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Der Pharma Chemica, 2013, 5(1):1-7
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and biological evaluation of 3-methyl- 2-pyrazolin-5-one derivatives containing thiazole and indole moieties

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ABSTRACT

*In the present work six 3-methyl-1-[(5-substituted-1H-indol-2-yl) carbonyl]-4-{[4- (substituted thiazol-2-yl)iminoethyl) phenyl]hydrazono}-2-pyrazolin-5-one derivatives were synthesized by conventional and microwave methods. The synthesized compounds were tested for their antimicrobial activity against six strains of bacteria and three fungal strains. Compound **5a** showed a broad spectrum of activity against bacteria and compound **5d** exhibited excellent antifungal activity, while most of the other compounds showed varying antimicrobial activity.*

Keywords: Indole derivatives, pyrazolin-5-ones, Thiazolyl Schiff bases, biological activity, Microwave irradiation.

INTRODUCTION

The chemistry of pyrazolone and its derivatives is particularly interesting because of their potential application in medicinal chemistry as herbicidal[1], fungicidal[2], bactericidal[3], anti-inflammatory[4], antipyretic[5], antiviral[6], blood pressure lowering [7] and SARS-corona virus 3C-like protease inhibitors[8] agents. Thiazole ring system and its derivatives are core structure in synthetic compounds displaying broad spectrum of biological actives. Penicillin and thiamine (Vitamin B_1) structure containing sulphur and nitrogen in five member ring system which is similar to thiazole and its derivatives. Thiazolyl Schiff bases have been reported to exhibit antibacterial activity [9] and antitumor activity against human cancer cell lines [10]. Indole derivatives are useful in antibacterial activity [11], antifungal activity [12], antitumor [13], antioxidant [14], and antiviral potency [15]. Microwave assisted organic synthesis has become increasingly popular in recent years to improve the yields and shorten reaction time in a variety of reactions [16,17]. Encouraged by the above observations, herein we report the synthesis of some new 3-methyl-1-[(5-substituted-*1H*-indol-2-yl)carbonyl]-4-{[4- (substituted thiazol-2-yl)iminoethyl) phenyl]hydrazono}-2-pyrazolin-5-one derivatives and evaluation of their antimicrobial activity.

MATERIALS AND METHODS

Melting points were taken on an Electrothermal capillary melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Jasco FTIR 460 plus spectrophotometer. ^{1}H- NMR spectra were recorded using a Bruker AV 500 MHz spectrometer using DMSO-d_6 as solvent and TMS as an internal standard. Elemental analyses were performed on a Perkin-Elmer 240 microanalyser in the Faculty of Science Cairo University. Microwave irradiations were carried out in a SANYO EM-700T domestic oven (700 W). Purity of compounds was checked by TLC.

Synthesis of 1-(4-aminophenyl)-1-(substituted thiazol-2-yl)iminoethanes 1a-c:
Conventional method:
A mixture of 4- aminoacetophenone (0.01 mole) and 2-aminothiazols namely (2-aminothiazole, 2-amino-5-methylthiazole and 2-aminobenzthiazole) (0.01 mole for each) in DMF (30 ml) was heated under reflux for 4h. The precipitated solid which formed after cooling was collected by filtration, washed with water, dried and crystallized to afford **1a-c** (Table 1).

Microwave method:
A solution of 4-aminoacetophenon (0.01 mole) in methanol (5ml) and 2-aminothiazoles (0.01mole) were taken in round-bottomed flask placed in a microwave oven and irradiated for 2.0-3.5 min. and then the solvent was removed by vacuum distillation. The solid product was filtered, dried and recrystallized from ethanol to give **1a-c** (Table 2).
1-(4-Aminophenyl)-1-(5-methylthiazol-2-yl)iminoethane (**1b**)**:**
IR (KBr,cm^{-1}): 3400-3312 (NH_2), 1640 (C=N), ^{1}H-NMR (□ppm)**:** 2.01 (s. 3H, CH_3), 2.72 (s. 3H, CH_3), 6.88 (s,2H, NH_2 , D_2O-exchangeable,7.22 – 7.82 (m, 5H, ArH).

1-(4-Aminophenyl)-1-(benzthiazol-2-yl)iminoethane **(1c**):
IR (KBr,cm^{-1}): 3400-3312 (NH_2), 1640 (C=N), ^{1}H-NMR(δppm)**:** 2.78 (s. 3H, CH_3), 6.10 (s,2H, NH_2 , D_2O-exchangeable),7.35 - 7.68 (m, 8H, ArH).

Synthesis of 2-{[4- (substituted thiazol-2-yl)iminoethyl)-phenyl]hydrazono}-3- oxo-butyric acid ethyl ester 2a-c:
Solution of sodium nitrite (0.01 mole) in water (10 ml) was added to an ice cooled mixture of **1a-c** (0.01 mole) in conc. HCl (10 ml) and water (10 ml). The diazotized compound was dropped while cooling with stirring over a cold mixture of ethyl acetoacetate (0.01 mole) and sodium acetate (2 g in 10 ml water) in ethanol (20 ml). The reaction mixture was stirred at room temperature for 8h. The precipitated solid was collected by filtration, washed with water, dried and recrystallized to afford **2a-c** (Table 1).

2-{[4-(5-Methylthiazol-2-yl)iminoethyl)phenyl]hydrazono}-3-oxo-butyric acid ethyl ester (**2b)**:
IR (KBr,cm^{-1}): 3431 (NH), 1760 (ester CO), 1713(acetyl CO),1610 (C=N), ^{1}H NMR (δppm)**:** 0.91 (s,3H,CH_3),1.21 (t,3H, OCH_2CH_3), 2.60 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 3.0 (s, 1H, CH), 4.20-4.22 (q, 2H, OCH_2CH_3), 6.70-7.60 (m,5H, ArH).

2-{[4-(Benzthiazol-2-yl)iminoethyl)phenyl]hydrazono}-3-oxo-butyric acid ethyl ester (**2c)**:
IR (KBr,cm^{-1}): 3442 (NH), 1752 (ester CO), 1718(acetyl CO),1605 (C=N).^{1}H NMR (δppm)**:** 1.27 (t, 3H, OCH_2CH_3), 2.57 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.22 (s, 1H, CH), 4.27-4.29 (q, 2H, OCH_2CH_3), 6.66 -7.98 (m,8H, ArH).

Ethyl 5-substituted-*1H*-indole-2-carboxylate (3a,b) [19-21]**:**
A mixture of *p*-toluenesulfonic acid (3 g, 0.0174 mole) in dry benzene (50 ml) was heated under reflux using Dean-stark apparatus for 1.5 h. A suspension of ethyl pyruvate 4-substituted phenylhydrazone (0.01 mole) in dry benzene (30 ml) was added and the whole mixture was refluxed for 5 h. The resulting solution was diluted with benzene, washed with aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and evaporated to dryness. The resulting product was recrystallized from ethanol. 3a, M.p.122-124°C and yield was 84%, 3b, M.P. 150-152 ^oC and yield was 80%.

5-Substituted-*1H*-indole-2-carbohydrazide (4a, b) [19]**:**
Conventional method:
A mixture of ethyl 5-substituted-*1H*-indole-2-carboxylates (0.01 mole) and hydrazine hydrate 99% (0.03 mole) was refluxed in 20 ml ethanol for 6 h. The precipitate formed after cooling was collected by filtration and recrystallized from DMF/ethanol mixture to give 4a,b. 4a, M.P. 228-230 ^oC and yield was 75%, 4b, M.P. 192 ^oC and yield was 82%.

Microwave method:
Hydrazine hydrate (0.01 mole), 3a,b (0.01 mole) and absolute ethanol (2 ml) were irradiated in an Erlenmeyer flask under MWI for 3 min. The reaction mixture was cooled, the solid which separated was filtered off and washed with water to yield **4a,b** (Table 2).

Synthesis of 3-methyl-1-[(5-substituted-*1H*-indol-2-yl) carbonyl]-4-{[4- (substituted thiazol-2-yl)iminoethyl) phenyl]hydrazono}-2-pyrazolin-5-one derivatives (5a-f):

Conventional method:
A solution of **4a,b** (0.002 mole for each) in acetic acid (15 ml) was added to a solution of **2a-c** (0.002 mole for each) in ethanol (5 ml). The mixture was refluxed for 12 h. The reaction mixture was then allowed to stand overnight. The solvent was removed under reduced pressure and the residue was triturated with water, then the product was extracted with dichloromethane. The combined extracts were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to give a buff solid product, which was recrystallized to afford **5a-f** (Table 1).

Microwave method:
A mixture of **4a,b** (0.01 mole for each), **2a-c** (0.01 mole for each) and glacial acetic acid (5 ml) in an Erlenmeyer flask was exposed to pulsed microwave irradiation using microwave oven for 5-6 min. The reaction mixture was poured onto crushed ice; the solid mass that separated was filtered, washed with water, and dried to give the pyrazolin-5-ones **5a-f** (Table 2).

3-Methyl-1-[(1H-indol-2-yl)carbonyl]-4-{[4-(thiazol-2-yl)iminoethyl)-phenyl]hydraz-ono} -2-pyrazolin-5-one (**5a**):
IR (KBr,cm^{-1}): 3415 (indole NH), 3273 (NH), 3061(=CH), 1680-1677(CO), 1615 (C=N); ^{1}H-NMR (δppm)**:** 2.03 (s, 3H, CH_3), 2.68-2.82 (s, 3H, CH_3), 6.90 (s, 1H, C_3-indole), 6.91-7.55 (m, 10H, ArH), 10.1 (s, 1H, NH, D_2O exchangeable), 11.2 (s,1H, NH indole, D_2O exchangeable).

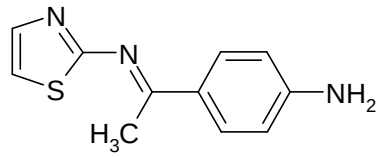
3-Methyl-1-[(1H-indol-2-yl)carbonyl]-4-{[4-(5-methylthiazol-2-yl)iminoethyl)-phenyl]-hydrazono} -2-pyrazolin-5-one (**5b**):
IR (KBr,cm^{-1}): 3410 (indole NH), 3298 (NH), 3086(=CH), 1685-1672(CO), 1610 (C=N). ^{1}H-NMR(δppm)**:** 1.44(s,3H,CH_3), 2.03 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 6.95(s, 1H, C_3 indole), 6.98-7.85 (m, 10H, ArH), 11.11 (s, 1H, NH,D_2O exchangeable), 11.46(s, 1H, indole NH, D_2O exchangeable).

3-Methyl-1-[(1H-indol-2-yl)carbonyl]-4-{[4-(benzthiazol-2-yl)iminoethyl)-phenyl]-hydrazono} -2-pyrazolin-5-one (**5c**):
IR (KBr,cm^{-1}): 3400 (indole NH), 3301(NH), 3079(=CH), 1668-1665(CO), 1590(C=N) . ^{1}H-NMR(δppm)**:** 2.45 (s, 3H, CH_3), 2.69-2.75 (s, 3H, CH_3), 6.89(s, 1H,C_3 indole) 6.91-7.89 (m, 12H, ArH),11.51 (s, 1H, NH, D_2O exchangeable), 11.92(s,1H, indole NH, D_2O exchangeable).

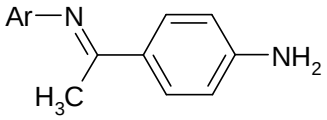
3-Methyl-1-[(5-floro-1H-indol-2-yl)carbonyl]-4-{[4-(thiazol-2-yl)iminoethyl)-phenyl]-hydrazono} -2-pyrazolin-5-one (**5d**):
IR (KBr,cm^{-1}): 3421 (indole NH), 3190(NH), 3065(=CH),1694-1660(CO), 1612(C=N) . ^{1}H-NMR(δppm)**:** 2.19 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 6.91(s, 1H, C_3 indole), 6.95-7.98 (m, 9H, ArH), 11.45 (s, 1H, NH, D_2O exchangeable), 11.6 (s, 1H, indole NH, D_2O exchangeable).

3-Methyl-1-[(5-floro-1H-indol-2-yl)carbonyl]-4-{[4-(5-methylthiazol-2-yl)iminoethyl)-phenyl]hydrazono} -2-pyrazolin-5-one (**5e**):
IR (KBr,cm^{-1}): 3415 (indole NH), 3158(NH), 3106(=CH),1682-1673(CO), 1551(C=N) . ^{1}H-NMR(δppm)**:** 1.31(s,1H,CH_3), 2.73(s, 3H, CH_3), 2.99 (s, 3H, CH_3), 6.93(s, 1H, C_3 indole),6.96-7.98 (m, 8H, ArH), 11.10 (s, 1H, NH, D_2O exchangeable), 11.85(s,1H, indole NH, D_2O exchangeable).

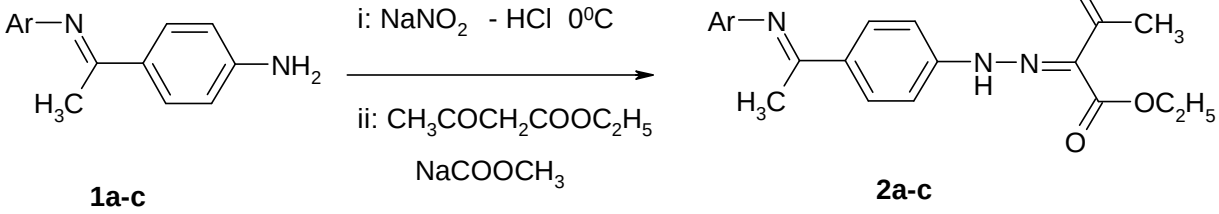
3-Methyl-1-[(5-floro-1H-indol-2-yl)carbonyl]-4-{[4-(benzthiazol-2-yl)iminoethyl)-phenyl]hydrazono} -2-pyrazolin-5-one (**5f**):
IR (KBr,cm^{-1}): 3410 (indole NH), 3210 (NH), 3103(=CH),1660-1658(CO) , 1625(C=N) .^{1}HNMR(δppm)**:** 2.19 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 6.91(s, 1H, C_3 indole), 6.96-8.10 (m, 11H, ArH), 11.03 (s, 1H, NH, D_2O exchangeable), 11.96(s, 1H, indole NH, D_2O exchangeable).



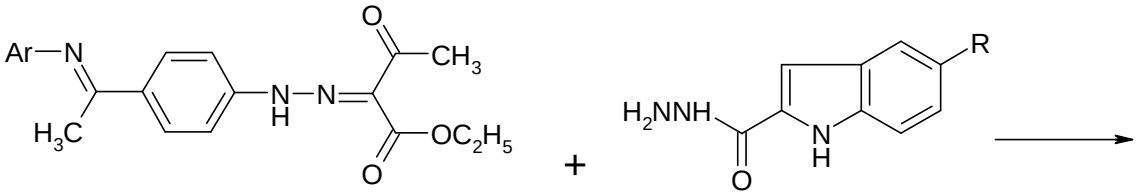
1a



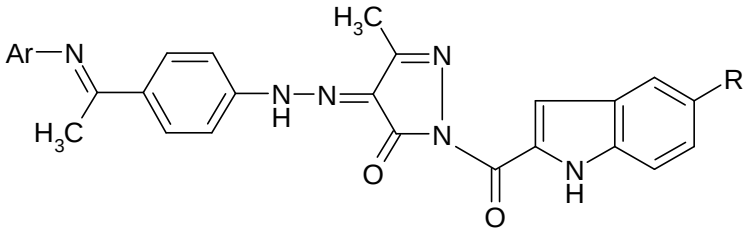
1b,c



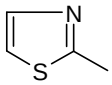
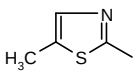
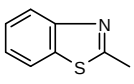
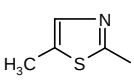
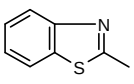
1a-c **2a-c**



2a-c **4a,b**



5a-f

5	a	b	c	d	e	f
R	H	H	H	F	F	F
Ar						

Scheme 1

RESULTS AND DISCUSSION

1-(4-Aminophenyl)-1-(thiazol-2-yl)iminoethane **1a** has been synthesized by treatment of 4-aminoacetophenone with 2-aminothiazole in boiling *N*,*N*-dimethyl-formamide as reported in the literature[18]. Similarly, 2-amino-5-methylthiazole and 2-aminobenzthiazole were condensed with 4-aminoacetophenone in DMF to give 1-(4-aminophenyl)-1-(substituted thiazol-2-yl)iminoethane derivatives (**1b,c)** (scheme1).

Compounds **1a-c** were also synthesized in excellent yield within few minutes (2-3.5 min) under microwave irradiation. Thiazolyl Schiff bases **1a-c** has been characterized on the basis of spectral studies and elemental analysis. IR spectrum (KBr) of **1b**, as an example, showed bands at 3400-3388 and 1640 cm^{-1} for NH_2 and C=N. The ^{1}H-NMR spectrum (DMSO-d_6) of **1c** showed signals at δ 2.78 ppm assigned to three protons of the methyl group and 6.10 ppm for NH_2.

The diazonium salts of **1a-c** when coupled with ethyl acetoacetate at 0-5 ºC in presence of sodium acetate gives 2-{[4-(substituted thiazol-2-yl)iminoethyl)-phenyl]hydrazono}-3- oxo-butyric acid ethyl esters **2a-c** (scheme 1). The ^{1}H-NMR spectrum (DMSO-d_6) of compound **2b**, as an example, exhibited signals at δ 0.91 (s,3H,CH_3),1.21 (t, 3H,OCH_2CH_3), 2.60 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 3.0 (s, 1H, CH), 4.20-4.22 (q, 2H, OCH_2CH_3), 6.70- 7.60 (m,5H, ArH). The IR spectrum of **2b** shows an absorption band at 3431 cm^{-1}, corresponding to the vibration of the NH group, a band at 1760 cm^{-1} , characteristic of the carboxylic ester moiety, while bands at 1713 cm^{-1} and 1610 cm^{-1} correspond to the characteristic acetyl CO and C=N groups respectively.

Heating under reflux a mixture of ethyl 5-substituted-1*H*-indole-2-carboxylate (**3a,b**) [19-21] and hydrazine hydrate in ethanol for 6h afforded 5-substituted-1*H*-indole-2-carbohydrazide derivatives[19] (**4a,b)**. These carbohydrazides were also obtained in a 96- 98 % yield by irradiation of (**3a,b**) with hydrazine hydrate in ethanol under MWI for 4 min.

Refluxing compounds **2a-c** and **4a,b** in a mixture of ethanol and acetic acid for 12 hrs furnishing 3-methyl-1-[(1*H*-indol-2-yl)carbonyl]-4-{[4-(substituted thiazol-2-yl)im-inoethyl)phenyl]hydrazono}-2-pyrazolin-5-one derivatives **5a-f** (scheme 1) . These pyrazolin-5-one derivatives were obtained in good yield through irradiation of a mixture of **2a-c** and **4a,b** using microwave oven for 5-6 min.

Table 1: Characterization data of synthesized compounds:

Comp	M.P. (ºC)	Solvent of Crystn.	Yield (%)	Formula (M.W.)	Analysis Calcd./ Found			
					C	H	N	S
1a[20]	201-204	Ethanol	62	$C_{11}H_{11}N_3S$ 217.29	60.80 60.81	5.10 5.13	19.33 19.38	14.75 14.71
1b	230-232	Ethanol	58	$C_{12}H_{13}N_3S$ 229.301	62.85 62.86	5.71 5.73	18.32 18.37	13.98 14.01
1c	271-273	EtOH-H_2O	50	$C_{15}H_{13}N_3S$ 267.35	67.38 67.40	4.90 4.91	15.71 15.69	11.99 11.96
2a[20]	165-167	Ethanol	66	$C_{17}H_{18}N_4O_3S$ 358.416	56.96 56.98	5.06 5.04	15.63 15.67	8.94 8.98
2b	186-188	Ethanol	62	$C_{18}H_{20}N_4O_3S$ 372.443	58.04 58.09	5.41 5.40	15.04 15.07	8.60 8.66
2c	140-142	Ethanol	60	$C_{21}H_{20}N_4O_3S$ 408.476	61.74 61.78	4.93 4.96	13.71 13.69	7.84 7.88
5a	294-297	$AcOC_2H_5$ - Pet. ether	57	$C_{24}H_{19}N_7O_2S$ 469.523	61.39 61.34	4.07 4.10	20.88 20.82	6.82 6.86
5b	258-260	Pet.ether 60-80	54	$C_{25}H_{21}N_7O_2S$ 483.55	62.09 62.10	4.37 4.32	20.27 20.24	6.63 6.60
5c	273-275	$AcOC_2H_5$ - Pet. ether	50	$C_{28}H_{21}N_7O_2S$ 519.583	64.72 64.77	4.07 4.10	18.87 18.81	6.17 6.13
5d	235-237	Ethanol	58	$C_{24}H_{18}FN_7O_2S$ 487.513	59.12 59.08	3.72 3.78	20.11 20.18	6.57 6.60
5e	216-218	Ethanol	48	$C_{25}H_{20}FN_7O_2S$ 501.54	59.87 59.88	4.02 4.02	19.54 19.51	6.39 6.41
5f	243-245	Ethanol	42	$C_{28}H_{20}FN_7O_2S$ 537.573	62.56 62.54	3.75 3.71	18.23 18.20	5.96 5.99

The ^{1}H-NMR spectrum (DMSO-d_6) of compounds **5a**, as an example, showed a singlet at δ 2.68-2.82 ppm assigned to three protons of the methyl group attached to the pyrazoline nucleus. Two broad signals at δ 11.12 and 11.60 ppm due to NH of hydrazino and indole, respectively were observed which were exchangeable with deuterium. A multiplet due to aromatic protons appeared at δ 6.24-7.55 ppm . The infrared spectrum of compounds **5a-f** showed strong bands in the 3325-3458 cm^{-1} region, attributed to NH groups stretching and the bands of the amidic and pyrazolinone ring C=O groups appearing at 1674 and 1680 cm^{-1}, respectively.

Table 2: Comparison of Conventional and Microwave synthesis:

Compd.	Conventional		Microwave	
	% yield	t/hrs	% yield	t/min
1a	64	4	82	3
1b	58	4	98	3.5
1c	50	4	89	2
4a	78	6	96	3
4b	85	6	98	3
5a	57	12	93	5
5b	54	12	88	5
5c	50	12	82	5
5d	58	12	91	5.5
5e	48	12	83	6
5f	42	12	81	6

Table 3: Antibacterial activity of prepared compounds:

Compd. No.	Gram +ve Bacteria			Gram –ve bacteria		
	S. aureus	*B. subtilis*	*B. cereus*	*P. aurignosa*	*E. coli*	*E. aerogenes*
1a	17	15	10	8	19	11
1b	19	17	14	8	11	10
1c	16	14	10	10	10	13
2a	11	13	12	10	16	11
2b	11	17	12	13	18	10
2c	8	22	11	10	16	12
5a	22	26	10	18	28	15
5b	20	19	16	11	18	14
5c	11	20	12	10	16	12
5d	15	16	11	8	19	13
5e	12	13	14	11	16	12
5f	13	14	10	12	18	11
Ampicillin	**20**	**25**	**22**	**18**	**21**	**12**

Table 4: Antifungal activity of prepared compounds:

Compd. No.	*A. niger*	*P. italicum*	*F. oxysporum*
1a	13	17	20
1b	20	20	18
1c	15	12	22
2a	14	16	14
2b	16	13	12
2c	12	15	11
5a	18	20	19
5b	10	16	22
5c	10	18	17
5d	12	22	26
5e	11	20	21
5f	10	16	19
Mycostatin	**12**	**20**	**26**

Biological Activity:

Some of the prepared compounds were screened for their activity against Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*), Gram-negative bacteria ((*Pseudomonas aurignosa*, *Echerichia coli*, *Enterobacter aerogenes*), as well as fungi (*Aspergillus niger*, *Penicillium italicum*, *Fusarium oxysporum*). Standard drugs, ampicillin for bacteria and mycostatin for fungi, were used at a concentration of 1000 ppm for comparisons. The biological activity of these compounds have been evaluated by filter paper disc method [22] after dissolving

them in *N*,*N*-dimethylformamide to obtain a 1mg/mL solution (1000 ppm). The inhibition zones of microbial growth surrounding the filter paper disc (5 mm) were measured in millimeters at the end of an incubation period of 3 days at 37°C for *Echerichia coli* and at 28°C for other bacteria and fungi. *N*,*N*-dimethylformamide alone showed no inhibition zone. The obtained results are listed in Tables 3 and 4.

CONCLUSION

A series of novel pyrazolin-5-one derivatives were prepared. The biological activity of these compounds was evaluated against various Gram-positive, Gram-negative bacteria and fungi. 3-Methyl-1-[(1*H*-indol-2-yl)carbonyl]-4-{[4-(thiazol-2-yl)iminoethyl)phenyl]hydrazono}-2-pyrazolin-5-one (**5a**) showed the highest antibact-erial activity, while compound **5c** showed moderate activity. As far as the antifungal activity is concerned, only compound **5d** exhibited the highest antifungal activity.

REFERENCES

[1]- P. N. Deshmukh, V.S. Jamode, *International Journal of Chemistry and Applications*, **2011**, 3, (3) , 291-302.
[2]- D. R. Gupta, R. K. Arora, *Acta Chim. Hung*. **1985**, 118, 79–83.
[3]- F. Thakor, P. Sanjay, MD. Patel, P. Manish, *Saudi Pharmaceutical Journal*. **2007**, 15(1), 48-54.
[4]- S. P. Hiremath, K. Rudresh, A. R. Saundan, *Indian J. Chem.* **2002**, 41B, 394–399.
[5]- F. R. Souza, V. T. Souaza, V. Ratzlaff, L. P. Borges, M. R. Olivera, H. G. Bonacorso, N. Zanatta, M. A. Martina, C. F. Mello, *Eur. J. Pharmacology* ,**2002**, 451, 141–147
[6]- AN. Evstropov, VE. Yavorovskaya, ES. Vorob'ev, ZP. Khudonogova, SG. Medvedeva, VD. Filimonov, TP. Prishchep, AS. Saratikov, *Pharm. Chem. J*, **1992**, 26(5), 426-430.
[7]- C. E. Rosiere, M. I. Grossmann, *Science* , **1951**,113 , 651.
[8]- R. Ramajayam, KP.Tan, HG. Liu, PH. Liang, *Bioorg. Medi.Chem.* **2010**,18, 7849–7854.
[9]- A. Iqbal, H. L. Siddiqui , C. M. Ashraf, M. Ahmad, G. W. Weaver, *Molecules* **2007**, 12, 245-254.
[10] – X. Zhou, L. Shao, Z. Jin, JB. Liu, H. Dai, J. Fang, *Heteroatom Chemistry*, **2007**, 18,1,55-59.
[11]- R. K. Tiwari, D. Singh, J. Singh, V. Yadav, A. K. Pathak, R. Dabur, A. K. Chhillar, R. Singh, G. L. Sharma, R. Chandraa and A. K. Verma, *Bioorg. Med. Chem*. **2006**, 16, 413–416.
[12]- E. R. El-Sawy, T. K. Mohamed and S. Y. El-Tablawy, *Egypt Pharm. J*. **2006**, 5 175–188.
[13]- A. R. Farghaly, *ARKIVOC*, **2010**, (xi), 177-187.
[14]- S. Suzen,; E. Buyukbingol, *II Farmaco*. **2000**, 55, 246.
[15]- D. Wang, D. Y. Sheng, F. Qin, L. Fang, P. Gong, *Chinese chemical letters*. **2004**, 15(1): 19-22.
[16]- D. Dallinger and C.O. Kappe, *Chem. Rev*, **2007,** 107, 2563.
[17]- P. Lidstrom, J. Tierney, B. Westman, J. Wathey, *Tetrahedron*, **2001**, 57, 9225.
[18]- F. E. Goda, A. R. Maarouf, E. R. EL-Bendary. *Saudi Pharmaceutical J*., **2003**,11, 3, 111-117.
[19]- N. Ghareb, P. A. Hanna , M. M. Said, *African Journal of Pharmaceutical Sciences and Pharmacy* , **2012**, 3(1), 41-65.
[20]- Y. Murakami, Y. Yokoyama, T. Mitura, H. Hirasawa, Y. Kamimura, M. Izaki, *Heterocycles*, **1984**, 22(5), 1211-1216.
[21]- MS Mohamed, G. Nagat, H. Pierre, A. El-Gendy. *Egypt J. Biomed. Sci*. **2009**, 30, 1-19.
[22]- National Committee for Clinical Laboratory Standards, Performance Standards For Antimicrobial Disk Susceptibility Test. Approved Standard M2-A6. National Committee for Clinical Laboratory Standards: Wayne, PA, USA, **1997**.