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SYNTHESIS AND ANTIBACTERIAL TESTING OF SOME NEW SELENADIAZOLE AND THIADIAZOLE CONTAINING AMINO ACID MOIETIES

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ABSTRACT

Several 4-{4-(substitutedglycylamino)-phenyl} -1,2,3-selenadiazols (IV) and 4{4-(substitutedglycylamino)phenyl}-1,2,3-thiadiazoles (V) were prepared for evaluation of their antimicrobial activity. 4-chloroacetylaminoacetophenone(I) when reacted with different amines gave 4-glycylaminoacetophenone derivatives(II). Condensation of II with semicarbazide furnished the corresponding semicrabazones (III). Oxidative cyclization of (III) either by selenium dioxide or thionyl chloride afforded IV and V respectively.

INTRODUCTION

Both selenadiazoles and thiadiazoles are known by their antibacterial and antifungal activities[1-5]. Also amino acids or its derivatives possess a very important role in biological aspects[6], these reports promoted us to synthesis 1,2,3-selena- and/or thiadiazole ring containing amino acid moieties with the hope that such incorporation will show improved antimicrobial activity .

EXPERIMENTAL

Melting points were determined in capillary tubes on a Thomas-Hoover-Uni-Melt apparatus and are uncorrected. The time allowed for the completion of the reaction and the purity of the prepared compounds were controlled by means of T.L.C. The ^{1}HNMR spectra were obtained in Me_2SO-d_6 with Me_4Si as internal standard. I R and ^{1}HNMR were consistent with assigned structures for all compounds:

1- 4-N-Glycylaminoacetophenones (II)

A mixture of 4-chloroacetylaminoacetophenone[7] I(0.01 mol) and the appropriate amine (0.015 mol) in dry toluene (50 ml)was refluxed for 3hr. The amine hydrochloride was filtered off and the organic layer extracted with 1N HCl (3 x 30 ml). The acidic extract was neutralized with sodium carbonate solution and the precipitated solid was then filtered, washed with sodium carbonate solution, dried and crystallised from the proper solvent (Table 1).

2- 4-Glycylaminoacetophenone Semicarbazone Derivatives (III):

To a solution of II (2g) in ethanol (50 ml) was added a solution of a mixture of semicarbazide hydrochloride (2g) and sodium acetate (3g) in water (20 ml). The reaction mixture was refluxed for one hour, evaporated to one half of its volume and then poured onto ice-water. The precipitated solid was filtered, washed with water, dried and crystallised from the appropriate solvent (Table 2).

3- 4{4-(substitutedglycylamino)Phenyl}-1,2,3-Selenadiazole (IV):

The semicarbazone III (2g) was dissolved in boiling acetic acid (40 ml). To this boiling solution was added, portion-wise with stirring,powdered selenium dioxide (0.82g).After complete addition, boiling and stirring was continued for 1h. The reaction mixture was then filtered on ice-water and the solid precipitate was extracted with chloroform. The organic layer was wa-

shed with 10% sodium bicarbonate solution, water and finally dried over anhydrous sodium sulphate. After evaporation of the solvent, the solid product was crystallised from the suitable solvent (Table 3).

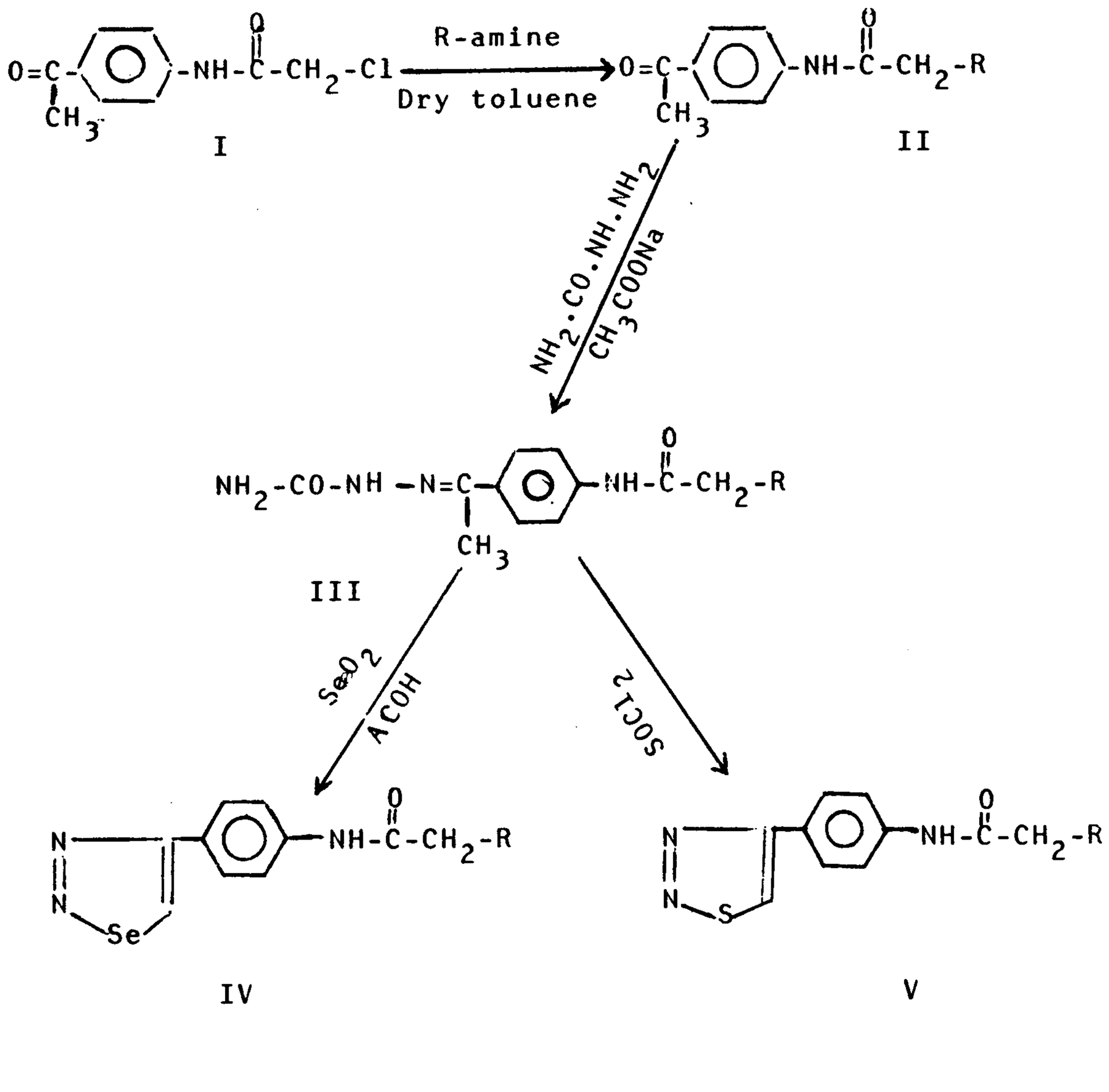
4- 4-{4-(Substitutedglycylamino)Phenyl}-1,2,3-thiadiazoles (V):

Thionyl chloride (9 ml) was gradually added to the semicarbazone III (3g) and the mixture was gently warmed and then left for 50 min at room temperature. An ice-cold saturated sodium bicarbonate solution was then added. The product was extracted with chloroform (120 ml) and the organic layer was washed and dried. After removal of the solvent in vacuo, the solid product was collected and crystallised from the suitable solvent (Table 4) .

RESULTS AND DISCUSSION

In a previous wark[5] we reported the synthesis and antibacterial activity of some thiadiazole and selenadiazole. In this context we describe the synthesis of some new 1,2,3-selena-and thiadiazole containing amino acid moieties and screened in vitro for their antibacterial activity. The starting 4-chloroacetylaminoacetophenone was prepared as detailed in literature[7]. The interaction of (I) with different amines such as piperazine, morpholine; piperidine; 2-aminopyridine, 2-aminothiazole, ethylamine, p-chloroaniline and -p-anisidine in dry toluene;4-glycylaminoacetophenones (II) were obtained in high yields. These compounds were easily condensed with semicarbazide hydrochloride in dilute ethanol solution to afford the corresponding semicarbazone derivatives (III). The purified semicarbazide derivatives III were subjected to oxidative cyclization[8] by either selenium dioxide in glacial acetic acid or thionyl chloride, where the 4-{4-(substitutedglycylamino)phenyl} 1,2,3,-selenadiazoles (IV) and 4-{4-(substitutedglycylamino)phenyl}1,2,3-thiazoles (V) were obtained, SCHEME I.

Scheme 1


R-amine
Dry toluene
I
II
$NH_2 \cdot CO \cdot NH \cdot NH_2$
CH_3COONa
III
SeO_2
AcOH
$SOCl_2$
IV
V

Synthesis and Antibacterial Testing of some New Selenadiazole and Thiadiazole Containing Amino Acid Moieties.

Antimicrobial Activity:

The selenadiazoles (IV) and thiadiazoles (V) were evaluated for their in vitro growth inhibitory activity against strains of gram-positive and gram-negative bacteria using agar cup diffusion technique[9,10]. The least square method was adopted to calculate the MIC (µg. mole/ml) values of the tested compounds[11,12] relative to tetracycline as a reference . Within the series of selenadiazoles IV, the morpholino IV_b and 2-aminothiazole IV_f derivatives showed more activity than the rest of the compounds tested. For the thiadiazole derivatives they are generally less active than the selenadiazoles. The most effective compounds being the morpholino V_b and 2-aminothiazole V_f and 2-aminopyridine V_e derivatives. (Table 5).

Acknowledgments:

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Table 1 : Physical data of compounds II

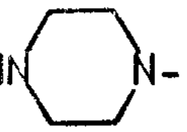
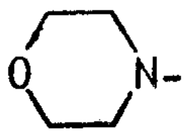
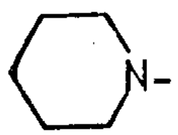
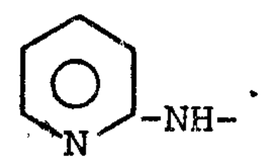
Compound	R	m.p.c°	Yield %	Solvent of Crystallisation	Molecular Formula	Analysis, calculated &(found)(%) C	H	N
II_a	$2H_2O.HN$ 	112	90	Benzene	$C_{14}H_{23}N_3O_4$	55.56 (56.7)	7.74 (7.7)	14.14 (14.2)
II_b		95	96	Toluene/petroleum ether	$C_{14}H_{18}N_2O_3$	64 12 (64.3)	6.87 (6.9)	10.68 (10.8)
II_c		107	95	Benzene/petroleum ether	$C_{15}H_{20}N_2O_2$	69.23 (69.3)	7.69 (7.7)	10.78 (10.8)
II_d	C_2H_5NH-	123	89	Toluene	$C_{12}H_{16}N_2O_2$	65.45 (65.5)	7.27 (7.3)	12.72 (12.9)
II_e		167	94	Dioxane	$C_{15}H_{15}N_3O_2$	66.91 (66.9)	5.58 (5.4)	15.61 (15.8)
II_f		120	93	Ethanol	$C_{13}H_{13}N_3O_2S$	56.72 (56.8)	4.72 (4.7)	15.27 (15.4)
II_g	p-ClC_6H_4NH-	176	88	Ethanol	$C_{16}H_{15}N_2O_2Cl$	63.47 (63.5)	4.95 (5.0)	9.26 (9.4)
II_h	p-$CH_3OC_6H_4NH$-	181	87	Methanol	$C_{17}H_{18}N_2O_3$	68.46 (68.6)	6.04 (6.0)	9.38 (9.1)

Table 2 : Physical data of compounds III

Compound	R	m.p.°C	Yield %	Solvent of crystallisation	Molecular Formula	Analysis ,calculated &(found)(%) C	H	N
III_a	$2H_2O$ H-N⟨⟩N-	230	80	Dioxane	$C_{15}H_{26}N_6O_4$	50.84 (50.9)	7.34 (7.2)	23.72 (23.9)
III_b	O⟨⟩N-	320	85	Dioxane	$C_{15}H_{21}N_5O_3$	56 42 (56.6)	6.58 (6.5)	21.94 (21.8)
III_c	⟨⟩N-	298	89	Dioxane/water	$C_{16}H_{23}N_5O_2$	60.56 (60.6)	7.25 (7.1)	22.08 (22.1)
III_d	C_2H_5NH-	250	91	Dioxane	$C_{13}H_{19}N_5O_2$	52.52 (52.8)	6 39 (6.5)	23.56 (23.3)
III_e	⟨⟩NH-	300	74	Dioxane	$C_{16}H_{18}N_6O_2$	58.89 (58.9)	5.52 (5.6)	25.76 (25.8)
III_f	⟨⟩NH-	237	86	Ethanol	$C_{14}H_{16}N_6O_2S$	50.60 (50.6)	4.81 (4.7)	25.30 (25.1)
III_g	p-Cl-C_6H_4NH-	260	75	Dioxane	$C_{17}H_{18}N_5O_2Cl$	56.74 (56.8)	5.01 (5.1)	19.47 (19 5)
III_h	p-$CH_3OC_6H_4NH$-	292	82	Acetone	$C_{18}H_{21}N_5O_3$	60.84 (60.8)	5.91 (5.9)	19.71 (19.6)

Table 3 : Physical data of compounds IV

Compound		m.p.c°	Yield %	Solvent of crystallisation	Molecular Formula	Analysis, calculated &(found)(%)		
						C	H	N
IV_a	$2H_2O \cdot H\text{-}N$ ⟨O⟩ $N\text{-}$	223	59	Ethanol	$C_{14}H_{21}N_5O_3Se$	43.52 (43.6)	5.44 (5.4)	18.13 (18.2)
IV_b	O ⟨⟩ $N\text{-}$	212	62	Ethanol	$C_{14}H_{16}N_4O_2Se$	47.86 (47.9)	4.55 (4.6)	15.95 (16.0)
IV_c	⟨⟩ $N\text{-}$	290	55	Ethanol	$C_{15}H_{18}N_4O$ Se	51.57 (51.6)	5.15 (5.2)	16.40 (16.1)
IV_d	$C_2H_5NH\text{-}$	260	66	Ethanol	$C_{12}H_{14}N_4O$ Se	46.60 (46.7)	4.53 (4.4)	18.12 (18 3)
IV_e	N ⟨⟩ $\text{-}NH\text{-}$	295	56	Dioxane	$C_{15}H_{13}N_5O$ Se	50.27 (50.4)	3.63 (3.6)	19.55 (19.6)
IV_f	S ⟨N⟩ $\text{-}NH\text{-}$	210	50	Methanol	$C_{13}H_{11}N_5O$ Se	42.85 (42.9)	3.02 (3.1)	19.23 (19.3)
IV_g	$P\text{-}ClC_6H_4NH\text{-}$	280	60	Ethanol	$C_{16}H_{13}N_4OClSe$	49.04 (49.1)	3.32 (3.2)	14.30 (14.4)
IV_h	$P\ CH_3OC_6H_4NH\text{-}$	271	58	Dioxane	$C_{17}H_{16}N_4O_2Se$	52.71 (52.8)	4.13 (4.2)	14.47 (14.3)

Table 4 : Physical data of compounds V.

Compound	R	m.p.c°	Yield %	Solvent of crystallisation	Molecular Formula	Analysis,calculated &(found)(%)		
						C	H	N
V_a	$2H_2O$ H-N⟨⟩N-	273	70	Ethanol	$C_{14}H_{21}N_5O_3S$	49.55 (49.6)	6.19 (6.2)	20.64 (20.8)
V_b	O⟨⟩N-	197	74	Methanol	$C_{14}H_{16}N_4O_2S$	55.26 (55.3)	5.26 (5.2)	18.42 (18.5)
V_c	⟨⟩N-	210	70	Ethanol	$C_{15}H_{18}N_4O\ S$	59.60 (59.7)	5.96 (6.0)	18.54 (18.5)
V_d	C_2H_5NH-	201	68	Ethanol/water	$C_{12}H_{14}N_4O\ S$	54.96 (54.8)	5.34 (5.3)	21.37 (21.4)
V_e	⟨N⟩- NH-	214	76	Ethanol	$C_{15}H_{13}N_5O\ S$	57.87 (57.9)	4.18 (4.1)	22.50 (22.7)
V_f	⟨N,S⟩- NH-	315	70	Dioxane	$C_{13}H_{11}N_5O\ S$	54.73 (54.8)	3.85 (3.8)	24.56 (24.7)
V_g	P-ClC_6H_4NH-	301	64	Methanol	$C_{16}H_{13}N_4ClOS$	55.73 (55.9)	3.77 (3.7)	16.25 (16.4)
V_h	P-$CH_3OC_6H_4NH$-	256	60	Dioxane	$C_{17}H_{16}N_4O_2S$	60.00 (60.1)	4.70 (4.6)	16.47 (16.5)

Table 5 : Molar Minimum Inhibitory Concentrations for Compounds IV_{a-h} and V_{a-h}

Compound No.	S.aureus	B.cereus	K.pneumonia	E.coli
IV_a	2.350(r=0.99)	1.735(r=0.99)	1.235(r=0.98)	0.970(r=0.99)
IV_b	0.710(r=0.96)	0.571(r=0.98)	0.509(r=0.99)	0.608(r=0.99)
IV_c	1.081(r=0.99)	1.230(r=0.96)	1.750(r=0.99)	1.583(r=0.99)
IV_d	1.230(r=0.99)	2.302(r=0.99)	1.650(r=0.99)	1.230(r-0.98)
IV_e	Inactive	Inactive	1.535(r=0.98)	Inactive
IV_f	0.356(r=0.99)	0.400(r=0.99)	0.356(r=0.99)	0.356(r=0.98)
IV_g	Inactive	Inactive	Inactive	1.356(r=0.99)
IV_h	2.350(r=0.98)	Inactive	Inactive	Inactive
V_a	2.350(r=0.99)	1.325(r=0.98)	Inactive	Inactive
V_b	0.356(r=0.98)	0.400(r=0.98)	0.366(r=0.99)	0.356(r=0.99)
V_c	Inactive	Inactive	2.580(r=0.99)	Inactive
V_d	1.650(r=0.99)	Inactive	1.750(r=0.98)	Inactive
V_e	1.750(r=0.99)	Inactive	Inactive	Inactive
V_f	0.356(r=0.98)	0.400(r=0.99)	0.356(r=0.99)	0.400(r=0.99)
V_g	Inactive	Inactive	Inactive	Inactive
V_h	Inactive	Inactive	Inactive	Inactive
Tetracycline	0.400(r=0.99)	0.750(r=0.98)	I·356(r=0.99)	0.400(r=0.99)

REFERENCES

1) *I. Latezari and A. Vahdat, J. Med. Chem., 14, 59 (1971).*

2) *H. Mirchamsy, I. Latezari, M. Kamaly, G. Niloufari and N. Rezvani Arch. Virusforch., 29, 267 (1970).*

3) *I. Latezari, A. Shafiee, S. Yazdany and Pour-nornorouz, J. Pharm. Sci., 62, 839 (1973).*

4) *I. Latezari, A. Shafiee and S. Yazdany, J. Pharm. Sci., 63, 268 (1974).*

5) *H.S. El-Kashef, M.A. Abd-Alla, B.E. Bayoumi and A.A.M. El-Timawy, J. Chem. Tech. Biotechnol. 33A, 294(1983).*

6) *A. Burger "Medicinal Chemistry", 2nd. Ed, Interscience publishers, Inc N.Y., 1960.*

7) *J.H. Ralf, J. Am. Chem. Sci., 41, 1469 (1919).*

8) *A. Shafiee, I. Latezari, S. Yazdani, F.M. Shahbazian, T. Partovi, J. Pharm. Sci., 65, 304 (1976).*

9) *P.G. Lawrence and Francis, Chemotherapy 3rd, Ed,Churchill, Livingstone, 1972, pp. 481.*

10) *M.L. Dhar, M.M. Dhar, B.N. Dhanan, B.N. Mehrolra and C. Ray Indian J. Exp. Biol., 2, 232 (1968).*

11) *F. Cavanagh, Anl. Microbial., 126 (1963).*

12) *R.T. Youssef and G. El-Tawil,Pharmazie 35 11, (1980).*

تخليق بعض المركبات الجديدة من مشتقات السيلينياديازول الثياديازول كمضادات للبكتريـــــــا

بشير بيومى ـ محمد عبد اللـــــــه ـ عبد الحميـــــد نجيب احمـــــد

كلية العلوم ـ قسم الكيمياء ـ جامعة الزقازيـــق ـ وكلية العلوم ـ قسم الكيمياء

جامعة اسيوط ـ وقسم الكيمياء الصيدلية ـ جامعـــــة اســـــيوط

لقد تم فى هذا البحث تخليق عديد من المركبات وهى من مشتقات ٤ـ٤ جليسيل امينو فينيل ١ر٢ر٣ سيلينادیازول (٤)٠ وكذلك تم تخليق عديد من مشـــــتقات ٤ر٤ فينيل ١ر٢ر٣ سياديازول (٥) ٠

ولقد تم تخليق هذه المركبات عن طريق التفاعل الكيميائى لـ ٤ كلوروا ستيل امينو اسيتوفينون (١) مع مشتقات مختلفة من الامين والتى نتج عنها تخليـــــق الجليسيل امينو اسيتوفينون (٢) والتى بتفاعلها مع السيمى كربازيد ثم تخليـــق مشتقات السيمى كاربازون المقابلة (٣) وبالاكسدة تم تخليق المركبات الحلقيـــة ٤ر٥ بواسطة استخدام اوكسيد السيلينيم وكذلك كلوريد السيانيل ٠

ولقد تم تجربة تلك المركبات كمضادات للبكتريا الموجبة والسالبة الجرام ٠

ولقد وجد أن مشتقات المورفيلينو ومشتق ٢ـ امينو ثيازول قداعطت نتائـــــج مشجعة كمضادات للبكتريـــــا ٠

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