2	C_6H_5	$CH_3S(CH_2)_2$	CH_3	44	64	197
IVe_3	C_6H_5	$CH_3S(CH_2)_2$	Na	109	136	151
IVf_1	o-ClC_6H_4	$CH_3S(CH_2)_2$	H	34	95	158
IVf_2	o-ClC_6H_4	$CH_3S(CH_2)_2$	CH_3	89	96	196
IVf_3	o-ClC_6H_4	$CH_3S(CH_2)_2$	Na	66	86	131
IVg_1	C_6H_5	$(CH_3)_2CH$	H	86	93	252
IVg_2	C_6H_5	$(CH_3)_2CH$	CH_3	114	222	267
IVg_3	C_6H_5	$(CH_3)_2CH$	Na	219	209	273
IVh_1	o-ClC_6H_4	$(CH_3)_2CH$	H	74	94	119
IVh_2	o-ClC_6H_4	$(CH_3)_2CH$	CH_3	67	68	123
IVh_3	o-ClC_6H_4	$(CH_3)_2CH$	Na	86	106	221

Table 4: Analgesic and Antipyretic activities of Compounds IVa-h.

Comp.	Analgesic minimum dose mg/100 g	Analgesic effect	Antipyretic minimum dose mg/100 g	Antipyretic effect
IVa_1	0.20	S	0.41	S
IVa_2	0.22	G	0.31	S
IVa_3	0.40	NO	0.45	S
IVb_1	0.31	S	0.46	G
IVb_2	0.22	S	0.32	S
IVb_3	0.36	NO	0.51	NO
IVc_1	0.24	NO	0.42	S
IVc_2	0.25	G	0.32	G
IVc_3	0.42	NO	0.41	S
IVd_1	0.21	S	0.33	S
IVd_2	0.41	NO	0.45	S
IVd_3	0.39	NO	0.55	NO
IVe_1	0.21	G	0.35	G
IVe_2	0.42	S	0.56	NO
IVe_3	0.38	S	0.42	S
IVf_1	0.23	S	0.36	G
IVf_2	0.19	G	0.25	G
IVf_3	0.30	S	0.37	G
IVg_1	0.24	V.G.	0.26	V.G.
IVg_2	0.18	G	0.21	V.G.
IVg_3	0.28	S	0.39	G
IVh_1	0.21	G	0.25	V.G.
IVh_2	0.25	G	0.33	G
IVh_3	0.34	G	0.35	G

S(slight), G(good) and V.G. (very good).

REFERENCES

1) J.T. Fishgold; J. Field; E. Hallo; Am. J. Physiol., 164, 727 (1951).
2) D.J. Engle, Prog. Exp. Biol. Med., 75, 673 (1950).
3) E. Franke, DENT., Med. Wochr., 80, 1449 (1955).
4) L.J.D. Duncan, J.D. Braid; Pharm. Rev., 12, 91(1960).
5) A.A. Abou-Ouf, Y.A. Mussa; J. Pharm. Sci., UAR, 12, 251 (1971).
6) K. Noda, A.Nakagawa, A. Yama-Zaki and H. Ide; Jap.Pat. 77 78888,C.A. (1977), 87, 168088 c.
7) S. Sato and G. Tsukamoto, Jap. Pat. 76, 133, 287,C.A. (1977), 87, 68405n.
8) S.S. Tiwari,R.K. Satsangi and S. Misra, Indian J.Pharm. Sci., 40, 40 (1978).
9) W. Boggam, J.S. Meyer, R.M. Steinberg and C. Washington; Psychopharmacology (Berlin) 54, 45(1977).
10) L.C. Weaver, R. Jones and T.L. Kaley ; Arch.int. Pharmacodyn., Ther. 43, 119 (1963).
11) L. Zhelyakov, R. Kolchagova, D. Steranova, L.Daliva; Tr. Nauchn. Khim. Farm. Inst., 8, 29 (1972).
12) J.P. Barthwal, S.K. Tandon, and K.S. Dixit; J. Pharm. Sci., 62, 613 (1973).
13) M.A. Ondetti (E.R. Squibb, and Sons) Ger. Offen, 2,753, 824 (Cl.007 Cl 53 109), 08 Jun. (1978), vs Appl. 747,282, 03 Dec. 26 pp., C.A., (1979), 90, 617.
14) S.S. Tiwari and V.K. Pandey; J. Indian Chem. Soc., 52, 736 (1975).
15) W.B. Hugo, A.D. Russell, "Pharmaceutical Microbiology" first edition, Blackwell Scientific Publications,Oxford London Edinburgh Melbourne (1977).
16) L.P. Garrod, O.F. Grady, "Antibiotic and Chemotherapy" Third edition, Chuchill Livingstone, Edinburgh and London (1972).
17) H.K. Beecher, Pharmacol. Rev. 9, 59 (1957).
18) S.M. Krane, N. Engl. J. Med., 286, 317 (1972).

تخليق بعض مشتقات جديدة لحامض السلسليك تحتوى على حلقة كينازولين -٤- اون ودراسة النشاط البيولوجى لها

محمد احمد عبد الله - امال ثابت بهنى - شعبان هاشم احمد - محمودحمدى عبد الرحيم
كلية العلوم - قسم الكيمياء - كلية الطب - جامعة اسيوط

لقد امكن تحضير سلاسل جديدة من مشتقات حمض السلسليك بتفاعل ٢ - اريل -٣ (هالوفورميل الكيل) - ٣و٤ - ثنائى هيدروكينازولين -٤-اون مع حمض السلسليك وسلسيلات المثيل وسلسيلات الصوديوم .

باختيار النشاط البيولوجى لهذة المركبات التى تم تخليقها ثبت ان لها فاعلية كمضادات للبكتريا وخافضة للحرارة .

received in 21/11/1983 & accepted in 22/1/1984