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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

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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, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ 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.

Keywords: Δ^2 -pynazolines, thiazoles, oxazoles, synthesis, antimicrobial 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 activities [24].

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.

EXPERIMENT SECTION

Melting points were determined by using Gallen camp digital melting point apparatus in capillary tubes and were uncorrected. ¹H-NMR and ¹³C NMR spectra (DMSO-d₄) 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:

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

Synthesis of 1,4-diaryl-1-thiocarbonyl-or-carbonyl-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 1ml 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 recrystallised from the proper solvent as **4a-e** and **7a-d**.

Synthesis of 1-(4-aryl-2-thiazolyl)-3,5-diaryl-2-pyrazolines (6a-i).

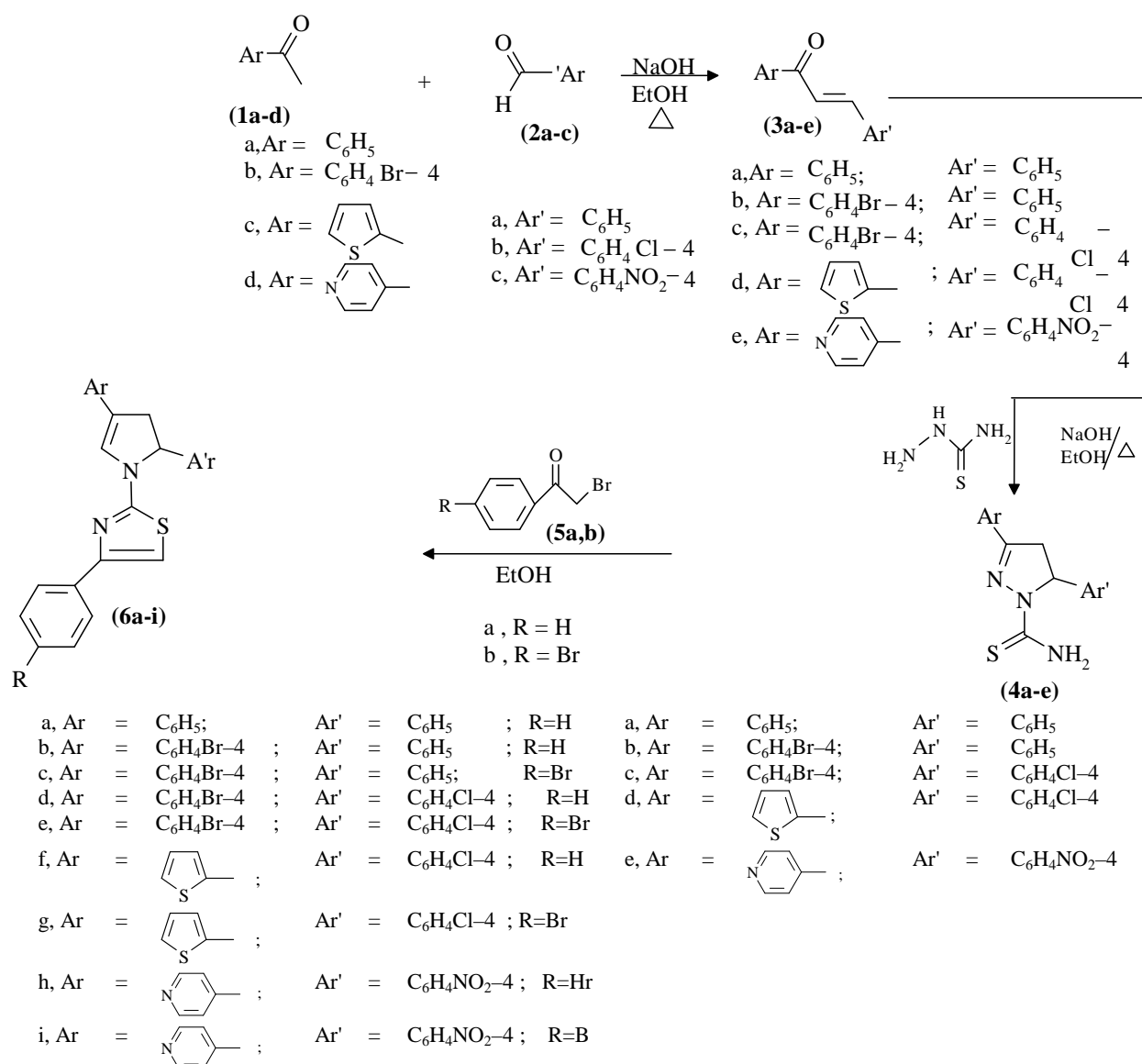
A mixture of **4a-e** (0.01mol), phenacylbromide derivatives (**5a,b**) (0.01mol) in 25ml of absolute ethanol was heated under reflux for 3h. The product that separated after concentration and cooling was collected and recrystallised from the proper solvent as **6a-i** (c.f. Table 1).

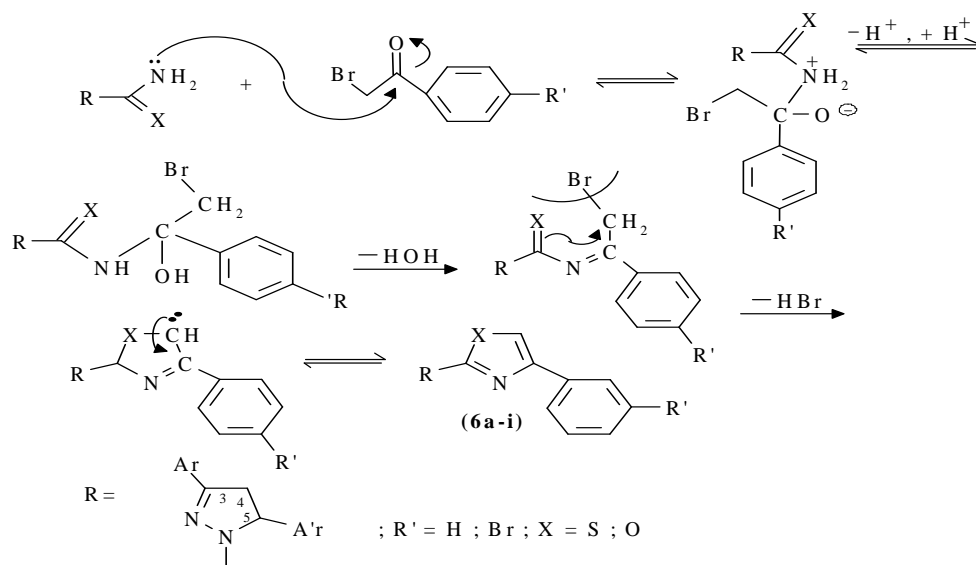
Synthesis of 1-(4-aryl-2-oxazolyl)-3,5-diaryl-2-pyrazolines (8a-f).

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** (c.f. Table 2).

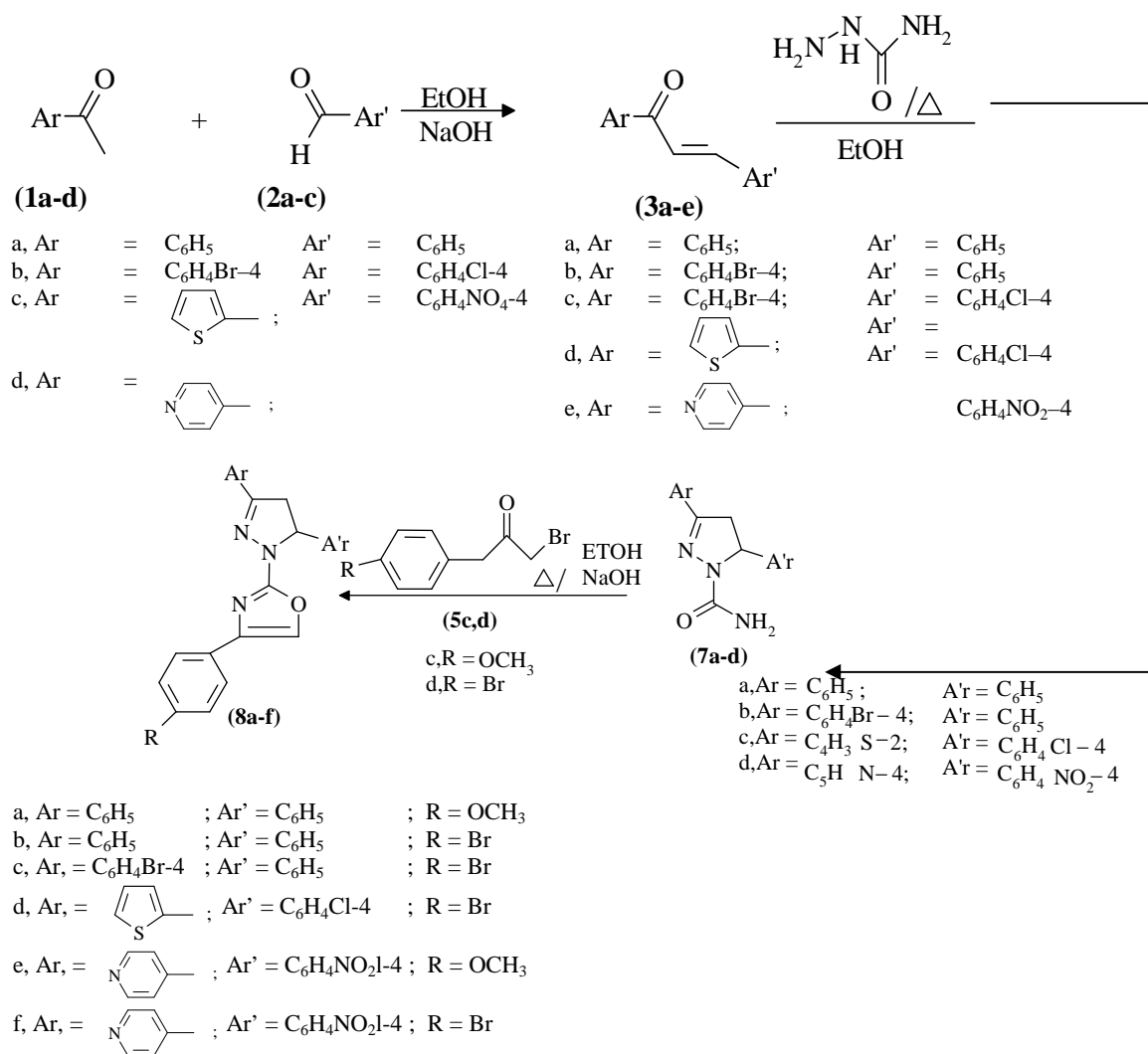
RESULTS AND DISCUSSION

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. Compounds 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 phenacylbromide derivative (5a-d) to give the corresponding 2-thiazolyl- and 2-oxazolyl-pyrazoline derivatives (6a-i) and (8a-f), respectively.





Scheme 2.



Scheme 3

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-chlorophenyl)-and/or-1-(4-pyridyl)-3-(4-nitrophenyl)-2-propen-1-ones (**3a-e**), were cyclised to the corresponding 3,5-diaryl-1-thiocarbamoyl-2-pyrazolines [26-28], (**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 1, 2).

The presence of a strong electron withdrawing group at the para position of the phenacylbromide 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 the reaction of compounds (**7a-d**) with phenacylbromide derivatives (**5c, d**) in boiling ethanol (Scheme 3).

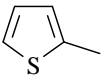
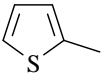
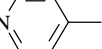
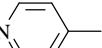
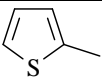
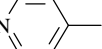
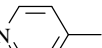
On the other hand, the presence of an electron-releasing group at the para position of the phenacylbromide derivative such as $-\text{OCH}_3$, in (**5c**) and a strong electron-withdrawing group such as Br in the para position in (**5d**) affected strongly the cyclization of 1-carbamoyl-3,5-diaryl-2 pyrazolines (**7a-f**) as the yields of the formed oxazoles (**8a-e**) differ completely than the oxazoles (**8b-d, 8f**) (c.f. Table 2).

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

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

The $^1\text{H-NMR}$ 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 $\delta 2.8-3.76\text{ppm}$ (H_b), the CH (H_x) proton appeared as a doublet of doublets at the region $\delta 3.25-3.96\text{ppm}$ due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 4 of the pyrazoline ring ($J_{ab} = 17.1-17.6\text{ Hz}$, $J_{ax} = 7.0-7.5\text{ Hz}$ and $J_{bx} = 12.0-12.1\text{ Hz}$). The H5-proton of the thiazole and/or the oxazole is observed as a singlet between $\delta 6.7-6.89\text{ppm}$. All the other aromatic and aliphatic protons were observed at the expected regions. The $^{13}\text{C-NMR}$ chemical shift values of the carbon atoms were measured at $\delta 42.25-44.93\text{ppm}$ (C-4), at $\delta 62.96-66.29\text{ppm}$ (C-5), at the region $\delta 50.79-152.96\text{ppm}$ (C-3), which supported the Δ^2 -pyrazoline character confirmed by the $^1\text{H-NMR}$ data (c.f. Tables 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 | mp.°C solvent of crystallization* | Molecule formula (Mol.wt.) | Analysis calcd./found% | | | | | | Yield % |
|------------|---|--|------------------|-----------------------------------|---|------------------------|--------------|---------------|---------------|---------------|-------------|---------|
| | | | | | | C | H | N | S | Br | Cl | |
| 6a | C ₆ H ₅ | C ₆ H ₅ | H | 292 EtOH | C ₂₄ H ₁₉ N ₃ S (381) | 75.59 75.6 | 4.98 5.0 | 11.02 11.1 | 8.39 8.4 | — — | — — | 55 |
| 6b | C ₆ H ₄ Br-4 | C ₆ H ₅ | H | 231 AcOH | C ₂₄ H ₁₈ N ₃ SBr (460) | 62.608 62.7 | 3.91 3.9 | 9.13 9.1 | 6.95 7.0 | 17.39 17.4 | — — | 64 |
| 6c | C ₆ H ₄ Br-4 | C ₆ H ₅ | Br | 240 EtOH | C ₂₄ H ₁₇ N ₃ SBr 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 ₆ H ₄ Br-4 | C ₆ H ₄ Cl-4 | H | 169 EtOH | C ₂₄ H ₁₇ N ₃ SBrCl (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 ₆ H ₄ Br-4 | C ₆ H ₄ Cl-4 | Br | 181 EtOH | C ₂₄ H ₁₆ N ₃ SBr ₂ Cl (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 ₆ H ₄ Cl-4 | H | 141 AcOH | C ₂₂ H ₁₆ N ₃ S ₂ Cl (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 ₆ H ₄ Cl-4 | Br | 157 EtOH | C ₂₂ H ₁₅ N ₃ S ₂ ClBr (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 ₆ H ₄ NO ₂ -4 | H | 134 P. E. | C ₂₃ H ₁₇ N ₅ O ₂ S (427) | 64.63 64.6 | 3.98 4.0 | 16.39 16.5 | 7.49 7.5 | — — | — — | 69 |
| 6i |  | C ₆ H ₄ NO ₂ -4 | Br | 149 P. E. | C ₂₃ H ₁₆ N ₅ O ₂ SBr (506) | 54.54 54.5 | 3.16 3.2 | 13.83 14.0 | 6.32 6.3 | 15.81 16.0 | — — | 63 |
| 8a | C ₆ H ₅ | C ₆ H ₅ | OCH ₃ | 217 EtOH | C ₂₅ H ₂₁ N ₃ O ₂ (395) | 75.94 76.0 | 5.31 5.3 | 10.63 10.6 | — — | — — | — — | 48 |
| 8b | C ₆ H ₅ | C ₆ H ₅ | Br | 227 AcOH | C ₂₄ H ₁₈ N ₃ OBr (444) | 64.86 65.0 | 4.05 4.1 | 9.45 9.6 | — — | 18.01 18.0 | — — | 69 |
| 8c | C ₆ H ₄ Br-4 | C ₆ H ₅ | Br | 211 EtOH | C ₂₄ H ₁₇ N ₃ OBr ₂ (523) | 55.06 55.1 | 3.25 5.3 | 8.03 8.1 | — — | 30.59 31.0 | — — | 73 |
| 8d |  | C ₆ H ₄ Cl ₄ -4 | Br | 169 P. E. | C ₂₂ H ₁₅ N ₃ OSClBr (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 ₆ H ₄ NO ₂ -4 | OCH ₃ | 198 AcOH | C ₂₄ H ₁₉ N ₅ O ₄ (441) | 65.306 65.4 | 4.308 4.3 | 15.87 16.0 | — — | — — | — — | 51 |
| 8f |  | C ₆ H ₄ NO ₂ -4 | Br | 205 EtOH | C ₂₃ H ₁₆ N ₅ O ₃ Br (478) | 57.74 57.7 | 3.34 3.3 | 14.64 14.7 | — — | 16.73 16.6 | — — | 68 |

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

Table (2): IR; ¹H-NMR; ¹³CNMR and MS of thiazolyl- and/or Oxazolyl-Pyrazolines (6a-i) and (8a-f).

| Comp. No | IR ν Cm^{-1} | ¹ H-NMR δ ppm | ¹³ C NMR δ ppm | Ms m/z (%) |
|----------|---|--|--|---|
| 6a | 2928,2826 (ν CH), 1623(ν C=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 (ν CH), 1619 (ν C=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)60(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(ν C-H), 1615(ν C=N),1071(C-N),518(ν C-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(ν CH), 1619(ν C=N), 1061(C-N), 879(ν C-Cl), 519(ν C-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(ν CH), 1618(ν C=N), 1071(C-N), 881(ν C-Cl), 529(ν C-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(ν CH),16 01(ν C=N), 1069(C-N), 872(ν C-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(ν CH), | | | |

| Com pd. No | IR ν Cm^{-1} | $^1\text{H-NMR}$ δ ppm | $^{13}\text{C NMR}$ δ ppm | Ms m/z (%) |
|------------|--|---|---|--|
| | 3.19, 1591($\nu\text{C}=\text{N}$), 1071 ($\text{C}-\text{N}$), 867($\nu\text{C}-\text{Cl}$), 528 ($\nu\text{C}-\text{Br}$). | | | |
| 8a | 3030,2928,2828 (νCH), 1601($\nu\text{C}=\text{N}$), 1027($\nu\text{O}-\text{C}-\text{N}$) | 3.07 (dd, 1H), 3.41 (s,3H,Ar-OCH ₃ , 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), 139.9(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). |
| 8b | 3010,2928,2818(νCH), 1619($\nu\text{C}=\text{N}$), 1072($\nu\text{O}-\text{C}-\text{N}$). | 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($\nu\text{C}-\text{H}$), 1622($\nu\text{C}=\text{N}$),1076($\nu\text{O}-\text{C}-\text{N}$), | 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(νCH), 1623($\nu\text{C}=\text{N}$), 1176($\nu\text{O}-\text{C}-\text{N}$). | 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(2CH), 137.9(CH), 141.1(C), 142.7(C), 154.3(C),163.9(C), 174.9(C). | |
| 8e | 308653, 2928, 2828(νCH), 1619($\nu\text{C}=\text{N}$), 1648(νNO_2), 1068($\nu\text{O}-\text{C}-\text{N}$). | 3.07(dd,1H),3.43(s,3H,ArOCH ₃),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(νCH), 1622($\nu\text{C}=\text{N}$),1660 (νNO_2), 1080($\nu\text{O}-\text{C}-\text{N}$). | 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). | |

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 flucanazole 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*.

Biological Evaluation

The new compounds (**6a-i**) and (**8a-f**) were screened for their antibacterial activity by disk-diffusion technique [29,30] against two Gram – positive bacteria namely, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, two Gram-negative bacteria namely, *Bacillus subtilis* and *Escherichia coli* and four pathogenic fungi namely, *Syncephalastrum racemosum*, *Aspergillus fumigatus*, *Candida albicans* and *Geotrichum candidum* at three concentrations 5,2.5 and 1.25 µg/ml. Chloramphenicol was used as standard antibacterial agent and flucanazole 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 3.9-250 µg/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 Flucanazole, 4 compounds were more active (MIC < 250µg/ml).

CONCLUSION

The synthesized compounds are identified by spectral data and compounds shows significant activity for antimicrobial property and further studies will be done.

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