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Conventional and micro wave assisted Synthesis Of Pyrazole Derivatives And Their Antimicrobial Activity

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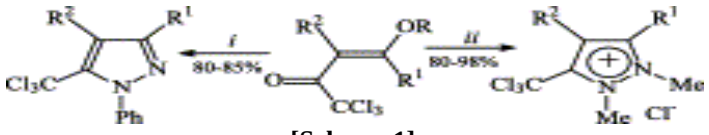
ABSTRACT: Pyrazoles have contend a vital half within the progression of theory in hetero-cyclic chemistry and conjointly used extensively in organic synthesis. Pyrazoles area unit 5 eight-membered heterocyclic compounds. Compounds that containing pyrazole derivatives area unit well-known and necessary nitrogen-containing 5-membered heterocyclic compounds. Among the 2 element atoms; one is basic and also the different is neutral in nature. Pyrazole and its derivatives have displayed broad spectrum of medicine necessary active scaffold that possesses the majority styles of medicine activities and biological activities like antimicrobial, antitumor, antiviral, medication, anti-convulsant, antihyperglycemic, and enzymes restrictive activities. gift paper is emphasizes on microwave assisted synthesis of some schemes Pyrazole Derivatives.

KEYWORDS: Pyrazole, heterocyclic, derivatives, pharmacological, activity.

I. INTRODUCTION:

Contagious conditions caused by microbes, similar as bacteria and fungi, are one of the leading causes of morbidity and mortality. The major reason for the increase in microbial infections is the resistance developed by these microbial organisms (1). The use of microwave oven irradiation in organic conflation has come decreasingly popular within the medicinal and academic arenas, because it's a new enabling technology for medicine discovery and development. By taking advantage of this effective source of energy, emulsion libraries for supereminent generation and optimization can be assembled in a bit of the time needed by classical thermals styles (2). Preparation of heterocyclic composites by using microwave oven fashion are preliminarily reported, where microwave oven irradiation considered as one of the green chemistry ways due to ameliorate the yield, friendly environmental and reducing the response times.(3) For the below- mentioned significance and according to our interest in synthesize new heterocyclic composites having natural and pharmacological conditioning.(4). In particular, applying Microwave oven supported Organic conflation (MAOS) becomes more common in heterocyclic chemistry and especially in pyrazole outgrowth conflation (5).

Different Approaches in Synthesis : A series of five 5-trichloromethyl-1-phenyl-1H-pyrazoles and six 5- trichloromethyl-1,2-dimethylpyrazolium chlorides have been synthesized in 80–98% yield by environmentally benign microwave induced techniques involving the cyclone condensation of 4-alkoxy-1,1,1- trichloro-3-alken-2-ones [Cl3C(O)C(R2)=C(R1)OR, where R2 =H, Me; R1 =H, alkyl, phenyl and R=Me, Et] with phenyl hydrazine and 1,2-dimethylhydrazine dihydrochloride, respectively, using toluene as solvent The use of microwave and classical methods are comparable for making pyrazolo's, but the formation of parazonium chlorides can be achieved in a significant shorter time, and in some cases better yield. A series of five 5-trichloromethylpyrazoles and six 5-trichloromethylpyrazolium chlorides have been synthesized by microwave (MW) induced techniques. Reaction conditions: (i) PhNHNH2, (ii) MeNHNHMe·2HCl, MW, 45 W, Ph.M., 85°C, 5–12 min.[6].



[Scheme 1]

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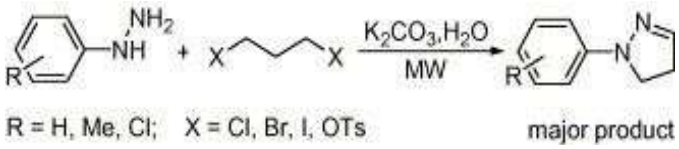
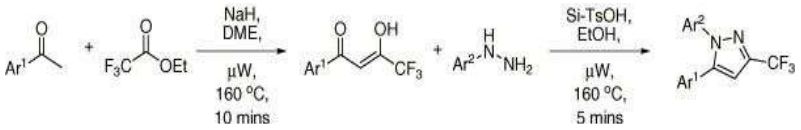
Direct microwave-assisted syntheses of 4, 5-dihydro- pyrazole, pyrazolidine and 1,2-dihydro-phthalazine derivatives from hydrazine's and alkyl dihalides or dissipates were achieved in aqueous alkaline media.



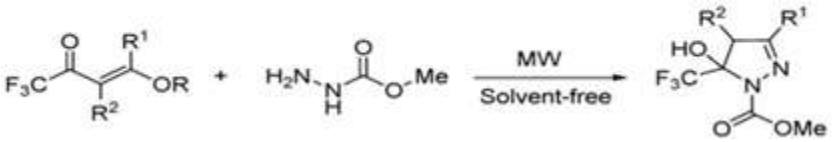
[Scheme 2]

The application of microwave heating to a silica assisted solution-phase synthesis technique has been utilized to develop a rapid and efficient two-step protocol for the preparation of Pyrazoles from arylmethyl ketone and aryl hydrazine monomers.[7]



[Scheme 3]

An efficient microwave-assisted synthesis of 1- carboxymethyl-5-trifluoromethyl-5-hydroxy-4. 5-dihydro-1H-pyrazoles from the cyclocondensation reaction between eonos [CF_3C (O) C (R^2) = C (R^1) (OR), where R^2 = H, Me;R^1 = H,Me,Et, Pr,i-Pr,t-Bu, i-Bu, Ph, 4-NO_2-Ph, 4-Cl-Ph, 4-Br-Ph, 4-F-PhandR = Me, Et] and methyl hydrazinocarboxylate under solvent- free conditions is reported. This process is an efficient alternative to the traditional thermal heating and furnishes the heterocyclic compounds in good to excellent yields in a short reaction time. To show the versatility of 1-carboxymethyl-5-trifluoromethyl-5- hydroxy-4, 5-dihydro-1H-pyrazoles, dehydration reactions of these compounds are also demonstrated.[8]



[Scheme 4]

A series of 1-(4-substitutedphenyl)-3-phenyl-1H- pyrazole-4-carbaldehydes **4a–l** have been synthesized and tested for their biological activities. Formation of the pyrazole derivatives was achieved by treating with Vilsmeier-Haack reagent. The newly synthesized compounds were evaluated for their anti- inflammatory and analgesic activities compared to Diclofenac sodium as standarddrug.[9]

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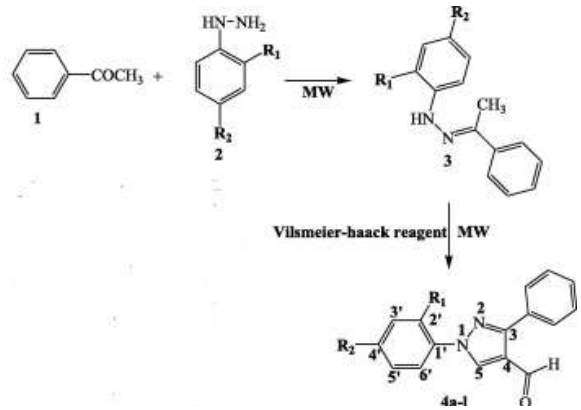

[Scheme 5]

Synthetic methods for compounds 2 to 9. Reagents and conditions: A, $PhCOCH_2Br$, EtOH, K_2CO_3, reflux 6 hours. B, $PhCOCH_2Br$,EtONa,reflux7hours.C,EtONa,reflux4hours.D)Glucose,EtOH/AcOH(1:1),reflux6hours.E,$PhCOCH_2Br$(2mole), EtOH,TEA,reflux9hours.F,$N_2H_4H_2O$,EtOH,reflux6hours.G,NH_2OHHCl,EtOH,reflux7hours.H,THF,EtOH,reflux8hours.I, Phthalic anhydride, AcOH, reflux 10hours thioglycolic acid to give the corresponding azetidinone 17 and thiazolidinone 18, respectively. This is according to the previous publications.[10,11]

The reactivity of compound 1 toward di-amino com- pounds as bi-nucleophilic was explored. Thus, treatment of 1 with ethylenediamine and/or O-phenylenediamine produced products which were formulated as pyrazoloimidazole 19 and pyrazolobenzoimidazole 20 derivatives, respectively. These structures weresupported by the disappearance of υ CN and presence of a strong absorption band specific for NH_2 in its IRspectrum.

Reaction of compound 1 with sodium azide afforded the pyrazolotetrazole derivative 21. This structure was supported by the disappearance υ CN and presence of a strong absorption band specific for tetrazole ring at1444 cm^{-1} in its IRspectrum.

The reaction of compound 1 with 1-amino-2-hydroxy- naphthalene-7-sulfonic acid gave compound 22 through nucleophilic attack of OH group on CN group followed by removal of one ammonia molecule forming the oxazole ring. The obtained compound structure was proved by IR, ^{1}HNMR, and mass spectra (Scheme 3).

Refluxing ethanolic solution ofcompound 1with diethyl malonate in 1:2 ratio gave the pyrazolomalonamide

23. The structure of 23 was illustrated by spectroscopic data were IR spectrum displayed the following bands at 3204 cm^{-1} (NH), 2208 (CN), 1652 (CO), and 1597 (CN)

and showed molecular ion peak m/z at 647 (0.2%). Com- pound 23 can also be obtained through treatment of com- pound 1 with malonyl chloride. The obtained product was identical in m.p, mixed m.p and TLC (benzene/acetone by 70%:30%) with compound 23.

While, the di-Schiff base 24 was synthesized by treatment of compound 1 with terephthalaldehyde in 1:2 ratio. Compound 24 showed molecular ion peak m/z at 704(0.74%).

Furthermore, compound 1 react with acetyl chloride togivetheN-monoacetylderivative25.Carryingthereaction using acetic anhydride the N, N-diacetyl derivative26 was obtained. Structure of compound 26 was confirmed by its treatment with O-phenylenediamine to give ben-zotriazepine derivative 27 (Scheme4).The cell membrane of bacterial is formed from a dense wall with several teichoic acid and peptidoglycan layersattachedbypolyhydricalcoholviaa“phospho rusbond” and surrounded by proteins andlipopolysaccharides(Figure 3). The heterocyclic biocides action mode toward bacteria was evaluated as the biocides adsorption mechanism on the outer bacteria cell membrane due to the adsorption characteristics via the heteroatoms.

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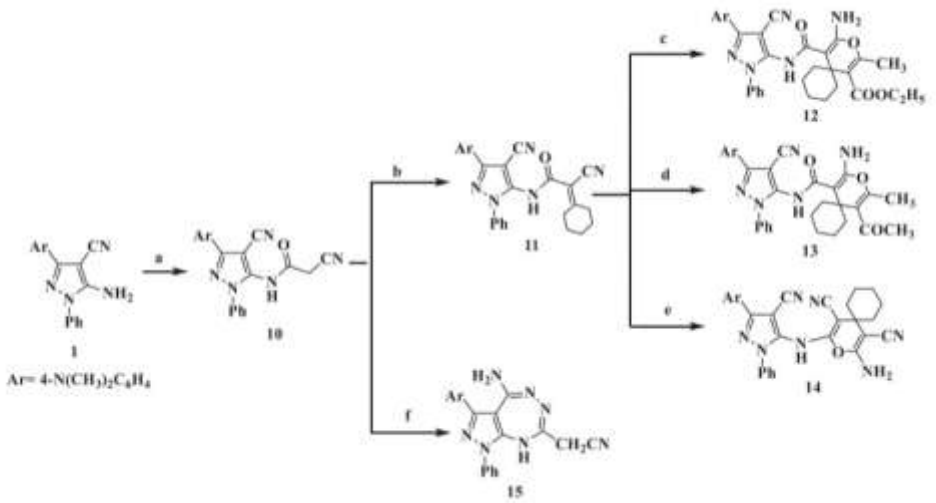
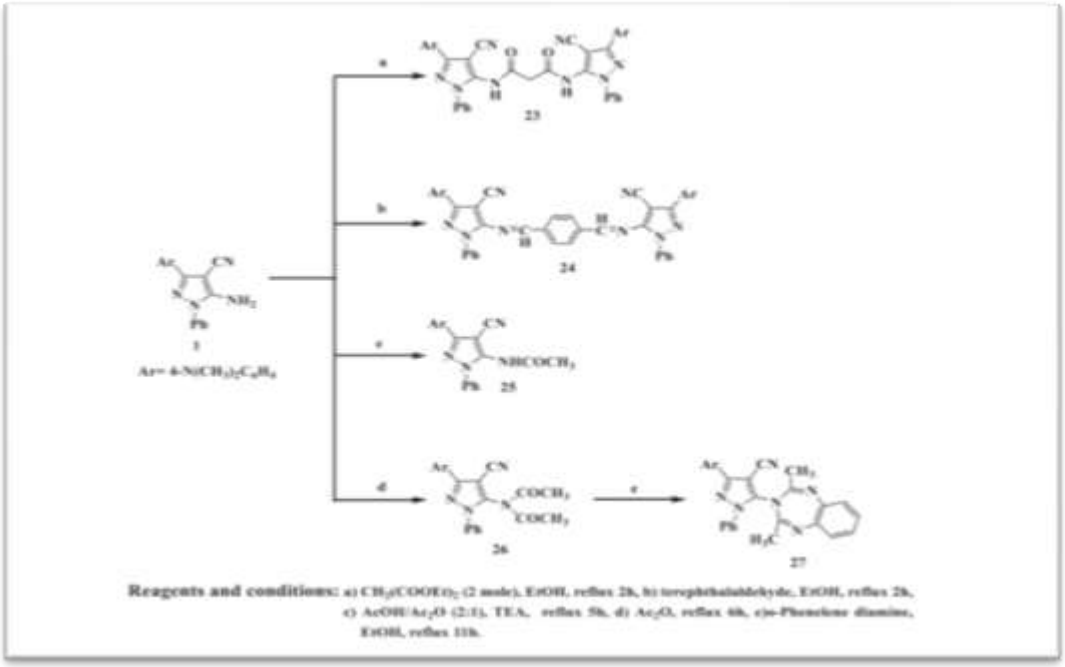


Reagent and Condition:

a) $CNCH_2COOH$, Ac_2O, reflux 7h, b) cyclohexanone, EtOH, TEA, reflux 5h, c) CH_3COCH_2COOEt, EtOH, reflux 4h, d) $CH_3COCH_2COCH_3$, EtOH, reflux 7h, e)$CNCH_2CN$, EtOH, reflux 8h, f)$N_2H_4.H_2O$, EtOH, reflux 5h.

[Scheme 6]



SCHEME 7

Synthetic methods for compounds 23 to 27. Reagents and conditions: A, CH2(COOEt)2 (2 mole), EtOH, reflux 2 hours. B, Terephthalaldehyde, EtOH, reflux 2 hours. C, AcOH/Ac2O (2:1), TEA, reflux 5 hours. D, Ac2O, reflux 6 hours. E, O-phenelene diamine, EtOH, reflux 11 hours.

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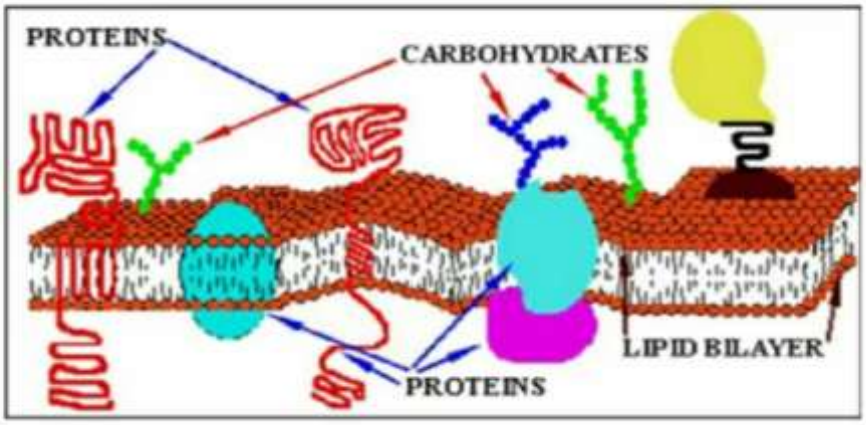

Fig structural bacterial outer cell membrane

Synthesized compounds have different heteroatoms which containing on lone electron pairs of nitrogen and/or oxygen atoms, also the electrons rich centers for the triple bonds of CN, double bonds, and phenyl rings. The synthesized molecules by the electron-rich centers, which adsorbed on the charged cites of the outer cellular membrane and begin in penetration into this membrane. The penetrated active molecules (8, 9, 19, 21, and 23) into the core of the cell begin various interactions inside the cell with breaking the proteins and companied by the "DNA" inside the nucleus. These interactions with the bacteria decompose the biological activities and leads the bacterial cells to death. The activity of returning to containing of compound 8 on additional pyrrolidine ring, containing of compound 9 on additional five carbonyl groups and dioxoisoindoline ring, containing of compound 19 on additional imidazole ring, and containing of compound 21 on additional tetrazole ring and compound 23 consider as bifunctional compound with two carbonyl groups by comparable with the starting martial

II. EXPERIMENTAL

Commercially available starting materials, solvents and reagents were used without further purification. All the uncorrected melting points are measured on a melting SCHEME 4 Synthetic methods for compounds 23 to 27. Reagents and conditions: A, CH2(COOEt)2 (2 mole), EtOH, reflux 2 hours. B, Terephthalaldehyde, EtOH, reflux 2 hours. C, AcOH/Ac2O (2:1), TEA, reflux 5 hours. D, Ac2O, reflux 6 hours. E, O-phenelene diamine, EtOH, reflux 11 hours Structure of the bacterial outer cell membrane 6 ANWER AND SAYED point apparatus which is digital Stuart "SMP3" electric. Microwave irradiation reactions were carried through microwave reactor Anton Paar "monowave 300" via using "borosilicate glass vials" of (10 mL). Infrared spectra (IR) measured on "Perkin-Elmer 293 spectrophotometer" (cm−1) using KBr disks. 1 H-NMR and 13C-NMR spectra measured on "Varian Mercury 400" (MHz) spectrometer in DMSO-d6 as a solvent, using an internal standard which is TMS. Chemical shift (δ) is measured in ppm. The mass spectra recorded on a Shimadzu Gas chromatography "GC-2010" instrument mass spectrometer (70 ev) with electron ionization technique. Elemental microanalyses measured on a CHN-2400 "Perkin-Elmer analyzer" where microanalyses within (±0.4%) comparative to the theoretical values. Pharmacological activities of the prepared compounds evaluated at Pharmacology Department, Faculty of Pharmacy, Mansoura University, Egypt.

3.1 | 5-Amino-3-(4-(dimethylamino) phenyl)-1-phenyl-1H-pyrazole4-carbonitrile

(1) An equimolar amount of N,N-dimethylaminobenzaldehyde (0.01 mol, 1.49 g), phenyl hydrazine (0.01 mol, 1.08 mL), and malononitrile (0.01 mol, 0.66 g) in methanol (40 mL) was refluxed for 24 hours. After cooling the solid precipitated was filtrated off, washed with ethanol, and crystallized from ethanol to give 1.

m.p. 106C to 108C. IR (KBr) ν cm−1 :3342, 3313 (NH2), 2212 (CN), 1600 (C N). 1 H-NMR

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(DMSO-d6) δ: 2.92 (s, 6H, N(CH3)2), 6.64 to 7.74 (m, 9H, Ar-H), 9.91 (s, 2H, NH2, D2O exchangeable). 13C NMR (DMSO-d6) δ (ppm): 40.2, 70.2, 109.9, 111.7, 121.3, 125.5, 126.2, 128.6, 131.6, 138.2, 147.1, 149.5 and 150.0. MS: m/z 303 [M+] (2%). Anal. Calcd for C18H17N5 (303): C, 71.27; H, 5.65; N, 23.09. Found: C, 71.09; H, 5.78; N, 23.13%.

3.2 | 3-(4-(Dimethylamino)phenyl)- 5-((2-oxo-2-phenylethyl)amino)-1-phenyl1H-pyrazole-4-carbonitrile (2)

Equimolar amount of 1 (0.01 mol, 3.03 g), phenacyl bromide (0.01 mol, 1.97 g) and potassium carbonate (0.01 mol, 1.37 g) in ethanol (25 mL) was refluxed for 6 hours. The solid precipitated after cooling was filtrated off, washed with ethanol, and crystallized from furnish to obtain 2.

m.p. > 300C. IR (KBr) ν cm−1 :3217 (NH), 2199 (CN), 1650 (C O), 1630 (C N). 1 H-NMR (DMSO-d6) δ: 2.93 (s, 6H, N(CH3)2), 4.33 (s, 2H, NHCH2CO), 6.66 to 7.79 (m, 14H, Ar-H), 11.19 (s, 1H, NH, D2O exchangeable). 13C NMR (DMSO-d6) δ (ppm): 40.3, 56.2, 70.6, 110.4, 110.9, 121.4, 125.4, 126.6, 127.1, 128.8, 130.7, 131.8, 136.2, 137.9, 140.1, 147.3, 150.2 and 166.5. MS: m/z 421 [M+] (13.4%). Anal. Calcd for C26H23N5O (421): C, 74.09; H, 5.50; N, 16.62. Found: C, 73.89; H, 5.78; N, 16.53%.

3.3 | (4-Amino-3-(4-(dimethylamino) phenyl)-1-phenyl-1,6-dihydropyrrolo[2,3-c] pyrazol-5-yl)(phenyl)methanone (3)

An equimolar of 1 (0.01 mol, 3.03 g), phenacyl bromide (0.01 mol, 1.97 g) and sodium ethoxide (0.01 mol, 0.23 g sodium in 25 mL ethanol) was refluxed for 7 hours. The solid precipitated after cooling was filtrated off, washed with ethanol, and crystallized from methanol forming 3.

m.p. 224C to 226C. IR (KBr) ν cm−1 :3420, 3306 (NH2), 3271 (NH), 1776 (C O), 1602 (C N). 1 H-NMR (DMSO-d6) δ: 2.90 (s, 6H, N(CH3)2), 6.61 to 7.50 (m, 14H, Ar-H), 9.72 (s, 2H, NH2, D2O exchangeable), 11.41 (s, 1H, NH, D2O exchangeable). 13C NMR (DMSO-d6) δ (ppm): 40.1, 100.2, 110.8, 118.2, 121.0, 125.3, 126.7, 127.4, 129.8, 130.1, 131.3, 133.2, 136.1, 137.5, 146.2, 147.0, 148.3, 149.7 and 168.9. MS: m/z 421 [M+] (9.2%). Anal. Calcd for C26H23N5O (421): C, 74.09; H, 5.50; N, 16.62. Found: C, 73.92; H, 5.74; N, 16.44%.

3.4 | (3-(4-(Dimethylamino)phenyl)- 4-((2,3,4,5,6-pentahydroxyhexylidene) amino)-1-phenyl-1,6-dihydropyrrolo[2,3-c] pyrazol-5-yl)(phenyl)methanone (4)

An equimolar amounts of 3 (0.01 mol, 4.21 g) and Dglucose (0.01 mol, 1.8 g) in 1:1 AcOH/EtOH (20 mL) was refluxed for 6 hours. The solid precipitated after cooling was filtrated off and crystallized from acetone to furnish 4.

m.p. 134C to 136C. IR (KBr) ν cm−1 :3479 (OH), 3199 (NH), 1649 (C O), 1602 (C N). 1 H-NMR (DMSOd6) δ: 2.94 (s, 6H, N(CH3)2), 3.61 to 3.67 (m, 3H, glucose moiety), 3.77 to 3.86 (m, 2H, CH2OH), 4.03 to 4.16 (m, 1H, N CHCHOH) 4.44, 4.61, 4.92, 5.96, 6.07 (s, 5H, OH, D2O exchangeable), 6.60 to 7.53 (m, 14H, Ar-H), 8.23 (d, 1H, CH N), 11.37 (s, 1H, NH, D2O exchangeable). 13C NMR (DMSO-d6) δ (ppm): 40.4, 60.2, 63.7, 66.1, 68.9, 71.2, 100.9, 112.2, 118.0, 119.2, 121.5, 126.1, 126.9, 127.0, 130.8, 131.1, 133.4, 136.4, 137.3, 138.3, 146.4, 147.6, 149.7, 158.0 and 169.9. MS: m/z 583 [M+] (3.7%). Anal. Calcd for C32H33N5O6 (583): C, 65.85; H, 5.70; N, 12.00. Found: C, 65.94; H, 5.87; N, 12.24%.

3.5|5-((2-((4-Cyano3-(4-(dimethylamino)phenyl)-1-phenyl-1Hpyrazol-5-yl)amino)-1-phenylethylidene) amino)-3-(4-(dimethylamino)phenyl)- 1-phenyl-1H-pyrazole-4-carbonitrile (5)

To solution of compound 1 (0.02 mol, 6.06 g) and phenacyl bromide (0.01 mol, 1.97 g) add TEA (0.5 mL) in ethanol (25 mL) was refluxed for 9 hours. The solid precipitated after cooling was filtrated off, washed with ethanol, and crystallized from acetone to obtain 5.

m.p. 262C to 264C. IR (KBr) ν cm−1 :3216 (NH), 2214 (CN), 1604 (C N) and was devoid of ν C O. 1 HNMR (DMSO-d6) δ: 2.91 (s, 6H, N(CH3)2), 2.98 (s, 6H, N(CH3)2), 3.03 (s, 2H, NHCH2CN), 6.67 to 8.09 (m, 23H, Ar-H), 10.28 (s, 1H, NH, D2O exchangeable). 13C NMR (DMSO-d6) δ (ppm): 33.4, 40.3, 42.7, 52.4, 70.2, 80.4, 111.6, 112.9, 113.4, 116.2, 122.7, 125.6, 126.1, 126.3, 127.4, 128.0, 130.9, 131.9, 136.1, 147.4, 148.2, 149.2, 150.2, 151.5 and 155.2. MS: m/z 706 [M+] (0.4%). Anal. Calcd for C44H38N10 (706): C, 74.77; H, 5.42; N, 19.82. Found: C, 74.90; H, 5.18; N, 19.92%.

3.6 | 4-(4-(Dimethylamino)phenyl)- 6-phenyl-1,6-dihydropyrazolo[3,4-c]pyrazol3-amine (6)

Equimolar amount of 1 (0.01 mol, 3.03 g) and hydrazine hydrate (0.01 mol, 0.5 mL) in acetic acid (10 mL) was refluxed for 6 hours. The solid precipitated after cooling was filtrated, washed

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with ethanol, and crystallized from ethanol to afford 6.

m.p. 262C to 264C. IR (KBr) ν cm−1 :3389, 3309 (NH2), 3212 (NH), 1603 (C N). 1 H-NMR (DMSO-d6) δ: 2.97 (s, 6H, N(CH3)2), 6.67 to 7.74 (m, 9H, Ar-H), 8.48 (s, 2H, NH2, D2O exchangeable), 9.91 (s, 1H, NH, D2O exchangeable). 13C NMR (DMSO-d6) δ (ppm): 40.1, 99.8, 110.9, 120.9, 125.3, 126.3, 128.6, 131.4, 138.7, 139.5, 146.6, 149.8 and 155.2. MS: m/z 318 [M+] (3.37%). Anal. Calcd for C18H18N6 (318): C, 67.90; H, 5.70; N, 26.40. Found: C, 67.66; H, 5.84; N, 26.50%.

3.7 | 4-(4-(Dimethylamino)phenyl)- 6-phenyl-6H-pyrazolo[4,3-d]isoxazol3-amine (7)

An equimolar amount of 1 (0.01 mol, 3.03 g) and hydroxylamine hydrochloride (0.01 mol, 0.69 g) in ethanol (25 mL) was refluxed for 7 hours. The solid precipitated after cooling filtrated off, washed with ethanol, and crystallized from methanol forming 7.

m.p. 121C to 122C. IR (KBr) ν cm−1 :3327, 3305 (NH2), 1601, 1597 (C N). 1 H-NMR (DMSO-d6) δ: 2.93 (s, 6H, N(CH3)2), 6.66 to 7.76 (m, 9H, Ar-H), 12.34 (s, 2H, NH2, D2O exchangeable). 13C NMR (DMSO-d6) δ (ppm): 40.0, 100.2, 111.0, 121.2, 125.7, 126.7, 126.9, 130.9, 138.2, 139.4, 146.5, 149.6 and 154.3. MS: m/z 319 [M+] (4.2%). Anal. Calcd for C18H17N5O (319): C, 67.70; H, 5.37; N, 21.93. Found: C, 67.54; H, 5.57; N, 21.77%.

3.8 | 3-(4-(Dimethylamino)phenyl)- 1-phenyl-5-(pyrrolidin-1-yl)-1H-pyrazole4-carbonitrile (8)

Equimolar amount of 1 (0.01 mol, 3.03 g) and tetrahydrofuran (0.01 mol, 0.72 g) in ethanol (10 mL) was refluxed for 8 hours. The solid precipitated after cooling was filtrated off, washed with ethanol, and crystallized from ethanol to give 8.

m.p. > 300C. IR (KBr) ν cm−1 :2194 (CN), 1598 (C N). 1 H-NMR (DMSO-d6) δ: 1.96 (t, 4H, 2CH2 CH2N), 2.91 (s, 6H, N(CH3)2), 3.11 (t, 4H, 2CH2 CH2N), 6.66 to 7.71 (m, 9H, Ar-H). 13C NMR (DMSO-d6) δ (ppm): 29.5, 40.0, 49.2, 70.8, 110.3, 110.9, 121.7, 124.8, 126.4, 128.2, 130.5, 138.0, 139.2, 145.9 and 150.7. MS: m/z 357 [M+] (5.9%). Anal. Calcd for C22H23N5 (357): C, 73.92; H, 6.49; N, 19.59. Found: C, 74.18; H, 6.62; N, 19.20%.

3.9 | N,N-Diacetyl-3-(4-(dimethylamino) phenyl)-5-(1,3-dioxoisoindolin-2-yl)- 1-phenyl-1H-pyrazole-4-carboxamide (9)

An equimolar amount of 1 (0.01 mol, 3.03 g) and phthalic anhydride (0.01 mol, 1.48 g) in acetic acid (25 mL) was refluxed for 10 hours. The solid precipitated after cooling was filtrated off, washed with ethanol, and crystallized from ethanol to give 9.

m.p. 180C to 182C. IR (KBr) ν cm−1 :1763, 1731, 1709 (C O), 1599 (C N). 1 H-NMR (DMSO-d6) δ: 2.34 (s, 6H, N(COCH3)2), 2.94 (s, 6H, N(CH3)2), 6.66 to 8.01 (m, 13H, ArH). 13C NMR (DMSO-d6) δ (ppm): 22.9, 23.6, 40.3, 70.2, 110.8, 122.3, 124.2, 125.2, 125.9, 128.3, 130.9, 135.1, 135.8, 138.2, 140.2, 146.7, 150.6, 165.2, 166.9, 167.2, 168.3 and168.6. MS: m/z 535 [M+] (1.2%). Anal. Calcd for C30H25N5O5 (535): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.09; H, 4.56; N, 13.24%.

3.10 | 2-Cyano-N-(4-cyano3-(4-(dimethylamino)phenyl)-1-phenyl-1Hpyrazol-5-yl)acetamide (10)

Equimolar amount of 1 (0.01 mol, 3.03 g) and cyanoacetic acid (0.01 mol, 0.85 g) in acetic anhydride (25 mL) 8 ANWER AND SAYED was refluxed for 7 hours. The reaction mixture leaved to cool, and then poured into crushed ice water (50 mL). The solid precipitated was collected by filtration and crystallized from methanol forming 10.

1 m.p. 240C to 242C. IR (KBr) ν cm−1 :3176 (NH), 2212, 2195 (CN), 1728 (C O), 1611 (C N). 1 H-NMR (DMSO-d6) δ: 3.03 (s, 6H, N(CH3)2), 3.88 (s, 2H, COCH2CN), 6.67 to 8.08 (m, 9H, Ar-H), 10.9 (s, 1H, NH, D2O exchangeable). 13C NMR (DMSO-d6) δ (ppm): 26.9, 40.1, 70.1, 111.5, 112.0, 112.2, 121.9, 125.1, 125.7, 126.2, 131.2, 138.0, 147.6, 149.2, 149.8 and 164.2. MS: m/z 370 [M+] (100%). Anal. Calcd for C21H18N6O (370): C, 68.09; H, 4.90; N, 22.69. Found: C, 68.24; H, 5.01; N, 22.54%.

3.11|2-Cyano-N-(4-cyano3-(4-(dimethylamino)phenyl)-1-phenyl-1Hpyrazol-5-yl)- 2-cyclohexylideneacetamide (11)

A mixture of 10 (0.01 mol, 3.70 g), cyclohexanone (0.01 mol, 0.98 mL) with TEA (0.5 mL) in ethanol (25 mL) was refluxed for 5 hours. The solid precipitated after cooling was filtrated, washed with ethanol, and crystallized from methanol forming 11.

m.p. 276C to 278C. IR (KBr) ν cm−1 :3214 (NH), 2261, 2209 (CN), 1681 (C O), 1618 (C N), 1601 (C C). 1 H-NMR (DMSO-d6) δ: 1.50 (m, 6H, 3CH2), 2.16 (t, 4H, 2CH2), 3.08 (s, 6H, N(CH3)2), 4.48 (s, 1H, NH, D2O exchangeable), 6.67 to 7.63 (m, 9H,

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Ar-H). 13C NMR (DMSO-d6) δ (ppm): 23.2, 26.1, 29.3, 40.2, 70.4, 88.2, 111.9, 112.3, 112.6, 122.8, 125.2, 125.7, 126.9, 131.2, 138.7, 142.3, 147.5, 149.7, 157.9, 158.7 and 160.1. MS: m/z 450 [M+] (0.9%). Anal. Calcd for C27H26N6O (450): C, 71.98; H, 5.82; N, 18.65. Found: C, 71.67; H, 5.71; N, 18.64%.

3.12 | Reaction of 11 with different nucleophiles: general procedure

A solution of 11 (0.01 mol, 4.50 g) in ethanol (25 mL) and equimolar amounts of ethyl acetoacetate, acetyl acetone, and/or malononitrile was added and the mixture was refluxed for 4 to 8 hours according to (TLC). While (2-3) drops of TEA was added in case of reaction with ethyl acetoacetate and acetyl acetone and sodium ethoxide in case of reaction with malononitrile. The crude material obtained after cooling was filtered off and crystallized from methanol in case of ethyl acetoacetate and acetyl acetone and from acetone in case of malononitrile to give compound 12 to 14, respectively.

3.13 | Ethyl-4-amino-5-((4-cyano3-(4-(dimethylamino)phenyl)-1-phenyl-1Hpyrazol-5-yl)carbamoyl)-2-methyl3-oxaspiro[5.5]undeca-1,4-diene1-carboxylate (12)

m.p. 192C to 194C. IR (KBr) ν cm−1 :3452, 3304 (NH2), 3192 (NH), 2208 (CN), 1774, 1646 (C O), 1597 (C N). 1 H-NMR (DMSO-d6) δ: 1.41 (t, 3H, OCH2CH3), 1.50 (m, 6H, 3CH2), 2.16 (t, 4H, 2CH2), 2.33 (s, 3H, CH3), 3.08 (s, 6H, N(CH3)2), 4.31 (q, 2H, OCH2CH3), 5.21 (s, 1H, NH, D2O exchangeable), 6.65 to 7.59 (m, 9H, Ar-H), 9.97 (s, 2H, NH2, D2O exchangeable). 13C NMR (DMSO-d6) δ (ppm): 15.3, 20.2, 20.4, 20.6, 22.1, 31.8, 40.4, 63.2, 70.3, 87.2, 100.5, 110.6, 113.2, 122.7, 125.6, 125.9, 126.8, 131.6, 138.8, 142.4, 147.8, 150.2, 151.2, 152.8, 165.6 and 169.2. MS: m/z 580 [M+] (1.2%). Anal. Calcd for C33H36N6O4 (580): C, 68.26; H, 6.25; N, 14.47. Found: C, 67.91; H, 6.32; N, 14.54%.

3.14 | 5-Acetyl-2-amino-N-(4-cyano3-(4-(dimethylamino)phenyl)-1-phenyl-1Hpyrazol-5-yl)-4-methyl-3-oxaspiro[5.5] undeca-1,4-diene-1-carboxamide (13) m.p. 168C to 170C. IR (KBr) ν cm−1 :3409, 3343 (NH2), 3234 (NH), 2210 (CN), 1776, 1648 (C O), 1598 (C N). 1 H-NMR (DMSO-d6) δ: 2.25 (s, 3H, COCH3), 1.52 (m, 6H, 3CH2), 2.12 (t, 4H, 2CH2), 2.33 (s, 3H, CH3), 3.08 (s, 6H, N(CH3)2), 5.19 (s, 1H, NH, D2O exchangeable), 6.61 to 7.68 (m, 9H, Ar-H) 10.09 (s, 2H, NH2, D2O exchangeable). 13C NMR (DMSO-d6) δ (ppm): 17.2, 20.2, 21.2, 23.5, 26.3, 31.2, 40.2, 70.1, 82.9, 110.6, 113.4, 120.4, 121.9, 125.5, 125.7, 126.8, 131.4, 138.6, 142.6, 147.9, 150.6, 153.2, 158.1, 160.9 and 166.9. MS: m/z 550 [M+] (1.4%). Anal. Calcd for C32H34N6O3 (550): C, 69.80; H, 6.22; N, 15.26. Found: C, 69.68; H, 6.19; N, 15.41%.

3.15 | 2-Amino-5-((4-cyano3-(4-(dimethylamino)phenyl)-1-phenyl-1Hpyrazol-5-yl)amino)-3-oxaspiro[5.5]undeca1,4-diene-1,4-dicarbonitrile (14)

m.p. > 300C. IR (KBr) ν cm−1 :3471, 3351 (NH2), 3233 (NH), 2214, 2200 (CN), 1632 (C N). 1 H-NMR (DMSO-d6) δ: 1.54 (m, 6H, 3CH2), 2.09 (t, 4H, 2CH2), 3.02 (s, 6H, N(CH3)2), 6.18 (s, 1H, NH, D2O exchangeable), 6.57 to 7.66 (m, 9H, Ar-H), 10.63 (s, 2H, NH2, D2O exchangeable). 13C NMR (DMSO-d6) δ (ppm): 16.2, 23.5, 26.7, 40.1, 57.7, 70.4, 111.6, 113.2, 114.1, 115.4, 122.0, 125.3, 126.0, 126.7, 131.4, 137.9, 142.8, 148.9, 151.2, 152.2 and 159.3. ANWER AND SAYED 9 MS: m/z 516 [M+] (4.9%). Anal. Calcd for C30H28N8O (516): C, 69.75; H, 5.46; N, 21.69. Found: C, 69.54; H, 5.23; N, 21.37%.

3.16 | 2-(4-Amino-3-(4-(dimethylamino) phenyl)-1-phenyl-1,8-dihydropyrazolo[3,4-e] [1,2,4]triazepin-7-yl)acetonitrile (15)

A mixture of 10 (0.01 mol, 3.70 g), hydrazine hydrate (0.01 mol, 0.5 mL) in ethanol (25 mL) was refluxed for 5 hours. The solid precipitated after cooling was filtrated, washed with ethanol, and crystallized from methanol forming 15. m.p. > 300C. IR (KBr) ν cm−1 :3421, 3358 (NH2), 3149 (NH), 2267 (CN), 1603 (C N). 1 H-NMR (DMSO-d6) δ: 2.94 (s, 6H, N(CH3)2), 3.82 (s, 2H, CH2CN), 6.75 to 7.76 (m, 9H, Ar-H), 8.49 (s, 3H, NH, NH2, D2O exchangeable). 13C NMR (DMSO-d6) δ (ppm): 22.5, 40.3, 89.2, 112.0, 113.2, 121.0, 124.9, 125.8, 127.6, 132.3, 134.2, 137.7, 144.2, 148.5, 150.9 and 158.2. MS: m/z 384 [M+] (1%). Anal. Calcd for C21H20N8 (384): C, 65.61; H, 5.24; N, 29.15. Found: C, 65.77; H, 5.41; N, 28.82%.

3.17 | 5-(Benzylideneamino)- 3-(4-(dimethylamino)phenyl)-1-phenyl-1Hpyrazole-4-carbonitrile (16)

To a reaction mixture of 1 (0.01 mol, 3.03 g) and benzaldehyde (0.01 mol, 1.06 mL) in acetic acid (25 mL), three drops of conc. HCl was added and refluxed for 9 hours. The solid precipitated

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after cooling was filtrated off, washed with ethanol, and crystallized from ethanol to give 16.
m.p. 200C to 202C. IR (KBr) ν cm−1 :2213 (CN), 1607 (C N). 1 H-NMR (DMSO-d6) δ: 2.97 (s, 6H, N(CH3)2), 6.66 to 8.28 (m, 14H, Ar-H), 9.49 (s, 1H, N CH). 13C NMR (DMSO-d6) δ (ppm): 40.3, 70.1, 111.2, 113.2, 121.1, 125.4, 125.8, 128.2, 128.4, 130.5, 131.1, 131.4, 133.2, 137.6, 146.6, 148.9, 149.7 and 155.2. MS: m/z 391 [M+] (0.79%). Anal. Calcd for C25H21N5 (391): C, 76.71; H, 5.41; N, 17.89. Found: C, 76.52; H, 5.25; N, 18.23%.

3.18 | 3-(4-(Dimethylamino)phenyl)- 5-(2-oxo-3,4-diphenylazetidin-1-yl)- 1-phenyl-1H-pyrazole-4-carbonitrile (17)

Equimolar amount of 16 (0.01 mol, 3.91 g), phenacyl bromide (0.01 mol, 1.97 g) and TEA (0.5 mL) in ethanol (25 mL) was refluxed for 4 hours. The solid precipitated after cooling was filtrated off, washed with ethanol, and crystallized from methanol forming 17.
m.p. 280C to 282C. IR (KBr) ν cm−1 :2208 (CN), 1694 (C O), 1565 (C N). 1 H-NMR (DMSO-d6) δ: 2.91 (s, 6H, N(CH3)2), 3.18 (d, 1H, NCHPh), 3.30 (d, 1H, COCHPh), 6.82 to 8.05 (m, 19H, Ar-H). 13C NMR (DMSO-d6) δ (ppm): 40.1, 47.2, 58.2, 70.4, 111.7, 113.3, 121.5, 124.3, 125.2, 125.6, 126.0, 127.3, 127.4, 129.0, 131.2, 133.1, 137.7, 140.9, 144.6, 149.4 and 162.5. MS: m/z 509 [M+] (5.32%). Anal. Calcd for C33H27N3O (509): C, 77.78; H, 5.34; N, 13.74. Found: C, 77.53; H, 5.24; N, 13.54%.

3.19 | 3-(4-(Dimethylamino)phenyl)- 5-(4-oxo-2-phenylthiazolidin-3-yl)-1-phenyl1H-pyrazole-4-carbonitrile (18)

A mixture of 16 (0.01 mol, 3.91 g) and thioglycolic acid (0.01 mol, 0.92 mL) in dioxane (20 mL) was refluxed for 12 hours. The solid obtained after cooling was filtered off and crystallized from acetone to form 18. m.p.

256C to 258C. IR (KBr) ν cm−1 :2213 (CN), 1665 (C O), 1600 (C N). 1 H-NMR (DMSO-d6) δ: 2.87 (s, 6H, N(CH3)2), 3.66 (s, 2H, SCH2CO), 6.88 to 8.34 (m, 15H, Ar-H). 13C NMR (DMSO-d6) δ (ppm): 29.5, 40.4, 66.2, 70.1, 112.1, 112.7, 122.0, 124.2, 125.6, 126.1, 127.7, 127.9, 129.0, 131.0, 133.4, 137.3, 140.1, 143.7, 149.2 and 166.2. MS: m/z 465 [M+] (5.21%). Anal. Calcd for C27H23N5O5 (465): C, 69.16; H, 4.69; N, 15.51. Found: C, 68.98; H, 4.31; N, 15.54%.

3.20 | 4-(4,5-Dihydro-1H-imidazol-2-yl)- 3-(4-(dimethylamino)phenyl)-1-phenyl-1Hpyrazol-5-amine (19)

To reaction mixture of 1 (0.01 mol, 3.03 g) in ethylene diamine (15 mL), (2 mL) of carbon disulfide was added. The mixture was refluxed for 16 hours, left to cool then poured into crushed ice water (200 mL). The solid obtained was filtrated off, washed with ethanol, and crystallized from ethanol to obtain 19. m.p.
150C to 152C. IR (KBr) ν cm−1 :3357, 3313 (NH2), 3101 (NH), 1598 (C N). 1 H-NMR (DMSO-d6) δ: 2.71 (s, 6H, N(CH3)2), 2.90 (d, 2H, C NCH2), 3.3 (d, 2H, NHCH2), 6.58 to 7.74 (m, 9H, Ar-H), 5.89 (s, 1H, NH, D2O exchangeable), 9.90 (s, 2H, NH2, D2O exchangeable). 13C NMR (DMSO-d6) δ (ppm): 40.1, 42.2, 42.8, 92.2, 110.8, 120.3, 125.1, 125.2, 128.4, 131.2, 137.9, 146.5, 147.5, 151.2 and 155.2. MS: m/z 346 [M+] (10.46%). Anal. Calcd for C20H22N6 (346): C, 69.34; H, 6.40; N, 24.26. Found: C, 69.18; H, 6.52; N, 24.30%

III. BIOLOGICALACTIVITY:

Antibacterialactivity:

Theanti-bacterialactivityofthesynthesizedcompoundswas tested against a panel of 2 g-negative bacteria (Escherichia coli, Pseudomonas aeuroginosa), and 2 g positive bacteria (Staphylococcusaureus,Bacillussubtilis[B.subtilis]). Eachof the compounds was dissolved in DMSO and solution of the concentration 1 mg /mL were prepared separately paper discs of Whatman filter paper were prepared with standard size (5 mm) were cut and sterilized in an autoclave. The paper discs soaked in the desired concentration of the com- plex solution were places aseptically in the petri dishes con- taining nutrient agar media (agar 20 g + beef extract 3 g + peptone 5 g) seeded with S aureus, B subtilis, E coli, and P aeuroginosa.Thepetridisheswereincubatedat36°Cand the inhibition zones were recorded after 24 hours of incubation. Each treatment was replicated three times with SD ±0.04 mm. The standard antibiotic ampicillin was also recordedusingthesameprocedureasaboveatthesame con-centrationandsolvents“1mg/mL.”The%activityindexfor the complex was calculated by the formula as under

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%Activity Index = Zone of inhibition by test compound ðdiametreÞ × 100
Zone of inhibition by standard ðdiametreÞ

Synthesis of compounds

2.2.1. 4-Benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole3-carboxylic acid (1a) An equimolar mixture of furandione F (0.278 g, 1 mmole) and 1-benzylidine-2-(2,5-dimethylphenyl)hydrazine (0.224 g, 1 mmole) were reacted in solid phase for approximately 40 min. The oily residue obtained was treated with dry ether. The crude product formed was crystallized from an ethyl alcohol to give 0.38 g (75%) of 1a, mp 202 C; IR (m, cm1): 3271 (OAH, COOH), 3040 (aromatic CAH), 2921 (aliph. CAH),

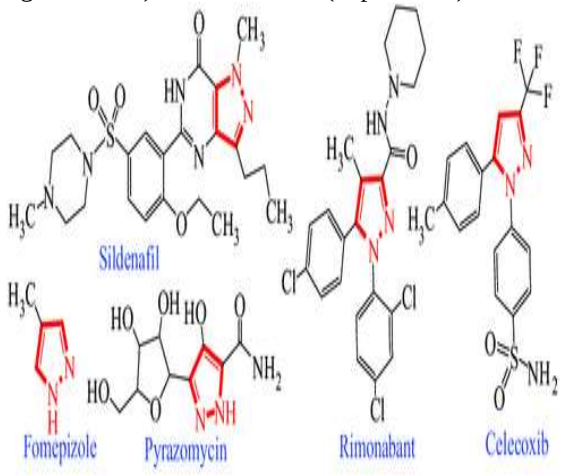

Figure- Some commercialized pyrazole-containing compounds.

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