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Synthesis, identification and *in vitro* biological evaluation of some novel 5-imidazopyrazole incorporated pyrazoline and isoxazoline derivatives†

Piyush N. Kalaria,* Shailesh P. Satasia and Dipak K. Raval

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In the present study, novel combinatorial libraries of substituted pyrazolines **6a–l** and isoxazolines **7a–l** have been synthesized *via* the reactions of chalcones with the hydrazine hydrate and hydroxylamine hydrochloride in ethanol. The title compounds were screened for their preliminary *in vitro* antibacterial activity against a panel of pathogenic strains, *in vitro* antituberculosis activity against *Mycobacterium tuberculosis* H37Rv, *in vitro* antimalarial activity against *Plasmodium falciparum* and *in vitro* antioxidant activity by the ferric-reducing antioxidant power method. Compounds **6k**, **6l**, **7h** and **7k** exhibited excellent antibacterial activity and a few of them exhibited moderate antituberculosis activity compared with the first line drugs. Half of the compounds exhibited terrific antimalarial activity and the majority of compounds showed highest antioxidant potency.

1. Introduction

Malaria remains one of the most imperative infectious diseases in the world. During the past decade, concerted efforts of prevalent countries, donors and global malaria partners led to strengthened malaria control around the world.[1] Malaria has placed the strongest known selective pressure on the human genome since the commencement of agriculture within the past 10 000 years.[2,3] *Plasmodium falciparum*, the most dangerous malarial parasite, is accountable for about 1 million deaths every year.[4–6] Infectious diseases are influencing the world through their morbidity and mortality among which tuberculosis is also a major infectious disease caused by *Mycobacterium tuberculosis*.[7] Solitary agent TB treatment quickly leads to drug-resistant organisms,[8] while multi-drug treatment needs to be extended as MTB divides gradually. It is metabolically capable of becoming drug insensitive and may become sequestered.[9,10] Therefore, the growth of new drugs with action besides MDR-TB, XDR-TB, and latent TB is a main concern. For this reason as drug-resistant strains of the parasite emerge, there is a vital need to recognize new pharmacological targets for developing antimalarial and antituberculosis therapeutics.

Five-membered heterocycles having a vicinal 1,2-diaryl substitution pattern are important scaffolds that are found in several pharmacologically active compounds, including kinase inhibitors, dopamine transporter inhibitors, GPCR antagonists and even agonists, cyclooxygenase inhibitors, and phosphatase inhibitors.[11] Pyrazole containing drugs having two adjacent aryl groups in a vicinal position have often been occupying a position in the list of top selling pharmaceutical products since the establishment of this decade.[12] Pyrazole signifies a key motif in heterocyclic chemistry and occupies a major position in medicinal and pesticide chemistry due to its wide range of bioactivities such as antibacterial,[13] anticancer,[14] analgesic,[15] anti-convulsant,[16] anti-depressant[17] and anti-inflammatory.[18] Whereas, the class of pyrazoles and isoxazolines possess a broad spectrum of pharmacological activities such as anti-bacterial,[19] antiviral[20] and antidepressant.[21] The synthesis of heterocyclic motifs containing multi-structure in one molecule has received much interest in recent years.[22]

After the pioneering work of Fischer and Knoevenagel in the late 19th century,[23] the reaction of α,β-unsaturated ketones and aldehydes with hydrazines became one of the most admired methods for the preparation of 2-pyrazolines. Many pyrazoline

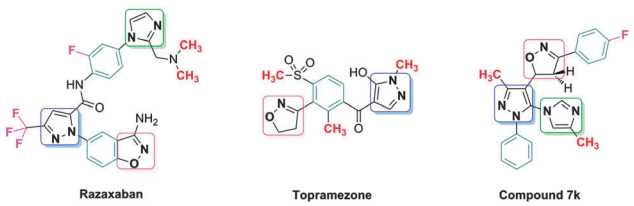

Fig. 1 Structural comparison of the representative compound with the standard drugs.

Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar-388 120, Gujarat, India. E-mail: piyush_kalaria@yahoo.com; Fax: +91-02692-236475; Tel: +91-02692-226856 ext. 211

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derivatives are reported to have a large spectrum of biological activities, such as antimalarial,[24] antibacterial,[25] antitubercular, analgesic,[26] antiviral,[27] antioxidant,[28] antidiabetic,[29] antifungal[30,31] and antimycobacterial.[32]

In view of these findings and in continuation of our research work,[33–41] we herein report the synthesis and pharmacological activity of substituted pyrazolines **6a–l** and isoxazolines **7a–l**. It was considered valuable to incorporate two five membered heterocyclic rings mutually in a molecular framework to study the synergistic effect of these rings towards the antibacterial, antituberculosis, antimalarial and antioxidant activities (Fig. 1).

2. Results and discussion

2.1. Chemistry

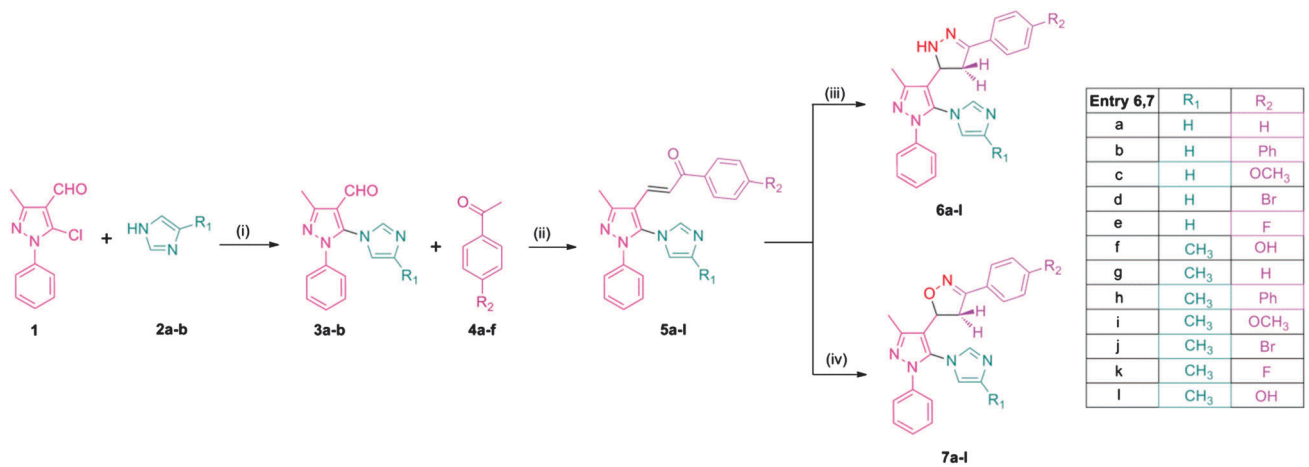
The synthetic route used to synthesize the unreported title compounds **6a–l** and **7a–l** is illustrated in Scheme 1. The starting material 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** was prepared according to Vilsmeier–Haack reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one.[42] 5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3a–b** were prepared by nucleophilic displacement of the chloro group at C5 in 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** with secondary amine of imidazole **2a–b** in refluxing DMF using anhydrous potassium carbonate as the base. The pyrazolic chalcones **5a–l** were prepared by the reaction of aldehydes **3a–b** with appropriately substituted acetophenones **4a–f** in ethanolic sodium hydroxide as the catalyst at room temperature. Finally pyrazolic chalcones **5a–l** were treated with hydrazine hydrate/hydroxylamine hydrochloride in ethanol containing a catalytic amount of glacial acetic acid giving pyrazoline **6a–l**/isoxazoline **7a–l** derivatives.

The structures of all the synthesized compounds were confirmed by ^{1}H NMR, FT-IR, mass spectrometry and elemental analysis. The IR spectrum of all the synthesized compounds showed absorption in the range of 1590–1654 cm^{-1} due to C═N stretching. The C–H stretching was observed at around 2935–3017 cm^{-1}. A strong absorption band was observed in the range of 1368–1379 cm^{-1} due to the presence of the CH_3 group. In the ^{1}H NMR spectra of these compounds the pro-chiral methylene protons of pyrazoline appeared as two distinct doublets of a doublet, thereby indicating that both the protons are magnetically non-equivalent and diastereotopic. The chiral C–H proton of pyrazoline appeared as a triplet. The aromatic protons resonate as multiplets at around δ 6.93–7.70 ppm. The mass spectrum of all the synthesized compounds showed a molecular ion peak at M + 1 corresponding to their molecular weights, which confirmed the respective chemical structures.

2.2. Biological evaluation

2.2.1. *In vitro* antimicrobial activity. All the synthesized compounds were evaluated for their antibacterial activity against three Gram positive bacteria (*Streptococcus pneumoniae* MTCC 1936, *Bacillus subtilis* MTCC 441 and *Clostridium tetani* MTCC 449) and three Gram negative bacteria (*Escherichia coli* MTCC 443, *Salmonella typhi* MTCC 98, and *Vibrio cholerae* MTCC 3906) by using ampicillin, norfloxacin and ciprofloxacin as the standard antibacterial drugs. Antifungal activity was screened against two fungal species (*Candida albicans* MTCC 3008 and *Aspergillus fumigatus* MTCC 227) where nystatin and griseofulvin were used as the standard antifungal drugs. The minimal inhibitory concentration (MIC) of all the synthesized compounds was determined by the broth microdilution method according to National Committee for Clinical Laboratory Standards (NCCLS).[43] The standard deviation value is expressed in terms of ±SD ($\leq$0.5). All the synthesized compounds (**6a–l**, **7a–l**) are screened for their antibacterial and antifungal activities in three sets (n = 3) against bacteria and fungi used in the present protocol. The results are summarized in Table 1.

The antibacterial screening of compounds **3a** and **3b** and their pyrazoline **6a–l** and isoxazoline **7a–l** derivatives (Table 1) pointed out that compounds **6k** and **7h** showed an outstanding inhibitory effect *i.e.* 62.5 μg mL^{-1} against *C. tetani* as compared



Entry 6,7	R_1	R_2
a	H	H
b	H	Ph
c	H	OCH_3
d	H	Br
e	H	F
f	CH_3	OH
g	CH_3	H
h	CH_3	Ph
i	CH_3	OCH_3
j	CH_3	Br
k	CH_3	F
l	CH_3	OH

Scheme 1 Synthesis of the substituted pyrazolines **6a–l** and isoxazolines **7a–l**. (i) DMF, K_2CO_3, reflux 2 h. (ii) 20% Ethanolic NaOH, room temperature. (iii) Hydrazine hydrate, glacial acetic acid, ethanol, reflux 1 h. (iv) Hydroxylamine hydrochloride, glacial acetic acid, ethanol, reflux 1 h.

Table 1 *In vitro* antimicrobial activity (MIC, μg mL^{-1}) of the synthesized compounds (**3a–b**, **6a–l**, **7a–l**)

	Gram positive bacteria			Gram negative bacteria			Fungi	
	S.P.	B.S.	C.T.	E.C.	S.T.	V.C.	C.A.	A.F.
	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC
Comp.	1936	441	449	443	98	3906	227	3008
3a	500	250	250	100	125	250	>1000	>1000
3b	500	250	**150**	250	200	250	**250**	500
6a	250	**100**	250	200	200	250	500	500
6b	500	500	**200**	100	200	500	500	1000
6c	250	250	**200**	250	250	250	1000	250
6d	250	**200**	**200**	125	500	500	500	1000
6e	200	**100**	**125**	100	250	250	1000	250
6f	500	**200**	**200**	200	200	500	**250**	250
6g	200	**125**	**100**	125	250	125	1000	1000
6h	100	**200**	250	125	250	100	>1000	>1000
6i	200	**200**	**200**	250	250	250	1000	500
6j	200	250	250	125	200	250	500	1000
6k	500	**100**	**62.5**	200	250	500	500	250
6l	250	**100**	**100**	100	200	**62.5**	>1000	500
7a	500	500	**200**	125	250	500	500	500
7b	500	250	250	100	200	500	1000	250
7c	500	**200**	**200**	100	500	250	1000	500
7d	200	**200**	250	200	250	250	500	1000
7e	500	**125**	**200**	100	125	500	1000	200
7f	250	**100**	**100**	250	200	250	1000	200
7g	250	**200**	250	200	250	200	>1000	>1000
7h	500	500	**62.5**	200	200	250	500	1000
7i	250	**200**	**200**	250	250	500	1000	500
7j	200	**200**	**200**	250	200	250	500	1000
7k	200	250	**200**	200	**62.5**	125	**250**	1000
7l	250	**200**	250	250	200	500	>1000	1000
A	100	250	250	100	100	100	n.t.[a]	n.t.
B	10	100	50	10	10	10	n.t.	n.t.
C	25	50	100	25	25	25	n.t.	n.t.
D	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	100	100
E	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	500	100

S.P.: streptococcus pneumoniae, B.S.: bacillus subtilis, C.T.: clostridium tetani, E.C.: escherichia coli S.T.: salmonella typhi, V.C.: vibrio cholerae, C.A.: candida albicans, A.F.: aspergillus fumigatus, MTCC: microbial type culture collection. A: ampicillin, B: norfloxacin, C: ciprofloxacin, D: nystatin, E: griseofulvin. [a] n.t.: not tested.

to ampicillin *i.e.* 250 μg mL^{-1} and ciprofloxacin. The majority of the compounds showed excellent activity against gram positive bacteria *B. subtilis* and *C. tetani* as that of the ampicillin. In the case of inhibiting *S. pneumoniae*, compound **6h** was found to be equipotent as ampicillin. Whereas in the case of inhibiting Gram negative bacteria, compounds **6l** and **7k** showed maximum activity against *V. cholera* and *S. typhi* as compared to ampicillin. Compounds **3a**, **6b**, **6e**, **6l**, **7b**, **7c**, and **7e** showed similar activity against *E. coli* upon comparison with the standard drug ampicillin. Compound **6h** was found to be equally active against *V. cholera* as compared to ampicillin. The antibacterial results revealed that most of the prepared compounds showed improved activity against the Gram-positive bacteria rather than Gram-negative bacteria.

From *in vitro* antifungal activity data, it is found that compounds **3b**, **6f** and **7k** displayed highest antifungal activity against *C. albicans* as compared to griseofulvin. Compounds **6a**, **6b**, **6d**, **6j**, **6k**, **7a**, **7d** and **7h** showed the same potency as griseofulvin. While none of the compounds were found to be active against *A. fumigatus*.

2.2.2. *In vitro* antituberculosis activity. All the synthesized compounds were tested for their *in vitro* antituberculosis activity against the *Mycobacterium tuberculosis* H37Rv strain. Primary screening of all the newly synthesized compounds was conducted at 250 μg mL^{-1} and 100 μg mL^{-1} by using Lowensteine–Jensen medium (conventional method) as described by Rattan.[44] The standard deviation value is shown in terms of ±SD ($\leq$0.75). All the newly synthesized compounds are screened for their antituberculosis activity in three sets (n = 3) against *M. tuberculosis* used in this study. The standard drugs rifampicin and isoniazid were used for comparison.

The bioassay results obtained for the efficacy of all the synthesized compounds **3a–3b**, **6a–l** and **7a–l** against *M. tuberculosis* H37Rv are summarized in Table 2. The antituberculosis screening data revealed that all the tested compounds showed moderate to very good inhibitory activity. The outcome of the results showed that compounds **6f**, **6j**, **7j** and **7f** are found to possess excellent activity, respectively, 92%, 88%, 90% and 88% at 250 μg mL^{-1} against *M. tuberculosis* H37Rv. Among the above four compounds, two compounds **6f** and **7j** also showed brilliant activity (*i.e.* 90%) at 100 μg mL^{-1} concentration. While compounds **6b** and **7b** were found to be

Table 2 *In vitro* antituberculosis activity (% inhibition) of the synthesized compounds (**3a–b**, **6a–l**, **7a–l**) against *M. tuberculosis* H37Rv (at concentrations 250 μg mL^{-1} and 100 μg mL^{-1})

	Inhibition (%)			Inhibition (%)	
Comp.	100 μg mL^{-1}	250 μg mL^{-1}	Comp.	100 μg mL^{-1}	250 μg mL^{-1}
3a	22	18	**7a**	68	54
3b	56	48	**7b**	75	54
6a	28	22	**7c**	48	32
6b	76	62	**7d**	40	34
6c	30	24	**7e**	46	34
6d	56	48	**7f**	**88**	**76**
6e	60	52	**7g**	47	30
6f	**92**	**90**	**7h**	32	28
6g	48	34	**7i**	48	36
6h	56	44	**7j**	**90**	**90**
6i	23	21	**7k**	46	39
6j	**88**	**82**	**7l**	86	82
6k	68	62	Rifampicin	98	98
6l	76	67	Isoniazid	99	99

Table 3 *In vitro* antimalarial activity of the synthesized compounds (**3a–b**, **6a–l**, **7a–l**)

Comp.	IC_{50} (μg mL^{-1})	Comp.	IC_{50} (μg mL^{-1})
3a	1.25	**7a**	**0.074**
3b	0.988	**7b**	**0.084**
6a	**0.081**	**7c**	0.70
6b	**0.067**	**7d**	**0.036**
6c	0.69	**7e**	0.78
6d	**0.012**	**7f**	1.24
6e	**0.058**	**7g**	**0.084**
6f	**0.036**	**7h**	1.047
6g	**0.089**	**7i**	**0.068**
6h	0.70	**7j**	1.046
6i	0.72	**7k**	0.32
6j	0.88	**7l**	**0.080**
6k	1.032	Chloroquine	0.020
6l	0.78	Quinine	0.268

moderately active against *M. tuberculosis* H37Rv. All other remaining compounds showed poor inhibition of *M. tuberculosis* growth. From the above results, it can be concluded that compounds **6f** and **7j** may become a new class of antitubercular agents in the future.

2.2.3. *In vitro* antimalarial activity. All the new pyrazoline **6a–l** and isoxazoline **7a–l** derivatives were tested for their antimalarial activity against the *P. falciparum* strain. The obtained results are presented in Table 3. The results of the pharmacological screening data are expressed as the drug concentration resulting in 50% inhibition (IC_{50}) of parasite growth.

The standard deviation value is expressed in terms of ±SD (≤0.5). Compounds **6a–l** and **7a–l** are screened for their malarial activity in three sets (n = 3) against *P. falciparum* used in the present procedure. Chloroquine and quinine were used as the standard drugs for comparison (Fig. 2).

All the synthesized compounds (**3a–b**, **7a–l** and **8a–l**) were screened for their antimalarial activity against chloroquine and quinine sensitive strains of *P. falciparum*. All experiments were performed in duplicate and the mean value of IC_{50} is mentioned in Table 3. Compounds **6a**, **6b**, **6d**, **6e**, **6f**, **6g**, **7a**, **7b**, **7d**, **7g**, **7i** and **7l** were found to have IC_{50} in the range of 0.012 to 0.089 for the *P. falciparum* strain. These compounds displayed excellent activity against the *P. falciparum* strain as compared to quinine with IC_{50} 0.268. Among all the above compounds, only compound **6d** demonstrates superior activity, *i.e.* IC_{50} 0.012, against chloroquine with IC_{50} 0.020. Moreover compounds **6f** and **7d** were found to possess moderate activity, *i.e.* IC_{50} 0.036 in agreement with chloroquine *i.e.* IC_{50} 0.020. All other remaining compounds were found to be not as much active as chloroquine and quinine against the *P. falciparum* strain.

2.2.4. *In vitro* antioxidant activity. The antioxidant activity of the entire series was investigated by using ascorbic acid as the standard antioxidant compound and results are listed in Table 4. Ferric reducing antioxidant power (FRAP) was measured by a modified method.[45] The antioxidant potentials of the compounds were estimated as their power to reduce the TPTZ–Fe(III) complex to the TPTZ–Fe(II) complex. The absorbance of the intense blue coloured [Fe(II)–TPTZ] complex was measured at 593 nm. The standard deviation value is shown in terms of ±SD (≤0.75). All the newly synthesized compounds are screened for their antioxidant activity in three sets (n = 3) in this study. The results were expressed as ascorbic equivalents (mmol per 100 g of the compound).

The measurement of ferric reducing power (FRAP) for the synthesized compounds (**6c**, **6d**, **6e**, **6f**, **6h**, **6k**, **7c**, **7e**, **7h** and **7k**) gave the FRAP value ranging from 421.71 to 497.49 mmol per 100 g of compounds. This indicates that these compounds are good antioxidants. Compound **6g** showed poor antioxidant

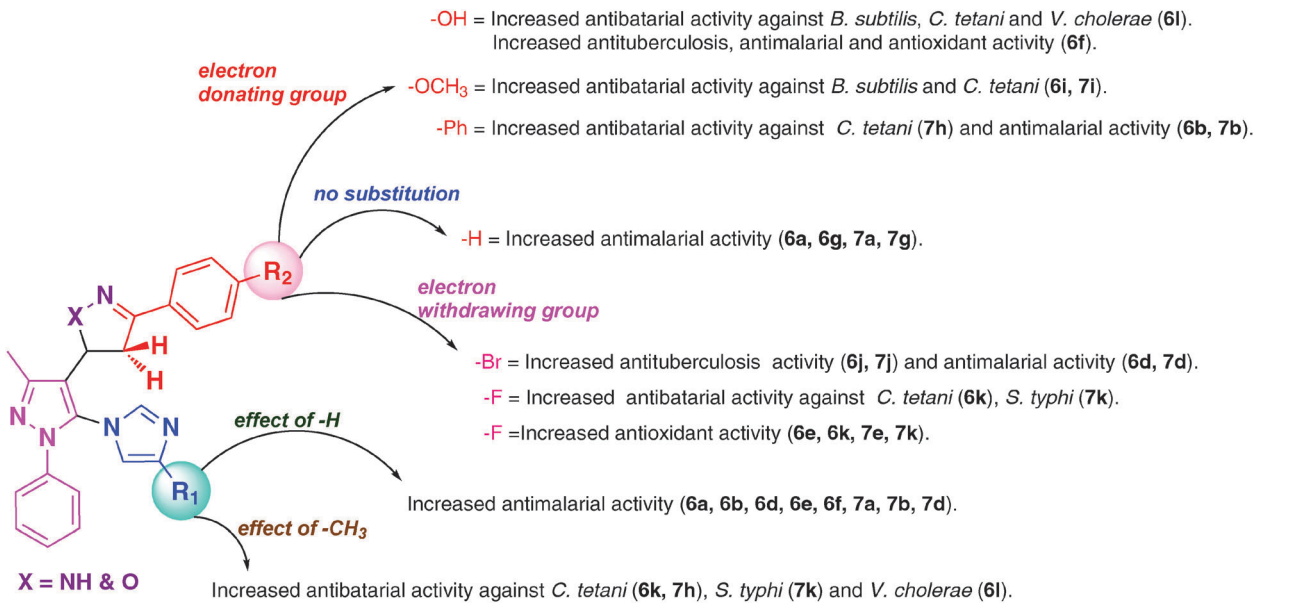


Fig. 2 Structure–activity relationship for antimicrobial, antituberculosis, antimalarial and antioxidant activities of the synthesized compounds.

Table 4 *In vitro* antioxidant activity of compounds **6a–l** and **7a–l**

Comp.	OD (593 nm)	Frap value[a]	Comp.	OD (593 nm)	Frap value[a]
3a	1.013	201.50	**7a**	1.789	355.86
3b	1.169	232.53	**7b**	1.818	361.63
6a	1.289	256.40	**7c**	**2.293**	**456.12**
6b	1.959	389.68	**7d**	1.846	367.20
6c	**2.120**	**421.71**	**7e**	**2.489**	**495.11**
6d	**2.206**	**438.81**	**7f**	1.986	395.05
6e	**2.488**	**494.91**	**7g**	1.105	219.80
6f	**2.212**	**440.01**	**7h**	**2.501**	**497.49**
6g	0.378	75.19	**7i**	1.959	389.68
6h	**2.501**	**497.49**	**7j**	1.745	347.11
6i	1.689	335.97	**7k**	**2.419**	**481.18**
6j	1.995	396.84	**7l**	1.732	344.52
6k	**2.485**	**494.31**	A.A.	2.501	
6l	1.824	362.83			

A.A. = ascorbic acid, concentration of compounds used = 200 mg mL^{-1}, concentration of standard (A.A.) = 176 mg mL^{-1}. [a] A.A. mmol per 100 g of the sample.

power while the remaining other compounds showed moderate antioxidant activity (Table 4).

2.3. Structure–activity relationship (SAR)

The substitution pattern of the aryl ring at the third position in the pyrazoline/isoxazoline ring was observed to affect biological activity. It emerged that the electron withdrawing and releasing groups were found to be responsible for variation in activity. The electronic nature of the substituents led to significant variation in all kinds of pharmacological activities. Compounds containing electron-donating substituents (–OH, $–OCH_3$) in the basic skeleton led to an increase in the antibacterial activity against *B. subtilis* and *C. tetani* (**6i**, **6l**, **7i**). While only the –OH group was found to increase antimalarial, antituberculosis and antioxidant activities. The phenyl group (weak electron donating) was found to be accountable for increasing antimalarial activity (**6b**, **7b**). The phenyl ring without any electron donating or withdrawing group also showed potent antimalarial activity (**6a**, **6g**, **7a**, and **7g**). In contrast, compounds bearing electron withdrawing groups (–Br) possessed stronger antituberculosis (**6j**, **7j**) and antimalarial activity (**6d**, **7d**). Whereas fluorine was observed to be responsible for intensified antibacterial and antioxidant activities. The substitution pattern (–H, $–CH_3$) at the fourth position in the imidazole moiety was also found to be responsible for discrepancy in activities. Compounds having hydrogen showed increased antimalarial activity while methyl substituted compounds showed higher antibacterial activity. On the basis of SAR, it has been observed that compounds having electron withdrawing fluoro groups show increased antimalarial and antioxidant activities. While the bromine group is responsible for enhancing the antimalarial activity and substitution of the methyl group on the imidazole ring enhances the antituberculosis activity.

The substitution pattern of pyrazoline and isoxazoline rings was also found to affect the biological activity. Compounds **6e** and **6f** have the pyrazoline ring, which enhanced the antimalarial activity. But the replacement of the nitrogen atom of the pyrazoline ring by the oxygen atom to form the isoxazoline ring worsens the antimalarial activity of **7e** and **7f**. The same kind of result was observed for the antioxidant activity. Compound **6d** has the pyrazoline ring, which increases its antioxidant potency. While compound **7d** has the isoxazoline ring, which decreases its antioxidant activity. Compounds **6k** and **6l** having the pyrazoline ring showed enhanced antibacterial activity against *C. tetani* and *V. cholerae* respectively. Whereas compounds **7k** and **7l** showed decreased antibacterial activity. In contrast, compound **7k** having the isoxazoline ring showed increased antibacterial activity against *S. typhi*, while compound **6k** has decreased potency because of the isoxaline ring.

3. Conclusion

A series of pyrazoline and isoxazoline derivatives carrying a 5-imidazo pyrazole moiety have been synthesized in good yield and screened for their biological activity with the aim of discovering innovative structure leads serving as potent antimicrobial, antituberculosis, antimalarial and antioxidant agents. Half of the compounds showed brilliant antimalarial activity against *P. falciparum* strains as compared to quinine. Two leading candidates (**6f** and **7j**) displayed modest antituberculosis activity. Most of the compounds were found to be active against *C. tetani* and *B. subtilis* and also illustrate good antioxidant activity. As for antifungal activity, compounds **3b**, **6f** and **7k** showed excellent activity against *C. albicans* as compared to griseofulvin. The results indicated that compounds bearing the electron withdrawing bromo group in the aryl moiety showed the highest antituberculosis and antimalarial activities.

4. Experimental section

4.1. Chemistry

All the chemicals were purchased from Sigma Aldrich and Merck – India. Commercial grade solvents were used and were distilled before use. Melting points were determined using a melting point apparatus μThermoCal$_{10}$ (Analab Scientific Pvt. Ltd, India) and are uncorrected. The completion of the reactions was checked by thin-layer chromatography (TLC) on aluminium plates coated with silica gel 60 F_{254}, 0.25 mm thickness (Merck) and detection of the components was made by exposure to iodine vapors or UV light. The IR spectra (in KBr pellets) were recorded on a Perkin-Elmer Spectrum GX FT-IR 157 spectrophotometer (Perkin-Elmer, USA) and only the characteristic peaks are reported in cm^{-1}. ^{1}H-NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using the residual solvent signal as an internal standard at 400 MHz. Chemical shifts (δ) are given in ppm and coupling constants (J) are in Hz. Mass spectra were recorded on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan) at Sardar Patel University (PURSE programme of DST), Vallabh Vidyanagar. The elemental analysis was carried out by using a Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all

compounds were found to be within ±0.4% of the theoretical compositions.

4.2. General procedure for the synthesis of substituted 5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehydes (3a–b)

5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** (1.1 g, 5 mmol), substituted imidazoles **2a–b** (7.5 mmol), anhydrous potassium carbonate (0.6 g, 10 mmol) and dimethylformamide (5 mL) were charged in a 50 mL round bottom flask equipped with a mechanical stirrer and a condenser. The reaction mixture was refluxed for 2 h and the progress of the reaction was monitored by TLC. After the completion of the reaction (as evidenced by TLC), the reaction mixture was cooled to room temperature and then poured into ice cold water (50 mL) with continuous stirring followed by neutralization with 1 N HCl to pH 7. The separated precipitates of substituted 5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazole-4 carbaldehydes **3a–b** were filtered, thoroughly washed with water, dried, and recrystallized from hot ethanol.

4.2.1. 5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3a). Yield 79%; m.p. 204 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.59 (s, 3H, CH_3), 7.07–7.46 (m, 7H, Ar–H), 7.94 (s, 1H, imidazole), 9.74 (s, 1H, CHO); ESI-MS (*m*/*z*): = 252.00 (M + 1).

4.2.2. 3-Methyl-5-(4-methyl-1*H*-imidazol-1-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3b). Yield 82%; m.p. 215 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.05 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 7.10–7.58 (m, 7H, Ar–H), 7.97 (s, 1H, imidazole), 9.59 (s, 1H, CHO); ESI-MS (*m*/*z*): = 267.00 (M + 1).

4.3. General procedure for the synthesis of (*E*)-3-(5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-phenylprop-2-en-1-one derivatives (pyrazolic chalcones 5a–l)

To a mixture of substituted 5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3a–b** (5.0 mmol) and acetophenones **4a–f** (5.0 mmol), 20% ethanolic NaOH (5 mL) was added. The reaction mixture was stirred at room temperature until formation of a precipitate. The solid obtained was isolated by filtration, washed with cold ethanol and recrystallized in $CHCl_3$.

4.4. General procedure for the synthesis of substituted 5′-(1*H*-imidazol-1-yl)-3′-methyl-1′,5-diphenyl-3,4-dihydro-1′*H*,2*H*-3,4′-bipyrazoles (6a–l)

The pyrazolic chalcones **5a–l** (1.0 mmol), hydrazine hydrate (1.5 mmol) and ethanol (5 mL) were refluxed for 1 h by using glacial acetic acid (1–2 drops) as the catalyst. After completion of the reaction (as monitored by TLC), the reaction mixture was cooled and poured into crushed ice. The resulting product was filtered, washed with cold water for several times and recrystallized from hot ethanol to give compounds **6a–l**.

4.4.1. 5′-(1*H*-Imidazol-1-yl)-3′-methyl-1′,5-diphenyl-3,4-dihydro-1′*H*,2*H*-3,4′-bipyrazole (6a). Yield 78%; m.p. 241 °C; IR (KBr, ν_{max}, cm^{-1}): 3288 (secondary amine –NH), 2950 (aromatic ring –CH), 1590 (–C═N), 1375 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 2.85 (dd, 1H, CH_2, *J* = 6.0 Hz, 12.4 Hz), 3.72 (dd, 1H, CH_2, *J* = 12.4 Hz, 17.2 Hz), 4.56 (t, 1H, CH, *J* = 10.8 Hz), 6.84–7.82 (m, 13H, Ar–H + 1H, NH); ESI-MS (*m*/*z*): = 369.40 (M + 1); anal. calcd (%) for $C_{22}H_{20}N_6$: C, 71.72; H, 5.47; N, 22.81. Found: C, 71.63; H, 5.53; N, 21.91.

4.4.2. 5-([1,1′-Biphenyl]-4-yl)-5′-(1*H*-imidazol-1-yl)-3′-methyl-1′-phenyl-3,4-dihydro-1′*H*,2*H*-3,4′-bipyrazole (6b). Yield 82%; m.p. 232 °C; IR (KBr, ν_{max}, cm^{-1}): 3284 (secondary amine –NH), 2944 (aromatic ring –CH), 1599 (–C═N), 1370 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.95 (dd, 1H, CH_2, *J* = 11.2 Hz, 16.4 Hz), 3.36 (dd, 1H, CH_2, *J* = 11.2 Hz, 16.4 Hz), 4.55 (td, 1H, CH, *J* = 3.2 Hz, 10.8 Hz), 7.07–7.84 (m, 17H, Ar–H + 1H, NH); ESI-MS (*m*/*z*): = 445.20 (M + 1); anal. calcd (%) for $C_{28}H_{24}N_6$: C, 75.65; H, 5.44; N, 18.91. Found: C, 75.63; H, 5.53; N, 18.71.

4.4.3. 5′-(1*H*-Imidazol-1-yl)-5-(4-methoxyphenyl)-3′-methyl-1′-phenyl-3,4-dihydro-1′*H*,2*H*-3,4′-bipyrazole (6c). Yield 75%; m.p. 262 °C; IR (KBr, ν_{max}, cm^{-1}): 3229 (secondary amine –NH), 3012 (aromatic ring –CH), 1651 (–C═N), 1375 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3), 2.94 (dd, 1H, CH_2, J = 6.0 Hz, 16.4 Hz, C_4-H pyrazoline), 3.13 (dd, 1H, CH_2, *J* = 10.2 Hz, 16.4 Hz, C_4-H pyrazoline), 3.92 (s, 3H, CH_3),4.51 (t, 1H, CH, *J* = 11.2 Hz, C_5-H pyrazoline), 7.09–8.23 (m, 12H, Ar–H + 1H, NH); ESI-MS (*m*/*z*): = 399.60 (M + 1); anal. calcd (%) for $C_{23}H_{22}N_6O$: C, 69,33; H, 5.57; N, 21.09. Found: C, 69.23; H, 5.55; N, 21.18.

4.4.4. 5-(4-Bromophenyl)-5′-(1*H*-imidazol-1-yl)-3′-methyl-1′-phenyl-3,4-dihydro-1′*H*,2*H*-3,4′-bipyrazole (6d). Yield 71%; m.p. 234 °C; IR (KBr, ν_{max}, cm^{-1}): 3306 (secondary amine –NH), 3017 (aromatic ring –CH), 1613 (–C═N), 1378 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.45 (s, 3H, CH_3), 2.90 (dd, 1H, CH_2, *J* = 11.6 Hz, 16.4 Hz, C_4-H pyrazoline), 3.28 (dd, 1H, CH_2, *J* = 16 Hz, 16.4 Hz, C_4-H pyrazoline), 4.48 (t, 1H, CH, *J* = 11.2 Hz, C_5-H pyrazoline), 7.12–8.12 (m, 12H, Ar–H + 1H, NH); ESI-MS (*m*/*z*): = 447.9 (M + 1), 449.80 (M + 2); anal. calcd (%) for $C_{22}H_{19}BrN_6$: C, 59.07; H, 4.28; N, 18.79. Found: C, 58.93; H, 4.23; N, 18.91.

4.4.5. 5-(4-Fluorophenyl)-5′-(1*H*-imidazol-1-yl)-3′-methyl-1′-phenyl-3,4-dihydro-1′*H*,2*H*-3,4′-bipyrazole (6e). Yield 78%; m.p. 263 °C; IR (KBr, ν_{max}, cm^{-1}): 3296 (secondary amine –NH), 2981 (aromatic ring –CH), 1651 (–C═N), 1370 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 3H, CH_3), 2.90 (dd, 1H, CH_2, *J* = 10.4 Hz, 15.6 Hz, C_4-H pyrazoline), 3.31 (dd, 1H, CH_2, *J* = 16.4 Hz, 27.6 Hz, C_4-H pyrazoline), 4.52 (t, 1H, CH, *J* = 10.4 Hz, C_5-H pyrazoline), 7.04–7.81 (m, 12H, Ar–H + 1H, NH); ESI-MS (*m*/*z*): = 387.30 (M + 1); anal. calcd (%) for $C_{22}H_{19}FN_6$: C, 68.38; H, 4.96; N, 21.75. Found: C, 68.44; H, 4.93; N, 21.80.

4.4.6. 4-(5′-(1*H*-Imidazol-1-yl)-3′-methyl-1′-phenyl-3,4-dihydro-1′*H*,2*H*-[3,4′-bipyrazol]-5-yl)phenol (6f). Yield 84%; m.p. 212 °C; IR (KBr, ν_{max}, cm^{-1}): 3289 (secondary amine –NH), 3012 (aromatic ring –CH), 1621 (–C═N), 1378 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.06 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.83 (dd, 1H, CH_2, *J* = 11.6 Hz, 16.4 Hz, C_4-H pyrazoline), 3.33 (dd, 1H, CH_2, *J* = 11.2 Hz, 16.4 Hz, C_4-H pyrazoline), 4.55 (td, 1H, CH, *J* = 11.2 Hz, 16.4 Hz, C_5-H pyrazoline), 6.76–7.81 (m, 11H, Ar–H + 1H, NH), 9.63 (1H, OH); ESI-MS (*m*/*z*): = 385.90 (M + 1); anal. calcd (%) for $C_{22}H_{20}N_6O$: C, 68.73; H, 5.24; N, 21.86. Found: C, 68.83; H, 5.25; N, 21.88.

4.4.7. 3′-Methyl-5′-(4-methyl-1*H*-imidazol-1-yl)-1′,5-diphenyl-3,4-dihydro-1′*H*,2*H*-3,4′-bipyrazole (6g). Yield 76%; m.p. 249 °C; IR (KBr, ν_{max}, cm^{-1}): 3339 (secondary amine –NH), 2996 (aromatic ring –CH), 1641 (–C═N), 1370 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.05 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.87 (dd, 1H, CH_2, J = 9.6 Hz, 16.4 Hz, C_4-H pyrazoline), 3.60 (dd, 1H, CH_2, J = 6.8 Hz, 17.2 Hz, C_4-H pyrazoline), 4.56 (t, 1H, CH, J = 6.0 Hz, C_5-H pyrazoline), 6.85–7.89 (m, 12H, Ar–H + 1H, NH); ESI-MS (m/z): = 383.50 (M + 1); anal. calcd (%) for $C_{23}H_{22}N_6$: C, 72.23; H, 5.80; N, 21.97. Found: C, 72.05; H, 5.80; N, 22.18.

4.4.8. 5-([1,1′-Biphenyl]-4-yl)-3′-methyl-5′-(4-methyl-1*H*-imidazol-1-yl)-1′-phenyl-3,4-dihydro-1′*H*,2*H*-3,4′-bipyrazole (6h). Yield 82%; m.p. 239 °C; IR (KBr, ν_{max}, cm^{-1}): 3286 (secondary amine –NH), 2999 (aromatic ring –CH), 1631 (–C═N), 1374 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.94 (dd, 1H, CH_2, J = 11.2 Hz, 16.4 Hz, C_4-H pyrazoline), 3.36 (dd, 1H, CH_2, J = 11.2 Hz, 16.4 Hz, C_4-H pyrazoline), 4.54 (td, 1H, CH, J = 3.2 Hz, 10.8 Hz, C_5-H pyrazoline), 7.05–7.89 (m, 16H, Ar–H + 1H, NH); ESI-MS (m/z): = 459.7 (M + 1); anal. calcd (%) for $C_{29}H_{26}N_6$: C, 75.96; H, 5.71; N, 18.33. Found: C, 76.05; H, 5.80; N, 28.08.

4.4.9. 5-(4-Methoxyphenyl)-3′-methyl-5′-(4-methyl-1*H*-imidazol-1-yl)-1′-phenyl-3,4-dihydro-1′*H*,2*H*-3,4′-bipyrazole (6i). Yield 76%; m.p. 249 °C; IR (KBr, ν_{max}, cm^{-1}): 3342 (secondary amine –NH), 2937 (aromatic ring –CH), 1651 (–C═N), 1375 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.12 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.88 (dd, 1H, CH_2, J = 6.0 Hz, 16.4 Hz, C_4-H pyrazoline), 3.13 (dd, 1H, CH_2, J = 7.6 Hz, 16.4 Hz, C_4-H pyrazoline), 3.93 (s, 3H, CH_3),4.41 (t, 1H, CH, J = 11.2 Hz, C_5-H pyrazoline), 6.10–7.78 (m, 11H, Ar–H + 1H, NH); ESI-MS (m/z): = 413.3 (M + 1); anal. calcd (%) for $C_{24}H_{24}N_6O$: C, 69.88; H, 5.86; N, 20.37. Found: C, 70.05; H, 5.80; N, 20.58.

4.4.10. 5-(4-Bromophenyl)-3′-methyl-5′-(4-methyl-1*H*-imidazol-1-yl)-1′-phenyl-3,4-dihydro-1′*H*,2*H*-3,4′-bipyrazole (6j). Yield 69%; m.p. 239 °C; IR (KBr, ν_{max}, cm^{-1}): 3321 (secondary amine –NH), 2981 (aromatic ring –CH), 1599 (–C═N), 1368 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.11 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.89 (dd, 1H, CH_2, J = 11.6 Hz, 16.4 Hz, C_4-H pyrazoline), 3.28 (dd, 1H, CH_2, J = 16 Hz, 16.4 Hz, C_4-H pyrazoline), 4.45 (t, 1H, CH, J = 11.2 Hz, C_5-H pyrazoline), 6.10–7.77 (m, 11H, Ar–H + 1H, NH); ESI-MS (m/z): = 462.30 (M + 1), 463.20 (M + 2); anal. calcd (%) for $C_{23}H_{21}BrN_6$: C, 59.88; H, 4.59; N, 18.22. Found: C, 59.76; H, 4.60; N, 18.28.

4.4.11. 4-(3-(4-Fluorophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)-3-methyl-5-(4-methyl-1*H*-imidazol-1-yl)-1-phenyl-1*H*-pyrazole (6k). Yield 86%; m.p. 219 °C; IR (KBr, ν_{max}, cm^{-1}): 3344 (secondary amine –NH), 2969 (aromatic ring –CH), 1611 (–C═N), 1372 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.11 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.89 (dd, 1H, CH_2, J = 11.6 Hz, 16.4 Hz, C_4-H pyrazoline), 3.27 (dd, 1H, CH_2, J = 15.6 Hz, 16.4 Hz, C_4-H pyrazoline), 4.43 (t, 1H, CH, J = 10.8 Hz, C_5-H pyrazoline), 6.02–7.72 (m, 11H, Ar–H + 1H, NH); ESI-MS (m/z): = 401.30 (M + 1); anal. calcd (%) for $C_{23}H_{21}FN_6$: C, 68.98; H, 5.29; N, 20.99. Found: C, 68.86; H, 5.18; N, 21.12.

4.4.12. 4-(5-(3-Methyl-5-(4-methyl-1*H*-imidazol-1-yl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenol (6l). Yield 86%; m.p. 219 °C; IR (KBr, ν_{max}, cm^{-1}): 2935 (secondary amine –NH), 2949 (aromatic ring –CH), 1591 (–C═N), 1375 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 3H, CH_3), 2.84 (dd, 1H, CH_2, J = 11.6 Hz, 16.4 Hz, C_4-H pyrazoline), 3.27 (dd, 1H, CH_2, J = 11.2 Hz, 16.4 Hz, C_4-H pyrazoline), 4.50 (td, 1H, CH, J = 11.2 Hz, 16.4 Hz, C_5-H pyrazoline), 6.73–7.89 (m, 11H, Ar–H + 1H, NH), 9.68 (1H, OH); ESI-MS (m/z): = 399.10 (M + 1); anal. calcd (%) for $C_{23}H_{22}N_6O$: C, 69.33; H, 5.57; N, 21.09. Found: C, 69.26; H, 5.58; N, 21.21.

4.5. General procedure for the synthesis of substituted 5-(5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-phenyl-4,5-dihydroisoxazoles (7a–l)

A mixture of pyrazolic chalcones **5a–l** (1.0 mmol), hydroxylamine hydrochloride (1.5 mmol) and ethanol (5 mL) was refluxed for 1 h by using glacial acetic acid (1–2 drops) as the catalyst. After completion of the reaction (as monitored by TLC), the reaction mixture was cooled and poured into crushed ice. The resulting product was filtered, washed with cold water for several times and recrystallized from hot ethanol to give compounds **7a–l**.

4.5.1. 5-(5-(1*H*-Imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-phenyl-4,5-dihydroisoxazole (7a). Yield 77%; m.p. 249 °C; IR (KBr, ν_{max}, cm^{-1}): 3010 (aromatic ring –CH), 1587 (–C═N), 1520 (N–O), 1374 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 2.90 (dd, 1H, CH_2, J = 3.2 Hz, 16.4 Hz, C_4-H isoxazoline), 3.30 (dd, 1H, CH_2, J = 3.2 Hz, 16.4 Hz, C_4-H isoxazoline), 4.55 (t, 1H, CH, J = 10.8 Hz, C_5-H isoxazoline), 6.33–7.87 (m, 13H, Ar–H); ESI-MS (m/z): = 370.10 (M + 1); anal. calcd (%) for $C_{22}H_{19}N_5O$: C, 71.53; H, 5.18; N, 18.96. Found: C, 71.46; H, 5.12; N, 19.06.

4.5.2. 5-(5-(1*H*-Imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-(biphenyl-4-yl)-4,5-dihydroisoxazole (7b). Yield 83%; m.p. 229 °C; IR (KBr, ν_{max}, cm^{-1}): 3017 (aromatic ring –CH), 1630 (–C═N), 1549 (N–O), 1374 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 3H, CH_3), 2.93 (dd, 1H, CH_2, J = 6.0 Hz, 12.4 Hz, C_4-H isoxazoline), 3.34 (dd, 1H, CH_2, J = 12.4 Hz, 17.6 Hz, C_4-H isoxazoline), 4.52 (t, 1H, CH, J = 10.8 Hz, C_5-H isoxazoline), 6.80–7.63 (m, 17H, Ar–H); ESI-MS (m/z): = 446.30 (M + 1); anal. calcd (%) for $C_{28}H_{23}N_5O$: C, 75.49; H, 5.20; N, 15.72. Found: C, 75.46; H, 5.12; N, 15.86.

4.5.3. 5-(5-(1*H*-Imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (7c). Yield 73%; m.p. 235 °C; IR (KBr, ν_{max}, cm^{-1}): 3010 (aromatic ring –CH), 1587 (–C═N), 1537 (N–O), 1379 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.94 (dd, 1H, CH_2, J = 6.4 Hz, 9.6 Hz, C_4-H isoxazoline), 3.23 (dd, 1H, CH_2, J = 6.0 Hz, 7.2 Hz, C_4-H isoxazoline), 3.92 (s, 3H, CH_3),4.60 (t, 1H, CH, J = 10.0 Hz, C_5-H isoxazoline), 7.26–8.23 (m, 12H, Ar–H); ESI-MS (m/z): = 400.50 (M + 1); anal. calcd (%) for $C_{23}H_{21}N_5O_2$: C, 69.16; H, 5.30; N, 17.53. Found: C, 68.98; H, 5.22; N, 17.91.

4.5.4. 5-(5-(1*H*-Imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-(4-bromophenyl)-4,5-dihydroisoxazole (7d). Yield 76%; m.p. 233 °C; IR (KBr, ν_{max}, cm^{-1}): 3019 (aromatic ring –CH), 1601 (–C═N), 1515 (N–O), 1379 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.44 (s, 3H, CH_3), 2.90 (dd, 1H, CH_2, J = 12 Hz, 16.4 Hz, C_4-H isoxazoline), 3.26 (dd, 1H, CH_2, J = 16.4 Hz, 16.4 Hz, C_4-H isoxazoline), 4.46 (t, 1H, CH, J = 10.8 Hz,

C_5-H isoxazoline), 6.00–7.73 (m, 12H, Ar–H); ESI-MS (*m*/*z*): = 449.00 (M + 1), 450.80 (M + 2); anal. calcd (%) for $C_{22}H_{18}BrN_5O$: C, 58.94; H, 4.05; N, 15.62. Found: C, 58.98; H, 3.96; N, 15.71.

4.5.5. 5-(5-(1*H*-Imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-(4-fluorophenyl)-4,5-dihydroisoxazole (7e). Yield 86%; m.p. 219 °C; IR (KBr, ν_{max}, cm^{-1}): IR (KBr, ν_{max}, cm^{-1}): 2979 (aromatic ring –CH), 1654 (–C═N), 1525 (N–O), 1369 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.43 (s, 3H, CH_3), 2.88 (dd, 1H, CH_2, *J* = 11.6 Hz, 16.4 Hz, C_4-H isoxazoline), 3.28 (dd, 1H, CH_2, *J* = 16.4 Hz, 16.8 Hz, C_4-H isoxazoline), 4.48 (t, 1H, CH, *J* = 11.2 Hz, C_5-H isoxazoline), 5.97–7.77 (m, 12H, Ar–H); ESI-MS (*m*/*z*): = 388.40 (M + 1); anal. calcd (%) for $C_{22}H_{18}FN_5O$: C, 68.21; H, 4.68; N, 18.08. Found: C, 68.18; H, 4.66; N, 18.01.

4.5.6. 4-(5-(5-(1*H*-Imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dihydroisoxazol-3-yl)phenol (7f). Yield 86%; m.p. 219 °C; IR (KBr, ν_{max}, cm^{-1}): 3015 (aromatic ring –CH), 1619 (–C═N), 1529 (N–O), 1378 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.87 (dd, 1H, CH_2, *J* = 11.6 Hz, 16.4 Hz, C_4-H isoxazoline), 3.28 (dd, 1H, CH_2, *J* = 10.8 Hz, 16.4 Hz, C_4-H isoxazoline), 4.48 (td, 1H, CH, *J* = 10.8 Hz, 16.4 Hz, C_5-H isoxazoline), 6.70–7.76 (m, 12H, Ar–H), 9.59 (1H, OH); ESI-MS (*m*/*z*): = 386.20 (M + 1); anal. calcd (%) for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17. Found: C, 68.45; H, 4.96; N, 18.29.

4.5.7. 5-(3-Methyl-5-(4-methyl-1*H*-imidazol-1-yl)-1-phenyl-1*H*-pyrazol-4-yl)-3-phenyl-4,5-dihydroisoxazole (7g). Yield 80%; m.p. 250 °C; IR (KBr, ν_{max}, cm^{-1}): 2995 (aromatic ring –CH), 1633 (–C═N), 1554 (N–O), 1370 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.87 (dd, 1H, CH_2, *J* = 11.2 Hz, 16.4 Hz, C_4-H isoxazoline), 3.31 (dd, 1H, CH_2, *J* = 15.6 Hz, 16.4 Hz, C_4-H isoxazoline), 4.53 (t, 1H, CH, *J* = 11.6 Hz, C_5-H isoxazoline), 6.90–7.84 (m, 12H, Ar–H); ESI-MS (*m*/*z*): = 384.50 (M + 1); anal. calcd (%) for $C_{23}H_{21}N_5O$: C, 72.04; H, 5.52; N, 18.26. Found: C, 71.90; H, 5.42; N, 18.38.

4.5.8. 3-(Biphenyl-4-yl)-5-(3-methyl-5-(4-methyl-1*H*-imidazol-1-yl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dihydroisoxazole (7h). Yield 85%; m.p. 241 °C; IR (KBr, ν_{max}, cm^{-1}): 2992 (aromatic ring –CH), 1632 (–C═N), 1532 (N–O), 1374 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.08 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.93 (dd, 1H, CH_2, *J* = 11.2 Hz, 16.4 Hz, C_4-H isoxazoline), 3.34 (dd, 1H, CH_2, *J* = 10.8 Hz, 16.4 Hz, C_4-H isoxazoline), 4.52 (td, 1H, CH, *J* = 3.2 Hz, 10.8 Hz, C_5-H isoxazoline), 6.99–7.74 (m, 16H, Ar–H); ESI-MS (*m*/*z*): = 460.5 (M + 1); anal. calcd (%) for $C_{29}H_{25}N_5O$: C, 75.80; H, 5.48; N, 15.24. Found: C, 76.10; H, 5.43; N, 14.98.

4.5.9. 3-(4-Methoxyphenyl)-5-(3-methyl-5-(4-methyl-1*H*-imidazol-1-yl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dihydroisoxazole (7i). Yield 78%; m.p. 243 °C; IR (KBr, ν_{max}, cm^{-1}): IR (KBr, ν_{max}, cm^{-1}): 2932 (aromatic ring –CH), 1651 (–C═N), 1539 (N–O), 1374 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.10 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.93 (dd, 1H, CH_2, *J* = 5.6 Hz, 16.4 Hz, C_4-H isoxazoline), 3.11 (dd, 1H, CH_2, *J* = 7.6 Hz, 16.4 Hz, C_4-H isoxazoline), 3.90 (s, 3H, CH_3),4.39 (t, 1H, CH, *J* = 10.8 Hz, C_5-H isoxazoline), 6.04–7.72 (m, 11H, Ar–H); ESI-MS (*m*/*z*): = 414.30 (M + 1); anal. calcd (%) for $C_{24}H_{23}N_5O_2$: C, 69.72; H, 5.61; N, 16.94. Found: C, 69.73; H, 5.53; N, 15.01.

4.5.10. 3-(4-Bromophenyl)-5-(3-methyl-5-(4-methyl-1*H*-imidazol-1-yl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dihydroisoxazole (7j). Yield 76%; m.p. 235 °C; IR (KBr, ν_{max}, cm^{-1}): 2989 (aromatic ring –CH), 1596 (–C═N), 1521 (N–O), 1368 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.09 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.89 (dd, 1H, CH_2, J = 12 Hz, 16.4 Hz, C_4-H isoxazoline), 3.28 (dd, 1H, CH_2, *J* = 16.4 Hz, 16.8 Hz, C_4-H isoxazoline), 4.46 (t, 1H, CH, *J* = 10.8 Hz, C_5-H isoxazoline), 5.98–7.78 (m, 11H, Ar–H); ESI-MS (*m*/*z*): = 463.20 (M + 1), 464.80 (M + 2); anal. calcd (%) for $C_{23}H_{20}BrN_5O$: C, 59.57; H, 4.36; N, 15.15. Found: C, 59.67; H, 4.33; N, 15.09.

4.5.11. 3-(4-Fluorophenyl)-5-(3-methyl-5-(4-methyl-1*H*-imidazol-1-yl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dihydroiso xazole (7k). Yield 86%; m.p. 219 °C; IR (KBr, ν_{max}, cm^{-1}): 2965 (aromatic ring –CH), 1613 (–C═N), 1542 (N–O), 1372 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.08 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.88 (dd, 1H, CH_2, *J* = 12 Hz, 16.4 Hz, C_4-H isoxazoline), 3.26 (dd, 1H, CH_2, *J* = 15.6 Hz, 16.8 Hz, C_4-H isoxazoline), 4.46 (t, 1H, CH, *J* = 11.2 Hz, C_5-H isoxazoline), 6.29–7.71 (m, 11H, Ar–H); ESI-MS (*m*/*z*): = 401.90 (M + 1); anal. calcd (%) for $C_{23}H_{20}FN_5O$: C, 68.81; H, 5.02; N, 17.45. Found: C, 69.04; H, 4.89; N, 17.69.

4.5.12. 3-(4-Bromophenyl)-5-(3-methyl-5-(4-methyl-1*H*-imidazol-1-yl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dihydroisoxazole (7l). Yield 86%; m.p. 219 °C; IR (KBr, ν_{max}, cm^{-1}): 3012 (aromatic ring –CH), 1621 (–C═N), 1560 (N–O), 1373 (Ar–CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3), 2.85 (dd, 1H, CH_2, J = 12.0 Hz, 16.4 Hz, C_4-H isoxazoline), 3.27 (dd, 1H, CH_2, *J* = 10.8 Hz, 16.4 Hz, C_4-H isoxazoline), 4.48 (td, 1H, CH, *J* = 11.2 Hz, 16.4 Hz, C_5-H isoxazoline), 6.72–7.76 (m, 11H, Ar–H), 9.62 (1H, OH); ESI-MS (*m*/*z*): = 400.30 (M + 1); anal. calcd (%) for $C_{23}H_{21}N_5O_2$: C, 69.16; H, 5.30; N, 17.53. Found: C, 69.34; H, 4.99; N, 17.61.

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