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Catalytic and Multicomponent Reactions for Green Synthesis of Some Pyrazolone Compounds and Evaluation as Antimicrobial Agents

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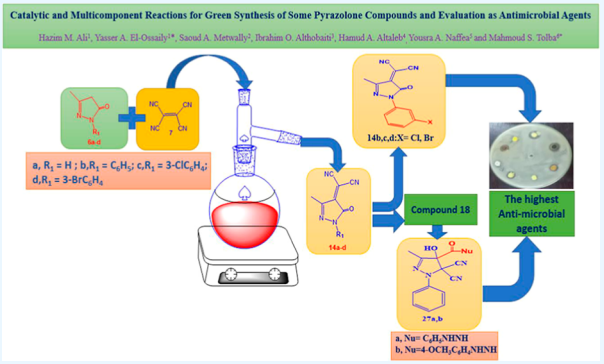
ABSTRACT: A green synthetic approach and facile method was developed to produce pyrazole compounds (**6a−d**) by the reaction of ethyl acetoacetate (**1**), hydrazines (**2a−d**), and catalytic imidazole (**3**) in aqueous media. 4-Dicyanomethylene-2-pyrazoline-5-one derivatives (**14a−d**) were synthesized through the reaction of 2-pyrazoline-5-one derivatives (**6a−d**) with tetracyanoethylene (TCE) (**7**) by using catalytic imidazole (**3**) in an aqueous medium. Moreover, the 4-dicyanomethylene derivative (**16**) was obtained via treatment of 1-phenyl-3,5-pyrazolidinedione (**15**) with TCE (**7**). The spiropyrazoleoxirane derivatives (**18** and **20**) were prepared by treating the precursor 4-dicyanomethylene-2-pyrazoline-5-one derivative (**14b**) with hydrogen peroxide in various polar solvents under alkaline conditions. The spiropyrazole oxirane derivative (**18**) was used as a precursor for the design of functionalized pyrazolone derivatives (**24** and **27a**, **b**). The chemical structure of the novel designed derivatives was ascertained based on elemental analyses, mp, thin-layer chromatography, and spectral analyses. Furthermore, some of the synthesized derivatives were examined against different pathogenic bacterial and fungal strains. Their results demonstrated that some of them revealed notable antimicrobial activities.



INTRODUCTION

The triple bottom line concept of green chemistry is used to analyze current chemical industries.[1] To minimize the environmental impact of pharmaceutical production, there is a growing interest in ecofriendly and green methods.[2,3] Ecologically friendly manufacturing techniques include atom economy, limited waste production, and environmentally acceptable reagents and solvents, with water as the preferred solvent wherever available.[4−6] Thus, the utilization of water as a nonclassical reaction medium has increased.[7−9] The multicomponent reactions (MCRs) have appropriate attributes, especially atom economy, where the number of used solvents and energy needed for separation and purification of reaction products is notably reduced to meet the demand of green chemistry.[10−12] The MCRs are characterized by the simplicity and versatility of the experimental procedures that unlock access to a wide range of products via the varied possibilities of reagent combinations.[13,14] Also, MCRs are very potent protocols in drug discovery and synthesis of useful bioorganic molecules.[15−20] Additionally, the pyrazole moiety is a versatile molecule, and its derivatives have been reported to have numerous biological activities,[21−23] including antimicrobial,[24] antifungal,[25] antitubercular,[26] anti-inflammatory,[27] anticonvulsant,[28] anticancer,[29] antiviral,[30] angiotensin-converting enzyme inhibitory, neuroprotective, cholecystokinin-1 receptor antagonist, and estrogen receptor ligand activity.[31−33] Whereas the resistance of microbial strains to conventional medications created in recent years is one of the key medical difficulties. Therefore, one of the study topics of chemists is the synthesis of novel molecules having antimicrobial characteristics.[34−36] Pyrazolone derivatives are considered essential components in antimicrobial drug discovery.[37] Throughout the continuation of our attempts is toward the methodologies for an ecofriendly synthetic facility with the significant benefits of rate acceleration in water as the reaction medium and utilizing a MCR approach.[38−45] The simple and practical water-assisted MCR method for the production of pyrazolone derivatives with the benefit of green chemistry and the expectation that they will have interesting biological activity applications is described.

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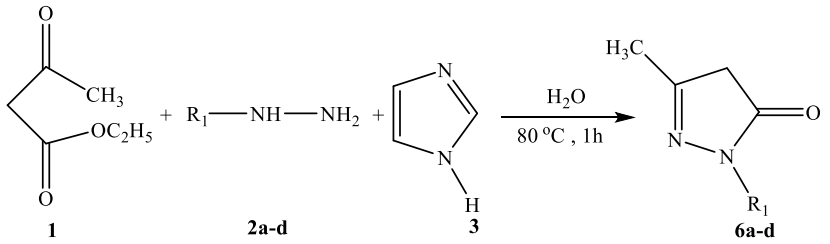
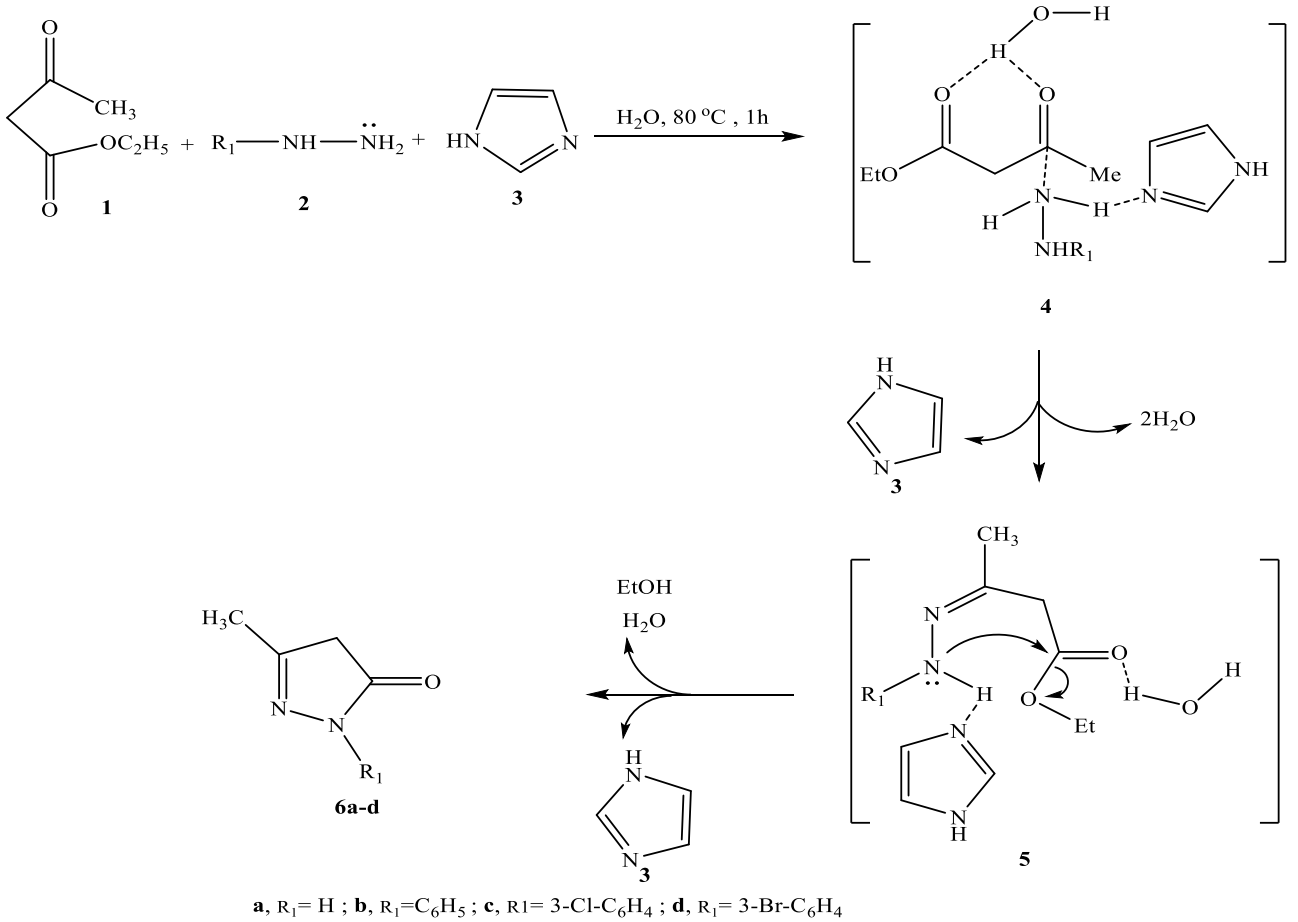
Scheme 1. Synthesis of Pyrazolineone Derivatives (6a−d)



a, R_1= H ; **b**, R_1=C_6H_5 ; **c**, R_1= 3-Cl-C_6H_4 ; **d**, R_1= 3-Br-C_6H_4

Scheme 2. Role of Water and Imidazole to Produce (6a−d)



a, R_1= H ; **b**, R_1=C_6H_5 ; **c**, R1= 3-Cl-C_6H_4 ; **d**, R_1= 3-Br-C_6H_4

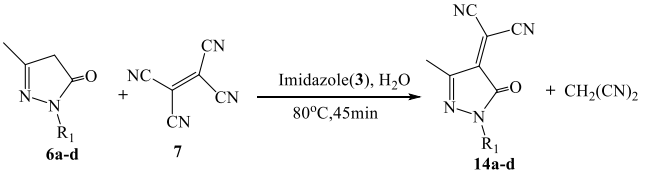
RESULTS AND DISCUSSION

The basic principles of green syntheses are that they are simple methods, require a short time, and involve easy product separation and purification. These advantages encouraged us to develop an easy green methodology to synthesize 2-pyrazoline-5-one derivatives (**6a−d**) (Scheme 1).

The pyrazolineone derivatives (**6a−d**) were produced by treatment of ethylacetoacetate (**1**), hydrazines (**2a−d**), and imidazole (**3**) as the catalyst in aqueous media.[46] A suggested mechanism to show the role of water and imidazole in the production of 2-pyrazoline-5-one derivatives (**6a−d**) has been depicted under Scheme 2, wherein water exerts electrophilic activation through a hydrogen bond.[10−12,16] Structural conformation of **6a−d** was established through comparison with reported physical and spectroscopic data by known methods.[47,48]

The use of TCE is based on the high reactivity of this reagent, which has potential use in organic synthesis. Consequently, 4-dicyanomethylene-2-pyrazolin-5-one derivatives (**14a−d**) were synthesized by a direct reaction of TCE (**7**) with 2-pyrazolin-5-one derivatives (**6a−d**) in the presence of a catalytic amount of imidazole (**3**) (Scheme 3). For a

Scheme 3. Catalytic Preparation of (14a−d)



a, $\mathbf{R_1}$ = H ; **b**, $\mathbf{R_1}$ = C_6H_5 ; **c**, $\mathbf{R_1}$ = 3-ClC_6H_4 ; **d**, $\mathbf{R_1}$ = 3-BrC_6H_4

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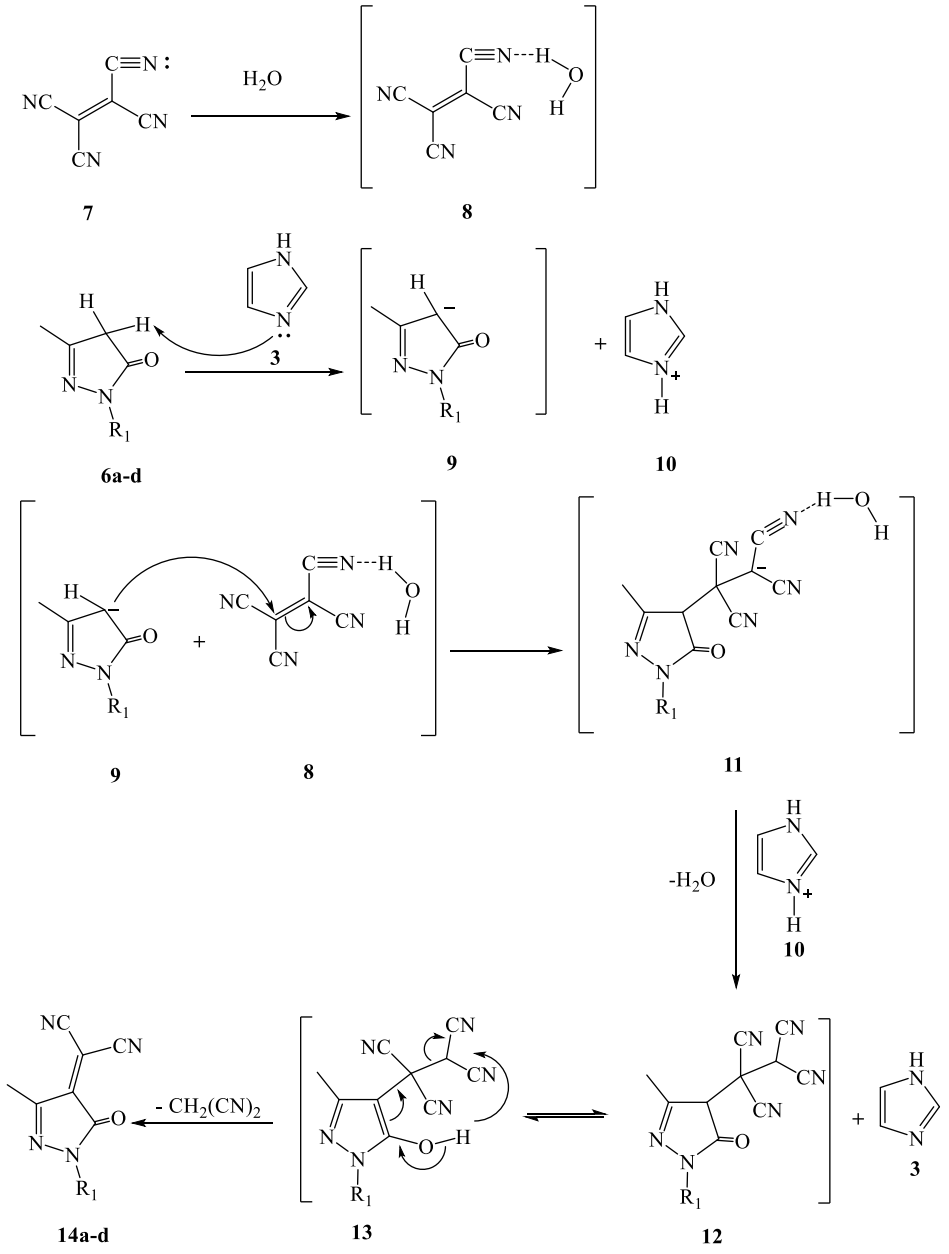
Scheme 4. Probable Mechanism Through which Water and Imidazole Generate 4-Dicyanomethylene-2-pyrazoline-5-one Derivatives (15a−d)



a, R_1 = H ; **b**, R_1 = C_6H_5 ; **c**, R_1 = 3-ClC_6H_4 ; **d**, R_1 = 3-BrC_6H_4

detailed explanation, the reaction process between 2-pyrazoline-5-one derivatives (**6a−d**) and TCE (**7**) is given. The influence of conventional organic solvents on the yield of the reaction pathway is studied in the presence of catalytic imidazole for the purpose of optimizing the catalytic quantity of the employed catalyst and determining the efficacy of conventional organic solvents. Initially, when the procedure was carried out in the absence of a catalyst, the products were produced with poor yields after 2−3 h. Also, addition of 0.2 mmol imidazole resulted in low product yields, and increasing the catalytic amount of imidazole to 0.5 mmol provided 4-dicyanomethylene-2-pyrazoline-5-one derivatives (**14a−d**) in good yields; however, increasing the catalytic amount further did not boost product yields. The solvent effect on the preparation of (**14a−d**) is initially investigated via the treatment of 2-pyrazoline-5-one derivatives (**6a−d**), TCE (**7**), and 0.5 mmol imidazole in various solvents such as water, acetonitrile, ethanol, methanol, tetrahydrofuran, and dioxane.[49−52] However, water afforded higher yields than their other counterparts. **14a−d** were elucidated via comparison with reported data by conventionally known methods.[38,39,53,54]

A tentative mechanism to produce imidazole-catalyzed 4-dicyanomethylene-2-pyrazoline-5-one derivatives (**14a−d**) in water is proposed in Scheme 4 wherein water activates the nitrile group in **7** through a hydrogen bond,[10−12,16] and imidazole activates the nucleophile **6a−d** through proton abstraction from the active methylene group. The feasibility of an active methylene hydrogen at 4-position of the 2-pyrazolone-5-one derivatives (**6a−d**) depends on the pK_a value of such active hydrogens.[55,56] In our present study, we

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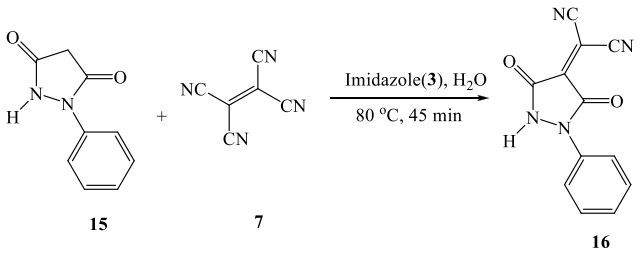
have found that the reaction of TCE with active methylenes will depend mainly on the pK_a value of the latter. With active methylenes of pK_a values less than 10, the formation of the dicyanomethylene derivative at position 4 in the 2-pyrazolin-5-one ring is favored (Scheme 3). Active methylenes with a pK_a value of 10 or higher react with TCE to give the tetracyanoderivative adduct.[57] The formation of 4-dicyanomethylene-2-pyrazoline-5-one derivatives (**14a−d**) may involve the protonation of TCE (**7**) by imidazole (**3**) to afford the two reactive intermediates (**8** and **9**), followed by an intermolecular attack of the deprotonated imidazole (**9**) on 2-pyrazoline-5-one derivatives (**6a−d**) to generate the more reactive carbanion intermediate (**10**) with the generation of imidazole (**3**). The intramolecular nucleophilic attack of the carbanion (**10**) on the protonated TCE intermediate (**8**) produced the intermediate (**11**), which rearranges easily to intermediate **12** and/or **13,** followed by the loss of a molecule of malononitrile via the retro Michael reaction to afford the expected products **14a−d** (Scheme 4).

Also, 4-dicyanomethylene-1-phenyl-3,5-pyrazolidinedione (**16**)[58] was prepared via the same manner through the reaction of 1-phenyl-3,5-pyrazolidinedione (**15**)[40] with TCE (**7**) in 0.5 mmol catalytic imidazole (**3**) (Scheme 5).

Scheme 5. Synthesis of 4-Dicyanomethylene Derivative (16)

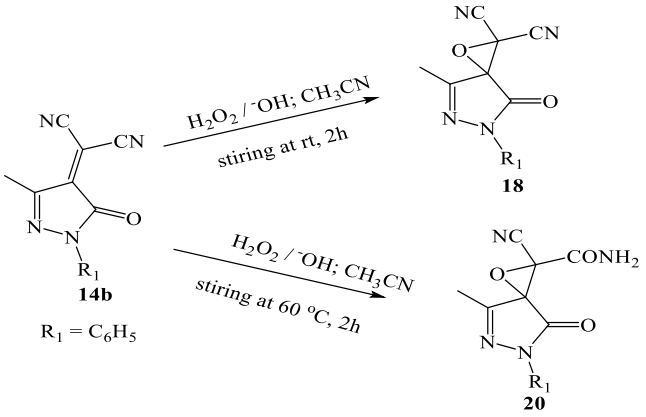


15 7 16

The derivative (**16**) was established by various spectral investigations, where the FT-IR spectrum revealed the characteristic absorption peaks: ν (cm^{-1}) at 3441 (NH), 2210 (CN), 1749 (CO), and 1706 (CO). The ^{1}H NMR (DMSO-d_6) spectrum showed a multiplet at δ values 7.04−7.91 (5H, C_6H_5) and a singlet at 8.51 (1H, NH). ^{13}C NMR in DMSO-d_6 revealed three characteristic signals in ppm: 166.6 (CO), 165.5 (CO), and 113.5 (CN). The mass spectrometric analysis revealed a peak at m/z 238 (100%), which represented its high stability under electron impact. Furthermore, this stability is proved by the appearance of a doubly charged ion at m/z 119 (17.1%). Moreover, dihydrospiropyrazoleoxirane derivatives (**18**) and (**20**) were synthesized by oxidation of **14b** using alkaline hydrogen peroxide (Scheme 6). The influence of temperature and the solvent on the synthesis of **18** and **20** was investigated by the reaction between 4-dicyanomethylene-2-pyrazoline-5-one derivatives (**14b**), hydrogen peroxide, and a few drops of 10% potassium hydroxide solution in different solvents such as *n*-hexane, cyclohexane, benzene, 1,4-dioxane, tetrahydrofuran, *t*-butyl alcohol, ethanol, and acetonitrile.[49−52] However, acetonitrile provided higher yields than its other counterparts (Table 1).

On the other hand, the corresponding monoamide product **20** was obtained by conducting the reaction of **14b** at 60 °C for 2 h (Scheme 6).[59] The mechanism to produce **18** and **20** by using alkaline hydrogen peroxide was illustrated in Scheme 7.

Scheme 6. Synthesis of Compounds 18 and 19 from 14b



14b 18 20

Table 1. Solvent Effectiveness on the Production of Dihydrospiropyrazoleoxirane Derivatives (18)

entry	solvent	time (h)	yield (%)
1	*n*-hexane	2	0.0
2	cyclohexane	2	0.0
3	benzene	2	0.0
4	1,4-dioxane	2	40
5	THF	2	55
6	*t*-BuOH	2	75
7	C_2H_5OH	2	80
8	CH_3CN	2	85

The spiropyrazole-4,3′-oxirane (**18**) was fully characterized by spectral analyses. ^{1}H NMR in $CDCl_3$ is in conformity with the suggested structure. It showed a signal at δ 2.27 (s, 3*H*, CH_3) and a multiplet extended at δ values: 7.82 (d, 2*H*, C_6H_5), 7.42 (t, 2*H*, C_6H_5), and 7.25 (t, 1*H*, C_6H_5). ^{13}CNMR in $CDCl_3$ revealed 11 signals in ppm: 13.6 (CH_3), 42.1 (C2′ oxirane), 64.7 (C3′ oxirane), 106.9 (CN), 109.1 (CN), 126.5, 129.0, 118.4, 136.7 (phenyl group), 148.9 (C3 pyrazole), and 158.4 (CO). Mass spectrometric analysis of the dihydrospiropyrazoleoxirane derivative (**18**) revealed a peak at m/z 252 with a high relative abundance (72.1%). The molecular ion loses a hydrogen radical to give an ion at m/z 251, representing the base peak. Also, compound (**20**) was characterized by ^{1}H NMR and showed a singlet at δ 1.96 (3*H*, CH_3) and a multiplet extended at δ values: 7.82 (d, 2*H*, ArH), 7.49 (t, 2*H*, ArH), 7.27 (t, 1*H*, ArH), and a singlet at 8.47 (2*H*, NH_2). The presence of NH_2 protons was confirmed by deuteration. ^{13}C NMR in DMSO-d_6 showed signals in ppm: 13.4 (CH_3), 42.9 (C2′ oxirane), 64.3 (C3′ oxirane), 112.3 (CN), 161.7 ($CONH_2$), 118.0, 129.1, 125.5, 137.4 (phenyl group), 151.6 (C3 pyrazole), and 159.2 (CO). The mass spectrometric analysis of **20** indicates the formation of a peak at m/z 270, which represented the molecular ion with a moderate relative abundance (31.1%). We reported herein the reactions of **18** with different nucleophilic reagents. Ammonia solution reacted rapidly with **18** with the formation of unexpected pyrazolone derivative (**24**) and not the dicyanopyrazole compound (**21**) in a good yield. The physical and spectroscopic data of **24** were identical to our previously reported work.[41,60]

The suggested reaction mechanism to produce pyrazolone derivative (**24**) is investigated. The formation of **24** may involve the nucleophilic ring opening of the oxirane ring through the attack of ammonia to produce the intermediate

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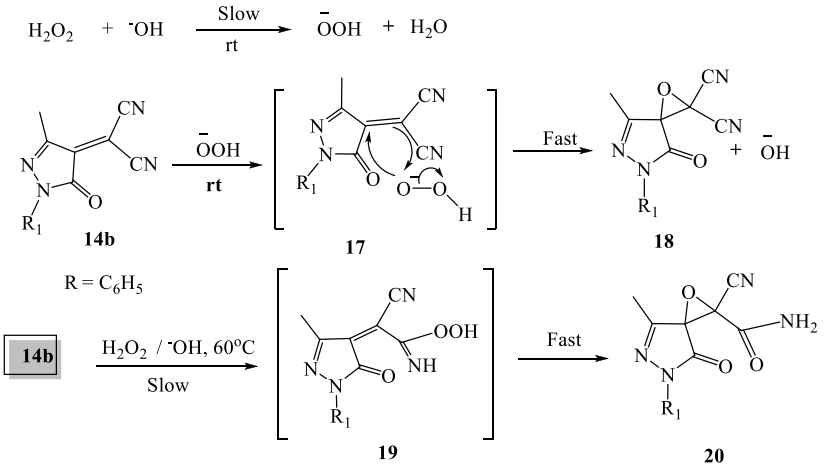
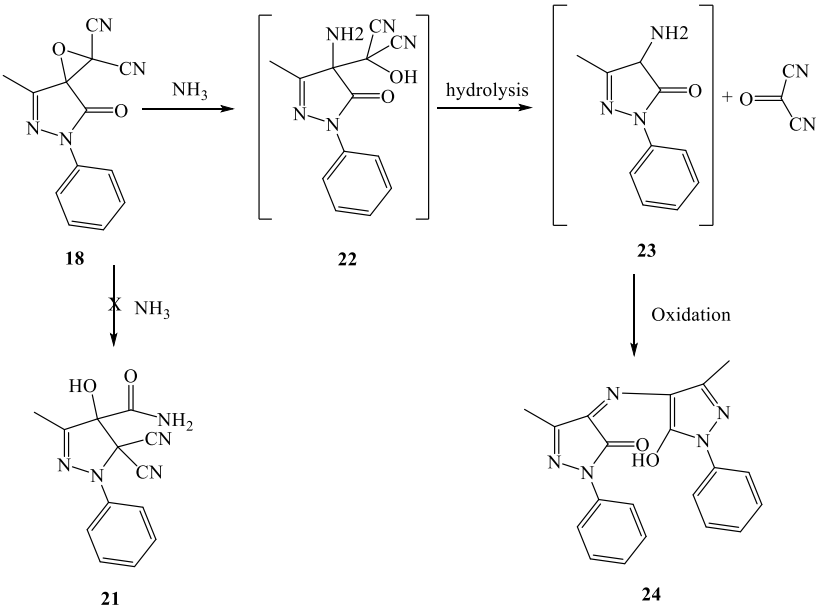
Scheme 7. Suggested Mechanism for the Assembly of Derivatives 18 and 20



Scheme 8. Suggested Mechanism for the Assembly of the Pyrazolone Derivative (24)



(**22**), which will be hydrolyzed to generate the 4-aminopyrazole intermediate (**23**), followed by air oxidation to produce the pyrazolone derivative (**24**) (Scheme 8). Moreover, **18** reacted with phenylhydrazine and/or 4-methoxyphenylhydrazine (**25a, b**) and imidazole (**3**) (0.5 mmol) to give the pyrazole-4-carboxylic acid derivatives (**27a,b**).[42,43] Such a ring transformation reaction may take place via the plausible nonisolated intermediates, as shown in the following suggested reaction mechanism (Scheme 9).

The two compounds **27a,b** were confirmed by using various spectral analyses. **27a,b** were proved by NMR spectroscopy. ^{1}H NMR of **27a** in DMSO-d_6 revealed a signal at δ 2.27 (s, 3H, CH_3) and a multiplet centered at δ 7.51 (13H, 10 ArH; 2H, 2NH; 1H, OH). The ^{13}C NMR measurement for compound **27a** in DMSO-d_6 gave the following signals in ppm: 13.1 (CH_3), 128.4 (C3), 96.5 (C4), 55.4 (C5), 109.9 (2CN), 123.8, 119.9, 124.9, 128.8 (C_6H_5NHNH), 118.0, 128.3, 112.4, 128.0 (C_6H_5), and 169.8 (CO). The mass spectrometric analysis of **27a** indicates a peak at m/z 360, which represented the molecular ion with a low relative abundance (1.6%). This reflects the low stability of the molecular ion under electron impact. ^{1}H NMR of **27b** in DMSO-d_6 indicates the following characteristic signals at δ values in ppm: a singlet at 2.14 (3H, CH_3), a singlet at 3.78 (3H, OCH_3), and a multiple centered at 7.29 (12H, 9ArH; 2H, 2NH; 1H, OH). The ^{13}C NMR measurement for compound **27b** in DMSO-d_6 gave the following signals in ppm: 11.4 (CH_3), 77.0 (OCH_3), 159.6 (C3), 106.7 (C4), 77.9 (C5), 117.9 (2CN), 156.6, 110.0, 113.8, 137.4 (C_6H_5NHNH), 118.7, 129.3, 113.8, 142.3 (C_6H_5), and 161.0 (CO). Mass spectrometric analysis of **27b** indicates a molecular ion peak at m/z 390 with a low relative abundance (10%), which reflects its low stability under electron impact. The suggested fragmentation pattern of **27b** showed ion (A) at m/z 155 (24%) and ion (B) at m/z 224 (23%). Therefore, the formation of the fragment ions A and B was considered a good proof for the proposed compound (**27b**) (Scheme 10).

Biological Evaluation. *Antimicrobial Activity.* Six types of bacteria and six fungal strains were used to assess the antibacterial and antifungal properties of the produced compounds (*Staphylococcus aureus, Bacillus cereus, Micrococcus luteus, Escherichia coli, Pseudomonas aeruginosa,* and *Serratia*

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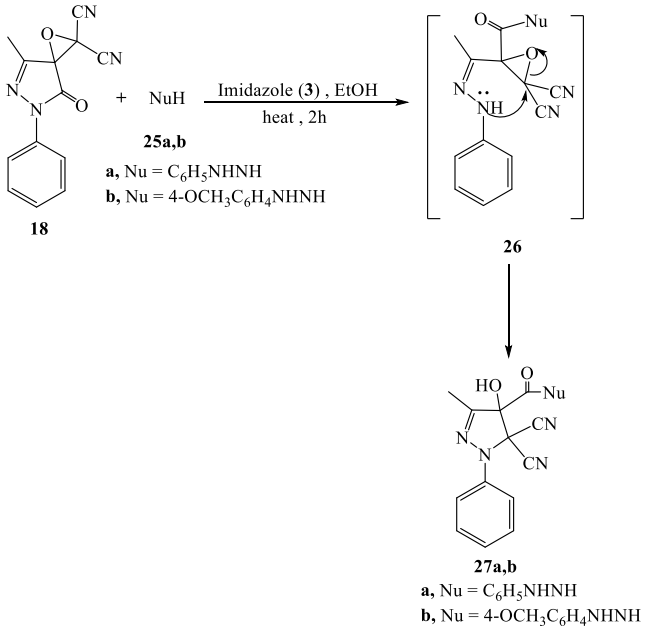
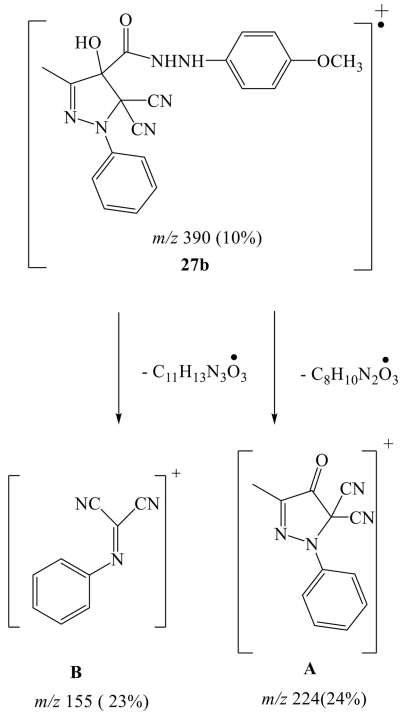
Scheme 9. Synthesis of Pyrazole-4-Carboxylic Acid Derivatives (27a, b)



Scheme 10. Fragmentation Pattern of Pyrazole-4-carboxylic Acid Derivative (27b)



marcescens) (Table 2), as well as six fungal strains (*Candida albicans*, *Trichophyton rubrum*, *Aspergillus flavus*, *Fusarium oxysporum*, and *Scopulariopsis brevica*) (Table 3). The inhibition zones of the studied compounds were compared with those of the antibacterial and antifungal reference drugs chloramphenicol and clotrimazole, respectively.

From the practical findings shown in Table 2, we extract the following: in the case of antibacterial activity, the results demonstrated outstanding activity of the chosen prepared compounds; therefore, compounds **14c**, **14d**, and **6b** displayed the maximum activity against *S. aureus* (+ve), whereas compounds **18** and **27a** showed moderate to strong activity compared to chloramphenicol. Additionally, compound **14c** had the highest activity (+ve) against *B. cereus*, while compounds **14d** and **27b** exhibited moderate activity in comparison to chloramphenicol. It was discovered that these chemicals **14c** and **14d** had the maximum biological activity against *Escherichia coli* (−ve). Conversely, compounds **14a** and **14b** had a moderate level of activity, but compounds **14b** and **18** showed a trivial level of action when compared to chloramphenicol. Compound **14d** was identified to have the highest biological activity against *P. aeruginosa* (−ve). In comparison to chloramphenicol, compounds **14c**, **27a**, and **27b** exhibited a moderate level of activity. Moreover, the **14d** derivative was shown to be the most efficient against all genera of bacteria, whether Gram positive or Gram negative. Alternatively, the **14b** derivative is ineffective against all genera of positive and negative bacteria.

Similarly, all compounds examined showed exceptional effectiveness against a variety of fungal species. Compound **14d** had the greatest effectiveness against *C. albicans*. Furthermore, compounds **14c**, **18**, **27a**, and **27b** had excellent to moderate antifungal efficacy, whereas compound **14b** demonstrated insufficient antifungal activity when compared to clotrimazole. Compounds **14c** and **14d** had high activity against *T. rubrum*, while compounds **18** and **27b** exhibited moderate activity. Furthermore, compounds **14a** and **27a** lacked antifungal efficacy when compared to clotrimazole. Additionally, compounds **14c**, **14d**, and **27a** showed excellent activity against *A. flavus*, respectively. While compounds **14b** and **18** showed moderate activity. According to the previous findings, compounds **14c** and **14d** were the most efficient at inhibiting all fungal species, whereas compounds **18**, **27a**, and **27b** performed well in the inhibition zones. Compound **14b** was the least effective (Table 3).

Structure–Activity Relationship. The structure and activity of the moiety 3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene malononitrile revealed that it has a significant influence on the inhibitory activity of microorganisms. Additionally, Table 2 revealed a significant action against Gram positive and Gram negative bacteria. The addition of alternate halogen groups to the phenyl ring increased the total inhibitory action much more than the original inhibitory activity. The replacement of the electron-withdrawing group bromo in phenyl **14d** seems to be more suited for producing an active antibacterial drug than the chloro group substitution in compound **14c**. Additionally, the findings in Tables 2 and 3 indicate that the derivative dihydrospiropyrazoleoxirane **18**, which has a closed oxirane ring, is less efficient than the **27a, b** derivatives, which have an opening oxirane ring and a phenyl hydrazide sidechain. Furthermore, it was discovered that the **27b** derivative had the maximum activity against all species of bacteria and fungi owing to the presence of the methoxy group in the hydrazide group's para position.

EXPERIMENTAL SECTION

General. All reactions were monitored via TLC. Elemental analysis was performed on an elemental analyze system GmbH-VarioEL V.3 microanalyzer. An electrothermal IA9100 melting point apparatus (UK) was used to monitor the melting points that were reported incorrectly. On a Shimadzu DR-8001 spectrometer, FT-IR was performed. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectroscopy

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Table 2. Inhibition Zone (mm) and MIC (μg mL^{-1}) of the Tested Compounds (14b, 14c, 14d, 18, 27a, and 27b) in the Case of Antibacterial Activity

	sample no.						
bacteria strains	**14b**	**14c**	**14d**	**18**	**27a**	**27b**	ref[a]
S. aureus (+ve)	**11**[b](9.0)[c]	15(7.0)	17(7.0)	13(8.0)	14 (7.0)	15(8.0)	18(5.0)
B. cereus (+ve)	10(8.0)	18(7.0)	15(8.0)	11(8.0)	12(7.0)	13(7.0)	22(4.0)
M. luteus (+ve)	8(9.0)	13(8.0)	18(8.0)	13(7.0)	14(8.0)	12(9.0)	20(4.0)
E. coli (−ve)	8(10)	16(8.0)	16(7.0)	10(9.0)	13(8.0)	14(8.0)	18(5.0)
P. aeruginosa (−ve)	10(9.0)	15(8.0)	17(8.0)	12(9.0)	13(10)	15(8.0)	18(5.0)
S. marcescens (−ve)	8(8.0)	17(7.0)	19(7.0)	14(8.0)	12(9.0)	11(7.0)	20(3.0)

[a]Ref = chloramphenicol as antibacterial reference; amount added to each pore = 50 μL. [b]The diameter of inhibition zone in (mm) of compounds (**14b**, **14c**, **14d**, **18**, **27a**, and **27b**). [c]MIC (minimum inhibition concentration) in (μg mL^{-1}) of compounds (**14b**, **14c**, **14d**, **18**, **27a**, and **27b**).

Table 3. Inhibition Zone (mm) and MIC (μg mL^{-1}) of the Tested Compounds (14b, 14c, 14d, 18, 27a, and 27b) in the case of Antifungal Activity

	sample no.						
fungal strains	**14b**	**14c**	**14d**	**18**	**27a**	**27b**	ref[a]
C. albicans	12[b](8.0)[c]	13(9.0)	18(7.0)	13(8.0)	13(7.0)	14(8.0)	20(5.0)
T. rubrum	10(11)	19(10)	26(8.0)	12(9.0)	10(9.0)	13(8.0)	36(5.0)
A. flavus	18(8.0)	24(8.0)	25(9.0)	20(10)	23(9.0)	10(9.0)	44(6.0)
F. oxysporum	15(9.0)	17(8.0)	18(8.0)	16(7.0)	15(9.0)	16(7.0)	28(4.0)
S. brevicaulis	10(11)	15(9.0)	16(8.0)	13(9.0)	10(10)	13(10)	20(5.0)
G. candidum	13(10)	16(8.0)	17(9.0)	14(8.0)	11(8.0)	13(8.0)	24(5.0)

[a]Ref = clotrimazole as antifungal reference; amount added to each pore = 50 μL. [b]The diameter of inhibition zone in (mm) of compounds (**14b**, **14c**, **14d**, **18**, **27a**, and **27b**). [c]MIC (minimum inhibition concentration) in (μg mL^{-1}) of compounds (**14b**, **14c**, **14d**, **18**, **27a**, and **27b**).

were measured on a Joel spectrometer, and chemical shifts were performed in ppm. Mass spectrometric analysis was performed on a Joel-JMS 600 spectrometer. All used chemicals are commercial and were used without further purification.

Synthesis of Some Pyrazolinone Derivatives (6a−d). *General Procedure.* The mixture of ethyl acetoacetate (10 mmol)-substituted hydrazine (10 mmol) and imidazole (0.5 mmol) in 20 mL of water was refluxed under stirring at 80 °C for 1 h. Then, the mixture was left at ambient temperature for 1 h. The formed precipitate was collected, washed three times with water (30 mL), and then desiccated carefully. The resulting solid precipitate was recrystallized from the suitable solvent.

*5-Methyl-2,4-dihydro-3H-pyrazol-3-one (**6a**).* Colorless flakes from EtOH, mp 220−221 °C, yield 92%. IR: ν (cm^{-1}) 3286 (NH), 2985 (sp^3-*H*), 1720 (CO), 1674 (C═N). ^{1}HNMR (400 MHz, DMSO-d_6): δ 2.04 (s, 3*H*, CH_3), 5.17 (s, 2*H*, CH_2) and 10.31 (s, 1*H*, NH). ^{13}CNMR (100 MHz, DMSO-d_6), four signals in ppm: 11.6 (CH_3), 89.4 (CH_2), 139.8 (C═N), 161.5 (CO). EI-MS *m*/*z* (%): 98.11 (M, 100). Anal. Calcd. for $C_4H_6N_2O$ (98.11): C, 48.97; H, 6.16; N, 28.56%. Found: C, 48.65; H, 6.13; N, 28.42%.

*5-Methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (**6b**).* Colorless needles from EtOH, mp 127 °C (lit. 126−128 °C),[48] yield 93%. IR: ν (cm^{-1}) 3100 (sp^2-*H*), 1597 (CO), 1674. ^{1}HNMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3*H*, CH_3), 4.52 (s, 2*H*, CH_2) and 7.52−8.03 (m, 5*H*, C_6H_5). ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.5 (CH_3), 86.2 (CH_2) and 163.4 (CO). Anal. Calcd. for $C_{13}H_8N_4O_2$ (174.2): C, 68.95; H, 5.79; N, 16.08%. Found: C, 68.91; H, 5.96; N, 15.98%.

*2-(3-Chlorophenyl)-5-methyl-2,4-dihydro-3H-pyrazol-3-one (**6c**).* A pale brown amorphous solid from acetonitrile, mp 173 °C, yield 83%, IR: ν (cm^{-1}) 3100 (sp^2-*H*), 1733 (CO) 1584 (C═N). ^{1}HNMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3*H*, CH_3), 4.89 (s, 2*H*, CH_2) and 7.42−8.06 (m, 4*H*, C_6H_4). ^{13}CNMR (100 MHz, DMSO-d_6): δ 14.6 (CH_3), 82.6 (CH_2) and 165.1 (CO). Anal. Calcd. for $C_{10}H_9ClN_2O$ (253.10): C, 57.57; H, 4.35; N, 13.43%. Found: C, 57.62; H, 4.47; N, 13.22%.

*2-(3-Bromophenyl)-5-methyl-2,4-dihydro-3H-pyrazol-3-one (**6d**).* Pale brown flakes from acetonitrile, mp 110 °C, yield 89%, IR: ν (cm^{-1}) 3100 (sp^2-*H*), 1582 (CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.13 (s, 3*H*, CH_3), 4.72 (s, 2*H*, CH_2) and 7.62−8.15 (m, 4*H*, C_6H_4). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.4 (CH_3), 79.2 (CH_2) and 164.1 (CO). Anal. Calcd. for $C_{10}H_9BrN_2O$ (253.10): C, 47.46; H, 3.58; N, 11.07%. Found: C, 47.62; H, 3.69; N, 11.25%.

Synthesis of 2-(3-Methyl-5-oxo-1-(substituted phenyl)-1,5-dihydro-4*H*-pyrazol-4-ylidene) Malononitrile (14a−c). *General Procedure.* A suspension of TCE (10 mmol), pyrazolinone derivatives (**8a−d**) (5 mmol), and imidazole (0.5 mmol) in water (30 mL) were refluxed with stirring for 45 min at 80 °C. The mixture was left at ambient temperature for 30 min and then filtered off. The filtrate was diluted with cold water to give heavy precipitate, which was collected and recrystallized from the suitable solvent.

*2-(3-Methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene)-malononitrile (**14a**).* Dark brown crystals from ethanol, mp 263−264 °C (lit. 263−264 °C),[38] yield 88%.

*2-(3-Methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)malononitrile (**14b**).* Black needles from EtOH, mp 178 °C (lit. 178 °C),[53,54] yield 80%. IR: ν (cm^{-1}) 3100 (sp^2-*H*), 2200 (CN), 1707 (CO) and 1590 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (s, 3*H*, CH_3) and 7.85−8.03 (m, 5*H*, C_6H_5). EI-MS *m*/*z* (%) = 236.23 (M, 77.6). Anal. Calcd. for $C_{13}H_8N_4O$ (263.23): C, 66.10; H, 3.41; N, 23.72%. Found: C, 66.22; H, 3.49; N, 23.58%.

*2-(1-(3-Chlorophenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene)malononitrile (**14c**).* Black tiny needles from EtOH, mp 133 °C, yield 72%, IR: ν (cm^{-1}) 3100 (sp^2-

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H), 2300 (CN), 1713 (CO) and 1593 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (s, 3*H*, CH_3) and 8.06−8.62 (m, 4*H*, C_6H_4). EI-MS *m*/*z* (%) = 270.68 (M, 100). Anal. Calcd. for $C_{13}H_7ClN_4O$ (270.68): C, 57.69; H, 2.61; N, 20.70%. Found: C, 57.46; H, 2.72; N, 20.79%.

*2-(1-(3-Bromophenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene)malononitrile (**14d**).* Black flakes from dioxane, mp 196 °C (lit. 196 °C),[39] yield 53%. IR: ν (cm^{-1}) 3093 (sp^2-*H*), 2320 (CN), 1711 (CO) and 1590 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.54 (s, 3*H*, CH_3) and 7.39−8.03 (m, 4*H*, C_6H_4). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.9 (CH_3), 116.0 (CN) and 157.4 (CO). EI-MS *m*/*z* (%) = 314 (M, 96.2), 316 (M, 100%) and doubly charged ion at 154.75 (54.2%). Anal. Calcd. for $C_{13}H_7BrN_4O$ (315.13): C, 49.55; H, 2.24; N, 17.78%. Found: C, 48.47; H, 2.20; N, 17.8%.

Synthesis of 2-(3,5-Dioxo-1-phenylpyrazolidin-4-ylidene)malononitrile (16). TCE (10 mmol), 1-phenylpyrazolidine-3,5-dione (5 mmol), and imidazole (0.5 mmol) in water (30 mL) were refluxed with stirring for 45 min at 80 °C. The mixture was left at ambient temperature for 30 min. After filtration of a few impurities, the produced filtrate was diluted with cold water to afford a black precipitate, which was collected and recrystallized from dioxane as black flakes, mp >350, yield 82%. IR: ν (cm^{-1}) 3219 (NH), 3100 (sp^2-*H*), 2219 (CN) and 1680 (CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.51 (s, 1*H*, NH) and 7.04−7.91 (m, 5*H*, C_6H_5). ^{13}CNMR (100 MHz, DMSO-d_6): δ 113.5 (CN), 166.6 (CO) and 165.5 (CO). EI-MS *m*/*z* (%) = 238 (M, 100), 316 (M, 100%). Anal. Calcd. for $C_{12}H_6N_4O_2$ (238.21): C, 60.51; H, 2.54; N, 23.52%. Found: C, 60.42; H, 2.37; N, 23.70%.

Synthesis of 2′,2′-Dicyano-3-methyl-1-phenyl-5-oxo-1,5-dihydrospiropyrazole-4,3′-oxirane (18). To a stirred solution of **14b** (10 mmol) in acetonitrile (30 mL) at ambient temperature for 2 h, few drops of sodium hydroxide (10%) and hydrogen peroxide (30%, 16.5 mL) were added dropwise until the dark violet color disappeared. The reaction mixture continued under stirring for 2 h. After filtration of a few impurities, the resulting filtrate was neutralized with dilute oxalic acid (5%) and diluted with water to afford a yellow precipitate. The formed precipitate was filtered, vacuum-desiccated, and recrystallized from chloroform/petroleum ether (1:1) as yellow fine crystals, mp 89−90 °C, yield 76.79%. IR: ν (cm^{-1}) 3050 (sp^2-*H*), 2900 (sp^3-*H*), 2220 and 2180 (CN), 1710 (CO), 1630 (C═N), 1120 (C−O), 910 (epoxide ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3*H*, CH_3), 7.82 (d, 2*H*, C_6H_5), 7.42 (t, 2*H*, C_6H_5), and 7.25 (t, 1*H*, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$), 11 signals in ppm: 13.6 (CH_3), 42.1 (C2′ oxirane), 64.7 (C3′ oxirane), 106.9 (CN), 109.1 (CN), 126.5, 129.0, 118.4, 136.7 (phenyl group), 148.9 (C3 pyrazole) and 158.4 (CO). EI-MS *m*/*z* (%) = 252(M, 72.1), 250 (M^+-2, 100). Anal. Calcd. for $C_{13}H_8N_4O_2$ (252.23): C, 61.90; H, 3.190; N, 22.21%. Found: C, 62.26; H, 4.628; N, 21.49%.

Synthesis of 2′-Cyano-3-methyl-1-phenyl-5-oxo-1,5-dihydrospiropyrazole-4,3′-oxirane-2′-carboxamide (20). To a hot stirred solution of **14b** (10 mmol) in 30 mL of acetonitrile at 60 °C for 2 h, few drops of sodium hydroxide (10%) and hydrogen peroxide (30%, 16.5 mL) were added dropwise until the dark violet color disappeared. The reaction mixture continued under stirring further for 1 h. After filtration of a few impurities, the resulting filtrate was neutralized with dilute oxalic acid (5%) and diluted with water to afford a dark yellow precipitate. The obtained precipitate was filtered, vacuum-desiccated, and recrystallized from chloroform/petroleum ether (1:1) as dark yellow fine crystals, mp 122−123 °C, yield 78%. IR: ν (cm^{-1}): 3400 and 3300 (NH_2), 3050 (sp^2-*H*), 2220 (CN), 2900 and 2850 (sp^3-*H*), 1700 (CO), 1610 (C═N), 1110 (C−O), 910 (epoxide ring). ^{1}H NMR (400 MHz, CDCl3): δ 1.96 (s, 3*H*, CH_3), 7.82 (d, 2*H*, C_6H_5), 7.49 (t, 2*H*, C_6H_5), 7.27 (t, 1*H*, C_6H_5), and 8.47 (s, 2*H*, NH_2). ^{13}CNMR (100 MHz, $CDCl_3$): 13.4 (CH_3), 55.9 (C2′ oxirane), 64.3 (C3′ oxirane), 112.3 (CN), 161.7 ($CONH_2$), 118.0, 129.1, 125.5, 137.4 (phenyl group), 151.6 (C3 pyrazole) and 159.2 (CO). EI-MS *m*/*z* (%) = 270 (M^+, 31.1). Anal. Calcd. for $C_{13}H_{10}N_4O_3$ (270.220): C, 57.78; H, 3.720; N, 20.73%. Found: C, 56.34; H, 3.491; N, 20.29%.

Synthesis of Pyrazolone Derivative (24). Compound (**18**) (1.5 mmol) and ammonia solution (5 mL) in EtOH (30 mL) were heated for 30 min. The mixture was continuously stirred for 1 h. After filtration, the resulting filtrate was neutralized with dilute oxalic acid (5%) to afford a red precipitate. The produced precipitate was filtered, vacuum-dried, and recrystallized from petroleum ether as red needless, mp 181 °C (lit. 181 °C),[41,60] yield 79.29%.

*5,5-Dicyano-4,5-dihydro-4-hydroxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic Acid Phenylhydrazide (**27a**) and 5,5-Dicyano-4,5-dihydro-4-hydroxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic Acid-4′-methoxyphenylhydrazide (**27b**).* A mixture of compound (**18**) (10 mmol) and substituted phenyl hydrazine (10 mmol) in EtOH (30 mL) was refluxed for 2 h in the presence of a catalytic amount of imidazole (0.5 mmol). The resulting solution was evaporated under vacuum to furnish a solid product, which was collected and recrystallized from the proper solvent.

*5,5-Dicyano-4,5-dihydro-4-hydroxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic Acid Phenylhydrazide (**27a**).* A brown amorphous solid from chloroform/petroleum ether (60−80) (1:1), mp 160 °C, yield 62.50%. IR: ν (cm^{-1}): 3200 (NH), 3050 (sp^2-*H*), 2900 and 2850 (sp^3-*H*), 2220 (CN), 1650 (CO), 1590 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3*H*, CH_3) and δ 7.51 (m, 13*H*, 10 ArH; 2*H*, 2NH; 1*H*, OH). ^{13}C NMR (100 MHz, DMSO-d_6): 13.1 (CH_3), 128.4 (C3), 96.5 (C4), 55.4 (C5), 109.9 (2CN), 123.8, 119.9, 124.9, 128.8 (C_6H_5NHNH), 118.0, 128.3, 112.4, 128.0 (C_6H_5) and 169.8 (CO). EI-MS *m*/*z* (%) = 360 (M, 1.6). Anal. Calcd for $C_{19}H_{16}N_6O_2$ (360.37): C, 63.32; H, 4.470; N, 23.32%. Found: C, 63.28; H, 4.262; N, 23.74%.

*5,5-Dicyano-4,5-dihydro-4-hydroxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic Acid-4′-methoxyphenylhydrazide (**27b**).* An orange granular solid from chloroform/petroleum ether (60−80) (1:1), mp 140 °C, yield 64.10%. IR: ν (cm^{-1}): 3210 (NH), 3050 (sp^2-*H*), 2900 and 2850 (sp^3-*H*), 2220 (CN), 1700 (CO), 1595 (C═N). ^{1}HNMR (400 MHz, DMSO-d_6): δ 2.14 (s, 3*H*, CH_3), δ 3.78 (s, 3*H*, OCH_3) and δ 7.29 (m, 12*H*, 9 ArH; 2*H*, 2NH; 1*H*, OH). ^{13}C NMR (100 MHz, DMSO-d_6): 11.4 (CH_3), 77.0 (OCH_3), 159.6 (C3), 106.7 (C4), 77.9 (C5), 117.9 (2CN), 156.6, 110.0, 113.8, 137.4 (C_6H_5NHNH), 118.7, 129.3, 113.8, 142.3 (C_6H_5) and 161.0 (CO). EI-MS *m*/*z* (%) = 390 (M, 10). Anal. Calcd. for $C_{20}H_{18}N_6O_3$ (390.40): C, 61.53; H, 4.640; N, 21.52%. Found: C, 62.15; H, 4.634; N, 21.73%.

Biological Assessment. *Procedure of the In Vitro Antibacterial Assay.* All used microorganisms were obtained from the microbiology department of Assiut University's Faculty of Medicine's culture collection. The effectiveness of the created compounds was determined using a range of Gram

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negative (*E. coli* and *P. aeruginosa*, and *S. marcescens*) and Gram positive (*S. aureus*, *B. cereus*, and *M. luteus*) bacterial strains in a 5 mL solution of the generated compounds in dimethyl sulfoxide (DMSO) as a solvent. The concentrations of the substances investigated were generally determined using the highest concentration at 100 μg/mL in DMSO and amoxicillin as a standard. Each Petri dish's sterile media (nutrient agar medium, 15 mL) was evenly coated with Gram positive and Gram negative bacterial cultures. For 24 h, the plates were incubated at 37 ± 2 °C.

Procedure of the In Vitro Antifungal Assay. The fungal strains (*C. albicans*, *T. rubrum*, *A. flavus*, *F. oxysporum*, *S. brevicaulis*, and *G. candidum*) were isolated from various human dermatophytosis situations (Assiut University Mycological Center, AUMC). The fungal strains were grown on sterile 9 cm Petri plates with Sabouraud's dextrose agar (SDA) supplemented with 0.05 percent amoxicillin to prevent bacterial contamination. The 10 mm diameter agar discs containing spores from these cultures were aseptically transferred to screw-topped vials containing 20 mL of sterile distilled water. After shaking, 1 mL of samples of the spore suspension was pipetted onto sterile Petri plates, followed by the addition of 15 mL of liquid SDA media. The screened compounds **14b**, **14c**, **14d**, **18**, **27a**, and **27b**, as well as the reference medication (clotrimazole), were dissolved in DMSO at a concentration of 2.0%. Plates were infected and incubated at ambient temperature for 4 days.

The antibacterial and antifungal activity of the investigated compounds were assessed using the technique outlined by Kwon-Chung and Bennett,[61] using wells with a diameter of 5 mm and 50 μL of the solution under investigation. Additionally, stock solutions of the standard medicines (chloramphenicol and clotrimazole) were produced in DMSO and tested for antibacterial and antifungal efficacy at a concentration of 100 μg/mL. The zones of inhibition were established and are presented in Tables 2 and 3.

The screened compounds (**14b**, **14c**, **14d**, **18**, **27a**, and **27b**) were dissolved in DMSO to yield a 2% concentration solution. Filter paper discs (Whatman no. 3) with a diameter of around 5 mm were soaked with 15 mL of the tested chemical solutions before being put on the surface of previously prepared agar plates seeded by the tested bacteria. Each disc was dipped to achieve thorough contact with the agar surface. After that, the agar plates were cultured for bacteria at 37 °C for 16−18 h and then at ambient temperature. The compound inhibition zones' sizes were measured and documented in the previous table. A similar procedure[61,62] was used for the commercial drug amoxicillin, which was used as a bacterium positive control. The microdilution technique was used to determine the MIC of each drug. The physiologically active compounds were diluted with DMSO and then incubated for 24 h in 10 mL broth tubes vaccinated with the tested culture. The MIC of each substance was calculated as the lowest concentration (μg mL^{-1}) at which no visible bacteria were found.

CONCLUSIONS

Using a catalytic quantity of imidazole, simple multicomponent processes for the green synthesis of 2-pyrazoline-5-one molecules and 4-dicyanomethylene-2-pyrazoline-5-one derivatives are described. Using hydrogen peroxide, a 1,5-dihydrospiropyrazole-4,3′-oxirane derivative was also produced. This compound has been used as an active synthon in the synthesis of potential novel pyrazole-4-carboxylic acid derivatives. Compounds **14c**, **14d**, **27a**, and **27b** were shown to be the most effective against all the tested fungi and bacteria.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c03070.

Analytical data of synthesized compounds (IR, ^{1}H NMR, ^{13}C NMR, and MS) (PDF)

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Notes

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