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Synthesis of New Salicylamide Derivatives with Evaluation of Their Antiinflammatory, Analgesic and Antipyretic Activities

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A new series of pyridazine, pyrazoles, pyrazolidine-3,5-dione, Semicarbazide, thiosemicarbazides, hydantoin, thiohydantoins, 1,2,4-triazoles, *S*-triazolo[3,4-b]-1,3,4-thiadiazoles incorporated indirectly into salicylamide moiety at position 2 were synthesized. Also the synthesis of novel series of 3-salicylamido-2-hydroxypropyl-amine derivatives were prepared. Several of these compounds were screened for antiinflammatory, analgesic, antipyretic and ulcerogenic activities.

Key words: Salicylamide derivatives, 1,2,4-Triazoles, *S*-Triazolo[3,4-b]-1,3,4-thiadiazoles, pyrazoles, Antiinflammatory, analgesic and antipyretic activities.

INTRODUCTION

Research on the nonsteroidal antiinflammatory and analgesic drugs is receiving continuous interest in industrial and academic laboratories. Due to the frequent presence with this class of drugs of undesirable side effects (Fahmy *et al.*, 1995), such as the gastrolesivity and the blood dyscrasia, the most desirable result would to obtain better tolerated new derivatives (Daidone *et al.*, 1989). A review of the literature revealed that salicylic acid and salicylates exhibit beside their antipyretic and analgesic properties a pronounced antiinflammatory activity (Coleman *et al.*, 1993).

Also, *S*-triazoles derivatives are reported to exhibit broad spectrum of biological activity such as antibacterial (Van reet *et al.*, 1979) antifungal (Modi *et al.*, 1977), analgesic (Pant *et al.*, 1983) and antiinflammatory activities (Wade *et al.*, 1979; Mueckter *et al.*, 1977). Moreover, it was reported that *S*-triazoles fused to 1,3,4-thiadiazoles possess antiinflammatory activity (Mody *et al.*, 1982). Based on these findings the purpose of the present work is to synthesize a variety of some new heterocycles, namely pyridazine, pyrazoles, pyrazolidinedione, triazole, *S*-triazolo[3,4-b]-1,3,4-thiadiazoles, imidazolidin-4, 5-diones and other related structure incorporated indirectly into the salicylamide moiety at its position 2 hoping that the resultant compounds might exhibit a promising antiinflammatory and analgesic activities.

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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 in KBr on a Perkin Elmer Model 137 infracord. The ^{1}H-NMR spectra were measured in DMSO 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

O-[*N*-(Benzilmonohydrazono)acetyl]salicylamide (2)

A mixture of compound **1** (2.09 g, 0.01 mole) and benzil (2.10 g, 0.01 mole) was refluxed in absolute ethanol (50 mL) for 6 h. The reaction mixture was concentrated then cooled. The solid separated was filtered off to give compound **2** (Table I, II).

O-[(4-Cyano-3-imino-5,6-diphenylpyridazine-2-yl)acetyl] salicylamide (3)

A mixture of **2** (4.01 g, 0.01 mole) and malononitrile (0.66 g, 0.01 mole) in methanol (100 mL) and DMF (10 mL) was refluxed for 10 h. The reaction mixture was

concentrated then cooled and the solid separated was filtered off to give compound **3** (Table I, II).

***O*-[(5-Amino-3-phenylpyrazol-1-yl)acetyl]salicylamide (4)**
A solution of **1** (2.09 g, 0.01 mole) and α-cyanoacetophenone (1.45 g, 0.01 mole) in DMF (20 mL) was refluxed for 5 h. The solvent was evaporated under reduced pressure and the precipitate was filtered, dried to give compound **4** (Table I, II).

***O*-[(5-Amino-3,4-dicyanopyrazol-1-yl)acetyl]salicylamide (6)**
Tetracyanoethylene (1.92 g, 0.015 mole) was added at room temperature with stirring to a solution of the hydrazide **1** (2.09 g, 0.01 mole) in DMF (20 mL), the reaction mixture was heated under reflux for 6 h. The solution was concentrated then cooled and the solid separated after addition of water was filtered off to give compound **6**. (Table I, II).

***O*-[(3,5-Dioxopyrazolidine-1-yl)acetyl]salicylamide (7)**
To a solution of sodium (0.198 g) in absolute ethanol (20 mL) was added freshly distilled diethyl malonate (0.68 g, 0.004 mole) followed by the addition of carbohydrazide **1** (0.58 g, 2.80 m mole). The reaction mixture was heated until all the alcohol has been distilled over and the residue was heated at 150-155°C for 6 h, it was cooled and dissolved in water, then filtered to remove unreacted materials, acidified with 10% hydrochloric acid, and the precipitate was filtered off and washed with cold water to give compound **7** (Table I, II).

***O*-[(5-Amino-4-cyano-3-methylthiopyrazol-1-yl)acetyl]salicylamide (8)**
A solution of compound **1** (2.09 g, 0.01 mole) and bis (methylthio)-methylene malononitrile (1.70 gm, 0.01 mole) in DMF (40 mL) was refluxed for 5 h. The reaction mixture was concentrated, cooled then poured on ice cold water, the resultant solid was filtered off to give compound **8** (Table I, II).

1-[*O*-(Salicylamido)acetyl]-4-(*p*-chlorophenyl)semicarbazide (9a) and 1-[*O*-(Salicylamido)acetyl]-4-substituted aryl thiosemicarbazides (9b,c)

General method
A mixture of compound **1** (2.09 g, 0.01 mole) and the suitable aryl isocyanate and/or isothiocyanate (0.01 mole) in dry benzene (50 mL) was refluxed for 6 h. The reaction mixture was concentrated, cooled and the solid formed after cooling was filtered off and recrystallized to give compounds **9a-c** (Table I, II).

1-(*p*-Chlorophenyl)-2-oxo-3-[*O*-(salicylamido)acetamido]-imidazolidin-4,5-dione (10a)
A mixture of **9a** (1.81 g, 0.005 mole) and oxalyl chloride (0.006 mole) in dry benzene (50 mL) was heated at 50°C for 6 h. The solvent was evaporated and the solid residue was recrystallized to give compound **10a** (Table I, II).

1-(Substituted aryl)-3-[*O*-(salicylamido)acetamido]-2-thioxoimidazolidin-4,5-dione (10b,c)
The foregoing procedure was carried out except that compound **9a** was replaced by **9b,c** to afford **10b,c**. (Table I, II)

***O*-[(4-Amino-5-mercapto-1,2,4-triazol-3-yl)methyl]salicylamide (12)**
To a solution of potassium dithiocarbazate **11** (Fahmy and El-Eraky, under publication) (3.23 g, 0.01 mole) in water (10 mL) hydrazine hydrate 99% (1.5 mL, 0.03 mole) was added. The reaction mixture was heated under reflux for 4 h, diluted with ice cold water and acidified with concentrated hydrochloric acid. The obtained white precipitate was filtered, washed with water and recrystallized to give compound **12** (Table I, II).

***O*-[(4-Arylideneamino-5-mercapto-1,2,4-triazol-3-yl)methyl]-salicylamide derivatives (13a-c).**
A mixture of **12** (2.65 g, 0.01 mole) and the appropriate aldehyde (0.01 mole) in ethanol (15 mL) was heated under reflux for 5 h. On cooling the precipitated solid was filtered, dried and recrystallized to give compounds **13a-c** (Table I, II).

6-Phenyl or substituted phenyl-3-(salicylamidomethyl)-1,2,4-triazolo[3,4-b]-[1,3,4]-thiadiazoles (14a,b)
A mixture of equimolar amounts of compound **12** (2.65 g, 0.01 mole) and the appropriate acid chloride (0.011 mole) in dry pyridine (20 mL) was heated under reflux for 6 h, poured over crushed ice, the precipitated solid was filtered, washed with water, dried and recrystallized to give compounds **14a,b** (Table I, II).

6-(2-Chlorophenyl)-3-(salicylamidomethyl)-1,2,4-triazolo [3,4-b][1,3,4]-thiadiazole (15)
A mixture of compound **12** (2.65 g, 0.01 mole) and 2-chlorobenzoic acid (1.56 g, 0.01 mole) in phosphorus oxychloride (5 mL) was heated under reflux for 1 h. The excess of phosphorus oxychloride was removed under reduced pressure, the residue was triturated with ice-cold water and neutralized with 10% solution of sodium bicarbonate. The resulting product was filtered, washed with water, dried and recrystallized to give compound **15** (Table I, II).

1,4-Benzoxazepine-3,5-dione (16)
Compound **12** (2.65 g, 0.01 mole) in acetic anhydride (15 mL) was heated under reflux for 2 h. The reaction mixture was neutralized with ammonium hydroxide solution and the precipitated product was filtered, washed with water, dried and recrystallized to give compound **16** (Table I, II).

Preparation of 3-salicylamido-2-hydroxypropylamine derivatives (18a-e)

A solution of epoxide **17** (Joullie *et al.*, 1971) (3.86 g, 0.02 mole) and the appropriate amine (0.02 mole) in ethanol (80 mL) was refluxed with stirring for 5 h. Evaporation of the solvent *in vacuo* gave an oily residue which was crystallized on trituration with petroleum ether, then the obtained solid was collected by filteration and recry-

Table I. Physical and analytical data of the newly synthesized compounds

Comp No.	m.p. (°C) solvent	Yield %	Formula M.wt	Analysis % Calculated/Found		
				C	H	N
2	158 EtOH	90	$C_{23}H_{19}N_3O_4$ 401.45	68.80 68.62	4.78 4.70	10.47 10.39
3	110 $CHCl_3$/pet.ether	63	$C_{26}H_{19}N_5O_3$ 449.50	69.46 69.33	4.26 4.20	15.58 15.61
4	190 EtOH/H_2O	65	$C_{18}H_{16}N_4O_3$ 336.38	64.27 64.32	4.80 4.68	16.66 16.80
6	150 EtOH/H_2O	90	$C_{14}H_{10}N_6O_3$ 310.30	54.19 54.26	3.25 3.30	27.09 27.15
7	228 EtOH	70	$C_{12}H_{11}N_3O_5$ 277.26	51.98 51.86	4.00 4.10	15.16 15.25
8	130 EtOH/H_2O	71	$C_{14}H_{13}N_5O_3S$ 331.38	50.74 50.81	3.96 4.00	21.14 21.25
9a	238 DMF	85	$C_{16}H_{15}ClN_4O_4$ 362.80	52.97 52.90	4.18 4.15	15.45 15.48
9b	200 EtOH	75	$C_{17}H_{18}N_4O_3S$ 358.45	56.96 56.94	5.07 5.11	15.63 15.67
9c	190 EtOH	70	$C_{16}H_{16}N_4O_3S$ 344.42	55.79 55.72	4.69 4.66	16.27 16.30
10a	210 EtOH/H_2O	90	$C_{18}H_{13}ClN_4O_6$ 416.80	51.87 51.79	3.15 3.13	13.45 13.51
10b	180 DMF/H_2O	85	$C_{19}H_{16}N_4O_5S$ 412.45	55.33 55.29	3.92 3.89	13.59 13.61
10c	230 DMF/H_2O	92	$C_{18}H_{14}N_4O_5S$ 398.42	54.26 54.35	3.55 3.58	14.07 14.15
12	222 EtOH	68	$C_{10}H_{11}N_5O_2S$ 265.32	45.27 45.32	4.19 4.10	26.40 26.42
13a	210 DMF/H_2O	60	$C_{17}H_{14}FN_5O_2S$ 371.42	54.97 54.78	3.81 3.78	18.86 18.77
13b	215 EtOH/H_2O	65	$C_{18}H_{17}N_5O_3S$ 383.46	56.38 56.31	4.48 4.45	18.27 18.31
13c	140 DMF/H_2O	75	$C_{20}H_{21}N_5O_5S$ 443.52	54.16 54.22	4.78 4.74	15.79 15.72
14a	190 $CHCl_3$/pet.ether	85	$C_{17}H_{13}N_5O_2S$ 351.41	58.10 58.18	3.74 3.87	19.93 19.86
14b	170 MeOH/H_2O	68	$C_{17}H_{12}ClN_5O_2S$ 385.85	52.91 52.85	3.14 3.17	18.15 18.11
15	180 $CHCl_3$/pet ether	65	$C_{17}H_{12}ClN_5O_2S$ 385.85	52.91 52.95	3.14 3.16	18.15 18.12
16	145 AcOH/H_2O	60	$C_9H_7NO_3$ 177.17	61.00 61.07	3.99 4.06	7.90 7.86
18a	180 $CHCl_3$/pet ether	60	$C_{14}H_{22}N_2O_3$ 266.38	63.12 63.20	8.34 8.28	10.52 10.49
18b	130 benzene	65	$C_{12}H_{18}N_2O_3$ 238.32	60.47 60.49	7.63 7.70	11.76 11.75
18c	170 $CHCl_3$/pet ether	90	$C_{15}H_{22}N_2O_3$ 278.39	64.71 64.77	7.98 7.80	10.06 10.12
18d	120 C_6H_6/pet.ether	92	$C_{17}H_{20}N_2O_3$ 300.39	67.96 67.92	6.72 6.65	9.82 9.78
18e	280 DMF/EtOH	65	$C_{17}H_{18}N_4O_3$ 326.39	62.55 62.52	5.57 5.54	17.17 17.20

stallized from the proper solvent (Table I, II).

Pharmacology

Materials and Methods

Male albino rats (100-200 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 5 animals. Each group was housed individually and fed on a standard Laboratory diet and water ad, libitum. Salicylamide (CiD company) carrageenan (BDH) were purchased.

Antiinflammatory activity

Table II. Spectral data of the newly synthesized compounds

Comp. No.	Spectral Data
	IR (KBr, cm^{-1}); ^{1}H-NMR, (DMSO, d_6) or $CDCl_3$, 270 MHz, δ ppm; MS, m/z (%)
2	IR: 3423, 3322 (NH_2, NH), 1702 (Ph-C=O), 1660, 1645 (CO-NH_2, CO-NH), 1600 (C=C), 1250 (C-O-C). ^{1}H-NMR (DMSO-d_6): 4.9 (2H, s, OCH_2), 7.0-7.8 (14H, m, Ar-H), 8.0 (2H, s, $CONH_2$), 10.5 (1H, s, NH), NH, NH_2 exchangeable with D_2O. MS: 402.15, M^+ (100)
3	IR: 3360, 3200 (NH_2, NH), 2200 (C½N), 1710 (O-CH_2-C=O), 1660 (CO-NH_2), 1600 (C=C), 1240 (C-O-C). ^{1}H-NMR (DMSO-d_6): 5.05 (2H, s, OCH_2), 7.0-7.7 (14H, m, Ar-H), 7.9 (2H, s, $CONH_2$), 8.7 (1H, s, NH). MS: 449.64, M^+ (4) and 134.01 (100)
4	IR: 3423.9,3321,3059.6 (two NH_2), 1653 (two C=O), 1598.3 (C=C), 1240 (C-O-C). ^{1}H-NMR (DMSO-d_6): 4.25 (2H, s, NH_2), 4.80 (2H, s, OCH_2), 7.05-7.80 (10H, m, Ar-H and pyrazole protons), 8.05 (2H, s, $CONH_2$). MS: 337.3, M^+ + 1 (100) which is the base peak.
6	IR: 3460, 3189, 3144 (two NH_2), 2226 (two C½N), 1714 (CO-CH_2O), 1653 (CO-NH_2), 1602 (C=C), 1238.8 (C-O-C). ^{1}H-NMR (DMSO-d_6): 4.8 (2H, s, NH_2), 5.05 (2H, s OCH_2), 7.0-7.9 (4H, m, Ar-H), 8.1 (2H, s, $CONH_2$), NH_2 exchangeable with D_2O. MS: 310.2, M^+ (100) which is the base peak.
7	IR: 3423, 3320, 3200 (NH_2, NH), 1720, 1680 (two C=O, of pyrazolidinedione), broad band at 1650 (two C=O), 1600 (C=C), 1240 (C-O-C). ^{1}H-NMR (DMSO-d_6): 4.80 (4H, s, OCH_2, and CH_2 of pyrazol-idinedione), 7.05-7.75 (4H, m, Ar-H), 8.0 (2H, s, $CONH_2$), 10.5 (1H, s, NH), NH, NH_2 exchangeable with D_2O. MS: 278, M^+ + 1 (13) and 218.09 (100).
8	IR: 3420, 3320 (two NH_2), 2200 (C½N), 1720 (CO-CH_2O), 1650 (CO-NH_2), 1600 (C=C), 1240 (C-O-C). ^{1}H-NMR (DMSO-d_6): 2.75 (3H, s, SCH_3), 4.75 (2H, s, NH_2), 4.95 (2H, s, OCH_2), 7.10-7.95 (4H, m, Ar-H), 8.10 (2H, s, $CONH_2$), NH_2 exchangeable with D_2O. MS: 330.93, M^+ (100) which is the base peak.
9a	IR: 3440, 3295 (NH_2, NH), 1660, 1640 (2 C=O), 1600 (C=C), 1240 (C-O-C), 750 (C-Cl). ^{1}H-NMR (DMSO-d_6): 4.9 (2H, s, OCH_2), 7.0-7.9 (8H, m, Ar-H), 8.1 (2H, s, $CONH_2$), 10.2, 10.6, 10.8 (3H, 3s, 3NH), NH, NH_2 exchangeable with D_2O.
9b	IR: 3350, 3163 (NH_2, NH), 1662 (2 C=O), 1241 (C-O-C), 1056 (C=S). ^{1}H-NMR (DMSO-d_6): 2.8 (3H, s, CH_3), 4.9 (2H, s, OCH_2), 7.0-7.8 (8H, m, Ar-H), 8.0 (2H, s, $CONH_2$), 10.0, 10.5, 10.7 (3H, 3s, 3NH), NH, NH_2 exchangeable with D_2O. MS: 256 (1.42), 209 (14.81), 192 (83.86), 150 (2.50), 120.9 (100), 104.9 (9.69), 91.9 (10.18).
9c	IR: 3420, 3320, 3240 (NH_2, NH), 1690, 1650 (2 C=O), 1600 (C=C), 1240 (C-O-C), 1050 (C=S). ^{1}H-NMR (DMSO-d_6): 4.95 (2H, s, OCH_2), 7.0-7.95 (9H, m, Ar-H), 8.1 (2H, s, $CONH_2$), 10.0, 10.5, 10.8 (3H, 3s, 3NH), NH, NH_2 exchangeable with D_2O. MS: 344.98, M^+ (5) and 326.98 (100).
10a	IR: 3400, 3250 (NH_2, NH), 1730 (3 C=O, of imidazolidin), 1640 (2 C=O of $CONH_2$, CONH), 1595 (C=C), 1250 (C-O-C), 750 (C-Cl). ^{1}H-NMR (DMSO-d_6): 4.9 (2H, s, OCH_2), 7.0-7.9 (8H, m, Ar-H), 8.1 (2H, s, $CONH_2$), 10.2 (1H, s, NH), NH, NH_2 exchangeable with D_2O. MS: 416.1, M^+ (44), 418, M^++2 (18), 152.9 (100).
10b	IR: 3440, 3280 (NH_2, NH), 1720 (2 C=O, of imidazolidin), 1670 (2 C=O of $CONH_2$, CONH), 1600 (C=C), 1240 (C-O-C), 1050 (C=S). ^{1}H-NMR (DMSO-d_6): 2.7 (3H, s, CH_3), 4.85 (2H, s, OCH_2), 7.0-7.8 (8H, m, Ar-H), 8.10 (2H, s, $CONH_2$), 10.0 (1H, s, NH), NH, NH_2 exchangeable with D_2O. MS: 412.3, M^+ (20) and 398.2 (100).
10c	IR: 3420, 3239 (NH_2, NH), 1710 (2 C=O, of imidazolidin), 1655 (2 C=O of $CONH_2$, CONH), 1600 (C=C), 1234 (C-O-C), 1050 (C=S). ^{1}H-NMR (DMSO-d_6): 4.95 (2H, s, OCH_2), 7.0-7.9 (9H, m, Ar-H), 8.1 (2H, s, $CONH_2$), 10.0 (1H, s, NH), NH, NH_2 exchangeable with D_2O. MS: 370.1 (0.5), 352.1 (0.72), 236.2 (4.03), 192 (25.94), 177 (12.83), 150 (9.29), 137 (19.01), 121 (100), 105 (27.72).

Table II. continued

Comp. No.	Spectral Data
12	IR: 3400, 3200 (NH, NH_2), 2560 (SH), 1650 (CO-NH_2), 1600 (C=C), 1245 (C-O-C), 1160 (C=S) it is indicate the keto enol form. ^{1}H-NMR (DMSO-d_6): 4.80 (2H, s, OCH_2), 7.0-7.9 (4H, m, Ar-H), 7.6 (2H, s, N-NH_2), 8.10 (2H, s, $CONH_2$), 13.3 (1H, s, SH), NH_2, SH exchangeable with D_2O. MS: 265.2, M^+ (30), 121 (100).
13a	IR: 3400, 3200 (NH_2), 2550 (SH), 1650 (CO-NH_2), 1600 (C=C), 1240 (C-O-C), 1120 (C=S), 1080 (C-F) it is indicate the keto enol form. ^{1}H-NMR (DMSO-d_6): 4.80 (2H, s, OCH_2), 7.0-7.9 (8H, m, Ar-H), 8.1 (2H, s, $CONH_2$), 8.5 (1H, s, CH=N), 11.0 (1H, s, SH), SH, NH_2 exchangeable with D_2O. MS: 270.3 (0.36), 249.7 (0.37), 196 (2.75), 151 (21.88), 134 (71.60), 121 (68.95), 105 (100), 93 (20.93), 77 (40.74).
13b	IR: 3400, 3200 (NH_2), 2540 (SH), 1648 (CO-NH_2), 1600 (C=C), 1250 (C-O-C), 1160 (C=S), it is indicate the keto enol form. ^{1}H-NMR (DMSO-d_6): 3.85 (3H, s, OCH_3), 4.80 (2H, s, OCH_2), 7.05-7.90 (8H, m, Ar-H), 8.10 (3H, s, CH=N and $CONH_2$), 9.90 (1H, s, SH). MS: 383.7, M^+ (4), 134 (100).
13c	IR: 3440, 3240 (NH_2), 2560 (SH), 1650 (CO-NH_2), 1610 (C=C), 1240 (C-O-C), 1125 (C=S), it is indicate keto enol form ^{1}H-NMR (DMSO-d_6): 3.70 (3H, s, p-OCH_3), 3.90 (6H, s, two m-OCH_3), 4.90 (2H, s, OCH_2), 7.0-7.9 (6H, m, Ar-H), 8.3 (2H, s, CO-NH_2), 8.70 (1H, s, CH=N), 12.0 (1H, s, SH), SH, NH_2 exchangeable with D_2O. MS: 444, M^+ (4), 64 (100).
14a	IR: 3440, 3230 (NH_2), 1650 (CO-NH_2), 1600 (C=C), 1250 (C-O-C). ^{1}H-NMR (DMSO-d_6): 4.85 (2H, s, OCH_2), 7.0-8.0 (9H, m, Ar-H), 8.1 (2H, s, CO-NH_2), which exchangeable with D_2O. MS: 350.7, M^+ (1.58), 105 (100).
14b	IR: 3400, 3200 (NH_2), 1660 (CO-NH_2), 1600 (C=C), 1260 (C-O-C), 750 (C-Cl). ^{1}H-NMR (DMSO-d_6): 4.80 (2H, s, OCH_2), 7.0-8.0 (8H, m, Ar-H), 8.1 (2H, s, CO-NH_2) which exchangeable with D_2O. MS: 386.2, M^+ (1.03), 120.9 (100).
15	IR: 3401, 3207 (NH_2), 1680 (CO-NH_2), 1595 (C=C), 1250 (C-O-C), 750 (C-Cl). ^{1}H-NMR (DMSO-d_6): 4.9 (2H, s, OCH_2), 7.0-8.0 (8H, m, Ar-H), 8.1 (2H, s, CO-NH_2) which exchangeable with D_2O. MS: 274 (0.49), 236 (4.4), 155 (20.57), 139 (100), 137.1 (99.79), 113.1 (10.59), 111.1 (33.91), 91.2 (69.49).
16	IR: 3200, 3160 (NH), 1714 (CO-CH_2O), 1654 (CO-NH), 1602 (C=C), 1240 (C-O-C). ^{1}H-NMR (DMSO-d_6): 4.80 (2H, s, OCH_2), 7.15-8.0 (4H, m, Ar-H), 11.30 (1H, s, NH, which exchangeable with D_2O). MS: 177.1. M^+ (90), 105 (100).
18a	IR: 3380, 3324, 3060 (OH, NH_2), 1660 (C=O), 1600 (C=C), 1230 (C-O-C). ^{1}H-NMR ($CDCl_3$): 1.03-1.2 (6H, t, $2CH_3$), 2.55-2.8 (6H, m, $3CH_2$), 4.0-4.1 (1H, m, CH), 4.2-4.25 (2H, d, OCH_2), 6.1 (1H, s, OH), 6.9-8.1 (4H, m, Ar-H), 8.0 (2H, s, CO-NH_2), OH, NH_2 exchangeable with D_2O. MS: 267.1, M^++1 (0.52), 120.8 (100).
18b	IR: 3853, 3751, 3649 (OH, NH, NH_2), 1650 (C=O), 1600 (C=C), 1250 (C-O-C). ^{1}H-NMR ($CDCl_3$): 1.05-1.15 (3H, t, CH_3), 2.6-2.8 (4H, m, $2CH_2$), 4.0 (1H, m, CH), 4.1-4.2 (2H, d, OCH_2), 6.1 (1H, s, OH), 6.9-8.1 (4H, m, Ar-H), 8.0 (2H, s, CO-NH_2), OH, NH_2 exchangeable with D_2O. MS: 239.1, M^++1 (91.01), 58 (100).
18c	IR: 3460, 3440, 3266 (OH, NH_2), 1660 (C=O), 1600 (C=C), 1240 (C-O-C). ^{1}H-NMR ($CDCl_3$): 1.4-1.55 (6H, m, $3CH_2$, of piperidine ring), 2.3-2.5 (4H, m, $N(CH_2)_2$, of piperidine ring), 2.6-2.7 (2H, d, CH_2-N), 3.95-4.05 (1H, m, CH), 4.15-4.20 (2H, d, OCH_2), 5.75 (1H, s, OH), 6.9-8.2 (4H, m, Ar-H), 8.01 (2H, s, CO-NH_2), OH, NH_2exchangeable with D_2O. MS: 279.2, M^+ +1 (49), 159.1 (100).
18d	IR: 3440, 3380, 3280 (OH, NH, NH_2), 1640 (C=O), 1600 (C=C), 1240 (C-O-C). ^{1}H-NMR ($CDCl_3$): 2.6-2.8 (2H, d, CH-CH_2), 3.4 (2H, s, CH_2-C_6H_5), 3.8-3.9 (1H, m, CH), 4.0-4.1 (2H, d, OCH_2), 4.2 (1H, s, NH), 6.2 (1H, s, OH), 6.9-8.1 (9H, m, Ar-H), 8.0 (2H, s, CO-NH_2), OH, NH, NH_2 exchangeable with D_2O. MS: 301.1, M^+ +1 (13.46), 120.1 (100).
18e	IR: 3400, 3326, 3080 (OH, NH_2, NH), 1660 (CO-NH_2), 1600 (C=C), 1230 (C-O-C). ^{1}H-NMR (DMSO-d_6): 2.1 (2H, s, CH_2), 4.15-4.25 (1H, m, CH), 4.35-4.45 (2H, d, OCH_2), 5.8 (1H, s, OH), 6.95-7.90 (8H, m, Ar-H), 7.90 (2H, s, CO-NH_2), 11.35, 12.25 (2H, 2s, 2NH), OH, NH, NH_2 exchangeable with D_2O. MS: 326.05, M^+ (4), 91.9 (100).

The antiinflammatory activity was evaluated following a modified method of (Winter *et al.*, 1962) using carrageenan as inflammagen, Seventy five rats of both sexes weighing 150-200 g were divided into fifteen groups. The thickness of the left hand paw of each rat was mein mm using a vernier caliber. One of these group was kept as a control and injected with carrageenan. Whereas, the other groups were subcutaneously injected with salicyl-

amide and the tested compounds in a dose of 20 mg/100 g body weight.

After 30 min of the drug administration, the inflammation was induced by subcutaneous injection of 0.05 ml of 1% solution of carageenan in normal saline into the left hand paw of each rat. The paw thickness was then measured hourly for a period of 4 h (Table III).

Analgesic activity

The writhing method was used to study the analgesic activity (El-Hakim and Ain-Shoka, 1995). Seventy five mice of both sexes weighing from 20-25 g were divided into fifteen groups. One group was kept as a control, whereas, the other groups were subcutaneously injected with salicylamide and the tested compounds in a dose of 20 mg/100 g body weight. After 30 min. each mouse was intraperitoneally injected with 0.25 ml of 20% aqueous solution of *p*-benzoquinone as an irritant. Mice of all groups were observed for 4 succesive hours to count the number of animals that protected against writhings (Table IV)

Antipyretic activity

Seventyfive rats of both sexes weighing 150-180 g were divided into fifteen groups. All rats were made hyperthermic by subcutaneous injection of 20% aqueous suspension of dry yeast in a dose of 2 ml/100 g body weight (El-Hakim and Ain-Shok, 1995). After 17 h, the initial body temperature of each rat was measured rectally. One group was kept as a control while the other groups were subcutaneously injected with salicylamide and the tested compounds in a dose of 20 mg/100 g body weight. The temperature of each rat was then recorded at 1 h interval after drug administration (Table V).

Ulcerogenic effect in RATS

Male rats (100-110 g) were fasted overnight and orally given the tested compounds (20 mg/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.*,

Table IV. Analgesic effect of salicylamide and the tested compounds in a dose of 20 mg/100 g body weight in mice (n = 5).

Compound	% Protection against writhing after (h)			
	1	2	3	4
Control	0	0	0	0
Salicylamide	100	100	80	60
2	0	0	0	0
6	0	0	0	0
8	60	60	40	20
9b	40	40	20	0
9c	80	80	60	20
10a	20	20	0	0
10c	20	20	0	0
12	0	0	0	0
13b	80	80	60	40
18b	80	80	60	20
18c	0	0	0	0
18d	80	80	60	20
18e	0	0	0	0

Table III. Antiinflammatory effect of salicylamide and the tested compounds in a dose of 20 mg/100 g body weight in rats (n =5).

Compound	Thickness of paw (mm) after (h)			
	1	2	3	4
Control	7.36 ± 0.21	7.48 ± 0.24	7.51 ± 0.22	7.60 ± 0.20
Salicylamide	6.30 ± 0.21**	6.35 ± 0.23**	6.40 ± 0.25**	6.48 ± 0.22**
2	7.17 ± 0.20	7.40 ± 0.24	7.46 ± 0.21	7.62 ± 0.21
6	6.80 ± 0.24	6.88 ± 0.22	6.93 ± 0.25	6.98 ± 0.23
8	6.43 ± 0.22**	6.63 ± 0.21*	6.72 ± 0.24*	6.84 ± 0.22*
9b	6.53 ± 0.24*	6.68 ± 0.22*	6.81 ± 0.21*	6.90 ± 0.23*
9c	6.36 ± 0.25**	6.42 ± 0.21**	6.48 ± 0.24**	6.71 ± 0.21**
10a	7.12 ± 0.23	7.33 ± 0.24	7.37 ± 0.21	7.49 ± 0.22
10c	7.08 ± 0.25	7.32 ± 0.21	7.38 ± 0.20	7.47 ± 0.24
12	6.66 ± 0.24	6.71 ± 0.25	6.87 ± 0.22	6.99 ± 0.23
13b	6.36 ± 0.20**	6.40 ± 0.23**	6.44 ± 0.20**	6.68 ± 0.22**
18b	6.36 ± 0.25**	6.41 ± 0.20**	6.48 ± 0.20**	6.69 ± 0.25*
18c	7.40 ± 0.22	7.49 ± 0.24	7.53 ± 0.20	7.76 ± 0.22
18d	6.57 ± 0.24*	6.70 ± 0.24*	6.85 ± 0.21*	6.94 ± 0.22*
18e	7.11 ± 0.23	7.38 ± 0.22	7.40 ± 0.21	7.58 ± 0.25

Significant at: *P≤0.05 **P≤0.01.

1979). A separate group which recived 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 student's t-test. A 0.05 level of probability was regarded as significant according to Sendecol and Cochran, (1971) (Table VI).

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.

Biological data

Antiinflammatory activity

From Table III some of the tested compounds (**9c, 13b, 18b, 8, 9b** and **18d**) in a dose of 20 mg/100 g body weight significantly reduced the carrageenan-induced oedema volume, these effects were nearly similar to that of salicylamide at the same dose level.

Analgesic activity

It is clear that compounds **9c, 13b, 18b** and **18d** produced 80% protection against writhing induced by *p*-benzoquinone in mice corresponding to 100% protection for salicylamide (standard). This indicates that these compounds possess, good analgesic activity.

3-Antipyretic activity

The results recorded in Table V showed that compounds **8, 9c, 13b, 18b** and **18d** possess a significant antipyretic activity when given to hyperthermic rats.

4-Ulcerogenic activity

The ulecrogenic activity of compounds in comparison with salicylamide clearly showed that compound **9c, 10a, 13b, 18c** and **18e** induce no ulcerogenic effect in a dose level of 20mg/100g body weight (Table VI).

On the other hand compounds **12** and **18d** showed

Table VI. Ulcerogenic effect of salicylamide and the tested compounds in a dose of 20 mg/100 g body weight in fasted rats (*n*=5)

Compound	Gastric lesion (M ± S.E)	
	Haemorrhagic spots	ulcers
Control	0	0
Salicylamide	4.92 ± 0.19	4.40 ± 0.18
2	3.27 ± 0.15	2.66 ± 0.14
6	3.96 ± 0.17	3.14 ± 0.19
8	3.11 ± 0.18	2.60 ± 0.14
9b	3.85 ± 0.18	3.02 ± 0.12
9c	0	0
10a	0	0
10c	3.14 ± 0.17	2.64 ± 0.18
12	2.72 ± 0.16	0
13b	0	0
18b	3.41 ± 0.14	2.97 ± 0.16
18c	0	0
18d	2.43 ± 0.17	0
18e	0	0

Table v. Antipyretic effect of salicylamide and the tested compounds in a dose of 20 mg/100 g body weight in rats (n=5)

Compound	Body temperature (°C) after (h)			
	1	2	3	4
Control	38.94 ± 0.37	38.87 ± 0.28	38.86 ± 0.29	38.76 ± 0.26
Salicylamide	37.41 ± 0.32**	37.40 ± 0.36**	37.47 ± 0.32**	37.78 ± 0.30**
2	38.80 ± 0.31	38.73 ± 0.36	38.66 ± 0.37	38.69 ± 0.30
6	38.81 ± 0.30	38.75 ± 0.37	38.69 ± 0.39	38.70 ± 0.31
8	38.04 ± 0.21*	37.96 ± 0.29*	38.11 ± 0.20*	38.38 ± 0.37
9b	38.13 ± 0.37	38.10 ± 0.36	38.24 ± 0.30	38.44 ± 0.36
9c	37.96 ± 0.27*	37.90 ± 0.24*	38.07 ± 0.23*	38.40 ± 0.36
10a	38.47 ± 0.36	38.35 ± 0.39	38.47 ± 0.30	38.56 ± 0.31
10c	38.52 ± 0.30	38.47 ± 0.39	38.66 ± 0.36	38.68 ± 0.37
12	38.61 ± 0.39	38.67 ± 0.37	38.66 ± 0.31	38.68 ± 0.32
13b	37.44 ± 0.36**	37.41 ± 0.36**	37.65 ± 0.27**	37.97 ± 0.31
18b	37.93 ± 0.30*	37.90 ± 0.30*	38.06 ± 0.24*	38.37 ± 0.39
18c	38.76 ± 0.39	38.60 ± 0.31	38.64 ± 0.36	38.65 ± 0.36
18d	37.98 ± 0.22*	37.98 ± 0.31*	38.09 ± 0.22*	38.38 ± 0.37
18e	38.66 ± 0.36	38.61 ± 0.36	38.60 ± 0.37	38.63 ± 0.37

Significant at *P≤0.05 **P≤0.01.

only two to three pin-point haemorrhagic spots. While compounds **2, 6, 8, 9b, 10c** and **18b** showed haemorrhagic spots and gastric ulcers with different degrees (Table VI). The finding correlates well and add a very important advantage to the antiinflammatory, analgesic, antipyritic activities of compounds **9c** and **13b**.

CONCLUSION

Some general features can be drawn by the pharmacological data:

1-Among the compounds **(6, 8, 10a, 10c, 12, 13b)** bearing a heterocyclic pentatomic nucleus, the triazole derivatives **(13b)** was the most active in all the pharmacological tests.

2-Thiosemicarbazide and 2-hydroxypropylamine of the new prepared salicylamides **(9c, 18b)** exhibited antiinflammatory, analgesic and antipyretic activities nearly similar to that of salicylamide.

3-Thiosemicarbazide, 2-hydroxypropylamine and heterocyclic ring. *O*-Substitution on the salicylamide molecule variously affects the antiinflammatory analgesic and antipyretic activities of the tested compounds whereas ulcerogenicity is advantagcously decreased.

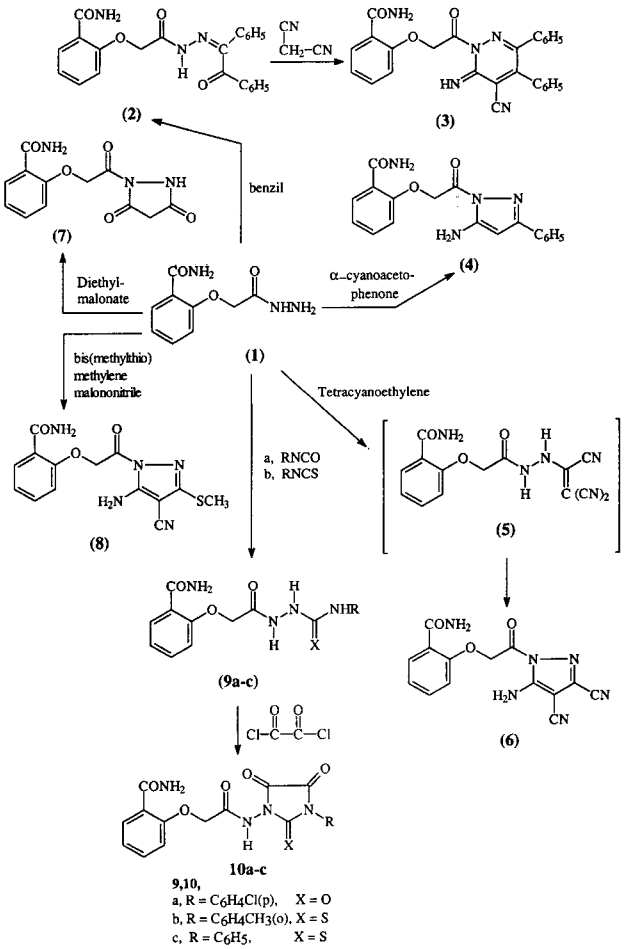
RESULTS AND DISCUSSION

In the present work, salicylamido acetic acid hydrazide **(1)** (Fahmy and El Eraky under publication) was used as the key intermediate for further synthesis so when compound **1** was refluxed with benzil in ethanol. Benzilmonohydrazone derivative **2** was obtained on treatment of **2** with malononitrile in ethanol, *O*-[(4-cyano-3-imino-5,6-diphenyl-pyridazine-2-yl) acetyl] salicylamide **(3)** was obtained. (Scheme 1).

On the other hand compound **1** condensed with a-cyanoacetophenone (Abel Motti *et al.*, 1997) in dimethylformamide to give *O*-[(5-amino-3-phenylpyrazol-1-yl) acetyl] salicylamide **(4)** (Scheme 1). Tetracyanoethylene reacted with compound **1** at room temperature (Abdel Motti *et al.*, 1997) to give 5-amino-3,4-dicyanopyrazolo derivative. The intial step involves the replacement of a cyano group to give a tricyanovinyl-hydrazine intermediate **5** which then cyclized to give compound **6**. (Scheme 1). Also, reaction of compound **1** with diethylmalonate in presence of sodium ethoxide (Fahmy., 1997) afforded 3, 5-pyrazolidinedione derivative **7**. (Scheme 1).

The reaction of bis(methylthio)methylene malononitrile (prepared according to the reported method (Tominage *et al.*, 1990) with the hydrazino compound **1** (Abdel Motti *et al.*, 1997) gave the corresponding 5-amino-4-cyano-3-methylthiopyrazolo-derivative **8**. (Scheme 1).

Reaction of salicylamidoacetic acid hydrazide **1** with isocyanate and isothiocyanate (Omer., 1997) in dry benzene afforded semicarbazide **9a** and thiosemicarbazides

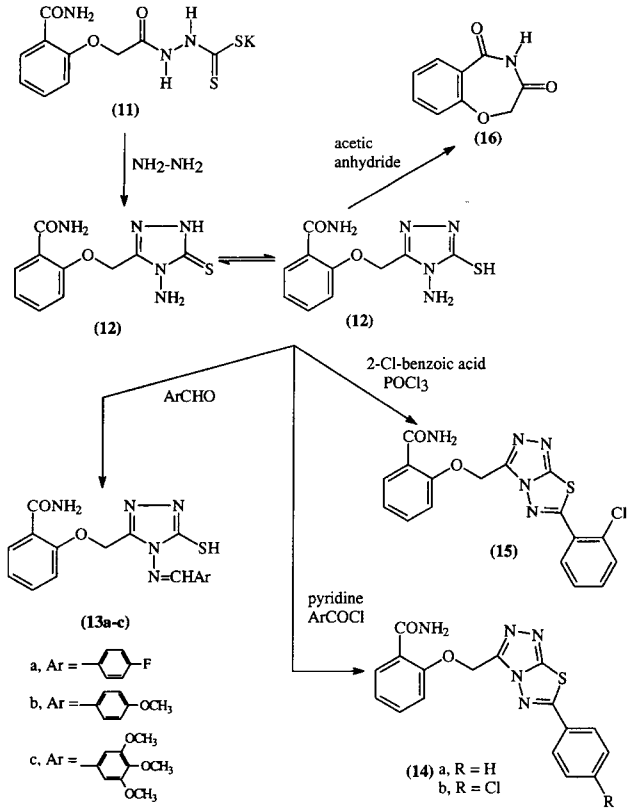


Scheme 1. Synthetic scheme for salicylamide derivatives I

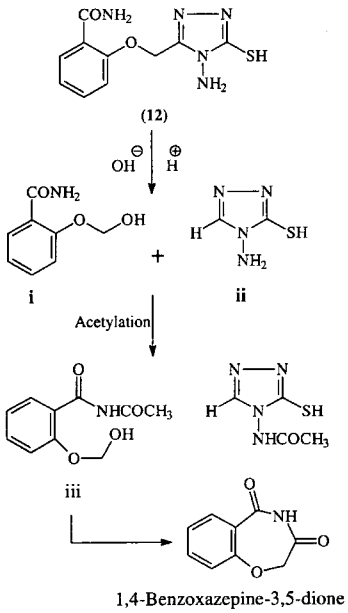
9b,c. Treatment of each **9a** and **9b,c** with oxalylchloride (Omar, 1997) in dry benzene furnished the hydantoin **10a** and the thiohydantoin **10b,c,** respectively. (Scheme 1).

On the other hand cyclocondensation of potassium dithiocarbazate (Fahmy and El Eraky under publication) with hydrazine hydrate afforded the correspoding O-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl] salicylamide **(12)** (Scheme 2). Reaction of compound **12** with different aromatic aldehydes in methanol (El-Ansary and Hassan., 1994) afforded the corresponding anils **13a-c**. (Scheme 2). 3,6-Disubstituted *S*-triazolo[3,4-b]-1,3,4-thiadiazoles **14a,b** were obtained by reacting compound **12** with equimolecular amounts of the appropriate acid chlorides, namely, benzoyl and /or *p*-chlorobenzoyl in pyridine. (El-Ansary and Hassan., 1994) Treatment of 4-amino-3-salicylamidomethyl-5-mercapto-1,2,4-triazole with 2-chlorobenzoic acid in the presence of $POCl_3$ (Pant *et al.*, 1983) afforded compound **15** (Scheme 2).

Attempted cyclization of compound **12** with excess acetic anhydride (El-Ansary and Hassan., 1994) under the reflux temperature for 2 h to produce 6-methyl-3-salicylamidomethyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole was unsucessful, instead we obtained 1,4-benzoxazepine-



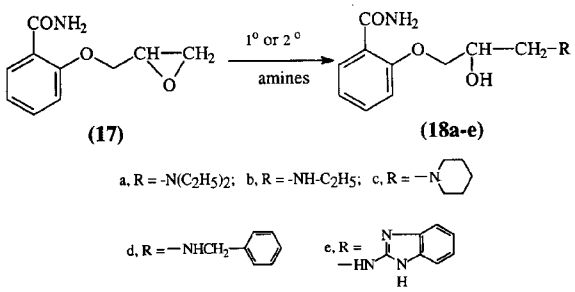
Scheme 2. Synthetic scheme for salicylamide derivatives II



Scheme 3. The mechanism of reaction between acetic anhydride and compound **12**

3,5-dione, and this was indicated from infrared, ^{1}H NMR and mass spectra, The mechanism of such reaction may be proposed as follow. (Scheme 3).

1-Hydrolysis of triazole **12**.



Scheme 4. Synthetic scheme for salicylamide derivatives III

2-Acetylation of the two amino groups of compound **i** and **ii**

3-Loss of one molecule of methanol from compound iii to give 1,4-benzoxazepine-3,5-dione. (Scheme 3).

The synthesis of compounds **18a-e** proceeded according to Scheme 4. The reaction of salicylamide with epichlorohydrin in the presence of potassium carbonate gave the epoxide **17** (Joullie *et al.*, 1971) which was used for the synthesis of the free amine bases **18a-e** by opening the epoxide through the reaction with the appropriate amines (Amin *et al.*, 1993) (Scheme 4).

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