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LETTER

Synthesis, antitubercular and antimicrobial activity of 1'-(4-chlorophenyl) pyrazole containing 3,5-disubstituted pyrazoline derivatives

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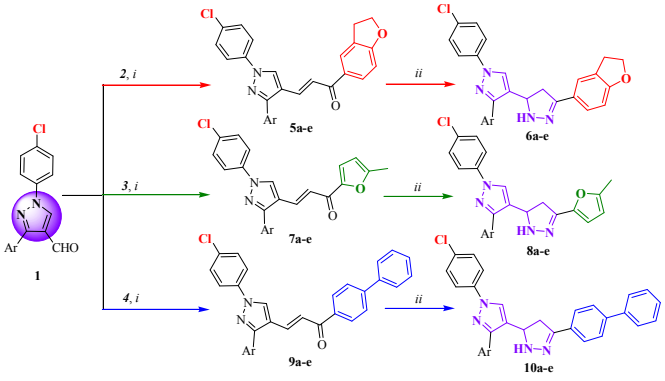
A new series of 1′-(4-chlorophenyl)-5-(substituted aryl)-3′-(substituted aryl)-3,4-dihydro-2*H*,1′*H*-[3,4′]bipyrazolyl (6a-e), (8a-e), (10a-e) have been synthesized, characterized and screened against antimicrobial and antitubercular activity. Among the synthesized compounds, Minimum Inhibition Concentration of 10e was found to be as low as 1.56 µg/ml and 10c had 6.25 µg/ml as compared to the standard anti-tb drugs Pyrazinamide and Streptomycin.

Mycobacterium Tuberculosis is one among the most dangerous bacteria, which causes the infectious disease and remains out of control in many developing countries.[1] It is a remarkable pathogenic bacteria, that has latently infected inside the body.[2] The control of the tuberculosis is most challenging in case of multi-drug resistance strains of *Mycobacterium tuberculosis*. The spread of multidrug-resistant TB (MDR-TB) and the appearance of extensively drug-resistant TB (XDR-TB) pose new challenges for the prevention, treatment and control of this deadly disease. Fewer new drugs were approved to treat tuberculosis with very long and complicated therapy.[3] It can be treated with multidrug combinations in an average span of six months.[2]

The azole class of drug derivatives and research has occupied an important role in the medicinal chemistry. Pyrazoles are well known nitrogen containing heterocyclic compounds. As per the literature, pyrazole and its derivatives represents one of the most desirable class of compounds with a wide variety of pharmacological activities *viz*., antitubercular,[4,5] antifungal,[6] antidepressant,[7,8] antimicrobial,[9] anti-angiogenic,[10] analgesic,[11] anticancer[12] and anticonvulsant.[13] Moreover, pyrazole containing pyrazoline derivatives are important drug molecules and exhibit an important pharmacophore activities *viz*. antioxidant,[14] antimicrobial[15] and antidiabetic.[16] Few of the literature reveals that, the presence of substituted phenyl *i.e.* 4-chlorophenyl or benzene sulfonamide at first position of pyrazole exhibit enhanced biological activities.[17] Based on the above considerations, we hereby report the synthesis of 1-(4-chlorophenyl) pyrazole containing pyrazoline derivatives and its antitubercular activity against *Mycobacterial tuberculosis*.

The targeted compounds 1′-(4-chlorophenyl)-5-(2,3-dihydrobenzofuran-5-yl)-3′-(substituted aryl)-3,4-dihydro-2*H*, 1′*H*-[3,4′]bipyrazolyl (**6a-e**), 1′-(4-chlorophenyl)-5-(5-methylfuran-2-yl)-3′-(substituted aryl)-3,4-dihydro-2*H*,1′*H*-[3,4′]bipyrazolyl (**8a-e**) and 5-biphenyl-4-yl-1′-(4-chlorophenyl)-3′-(substituted aryl)-3,4-dihydro-2*H*,1′*H*-[3,4′]bipyrazolyl (**10a-e**) were synthesized according to the steps outlined in Scheme 1.



Where: *2*= 5-Acetyl-2,3-dihydrobenzofuran; *3*= 5-Acetyl-2-methylfuran; *4*= Monoacetyl biphenyl
i= Methanol, cat. NaOH, RT, 4 h; *ii*= Hydrazine hydrate, Ethanol, Reflux, 3 h.

Scheme 1: Synthetic route for the pyrazole bearing pyrazoline derivatives

The basic pyrazole skeleton *i.e.* 1,3-disubstituted pyrazole-4-carbaldehydes **1** were synthesized by Vilsmeier-Haack reaction in moderate to good yields.[9] The other key starting materials 5-acetyl-2,3-dihydrobenzofuran **2**, 2-acetyl-5-methylfuran **3** and 4-monoacetylbiphenyl **4** were prepared as per the reported literature[18] and confirmed by IR and NMR. The 1,3-disubstituted pyrazole-4-carbaldehyde **1** reacted with **2**, **3** and **4** individually to give chalcone derivatives (**5a-e**, **7a-e, 9a-e)** respectively. Which on reacting with hydrazine hydrate in ethanol media under reflux temperature to give (**6a-e**, **8a-e**, **10a-e)** in reasonable yields.

Formation of **6a-e**, **8a-e**, **10a-e** were confirmed by recording their IR, ^{1}H NMR, ^{13}C NMR and mass spectra. IR analysis of compound **6a** showed the peak at 3322 cm^{-1} is due to the NH group. The absorption band at 1607cm^{-1} was due to the -C=N group and -C=C stretching was observed at 1497 cm^{-1}. The ^{1}H NMR spectrum of **6a** in DMSO-d_6 solvent showed a triplet at δ 2.90-2.96 which was attributed to H_A proton, and triplet at δ 3.42-3.49 was due

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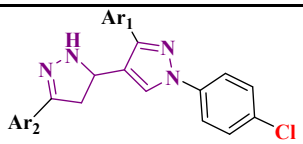
to the H_B proton of the pyrazoline ring. The characteristic peak of -NH proton of pyrazoline was observed as a singlet at δ 8.62. The detailed ^{1}H NMR resonances are summarized in the experimental section. The mass spectrum of **6a** showed a molecular ion peak at *m/z* = 441.2 (M^+). This in turn confirmed the formation of a compound having the molecular formula $C_{26}H_{21}ClN_4O$. The other compounds **8a-e** and **10a-e** were explained in the supplementary material. The characterization data of the newly synthesized compounds **6a-e**, **8a-e** and **10a-e** were presented in Table 1.

Table 1 Characterization data of the compounds **6a-e**, **8a-e** and **10a-e**



Compounds	Ar_1	Ar_2	Mol. F/ Mol. wt	M.P (°C)	Color & nature
6a	Phenyl	5-(2,3-dihydrobenzofuran)	$C_{26}H_{21}ClN_4O$/ 440.92	156-157	White solid
6b	4-Methylphenyl	5-(2,3-dihydrobenzofuran)	$C_{27}H_{23}ClN_4O$/ 454.95	151-153	Off-white solid
6c	4-Methoxyphenyl	5-(2,3-dihydrobenzofuran)	$C_{27}H_{23}ClN_4O$/ 470.95	132-134	Off-white solid
6d	4-Chlorophenyl	5-(2,3-dihydrobenzofuran)	$C_{26}H_{20}Cl_2N_4O$/ 475.37	171-172	white solid
6e	2-Thiophene	5-(2,3-dihydrobenzofuran)	$C_{24}H_{19}ClN_4OS$/ 446.95	140-141	White solid
8a	Phenyl	5-(2-methylfuran)	$C_{23}H_{19}ClN_4O$/ 402.88	144-145	White solid
8b	4-Methylphenyl	5-(2-methylfuran)	$C_{24}H_{21}ClN_4O$/ 416.90	206-208	Off-white solid
8c	4-Methoxyphenyl	5-(2-methylfuran)	$C_{24}H_{21}ClN_4O_2$/ 432.9	156-157	Off-white solid
8d	4-Chlorophenyl	5-(2-methylfuran)	$C_{23}H_{18}Cl_2N_4O$/ 437.32	198-200	Off-white solid
8e	2-Thiophene	5-(2-methylfuran)	$C_{21}H_{17}ClN_4OS$/ 408.9	186-187	Off-white solid
10a	Phenyl	4-(biphenyl)	$C_{30}H_{23}ClN_4$/ 474.98	164-165	Off-white solid
10b	4-Methylphenyl	4-(biphenyl)	$C_{31}H_{25}ClN_4$/ 489.01	157-158	Off-white solid
10c	4-Methoxyphenyl	4-(biphenyl)	$C_{31}H_{25}ClN_4O$/ 505.01	160-162	Off-white solid
10d	4-Chlorophenyl	4-(biphenyl)	$C_{30}H_{22}Cl_2N_4$/ 509.43	184-186	white solid
10e	2-Thiophene	4-(biphenyl)	$C_{28}H_{21}ClN_4S$/ 481.01	217-219	Off-white solid

Antimicrobial activity of all the synthesized compounds were screened against *Staphylococcus aureus* (Gram positive bacteria), *Mycobacterium smegmatis* (tubercular variant), and *Candida albicans* (fungi). The Minimum Inhibitory Concentration (MIC) of all the organisms tested at different concentrations ranging from 500 to 3.9 µg/ml. Most of the compounds were exhibited the activity with MIC ranging between 62.5 to 7.8 µg/ml. Structure activity relationship of the synthesized compound was explained based on MIC. The compound **10e** showed lowest MIC against all tested organisms due to the presence of 2-thiophene group at third position of the pyrazole ring and biphenyl at third position of the pyrazoline ring. The second lowest MIC showed for compounds **6a** is due to the presence of 2,3-dihydrobenzofuran at third position of pyrazoline ring and phenyl group at third position of pyrazole, compound **10c** is due to biphenyl at third position of pyrazoline and 4-methoxyphenyl at third position of pyrazole and compound **10d** is due to biphenyl substitution on pyrazoline at third position and *p*-chlorophenyl at third position of pyrazole ring. Other compounds **6d**, **6e**, **8b**, **8c**, **8d** showed moderate activity with MIC value 62.5 to 125 µg/ml against tested organisms. Antimicrobial results of final compounds **6a-e**, **8a-e**, **10a-e** were tabulated in Table 2.

The MIC against pathogenic bacteria *Mycobacterium tuberculosis* $H_{37}Rv$ at different concentrations ranging from 100 to 0.8 µg/ml was also represented in Table 2. Most of the compounds were exhibited the activity with MIC ranging between 50 µg/ml to 1.56 µg/ml. The compound **10e** showed lowest MIC (1.56 µg/ml) among all other compounds and it was more active than the standard first-line anti-tb drug Pyrazinamide (MIC value 3.12 µg/ml). The second lowest MIC (6.25 µg/ml) obtained for compound **10c** against the tested microorganism and it was similarly active with the standard anti-tb drug Streptomycin (MIC value 6.25 µg/ml). The compound **6a** showed third lowest MIC (12.5 µg/ml). Other compounds **6d**, **6e**, **8a**, **8b**, **8c**, **8d** showed moderate activity with MIC value 25 µg/ml against tested *Mycobacterium tuberculosis.* This indicates that, most of the pyrazole containing pyrazoline compounds with 5-methylfuran substitution at third position is able to give moderate activity against *M. Tuberculosis*. Compounds **6b, 6c, 8e, 10a, 10b, 10d** were showing less activity against tested organisms with MIC value 50 µg/ml.

Table 2: The Minimum Inhibitory Concentration (MIC) of **6a-e**, **8a-e** and **10a-e** against various antimicrobial and antitubercular agents

Synthesized Compound	MIC in µg/mL			
	M. smegmatis	*S. aureus*	*C. albicans*	*M. Tuberculosis*
6a	15.6	15.6	31.25	12.5
6b	500	500	500	50
6c	500	500	500	50
6d	62.5	62.5	62.5	25
6e	62.5	125	62.5	25
8a	250	125	125	25
8b	62.5	125	62.5	25
8c	62.5	62.5	62.5	25
8d	62.5	62.5	62.5	25
8e	125	31.25	125	50
10a	125	125	125	50
10b	500	500	500	50
10c	15.6	15.6	31.25	6.25
10d	15.6	62.5	31.25	50
10e	7.8	15.6	31.25	1.56
ABS	<5	<5	--	3.12

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AFS	--	--	<10	--
PZA	--	--	--	3.12
Streptomycin	--	--	--	6.25

ABS; antibacterial standard Ciprofloxacin; AFS; antifungal standard Fluconazole; PZA; anti-tb standard Pyrazinamide; --: not detected inhibition; control; dimethylsulfoxide

The *in vitro* cytotoxicity study was carried out using HeLa cells at Stellixir Biotech Pvt. Ltd, Bangalore. The five compounds **6a**, **6d**, **8b**, **10c** and **10e** which had highest to moderate activity for antimicrobial and antituberculosis were tested for cytotoxicity with HeLa cells represented in Figure 1. The IC_{50} value of synthetic compound found to be moderately effective for the HeLa cells. The control cells which are not treated with any compound have shown 100% viability. One of the synthetic compound **8b** has shown highest cytotoxicity (12.83 µg/mL) among tested compounds. The compounds having cytotoxicity below 50 µg/mL IC_{50} value are usually considered as toxic compounds.

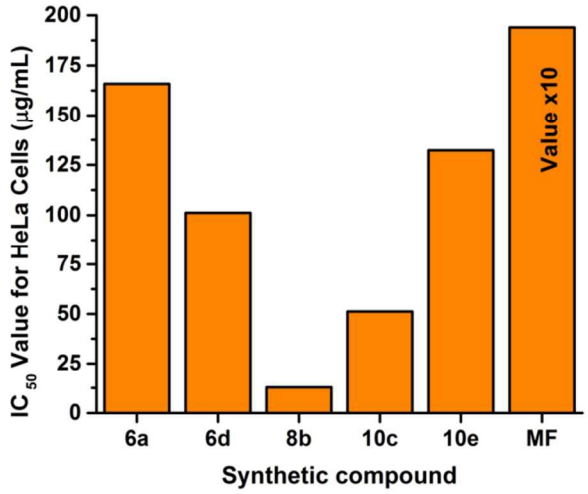

Figure 1: Cytotoxicity of **6a**, **6d**, **8b**, **10c** and **10e** with HeLa cell line

This concludes that, compounds 6a-e, 8a-e and 10a-e derivatives were synthesized, characterized and investigated for their *in-vitro* antimicrobial by Resazurin reduction method and was used for determining the MIC in 96 well microplates.[19] and antitubercular activity by microplate alamar blue assay (MABA) method[20] and proved to be very good antimicrobial and antitubercular agents. The results are consistent with specific substitution to utility of tuberculosis chemotherapy and antimicrobial agents. The compounds 10e, 10c showed best screening results among all the synthesized compounds. This indicates, newly synthesized pyrazole containing pyrazoline compounds might emerge as one of the antituberculosis drugs.

Experimental

All the chemicals were purchased from Sigma Aldrich and Spectrochem-India. Melting points were determined by open capillary method and are uncorrected. The IR spectrums (in KBr pellet) were recorded on Perkin-Elmer FTIR-4000-400 cm^{-1} spectrophotometer. NMR spectra were obtained on a Bruker Avance-400 spectrometer (400 MHz) for ^1H NMR and ^{13}C NMR using tetramethylsilane (TMS) as internal standard. The mass spectrum was recorded on LC-MS Applied biosystems MDS SCIEX-API 4000 spectrometer. Elemental analysis was performed on a Flash EA 1112 series CHNS-O analyzer. The completion of the reaction was checked by thin layer chromatography (TLC) with readymade aluminium sheets (Merck F_{254}). The names of the structures were mentioned as per chemdraw.

A mixture of 1,3-disubstituted pyrazole-4-carbaldehyde (**1a-e**) (0.01mol), acetyl derivative (**2**, **3** and **4**) (0.91 g, 0.01mol) in ethanol (10 ml) were stirred in the presence of 10% sodium hydroxide solution (2 ml) at an ambient temperature for 5 h. The resultant yellow color reaction mass was filtered and washed with 5 ml of ethanol to get chalcone intermediate (**5a-e**), (**7a-e**) and (**9a-e**) respectively in reasonably good yields (80-95%). The compound (**5a-e**), (**7a-e**) and (**9a-e**) (0.005 mol) was taken in ethanol (10 ml) and added excess amount of hydrazine hydrate (1.3 g, 0.005 mol). The reaction mixture was heated at reflux temperature for 2 h and reaction was monitored by TLC [Hexane : Ethylacetate (4:1)]. The reaction mass was cooled to room temperature and stirred for 0.5 h. The solid product was filtered and washed with ethanol to get (**6a-e**), (**8a-e**) and (**10a-e**) respectively.

1′-(4-chlorophenyl)-5-(2,3-dihydrobenzofuran-5-yl)-3′-phenyl-3,4-dihydro-2*H*,1′*H*-[3,4′]bipyrazolyl (6a). IR (KBr ν_{max} cm^{-1}): 3322 (N-H str), 3064 (Ar-H str), 2919 (C-H aliphatic str), 1607 (C=N str), 1497 (C=C str), 824 (C-Cl str); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.90-2.96 (t, 1H, H_A, J = 12.8 Hz), 3.19 (t, 2H, -CH_2), 3.42-3.49 (t, 1H, H_B, J = 13.6 Hz), 4.56 (t, 2H, -CH_2), 4.89-4.92 (t, 1H, H_X, J = 10.4 Hz), 6.77 (m, 1H, Ar-H), 7.33-7.36 (m, 2H, Ar-H), 7.43-7.56 (m, 6H, Ar-H), 7.77-7.95 (m, 4H, Ar-H), 8.62 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 160.5, 151.2, 138.8, 133.2, 130.7, 130.1, 129.9, 129.7, 129.1, 128.6, 128.4, 128.2, 128.0, 126.3, 122.9, 121.0, 120.2, 109.2, 71.7, 55.5, 29.3; MS: m/z = 441.2 (M^+), ANAL. Calcd. for $C_{26}H_{21}ClN_4O$; calcd: C, 70.82; H, 4.80; N, 12.71; found: C, 70.83; H, 4.80; N, 12.72.

1′-(4-chlorophenyl)-5-(5-methylfuran-2-yl)-3′-phenyl-3,4-dihydro-2*H*,1′*H*-[3,4′]bipyrazolyl (8a). IR (KBr ν_{max} cm^{-1}): 3316 (N-H str), 3117 (Ar-H str), 2923 (C-H aliphatic str), 1594 (C=N str), 1499 (C=C str), 829 (C-Clstr); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.31 (s, 3H, -CH_3), 2.84-2.90 (t, 1H, H_A, J = 13.0 Hz), 3.31 (m, 1H, H_B), 4.89-4.95 (t, 1H, H_X, J =10.6 Hz), 6.17 (s, 1H, Ar-H), 6.50 (s, 1H, Ar-H), 7.44-7.76 (m, 8H, Ar-H), 7.94-7.95 (d, 2H, Ar-H, J = 6.0 Hz), 8.59 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 152.9, 151.1, 147.3, 142.1, 138.7, 133.2, 130.7, 129.9, 129.1, 128.6, 128.4, 128.0, 123.7, 120.2, 110.9, 108.3, 55.2, 13.9; MS: m/z =403.2 (M^+), ANAL. Calcd. for $C_{23}H_{19}ClN_4O$; calcd: C, 68.57; H, 4.75; N, 13.91; found: C, 68.60; H, 4.76; N, 13.92.

5-Biphenyl-4-yl-1′-(4-chlorophenyl)-3′-phenyl-3,4-dihydro-2*H*,1′*H*- [3,4′]bipyrazolyl (10a). IR (KBr ν_{max} cm^{-1}): 3312 (N-H str), 3073 (Ar-H str), 2921 (C-H aliphatic str), 1593 (C=N str), 1497 (C=C str), 830 (C-Cl str); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.97-3.03 (dd, 1H, H_A, J = 10.9 Hz), 3.49-3.56 (dd, 1H, H_B, J = 10.7 Hz), 4.97-5.03 (dt, 1H, Hx), 7.30-7.38 (m, 2H, Ar-H), 7.45-7.55 (m, 6H, Ar-H), 7.64-7.65 (d, 1H, Ar-H, J =3.3 Hz), 7.68 (s, 1H, pyrazole-5H), 7.70-7.71 (dd, 5H, Ar-H, J = 1.4 Hz), 7.80-7.82 (d, 2H, Ar-H, J = 8.5 Hz), 7.89-7.91 (d, 2H, Ar-H, J = 7.7 Hz), 8.61(s, 1H, -NH); MS: m/z = 475.1 (M^+), ANAL. Calcd. for $C_{30}H_{23}ClN_4$; calcd: C, 75.86; H, 4.88; N, 11.80; found: C, 75.90; H, 4.90; N, 11.90.

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Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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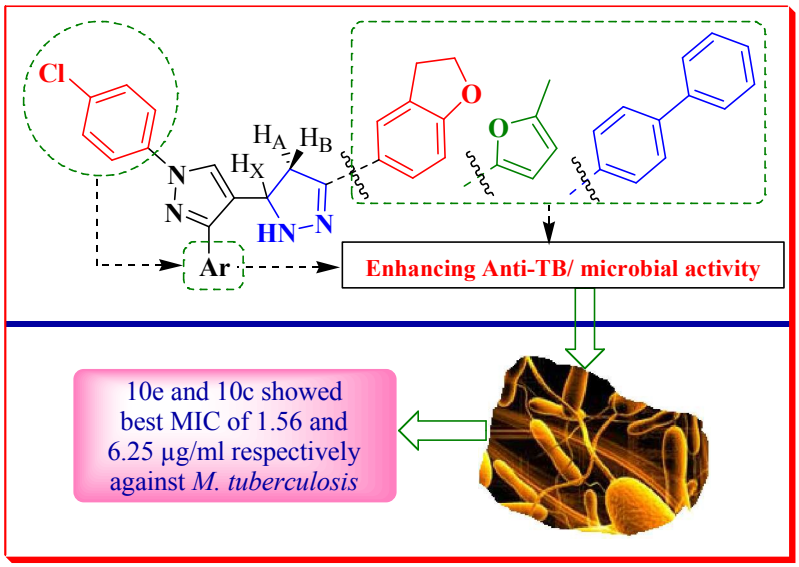
Drugs of Pyrazinamide and Streptomycin.



New series of pyrazoline derivatives was synthesized and characterized by spectral techniques. Synthesized compounds were evaluated for their antitubercular and antimicrobial activities. Most of the compounds are found to be biologically potent.