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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 1-(4-ARYL-2-THIAZOLYL) - AND 1-(4-ARYL-2-OXAZOLYL)-3, 5-DIARYL Δ^2-PYRAZOLINE DERIVATIVES

Nadia T. A. Dawood

Chemistry Department, Faculty of Science, Girl's, Al-Azhar University, Nasr City, Cairo, Egypt

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Correspondence to Author:

Nadia T. A. Dawood

Chemistry Department, Faculty of Science, Girl's, Al-Azhar University, Nasr City, Cairo, Egypt

ABSTRACT

A series of nine 1-(4-aryl-2-thiazolyl)-3, 5- diaryl and six of 1- (4- aryl- 2-oxazolyl)-3, 5- diaryl- 2- pyrazolin derivatives were prepared by reacting 3, 5-diaryl-1- thiocarbamoyl-/or 3, 5- diaryl- 1- carbamoyl- Δ^2- pyrazolines with substituted phenacyl bromide in ethanol. The structures of the synthesized derivatives were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR as well as EIMS spectral data. Some of these derivatives were screened for their antimicrobial activity against Gram-positive, Gram- negative and pathogenic fungi, and showed a significant activity.

INTRODUCTION: Heterocyclic compounds have played an invaluable role in pharmaceutical and agrochemical discovery processes. In recent years a substantial number of substituted pyrazolines have been reported to possess various pharmacological activities such as antimicrobial [1-3], anti-inflammatory [4], antihypertensive [5], antiamoebic [6, 7], antimycobacterial [8, 9], antitumor [10], antidepressant [11] and antidiabetic [12], and since the combat against bacterial infections has resulted in the development of a wide variety of antibiotics, therefore, recent efforts have been directed toward exploring novel antibacterial agents [13].

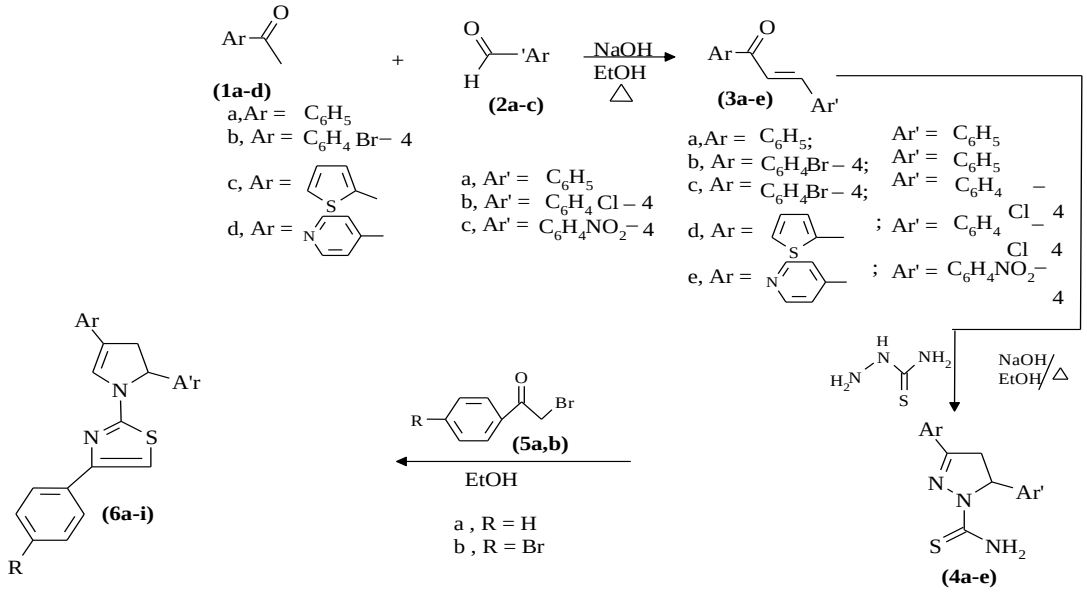
Apart from this, during the past 20 years an increase of invasive fungal infections has been observed, particularly in immunosuppressed patients, which are now, cause of morbidity and mortality. Since the discovery of amphotericin B a number of different classes of antifungal agents have been discovered, however, there is still a critical need for new antifungal agents to treat life threatening invasive mycoses [14].

In order to overcome the rapid development of drug resistance, new agents should preferably consist of chemical characteristics that clearly differ from those existing agents. Certain small heterocyclic molecules act as highly functionalized scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules [15, 16]. Electron-rich nitrogen heterocycles play an important role in diverse biological activities. Second nitrogen in the five membered rings also influences the antibacterial or pharmacokinetic properties [17-19].

On the other hand, sulphur and/or nitrogen heterocycles that possess pharmaceutical activities widely occur in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cells. Penicillins containing a thiazole ring system (thiazolidine) [20] are also important naturally occurring products. Thiazoles and their derivatives are found to be associated with various biological activities such as antimicrobial [21, 22], antituberculosis [23], and anti-HIV [24] activities.

In the interest of the above suggestion, the present investigation was planned to synthesize a system that combines together two biolabile components that are 2-pyrazolines and thiazoles or oxazole, to give a compact structure like the title compounds.

Chemistry: The synthetic routes of 1-(4-aryl-2-thiazolyl)-3, 5-diaryl pyrazolines (6a-i) and 1-(4-aryl-2-oxazolyl)-3, 5-diaryl pyrazolines (8a-f) are outlined in schemes 1, 2 and 3.

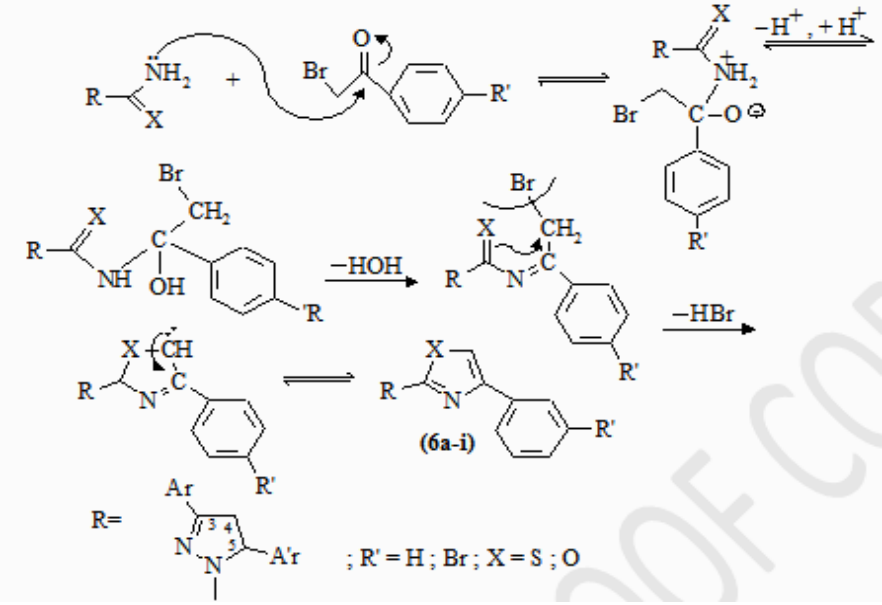


a, Ar	=	C_6H_5;	Ar'	=	C_6H_5 ; R=H	a, Ar	=	C_6H_5;	Ar'	=	C_6H_5
b, Ar	=	C_6H_4Br–4 ;	Ar'	=	C_6H_5 ; R=H	b, Ar	=	C_6H_4Br–4;	Ar'	=	C_6H_5
c, Ar	=	C_6H_4Br–4 ;	Ar'	=	C_6H_5; R=Br	c, Ar	=	C_6H_4Br–4;	Ar'	=	C_6H_4Cl–4
d, Ar	=	C_6H_4Br–4 ;	Ar'	=	C_6H_4Cl–4 ; R=H	d, Ar	=	;	Ar'	=	C_6H_4Cl–4
e, Ar	=	C_6H_4Br–4 ;	Ar'	=	C_6H_4Cl–4 ; R=Br						
f, Ar	=	;	Ar'	=	C_6H_4Cl–4 ; R=H	e, Ar	=	;	Ar'	=	$C_6H_4NO_2$–4
g, Ar	=	;	Ar'	=	C_6H_4Cl–4 ; R=Br						
h, Ar	=	;	Ar'	=	$C_6H_4NO_2$–4 ; R=Hr						
i, Ar	=	;	Ar'	=	$C_6H_4NO_2$–4 ; R=B						

SCHEME 1

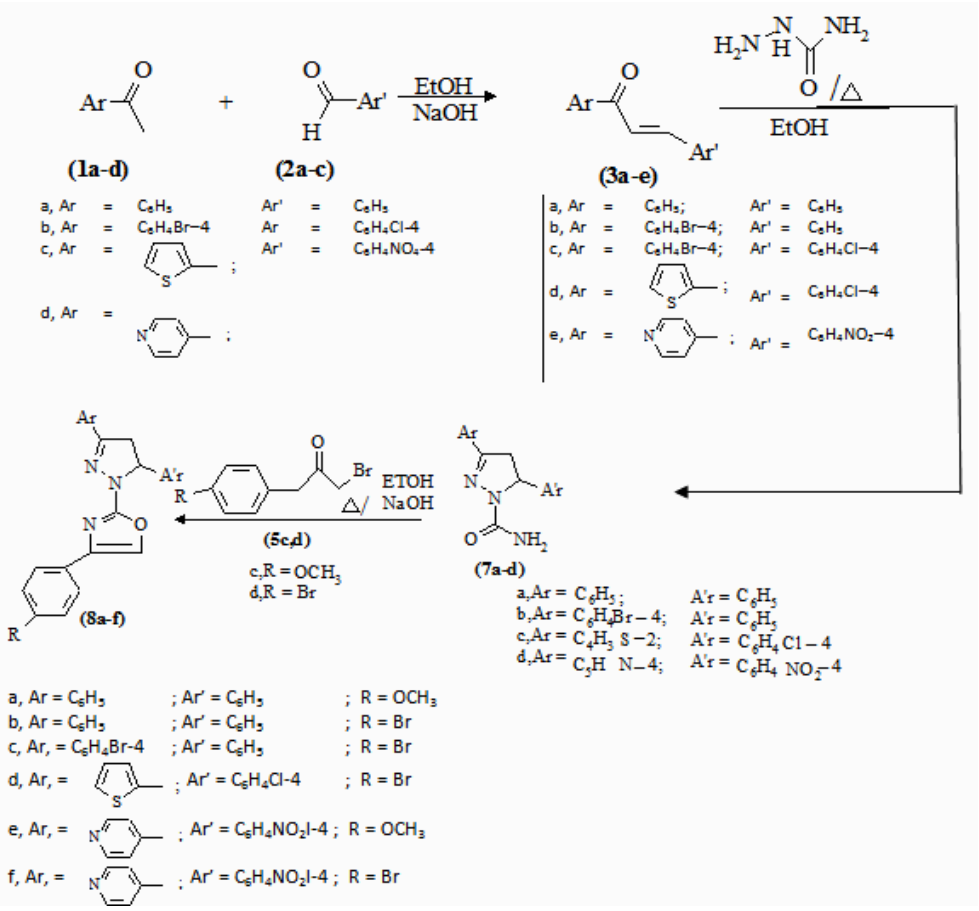
In the present work, 1-phenyl-1-(4-bromophenyl), 1-(2-thienyl) and 1-(4-pyridyl)-3-aryl-2-propen-1-ones **(3a-e)** were prepared by reacting acetophenone, 4-bromoacetophenone, 2-acetylthiophene and/or 4-acetylpyridine **(1a-d)** with aromatic aldehydes namely, benzaldehyde, 4-chlorobenzaldehyde and/or 4-nitrobenzaldehyde **(2a-c)** according to the method described in the literature [25], They were then subjected to reaction with thiosemicarbazide and/or semicarbazide followed by reaction with phenacyl bromide derivative **(5a-d)** to give the corresponding 2-thiazolyl- and 2-oxazolyl-pyrazoline derivatives **(6a-i)** and **(8a-f),** respectively.

RESULTS, DISCUSSION AND CONCLUSION: In the present investigation a series of 9 and 6 new compounds were prepared. Thus, starting with 1, 3-(diphenyl)-, 1-(4-bromophenyl)-3-(phenyl)-, 1-(4-bromophenyl)-3-(4-chlorophenyl), 1-(2-thienyl)-3-(4-chlo-rophenyl)-and/or-1-(4-pyridyl)-3-(4-nitrophenyl)-2-propen-1-ones **(3a-e)** prepared according to the literature [25] were cyclized to the corresponding 3, 5-diaryl- 1- thiocarbamoyl- 2- pyrazolines **(4a-e)** by treatment with thiosemicarbazide in boiling ethanol containing aqueous NaOH. Treatment of (4a-e) with phenacylbromide derivatives **(5a, b)** in boiling ethanol affected cyclization to the corresponding title compounds **(6a-i),** respectively (c.f. **Scheme 2**)



SCHEME 1

The presence of a strong electron withdrawing group at the para position of the phenacyl bromide such as Br played an important role in the thiazole formation since it appears to increase its polar character and therefore its tendency to undergo cyclocondensation in the para position of the benzene ring since it enhances the reaction to the forward and so gave higher yield compared to other derivative which didn't contain it (c.f. **Tables 1, 2**). In a similar manner, the interaction of 1, 3-diaryl-propen-1-one (**3a-e)** with semicarbazide in ethanolic NaOH gave the corresponding 3, 5-diaryl-1-carbamoyl-2-pyrazolines **(7a-d).** Compounds **(8a-f)** were obtained by reacting compounds **(7a-d)** with phenacylbromide derivatives **(5c, d)** in boiling ethanol (**Scheme 3**).



SCHEME 2

On the other hand, the presence of an electron-releasing group at the para position of the phenacyl bromide derivative such as $–OCH_3$, in **(5c)** and a strong electron-withdrawing group such as Br in the para position in **(5d)** affected strongly the cyclization of 1-carbamoyl-3, 5-diaryl-2 pyrazolines **(7a-f)** as the yields of the formed oxazoles **(8a-e)** differ completely than the oxazoles **(8b-d, 8f)** (c.f. Table 2).

* Where EtOH = absolute ethanol; AcOH = acetic acid and P.E. = Petroleum ether (B.P. 60-80°C)

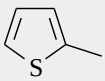
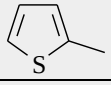
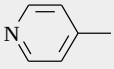
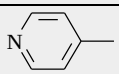
The structures of compounds **(6a-i)** and **(8a-f)** were confirmed by their IR, ^{1}H-NMR, ^{13}C-NMR and EIMS spectral data (c.f. Tables 2). The IR spectra of **(6a-i)** has shown strong absorption bands at the region 1591-1623cm^{-1} for υC=N, at the region 1061-1071cm^{-1} for υC=N–N–C and at the region 1100-1159cm^{-1} for υN=C–X (X=S).

The IR spectra of **(8a-f)** has shown characteristic absorption bands in the region 1601-1623cm^{-1} for υC=N, at the region 1069-1073cm^{-1} for υC=N–N–C and at the region 1097-1176 for υC–C–X (X=O).

The ^{1}H–NMR spectra of compounds **(6a-i)** have shown the CH_2 protons of the pyrazoline ring resonated as a pair of doublets of doublets at the region δ2.8-3.76ppm (Hb), the CH (Hx) proton appeared as a doublet of doublets at the region δ3.25-3.96ppm due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 4 of the pyrazoline ring (Jab = 17.1-17.6 Hz, J_{ax} = 7.0-7.5 H_2 and J_{bx}=12.0-12.1 Hz). The H5-proton of the thiazole and/or the oxazole is observed as a singlet between δ6.7-6.89ppm.

All the other aromatic and aliphatic protons were observed at the expected regions. The ^{13}C–NMR chemical shift values of the carbon atoms were measured at δ42.25-44.93ppm. (C–4), at δ62.96-66.29ppm (C–5), at the region δ50.79-152.96ppm (C–3), which supported the Δ^2-pyrazoline character confirmed by the ^{1}H–NMR data (c.f. Table 2). The EIMS spectra of the prepared compounds **(6a–i)** were also in agreement with the proposed structures. The analytical as well as physical and spectral data of compounds **(6a-i)** and compounds **(8a-f)** which confirmed the structure of these compounds are listed in **Table 1, 2**.

TABLE 1: PHYSICAL DATA OF THE THIAZOLYLPYRAZOLINES (6a-i) AND OXAZOLYLPYRAZOLINES (8a-f)

Compd. No.	Ar	Ar′	R	M. pt. °C solvent of crystallization*	Mol. formula (Mol. wt.)	Analysis calcd./found%						Yield %
						C	H	N	S	Br	Cl	
6a	C_6H_5	C_6H_5	H	292 EtOH	$C_{24}H_{19}N_3S$ (381)	75.59 75.6	4.98 5.0	11.02 11.1	8.39 8.4	—	—	55
6b	C_6H_4Br–4	C_6H_5	H	231 AcOH	$C_{24}H_{18}N_3SBr$ (460)	62.608 62.7	3.91 3.9	9.13 9.1	6.95 7.0	17.39 17.4	—	64
6c	C_6H_4Br–4	C_6H_5	Br	240 EtOH	$C_{24}H_{17}N_3SBr_2$ (539)	53.43 53.5	3.15 3.2	7.79 7.8	5.93 6.0	29.68 30.0	—	74
6d	C_6H_4Br–4	C_6H_4Cl–4	H	169 EtOH	$C_{24}H_{17}N_3SBrCl$ (494.5)	58.24 58.3	3.43 3.5	8.49 8.5	6.47 6.5	16.17 16.2	7.17 7.3	69
6e	C_6H_4Br–4	C_6H_4Cl–4	Br	181 EtOH	$C_{24}H_{16}N_3SBr_2Cl$ (573.5)	50.21 50.2	2.78 2.8	7.32 7.3	5.57 5.6	27.89 28.0	6.19 6.2	73
6f		C_6H_4Cl–4	H	141 AcOH	$C_{22}H_{16}N_3S_2Cl$ (421.5)	62.63 62.6	3.79 3.8	9.96 10.1	15.18 15.2	—	8.42 8.5	59
6g		C_6H_4Cl–4	Br	157 EtOH	$C_{22}H_{15}N_3S_2ClBr$ (500.5)	52.74 52.8	2.99 3.0	8.39 8.4	12.78 13.0	15.98 16.0	7.09 7.1	71
6h		$C_6H_4NO_2$–4	H	134 P. E.	$C_{23}H_{17}N_5O_2S$ (427)	64.63 64.6	3.98 4.0	16.39 16.5	7.49 7.5	—	—	69
6i		$C_6H_4NO_2$–4	Br	149 P. E.	$C_{23}H_{16}N_5O_2SBr$ (506)	54.54 54.5	3.16 3.2	13.83 14.0	6.32 6.3	15.81 16.0		63
8a	C_6H_5	C_6H_5	OCH_3	217 EtOH	$C_{25}H_{21}N_3O_2$ (395)	75.94 76.0	5.31 5.3	10.63 10.6	—	—	—	48
8b	C_6H_5	C_6H_5	Br	227 AcOH	$C_{24}H_{18}N_3OBr$ (444)	64.86 65.0	4.05 4.1	9.45 9.6	—	18.01 18.0	—	69
8c	C_6H_4Br–4	C_6H_5	Br	211	$C_{24}H_{17}N_3OBr_2$	55.06	3.25	8.03	—	30.59	—	73

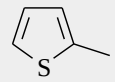
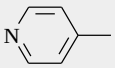
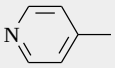
				EtOH	(523)	55.1	5.3	8.1		31.0		
8d		$C_6H_4Cl_4$–4	Br	169 P. E.	$C_{22}H_{15}N_3OSClBr$ (484.5)	54.48 54.5	3.09 3.1	8.66 8.7	6.604 6.7	16.51 16.5	7.32 7.3	61
8e		$C_6H_4NO_2$–4	OCH_3	198 AcOH	$C_{24}H_{19}N_5O_4$ (441)	65.306 65.4	4.308 4.3	15.87 16.0	—	—	—	51
8f		$C_6H_4NO_2$–4	Br	205 EtOH	$C_{23}H_{16}N_5O_3Br$ (478)	57.74 57.7	3.34 3.3	14.64 14.7	—	16.73 16.6		68

TABLE 2: IR; ^{1}H–NMR; ^{13}CNMR AND MS OF THIAZOLYL- AND/OR OXAZOLYL-PYRAZOLINES (6a-i) AND (8a-f)

Compd. No	IR υ Cm^{-1}	1H-NMR δ ppm	13C NMR δ ppm	Ms m/z (%)
6a	2928,2826 (υCH), 1623(υC=N), 1061(C–N)	2.23 (dd, 1H), 2.91 (dd, 1H), 3.25 (dd, 1H), 6.70(s, 1H, CH), 6.95–7.61 (m, 15H, Ar–H)	40.72(CH_2), 66.1(CH), 1017(CH), 126.8(2CH), 127.0(2CH), 128.6(2CH), 128.9(2CH), 129.2(2CH), 131.1(CH), 134.0(CH), 143.5(C), 151.8(C), 173(C).	382(2.7), 381(17.2), 221(8.7), 215(12.7), 201(33.1), 174(4.9), 161(23.7), 130(19.2), 103(11.4), 77(100), 72(59.3), 67(37.1), 59(19.2), 58(13.4), 54(12.2).
6b	3010,2928,2880(υCH), 1619(υC=N), 1069(C–N), 529(C–Br).	2.81 (dd, 1H), 3.12 (dd, 1H), 3.91 (dd, 1H), 6.72 (s, 1H, CH) 7.08-7.59(m,14H,Ar–H)		462(1.8), 461(17.3), 460(22.1), 446(19.7), 384(11.3), 366(7.1), 306(1.1), 304(15.2), 303(12.9), 290(25.3), 277(61.1), 234(1.7) 226(33.7), 215(16.3)156(100), 151(23.1), 83(16.3), 67(11.1), 77(51.9), 76(2.1).
6c	3030,2967,2889(υC–H), 1615(υC=N), 1071(C–N), 518(υC–Br).	2.89(dd,1H), 3.39(dd, 1H), 3.95(dd,1H), 6.80 (s, 1H, CH),7.19-8.13 (m,13H,Ar–H)	42.6(CH_2), 67.3(CH), 102.1(CH), 119.3(CH), 125.4(2CH), 128.2 (2CH), 128.7(CH), 131.4(CH), 131.8(2CH), 132.3(CH), 1331.0(CH), 143.5(C), 151.8(C), 173.2(C).	
6d	3010, 2922, 2886(υCH), 1619(υC=N), 1061(C–N), 879(υC–Cl), 519((υC–Br).	2.81(dd, 1H), 3.15(dd, 1H), 3.90(dd, 1H), 3.90 (dd, 1H) 6.81 (s, 1H, CH), 7.02-7.89 (m, 13H, Ar–H)		497(1.1), 496(12.9), 495(13.3), 458(21.3), 414(53.1), 379(50.3),339(37.2),327(18.2), 326(35.1),313(12.6), 238(27.4), 225(21.5), 223(14.3), 211(1.6), 201(19.6), 179(22.2), 161(89.1),156(89.1),151(43.3), 145(16.1), 143(1.1), 112(7.1), 76(23.3), 68(100), 55(56.1).
6e	3053, 2986, 2822(υCH), 1618(υC=N), 1071(C–N), 881(υC–Cl), 529(υC–Br).	3.32(dd, 1H), 3.76(dd, 1H), 3.96(dd, 1H), 6.89(s, 1HCH) 7.03-8.12 (m, 12H, Ar–H).		
6f	3003, 2928, 2826(υCH), 1601(υC=N), 1069(C–N), 872(υC–Cl).	2.80(dd, 1H), 3.12(dd, 1H), 3.90 (dd, 1H), 6.82 (s, 1H, CH), 7.06-7.28 (m, 12H, Ar–H).	37.8(CH_2), 66.9(CH), 103.2 (CH), 117(2CH), 122.3 (2CH), 128.4(2CH), 128.7(2CH), 137(CH), 139.0(C), 141.6(C), 149.4(C), 173.2(C).	
6g	2986, 2886, 2828(υCH), 3.19, 1591(υC=N), 1071 (C–N), 867(υC–Cl), 528 (υC–Br).			
8a	3030,2928,2828 (υCH),1601(υC= N), 1027(υO–C– N)	3.07 (dd, 1H), 3.41 (s,3H,Ar-OCH3, 1H), 3.81 (dd, 1H), 5.4 (dd, 1H), 6.13(s,1H,CH),7.01–7.85 (m,14H,Ar–H)	40.37(CH_2), 68.1(CH), 104.1(CH), 111.8(2CH), 121.9(2CH), 128.4(2CH), 128.7(2CH), 137.8(CH), 39.9(H), 142.7(H), 153.7(C), 174.1(C).	395(18.1), 396(3.3), 397(1.2), 263(19.1), 185(23.3), 109(50.1), 108(23.1), 107(16.5), 106(27.2), 94(17.9), 83(17.3), 77(100), 67(7.1), 53(14.9).

Compd. No	IR υ Cm^{-1}	1H-NMR δ ppm	13C NMR δ ppm	Ms m/z (%)
8b	3010, 2928, 2818(υCH), 1619(υC=N), 1072(υO–C–N).	3.08 (dd, 1H), 3.82 (dd, 1H), 5.45 (dd, 1H), 6.76 (s, 1H, CH), 7.15-7.91(m,14H,Ar–H)		
8c	3008,2928,2828(υC–H),1622(υC=N),1076(υO–C–N),	3.21(dd,1H), 3.84(dd,1H), 5.45(dd,1H), 6.76(s,1H,CH), 7.19-7.85(m, 13H, Ar–H)		523(11.1),524(7.7),525(1.4),342(19.3)278(11.2),272(12.1),264(1.3),224(11.3)197(35.4),135(20.9),123(11.1),109(71.3),83(100),77(55.1),76(24.9),69(13.9),67(1.3).
8d	3055, 2928, 2818(υCH), 1623(υC=N), 1176(υO–C–N).	3.08(dd,1H), 3.80(dd, 1H), 5.41(dd,1H), 6.65(s, 1H, CH), 7.09-7.89 (m, 11H, Ar–H)	44.3(CH_2), 69.01(CH), 114.3(CH), 118.7(2CH), 121.9(2CH), 128.7(2CH), 129.1(2C), 137.9(CH), 141.1(C), 142.7(C), 154.3(C), 163.9(C), 174.9(C).	
8e	308653, 2928, 28282υCH), 1619(υC=N), 1648(υNO2), 1068(υO–C–N).	3.07(dd,1H),3.43(s,3H,ArOCH3), 3.82(dd, 1H), 6.39(dd, 1H), 6.79-7.80(m, 12,Ar-H).		441(17.1), 442(9.7), 443(3.2), 425(11.1), 409(17.2), 355(23.1), 324(14.2), 318(19.2),313(2.4), 266(21.3), 251(20.4), 249(15.3), 212(11.3), 185(30.4), 159(1.3), 145(17.9), 118(12.3), 90(15.4), 79(58.1), 77(20.3), 76(12.9), 68(11.1), 66(100), 51(98.1)
8f	3065, 2928, 2828(υCH), 1622(υC=N), 1660(υNO2), 1080((υO–C–N).	3.10(dd, 1H), 3.81(dd, 1H), 5.43 (dd, 1H), 6.67 (s, 1H, CH), 7.04-7.80 (m, 12H, Ar–H).	37.9(CH_2), 66.7(CH), 103.9(CH), 114.7(2CH), 118.1(2CH), 121.4 (2CH), 127.9(2CH), 129.4 (CH), 131.3(CH), 133.4(C), 139.1(C), 141.3(C).151.1(C), 163.2(C).	

Antimicrobial Activity:

Biology: The new compounds **(6a-i)** and **(8a-f)** were screened for their antibacterial activity by disk-diffusion technique[26] against two Gram – positive bacteria namely, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, two Gram-negative bacteria namely, *Bacillus subtillis* and *Escherichia coli* and four pathogenic fungi namely, *Syncephalastrum racemosum*, *Aspergillus fumigatus*, *Candida albicans* and *Geotrichum candidum* at three concentrations 5,2.5 and 1.25µg/ml. Chloramphenicol was used as standard antibacterial agent and fluconazole was used as standard antifungal agent. The minimal inhibitory concentrations (MIC) of the compounds are listed in **Table 3**.

MIC'S were recorded as the minimum concentration of a compound that inhibits the growth of tested microorganisms. All of the compounds tested have shown significant antibacterial and antifungal activity as compared with the reference drugs. The antibacterial assessment revealed that most of the tested compounds possess weak to moderate activity. The MIC values are generally within the range 3.9-250µg/ml against all the tested strains.

In comparing the MIC values with the references chloramphenicol, it is obvious that most of the compounds are effective against *P. aeruginosa, A. fumigatus, C. albicans* and *G. eandidum*. Compound **6a** has shown a relatively high activity against *S. aureus, P. aeruginosa*, *S. racemosum, A. fumigatus* and *B. subtilis*. Compounds **6d** were highly active against *S. aureus, B. subtilis, P. aeruginosa, S. racemosum* and *A. fumigatus*.

Compounds **6a-i** and **8a-f** have shown no activity towards *E. coli*. Compound **6a** has shown the highest activity towards *E.coli*. Compound **6a** has shown the highest activity towards *S. aureus* as compared to the references, while the activity of compounds **8a** was the same as the references chloramphenicol.

Compounds **6a, 6d** have shown the same moderate activity against *B. subtilis*. Compound **6i** has shown the highest activity towards *P. aeruginosa,* while compounds **6b-e**, **8a** and **8d** have shown the same moderate activity and compound **6a** showed the same activity as the standard reference. Compound **6a**, **8a**, have shown the same activity against *S. racemosum* and *A. fumigatus,* while compounds **6d**, **8b-d** have shown the same moderate activity. Compounds **6c, 8a-d** have shown high activity towards *C. albicans,* while compounds **6c,d** and **8a-d** have shown the same high level of activity towards *G. eandidum* (c.f. **Table 3**). The results are summarized in Table 3. Most of the compounds have shown good antifungal activity, when compared to Fluconazole, **4** compounds were more active (MIC < 250µg/ml).

TABLE 3: MIC VALUES (mg/ml) OF COMPOUND 6a-i AND 8a-f.

Compound	A	B	C	D	E	F	G	H
6a	250	15.6	62.5	31.25	31.25	31.25	250	250
6b	250	125	125	62.5	250	125	125	125
6c	125	125	125	62.5	250	125	62.5	62.5
6d	125	62.5	62.5	62.5	62.5	62.5	125	62.5
6e	125	125	125	62.5	250	125	125	125
6f	250	125	250	250	250	250	250	250
6g	250	125	125	125	250	250	125	125
6h	250	250	125	250	250	125	125	125
6i	250	250	250	3.9	125	250	250	250
8a	250	31.25	125	62.5	125	31.25	62.5	62.5
8b	125	250	125	125	250	62.5	62.5	62.5
8c	125	250	125	125	250	62.5	62.5	62.5
8d	125	125	125	62.5	250	62.5	62.5	62.5
8e	125	250	250	250	250	125	125	125
8f	125	250	250	250	500	125	125	125
Reference-1	15.60	31.25	31.25	31.25	—	—	—	—
Reference-2	—	—	—	—	250	125	250	250

Reference 1: Chloramphenicol, Reference-2 fluconazole where:

A: *Escherichia coli* (RCMB 000103), B: *Staphylococcus aureus* (RCMB 000106), C: *Bacillus subtilis* (RCMB 000107), D: *Pseudomonas aeruginosa* (RCMB 000102), E: *Syncephalastrum racemosum* (RCMB 005003), F: *Aspergillus fumigatus* (RCMB 002003), G: *Candida albicans* (RCMB 005002), H: *Geotrichum eandidum.*

Experimental:

Chemistry: Melting points were determined by using Gallen camp digital meeting point apparatus in capillary tubes and were uncorrected. ^{1}H-NMR and ^{13}C NMR spectra (DMSO-d_4) using TMS as internal standard were recorded at 400 and 1000 MHZ with a Bruker apparatus. MS spectra were performed with apparatus Jeol JMS-D300 at 70eV.

General procedure for the synthesis of the compounds:

1, 3-diaryl-2-propen-1-ones(3a-e): A mixture of acetophenone, 4-bromoacetophenon,2-acetyl-thiophene and/or 4-acetyl pyridine (0.02mol) **(1_{a-d}),** aromatic aldehyde namely, benzaldehyde, 4-chlorobenzaldehyde and/or 4-nitrobenzaldehyde (0.02 mol) **(2_{a-c})** and 10% aqueous sodium hydroxide (10 ml) in ethanol (30ml) was stirred while cooling (0-5ºC) for 3h; The resulting solid was collected, washed well and recrystallized from ethanol as **3a-e** [25].

1, 4- diaryl- 1- thiocarbamoyl- or- carbamoyl- 2-pyrazolines (4a-e) and (7a-d): A mixture of 1,3-diaryl-2-propen-1-one derivatives **(3a-e)** (0.01mol), aqueous sodium hydroxide [(1g, 0.025mol), dissolved in 1m1 of water] in 30ml of absolute ethanol and thiosemicarbazide (0.01 mol, 0.9g)/or semicarbazide (0.01mol, 0.7g) was refluxed for 6h. The product was poured into cold water and the solid product was collected, washed well and recrystallized from the proper solvent as **4a-e** and **7a-d**.

1-(4-aryl-2-thiazolyl)-3, 5-diaryl-2-pyrazolines (6a-i): A mixture of **4a-e** (0.01mol), phenacylbromide derivatives **(5a, b)** (0.01mol) in 25ml of absolute ethanol was heated under reflux for 3h. The product that separated after concentration and cooling was collected and recrystallized from the proper solvent as (**6a-i)**.

1-(4-aryl-2-oxazolyl)-3, 5-diaryl-2-pyrazolines (8a-f): A mixture of **7a-d** (0.01mol), phenacylbromide derivatives **(5c, b)** (0.01mol) in 25ml of absolute ethanol was heated under reflux for 3h and the products were treated as above to give (**8a-f).**

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