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Synthesis and Evaluation of the Analgesic and Antiinflammatory Activities of *O*-Substituted Salicylamides

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The present investigation deals with the synthesis of some new salicylamidoacetyl sulfonamides **3a,b**, salicylamido ethylacetate **4**, salicylamido acetic acid hydrazide **5**, which is considered as the key intermediate for the synthesis of several series of new compounds such as salicylamido pyrazol 6 and pyrazolone **7**. *N*-imido-derivatives **9, 10, 11**, thiadiazole **13**, oxadiazole **14, 15**, Schiffs bases **16a-f**. Cyclocondensation of Schiffs bases with thioglycolic acid gave thiazolidinone **18a-c** while with acetylchloride afforded azitidinones **19a-c** and with acetic anhydride gave 1,4-benzoxazepine-3,5-dione. Some of the compounds were tested for their analgesic and antiinflammatory activities as well as ulcerogenic effects. Some derivatives were more effective than salicylamide and ulcerogenic activity was variably lowered.

Key words: *O*-Substituted salicylamides, Pyrazol, Pyrazolone, Oxadiazole, Thiadiazole, Analgesic and antiinflammatory activities

INTRODUCTION

The diversed undesirable side effect of glucocorticoids as antiinflammatory agents increased the interest in the non-steroidal antiinflammatory drugs hoping to obtain compounds that may possess potent therapeutic effect but lacking any undesirable side effects (Fahmy *et al.*, 1995). It has been reported that salicylic acid derivatives represent a class of these non-steroidal antiinflammatory, analgesic and antipyretic drugs. The antiinflammatory derivatives of salicylic acid derivatives are typified by aspirin, salicylamide (Coleman *et al.*, 1993). A review of the literature revealed that some *N*-alkyl substituted salicylamide are more effective than salicylamide and in some cases, less toxic (Daidon *et al.*, 1989).

In the present investigation, interest was emphasized to synthesize some new *O*-heterocyclic substituted salicylamides. In order to ascertain if it would offer any advantage over the unsubstituted compound with regard to analgesic and antiinflammatory activities as well as to toxicity. The influence of the different substitutents on pharmacological properties was also investigated.

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MATERIALS AND METHODS

All melting points are uncorrected and were taken in open capillaries on a Gallenkamp apparatus. Infrared spectra were determined on KBr discs with FT IR 300E Fourier Transform-Infrared Spectrometer. The ^{1}H-NMR spectra were measured in DMSO-d_6 or $CDCl_3$ using Jeol EX-270 MHz spectrometer. The mass spectra were recorded on GCMS-QP 1000 EX Schimadzu gas chromatography MS apparatus. Microanalyses were performed at National Research Centre, Cairo, Egypt.

Chemistry

Synthesis of compounds

2-(Chloroacetyloxy)benzonitrile (1)

A solution of salicylamido-acetic acid (El-Sebai *et al.*, 1974), (0.01 mol) in 10 ml thionyl chloride and 10 ml dry benzene was refluxed for 10 h. Excess thionyl chloride and benzene was distilled under vacuum, washed with benzene and pet. ether to give compound **1** the product obtained is nearly quantitative yield, was employed in the next reaction without further purification.

O-[*N*-(Sulphanilamido)acetyloxy]benzonitrile (2)

A mixture of compound **1** (1.96 g, 0.01mol) and sulphanilamide (2.06 g, 0.012 mol) and triethylamine (0.5 ml)

in 100 ml dioxan was refluxed for 6 h. The reaction mixture was concentrated, cooled and the formed precipitate was filtered off and recrystallized from DMF/H_2O, m.p. 214 °C, yield 70%.

Analysis : $C_{15}H_{13}N_3O_4S$ (331.38)
Calculated : C, 54.36 H, 3.96 N, 12.68
Found : C, 54.50 H, 4.06 N, 12.59

IR (KBr, cm^{-1}): 3396, 3338, 3247 (NH_2, NH), 2225 (C N), 1704 (CO-OCH_2), 1330, 1150 (SO_2), 1260 (C-O-C). ^{1}H-NMR (DMSO-d_6-δ ppm): 4.95 (2H, s, OCH_2), 7.1-7.7 (10H, m, 8 aromatic protons and NH_2 protons), NH out of the scale. The mass spectrum showed the molecular ion peak (M^+, $C_{15}H_{13}N_3O_4S$) at *m/z* 331.1 (82.27%) and the base peak at *m/z* 133 (100%).

O-[*N*-(Sulpha drug)acetyl]salicylamides (3a,b)

Equimolecular quantities of salicylamido-acetic acid and sulpha drugs (0.01 mol) namely, sulphanilamide and sulphamethoxazole were heated to fussion at 150-180°C in a sand bath for 4 h. The reaction mixture was triturated with hot ethanol and the product was filtered and recrystallized from the proper solvent to give the title compounds. The physical and analytical data of these compounds are shown in Table I.

IR (KBr, cm^{-1}) of compounds **3a,b**: 3440, 3369, 3338 (NH_2, NH), 1680, 1660 (two C=O), 1600 (C=C), 1320, 1160 (SO_2), 1250, 1240 (C-O-C). The mass spectrum of compound **3b** showed the fragment at *m/z* 341 (19.02%), *m/z* 256 (13.32%), *m/z* 172 (12.28%), *m/z* 137

Table I. Physical and analytical data of compounds **3a,b, 9, 10, 11, 16a-f, 17a,b, 18a-c** and **19a-c**

Comp. No.	M.P. úC (Solvent)	Yield %	Formulae (M.wt.)	Analysis %, Calculated/Found		
				C	H	N
3a	>300 DMF/H_2O	61	$C_{15}H_{15}N_3O_5S$ (349.4)	51.55 51.68	4.33 4.26	12.02 11.88
3b	>300 DMF/Ethanol	53	$C_{19}H_{18}N_4O_6S$ (430.48)	53.00 53.16	4.22 4.35	13.01 12.89
9	189 Ethanol/H_2O	80	$C_{17}H_{13}N_3O_5$ (339.33)	60.17 59.89	3.86 3.75	12.39 12.41
10	180 Ethanol/H_2O	60	$C_{13}H_{11}N_3O_5$ (289.27)	53.97 53.90	3.84 4.10	14.52 14.78
11	176 Methanol/H_2O	54	$C_{13}H_{13}N_3O_5$ (291.29)	53.59 53.82	4.50 4.61	14.42 14.53
16a	206 Ethanol	83	$C_{16}H_{15}N_3O_3$ (297.34)	64.63 64.56	5.09 4.91	14.14 14.21
16b	248 DMF	95	$C_{16}H_{14}ClN_3O_3$ (331.88)	57.90 58.16	4.26 4.32	12.66 12.48
16c	242 Ethanol	70	$C_{16}H_{14}N_3O_3F$ (315.33)	60.93 61.20	4.48 4.57	13.32 13.40
16d	192 Ethanol	95	$C_{17}H_{17}N_3O_3$ (311.37)	65.57 65.49	5.51 5.39	13.49 13.61
16e	238 DMF/MeOH	90	$C_{19}H_{21}N_3O_6$ (387.43)	58.89 59.96	5.47 5.62	10.84 10.67
16f	212 Ethanol	70	$C_{14}H_{13}N_3O_3S$ (303.37)	55.42 55.29	4.33 4.30	13.85 13.90
17a	242 Ethanol	84	$C_{16}H_{15}N_3O_4$ (313.34)	61.32 61.19	4.83 4.75	13.41 13.35
17b	210 $CHCl_3$	53	$C_{14}H_{13}N_3O_5$ (303.3)	55.43 55.28	4.32 4.25	13.85 13.90
18a	210 $CHCl_3$/Pet.ether	60	$C_{18}H_{17}N_3O_4S$ (371.45)	58.19 58.31	4.62 4.68	11.32 11.23
18b	130 $CHCl_3$/Pet.ether	50	$C_{18}H_{16}ClN_3O_4S$ (405.89)	53.26 53.19	3.98 3.85	10.35 10.28
18c	178 $CHCl_3$/Pet.ether	47	$C_{16}H_{15}N_3O_4S_2$ (377.48)	50.90 50.81	4.01 3.89	11.13 11.20
19a	110 $CHCl_3$/Pet.ether	53	$C_{18}H_{16}ClN_3O_4$ (373.82)	57.82 57.97	4.32 4.40	11.24 11.32
19b	170 Benzene/Pet.ether	75	$C_{21}H_{23}N_3O_7$ (429.47)	58.72 58.55	5.40 5.31	9.78 9.67
19c	145 Benzene/Pet.ether	63	$C_{16}H_{15}N_3O_3S$ (329.41)	58.33 58.45	4.59 4.70	12.75 12.68

(10.62%), *m/z* 121 (7.33%) and the base peak) at *m/z* 97 (100%).

Salicylamido ethyl acetate (4)

A mixture of salicylamide (0.69 g, 0.005 mol) and K_2CO_3 anhydrous (0.7 g, 0.005 mol) was refluxed in absolute ethanol (50 ml) for 15 min. Then ethylchloro-acetate (0.8 ml, 0.005 mol) was added. The reaction mixture was refluxed for 10 h. the precipitated anhy-drous K_2CO_3 was filtered off and the alcoholic solution was conc., cooled, the separated solid was filtered washed with water and then recrystallized from ethanol, m.p. 124°C, yield 80%.

Analysis :	$C_{11}H_{13}NO_4$ (223.25)		
Calculated :	C, 59.17	H, 5.88	N, 6.27
Found :	C, 58.98	H, 5.80	N, 6.31

IR (KBr, cm^{-1}): 3400, 3200 (NH_2), 1720 (CO-OC_2H_5), 1660 (CONH_2), 1600 (C=C), 1240 (C-O-C). ^{1}H-NMR (DMSO-d_6- δ ppm): 1.2 (3H, t, CH_3), 4.2 (2H, q, CH_2 CH_3) 4.9 (2H, s, OCH_2), 7-7.9 (4H, m, aromatic protons), 8 (2H, s, NH_2). The mass spectrum showed the molecular ion peak (M^+, $C_{11}H_{13}NO_4$) at *m/z* 223.25 (44%) and the base peak at *m/z* 121(100%).

Salicylamidoacetic acid hydrazide (5)

A mixture of compound **4** (2.2 g, 0.01 mol) and hydrazine hydrate 98% (2.2 ml) was refluxed in (25 ml ethanol for 3 h. The reaction mixture was cooled and the separated solid was filtered, and then recrystallized from ethanol, m.p. 190°C, yield 95%.

Analysis :	$C_9H_{11}N_3O_3$ (209.23)		
Calculated :	C, 51.66	H, 5.30	N, 20.08
Found :	C, 51.52	H, 5.27	N, 19.93

IR (KBr, cm^{-1}): 3350, 3150 (NH_2, NH), 1660, 1640 (two C=O), 1240 (C-O-C).^{1}H-NMR (DMSO-d_6- δ ppm): 4.4 (2H, s, NH-NH_2), 4.7 (2H, s, OCH_2), 7-7.7 (4H, m, aromatic protons), 8.1 (2H, s, CO-NH_2), 9.5 (1H, s, NH). The mass spectrum showed the molecular ion peak (M+, $C_9H_{11}N_3O_3$) at *m/z* 209 (6.37%) and the base peak at *m/z* 121 (100%).

***O*-[(3,5-Dimethylpyrazol-1-yl)acetyl]salicylamide (6)**

A mixture of compound **5** (0.58 g, 0.0028 mol) and acetylacetone (0.0028 mol) in 50 ml absolute ethanol was heated at reflux temp. for 7 h. The reaction mixture was cooled and the formed precipitate was filtered off and recrystallized from ethanol, m.p. 204°C, yield 85%.

Analysis :	$C_{14}H_{15}N_3O_3$ (273.32)		
Calculated :	C, 61.51	H, 5.54	N, 15.37
Found :	C, 61.36	H, 5.50	N, 15.48

IR (KBr, cm^{-1}): 3400, 3240 (NH_2), 1670, 1640 (two C=O), 1600 (C=C), 1250 (C-O-C).^{1}H-NMR (DMSO-d_6- δ ppm): 1.8, 2 (6H, 2s, $2CH_3$), 5 (2H, s, OCH_2), 6.5 (1H, s, CH of pyrazole), 7-8 (4H, m, aromatic protons), 8.5 (2H, s,NH_2).

***O*-[(3-Methyl-5-oxo-pyrazolin-1-yl)acetyl]salicylamide (7)**

A mixture of the carbohydrazide **5** (0.58 g, 0.0028 mol) and ethylacetoacetate (0.0028 mol) in absolute ethanol (50 ml) was reacted according to the procedure described above. It gave compound **7** in 90% yield m.p. 198°C, cryst. solvent DMF/ethanol.

Analysis :	$C_{13}H_{13}N_3O_4$ (275.29)		
Calculated :	C, 56.71	H, 4.76	N, 15.27
Found :	C, 56.85	H, 4.81	N, 15.16

IR (KBr, cm^{-1}): 3400, 3200 (NH_2), 1730 (C=O of pyrazolone), 1700 (CO-CH_2O), 1660 (CONH_2), 1600 (C =C), 1240 (C-O-C). ^{1}H-NMR (DMSO-d_6- δ ppm): 2.1 (3H, s, CH_3), 4.9 (2H, s, OCH_2), 5.1 (2H, s, CH_2 of pyrazolin), 7-8 (4H, m, aromatic protons), 8.4 (2H, s, NH_2).

***O*-[*N*-(2-Oxo-3-indolinylidene)acetic acid hydrazido]salicylamide (8)**

A mixture of compound **5** (1.046 g, 0.005 mol) and isatin (0.66 g, 0.005 mol) in 10 ml glacial acetic acid was heated under reflux temp. for 8 h. The reaction mixture was cooled, poured into crushed ice and the separated solid was filtered off and recrystallized from DMF/H_2O m.p. 238°C, yield 73%.

Analysis :	$C_{17}H_{14}N_4O_4$ (338.35)		
Calculated :	C, 60.34	H, 4.10	N, 16.56
Found :	C, 60.18	H, 3.91	N, 16.70

IR (KBr, cm^{-1}): 3424, 3340, 3240 (NH_2, NH), 1720 (C=O of isatin), 1650, 1640 (two C=O), 1600 (C=C), 1240 (C-O-C). ^{1}H-NMR (DMSO-d_6- δ ppm): 4.9 (2H, s, OCH_2), 7-7.9 (8 H, m, aromatic protons), 8.2 (2H, s,NH_2), 10.3 (1H, s, NH).

***O*-[*N*-(Phthalimido, maleimido and/or succinimido) acetamido] salicylamides (9, 10, and 11)**

A mixture of compound **5** (1.046 g, 0.005 mol) and (0.005 mol) of phthalic, maleic or succinic anhydride in 20 ml glacial acetic acid was refluxed for 8 h. The reaction mixture was cooled then poured into crushed ice. The separated solid product was filtered off, washed with water and recrystallized from the proper solvent to give the title compounds. The physical and analytical data of these compounds were shown in Table I.

IR (KBr, cm^{-1}) of compound **9**: 3400, 3200 (NH_2, NH), 1740, 1680 (two C=O, cyclic imide), 1660 (two C=O of CONH, $CONH_2$), 1600 (C=C), 1240 (C-O-C). And that of compound **11**: 3400, 3200 (NH_2, NH), 1720 (two C=O, cyclic imide), 1650 (two C=O), 1600 (C=C), 1250 (C-O-C). ^{1}H-NMR (DMSO-d_6- δ ppm) of compound **9**: 4.9 (2H, s, OCH_2), 7-7.9 (8H, m, aromatic protons), 8.1 (2H, s,NH_2), 10.3 (1H, s, NH), NH and NH_2

exchangeable with D_2O.

***O*-[(5-Thioxo-1,3,4-thiadiazol-2-yl)methyl]salicylamide (13)**

Carbon disulphide (0.005 mol) was added dropwise to an ice cold solution of KOH (0.0025 mol) in absolute ethanol (50 ml) containing the hydrazide derivative **5** (0.0025 mol). The mixture was stirred at room temperature for 20 h. The separated solid of potassium dithiocarbazate **12** was filtered and washed with ether. The product obtained is nearly quantitative yield, was employed in the next reaction without further purification.

Compound **12** (2 g) was added portion wise to concentrated sulphuric acid 20 ml with stirring and cooling, and left to stand for 2 h. at room temperature. The solution was poured on ice and neutralized with NH_4OH. The solid obtained was filtered off and washed with water, and recrystallized from DMF/H_2O to give **13** in 90%yield m.p. 170°C.

Analysis :	$C_{10}H_9N_3O_2S_2$ (267.34)		
Calculated :	C, 44.92	H, 3.40	N, 15.72
Found :	C, 44.79	H, 3.34	N, 15.81

The mass spectrum showed the molecular ion peak (M^+, $C_{10}H_9N_3O_2S_2$) at *m/z* 267 (18.95%) and the base peak at *m/z* 131.9 (100%).

***O*-[(5-Thioxo-1,3,4-oxadiazol-2-yl)methyl]salicylamide (14)**

To a mixture of (2.09 g, 0.01 mol) of carbohydrazide **5** in 200 ml ethanol was added a solution of potassium hydroxide (0.84 g, 0.015 mol) followed by 20 ml of carbon disulphide. The reaction mixture was heated under reflux for 8 h. concentrated, acidified with dil. HCl and the resulting solid was collected, washed with water and recrystallized from a mixture of DMF/H_2O m.p. 220°C, yield 72%.

Analysis :	$C_{10}H_9N_3O_3S$ (251.28)		
Calculated :	C, 47.79	H, 3.61	N, 16.72
Found :	C, 47.91	H, 3.70	N, 16.59

IR (KBr, cm^{-1}): 3456, 3347 (NH_2), 1650 ($\underline{CO}NH_2$), 1600 (C=C), 1240, 1090 (two C-O-C), 1140 (C=S). The mass spectrum showed the molecular ion peak (M^+, $C_{10}H_9N_3O_3S$) at *m/z* 251 (18.44%) and the base peak at *m/z* 120.1 (100%).

***O*-[(5-Phenyl-1,3,4-oxadiazol-2-yl)methyl]salicylamide (15)**

A mixture of the carbohydrazide **5** (1.046 g, 0.005 mol) and benzoic acid (0.61 g, 0.005 mol) in 5 ml $POCl_3$ was heated at reflux temp. for 2 h, cooled down and slowly added to ice-water. The precipitated solid was filtered off, washed with water and recrystallized from ethanol/H_2O m.p. 158°C, yield 56%.

Analysis :	$C_{16}H_{13}N_3O_3$ (295.32)		
Calculated :	C, 65.06	H, 4.44	N, 14.23
Found :	C. 65.32	H, 4.52	N, 14.41

The mass spectrum showed the molecular ion peak (M^+, $C_{16}H_{13}N_3O_3$) at *m/z* 295 (<5%) and the base peak at *m/z* 105.1 (100%).

Salicylamido acetic acid hydrazide Schiffs bases (16a-f)

To a solution of the carbohydrazide **5** (1.046 g, 0.005 mol) in 30 ml of ethanol was added (0.005 mol) of the appropriate aromatic and/or heterocyclic aldehydes. The reaction mixture was refluxed for 5 h. The solid formed after cooling was filtered off, washed with water and recrystallized from the proper solvent to give the title compounds. The physical and analytical data of these compounds are shown in Table I.

IR (KBr, cm^{-1}) of compound **16a**: 3400, 3200 (NH_2, NH), 1700, 1660 (two C=O), 1600 (C=C), 1240 (C-O-C). ^{1}H-NMR (DMSO-d_6- δ ppm) of compound **16c**: 4.9 (2H, s, OCH_2), 7-8 (8H, m, aromatic protons), 8.2 (2H, s,NH_2), 8.5 (1H, s, CH), 11.7 (1H, s, NH). And that of **16d**: 2.4 (3H, s, CH_3), 4.9 (2H, s, OCH_2), 7-8 (8H, m, aromatic protons), 8.2 (2H, s,NH_2), 8.5 (1H, s, CH), 11.6 (1H, s, NH). And that of **16e**: 3.7 (3H, s, *p*-OCH_3), 3.9 (6H, s, two *m*-OCH_3) 4.9 (2H, s, OCH_2), 7-8 (6H, m, aromatic protons), 8.2 (2H, s,NH_2), 8.5 (1H, s, CH), 11.7 (1H, s, NH). And that of **16f**: 4.9 (2H, s, OCH_2), 7-8.2 (7H, m, 3 thiophene protons and 4 aromatic protons), 8.4 (2H, s, NH_2), 8.5 (1H, s, CH), 11.7 (1H, s, NH), NH and NH_2 exchangeable with D_2O. The mass spectrum of compound **16a** showed the molecular ion peak (M^+, $C_{16}H_{15}N_3O_3$) at *m/z* 298 (2.99 %) and the base peak at *m/z* 121 (100%). And that of compound **16c** showed the molecular ion peak (M^+, $C_{16}H_{14}FN_3O_3$) at *m/z* 316 (17.24%) and the base peak at *m/z* 121 (100%).

Salicylamido acetic acid benzoyl or furan-2-carbonyl hydrazides (17a,b)

(2.09 g, 0.01 mol) of the hydrazide **5** was dissolved in 10 ml dry pyridine with stirring then (0.01 mol) of the requested acid chloride namely benzoyl chloride, and furan-2-carbonyl chloride was added during stirring the reaction mixture was refluxed for 4 h. cooled and poured over crushed ice. The formed solid was filtered off, washed with water and petroleum ether then recrystallized from the proper solvent to give **17a,b** respectively. Table I.

IR (KBr, cm^{-1}) of compound **17a**: 3444, 3326, 3244 (NH_2, NH), 1702 (C=O aromatic ketone), 1660, 1640 (two C=O), 1604 (C=C), 1240 (C-O-C). And that of compound **17b**: 3400, 3200 (NH_2, NH), 1680, 1640 (three C=O), 1600 (C=C), 1230 (C-O-C). ^{1}H-NMR (DMSO-d_6- δ ppm) of compound **17a**: 4.9 (2H, s, OCH_2), 7-7.8 (9H, m, aromatic protons), 8.1 (2H, s,NH_2), 11.7, 12 (2H, 2s, 2NH), NH and NH_2 exchange-able with D_2O.

***O*-[*N*-(2-Substituted aryl-4-oxo-thiazolidin-3-yl)acetamido] salicylamides (18a-c)**

Thioglycolic acid (0.18 g, 0.002 mol) in 15 ml dry benzene

was added dropwise to (0.002 mol) of the appropriate Schiffs bases **16a,b,** and **f** in 10 ml dry benzene during 10 min. with stirring, which continued with reflux for 10 h. The solvent was distilled off and the residue neutralized with sodium bicarbonate solution. The precipitate material was filtered off and recrystallized from the proper solvent. The physical and analytical data of these compounds are shown in Table I.

^{1}H-NMR (DMSO-d_6- δ ppm) of compound **18c**: 3.7 (2H, s, CH_2 of thiazolidinone at C_5) 4.9 (2H, s, OCH_2), 6 (1H, s, CH of thiazolidinone at C_2), 6.9-7.9 (7H, m, 3 thiophene protons and 4 aromatic protons), 8.2 (2H, s,NH_2), NH out of scale. The mass spectrum of compound **18a** showed the molecular ion peak (M^+, $C_{18}H_{17}N_3O_4$ S) at *m/z* 371 (<5%) and the base peak at *m/z* 121 (100%). And that of compound **18b** showed the molecular ion peak (M^+, $C_{18}H_{16}ClN_3O_4S$) at *m/z* 405 and at *m/z* 407 (<5%) and the base peak at *m/z* 211.9 (100%). And that of compound **18c** showed the molecular ion peak (M^+, $C_{16}H_{15}N_3O_4S_2$) at *m/z* 337 (<5%) and the base peak at *m/z* 121 (100%).

O-[*N*-(4-Substituted aryl-2-oxo-azetidin-1-yl)acetamido] salicylamides (19a-c)

A solution of acetyl chloride (0.1 mol) in dry dioxane was added dropwise to a cooled well-stirred solution of Schiffs bases **16b,e,** and **f** (0.1 mol) and triethylamine (0.2 mol) in 50 ml dry dioxane and the mixture was stirred for 6 h. at room temperature then refluxed for 5 h. The precipitated amine hydrochloride was filtered off and dioxane removed. The residue was poured into water and the resulting solid was filtered off, washed with water and recrystallized from the proper solvent. The physical and analytical data of these compounds are shown in Table I.

IR (KBr, cm^{-1}) of compound **19c**: 3400, 3200 (NH_2, NH), 1700 (C=O of azetidinone), 1660 (two C=O), 1600 (C=C), 1250 (C-O-C). ^{1}H-NMR (DMSO-d_6- δ ppm) of compound **19b**: 3.5 (2H, s, CH_2 of azitidinone), 3.7 (3H, s, *p*-OCH_3), 3.9 (6H, s, two *m*-OCH_3), 4.8 (1H, s, CH of azitidinone), 4.9 (2H, s, OCH_2), 7-7.9 (6H, m, aromatic protons), 8.1 (2H, s,NH_2), NH out of scale. And that of compound **19c**: 3.1 (2H, s, CH_2 of azitidinone), 4.8 (2H, s, OCH_2), 5.2 (1H, s, CH of azitidinone), 6.9-8 (7H, m, 3 thiophene protons and 4 aromatic protons), 8.5 (2H, s, NH_2), 11.7 (1H, s, NH). The mass spectrum of compound **19a** showed the molecular ion peak (M^+, $C_{18}H_{16}$ Cl N_3O_4) at *m/z* 374 (2.19%) and at *m/z* 376 (2.90%) and the base peak at *m/z* 121 (100%). And that of compound **19b** showed the molecular ion peak (M^+, $C_{21}H_{23}N_3O_7$) at *m/z* 429 (<5%) and the base peak at *m/z* 120.9 (100%).

1,4-Benzoxazepine-3,5-dione (20)

A mixture of **16a,c,e,** and **f** (0.005 mol) and 15 ml of acetic anhydride was refluxed for 5 h. The reaction mixture was concentrated, cooled poured into ice cold water the formed precipitate was filtered off and recrystallized from benzene to give the title compound m.p. 144°C, yield (40-50)%. The four products were the same and this was indicated from m.p. and IR spectra.

Analysis :	$C_9H_7NO_3$ (177.17)		
Calculated :	C, 61.00	H, 3.99	N, 7.90
Found :	C, 61.25	H, 4.06	N, 7.79

IR (KBr, cm^{-1}): 3200 (NH), 1720 (CO-CH_2O), 1660 (CONH), 1600 (C=C), 1240 (C-O-C). ^{1}H-NMR (DMSO-d_6 - δ ppm): 4.8 (2H, s, OCH_2), 7.1-8 (4H, m, aromatic protons), 11.35 (1H, s,NH). The mass spectrum showed the molecular ion peak (M^+, $C_9H_7NO_3$) which is the base peak at *m/z* 177 (100%).

Pharmacology

Materials and methods

Male albino rats (100-110 g body weight) were obtained from the animal house colony of the National Research Centre, Dokki, Cairo (Egypt). They were randomly assigned to groups each group contain 6 animals. Each group was housed individually and fed on a standard laboratory diet and water ad. Libitum.

Acute anti-inflammatory activity

The inflammatory oedema was induced in one hind paw of the rats by s. c. injection of 0.05 ml of 1% carrageenan into the subplantar tissue according to the method of (Winter *et al.*, 1962) the first group (negative control group) received propylene glycol and water 10% v/v the second group (positive control group) received salicylamide in a single oral dose of 20 mg/100g body weight orally. The other groups received the tested compounds in a dose of 0.14 mmol/100 g body weight (dissolved in 10% propylene glycol) one hour before carrageenan challenge. Initial foot paw volume was measured immediately following carrageenan challenge. The swelling in each test group of animals (n=6), after 3 hour treatment carrageenan administration was used to calculate percent oedema achieved by the reference and tested compounds compared with the control group.

Carrageenan-induced pleurisy in rats

Rats (100-110 g) were fasted over night and in the morning they were P. O. given the tested compounds (0.14 mmol/100 g body weight) dissolved in 10% propylene glycol. One hour latter, the animals were lightly anaesthetised; carrageenan (0.1 of 2% carrageenan solution in saline) was intrapleurally injected between the 8th and 9th rib.

Three hours latter rats was again anaesthetised, bled to death and the volume of the pleural exudate was measured for each group (n=6). A standard positive control group

receiving salicylamide (10 mg/100 g body weight) was treated in the same way and the results were compared to a control non-treated group (only received 10% propylene glycol), (Velo *et al.*, 1973).

Analgesic activity

Electric current as a noxious stimulus was used as described by (Charlier *et al.*, 1961) and the minimum voltage that causes the rats to emit a cry was determined. Electrical stimulation of the tail was applied by means of 515 Master Shocker (Lafayette Inst. Co.). The minimum voltage required for the animal to emit a cry was recorded for the control and treated groups with the tested compounds and salicylamide as reference standard (dose=0.14 mmol /100 g body weight, n=6). Three hours latter the electric current was applied and the minimum voltage that causes the animal to emit a cry was determined.

Ulcerogenic effect in rats

Male rats (100-110 g.) were fasted overnight, and orally given the tested compounds (0.14 mmol/100 g body weight). Five hours later, animals were killed, their stomachs removed, opened along the greater curvature, and the number of ulcers assessed by the method of (Corell *et al.*, 1979). A separate group which received salicylamide (20 mg/100 g body weight) as a positive control was used. The results were compared with a propylene glycol (10% solution) treated group as negative control.

Statistical analysis of the data was computed via the students-test. A 0.05 level of probability was regarded as significant according to (Snedecol and Cochran, 1971).

RESULTS

During the biological evaluation, the animals tolerated the tested compounds quit well and no mortalities have been recorded among them such preliminary results encourage further studies.

From Table II some of the tested compounds show antiinflammatory activity especially compounds **7, 3a, 8, 6, 15, 17a,** and **4** in descending order, where the first five compounds showed activity superior to salicylamide itself in respect to the volume of the pleural fluid & analgesic activity. Compound **6** showed activity superior to salicylamide in respect to the % oedema, volume of pleural fluid and the number of ulcers found.

The tested compounds **3a, 9, 4, 2, 17a, 6, 8, 7, 4, 16f, 16c, 5,** and **16a** were found to have significant analgesic activity in descending order. This latter finding represent an important advantage to their antiinflammatory activity, where the first nine compounds showed analgesic activity superior to that of salicylamide itself (Table II).

The ulcerogenic activity of the compounds in comparison with salicylamide clearly showed that compound **15** induce no ulcerogenic effect. The finding correlates well and add a very important advantage to its antiinflammatory activity mean while compounds **5, 8, 4, 16f, 6, 3a, 16a, 9, 7, 16c, 2,** and **17a** showed ulcerogenicity less than that of the positive control as shown in Table II.

RESULTS AND DISCUSSION

Salicylamido-acetic acid was prepared using literature method (El-Sebai *et al.*, 1974), treatment of it with thionyl chloride (Furniss *et al.*, 1989), in dry benzene afforded

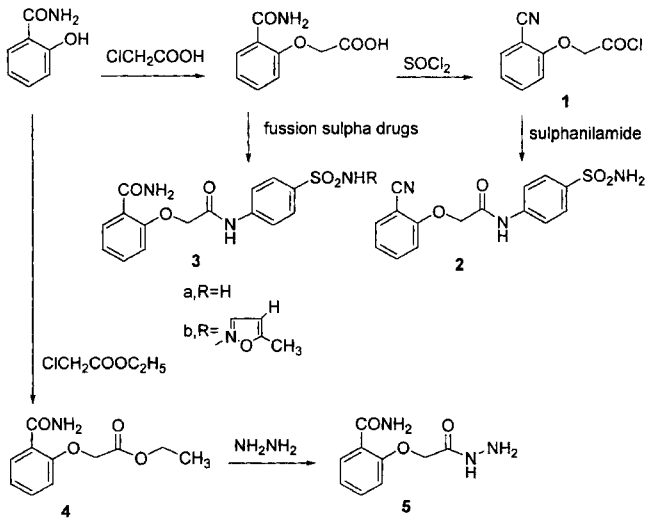
Table II. Antiinflammatory, analgesic and ulcerogenic effect of compounds (2, 3a, 4, 5, 6, 7, 8, 9, 15, 16a,c,f and 17a)

Animal group	Tested material	% Oedema (mean ± s.e.)	Pleural fluid (mean ± s.e.)	Analgesic activity (Volts) (mean ± s.e.)	Number of ulcers (mean ± s.e.)
Control	Propylene glycol+water	61.87 ± 1.34	0.63 ± 0.007	72.7 ± 1.73	0 ± 0
Positive Control	Salicylamide	28.95* ± 1.11	0.42* ± 0.009	139* ± 5.93	6.0* ± 1.66#
1	2	66.99 ± 1.99	0.64 ± 0.019	153.1* ± 3.17	4.9* ± 0.59#
2	3a	31.18* ± 3.91	0.21* ± 0.021	169* ± 1.16	2.00* ± 0.54#
3	4	52.39* ± 1.19	0.62 ± 0.016	143* ± 5.03	1.55* ± 0.29
4	5	66.23 ± 3.38	0.63 ± 0.020	128* ± 3.44	0.54* ± 0.29
5	6	38.17* ± 2.94	0.40* ± 0.026	151* ± 3.55	0.20* ± 0.21
6	7	28.92* ± 1.87	0.34* ± 0.010	145.9* ± 5.44	2.91* ± 0.54
7	8	35.17* ± 2.19	0.40* ± 0.004	152.2* ± 5.11	1.00* ± 0.28#
8	9	63.17 ± 1.97	0.65 ± 0.011	157* ± 7.03	2.5* ± 2.17#
9	15	45.11* ± 3.13	0.40* ± 0.013	154* ± 1.99	0 ± 0
10	16a	62.95 ± 1.24	0.66 ± 0.004	123.1* ± 3.33	2.25* ± 0.98
11	16c	65.19 ± 1.8	0.64 ± 0.001	129.0* ± 5.42	3.50* ± 0.31
12	16f	67.13 ± 1.21	0.63 ± 0.009	139* ± 3.99	1.50* ± 0.21
13	17a	50.11* ± 0.99	0.62 ± 0.009	151.7* ± 3.39	5.30* ± 1.77

*Significantly different from control values at P 0.05
#Congestion

2-(chloroacetyloxy)benzonitrile. Further, reaction of compound **1** with an equimolecular amount of sulfanilamide in presence of few drops of triethylamie afforded *O*-[*N*-(sulphanilamido)acetyloxy] benzonitrile **2**. (Scheme 1). When salicylamido-acetic acid was allowed to react with an equimolecular amount of sulpha drugs namely sulfanilamide and sulphaoxazole by fussion the corresponding *O*-[*N*-(sulpha drug)acetyl]salicylamides (**3a, b**) were obtained. (Scheme 1). Synthesis of the ester derivatives **4** was achieved by the reaction of salicylamide with ethyl chloroacetate in presence of anhydrous potassium carbonate. Reaction of **4** with hydrazine hydrate 99% afforded the hydrazide **5**. (Scheme 1). Hydrazide **5** was considered as the key intermediate for the synthesis of several series of new compounds. Reaction of hydrazide **5** with acetylacetone and/or ethyl acetoacetate gave O-[(3, 5-dimethylpyrazol-1-yl)acetyl] salicylamide (**6**), and *O*-[(3-methyl-5-oxo-pyrazolin-1-yl)acetyl]salicylamide (**7**). (Fig. 1). Also, reaction of hydrazide **5** with isatin (Fahmy *et al.*, 1997), lead to the formation of *O*-[*N*-(2-oxo-3-indolinylidene)acetic acid hydrazido]salicylamide (**8**). The *N*-imido derivatives **9, 10,** and **11**, were obtained by treating the hydrazide **5** with phthalic, maleic and/or succinic anhydrides respectively (Abdel-motti *et al.*, 1995), (Fig. 1). On the other hand, reaction of hydrazide **5** with carbon disulphide in ethanolic potassium hydroxide at room temperature (Kassem and El-Masry., 1995), afforded the potassium dithiocarbazate **12**, cycloconden-sation of **12** with sulphuric acid at room temperature (Kassem and El-Masry, 1995) afforded the corresponding *O*-[(5-thioxo-1,3,4-thiadiazol-2-yl)methyl]salicylamide (**13**).

Compound **14** was prepared according to Young & Wood (Abdel-motti *et al.*, 1995), by heating the hydrazide **5** with CS_2 in presence of ethanolic potassium hydroxide. *O*-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]salicylamide (**15**) was obtained by treating the hydrazide **5** with benzoic acid in $POCl_3$ (Fahmy, 1997). Synthesis of the desired Schiffs bases **16a-f** was achieved by allowing



Scheme 1. Synthesis of compound **1~5**

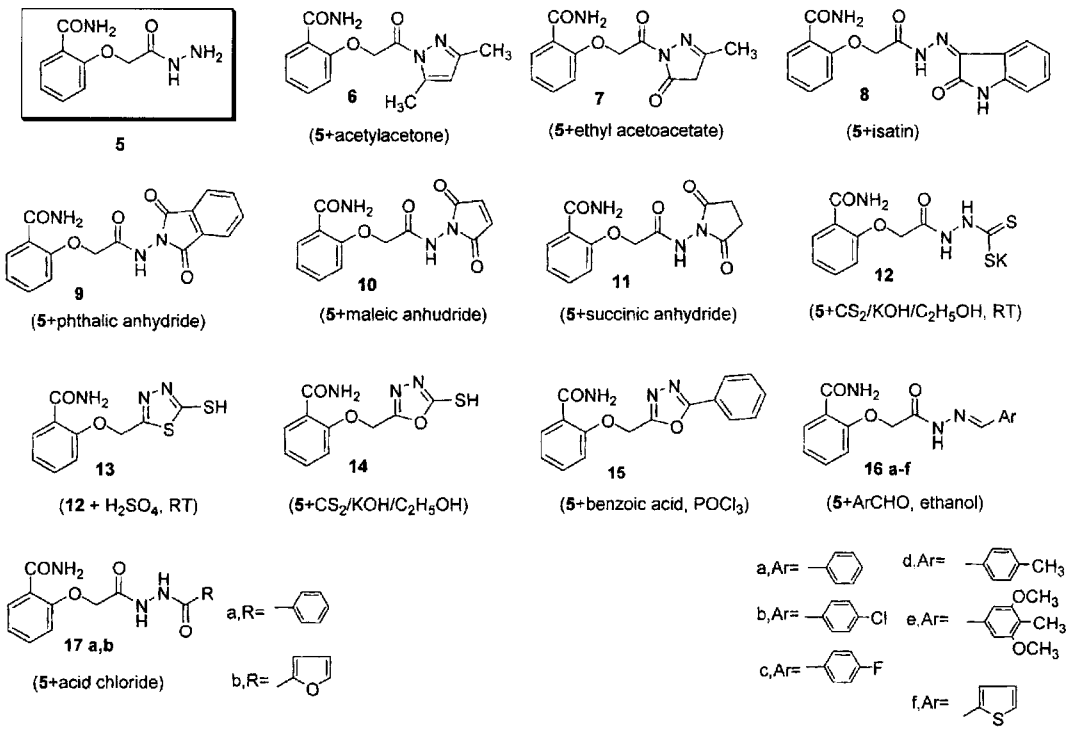


Fig. 1. Structure of compound **6~17**

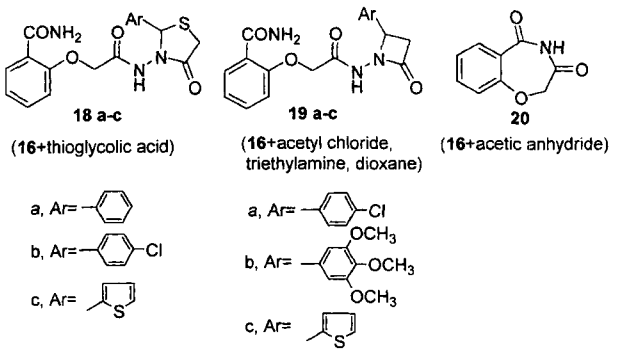
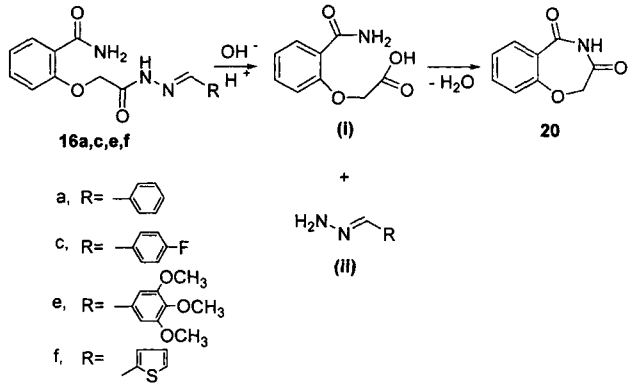


Fig. 2. Structure of compound **18~20**



Scheme 2. Transformation to compound **20**

the hydrazide **5** to react with different aromatic and/or heterocyclic aldehydes namely, benzaldehyde, *p*-chorobenzaldehyde, *p*-florobenzaldehyde, *p*-methylbenzaldehyde, 3,4,5-trimethoxy-benzaldehyde and/or thiophene-2-carboxaldehyde. Whereby the compounds **16a-f** were obtained in high yields. Also, compound **5** was reacted with acid chlorides namely, benzoyl chloride and furan-2-carbonyl chloride to give compounds **17a,b** respectively (Fig. 1).

Cyclocondensation of the Schiffs bases **16a,b** and **f** with thioglycolic acid (Kassem *et al.*, 1993), afforded the corresponding thiazolidinones **18a-c** respectively (Fig. 2). Attempted cyclocondensation of the Schiffs bases **16a,c,e,f** with acetic anhydride to give the desired 1,3,4-oxadiazole derivatives (Abbas *et al.*, 1994) have been failed, only 1,4-bezoxazepine-3,5-dione (**20**) was obtained from all reactions and this was indicated from mixed melting points and infrared (Fathalla *et al.*, 1995) spectra. The mechanism of such reaction may be passes through two steps as indicated in Scheme 2.

Hydrolysis of the Schiffs bases **16a,c,e,f** to give the hydrazone ii and salicylamido-acetic acid (i). Loss of one molecule of water from O-salicylamido-acetic acid (**i**) gave 1,4-benzoxazepine-3,5-dione (**20**) (Scheme 2). The structure of compound **20** was confirmed with concordant microanalytical data, IR, ^{1}H-NMR and mass spectra.

REFERENCES

Abbas, S. E., El-Ansary, S. L., and Mikhael, A. N., Synthesis of Some 1,3,4-Oxadiazolines and Thiazolidinones of Expected Antibacterial Activity. *Egypt. J. Pharm. Sci., 35*, 21-30 (1994).

Abdel-Motti, F. M., Alafaleg, E. I., and Almehbad, N. Y. F., Synthesis and Reaction of Some Derivatives of Pyridazinylthioglycolic Acid Hydrazide with Possible Antimicrobial Activity. *ibid*, 36, 117-124 (1995).

Charlier, R., M. Prost, F. Binon, and G. Deltour, Pharmacology of an Anti-tussive-1-Phenyl-2-propynyl-4-propinoxypiperidine acid Fumarate. *Arch. Intern. Pharamacodyn.*, 134, 306 (1961).

Coleman, D. L., Wood, N. L., and Darling, W. M. Martindale the Extrapharmacopoei Edited by James E. E. Reynolds Published by Direction of The Council of Royal Pharmaceutical Society of Great Britain. Thirtieth Edition, 1-36 (1993).

Corell, T., Moller, J. K., and Splawinskim, J., A New Anti-inflammatory Derivative of Indiazole Which Is Less Ulcerogenic than Indomethacin in Rats. *Acta Pharmacol., er. Toxicol.*, 45, 232-239 (1979).

Daidone, G., Raffa, D., and Piescia, S., Synthesis and Evaluation of the Analgesic and Antiinflammatory Activities of *N*-Substituted Salicylamides, *IL. Farmaco* 44 (5), 465-473 (1989).

El-sebai, A. I., Rida, S. M., Beltagy, Y. A., and Abdel-Khalek, M. M. Synthesis of Some New Semisynthetic Penicillins. *Pharmazie*, 29 (9), 581 (1974).

Fahmy, H. H., Synthesis of Some New Quinoline Derivatives of Potential Antimicrobial Activity. *Egypt. J. Pharm. Sci.*, 38, 403-414 (1997).

Fahmy, H. H., W. Abdou, A. M., and El-eraky, W., Synthesis of some new pyrazolones as potent antiinflammatory agent. *Bull. Fac. Pharm.* Cairo Univ., 33, 85-92 (1995).

Fathalla, O. A., E. Kassem, and M. M., Farouk, A., Synthesis of Some New Oxadiazoles and Thiazoles of Quinoline Derivatives as Antimicrobial Agents, Proceedings of the First International Scientific Conference (Science & Development), Fac. of Science Al-Azhar University, Cairo, 20-23 March, 101-112 (1995).

Furniss, B. S., Hannaford, A. N., Smith, P. W. G., and Tachel, A. R., Vogels Text Book of Practical Organic Chemistry, edited by Longmann, Singapore Publishers, Singapore, Pte Ltd. 716 (1989).

Kassem, E. M. M. and El-Masry, A., Synthesis of Some New Benzothiazole-2-Acrylic Acid Hydrazide Derivatives of Possible Biological Activity, Proceedings of the First International Scientific Conference (Science & Development), Fac. of Science Al-Azhar University, Cairo, 20-23 March, 114-134 (1995).

Kassem, E. M. M., El-difrawy, S., Fathalla, O. A., El-Ansary

A., and Abdou, W. A. M., Synthesis of Some New Thiazolidinone Amide and Pyrazolidinones of Possible Inhibitory Effect on Biomphalaria Alexandrina Snail Enzymatic Activities. *Egypt. J. Bilh.*, 15, 171-181 (1993).

Kumar, R. and Giri, S., Nizamuddin, Synthesis of Some 1-[5'-(Substituted-Phenoxymethyl)-1',3',4'-Thiadiazol-2'-yl]-4-Substituted-2-azetidinones as Potential Fungicides. *J. Indian Chem. Soc.*, LXV, 571-573 (1998).

Snedecol, W. G. and Cochran, G. W., Statistical Methods, Iowa State University, press, Ames., Iowa State. Ames., (1971).

Velo, G. P., Dunn, C. T., Giroud, J. P., Timisit, J., and Willoughby, D. A., Distribution of Prostaglandin in Inflammatory Exudate. *J. Path.*, 111, 149 (1973).

Winter, C. A., Risley, E. A., and Nuss, G. W., Carrageenan Induced Oedema in Hind Paw of the Rat as an Assay for Antiinflammatory Drug. *Proc. Soc. Exp. Biol. Med.*, 111, 544-547 (1962).