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SYNTHESIS AND ANTIBACTERIAL EVALUATION OF CERTAIN 1,2,4- TRIAZOLE AND THIAZOLIDINONE DERIVATIVES

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ABSTRACT

The synthesis of certain 3 - [(4- chloro - 3,5 - dimethyl - phenoxy) methyl] 4-alkyl or aryl -5 - mercapto - 1,2,4 - triazoles (5a - e) is described .The preparation of these triazoles was achieved by the cyclization of the corresponding thiosemicarbazides (Af- j) using piperidine in refluxing ethanol. Also , series of thioethers (6a,b) and (7a-g) were obtained by reacting (5) with different halo- compounds .The thiazolidinone derivatives (8 a - d) were prepared by reacting (4f - j) with ethyl bromoacetate .The new compounds were proved by elemental analysis, ir and ^{1}H- nmr . The antibacterial activity was carried out for eight representative compounds .

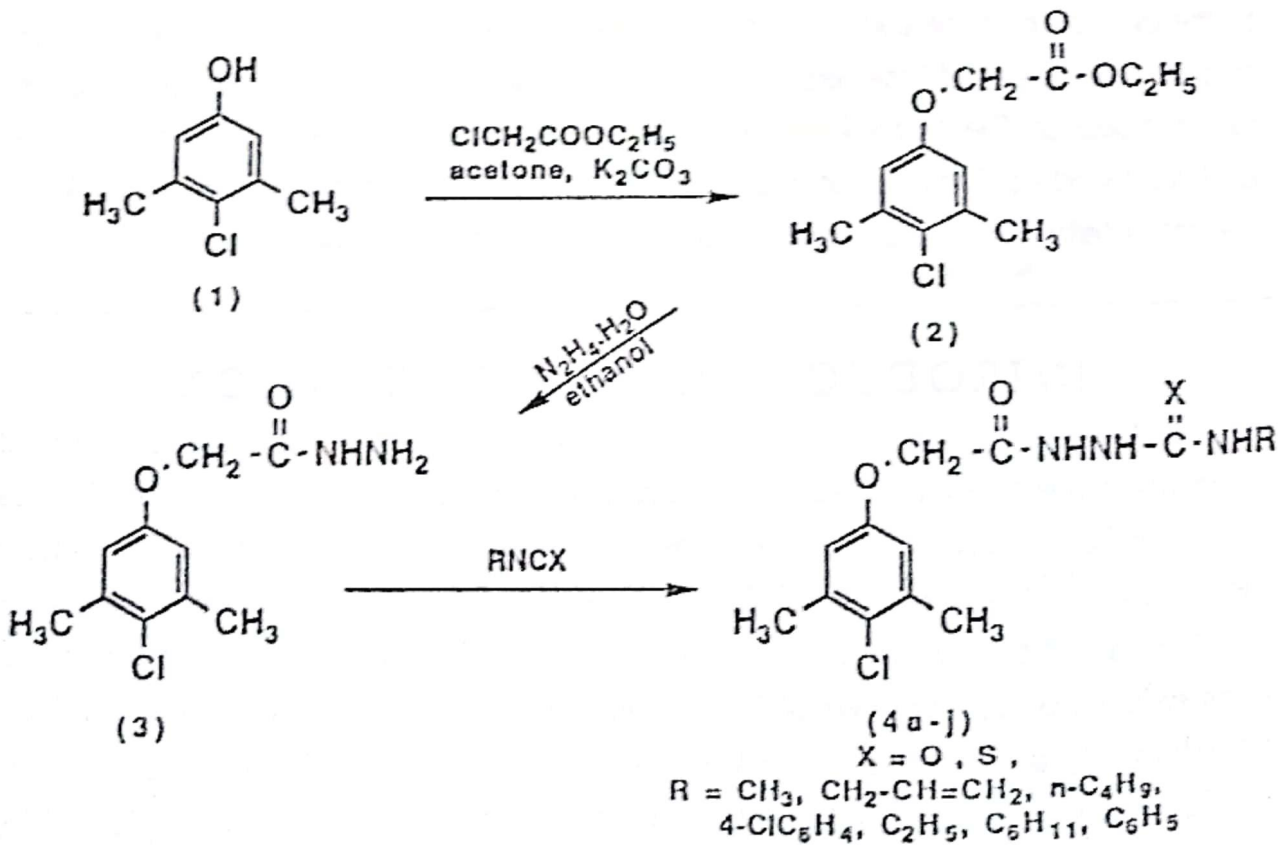
INTRODUCTION AND DISCUSSION

Certain compounds containing N^4-substituted thiosemicarbazide moieties have shown broad spectrum of chemotherapeutic activities [1], the antimicrobial activity of some thiosemicarbazides is comparable to that of penicillin [2]. Also,various 1,2,4- triazole derivatives are reported to display antifungal[3,4]and antibacterial[5]effects. Furthermore,many thiazolidin-ones exhibit a wide range of biological activities including anticonvulsant, amaebicidal, antihistaminic and antibacterial activities [6,11].

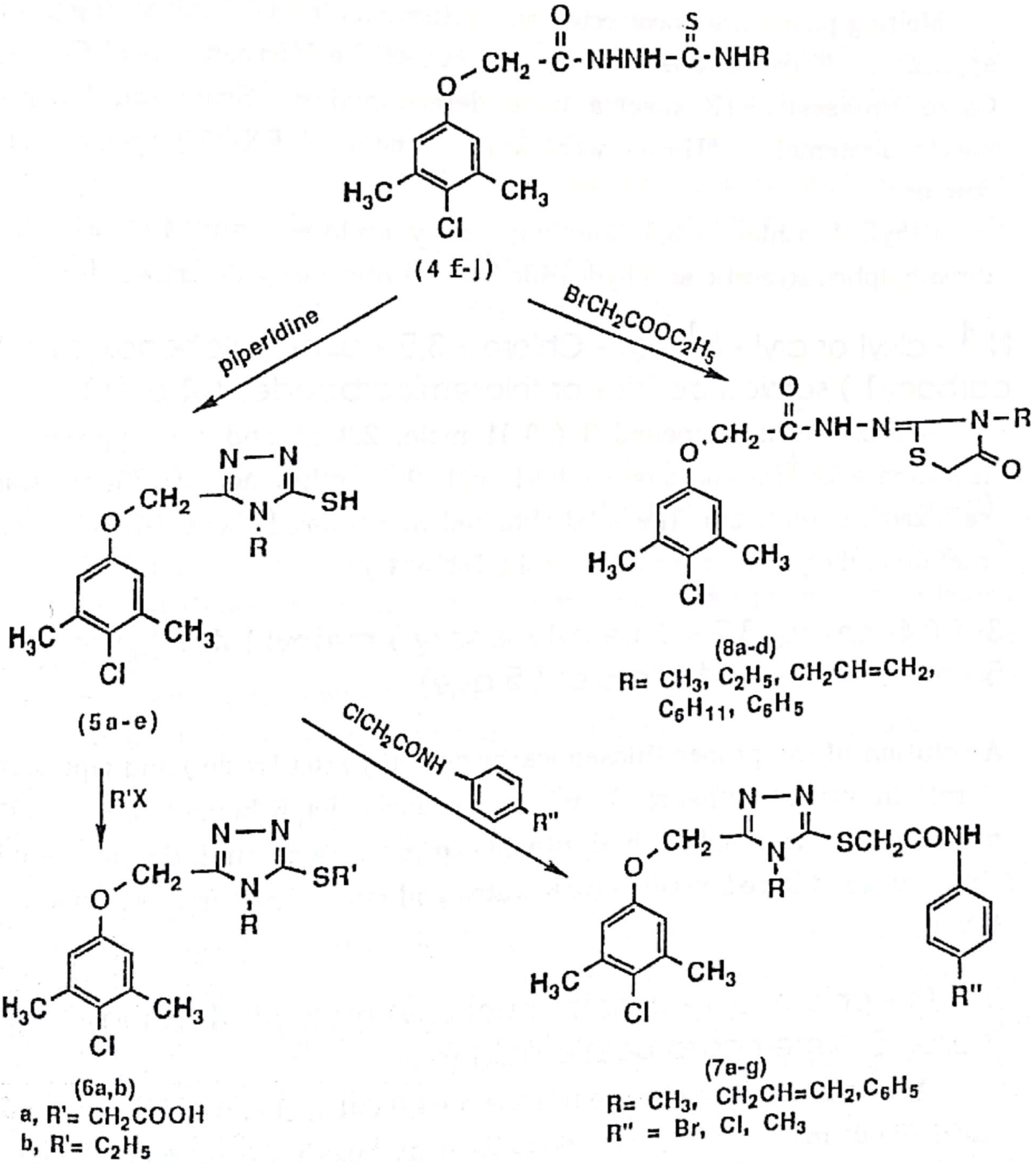
In this work, certain 1,2,4-triazole (5a-e) and thiazolidinone derivatives (8a-d) were prepared with the objective that the new compounds may show promising antibacterial properties. The ethyl ester 2 was prepared by reacting 4- chloro-3,5-dimethylphenol 1 with ethyl chloroacetate. The corresponding acid hydrazide 3 was obtained by hydrazinolysis of 2. Reacting 3 with the appropriate isocyanate or isothiocyanate in refluxing ethyl acetate gave (4a- j). The preparation of 1,2,4- triazole derivatives (5a - e) was achieved by cycliztion of the corresponding thiosemicarbazides (f - j) in refluxing ethanol and in the presence of piperidine. The thioether (6a)

was prepared by reacting (5e) with chloroacetic acid in refluxing ethanol and in presence of potassium hydroxide. The other thioether derivatives (6b) and (7 a - g) were obtained by refluxing the corresponding triazoles with different halo compounds in acetone and in presence of anhydrous potassium carbonate. Thiazolidinone derivatives (8a - d) were synthesized by refluxing the thiosemicarbazides (4f-j) with ethyl bromoacetate and anhydrous sodium acetate in ethanol.

The route adopted for the preparation of the new compound was summarized in the following schemes.



Scheme 1


piperidine
BrCH2COOC2H5
ClCH2CONH
R'X
(4 f-j)
(5a-e)
(8a-d)
R= CH3, C2H5, CH2CH=CH2, C6H11, C6H5
(6a,b)
a, R'= CH2COOH
b, R'= C2H5
(7a-g)
R= CH3, CH2CH=CH2, C6H5
R" = Br, Cl, CH3

Scheme 2

EXPERIMENTAL

Melting points are uncorrected and determined on Griffin melting point apparatus . Microanalyses were carried out at the Microanalytical Center, Cairo University. IR spectra were determined on Schimadu IR 435 spectrophotometer. ^{1}H-nmr were scanned on Jeol FX-90Q spectrophotometer.

Ethyl, 4- Chloro - 3,5-dimethylphenoxy acetate 2 and 4-chloro 3,5 - dimethylphenoxyacetic acid hydrazide 3 were previously described (12).

N^4 - alkyl or aryl - N^1 - (4 - Chloro - 3,5 - dimethylphenoxymethl carbonyl) semicarbazides or thiosemicarbazides (4 a - j) :

A mixture of compound 3 (0.01 mole, 2.3 g) and the appropriate isocyanate or isothiocyanate (0.01 mole) in ethyl acetate (30ml) was refluxed for 4-6 hours .The solid obtained was filtered , washed with ethyl acetate and crystallized from ethanol (Table 1).

3- ((4- chloro -3,5 - dimethylphenoxy) methyl) 4- alkyl or aryl - 5 - mercapto - 1,2,4- triazoles (5 a- e) :

A solution of the proper thiosemicarbazide (4f-j) (0.01mole) and piperidine (1 ml) in absolute ethanol (20 ml) was refluxed for 6 hours. The reaction mixture was acidified with dilute hydrochloric acid and the precipitate obtained was filtered, washed with water and crystallized from ethanol table (2).

3- ((4 - chloro -3,5 - dimethlyphenoxy) methyl) -4- phenyl- 1,2,4- triazol -5- lymercapte acetic acid (6a) :

A mixture of the mercapto triazole 5 e (0.001 mole , 0.35g), chloroacetic acid (0.001 mole , 0.09g) and potassium hydroxide (0.002 mole ,0.11g) in absolute ethanol (30 ml) was refluxed for 6 hours. The mixture was cooled, concentrated, diluted with water and acidified with dilute hydrochloric acid. The solid obtained was filtered, washed with water and crystallized from ethanol ; m.p. 104 - 5° C; yield : 80%. Analysis $C_{19}H_{18}ClN_3O_3S$

	% C	%H	%N
Calcd .	56.50	4.46	10.41
Found	56	5.0	10.6

3- ((4 - Chloro - 3,5 - dimethylphenoxy) methyl) 5- ethylthio -4-phenyl -1,2,4- triazole (6b) :

A mixture of compound 5 e (0.001 mole , 0 .35g) ethyl iodide (0.001 mole) and anhydrous potassium carbonate (0.001mole , 0.16g) in dry acetone (30 ml) was refluxed for 18 hours . The mixture was filtered while hot, concentrated , the solid separated was washed with water and crystallized from chloroform - petroleum ether (60- 80° C) ; m.p. 107 - 8°C, yield : 70%. Analysis for $C_{19} H_{20} ClN_3OS$

Calcd .	%C	%H	%N
	61.04	5.35	11.24
Found	60 .5	5.8	11.7

3- ((4- chloro - 3,5- dimethylphenoxy) methyl) -4-alkyl or aryl-5-(4-substituted phenylaminocarbonyl thio)-1,2,4-triazoles (7a-g):

Equimolar amounts of the proper mercaptotriazole 5, the appropriate N-substituted chloroacetamide derivative and anhydrous potassium carbonate (0.001 mole of each) in dry acetone (30 ml) was refluxed for 12 - 18 hours. The reaction mixture was filtered while hot. The crude solid obtained was filtered, washed with water and crystallized from ethanol (Table 3).

3- substituted -2- ((4-Chloro - 3,5 dimethylphenoxy) - acetyl hydrazone) - 1,3 - thiazolidin - 4 - one :

A mixture of the appropriate thiosemicarbazide (4f - j) (0.001 mole), ethyl bromoacetate (0.001 mole , 0. 12 ml) and fused sodium acetate (0.004 mole, 0.33 g) in absolute ethanol (30 ml) was refluxed for 2 hours .The reaction mixture was filtered while hot. The solvent was removed by distilation and the residue obtained was crystallized from ethanol (Table 4).

Antibacterial Activity :

Eight representative compounds (3 , 4 d , 4 h , 5 b , 6 a, 6 b, 7 g and 8 a) were tested for their antibacterial activity using the agar diffusion method[13]. Testing the sensitivity of the new compounds was carried out using the disc method.

Preparation of Discs for Study :

50 mg of each compound were dissolved in 2 ml alcohol. Sterile filter paper discs (Whatman No .1) were impregnated with each solution and left to dry. Methylene blue impregnated disc was used as a control for antibacterial activity .The microorganisms used for this study were : E. Coli (8 strains) , Diphteroids (7 strains) , Kleb. pneumonia (6 strains) , Staph . aureus (8 strains) and Staph . epidermis (6 strains).

RESULTS

Compound 6a showed a marked activity against Staph. epidermis (6 strains) and Diphteroids (7 strains) , whereas the other chosen compounds were inactive against the tested microorganisms.

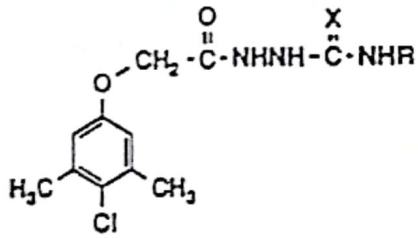


Table (1):

Compd No.	X	R	Yield %	M.P.°C	Molecular Formula	Microanalysis(%) Calcd.		Found
4- a	O	-CH(CH$_3$)$_2$	90	193-4	$C_{14}H_{20}ClN_3O_3$	C	53.58	53.5
						H	6.37	6.0
						N	13.39	13.0
b	O	n-C$_4$H$_9$	87	148-9	$C_{15}H_{22}ClN_3O_3$	C	54.96	54.8
						H	6.71	6.8
						N	12.82	12.5
c	O	C$_6$H$_{11}$	90	182-3	$C_{17}H_{24}ClN_3O_3$	C	57.71	57.8
						H	6.78	6.8
						N	11.88	11.4
d	O	C$_6$H$_5$	95	180-1	$C_{17}H_{18}ClN_3O_3$	C	58.70	59.1
						H	5.17	5.4
						N	12.08	11.8
e	O	4-ClC$_6$H$_4$	90	242-3	$C_{17}H_{17}Cl_2N_3O_3$	C	53.40	53.4
						H	4.45	4.8
						N	10.99	10.6

Table (1) Continued:

Compd No.	X	R	Yield %	M.P.°C	Molecular Formula	Microanalysis(%)		
						Calcd.		Found
f	S	CH_3	85	186-7	$C_{12}H_{16}ClN_3O_2S$	C	47.76	47.5
						H	5.30	5.6
						N	13.93	14.1
g	S	C_2H_5	90	180-1	$C_{13}H_{18}ClN_3O_2S$	C	49.44	49.0
						H	5.70	5.7
						N	13.31	12.9
h	S	C_6H_{11}	85	200-1	$C_{17}H_{24}ClN_3O_2S$	C	55.20	55.7
						H	6.49	6.0
						N	11.36	11.7
i	S	CH_2-CH=CH_2	80	166-7	$C_{14}H_{18}ClN_3O_2S$	C	51.29	51.3
						H	5.49	5.7
						N	12.82	12.4
j	S	C_6H_5	90	167-8	$C_{17}H_{18}ClN_3O_2S$	C	56.12	55.7
						H	4.95	4.8
						N	11.55	11.5

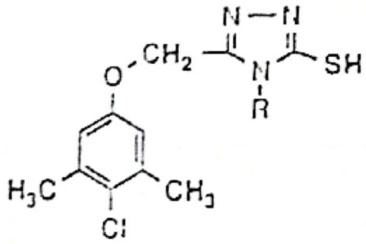
IR (KBr, cm^{-1}) of compound 4-j : NH (3200) and CO (1680).

^{1}H-nmr (DMSO, δ ppm) of compound 4-g:

1.10 (t, 3H, CH_2CH_3); 2.40 (s, 6H, $2CH_3$); 3.60(q, 2H, CH_2CH_3); 4.75 (S, 2H, OCH_2),

7.15 (S, 2H, aromatic proton of the phenoxy residue); 8.40 (S, 1H NH) and 9.50 (S, 1H, NH).

Table (2):



(5a-e)

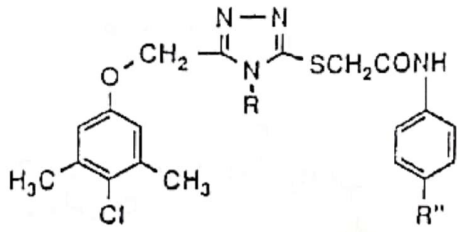
Compd No.	R	Yield %	M.P.°C	Molecular Formula	Microanalysis(%)		
					Calcd.		Found
5- a	CH_3	85	190-1	$C_{12}H_{14}ClN_3OS$	C	50.79	50.5
					H	4.93	5.0
					N	14.81	14.5
b	C_2H_5	80	144-5	$C_{13}H_{16}ClN_3OS$	C	52.43	52.8
					H	5.37	5.4
					N	14.11	13.8
c	CH_2-CH=CH_2	75	143-4	$C_{14}H_{16}ClN_3OS$	C	54.28	54.5
					H	5.16	5.0
					N	13.57	13.3
d	C_6H_{11}	80	204-5	$C_{17}H_{22}ClN_3OS$	C	58.03	58.2
					H	6.25	6.4
					N	11.94	12.3
e	C_6H_5	85	178-9	$C_{17}H_{16}ClN_3OS$	C	59.04	58.6
					H	4.63	4.7
					N	12.15	12.1

^{1}H-nmr (DMSO, δ ppm) of compound 5-d:

1.60 - 2.00 (m, 10 H, C_6H_{11}); 2.40 (S, 6H, $2CH_3$); 4.80 (m, 1H, C_6H_{11});

5.20 (S, 2H, OCH_2) and 7.00 (S, 2H, aromatic protons of the phenoxy residue)

Table (3):



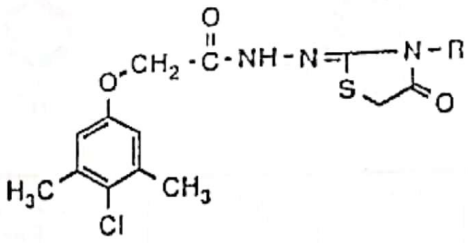
(7a-g)

Compd No.	R	R''	Yield %	M.P.°C	Molecular Formula	Microanalysis(%)		
							Calcd.	Found
7- a	CH_3	Br	90	191-2	$C_{20}H_{20}BrClN_4O_2S$	C	48.43	48.8
						H	4.03	4.0
						N	11.30	11.6
b	CH_3	CH_3	95	180-1	$C_{21}H_{23}ClN_4O_2S$	C	58.53	58.6
						H	5.34	5.4
						N	13.01	13.4
c	CH_2-CH=CH_2	Br	98	198-9	$C_{22}H_{22}BrClN_4O_2S$	C	50.62	50.9
						H	4.21	4.7
						N	10.73	10.4
d	CH_2-CH=CH_2	Cl	98	190-1	$C_{22}H_{22}Cl_2N_4O_2S$	C	55.34	55.6
						H	4.61	5.2
						N	11.74	11.4
e	CH_2-CH=CH_2	CH_3	95	163-4	$C_{23}H_{25}ClN_4O_2S$	C	60.46	60.1
						H	5.47	5.5
						N	12.26	11.9
f	C_6H_5	Br	98	197-8	$C_{25}H_{22}BrClN_4O_2S$	C	53.81	54.0
						H	3.94	4.3
						N	10.04	10.4
g	C_6H_5	CH_3	95	183-4	$C_{26}H_{25}ClN_4O_2S$	C	63.35	63.3
						H	5.07	5.4
						N	11.37	11.3

IR (KBr, cm^{-1}) of compound 7b: NH (3250) and CO (1680).

^{1}H-nmr (DMSO, δ ppm) of compound 7a: 2.40 (S, 6H, $2CH_3$); 380 (S, 3H, NCH_3); 4.10 (S, 2H, SCH2CO); 5.40 (S, 2H, OCH2); 7.20 (S, 2H, aromatic protons of the phenoxy residue); 7.60 - 7.80 . (d, 4H, aromatic protons of 4-Br phenyl C_6H_4) and 10.80 (S, 1H, NH)

Table (4):



(8a-d)

Compd No.	R	Yield %	M.P.°C	Molecular Formula	Microanalysis(%)		
					Calcd.		Found
8- a	CH_3	70	192-3	$C_{14}H_{16}ClN_3O_3S$	C	49.19	49.6
					H	4.68	5.0
					N	12.29	12.5
- b	CH_2·CH=CH_2	75	174-5	$C_{16}H_{18}ClN_3O_3S$	C	52.24	52.8
					H	4.89	5.4
					N	11.42	11.0
- c	C_2H_5	75	184-5	$C_{15}H_{18}ClN_3O_3S$	C	50.63	50.3
					H	5.06	5.4
					N	11.81	11.5
- d	C_6H_5	80	177-8	$C_{19}H_{18}ClN_3O_3S$	C	56.51	56.2
					H	4.46	4.5
					N	10.41	10.8

IR (KBr. Cm-1) of compound. 8a: NH (3250) and CO (1680, 1720).

^{1}H-nmr (DMSO. δ ppm) of the same compound: 1.80 (t, 3H, CH_2CH_3); 2.20 (S, 6H, $2CH_3$); 380 (S, 2H, CH_2 of thiazolidinone); 4.40 (q, CH_2 , CH_2); 4.90 (S. 2H, OCH_2); 7.00 (S, 2H, aromatic protons of the phenoxy residue) and 9.50 (S, 1H, NH).

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تشييد وتقييم النشاط المضاد للميكروبات لبعض مشتقات الـ ١ ، ٢ ، ٤- تريازول والثيازوليدينون

عواطف السعيد فرج ، صافيناز السيد عباس ، أنور نصر ميخائيل

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تم في هذا البحث تحضير بعض السيمي والثيوسيمي كاربازايد (4a - j) وذلك لتفاعل الهيدرازيد (3)مع بعض الأيزوسيانيت والأيزوثيوسيانيت ، وقد استخدم الثيوسيمي كاربازيد (4f - j) كمركب وسيط لتحضير كل من الـ ١ ، ٢ ، ٤ - تريازول (5a - e) والثيازوليدينونات (8 a- d) .

هذا وقد تم تحضير مجموعة الـ ١ ، ٢ ، ٤ - تريازول (5 a - e) بتفاعل (4f -j) مع البيبريدين . كما تم أيضاً تحضير بعض الثيوايثر (6a- b) ، (7a- g) وذلك بتفاعل (5a-e) مع بعض المركبات الهالوجينية .

أما مجموعة الثيازوليدينون (8 a - d) فقد تم الحصول عليها بتفاعل (4f-j) مع الأيثيل بروموأسيتات والصوديوم اسيتات .

وقد تم اجراء اختيار ثمان من المركبات الجديدة لدراسة تأثيرها كمضاد للميكروبات وقد ثبت أن المركب (6a) له تأثير واضح ضد الـ Staph- epidermis والـ Diphteroids .