Synthesis, Antimicrobial Activity and Molecular Modeling of Some Novel 5-Aminopyrazole, Pyrazolo[1,5-*a*]pyrimidine, Bispyrazole and Bispyridone Derivatives Containing Antipyrinyl Moiety

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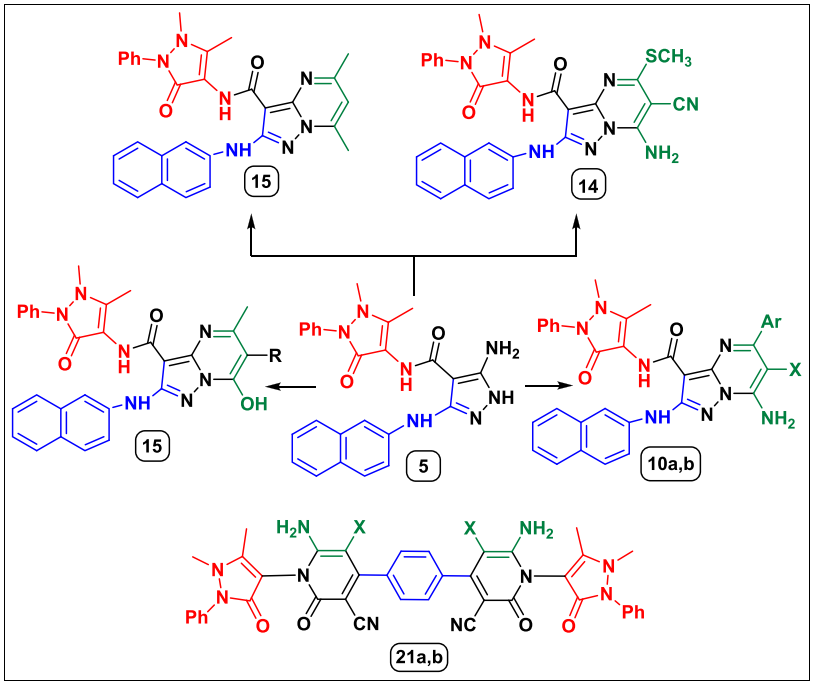


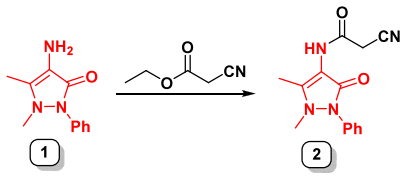
2-Cyano-N-(antipyrin-4-yl)-3-(ethylthio)-3-(naphthalen-1-ylamino)acryl-amide **4** was achieved via a one-pot, three-component reactions of cyanoacetamide derivative **2**, 2-naphthyl isothiocyanate, and diethyl-sulphate. The cyano acrylamide derivative **4** was hydrazinolysis to furnish 5-aminopyrazole **5**; many pyrazolo [1,5-*a*]pyrimidines **10a,b, 14, 15, 16, 18,** and **20** have been synthesized via treatment of **5** with some electrophilic reagents. Also, ternary condensation of cyanoacetamide derivative **2**, terephthalaldehyde, and active methylene derivatives afforded bispyridone derivatives **21a,b**. The structures of the new compounds were confirmed on the basis of elemental analysis and spectral data. Representative compounds of the synthesized products were tested and evaluated as antimicrobial. In general, the novel-synthesized compounds showed a good antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria, and antifungal activity against *Azithromycin* and *Ketoconazole*. The molecular modeling of the **21a** and **21b** as representative examples of the synthesized compounds has been drawn, and their molecular parameters were calculated.

INTRODUCTION

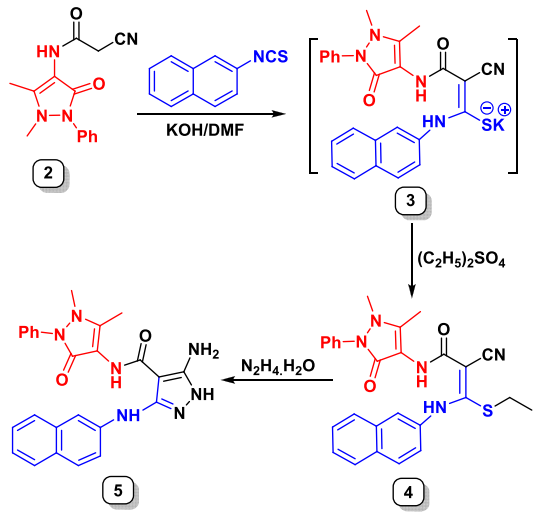
Infectious diseases caused by microorganisms are one of the main reasons of death in the world. This may be attributed to resistance and morphological modifications of microorganisms to currently market antibiotics. Hence, there will always be a vital need to discover new chemotherapeutic agents to avert the emergence of resistance and ideally shorten the duration of therapy, that is, it is desirable to find drugs with improved potency and wide activity spectrum. Pyrazoles showed more excellent antimicrobial and antifungal activities than control drugs [1–4]. Also, the synthesis of pyrazolo [1, 5-*a*] pyrimidine and their derivatives have attracted attention due to their interesting pharmacological properties [5–9]. Antipyrine derivatives are well known compounds used mainly as analgesic and antipyretic drugs antitumor agent, antivirus, anticancer, and radiosensitizing agent [10–12]. One of the

best known antipyrine derivatives is 4-aminoantipyrine (4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one), which presents a structural similarity with metamizole, a well-known and very effective analgesic, anti-inflammatory agent [13]. In continuation of our research program directed towards synthesis and investigation of biologically active compounds [14–23]. It seems therefore to be of considerable interest to synthesize novel aminopyrazole, pyrazolo [1,5-*a*] pyrimidine, bispyrazole and bispyridone derivatives containing antipyrinyl moiety. Additionally, our objective is also to study the antibacterial and antifungal activities of the synthesized compounds.

Scheme 1. Schematic illustration of the synthesis for cyanoacetamide derivative 2. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 2. Synthetic pathways for compounds **4** and **5**. [Color figure can be viewed at wileyonlinelibrary.com]



RESULTS AND DISCUSSION

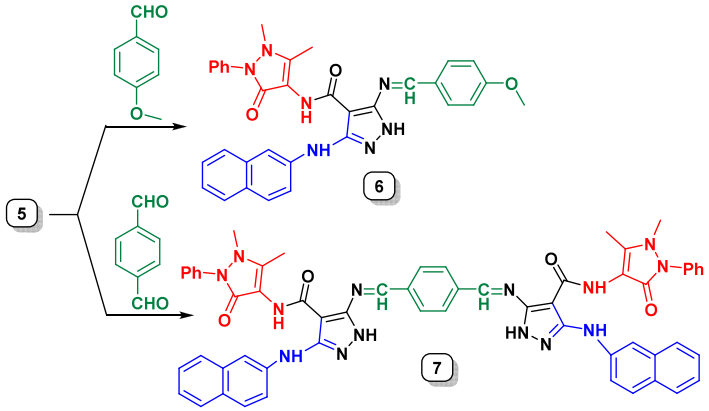
Chemistry. The reaction sequences used for synthesis of the title compounds are depicted in Schemes 1–4 and 5. The starting material 2-cyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)acetamide **2** was achieved in a good yield (92%) via treatment of 4-aminoantipyrine **1** with ethyl cyanoacetate in *m*-xylene under reflux [24], (Scheme 1).

Treatment of cyanoacetamide derivative **2** with 2-naphthyl isothiocyanate in the presence of potassium hydroxide gave the non-isolated adduct **3** which was then treated with diethyl sulfate to furnish the 2-cyano-*N*-(antipyrin-4-yl)-3-(ethylthio)-3-(naphthalen-1-ylamino)acrylamide **4**. Cycl-ocondensation of compound **4** with hydrazine hydrate in refluxing ethanol furnished the novel 5-aminopyrazole derivative **5** (Scheme 2). The mass spectrum of compound **5** revealed a molecular ion peak at *m/z* = 453 (24.3%) with a base peak at *m/z* = 69 (Chart 1).

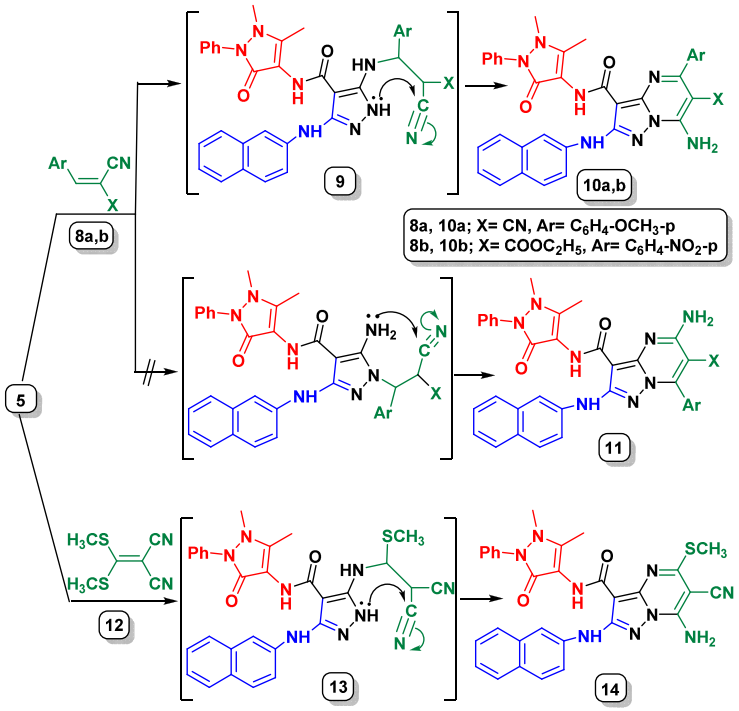
The reactivity of 5-aminopyrazole derivative **5** towards some electrophilic reagents was investigated. Schiff base derivatives were reported to possess significant biological activities and new series have been tested for their antitumor, antimicrobial, and antiviral activities [11,25]. In the light of these facts, we report the synthesis of azomethine derivative **6** via condensation of compound **5** with 4-methoxy-benzaldehyde in ethanol in the presence of piperidine under reflux. Also, bis(azomethine) derivative **7** was obtained by condensation of compound **5** with terephthalaldehyde (2 : 1 molar ratio) (Scheme 3).

The derivatives of pyrazolopyrimidines have been the focus of great interest over many years. This is due to the

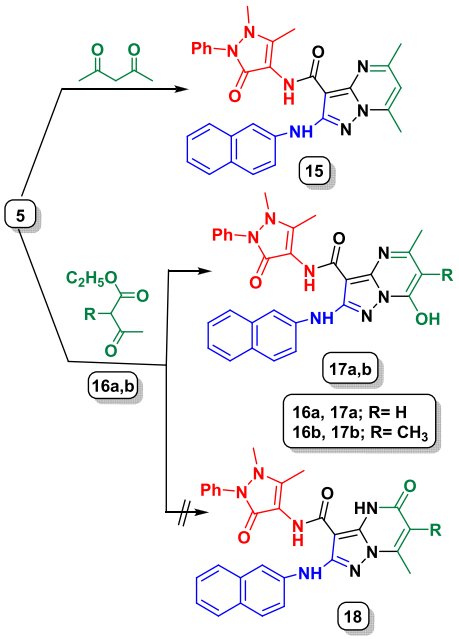
Scheme 3. Synthetic pathways for azomethine derivatives 6 and 7. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 4. Synthetic pathways for compounds **10–14**. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 5. Synthetic pathways for compounds pyrazolo[l,5-a]pyrimidine derivatives 15 and 17. [Color figure can be viewed at wileyonlinelibrary.com]



wide range of biological activities associated with this heterocyclic scaffold [12], so the reactivity of compound **5** towards α-cinnamonitriles was investigated. Therefore, treatment of 5-aminopyrazole **5** with α-cinnamonitriles **8a,b** in refluxing pyridine yielded a single product for which structure **10a,b** or **11a,b** seemed possible. Structure of **10a,b** appears more likely than **11a,b** on the basis of single crystal X-ray structure analysis [26] and HMBC-^{15} N [27]. The formation of **10a,b** is assumed to proceed via an initial *Michael* addition of the oxocyclic amino in **5** to the double bond in **8** to yield the non-isolable intermediate **9** followed by intramolecular cyclization and aromatization by loss of hydrogen molecule (Scheme 4). Similar to its behavior towards α-substituted cinnamonitrile [28,29], compound **5** was reacted with 2-(bis(methylthio)methylene)malononitrile **12** in ethanol containing a catalytic amount of piperidine as catalyst to produce pyrazolo[1,5-*a*]pyrimidine derivative **14** (Scheme 4).

This work was extended to cover the reactivity of compound **5** towards carbonyl compounds to synthesized pyrazolo[1,5-*a*]pyrimidines via the cyclocondensation of aminopyrazole **5** with β-ketoester. Thus, cyclocondensation of compound **5** with acetylacetone in refluxing glacial acetic acid gave the pyrazolo[l,5-*a*]pyrimidine derivative **15** (Chart 2). In addition, reaction of aminopyrazole **5** with ethyl acetoacetate **16a** and ethyl 2-methyl-3-oxobutanoate **16b** afforded two possible isomeric products **17** and **18**. Structure **18** was excluded on the basis of spectral data and analogy with previous work [30–33]. The formation of **17** is assumed to proceed through the condensation of the oxocyclic amino group in **5** with the carbonyl of acetyl moiety followed by *in situ* heterocyclization through elimination of ethanol (Scheme 5).

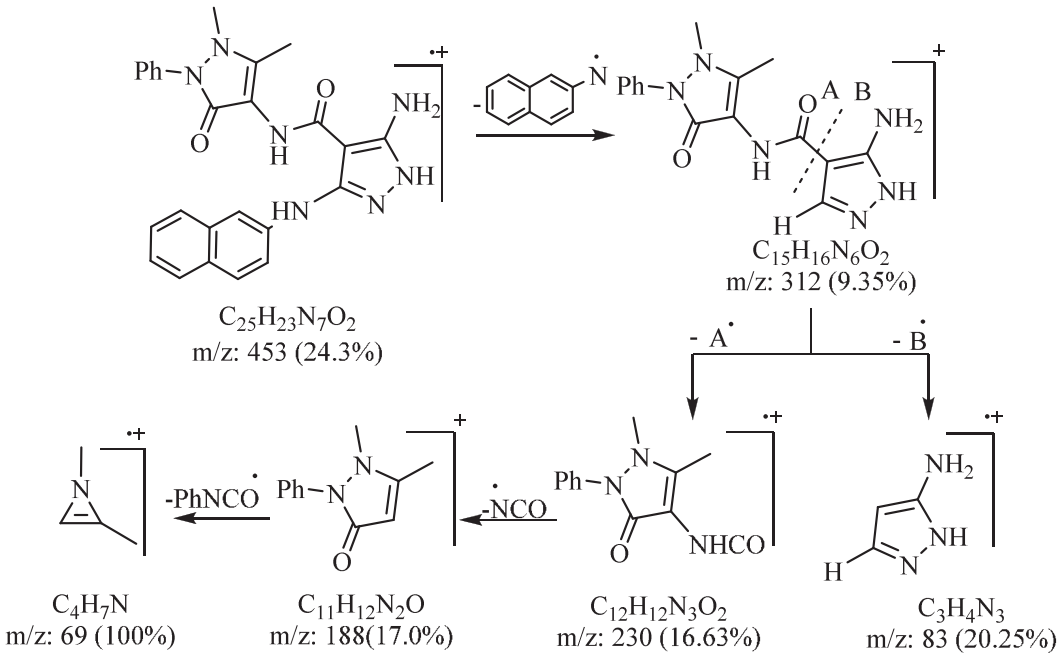


Chart 1. Fragmentation pattern of compound **5**.

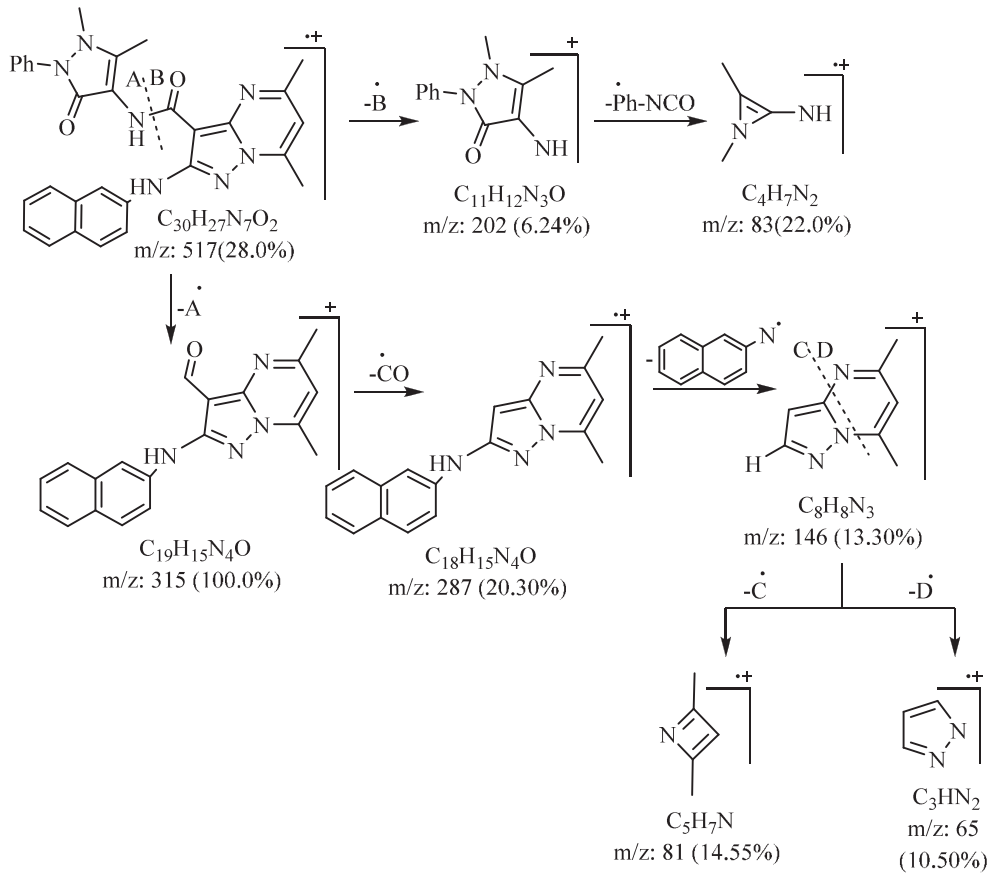


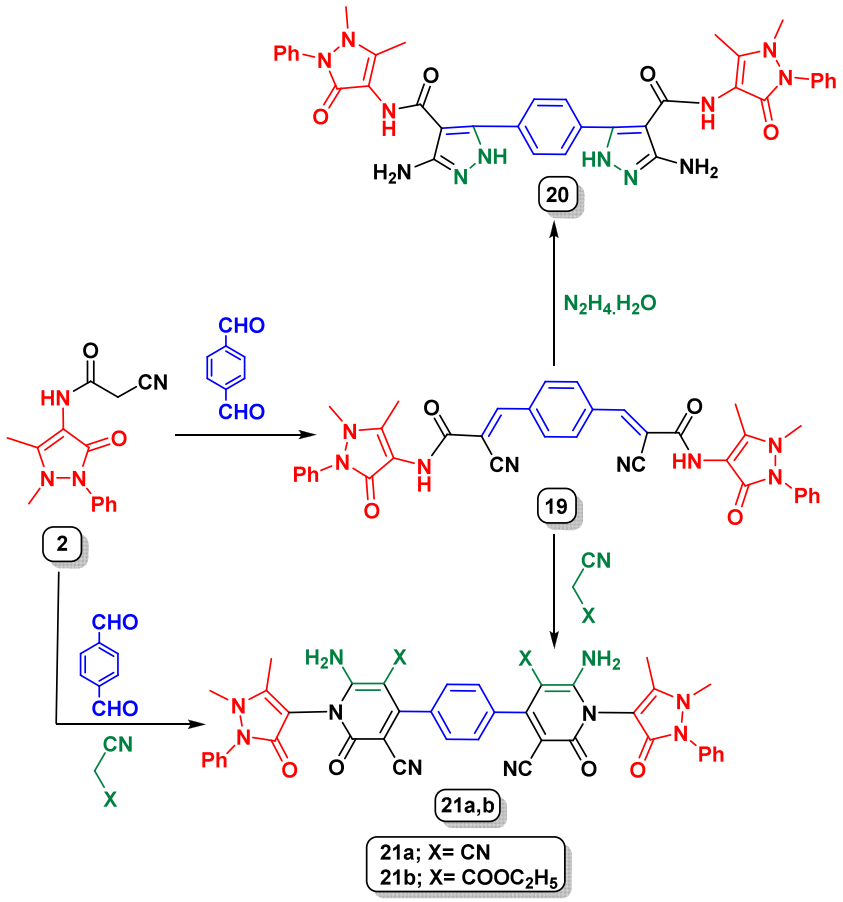
Chart 2. Fragmentation pattern of compound **15**.

A Knoevenagel Condensation of compound **2** with terephthalaldehyde (2 : 1 M ratio) in ethanolic piperidine under reflux furnished the bis(benzylidene) derivative **19** in high yield. Bis pyrazole derivative **20** was obtained through the reaction of bis(benzylidene) derivative **19** with hydrazine hydrate. The synthesis of functionalized pyridine is important because of their widespread occurrence in nature and biological activity [34]. Thus, to explore the synthetic potentiality of cyanoacetamide **2** in bipyridone synthesis, we investigated the reactivity of compound **19** towards some active methylene reagents. Refluxing of compound **19** with malononitrile and/or ethylcyanoacetate in ethanol in the presence of piperidine yielded the novel bis(aminopyridone) derivatives **21a,b.** Additionally, the structures of **21a,b** were established chemically through ternary condensation of cyanoacetamide derivative **2**, terephthalaldehyde and active methylene derivative (2 : 1 :2 M ratio) by refluxing in ethanol in the presence of piperidine (Scheme 6).

Antimicrobial screening. The in vitro antimicrobial activity of all the synthesized compounds was carried out by broth micro dilution method [35]. Mueller Hinton broth was used as nutrient medium to grow and dilute the compound suspension for the test bacteria and Sabouraud Dextrose broth used for fungal nutrition. Inoculum size for test strain was adjusted to 108 CFUmL-1 (Colony Forming Unit per milliliter) by comparing the turbidity. The strains employed for the activity were procured from (MTCC–Micro Type Culture Collection) Institute of Microbial Technology, Chandigarh.

The antipyrine derivatives were screened for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Enterococcus faecalis* and *Staphylococcus pyogenes* (as gram positive bacteria), *Pseudomonas aeruginosa, Escherichia coli, Salmonella Typhimurium* and *Klebsiella pneumonia* (as gram negative bacteria) as well as antifungal activity against *C. albicans, P. sasakii, G. azeae, F. oxysporum, C. mandshurica, and P. infestans*. DMSO was used as vehicle to obtain desired concentration of compounds to test upon microbial strains. The lowest concentration, which showed no visible growth after spot subculture was considered as MIC for each compound. *Azithromycin* was used as standard antibacterial drugs, whereas

Scheme 6. Synthetic pathways for compounds **19–21**. [Color figure can be viewed at wileyonlinelibrary.com]



Ketoconazole was used as standard antifungal drugs. The protocols were summarized in (Tables 1 and 2).

The examination of the data (Tables 1 and 2) reveals that most of the compounds showed good to moderate antimicrobial activity when compared with *Azithromycin* and *Ketoconazole*. Against Gram positive *Bacillus subtilis*, compounds **4, 6, 10a,** and **20** were found to be more efficient than *Azithromycin*. Furthermore, compound **20** was more potent than *Azithromycin* against *Enterococcus faecalis*. Towards Gram negative strain *Pseudomonas aeruginosa*, compounds **5** and **21b** were found to be more efficient than *Azithromycin*. None of the tested compounds found to be potent against *Staphylococcus aureus*, and *Staphylococcus pyogenes* (as gram positive bacteria), *Escherichia coli, Salmonella Typhimurium* and *Klebsiella pneumonia* (as gram negative bacteria) compared with standard drug.

Against fungal pathogen *C. albicans*, compounds **4, 5, 20,** and **21b** found better activity, whereas, **21a** was found to be equipotent compared with *Ketoconazole*. Most of the tested compounds possess higher to similar activities compared with *Ketoconazole* against *P. sasakii* and *P. infestans*. Furthermore, compounds **5** and **10b** found equipotent to *Ketoconazole* against *G. azeae*.

Table 1

Antibacterial activity of the synthesized compounds.

	Minimum inhibitory concentration (MIC, μgmL^{-1})							
	Gram positive bacteria				Gram negative bacteria			
Compounds No.	*S. aureus*	*B. subtilis*	*E. faecalis*	*S. pyogenes*	*P. aeruginosa*	*E. coli*	*S. typhimurim*	*K. pneumonia*
4	5.43	5.40	4.09	5.30	5.67	3.33	4.30	12.78
5	7.65	6.43	6.08	2.40	7.80	4.39	7.69	23.23
6	8.76	7.65	6.67	3.45	6.54	5.49	4.50	32.87
7	9.87	6.59	6.98	3.20	3.65	5.49	6.70	3.89
10a	4.34	9.43	6.49	9.65	8.76	5.40	6.78	2.38
10b	8.76	5.76	7.54	6.54	6.43	7.65	4.50	7.69
14	4.76	8.79	3.49	7.86	4.76	6.90	5.49	3.78
15	9.87	3.54	3.65	7.65	6.53	7.89	6.70	9.87
18a	9.50	7.69	6.54	4.67	6.56	6.50	8.70	9.87
18b	6.53	9.80	7.87	4.32	5.43	4.56	5.60	4.39
19	6.53	8.65	3.67	3.45	6.54	5.55	7.50	4.58
20	6.54	2.57	6.70	5.80	4.67	0.65	4.50	6.59
21a	6.78	8.09	5.49	3.42	7.54	6.59	8.06	8.79
21b	2.45	7.65	8.76	3.12	8.76	7.59	7.65	5.67
Azithromycin	1.32	0.91	1.02	3.2	3.1	1.03	4.56	1.23

Table 2

Antifungal activity of the synthesized compounds.

	Minimum inhibitory concentration (MIC, μgmL^{-1})					
Compounds No.	*C. albicans*	*P. sasakii*	*G. azeae*	*F. oxysporum*	*C.mandshurica*	*P. infestans*
4	2.34	4.32	4.54	3.54	3.45	4.39
5	2.32	1.32	2.54	6.7	6.78	5.67
6	4.45	1.54	6.54	8.9	5.43	4.34
7	7.65	1.23	8.76	6.5	3.56	2.56
10a	8.65	1.65	6.32	2.45	9.87	3.45
10b	3.21	4.32	2.3	5.64	6.54	2.34
14	8.76	1.32	4.23	3.56	8.76	7.65
15	3.21	4.65	4.6	3.45	3.56	6.54
18a	7.65	1.43	4.76	4.6	2.45	7.65
18b	2.54	1.34	4.3	8.09	9.87	2.34
19	9.54	2.34	7.54	2.45	6.54	3.24
20	2.34	3.21	3.4	2.45	6.4	3.45
21a	1.23	1.32	6.87	6.7	5.21	2.56
21b	2.13	1.58	9.6	8.9	4.67	4.32
Ketoconazole	1.09	2.01	2.34	1.23	2.17	5.4

Moreover, 1**8a** were found to exhibit comparable activity towards *C. mandshurica.* None of the tested compounds found to be potent *F. oxysporum*.

Structure activity relationships (SAR) of the tested compounds for anti-microbial activity. Comparing the results obtained for the anti-microbial properties of the compounds reported in this study with their structures, the following SAR are postulated, it seems that most of the antipyrine derivatives have good antimicrobial activities which may be due to the presence of the $NHCOCH_2CN$, aminopyrazole, azomethine, pyrazolo-pyrimdine, and aminopyridine moieties, respectively.

Quantum chemical calculations and equilibrium studies. Energy minimization studies were carried out on the basis of the semi-empirical PM3 level provided by HyperChem 7.5 software. The most stable structures for the 21a and 21b as representative compounds of the synthesized compounds subsequently optimized to the closest local minimum at the semiempirical level using PM3 parameterizations. The values of the following parameters: the highest occupied molecular orbital energy (EHOMO), the lowest unoccupied molecular orbital energy (ELUMO), the difference between HOMO and LUMO energy levels (ΔE), Mulliken electronegativity (χ), chemical potential (Pi), global hardness (η), global softness (S), and global electrophilicity (ω) [36–42] have been calculated [42] using semi-empirical PM3 method as implemented in HyperChem [43]. In a first step, the molecular geometries of all compounds were fully optimized in the gas phase to gradients of 0.01 kcal. mol^{-1} $Å^{-1}$ and afterwards the molecular descriptors were determined.

Equations 1–6 are used in calculations of molecular parameters as given below:

$$\chi = -1/2\,(E_{LUMO} - E_{HOMO}) \quad (1)$$

$$Pi = -\chi \quad (2)$$

$$\eta = 1/2\,(E_{LUMO} - E_{HOMO}) \quad (3)$$

$$S = 1/2\,\eta \quad (4)$$

$$\omega = Pi^2/2\eta \quad (5)$$

$$\sigma = 1/\eta \quad (6)$$

The concepts of the parameters χ and Pi are related to each other. The inverse of the global hardness is designated as the absolute softness σ. The energies and molecular parameters are given in Tables 3 and 4.

The reactivity index measures the stabilization in energy when the system acquires an additional electronic charge (ΔN_{max}) from the environment. The electrophilicity index is positive quantity and the direction of the charge transfer is completely determined by the electronic chemical potential (Pi) of the molecule because an electrophile is a chemical species capable of accepting electrons from the environment and its energy must decrease upon accepting electronic charge. Therefore, the electronic chemical potential must be negative, exactly as supported by the values in Table 4.

In most of the cases, the actual bond lengths and bond angles (Tables 5 and 6) are close to the optimal values, and thus the proposed structure of these compounds is acceptable.

The energies of HOMO and LUMO are negative, which indicates that the studied heterocyclic compounds are stable molecules [44,45]. The optimized structures for the **21a** and **21b** with the atomic numbering scheme as a representative example of the synthesized heterocyclic compounds are shown in the Figs. 1 and 2.

Table 3

Some energies of compounds **21a** and **21b** calculated by PM3 method.

The assignment of the theoretical parameters	The compound investigated	The theoretical data
Total energy	**21a**	−197208.1 kcal/mol
Binding energy		−10123.7 kcal/mol
Electronic energy		−2247067.6 kcal/mol
Core–core interaction		2049859.5 kcal/mol
Heat of formation		210.96 kcal/mol
Hydration energy		−22.33 kcal/mol
HOMO		−8.821 eV
LUMO		−1.142 eV
Dipole moment		9.208
Total energy	**21b**	−231347.6 kcal/mol
Binding energy		−11567.6 kcal/mol
Electronic energy		−2876169.1 kcal/mol
Core–core interaction		2644821.5 kcal/mol
Heat of formation		−16.11 kcal/mol
Hydration energy		−16.37 kcal/mol
HOMO		−8.758 eV
LUMO		−1.086 eV
Dipole moment		15.87

Table 4

Calculated E_{HOMO} (E_H), $E_{L\ UMO}$ (E_L), energy band gap (ΔE), chemical potential (IP), electronegativity (χ), global hardness (η), absolute softness (σ), global softness (S), and electrophilicity index (ω) for compounds **21a** and **21b**.

Compound	HOMO	LUMO	ΔE	IP	EA	χ	η	σ	S	ω
21a	−8.821	−1.142	7.679	8.821	1.142	4.9815	3.8395	0.260	0.130	3.232
21b	−8.758	−1.086	7.672	8.758	1.09	4.922	3.84	0.261	0.130	3.158

Table 5

Various bond lengths (Å) of compound 21a.

Atoms	Actual bond length (Å)	Optimal bond length (Å)
C(56)-H(88)	1.096	1.1
C(55)-H(87)	1.095	1.1
C(55)-C(56)	1.391	1.42
C(54)-H(86)	1.095	1.1
C(54)-C(55)	1.391	1.42
C(53)-H(85)	1.095	1.1
C(53)-C(54)	1.391	1.42
C(52)-H(84)	1.098	1.1
C(52)-C(53)	1.39	1.42
C(51)-H(83)	1.098	1.1
C(50)-H(82)	1.095	1.1
C(50)-C(51)	1.39	1.42
C(49)-H(81)	1.095	1.1
C(49)-C(50)	1.391	1.42
C(48)-H(80)	1.095	1.1
C(48)-C(49)	1.391	1.42
C(47)-H(79)	1.096	1.1
C(47)-C(48)	1.391	1.42
N(44)-H(78)	0.996	1.05
N(44)-H(77)	0.995	1.05
C(43)-N(46)	1.161	1.158
C(42)-N(58)	1.16	1.158
N(39)-H(76)	0.994	1.05
N(39)-H(75)	0.995	1.05
C(38)-N(45)	1.161	1.158
C(37)-N(57)	1.16	1.158
C(36)-C(37)	1.42	1.469
C(35)-O(40)	1.221	1.208
C(35)-C(36)	1.463	1.517
N(34)-C(35)	1.452	1.369
C(33)-N(39)	1.407	1.462
C(33)-N(34)	1.405	1.345
C(32)-C(38)	1.418	1.469
C(32)-C(33)	1.399	1.337
C(31)-C(43)	1.419	1.469
C(30)-N(44)	1.413	1.462
C(30)-C(31)	1.396	1.337
N(29)-C(30)	1.405	1.345
C(28)-O(41)	1.22	1.208
C(28)-N(29)	1.453	1.369
C(27)-C(42)	1.42	1.469
C(27)-C(28)	1.464	1.517
C(26)-H(74)	1.1	1.113
C(26)-H(73)	1.1	1.113
C(26)-H(72)	1.098	1.113
C(25)-H(71)	1.1	1.113
C(25)-H(70)	1.1	1.113
C(25)-H(69)	1.098	1.113
C(24)-C(51)	1.398	1.42
C(24)-C(47)	1.398	1.42
C(21)-C(56)	1.398	1.42
C(21)-C(52)	1.399	1.42
C(20)-H(68)	1.103	1.113
C(20)-H(67)	1.1	1.113
C(20)-H(66)	1.098	1.113
C(19)-H(65)	1.098	1.113
C(19)-H(64)	1.104	1.113
C(19)-H(63)	1.1	1.113
C(18)-O(23)	1.21	1.208
N(17)-C(24)	1.459	1.462
N(17)-C(18)	1.469	1.462
N(16)-C(25)	1.474	1.47
C(15)-C(26)	1.478	1.497
C(15)-N(16)	1.429	1.462
C(14)-C(19)	1.477	1.497
N(13)-C(20)	1.475	1.47
N(13)-C(14)	1.43	1.462
N(12)-C(21)	1.459	1.462
C(11)-O(22)	1.212	1.208
C(11)-N(12)	1.468	1.462
C(10)-N(34)	1.443	1.345
C(10)-C(18)	1.486	1.517
C(10)-C(15)	1.37	1.337
C(9)-N(29)	1.442	1.345
C(9)-C(14)	1.369	1.337
C(9)-C(11)	1.485	1.517
C(8)-C(36)	1.372	1.337
C(8)-C(32)	1.429	1.503
C(7)-C(31)	1.431	1.503
C(7)-C(27)	1.371	1.337
C(6)-C(7)	1.475	1.503
C(5)-H(62)	1.096	1.1
C(5)-C(6)	1.396	1.42
C(4)-H(61)	1.096	1.1
C(4)-C(5)	1.39	1.42
C(3)-C(8)	1.475	1.503
C(3)-C(4)	1.396	1.42
C(2)-H(60)	1.096	1.1
C(2)-C(3)	1.396	1.42
C(1)-H(59)	1.096	1.1
C(1)-C(6)	1.395	1.42
C(1)-C(2)	1.39	1.42

(*Continued*)

Table 5

(Continued)

EXPERIMENTAL

Chemistry. All melting points are in degree centigrade (uncorrected) and were determined on Gallenkamp electric melting point apparatus. TLC analysis was carried out on silica gel 60 F254 precoated aluminum sheets. The IR spectra were recorded (KBr) on a Perkin–Elmer 1430 spectrometer (λ, cm^{-1}) in National Research Center, Egypt. ^{1}HNMR/^{13}CNMR Spectra were measured on JEOL-ECA 500 and JEOL JNM-LA-400 FT NMR Spectrometers at 500, 125 MHz, respectively, using tetramethylsilane (TMS) as an internal reference and DMSO-d_6 as solvent at the Microanalytical Center in National Research Center, Egypt. The mass spectra (EI) were recorded on GCMS-QP 1000 EX (Shimadzu) at National Research Center, Egypt. Elemental analyses (C, H, and N) were carried out at the Microanalytical Center in National Research Center, Egypt. The elemental analyses were found to agree favorably with the calculated values. Biological activities were carried in Regional Center for Mycology and Biotechnology, Al-Azhar University, Nasr City, Cairo, Egypt.

Synthesis of 2-cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-(ethylthio)-3-(naphthalen-1-ylamino)acrylamide (4). To a stirred suspension of finely powdered potassium hydroxide (0.01 mol) in dry dimethyl formamide (10 mL), 2-naphthylisothiocyanate (0.01 mol) and

Table 6

Various bond angles of compound 21a.

Atoms	Actual bond length (Å)	Optimal bond length (Å)
H(88)-C(56)-C(55)	119.902	120
H(88)-C(56)-C(21)	120.804	120
H(87)-C(55)-C(56)	119.727	120
H(87)-C(55)-C(54)	119.911	120
H(86)-C(54)-C(55)	119.989	120
H(86)-C(54)-C(53)	119.913	120
H(85)-C(53)-C(54)	120.087	120
H(85)-C(53)-C(52)	119.624	120
H(84)-C(52)-C(53)	119.629	120
H(84)-C(52)-C(21)	120.994	120
H(83)-C(51)-C(50)	119.696	120
H(83)-C(51)-C(24)	120.974	120
H(82)-C(50)-C(51)	119.625	120
H(82)-C(50)-C(49)	120.056	120
H(81)-C(49)-C(50)	119.912	120
H(81)-C(49)-C(48)	119.974	120
H(80)-C(48)-C(49)	119.916	120
H(80)-C(48)-C(47)	119.747	120
H(79)-C(47)-C(48)	119.842	120
H(79)-C(47)-C(24)	120.862	120
H(78)-N(44)-H(77)	112.706	118.8
N(46)-C(43)-C(31)	179.1	180
N(58)-C(42)-C(27)	178.98	180
N(45)-C(38)-C(32)	179.486	180
N(57)-C(37)-C(36)	179.011	180
C(37)-C(36)-C(8)	121.936	120
C(36)-C(35)-N(34)	116.512	112.74
C(35)-N(34)-C(33)	121.086	122
N(39)-C(33)-N(34)	118.655	120
N(39)-C(33)-C(32)	121.531	120
N(34)-C(33)-C(32)	119.695	120
C(38)-C(32)-C(33)	119.442	120
C(38)-C(32)-C(8)	119.552	120
C(33)-C(32)-C(8)	121.006	120
C(43)-C(31)-C(30)	119.677	120
C(43)-C(31)-C(7)	119.38	120
C(30)-C(31)-C(7)	120.94	120
N(44)-C(30)-C(31)	121.818	120
N(44)-C(30)-N(29)	118.012	120
C(31)-C(30)-N(29)	119.875	120
C(30)-N(29)-C(28)	121.016	122
C(42)-C(27)-C(7)	122.003	120
H(74)-C(26)-H(73)	107.681	109
H(74)-C(26)-H(72)	107.417	109
H(74)-C(26)-C(15)	110.181	110
H(73)-C(26)-C(15)	112.031	110
H(72)-C(26)-C(15)	111.729	110
H(71)-C(25)-H(70)	108.435	109
H(71)-C(25)-H(69)	108.416	109
H(70)-C(25)-H(69)	108.696	109
C(51)-C(24)-C(47)	120.607	120
C(51)-C(24)-N(17)	121.778	120
C(47)-C(24)-N(17)	117.613	120
C(56)-C(21)-C(52)	120.583	120
C(56)-C(21)-N(12)	117.742	120
C(52)-C(21)-N(12)	121.671	120
H(68)-C(20)-H(67)	108.699	109
H(68)-C(20)-H(66)	109.275	109
H(67)-C(20)-H(66)	108.468	109
H(65)-C(19)-H(64)	108.006	109
H(65)-C(19)-H(63)	107.664	109
H(65)-C(19)-C(14)	111.402	110
H(64)-C(19)-H(63)	107.816	109
H(64)-C(19)-C(14)	111.618	110
H(63)-C(19)-C(14)	110.175	110
O(23)-C(18)-N(17)	123.29	122.6
O(22)-C(11)-N(12)	123.41	122.6
O(22)-C(11)-C(9)	130.189	123
N(12)-C(11)-C(9)	106.284	122
N(34)-C(10)-C(18)	123.156	120
N(34)-C(10)-C(15)	126.438	120
C(18)-C(10)-C(15)	109.911	117.6
N(29)-C(9)-C(14)	127.062	120
N(29)-C(9)-C(11)	122.567	120
C(14)-C(9)-C(11)	109.833	117.6
C(36)-C(8)-C(32)	119.898	120
C(36)-C(8)-C(3)	120.857	120
C(32)-C(8)-C(3)	119.245	120
C(31)-C(7)-C(27)	119.924	120
C(31)-C(7)-C(6)	119.112	120
C(27)-C(7)-C(6)	120.946	120
C(7)-C(6)-C(5)	119.288	120
C(7)-C(6)-C(1)	120.561	120
C(5)-C(6)-C(1)	120.148	120
H(62)-C(5)-C(6)	120.092	120
H(62)-C(5)-C(4)	119.937	120
H(61)-C(4)-C(5)	119.922	120
H(61)-C(4)-C(3)	120.173	120
C(8)-C(3)-C(4)	119.981	120
C(8)-C(3)-C(2)	119.914	120
C(4)-C(3)-C(2)	120.103	120
H(60)-C(2)-C(3)	120.088	120
H(60)-C(2)-C(1)	119.908	120
H(59)-C(1)-C(6)	120.204	120
H(59)-C(1)-C(2)	119.925	120

the active methylene **2** (0.01 mol) were added gradually. The reaction was stirred at room temperature for 3 h, then treated with diethyl sulfate and stirred at room temperature for an additional 6 h. Then it was poured into ice/water and acidified with 0.1 *N* HCl at pH 3–4.; the resulting precipitate was filtered off, dried and recrystallized from ethanol as yellow crystals. Yield 70%; mp 189–190°C; IR (KBr): (ν/cm^{-1}) = 3371(NH), 2935 (CH aliph.), 2191(C ≡ N), 1631(C = O; amide); ^{1}H NMR (DMSO-d$_6$): δ (ppm):1.22 (t, 3H, CH_3), 2.18(s, 3H, CH_3), 2.90 (s, 3H, N-CH_3), 3.46(q, 2H, CH_2), 7.12–8.08 (m, 12H, Ar-H), 9.80, 13.11 (2 s, 2H, 2NH); m/z (%) = 483 (M^+, 45%), 64 (100%); *Anal*. Calcd. for $C_{27}H_{25}N_5O_2S$: Calcd.: C, 67.06; H, 5.21; N, 14.48%; Found: C, 66.90; H, 4.95; N, 14.10%:

Synthesis of 5-amino-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-(naphthalen-1-ylamino)-1H-pyrazole-4-carbox-amide (5). A mixture of **4** (0.01 mol) and hydrazine hydride (0.01 mol) in ethanol (30 mL) was heated under reflux for 2 h. Then it was poured into ice/water and acidified with 0.1 *N* HCl at pH 3–4.; the resulting precipitate was filtered off, dried and recrystallized from ethanol as white crystals. Yield 65%; mp 250–251°C; IR (KBr): (ν/cm^{-1}) = 3289, 3189 (NH_2/NH), 1635(C = O; amide); ^{1}H NMR (DMSO-d$_6$): δ (ppm):

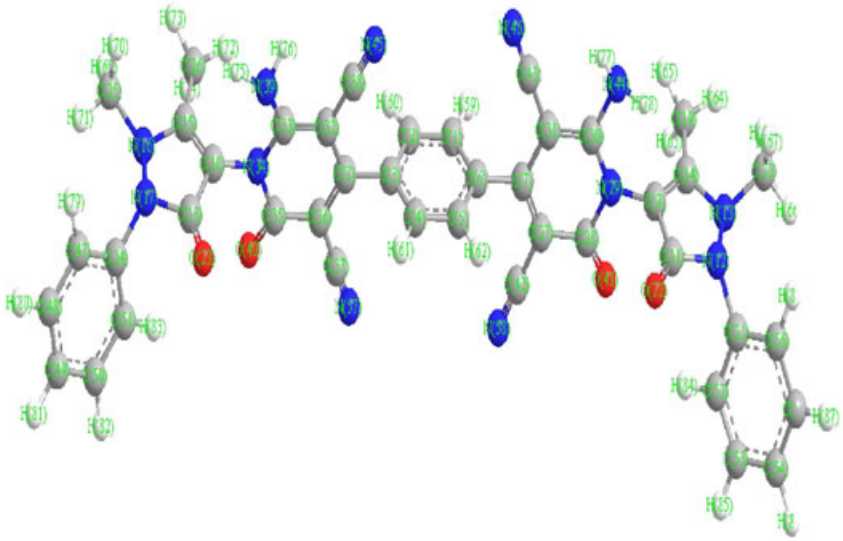


Figure 1. The molecular structure of compound **21a** along with the atom numbering scheme. [Color figure can be viewed at wileyonlinelibrary.com]

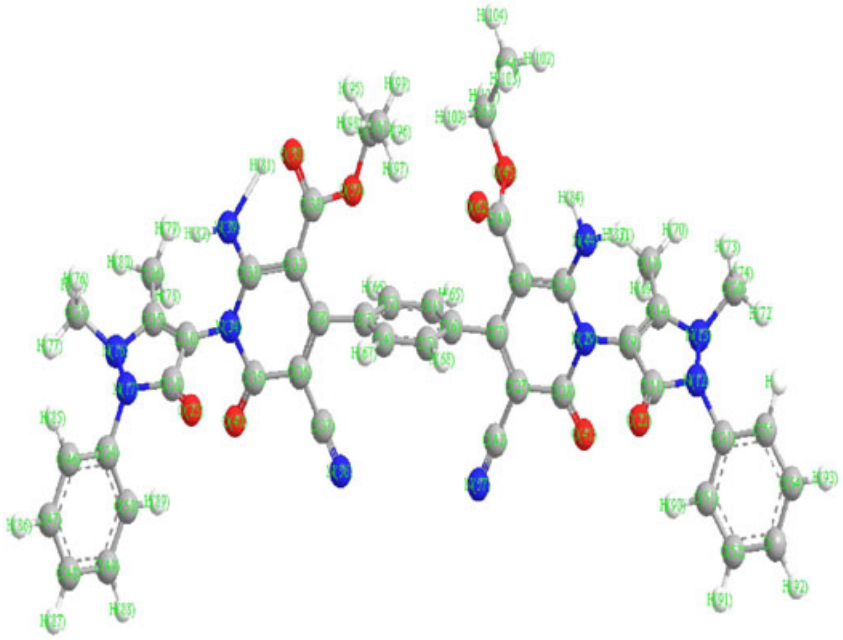


Figure 2. The molecular structure of compound **21b** along with the atom numbering scheme. [Color figure can be viewed at wileyonlinelibrary.com]

2.18 (s, 3H, CH_3), 3.10 (s, 3H, N-CH_3), 6.06 (s, 2H, NH_2), 7.30–7.93 (m, 12H, Ar-H), 8.03, 10.02, 11.24 (3 s, 3H, 3NH); ^{13}C NMR (DMSO-d_6): δ (ppm):10.97, 56.60 (2 CH_3), 86.38 (pyrazole-C4), 107.46, 109.26 (antipyrine-C4,C5), 118.86, 120.26, 123.30, 125.41, 125.72, 126.23, 128.33, 129.11 (Ar-C), 151.67, 152.81 (pyrazole-C3,C5), 162.20 (antipyrine-C3), 164.66 (C = O); m/z (%) = 453 (M^+, 24.3%), 69 (100%); *Anal*. Calcd. for $C_{25}H_{23}N_7O_2$: Calcd.: C, 66.21; H, 5.11; N, 21.62%; Found: %: C, 66.00; H, 5.05; N, 21.50%.

Synthesis of N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-5-(4-methoxybenzylideneamino)-3-(naphthalen-1-ylamino)-1H-pyrazole-4-carboxamide (6). A mixture of compound **5** (0.01 mol), 4-anisaldehyde (0.01 mol) and piperidine (0.01 mol) in ethanol (30 mL) was heated under reflux for 1 h; the solid product which was produced on heating was collected and recrystallized from dioxane as yellow solid. Yield 50%; mp 280–281°C; IR (KBr): (ν/cm^{-1}) = 3417 (NH), 2939 (CH-arom), 1635 (C = O; amide), 1593 (CH = N); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.35, 3.13 (2 s, 6H, 2 CH_3), 3.86 (s, 3H, OCH_3), 6.96–8.17 (m, 16H, Ar-H), 8.42 (s, 1H, N = CH), 9.87, 10.01, 12.96 (3 s, 3H, 3NH); ^{13}C NMR (DMSO-d_6): δ (ppm): 11.50, 35.80 (2 CH_3), 56.60 (OCH_3), 86.38 (pyrazole-C4), 107.46, 132.28 (antipyrine-C4,C5), 114.25, 118.86, 120.26, 123.30, 125.41, 125.72, 126.23, 128.33, 129.11 (Ar-C), 151.67, 152.81 (pyrazole-C3,C5), 163.85 (C-OCH_3), 159.55 (N = CH), 163.20 (antipyrine-C3),

169.96 (C = O); m/z (%) = 571 (M^+, 15%), 56 (100%); *Anal*. Calcd. For $C_{33}H_{29}N_7O_3$: Calcd.: C, 69.34; H, 5.11; N, 17.15%; Found: C, 69.10; H, 5.00; N, 17.25%.

Synthesis of 5,5''-(1,4-phenylenebis(methan-1-yl-1-ylidene))bis (azan-1-yl-1-ylidene)-bis(N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-(naphthalen-2-ylamino)-1H-pyrazole-4-carboxamide) (7). A mixture of compound **5** (0.02 mol), terephthalaldehyde (0.01 mol), and piperidine (0.01 mol) in ethanol (30 mL) was heated under reflux for 1 h; the solid product which was produced on heating was collected and recrystallized from dioxan as red solid. Yield 45%; mp 298–290°C; IR (KBr): (ν/cm^{-1}) = 3363 (br,4NH), 2981(CH arom.), 1631 (C = O; amide), 1593,1599 (2CH = N); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.93, 3.13 (2 s, 12H, 4CH_3), 7.25–8.11(m, 28H, Ar-H), 8.27(s, 2H, 2 N = CH), 10.01, 10.09, 10.14 (3 s, 6H, 6NH); m/z (%) =1004 (M^+, 10%), 158 (100%); *Anal*. Calcd. For $C_{58}H_{48}N_{14}O_4$: Calcd.: C, 69.31; H, 4.81; N, 19.51%; Found: C, 69.10; H, 4.50; N, 19.10%.

Synthesis of Synthesis of compounds (10a and **10b**). A mixture of 5(0.01 mol), α-cinnamonitrile **8** (0.01 mol) in pyridine (20 mL) was heated under reflux for 3 h; the solid product which was produced on heating was collected and recrystallized from the proper solvent to give **10**.

5-Amino-6-cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-7-(4-methoxyphenyl)-2-(naphthalen-1-ylamino)pyrazolo[1,5-a]pyrimidine-3-carboxamide (10a). Yield 50%; brown solid (Dioxane); mp 290–291°C; IR (KBr): (ν/cm^{-1}) = 3417, 3398 (br NH_2/NH), 2194 (C ≡ N), 1631 (C = O; amide); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.15, 3.16 (2 s, 6H, 2CH_3), 3.87 (s, 3H, OCH_3), 6.76–7.73 (m, 16H, Ar-H), 7.99 (br, 2H, NH_2), 8.62, 8.76 (s, 2H, 2NH); ^{13}C NMR (DMSO-d_6): δ (ppm):11.27, 34.37 (2CH_3), 56.45 (OCH_3), 84.65 (pyrazole-C4), 108.14 (antipyrine-C4), 112.65 (pyrimidine-C5), 117.35, 120.10, 121.24, 123.42, 126.72, 126.15, 128.24, 129.71, 132.33 (Ar-C), 133.54 (antipyrine-C5), 134.30 (pyrazole-C3), 135.48 (pyrimidine-C6), 151.87, (pyrazole-C5), 162.70 (pyrimidine-C4), 161.70 (C-OCH_3), 147.20 (C ≡ N), 163.33 (antipyrine-C3), 174.92 (C = O); m/z (%) = 635 (M^+, 15%), 268 (100%); *Anal*. Calcd. For $C_{36}H_{29}N_9O_3$: Calcd.: C, 68.02; H, 4.60; N, 19.83%; Found: C, 67.70; H, 4.20; N, 19.50%.

Ethyl 5-amino-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylcarbamoyl)-2-(naphthalen-1-ylamino)-7-(4-nitrophenyl)-pyrazolo[1,5-a]pyrimidine-6-carboxylate (10b). Yield 52%; brown solid (Dioxane); mp 300–301°C; IR (KBr): (ν/cm^{-1}) = 3383, 3360 (br NH_2/NH), 1670(C = O; ester), 1631 (C = O; amide); ^{1}H NMR (DMSO-d_6): δ (ppm):1.09(t, 3H, CH_3), 2.21, 3.18 (2 s, 6H, 2CH_3), 4.27 (q,2H,CH_2), 7.11–8.11 (m, 16H, Ar-H), 8.21 (br, 2H, NH_2), 8.41, 9.22 (s, 2H, 2NH); ^{13}C NMR (DMSO-d_6): δ (ppm): 11.27, 15.32, 34.37 (3CH_3), 63.54 (CH_2), 86.47 (pyrazole-C4), 109.25 (antipyrine-C4), 112.90 (pyrimidine-C5), 119.32, 120.20, 122.15, 123.42, 126.72, 126.15, 128.24, 129.71, 132.33 (Ar-C), 134.20 (antipyrine-C5), 135.30 (pyrazole-C3), 136.24 (pyrimidine-C6), 151.87 (pyrazole-C5), 162.70 (pyrimidine-C4), 163.33 (antipyrine-C3), 167.54, 173.92 (2C = O); m/z (%) = 697 (M+, 22%), 58 (100%); *Anal*. Calcd. For $C_{37}H_{31}N_9O_6$: Calcd.: C, 63.69; H, 4.48; N, 18.07%; Found: C, 63.90; H, 4.53; N, 18.17%.

Synthesis of 5-amino-6-cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-7-(methylthio)-2-(naphthalen-1-ylamino)pyrazolo [1,5-a]pyrimidine-3-carboxamide (14). Yield 45%; brown solid (MeOH); mp 290–291°C; IR (KBr): (ν/cm^{-1}) =3452, 3398, 3336 (NH_2/ NH), 2191 (C ≡ N), 1631 (C = O; amide); ^{1}HNMR spectrum, δ, ppm: 2.21, 3.13 (2 s, 6H, 2CH_3), 2.41 (s, 3H, SCH_3), 7.34–8.36 (m, 12H, Ar-H), 8.65 (br, 2H, NH_2), 10.40, 12.60 (2 s, 2H, 2NH); m/z (%) = 575 (M^+, 28.29%), 115 (100%); *Anal*. Calcd. For $C_{30}H_{25}N_9O_2S$: Calcd.: C, 62.59; H, 4.38; N, 21.90%; Found: C, 62.65; H, 4.31; N, 21.75%.

Synthesis of compounds (15, **17a,** and **17b**). **A** mixture of compound **5** (0.01 mol) and 1,3-dicarbonyl compound (namely; acetylacetone, ethyl acetoacetate and ethyl 2-methyl-3-oxobutanoate) (0.01 mol) in glacial acetic acid (10 mL) was heated under reflux for 3 h, then allowed to cool. The solid was collected and recrystallized from the proper solvent to give **15**, **17a,** and **17b**, respectively.

N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl) 5,7-dimethyl-2-(naphthalen-1-ylamino)pyrazolo[1,5-a] pyrimidine-3-carboxamide (15). Yield 55%; white solid (Dioxane); mp 279–280°C; IR (KBr): (ν/cm^{-1}) = 3367 (NH), 1631 (C = O; amide); ^{1}HNMR spectrum, δ, ppm: 2.34, 2.58, 2.79, 3.16 (4 s, 12H, 4CH_3), 7.03 (s, 1H, pyrimidine-H), 7.36–8.58 (m, 12H, Ar-H), 8.97, 10.47 (2 s, 2H, 2NH); ^{13}C NMR spectrum, δ, ppm: 10.27, 17.14, 21.80, 35.37 (4CH_3), 85.97 (pyrazole-C4), 106.85 (antipyrine-C4), 115.40 (pyrimidine-C5), 120.10, 121.24, 123.42, 126.70, 126.10, 128.20, 129.70, 132.33 (Ar-C), 132.50 (antipyrine-C5), 136.36 (pyrazole-C3), 135.48 (pyrimidine-C6),154.87, (pyrazole-C5), 161.96 (pyrimidine-C4),163.33 (antipyrine-C3), 172.92 (C = O); m/z (%) = 517 (M^+, 28%), 315 (100%); *Anal*. Calcd. For $C_{30}H_{27}N_7O_2$: Calcd.: C, 69.62; H, 5.26; N, 18.94%; Found: C, 69.80; H, 5.21; N, 18.84%.

N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-7-hydroxy-5-methyl-2-(naphthalen-2-ylamino)pyrazolo[1,5-a]pyrimidine-3-carboxamide (17a). Yield 60%; white solid (Dioxane); mp 289–290°C; IR (KBr): (ν/cm^{-1}) = 3356 (NH/ OH), 2943 (CH arom.), 1631 (C = O; amide); ^{1}HNMR spectrum, δ, ppm: 2.24, 2.49, 3.16 (3 s, 9H, 3CH_3), 5.82 (s, 1H, pyrimidine-H), 7.36–8.04 (m, 12H, Ar-H), 8.53, 8.88, 10.44 (3 s, 3H, 3NH); ^{13}C NMR spectrum, δ, ppm: 10.27, 17.14, 35.37 (3CH_3), 86.95 (pyrazole-C4), 106.15 (antipyrine-C4), 114.40 (pyrimidine-C5), 119.15, 122.35, 123.42, 126.70, 126.10, 128.30, 129.70, 132.33 (Ar-C), 134.50 (antipyrine-C5), 134.30 (pyrazole-C3), 136.30 (pyrimidine-C6), 153.65 (pyrazole-C5), 163.96 (pyrimidine-C4), 165.33 (antipyrine-C3), 174.36 (C = O); m/z (%) = 519 (M^+, 20%), 77 (100%); *Anal*. Calcd. For $C_{29}H_{25}N_7O_3$: Calcd.: C, 67.04; H, 4.85; N, 18.87%; Found: C, 66.95; H, 4.95; N, 18.66%.

N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-7-hydroxy-5,6-dimethyl-2-(naphthalen-2-ylamino)pyrazolo [1,5-a]pyramidine-3-carboxamide (17b). Yield 55%; white solid (Dioxane); mp< 300°C; IR (KBr): (ν/cm^{-1}) = 3364 (NH), 2953 (CH arom.), 1631 (C = O; amide); ^{1}HNMR spectrum, δ, ppm: 1.19, 2.19, 2.38, 3.19 (4 s, 12H, 4CH_3), 7.36–8.04 (m,12H, Ar-H), 8.53, 8.80, 10.59 (3 s, 3H, 3NH); ^{13}C NMR spectrum, δ, ppm:10.27, 17.14, 20.98, 35.37 (4CH_3), 84.87 (pyrazole-C4), 105.73 (antipyrine-C4), 112.20 (pyrimidine-C5), 119.76, 120.26, 123.42, 125.79, 126.38, 127.14, 128.67, 129.33 (Ar-C), 133.68 (antipyrine-C5), 134.30 (pyrazole-C3), 135.48 (pyrimidine-C6),151.87, (pyrazole-C5), 161.96 (pyrimidine-C4),163.33 (antipyrine-C3), 171.92 (C = O); *Anal*. Calcd. For $C_{30}H_{27}N_7O_3$: Calcd.: C, 67.53; H, 5.10; N, 18.38% ; Found: C, 67.45; H, 4.99; N, 18.25%.

Synthesis of 3,3''-(1,4-phenylene)bis(2-cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl) acrylamide) (19). To a solution of 2 (0.02 mol) in ethanol (30 mL), terephthalaldehyde (0.01 mol), and piperidine (0.5 mL) were added. The mixture was refluxed, then it was poured into ice/water and acidified with 0.1 *N* HCl at pH 3–4; the resulting precipitate was filtered off, dried and recrystallized from ethanol as red crystals. Yield 70%; mp 291–220°C; IR (KBr): (ν/cm^{-1}) = 3394 (NH), 2947 (CH arom.), 1635 (C = O; amide); ^{1}HNMR spectrum, δ, ppm: 2.32 3.20 (2 s, 12H, $4CH_3$), 7.29–8.32 (m, 14H, Ar-H), 9.58 (s, 2H, 2 = CH), 11.71 (1 s, 2H, 2NH); m/z (%) = 624 (M^+, 25%), 72 (100%); *Anal*. Calcd. For $C_{36}H_{30}N_8O_4$: Calcd.: C, 67.70; H, 4.73; N, 17.54%; Found: C, 67.50; H, 4.25; N, 17.45%.

5,5''-(1,4-phenylene)bis(3-amino-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-1H-pyrazole-4-carboxamide) (20). To a solution of **19** (0.01 mol) in ethanol (30 mL), hydrazine hydrate (0.02 mol) was added. The mixture was heated under reflux for 3 h, then allowed to cool. The solid was collected and recrystallized from the MeOH to give **20**. Yield 40%; white solid; mp 279–280°C; IR (KBr): (ν/cm^{-1}) = 3460, 3406 (NH_2/NH), 2943 (CH arom.), 1635 (C = O; amide); m/z (%) = 698 (M^+, 15%), 69 (100%); *Anal*. Calcd. For $C_{36}H_{34}N_{12}O_4$: Calcd.: C, 61.88; H, 4.90; N, 24.06%; Found: C, 62.00; H, 4.77; N, 23.85%.

Synthesis of compounds (21a and **21b**). ***Method A.*** A mixture of **19** (0.01 mol), active methylene compound (0.02 mol) and piperidine (0.5 mL) in ethanol (30 mL) was heated under reflux for 3 h, the solid product which produced on heating was collected and recrysta-llized from common solvents to afford products **21a,b**.

Method B. A mixture of cyanoacetamide derivative **2** (0.02 mol), active methylene compound (0.02 mol), terephthalaldehyde (0.01 mol) and piperidine (0.5 mL) in dioxane (30 mL) was heated under reflux for 3 h. The product which produced on heating was collected and recrystallized to give **21a,b**.

4,4''-(1,4-Phenylene)bis(6-amino-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile) (21a). Yield 50%; brown solid (AcOH); mp 259–260°C; IR (KBr): (ν/cm^{-1}) = 3394, 3184 (NH_2), 3043 (CH-arom.), 2209 (C ≡ N), 1637 (C = O; amide); ^{1}HNMR spectrum, δ, ppm: 2.18, 3.12 (2 s, 12H, $4CH_3$), 7.31–8.54 (m, 14H, Ar-H), 9.47 (s, 4H, $2NH_2$); m/z (%) = 766 (M^+, 27%), 69 (100%); *Anal*. Calcd. For $C_{42}H_{30}N_{12}O_4$: Calcd.: C, 65.79; H, 3.94; N, 21.92%; Found: C, 65.60; H, 4.10; N, 21.75%.

Diethyl 4,4''-(1,4-phenylene)bis(2-amino-5-cyano-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxylate) (21b). Yield 50%; brown solid (AcOH); mp 269–270°C; IR (KBr): (ν/cm^{-1}) = 3444, 3417 (NH_2), 2985 (CH arom.), 2215 (C ≡ N), 1674 (C = O; ester); ^{1}HNMR spectrum, δ, ppm: 1.32 (t, 6H, $2CH_3$), 2.14, 3.19 (2 s, 12H, $4CH_3$), 4.15 (q, 4H, $2CH_2$), 7.30–8.59 (m, 14H, Ar-H), 9.50 (br, 4H, $2NH_2$); m/z (%) = 860 (M^+, 30%), 108 (100%); *Anal*. Calcd. For $C_{46}H_{40}N_{10}O_8$: Calcd.: 64.18; H, 4.68; N, 16.27%; Found: 64.00; H, 4.80; N, 16.35%.

Molecular modeling studies. An attempt to gain a better insight on the molecular structure of the compounds, geometric optimization and conformation analysis has performed using semi-empirical method PM3 as implemented in HyperChem 7.5 [45]. The structures of synthesized compounds were optimized with semi-empirical method PM3 (Parametric Method-3). A gradient of 0.01 kcal/Å was set as a convergence criterion in all the molecular mechanics and quantum calculations. The lowest energy structure was used for each molecule to calculate physicochemical properties.

CONCLUSIONS

Novel bispyrazole, pyrazolopyrimidine, and pyridine derivatives incorporating the antipyrinyl moiety have been synthesized and their microbial activity evaluated. The results clearly showed that most of the compounds had good to moderate activity, and that coupling of aminopyrazole moiety to arylcarboxaldehydes through a azomithine linkage improves the antimicrobial activity. These preliminary results of biological screening of the tested compounds could offer an encouraging framework in this field that may lead to the discovery of novel antimicrobial agent.

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