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Synthesis, Identification and Anti-candidaProperties of Some NewBis (Five, Six, Seven-membered Heterocycles) AttachedPyrrole Rings

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Abstract:

This research involves preparation of many bisheterocycles attached to pyrrole rings have been synthesized by the stepwise procedure such asbis(1,2-dihydropyridazine-3,6-dione) (3),bis(2,3-dihydrophthalazine-1,4-dione) (4) and bis(tetrahydropyridazine-3,6-dione) (5) derivatives of pyrrole. Further the bis(3,5-dimethyl-1*H*-pyrazol-1-yl)methanone (6), bis(3-methyl-1*H*-pyrazol-5(4*H*)-one) (7) and bis(4H-1,3,4-oxadiazin-6(5*H*)-one) (8) pyrrole derivatives also prepared in good yields. Furthermore, series of bis-benzothiazine (10a-c), bis-benzoxathiazepine (11a-c)and bis-quinazoline compounds (12a-c) attached to pyrrole moieties also have been synthesized successfully.Structures of the newly synthesized compounds were established by physicochemical, elemental analysis CHNS, FTIR, H-NMR and C-NMR spectroscopic methods. The new synthesized agents were evaluated for their *in vitro* inhibitory effectagainst several candida isolates. Some of the evaluated compounds possessed good activities compared to a fluconazole, nystatin and clotrimazole standard antifungal drugs.

Keywords: Synthesis, identification,anti-candida,bis heterocycles,pyrrole rings.

Introduction:

Pyrrole rings is one of the great important heterocycles, which is found in a large number of drug molecules, [1]naturallyoccurring alkaloids. [2] Many biomolecules such as bile pigments, heme, vitamin B_{12} and chlorophyll containing pyrroles as subunits. [3]Synthetic pyrroles exhibit extensive pharmacological and biological properties, such as analgesic,[4] antimycobacterial,[5]antifungal,[6]anti-inflammatory,[7] antioxidant,[8] and immune suppressant activities.[9]

Pyrrole and the simple alkyl Pyrrole are colorless liquids, with relatively weak odors rather like that of aniline, which also like anilines, darkens by auto oxidation. The pyrrole scaffold is a useful structural pattern for exhibiting chemical functionality in biologically active molecules .It has established broad application in the drug development.[10]

There are several methods for the synthesis of Pyrrole in the literature from classical hantzsch procedure, [11] 1,3-dipolar cyclo addition reaction,[12]aza-wittig reaction, [13] reductive coupling, [14] titanium catalyzed hydro amination of dynes [15] and other stepwise synthesis operations. The most widely used method is the Paal-Knorr synthesis, which involves the cyclo condensation reaction of 1,4-dicarbonyl compounds with primary amines to produce substituted pyrrole. [16]

The objectives of this research to synthesize of new class of pyrrole moieties it wasthought to incorporate bis-five, six and seven membered heterocycles in a single molecular frame work and to evaluate their anti-candida activity as type of fungal strains.

Materials and Methods:

All the chemicals used in this work were procured from Sigma–Aldrich BDH, Fluka,

and some other commercial suppliers were used without further purification. Melting points were recorded by digital melting point equipment (Stuart Scientific SMP30). Infrared spectra were record for KBr disks on a Shimadzu 8400S spectrometerin the spectral range (400-4000) cm^{-1}.^{13}CNMR, ^{1}HNMR spectra were recorded on Bruker spectrometer ultra-shield model in dimethyl sulfoxide-d^6 as solvent at 300 MHz using tetra methyl saline as an internal reference standard.Elemental micro analysis (C,H,N and S) was carried out using micro analytical techniques on Perkin Elmer 2400 (IEES).Thin layer chromatographycontrols were carried out using Fertigfollenprecoated silica gel plateswere visualizedby exposure to iodine vapour.

Synthesis of 3,5-dimethyl-1H-pyrrole-2,4-diethyl carboxylate (1)

Ethyl acetoacetate (1.9mL) mixed well with glacial acetic acid (4.5mL) in three necked round bottom flask with stirring. The mixture then cooled below 5^{o}C while adding a solution of sodium nitrite (0.535g) in water (0.9mL) with stirring vigorously. After removing the cooling bath, and stir for a further 1hr. the flask contents attain room temperature. Zinc dust (0.98g) portion wise over 0.5 hr. with continuous stirring, and then further acetic acid (1.5mL) adding and the mixture heat under reflux for 2hrs. The solution allowed cooling then decanting from excess of zinc into stirred water (10mL). The mixture stands overnight then filtered. The crude product and wash with water and recrystallized from absolute ethanol.[17]

Color:orange crystals;m.p:137-140°C; yield:58%; $R_f$value:0.65; anal. calc. for $C_{12}H_{17}NO_4$(239.27g/mol.); calc. C:60.24; H:7.16; N:5.85; found: C:60.30; H:7.32; N:5.61

FT-IR (cm^{-1}): 3443(N-H);2981(C-H) aliphatic;1747(C=O) ester; 1534(C=C); 1344(C-N).

^{1}HNMR(δ ppm): 1.91 (C$\underline{H}_3$)protons; 4.82(C$\underline{H}_2$) protons; 5.35 (N$\underline{H}$) pyrrole ring proton.

^{13}CNMR (δ ppm): 16.12 ($\underline{C}H_3$); 70.03 ($\underline{C}H_2$); 122.62, 139.51(2$\underline{C}$) pyrrole ring; 160.33 ($\underline{C}O$)

Synthesis of 3,5-dimethyl-*1H*-pyrrole-2,4-dicarbohydrazide (2)

To solution of compound (1) (1g, 0.0041mol) in absolute ethanol (20mL), hydrazine hydrate (0.0082mol) was added gradually with continuous stirring. The reaction mixture was reflexed under water bath for 5hrs. Cooling the mixture formed the final product as precipitate was then filtered and recrystallized from ethanol. [18]

Color: brown; m.p: 168-170^{o}C; yield: 66%;$R_f$value: 0.59; anal. calc. for $C_8H_{13}N_5O_2$ (211.23 g/mol.); calc. C: 45.49; H: 6.20; N: 33.16; found: C: 45.59; H: 6.29; N: 33.35.

FT-IR (cm^{-1}):3359, 3265 (NH$\underline{N}H_2$) hydrazide; 2967 (C-H) aliphatic; 1708 (C=O) amide; 1581 (C=C); 1350 (C-N).

^{1}HNMR(δ ppm):1.83 (C$\underline{H}_3$) protons; 4.14(N$\underline{H}_2$) protons; 5.61 (N$\underline{H}$) pyrrole ring proton; 7.96 (N$\underline{H}$) hydrazide proton.

^{13}CNMR (δ ppm):16.12 ($\underline{C}H_3$); 124.91, 137.22 (2$\underline{C}$) pyrrole ring; 162.42 ($\underline{C}O$) amide.

Synthesis of (3,5-dimethyl-1H-pyrrole-2,4-dicarbonyl)bis(1,2-dihydropyridazine-3,6-dione) (3),(3,5-dimethyl-1H-pyrrole-2,4-dicarbonyl)bis(2,3-dihydrophthalazine-1,4-dione) (4) and(3,5-dimethyl-1H-pyrrole-2,4-dicarbonyl)bis(tetrahydropyridazine-3,6-dione) (5)

Compound (2)(1g, 0.0047mol) were mixed with appropriate anhydride of (maleic, phthalic or succinic) (0.0094mol) respectively in glacial acetic acid (10mL). The reaction mixture was refluxed between (8-10hrs.) and then cooled to room temperature. Crushed ice added to

precipitate the crude products was filtered, washed with distilled water and recrystallized from suitable solvents.[19]

(3,5-dimethyl-1H-pyrrole-2,4-dicarbonyl)bis(1,2-dihydropyridazine-3,6-dione) (3)

Color: white; m.p: 186-187^{o}C; yield:63%;$R_f$value: 0.70; anal. calc. for $C_{16}H_{13}N_5O_6$(371.31g/mol.); calc. C: 51.76; H: 3.53; N: 18.86; found: C: 51.80; H:3.44; N: 18.57.

FT-IR (cm^{-1}):3151(N-H); 2962(C-H) aliphatic; 1720(C=O) pyridazine;1676(C=O); 1593(C=C); 1355(C-N).

^{1}HNMR(δ ppm):1.88(C<u>H</u>$_3$) protons; 5.52(N<u>H</u>) pyrrole ring proton; 7.18(C<u>H</u>) pyridazine ring proton; 8.20(N<u>H</u>) pyridazine ring proton.

^{13}CNMR (δ ppm):15.80(<u>C</u>H$_3$);121.50, 136.03(2<u>C</u>) pyrrole ring; 128.79, 130.32, 131.51(3<u>C</u>) pyridazine ring; 158.11(<u>C</u>O) pyridazine ring; 163.81(<u>C</u>O).

(3,5-dimethyl-1H-pyrrole-2,4-dicarbonyl)bis(2,3-dihydrophthalazine-1,4-dione) (4)

Color:dark brown; m.p:201-204^{o}C; yield: 72%;$R_f$value:0.64; anal. calc. for$C_{24}H_{17}N_5O_6$ (471.43g/mol.); calc. C: 61.15; H: 3.63; N: 14.86; found: C: 60.94; H: 3.78; N: 15.20.

FT-IR (cm^{-1}): 3340 (N-H); 3047 (C-H) aromatic; 2966(C-H) aliphatic; 1709 (C=O) phthalazine; 1650 (C=O);1489 (C=C) aromatic; 1320 (C-N). As shown in figure (1).

^{1}HNMR(δ ppm):1.79 (C<u>H</u>$_3$)protons; 5.67 (N<u>H</u>) pyrrole ring proton; 7.25- 7.73 aromatic ring protons; 8.33 (NH) phthalazine ring proton. As shown in figure (2).

^{13}CNMR (δ ppm):15.74 (<u>C</u>H$_3$); 129.34, 135.82 (2<u>C</u>) pyrrole ring;122.41-133.59 aromatic carbons; 157.11 (<u>C</u>O) phthalazine ring; 166.04 (<u>C</u>O). As shown in figure (3).

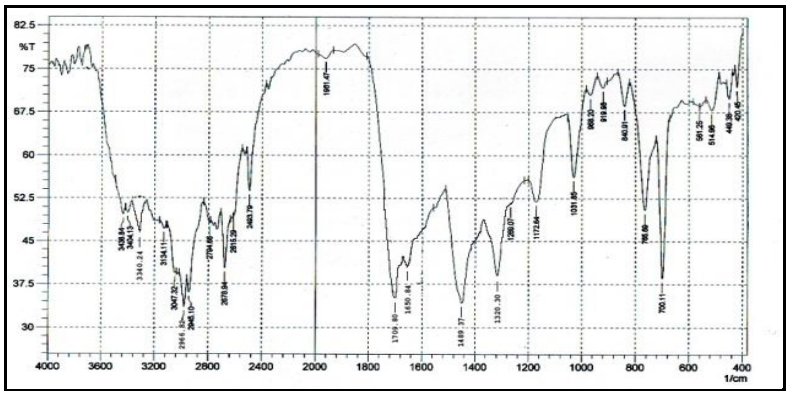


Figure (1): FTIR spectrum for compound(4)

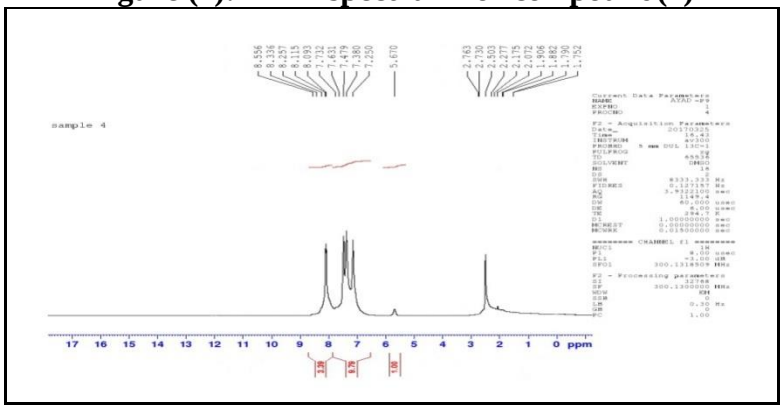


Figure (2): ^{1}HNMR Spectrum for compound (4).

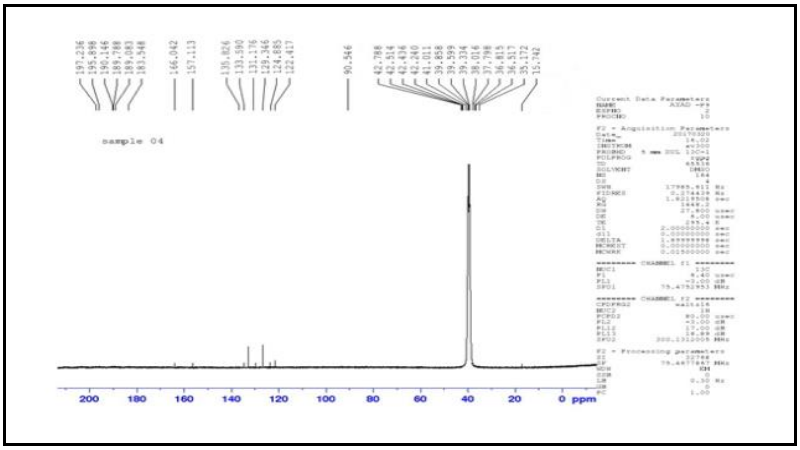


Figure (3): ^{13}CNMR Spectrum for compound (4).

(3,5-dimethyl-1H-pyrrole-2,4-dicarbonyl)bis(tetrahydropyridazine-3,6-dione)(5)

Color:off white; m.p: 155-157^{o}C; yield: 59%;$R_f$value: 0.55; anal. calc. for $C_{16}H_{17}N_5O_6$(375.34g/mol.); calc. C: 51.20; H: 4.57; N: 18.66; found: C: 50.88; H: 4.33; N: 18.91.

FT-IR (cm^{-1}): 3174(N-H); 2978(C-H) aliphatic; 1712 (C=O) pyridazine; 1666 (C=O); 1589(C=C); 1357(C-N).

^{1}HNMR (δ ppm): 1.64 (C<u>H</u>$_3$)protons; 3.25 (C<u>H</u>$_2$) pyridazine ring proton; 4.98 (N<u>H</u>)pyrrole ring proton; 9.14 (N<u>H</u>) pyridazine ring proton.

^{13}CNMR (δ ppm):16.92 (<u>C</u>H$_3$); 33.90, 35.66(2<u>C</u>)pyridazine ring; 127.62, 137.44(2<u>C</u>) pyrrole ring; 161.59 (<u>C</u>O) pyridazine ring; 168.33 (<u>C</u>O).

Synthesis of (3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis((3,5-dimethyl-1*H*-pyrazol-1-yl)methanone) (6), (3,5-dimethyl-1*H*-pyrrole-2,4-dicarbonyl)bis(3-methyl-1*H*-pyrazol-5(4*H*)-one) (7)

A mixture of compound (2)(1g, 0.0047mol) appropriate ketone compound (acetyl acetoneethyl, acetoacetate)(0.0094mol) respectively and absolute ethanol (15mL) was reflexed for 6-7hrs. The mixture then concentrated and cooled to form the product was filtered and recrystallized from ethanol.[20]

(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis((3,5-dimethyl-1*H*-pyrazol-1-yl) methanone) (6)

Color: white powder; m.p:168-171^{o}C; yield:62%;$R_f$value: 0.57; anal. calc. for $C_{18}H_{25}N_5O_2$ (343.43g/mol.); calc. C: 62.95; H:7.34; N: 20.39; found: C: 63.12; H: 7.76; N: 20.55.

FT-IR (cm^{-1}): 3248(N-H);2931(C-H) aliphatic; 1705 (C=O);1608 (C=N); 1544 (C=C); 1346 (C-N).

^{1}HNMR (δ ppm): 1.85 (C<u>H</u>$_3$)protons;5.33 (N<u>H</u>) pyrrole ring proton; 6.33 (C<u>H</u>)pyrazole ring proton.

^{13}CNMR (δ ppm):17.03 (CH$_3$);125.66, 134.51(2<u>C</u>) pyrrole ring; 148.62, 149.19, 149.77(3<u>C</u>)pyrazole ring;165.84 (CO).

(3,5-dimethyl-1*H*-pyrrole-2,4-dicarbonyl)bis(3-methyl-1*H*-pyrazol-5(4*H*)-one) (7)

Color: white; m.p:144-146^{o}C; yield:71%;$R_f$value: 0.73; anal. calc. for $C_{16}H_{17}N_5O_4$(343.34g/mol.); calc. C: 55.97; H: 4.99; N: 20.40; found: C: 56.22; H: 4.72; N: 20.71.

FT-IR (cm^{-1}): 3190 (N-H); 2974(C-H) aliphatic; 1728 (C=O) pyrazole; 1662 (C=O); 1616(C=N); 1589(C=C);1340 (C-N).
^{1}HNMR (δ ppm): 1.80 (C<u>H</u>$_3$)protons; 3.08 (C<u>H</u>$_2$)pyrazole ring protons;5.44 (N<u>H</u>) pyrrole ring proton.
^{13}CNMR (δ ppm): 15.16 (<u>C</u>H$_3$); 35.54, 120.49(2<u>C</u>)pyrazole ring; 123.11, 138.27(2C) pyrrole ring; 164.31 (<u>C</u>O)pyrazole ring; 169.04 (<u>C</u>O).

Synthesis of (3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(4H-1,3,4-oxadiazin-6(5*H*)-one) (8)

To a solution of compound (2)(1g, 0.0047mol), chloroacetylchloride(1.06g, 0094mol) was added in the presence of sodium acetate (0.771g, 0.0094mol) and glacial acetic acid. The mixture refluxed for (5hrs) and then poured on ice water. Solid product was obtained filtered and recrystallized from ethanol.[21]
Color: dusty; m.p: 162-165^{o}C; yield:75%;$R_f$value: 0.72; anal. calc. for $C_{12}H_{13}N_5O_4$ (291.27g/mol.); calc. C: 49.48; H: 4.50; N: 24.04; found: C: 49.70; H: 4.28; N: 23.63.
FT-IR (cm^{-1}): 3232 (N-H);2977 (C-H) aliphatic;1724 (C=O) oxadiazine;1604 (C=N);1571 (C=C); 1355 (C-N).
^{1}HNMR(δ ppm):1.99 (C<u>H</u>$_3$) protons; 3.16 (C<u>H</u>$_2$)oxadiazine ring; 5.72 (N<u>H</u>) pyrrole ring proton; 7.23 (N<u>H</u>) oxadiazine ring proton.
^{13}CNMR (δ ppm): 16.05 (<u>C</u>H$_3$); 40.73, 128.04(2<u>C</u>) oxadiazine ring; 129.33, 134.81(2<u>C</u>) pyrrole ring; 167.22 (<u>C</u>O) oxadiazine ring.

Synthesis of 3,5-dimethyl - N2,N4-bis(substituted benzylidene)-1H-pyrrole-2,4-dicarbohydrazide (9a-c)

Compound (2) (1g, 0.0047mol) and appropriate aromatic aldehyde (0.0094 mol) in absolute ethanol was refluxed for 5-7hrs. and then cooled to room temp. The solid product was filtered off and recrystallized from suitable solvents.[22]

3,5-dimethyl -*N*^{2},*N*^{4}-bis(benzylidene)-1*H*-pyrrole-2,4-dicarbohydrazide (9a)

Color: off white; m.p:149-152^{o}C; yield: 67%; $R_f$value: 0.76; anal. calc. for $C_{23}H_{23}N_5O$(385.47 g/mol.); calc. C: 71.67; H: 6.01; N: 18.17; found: C: 71.33; H: 5.86; N: 18.42.
FT-IR (cm^{-1}): 3394 (N-H); 2908 (C-H) aliphatic; 1688 (C=O) amide; 1631 (C=N) imine; 1582 (C=C) aromatic; 1340 (C-N).
^{1}HNMR (δ ppm): 2.04 (C<u>H</u>$_3$)protons; 5.20 (N<u>H</u>) pyrrole ring proton; 6.34 (C<u>H</u>) imine proton;7.01-7.87 aromatic ring protons;8.01 (N<u>H</u>) amide proton.
^{13}CNMR (δ ppm): 16.22 (<u>C</u>H$_3$); 121.34, 139.49(2<u>C</u>) pyrrole ring; 128.31-132.95 aromatic carbons; 144.56 (<u>C</u>H) imine; 163.18 (<u>C</u>O) amide.

3,5-dimethyl-*N*^{2},*N*^{4}-bis(4-chloro benzylidene)-1*H*-pyrrole-2,4-dicarbohydrazide (9b)

Color: white; m.p: 146-147^{o}C; yield: 69%; $R_f$value: 0.56; anal. calc. for $C_{23}H_{21}N_5OCl_2$ (454.36g/mol.); calc. C:60.80; H:4.66; N: 15.41; found: C: 61.11; H: 4.37; N: 15.67.
FT-IR (cm^{-1}): 3221 (N-H); 2966 (C-H) aliphatic; 1685 (C=O) amide; 1628 (C=N) imine; 1585 (C=C) aromatic; 1344(C-N); 1091 (C-Cl).
^{1}HNMR (δ ppm): 1.96 (C<u>H</u>$_3$)protons; 5.12 (N<u>H</u>) pyrrole ring proton; 6.55 (C<u>H</u>) imine proton;6.80-7.69 aromatic ring protons; 8.19 (N<u>H</u>) amide proton.
^{13}CNMR (δ ppm): 17.09 (<u>C</u>H$_3$); 122.88, 138.63(2<u>C</u>) pyrrole ring; 129.72-134.62 aromatic carbons; 143.48 (<u>C</u>H) imine; 164.51 (<u>C</u>O)amide.

3,5-dimethyl-*N*^{2},*N*^{4}-bis(4-nitro benzylidene)-1*H*-pyrrole-2,4-dicarbohydrazide (9c)

Color: deep yellow; m.p: 153-155^{o}C; yield: 70%; $R_f$value: 0.58; anal. calc. for

$C_{23}H_{21}N_7O_5$(475.47g/mol.); calc. C: 58.10; H:4.45; N: 20.62; found: C: 58.34; H:4.20; N: 20.35.
FT-IR (cm^{-1}): 3143 (N-H); 2943 (C-H) aliphatic;1705 (C=O) amide; 1624 (C=N) imine;1581 (C=C) aromatic;1498(NO_2);1360 (C-N).
^{1}HNMR (δ ppm): 2.10 (C<u>H</u>$_3$)protons; 5.38 (N<u>H</u>) pyrrole ring proton;6.62(C<u>H</u>) imine proton;6.63-7.90 aromatic ring protons; 8.30 (N<u>H</u>) amide proton.
^{13}CNMR (δ ppm): 17.21 (<u>C</u>H$_3$);123.61, 137.85(2<u>C</u>) pyrrole ring;126.10-136.33 aromatic carbons; 145.62 (<u>C</u>H) imine;165.93 (<u>C</u>O)amide.

Synthesis of 3,5-dimethyl-*N*^{2},*N*^{4}-bis (4-oxo-2-(substituted benzene)-2*H*-benzo[e][1,3]thiazin-3(4*H*)-yl)-1*H*-pyrrole-2,4-dicarboxamide (10a-c)
A mixture of appropriate Schiff basis (9a-c) (0.001mol) and 2-mercaptobenzoic acid (0.002mol) was added with stirring to dry benzene (25mL)and few drops of triethylamine. The mixture was refluxed for 3-4hrs.then the solvent was evaporated. The product washed with 5% sodium bicarbonate, filtered and recrystallized with suitable solvents. [23]

3,5-dimethyl-*N*^{2},*N*^{4}-bis(4-oxo-2-(phenyl)-2*H*-benzo[e][1,3]thiazin-3(4*H*)-yl)-1*H*-pyrrole-2,4-dicarboxamide (10a)
Color: brown; m.p: 188-190^{o}C; yield: 78%; $R_f$value: 0.62; anal. calc. for $C_{36}H_{29}N_5O_4S_2$(659.78g/mol.); calc. C: 65.54; H: 4.43; N: 10.61; S: 9.72; found: C: 65.76; H: 4.18; N: 10.45;S: 9.33.
FT-IR (cm^{-1}): 3186 (N-H); 2931 (C-H) aliphatic; 1710 (C=O) benzothiazine; 1651 (C=O) amide; 1539 (C=C) aromatic; 1360 (C-N).
^{1}HNMR (δ ppm): 2.08 (C<u>H</u>$_3$)protons; 4.71 (C<u>H</u>) benzothiazine ring proton; 5.11 (N<u>H</u>) pyrrole ring proton; 6.22-7.83 aromatic ring protons;8.28 (N<u>H</u>) amide proton.
^{13}CNMR (δ ppm): 14.78 (<u>C</u>H$_3$);55.16 (<u>C</u>) benzothiazine ring; 121.44, 136.92(2<u>C</u>) pyrrole ring;127.62-139.38 aromatic carbons;161.03 (<u>C</u>O) benzothiazine ring;165.62 (<u>C</u>O)amide.

3,5-dimethyl-*N*^{2},*N*^{4}-bis(4-oxo-2-(4-chlorobenzene)-2*H*-benzo[e][1,3]thiazin-3(4*H*)-yl)-1*H*-pyrrole-2,4-dicarboxamide (10b)
Color: lightbrown; m.p: 182-185^{o}C; yield:73%; $R_f$value: 0.68; anal. calc. for $C_{36}H_{27}N_5O_4S_2Cl_2$(728.66g/mol.); calc. C:59.34; H:3.73; N:9.61; S: 8.80; found: C: 59.69; H: 3.90; N: 9.28; S: 9.14.
FT-IR (cm^{-1}): 3240 (N-H); 2924 (C-H) aliphatic; 1718(C=O) benzothiazine; 1628 (C=O) amide; 1546(C=C) aromatic; 1344 (C-N); 1078(C-Cl).
^{1}HNMR (δ ppm): 1.90 (C<u>H</u>$_3$)protons;4.52 (C<u>H</u>)benzothiazine ring proton;5.25 (N<u>H</u>) pyrrole ring proton; 6.18-7.23 aromatic ring protons; 8.01 (N<u>H</u>) amide proton.
^{13}CNMR (δ ppm): 15.37 (<u>C</u>H$_3$);54.68 (<u>C</u>)benzothiazine ring;122.72, 135.06(2<u>C</u>) pyrrole ring;126.57-139.90 aromatic carbons;160.83 (<u>C</u>O)benzothiazine ring;166.71 (<u>C</u>O)amide.

3,5-dimethyl-*N*^{2},*N*^{4}-bis(4-oxo-2-(4-nitrobenzene)-2*H*-benzo[e][1,3]thiazin-3(4*H*)-yl)-1*H*-pyrrole-2,4-dicarboxamide (10c)
Color: white; m.p: 191-193^{o}C; yield: 74%; $R_f$value: 0.52; anal. calc. for $C_{36}H_{27}N_7O_8S_2$(749.14g/mol.); calc. C: 57.67; H: 3.63; N: 13.08;S: 8.55; found: C: 58.02; H: 3.55; N: 12.64; S: 8.84.
FT-IR (cm^{-1}): 3278 (N-H);2971 (C-H) aliphatic;1701(C=O) benzothiazine; 1633 (C=O) amide; 1537(C=C) aromatic;1496, 1305 (NO_2);1361 (C-N).
^{1}HNMR (δ ppm): 1.73 (C<u>H</u>$_3$)protons;4.91 (C<u>H</u>)benzothiazine ring proton;5.62 (N<u>H</u>) pyrrole ring proton;7.03-7.64 aromatic ring protons;8.33 (N<u>H</u>) amide proton.

^{13}CNMR (δ ppm): 15.18 (CH_3); 56.43 (C)benzothiazine ring;121.79, 136.12 (2C) pyrrole ring;125.53-138.88 aromatic carbons; 162.79 (CO)benzothiazine ring 167.81 (CO)amide.

Synthesis of 3,5-dimethyl-*N*^{2},*N*^{4}-bis(1,1-dioxido-5-oxo-3-(substituted benzene)-3,5-dihydro-2*H*-benzo[1,4,3]oxathiazepin-2-yl)-1*H*-pyrrole-2,4-dicarboxamide (11a-c)

Solution of orthosulfobenzoic anhydride (0.002mol) in (2mL) of dry benzene added to solution of appropriate Schiff basis (9a-c) (0.001mol) in (5mL) of dry benzene with few drops of tetrahydrofuran. The mixture was refluxed gently on water bath for 6-8hrs. After the color of reaction mixture exchanged, then cooled into room temperature, the precipitate was filtered and washed with little amount of dry benzene. [24]

3,5-dimethyl-*N*^{2},*N*^{4}-bis(1,1-dioxido-5-oxo-3-(phenyl)-3,5-dihydro-2*H*-benzo[1,4,3] oxathiazepin-2-yl)-1*H*-pyrrole-2,4-dicarboxamide (11a)

Color: light yellow; m.p: 163-166^{o}C; yield:51%; $R_f$value: 0.64; anal. calc. for $C_{36}H_{29}N_5O_{10}S_2$ (755.77 g/mol.); calc. C: 57.21; H: 3.87; N: 9.27;S:8.49; found: C: 57.55; H: 3.68; N: 9.51;S: 8.66.

FT-IR (cm^{-1}): 3201 (N-H);2983(C-H) aliphatic; 1698 (C=O) benzoxathiazepine;1666 (C=O) amide; 1544 (C=C) aromatic;1390, 1170 (SO_2);1351(C-N).

^{1}HNMR (δ ppm): 1.84 (CH_3)protons; 4.11 (CH)benzoxathiazepinering proton; 5.29 (NH)pyrrole ring proton; 6.80-7.55 aromatic ring protons; 8.07 (NH) amide proton.

^{13}CNMR (δ ppm): 16.12 (CH_3);61.73 (C)benzoxathiazepine ring;120.69, 137.16(2C) pyrrole ring;125.34-139.19 aromatic carbons;167.92 (CO)benzoxathiazepine ring;169.49 (CO)amide.

3,5-dimethyl-*N*^{2},*N*^{4}-bis(1,1-dioxido-5-oxo-3-(4-chlorobenzene)-3,5-dihydro-2*H*-benzo[1,4,3] oxathiazepin-2-yl)-1*H*-pyrrole-2,4-dicarboxamide (11b)

Color: off white; m.p: 170-171^{o}C; yield: 61%; $R_f$value: 0.66; anal. calc. for $C_{36}H_{27}N_5O_{10}S_2Cl_2$ (824.66 g/mol.); calc. C: 52.43; H: 3.30; N: 8.49;S: 7.78; found: C: 52.58; H: 3.56; N: 8.17;S: 7.60.

FT-IR (cm^{-1}): 3267 (N-H); 2991 (C-H) aliphatic; 1697 (C=O) benzoxathiazepine; 1670 (C=O) amide; 1535 (C=C) aromatic;1365, 1188(SO_2); 1341(C-N);1090 (C-Cl).

^{1}HNMR (δ ppm): 1.99 (CH_3)protons; 4.18 (CH)benzoxathiazepine ring proton; 5.54 (NH)pyrrole ring proton; 6.93-7.88 aromatic ring protons; 8.38 (NH) amide proton.

^{13}CNMR (δ ppm): 16.29 (CH_3);62.47 (C)benzoxathiazepine ring;121.64, 136.72(2C) pyrrole ring; 126.39-138.46 aromatic carbons; 164.53 (CO)benzoxathiazepine ring; 168.62 (CO)amide.

3,5-dimethyl-*N*^{2},*N*^{4}-bis(1,1-dioxido-5-oxo-3-(4-nitrobenzene)-3,5-dihydro-2*H*-benzo[1,4,3] oxathiazepin-2-yl)-1*H*-pyrrole-2,4-dicarboxamide (11c)

Color: pale yellow;m.p: 159-161^{o}C; yield: 58%; $R_f$value: 0.63; anal. calc. for $C_{36}H_{27}N_7O_{14}S_2$(845.77g/mol.); calc. C: 51.12; H: 3.22; N: 11.59;S: 7.58; found: C: 50.72; H: 3.48; N: 11.14; S: 7.88.

FT-IR (cm^{-1}): 3213 (N-H);2956 (C-H) aliphatic;1695 (C=O) benzoxathiazepine;1665(C=O) amide; 1546 (C=C) aromatic;1469, 1300(NO_2);1373, 1165(SO_2);1330(C-N).

^{1}HNMR (δ ppm): 1.78 (CH_3)protons;4.25 (CH)benzoxathiazepine ring proton;5.38 (NH)ring proton; 7.08-7.60 aromatic ring protons; 8.20 (NH) amide proton.

^{13}CNMR (δ ppm): 17.15 (CH_3);60.38 (C)benzoxathiazepine ring;122.94, 135.499 (2C) pyrrole ring;125.31-139.40 aromatic

carbons;163.75 (CO)benzoxathiazepine ring;167.85 (CO)amide.

Synthesis of3,5-dimethyl-*N*^{2},*N*^{4}-bis(4-oxo-2-(substituted benzene)-1,2-dihydroquinazolin-3(4*H*)-yl)-1*H*-pyrrole-2,4-dicarboxamide (12a-c)

To a solution of 2-amino benzoic acid (0.002mol) appropriate Schiff basis (9a-c)(0.001mol) in (2mL) of dioxane was added. This mixture was refluxed overnight and the completion of reaction was monitored by thin layer chromatography. The solvent was evaporated and the solid product washed with (5%) sodium hydrogen carbonate, filtered and recrystallized from suitable solvents.[25]

3,5-dimethyl-*N*^{2},*N*^{4}-bis(4-oxo-2-(phenyl)-1,2-dihydroquinazolin-3(4*H*)-yl)-1*H*-pyrrole-2,4-dicarboxamide (12a)

Color: brown; m.p: 175-177^{o}C; yield: 80%; $R_f$value: 0.69; anal. calc. for $C_{36}H_{31}N_7O_4$ (625.69 g/mol.); calc. C: 69.11; H: 4.99; N: 15.67; found: C: 68.80; H: 5.24; N: 15.33.
FT-IR (cm^{-1}): 3376 (N-H);2951(C-H) aliphatic;1691 (C=O) quinazoline; 1670 (C=O) amide; 1539 (C=C) aromatic;1327(C-N).
^{1}HNMR (δ ppm): 1.82 (C<u>H</u>$_3$)protons; 5.40 (N<u>H</u>)pyrrole ring proton; 5.84 (C<u>H</u>)quinazoline ring proton; 6.18 (N<u>H</u>)quinazoline ring proton; 6.72-7.68 aromatic ring protons; 8.29 (N<u>H</u>) amide proton.
^{13}CNMR (δ ppm): 15.18 (<u>C</u>H$_3$);56.78 (<u>C</u>)quinazoline ring;118.23, 133.58(2<u>C</u>) pyrrole ring;126.27-138.57 aromatic carbons;159.66 (<u>C</u>O)quinazoline ring;164.51 (<u>C</u>O)amide.

3,5-dimethyl-*N*^{2},*N*^{4}-bis(4-oxo-2-(4-chlorobenzene)-1,2-dihydroquinazolin-3(4*H*)-yl)-1*H*-pyrrole-2,4-dicarboxamide (12b)

Color: gray; m.p: 179-182^{o}C; yield: 65%; $R_f$value: 0.70; anal. calc. for $C_{36}H_{29}N_7O_4Cl_2$ (694.57g/mol.); Calc. C: 62.25; H: 4.21; N: 14.12; Found: C: 60.92; H: 4.02; N: 14.23.
FT-IR (cm^{-1}): 3387 (N-H);2969(C-H) aliphatic;1696 (C=O) quinazoline;1675 (C=O) amide; 1550 (C=C) aromatic;1323(C-N); 1081 (C-Cl).
^{1}HNMR (δ ppm): 1.92 (C<u>H</u>$_3$)protons; 4.99 (N<u>H</u>)pyrrole ring proton; 5.76 (C<u>H</u>)quinazoline ring proton;6.19 (N<u>H</u>)quinazoline ring proton; 6.94-7.81 aromatic ring protons; 8.50 (N<u>H</u>) amide proton.
^{13}CNMR (δ ppm): 16.82 (<u>C</u>H$_3$);58.66 (<u>C</u>)quinazoline ring;118.75, 132.89(2<u>C</u>) pyrrole ring;127.71-139.06 aromatic carbons;158.31 (<u>C</u>O)quinazoline ring;166.48 (<u>C</u>O)amide.

3,5-dimethyl-*N*^{2},*N*^{4}-bis(4-oxo-2-(4-nitrobenzene)-1,2-dihydroquinazolin-3(4*H*)-yl)-1*H*-pyrrole-2,4-dicarboxamide (12c)

Color: yellow-orange; m.p: 173-175^{o}C; yield: 79%; $R_f$value: 0.68; anal. calc. for $C_{36}H_{29}N_9O_8$ (715.68g/mol.); calc. C: 60.42; H: 4.08; N: 17.61; found: C: 59.98; H: 4.30; N: 17.28.
FT-IR (cm^{-1}): 3182 (N-H);2964 (C-H) aliphatic; 1689 (C=O) quinazoline;1674 (C=O) amide; 1530(C=C) aromatic;1496 (NO_2); 1344(C-N).
^{1}HNMR (δ ppm): 1.87 (C<u>H</u>$_3$)protons; 5.12 (N<u>H</u>)pyrrole ring proton; 5.69 (C<u>H</u>)quinazoline ring proton; 6.27 (N<u>H</u>)quinazoline ring proton; 6.88-7.96aromatic ring protons; 8.44 (N<u>H</u>) amide proton.
^{13}CNMR (δ ppm): 16.44 (<u>C</u>H$_3$);57.34 (<u>C</u>)quinazoline ring;119.69, 132.15(2<u>C</u>) pyrrole ring;127.14-139.36 aromatic carbons;161.32 (<u>C</u>O)quinazoline ring;166.28 (<u>C</u>O)amide.

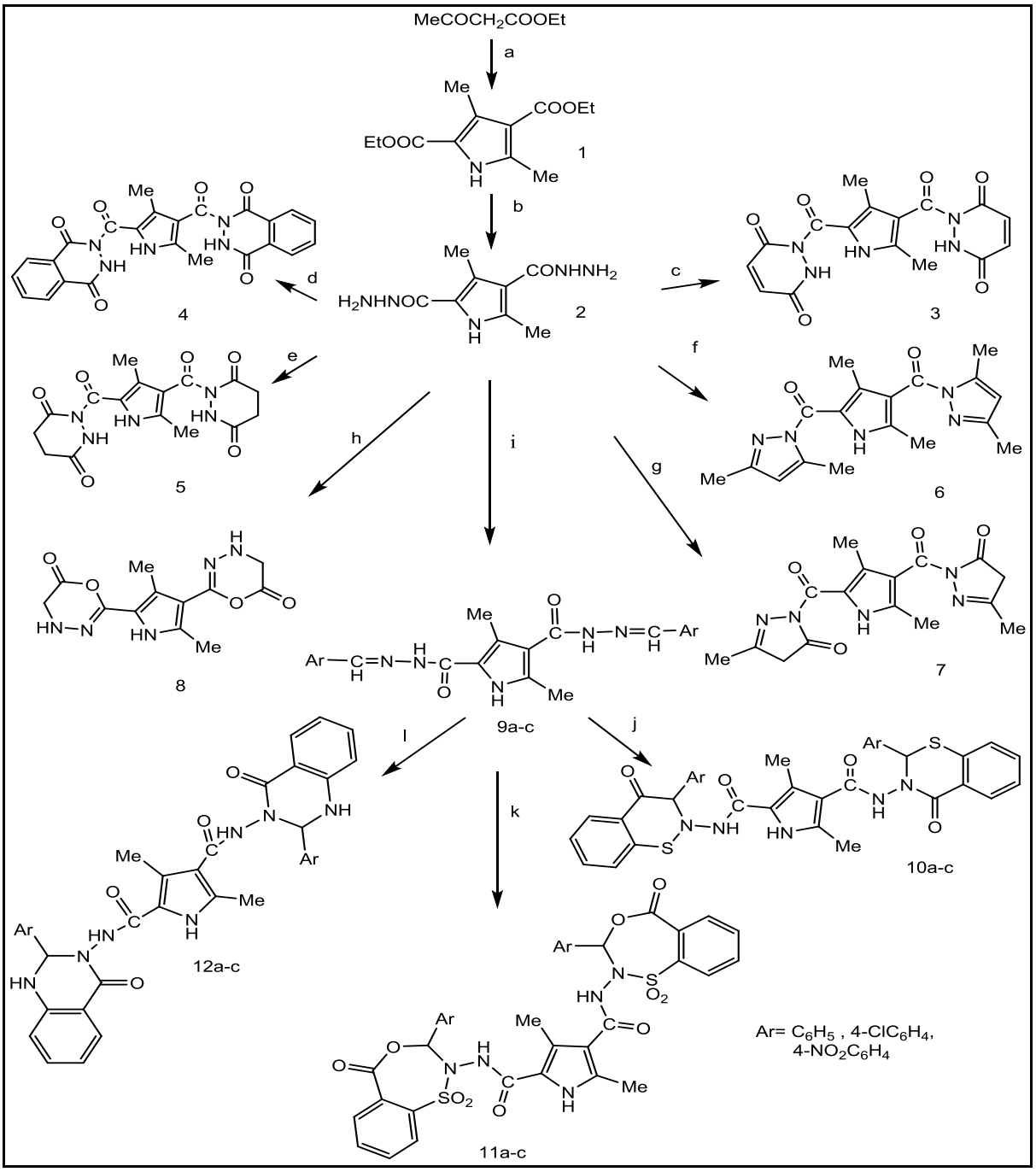
Anti-Candida Activity

Anti-candida susceptibility test was done by disc diffusion method [26]usingSabouraud dextrose agar (SDA) medium. We have

tested three*Candida* strains,*Candida albicans,Candida glabrata*and*Candida spp*.) Isolated from clinical specimens were obtained from Al-Yarmuk teaching hospital.After sterilization the medium was inoculated with Candida strains. The standard antifungal agentFluconazole, Nystatin and Clotrimazole (100mg.L^{-1}) were tested, Stock solution of each drug was prepared in dimethyl sulphoxide (DMSO) as solvent control (0.5% v/v) and the newly synthesized compounds in a concentration of (100mg.L^{-1})were then added by sterilized micro pipette. The plates were the incubated at 37°C for 24-48 hrs. The diameter and percentageof inhibition zone were observed and recorded.

RESULTS AND DISCUSSION

The synthetic routes for preparation of series of new bis heterocyclic compounds such as pyridazine, phthalazine, pyrazole, oxadiazine, benzothiazine, benzoxathiazepine and quinazoline bearing pyrrole rings areshown in (Scheme 1).



Scheme 1: Synthetic route of compounds [1-12a-c], reactions and reagents: a) 1) HNO_2, 2) Zn/AcOH b) $NH_2NH_2.H_2O$/EtOH c) maleic anhydride/AcOH d)phthalic anhydride/AcOH e) succinic anhydride/AcOH f) acetylacetone/EtOH g)ethylacetoacetate/EtOH h) chloroacetylchloride/AcONa, glacial AcOH i) aryl aldehydes/EtOH j) 2-mercaptobenzoic acid/dry benzene k) orthosulfobenzoic anhydride/dry benzene l) 2-amino benzoic/dioxane

Identification of 3,5-dimethyl-1*H*-pyrrole-2,4-diethyl carboxylate (1)

The first prepared compound3,5-dimethyl-1*H*-pyrrole-2,4-diethyl carboxylate (1)was obtained by the reaction of excess ethyl acetoacetatewith sodium nitriteand the resulting nitroso compound is reduced byzinc and acetic acid. This reduced product reacts with unchanged ethyl acetoacetate yielding the desired product according to Knorr procedure.[27]

The FT-IR spectrum of thisproduct indicated the presence of absorption bands due to(N-H) group of pyrrole of glycine and the presence of a (C-H) aliphatic; (C=O) group of ester; (C=C) and (C-N) absorption bandsrespectively.

Also the ^{1}HNMR spectrum of this compound showed a signals integrating for protons of the(CH_3), (CH_2) and (NH) groupsrespectively.

Further the ^{13}CNMRspectrumshowed signalsdue to carbons of (CH_3), (CH_2),(CO) groups and two carbons of pyrrole ring.

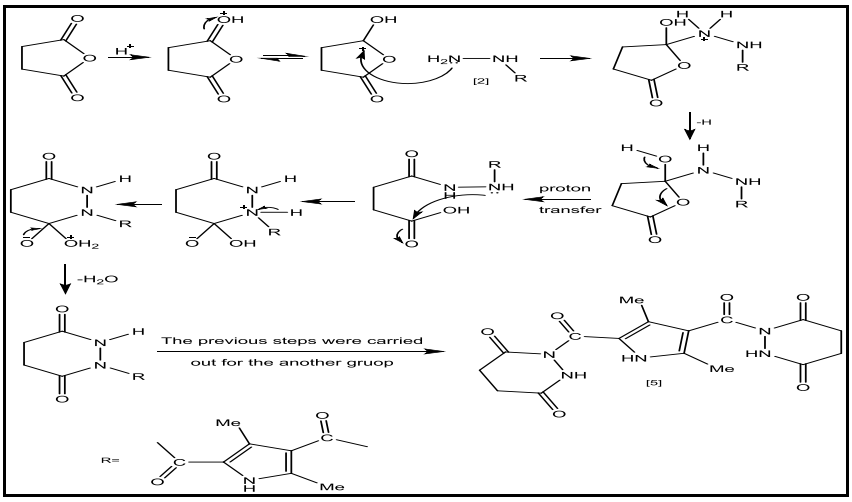
Identification of 3,5-dimethyl-*1H*-pyrrole-2,4-dicarbohydrazide (2)

Treatment of prepared ester3,5-dimethyl-1*H*-pyrrole-2,4-diethyl carboxylate (1)with hydrazine hydrate in absolute ethanolgive the acid hydrazide3,5-dimethyl-*1H*-pyrrole-2,4-dicarbohydrazide (2).The reaction occursvianucleophilic substitution and its mechanism involvednucleophilic attack of amino group in hydrazine on carbonyl group in ester followed by elimination of ethanol molecule. FTIR spectrum of compound (2) showed disappearance of absorptions due to υ(C=O) of ester at (1747) cm^{-1} and appearance of Asym. υ(NH_2) absorption bands at (3359) cm^{-1} and sym. υ(NH_2) at (3265) cm^{-1} proving success of hydrazide formation .

^{1}HNMR spectrum of compound (2) displayed signals attributed to protons of (CH_3), (NH_2), (NH) pyrrole ring and (N<u>H</u>) hydraziderespectively.^{13}CNMR spectrum of compound (2) showed signals belong to carbons of (CH_3), two carbons of pyrrole ringand (C=O) amidic carbonyl respectively.

Identification of bis-phthalazine and bis-pyridazin-dione derivatives (3), (4) and (5)

Compounds (3), (4) and (5) were synthesized from the reaction of compound (2) with maleic anhydride, phthalic anhydride and succinic anhydride respectively, in the presence of acetic acid as a solvent and catalyst. The suggested mechanism for the synthesis of the compound (5) is shown in (Scheme 2). The synthesis of compounds (3) and (4) were followed the same mechanism as in compound (5). The first step of the reaction includes a takes place of protonation process by the acid, followed by a nucleophilic attack by the hydrazide on the carbon atom bearing the positive charge. Losing a proton and rearrangement lead to cyclization with losing a water molecule.



Scheme 2:The suggested mechanism for the synthesis of compound (5)

The FTIR spectra of compounds (3), (4) and (5) respectively show the disappearance of (NH_2) band at (3359, 3265) cm^{-1} of compound (2).

^{1}H-NMR spectrum of these compounds shows the following characteristic chemical shifts suggested the attribution of the protons of($C\underline{H}_3$), (CH_2) groups of pyridazine ring, (NH) group pyrrole ring and (NH) for pyridazine ring.Also ^{13}CNMR shows characteristic signals for carbons of (CH_3), carbons of pyrrole ring, carbons of pyridazine ring, (CO)of pyridazine ring and other (CO).

Identification of bis-pyrazole derivatives (6) and (7)

Compounds (6) and (7) were synthesized from the reaction of compound (2) with acetyl acetone and ethyl acetoacetate, respectively in the presence of acetic acid using absolute ethanol as a solvent.

The FTIR spectra of compounds (6) and (7) show the disappearance of (NH_2) bands at (3349, 3265) cm^{-1} of the starting material (2).^{1}H-NMR spectra showed the following characteristics chemical shifts (DMSO as a solvent) were appeared signals suggested the attribution of the protons of (CH_3),($N\underline{H}$) pyrrole ring and($C\underline{H}$) for pyrazole ring. ^{13}CNMR shows characteristic signals for carbons of these compounds.

Identification of bis-oxadiazine derivative (8)

3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(4H-1,3,4-oxadiazin-6(5*H*)-one) were obtained from the reaction of compound (2) with chloroacetylchloride to give a product with characteristic FT-IR band at 1724 $cm^{-1}$for carbonyl of oxadiazine ring.^{1}HNMR signal at3.16 ppm(CH_2) belongs to proton of oxadiazine ring. ^{13}CNMR 40.73, 128.04 ppmrefer to two carbons of oxadiazine ring.

Identification of bis-Schiff basesderivatives (9a-c)

The hydrazide (2) was converted into derivatives of Schiff base (9a-c) by the reaction withdifferent aromatic aldehyde, FT-IR spectra of compounds (9a-c) showing disappearance of absorptions bands due to υ(NH_2) for compound (2) and appearance of υ(NH) absorption bands for compounds (9a-c).

The spectra shows other characteristic bands υ (C=N) due to imine groups. ^{1}HNMR and ^{13}CNMR spectral data of compounds (9a-c) shows results confirmed the structure of the synthesized compounds.

Identification of bis-benzothiazine derivatives (10a-c)

Treatment of compounds (9a-c)with 2-mercaptobenzoic acid in the presence oftriethylamine as catalytic amount in dry benzene affords intramolecular cyclization to give bis-benzothiazine derivatives characterized by FT-IR spectra showed a fundamentalstretching band due to υ(C=O)about (1710) cm^{-1}. The ^{1}HNMR spectrum of compounds [10a-c]showed proton signalsabout 4.7ppm for benzothiazine ring as characteristic signal besides the others for(CH_3), (NH) pyrrole ring, benzene rings and (NH) amide protons.Further^{13}CNMRspectra of compounds (10a-c) give essential results for signals of carbons benzothiazine ring about 55ppm.

Identification of bis-benzoxathiazepine derivatives (11a-c)

Preparation of thesederivatives includes reactions of desired Schiff bases (9a-c) with orthosulfobenzoic anhydride in dry benzene solvent to produce corresponding desirable benzoxathiazepine heterocycles.FT-IR spectra improve the presence bands due to stretching carbonyl group of benzoxathiazepine rings about (1698) cm^{-1}besides bands about 1390, 1170for stretching(SO_2)group.^{1}HNMR spectra give important signals for characterization proton of benzoxathiazepinering about 4ppm. The other evidence to improve the structure of benzoxathiazepine derivatives by ^{13}CNMR which give signals about 61ppm for carbon benzoxathiazepine ring.

Identification of bis-quinazoline derivatives (12a-c)

Conversions of appropriate Schiff bases (9a-c) intobis-quinazoline derivatives take place via intramolecular cyclization by using 2-amino benzoic in dioxane.

^{1}HNMR and ^{13}CNMR proved the presence of proton and carbon of quinazoline ring by giving signals about 5 and 58 ppm respectively. More FT-IR spectra give bands about (1696) cm^{-1} due to stretching of carbonyl(C=O) quinazoline ring.

Anti-candida screening

The zone of inhibition around incubational cups were observed and measuredin (mm.).The results are summarized in (Table 1).

Table 1:Anti-candida activitydata of some new synthesized derivatives

Compound	*Candida albicans* inhibition zone (mm)	Inhibition (%)	*Candida glabrata* inhibition zone (mm)	Inhibition (%)	*Candida spp.* inhibition zone (mm)	Inhibition (%)
fluconazole	16	80.00	13	76.00	13	76.00
nystatin	19	95.00	17	94.00	15	88.00
clotrimazole	20	100.00	18	100.00	17	100.00
Control (DMSO)	No inhibition					
3	13	65.00	11	61.00	12	70.00
4	11	55.00	10	55.00	8	47.00
5	14	70.00	11	61.00	0	0

6	11	55.00	9	50.00	13	76.00
7	14	70.00	10	55.00	9	52.00
8	10	50.00	8	44.44	12	70.00
10a	8	40.00	7	38.00	7	41.17
10b	7	35.00	0	0	0	0
10c	9	45.00	9	50.00	8	47.05
11a	11	55.00	12	66.00	10	58.82
11b	10	50.00	10	55.00	7	41.17
11c	12	60.00	9	50.00	9	52.00
12a	11	55.00	0	0	0	0
12b	10	50.00	11	61.00	7	41.17
12c	13	65.00	0	0	0	0

In general, the derivatives of bis-phthalazine (3),bis-pyridazin-dione (5),bis-pyrazole (6,7) and bis-oxadiazine (8) showed good anti-candida activity against the three types of candida isolates *Candida albicans, CandidaGlabrata and Candida spp.*respectively when compared with the other derivatives of bis-benzothiazine (10a-c), bis-benzoxathiazepine (11a-c) andbis-quinazoline (12a-c).Compounds (5 and 7) showed goodactivities against *Candida albicans*compared with clotrimazole and nystatin as standard drugs.Compounds (3,6 and 8) observedgood activities against *Candida spp.* isolatescompared with clotrimazole and nystatin standards.Compound (6)showed potent activity against *Candida spp.*compared with fluconazole standard.The other synthesized compounds were also found to be moderate effective against candida.

In some cases no inhibition zone was observed specially in cases of compounds (10b, 12a and 12c) against *CandidaGlabrata and Candida spp.*respectively.

Conclusions:

Pyrrole derivatives have great relevance in organic chemistry. The present research reports a new investigation of bis-heterocyclic systems (phthalazine, pyridazin-dione, pyrazole, oxadiazine, benzothiazine, benzoxathiazepineand quinazoline)derived from pyrrole. All thesesystemswere synthesized with the aimto developing better anti-candidamolecules. Someof tested prepared compounds (3,4, 5,6, 7and 8) showed maximum activity compared to other compounds.The other prepared compounds also showed moderateactivity compared to standard drugs.I hope that this work will serve to stimulate research in this fieldand better useful area of organic synthesis.

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