Heterocyclic Letters
Vol. 7| No.2|347-356|Feb-April| 2017
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS AND BIOLOGICAL EVALUATION OF CERTAIN PYRAZOLE CLUBBED 1, 3-THIAZOLONE DERIVATIVES BEARING PYRAZOLINE MOIETY

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ABSTRACT:
Pyrazole based fluoromethyl substituted fused thiazolo - pyrazoline scaffold derivatives ((*Z*)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-5-((3-methyl-5-subtituted phenoxy-1-phenyl-1H-pyrazol-4-yl)methylene)thiazol-4(5H)-one) have been synthesized by a tandem type reaction. The targeted compounds were synthesized in good to excellent yield (75-88%).All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectra & elemental analysis. They were tested for their *in vitro* antitubercular activity against *Mycobacterium tuberculosis* H_{37}Rv strain and *in vitro* antimalarial activity against *P. falciparum* strain. The synthesized compounds showed potent inhibitory action against the test organisms.

KEY WORDS : pyrazole; pyrazoline; thiazolone; Biological evaluation

INTRODUCTION:

Malaria, a mosquito-borne disease, is one of the most critical health evils in the world at the current time [i]. Due to malaria approximate 500 million people get affected annually and about 3 million deaths occur due to malaria [ii-iv]. The spread of multidrug-resistant *Plasmodium falciparum* has highlighted the urgent need of discovering new antimalarial drugs.

TB (Tuberculosis) is also a threatful global health problem and is the second prominent cause of death from an infectious sickness worldwide. It is an infectious disease for both animals and humans. caused by bacilli belonging the mycobacterium tuberculosis complex [v]. In present work all the synthesized compounds were tested in-vitro for their antitubercular activity and towards bacterial and fungal strains.

Pyrazole and thiazolone are extensively found in drugs as well as natural products [vi]. Their cores possess *E. coli* FabH inhibitory activity [vii-x]. Pyrazole and pyrazoline based compounds have been constantly considered over the years because of their biological

activity and strong efficiency as antimalarial, antituberculosis, antibacterial, antifungal and antioxidant [xi]. A combination of thiazolone and pyrazoline has been reported as the vital component of novel compounds having inputs in drug development as antimicrobial [xii], anticancer [xiii-xiv], antiviral [xv], oxidase inhibitors, free radical scavengers [xvi] and as potential COX-2 inhibitors [xvii].

In the current investigation our intention is to develop a variety of heterocycles incorporating pyrazole, pyrazoline and thiazolone in one molecule which may play essential role in title compounds. In continuation of our efforts to synthesize some novel heterocyclic motifs with biological interest [xviii-xx], herein we report the synthesis and biological screening of novel heterocyclic products by conventional method.

EXPERIMENTAL:

All the reagents were of commercial grade and used without further purification. Melting points were determined using mThermoCal10 (Analab scientific Pvt. Ltd.) melting point apparatus and are uncorrected. TLC was performed on aluminum plates coated with silica gel 60 F254, 0.25 mm thickness, Merck, Germany and pots were visualized by iodine vapors or irradiation with UV light (254 nm). ^{1}H NMR spectra (in DMSO-d_6& $CDCl_3$) were recorded on Bruker avance 400 MHz instruments using TMS as the internal standard. Chemical shifts are reported in parts per million (ppm). Splitting patterns were designated as follows: s, singlet; d, doublet; dd, doublet of doublets and m, multiplet. Mass spectra were recorded on Shimadzu LCMS 2010 mass spectrometer. Elemental analyses were carried out using a Perkin-Elmer 2400 Series II C, H, N- analyzer. The IR spectra were recorded in KBr on a Perkin-Elmer Spectrum GX FT-IR spectrophotometer.

General procedure for synthesis of chalcone-3

To a solution of aldehyde **2** (1 mmol) and 4-fluoro acetophenone **1** (1 mmol) in ethanol (10.0 mL), 4mL 20% NaOH was added. The reaction mixture was stirred at room temperature until the formation of precipitate. Progress of the reaction was monitored by TLC. After completion of reaction, the solid mass separated was collected by filtration, and recrystallized from methanol to afford pure compound **3**.

General procedure for synthesis of 4

A 100 ml round bottomed flask, was charged with a mixture of **3** (1 mmol), thiosemicarbezide (1 mmol) and NaOH in ethanol (5mL).The content were refluxed and completion of the reaction was confirmed by TLC. The isolated product was purified by crystallization from methanol. The product **4** was produced in good yield & purity.

General procedure for synthesis of 5

To a suspension of compound **4** (1mmol) in ethanol (20 mL), ethyl bromoacetate (1mmol) was added and heated at reflux for 1h. Completion of the reaction was confirmed by TLC. The product obtain **5** obtained was purified by recrystallization from methanol and dried.

General procedure for synthesis of 6a-n

3-methyl-5-substituted phenoxy-1-phenyl-1H-pyrazole-4-carbaldehyde **6a-n** was prepared by refluxing 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (1mmol) and substituted phenols (1mmol) in presence of anhydrous K_2CO_3 (3mmol) as basic catalyst in DMF (20ml) as solvent. After the completion of reaction the reaction mixture was cooled to room

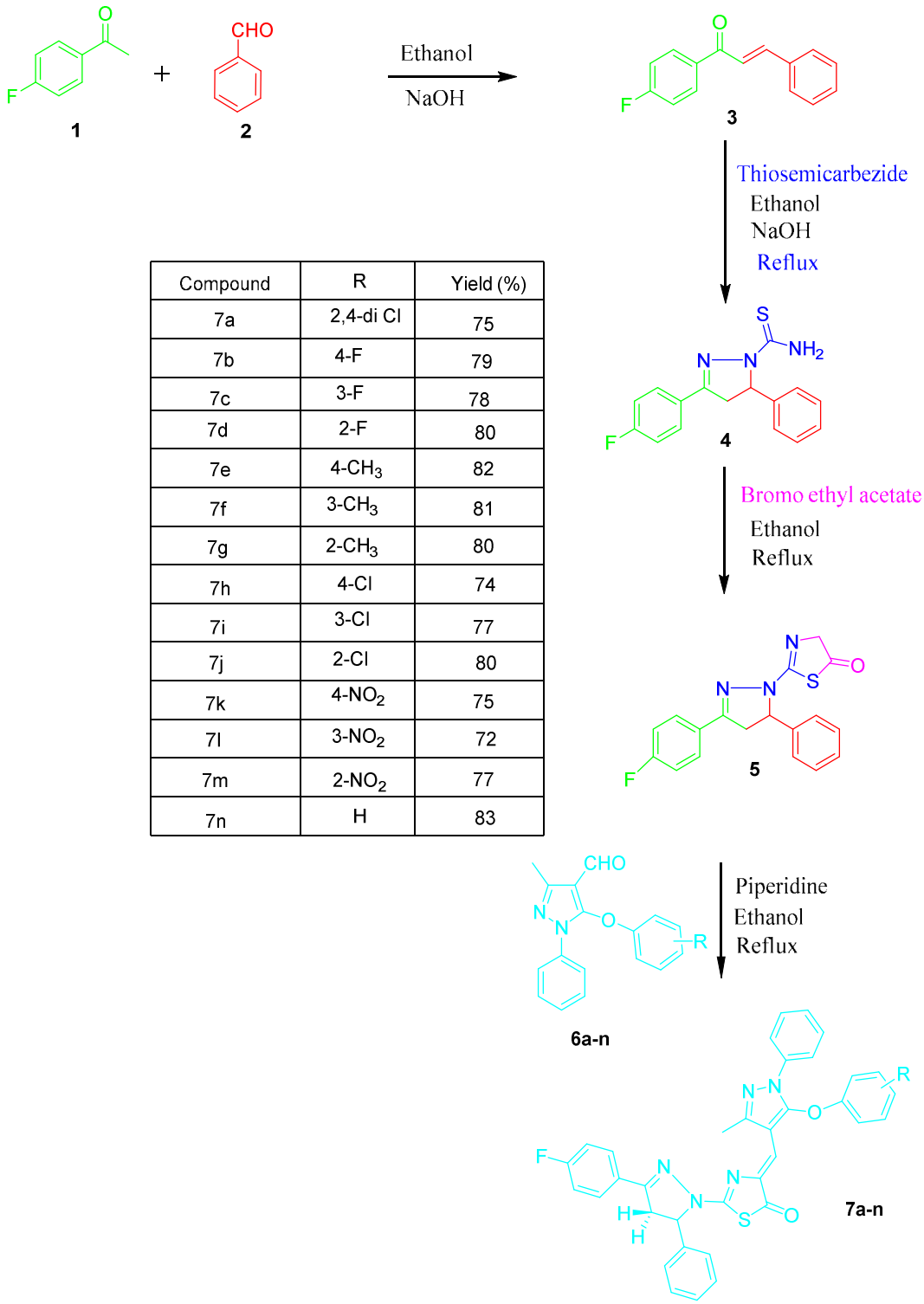
temperature and then poured into ice cold water (40 mL) with continuous stirring .The separated precipitates dried and recrystallized from hot ethanol.

General procedure for synthesis of substituted (Z)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-5-((3-methyl-5-substituted phenoxy-1-phenyl-1H-pyrazol-4-yl)methylene)thiazol-4(5H)-one 7a–n.

A compound **6** (1 mmol) and 3-methyl-5-phenoxy-1-phenyl-1H-pyrazole-4-carbaldehyde derivatives **5** (1mmol) and catalytic amount of piperidine in 20 mL ethanol was stirred at room temperature for 1 h. After completion of the reaction (as detected by TLC), the solid phase was filtered and washed with ethanol 10 mL to obtain pure product (**7a–n**) Compounds.

RESULTS AND DISCUSSION:

The structures of all the newly synthesized compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR, Mass spectrometry and elemental analysis. The IR spectrum of all compound showed absorption in the range of 1686-1710 cm^{-1} due to carbonyl group. The C-O-C stretching was observed around 1212-1228 cm^{-1} and strong absorption band was observed in the range of 1365-1380 cm^{-1} due to the presence CH_3 group. In the 400 MHz ^{1}H NMR spectrum of compounds, the C_4 protons of the pyrazoline ring resonated as multiplet at 3.24-3.60 ppm (Ha), 3.82-4.10 ppm (Hb). The C_5 proton of pyrazoline appeared as multiplet at 5.79-5.84 ppm due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 4 of the pyrazoline ring. All compounds gave satisfactory elemental analysis. The mass spectrum of all the synthesized compounds showed molecular ion peak at M + 1 corresponding to their molecular weights.



Compound	R	Yield (%)
7a	2,4-di Cl	75
7b	4-F	79
7c	3-F	78
7d	2-F	80
7e	4-CH_3	82
7f	3-CH_3	81
7g	2-CH_3	80
7h	4-Cl	74
7i	3-Cl	77
7j	2-Cl	80
7k	4-NO_2	75
7l	3-NO_2	72
7m	2-NO_2	77
7n	H	83

Scheme 1. Synthesis of substituted (*Z*)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-5-((3-methyl-5-phenoxy-1-phenyl-1H-pyrazol-4-yl)methylene)thiazol-4(5H)-derivatives **7a-n.**

BIOLOGICAL SECTION:

In vitro Antituberculosis activity

In vitro antituberculosis activity of all the synthesized compounds against *M. tuberculosis* $H_{37}Rv$ strain was determined by using Lowenstein Jensen slope method [20].The observed results are shown in Table 2 in the form of % inhibition, relative to that of standard antitubercular drugs Rifampicin and isoniazid. Compounds **7a** (R = 2,4-di Cl), **7b** (R = -F) **7e** (R = 4-CH_3) and **7h** (R = 4-Cl) were found to possess excellent activity (i.e. 95%,93%,89% and 91% at 250 µg/mL) against M. tuberculosis $H_{37}Rv$ and remaining all other compounds showed poor inhibition against *M. tuberculosis* $H_{37}Rv$ growth (**Table2**).

Table 2. In vitro anti tuberculosis activity (% Inhibition) of **7a-n** against M. tuberculosis $H_{37}Rv$ (at concentration 250 µg/mL)

Compounds	**%Inhibition**	**Compounds**	**%Inhibition**
7a	**95**	7i	65
7b	**93**	7j	49
7c	76	7k	75
7d	62	7l	52
7e	**89**	7m	39
7f	58	7n	53
7g	74	**Rifampicin**	**98**
7h	**91**	**Isoniazide**	**99**

***In vitro* antimalarial activity**

In vitro antimalarial activity of the synthesized compounds **7a-n** against *P. falciparum* strain was tested using quinine and chloroquine as the reference compounds. The consequences of the antimalarial screening are communicated as the drug concentration resulting in 50% inhibition (IC_{50}) of parasite growth and are listed in **Table 3**. The compounds **7a** (R = 2,4-di Cl), **7b** (R =4-F), **7g** (R = 2-CH_3), **7j** (R = 2-Cl), were found to have IC_{50} in the range of 0.045 to 0.083 upon *P. falciparum* strain as compared to quinine IC_{50} 0.268.

Table 3. *In vitro* antimalarial activity of derivatives 7a-n

Compound	**IC_{50} (µg/mL)**	**Compound**	**IC_{50} (µg/mL)**
7a	**0.083**	7i	0.64
7b	**0.073**	**7j**	**0.045**
7c	0.16	7k	0.95
7d	1.40	7l	0.52
7e	0.79	7m	1.30
7f	1.22	7n	1.59
7g	**0.068**	**Chloroquine**	**0.020**
7h	1.08	**Quinine**	**0.268**

^{1}H, ^{13}C, IR and Mass spectra of synthesized compound 7a-n.

(*Z*)-5-((5-(2,4-dichlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one (7a)

Yellow solid; mp 225-228 C; IR (KBr, *v*max, cm^{-1}) = 2934 (Ar-C-H), 1616 (C=O str.);1379

(–CH3 str.), 1218 (C-O-C); 1H NMR (400 MHz, DMSO-*d6*) δ = 2.41 (s, 3H, CH_3) 3.47 (dd, 1H,C_4 of Pyrazoline) 4.10 (dd, 1H , C_4 of pyrazoline) 5.82 (dd, 1H , C_5 of pyrazoline) 6.69-7.85 (m,Ar-H + -C-H),13C NMR (100 MHz DMSO-d_6) δ: 12.93, 43.38, 62.82, 104.99, 115.49, 115.71, 115.82, 118.81, 121.99, 122.30, 127.22, 127.78, 127.91, 128.11, 128.87, 129.20, 129.58, 130.13, 131.53, 136.07, 136.52,142.92, 149.75, 150.15, 160.41, 160.52, 162.84, 170.72, 178.90.LC-MS: 668.4 $(M)^+$; Anal.Calc. For $C_{35}H_{24}Cl_2FN_5O_2S$: C, 62.88; H, 3.62; N, 10.48; Observed, C, 62.80; H, 3.66; N, 10.40 %.

(*Z*)-5-((5-(4-fluorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one (7b)

Yellow solid; yield: mp 230-223 ºC; IR (KBr, *ν*max, cm^{-1}) = 2938 (Ar-C-H), 1686 (C=O str.);1378 (-CH3 str.), 1216 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.45 (s, 3H, CH_3) 3.38 (dd, 1H, C_4 of pyrazoline) 3.96 (dd, 1H, C_4 of pyrazoline) 5.82 (dd, 1H, C_5 of pyrazoline) 6.81-7.52 (m,Ar-H + -C-H) ,^{13}C NMR (100 MHz DMSO-d_6) δ: 13.04, 43.36, 63.05, 105.66, 115.58, 115.80, 116.47, 116.85, 119.57, 122.26, 127.40, 128.04, 128.12, 129.55, 131.68, 136.28, 136.81, 144.78, 149.44, 152.16, 156.87, 159.26, 160.41, 160.90, 162.83, 170.64, 178.79 , LC-MS: 617.6 $(M)^+$; Anal.Calc. For $C_{35}H_{25}F_2N_5O_2S$: C, 68.06; H, 4.08; N, 11.34; Observed, C, 68.02; H, 4.04; N, 11.36 %.

(*Z*)-5-((5-(3-fluorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one (7c)

White solid; yield: mp 220-222 ºC; IR (KBr, *ν*max, cm^{-1}) = 2940 (Ar-C-H), 1691 (C=O str.);1372 (-CH3 str.), 1221 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.42 (s, 3H, CH_3) 3.40(dd, 1H, C_4 of pyrazoline) 3.96 (dd, 1H, C_4 of pyrazoline) 5.84 (dd, 1H, C_5 of pyrazoline) 6.79-7.521(m,Ar-H + -C-H) .^{13}C NMR (100 MHz DMSO-*d*6 + $CDCl_3$) δ:13.09, 43.32, 62.58, 104.60, 115.70, 116.10, 116.40, 116.70, 119.50, 122.20, 127.30,127.66, 128.04, 128.32, 129.48, 129.55, 131.60, 136.28, 136.70, 144.60, 149.34, 152.10, 156.57, 159.06, 160.21, 160.90, 162.80, 170.64, 178.86.LC-MS: 617.6 $(M)^+$; Anal.Calc. For $C_{35}H_{25}F_2N_5O_2S$: C, 68.06; H, 4.08 ; N, 11.34. Observed, C, 68.02; H, 4.04; N, 11.36 %.

(*Z*)-5-((5-(2-fluorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one (7d)

White solid; yield: mp 228-230 ºC; IR (KBr, *ν*max, cm^{-1}) = 2941 (Ar-C-H), 1697 (C=O str.);1375 (-CH3 str.), 1220 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.43 (s, 3H, CH_3) 3.39(dd, 1H, C_4 of pyrazoline) 3.98 (dd, 1H, C_4 of pyrazoline) 5.82 (dd, 1H, C_5 of pyrazoline) 6.79-7.521(m,Ar-H + -C-H)^{13}C NMR (100 MHz DMSO-d_6) δ:13.06, 43.38, 62.60, 104.61, 115.54, 115.80, 116.45, 116.90, 119.48, 122.32, 127.45, 127.51, 128.14, 128.26, 129.41, 129.62, 132.18, 136.28, 136.85, 144.70 149.21, 152.26, 155.87, 159.36, 160.49, 170.00, 162.63, 170.70, 179.09. LC-MS: 617.6 $(M)^+$; Anal.Calc. For $C_{35}H_{25}F_2N_5O_2S$: C, 68.06; H, 4.08; N, 11.34; Observed, C, 68.02; H, 4.04; N, 11.36 %.

(*Z*)-2-(5-(4-fluorophenyl)-3-phenyl-4, 5-dihydro-1*H*-pyrazol-1-yl)-5-((3-methyl-1-phenyl-5-(p-tolyloxy)-1*H*-pyrazol-4-yl)methylene)thiazol-4(5*H*)-one (7e)

White solid; yield: mp 235-238 ºC; IR (KBr, *ν*max, cm^{-1}) = 2950 (Ar-C-H), 1710 (C=O str.);1380 (-CH3 str.), 1225 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.21 (s, 3H, CH_3) 3.36 (dd, 1H, C_4 of pyrazoline) 3.94 (dd, 1H, C_4 of pyrazoline) 5.81 (dd, 1H, C_5 of pyrazoline) 6.75-7.50 (m,Ar-H + -C-H)^{13}C NMR (100 MHz DMSO-*d*6) δ:13.05, 19.99, 43.35, 62.87, 104.76, 115.58, 115.79, 119.68, 122.06, 126.90, 127.40, 127.53,128.05, 128.13, 129.27, 129.58, 131.69, 132.78, 136.32, 136.91, 144.90, 149.40, 154.12, 160.32, 160.95, 162.82, 170.76, 178.84 LC-MS: 613.7 $(M)^+$; Anal.Calc. For$C_{36}H_{28}FN_5O_2S$: C, 70.46; H, 4.60; N, 11.41; Observed: C, 70.42; H, 4.62 , N, 11.40 %.

(*Z*)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-5-((3-methyl-1-phenyl-5-(m-tolyloxy)-1*H*-pyrazol-4-yl)methylene)thiazol-4(5*H*)-one (7f)

White solid; yield: mp 230-232 ºC; IR (KBr, *v*max, cm^{-1}) = 2948 (Ar-C-H), 1695 (C=O str.);1378 (-CH3 str.), 1228 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.20 (s, 3H, CH_3) 3.34 (dd, 1H, C_4 of pyrazoline) 3.93 (dd, 1H, C_4 of pyrazoline) 5.79 (dd, 1H, C_5 of pyrazoline) 6.72-7.51 (m,Ar-H + -C-H)^{13}C NMR (100 MHz DMSO-*d*6) δ: 13.09, 20.10, 43.50, 62.88, 104.76, 115.54, 115.80, 119.70, 122.16, 127.00, 127.38, 127.53,128.10, 128.23,129.00, 129.20, 129.51,130.39, 131.72, 132.59, 136.32, 137.00, 145.10, 149.20, 154.10, 160.32, 160.85, 162.72, 170.46, 178.90 , LC-MS: 613.7 $(M)^+$; Anal.Calc. For$C_{36}H_{28}FN_5O_2S$: C, 70.46; H, 4.60; N, 11.41; Observed: C, 70.42; H, 4.62; N, 11.40 %.

(*Z*)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-5-((3-methyl-1-phenyl-5-(o-tolyloxy)-1*H*-pyrazol-4-yl)methylene)thiazol-4(5*H*)-one (7g)

White solid; yield: mp 233-235 ºC; IR (KBr, *v*max, cm^{-1}) = 2965 (Ar-C-H), 1683 (C=O str.);1379 (-CH3 str.), 1219 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.22 (s, 3H, CH_3) 3.36 (dd, 1H, C_4 of pyrazoline) 3.91 (dd, 1H, C_4 of pyrazoline) 5.80 (dd, 1H, C_5 of pyrazoline) 6.71-7.54 (m,Ar-H + -C-H)^{13}C NMR (100 MHz DMSO-*d*6) δ:13.06, 19.94, 43.35, 62.77, 104.70, 115.69, 115.72, 119.65, 122.10, 127.10, 127.45, 127.63,127.00, 128.18, 129.13, 129.37, 129.58, 130.35, 131.75, 132.70, 136.30, 136.95, 145.00, 149.14, 154.32, 160.30, 170.00, 162.85, 170.66, 179.01 LC-MS: 613.7 $(M)^+$; Anal.Calc. For $C_{36}H_{28}FN_5O_2S$: C, 70.46; H, 4.60; N, 11.41; Observed C, 70.42; H, 4.62; N, 11.40 %.

(*Z*)-5-((5-(4-chlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one(7h)

Orange solid; yield: mp 222-224 ºC; IR (KBr, *v*max, cm^{-1}) = 2946 (Ar-C-H), 1696 (C=O str.);1369 (-CH_3 . Observed str.), 1220 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.26 (s, 3H, CH_3) 3.30 (dd, 1H, C_4 of pyrazoline) 3.86 (dd, 1H, C_4 of pyrazoline) 5.80 (dd, 1H, C_5 of pyrazoline) 6.65-8.00 (m,Ar-H + -C-H)^{13}C NMR (100 MHz DMSO-*d*6) δ:13.02, 43.39, 62.78, 104.71, 115.58, 115.80, 119.31, 122.28, 127.26, 127.40, 127.69, 129.58, 136.28, 136.73, 139.16, 140.54, 141.89, 144.24, 149.54, 154.79,154.94, 160.38, 161.60, 162.86, 170.31, 175.91, 178.73 LC-MS: 634.1 $(M)^+$; Anal.Calc. for $C_{35}H_{25}ClFN_5O_2S$: C, 66.29; H, 3.97; N, 11.04; Observed C, 66.26; H, 3.96; N, 11.02 %.

(*Z*)-5-((5-(3-chlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one(7i)

Orange solid; yield: mp 227-230 ºC; IR (KBr, *v*max, cm^{-1}) = 2939 (Ar-C-H), 1689 (C=O str.);1365 (-CH_3, Observed str.), 1215 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.23 (s, 3H, CH_3)3.32 (dd, 1H, C_4 of pyrazoline) 3.85 (dd, 1H, C_4 of pyrazoline) 5.81 (dd, 1H, C_5 of pyrazoline) 6.64-7.96 (m,Ar-H + -C-H)^{13}C NMR (100 MHz DMSO-*d*6) δ)13.00, 43.32, 62.65, 104.70, 115.50, 116.00, 119.29, 122.20, 126.81, 127.27, 127.45, 127.60, 128.06, 129.54, 136.28, 136.53, 139.90, 140.49, 141.79, 145.04, 149.10, 154.80, 154.94, 159.10, 160.20, 161.96, 170.11, 176.00, 178.60LC-MS: 634.1 $(M)^+$; Anal.Calc. For$C_{35}H_{25}ClFN_5O_2S$: C, 66.29; H, 3.97; N, 11.04; Observed C, 66.26; H, 3.96; N, 11.02 %.

(*Z*)-5-((5-(2-chlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one (7j)

Orange solid; yield: mp 223-225 ºC; IR (KBr, *v*max, cm^{-1}) = 2964 (Ar-C-H), 1700 (C=O str.);1370 (-CH_3, Observed str.), 1217 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.22 (s, 3H, CH_3 3.30 (dd, 1H, C_4 of pyrazoline) 3.86 (dd, 1H, C_4 of pyrazoline) 5.49 (dd, 1H, C_5 of pyrazoline) 6.67-7.99 (m,Ar-H + -C-H)^{13}C NMR (100 MHz DMSO-*d*6) δ:13.08, 43.40, 62.70, 104.60, 115.48, 115.90, 119.35, 122.18, 125.08, 127.25, 127.34, 128.09, 128.00, 129.48, 137.08, 136.63, 140.09, 140.44, 141.90, 145.10, 149.24, 154.79, 155.00, 159.09,

160.38, 161.76, 171.12, 175.95, 178.69 LC-MS: 634.1 $(M)^+$; Anal.Calc. for $C_{35}H_{25}ClFN_5O_2S$: C, 66.29; H, 3.97; N, 11.04; Observed: C, 66.26; H, 3.96; N, 11.02 %.

(*Z*)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-5-((3-methyl-5-(4-nitrophenoxy)-1-phenyl-1*H*-pyrazol-4-yl)methylene)thiazol-4(5*H*)-one (7k)

Yellow solid; yield: mp 245-247 ºC; IR (KBr, *v*max, cm^{-1}) = 2958 (Ar-C-H), 1705 (C=O str.);1374 (-CH_3, Observed str.), 1212 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.24 (s, 3H, CH_3) 3.26 (dd, 1H, C_4 of pyrazoline) 3.80 (dd, 1H, C_4 of pyrazoline) 5.80 (dd, 1H, C_5 of pyrazoline) 6.65-8.50 (m,Ar-H + -C-H)^{13}C NMR (100 MHz DMSO-*d*6) δ:12.53, 42.80, 63.04, 105.94, 115.25, 116.36, 119.64, 123.27, 125.58, 127.39, 127.60, 131.23, 136.48, 137.70, 139.36, 141.04, 141.89, 144.24, 150.38, 153.50, 155.54, 160.18, 161.29, 163.56, 171.42, 175.89, 177.93LC-MS: 644.6 $(M)^+$; Anal.Calc. For$C_{35}H_{25}FN_6O_4S$: C, 65.21; H, 3.91; N, 13.04; Observed: C, 65.22; H, 3.89; N, 13.01 %.

(*Z*)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-5-((3-methyl-5-(3-nitrophenoxy)-1-phenyl-1*H*-pyrazol-4-yl)methylene)thiazol-4(5*H*)-one (7l)

Yellow solid; yield: mp 249-251 ºC; IR (KBr, *v*max, cm^{-1}) = 2942 (Ar-C-H), 1685 (C=O str.);1379 (-CH_3, Observed str.), 1224 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.22 (s, 3H, CH_3) 3.24 (dd, 1H, C_4 of pyrazoline) 3.81 (dd, 1H, C_4 of pyrazoline) 5.81 (dd, 1H, C_5 of pyrazoline) 6.68-8.52 (m,Ar-H + -C-H)^{13}C NMR (100 MHz DMSO-*d*6) δ :12.83, 42.56, 62.96, 106.18, 115.20, 117.20, 119.44, 122.56, 124.18, 125.98, 126.94, 128.42, 131.53, 135.35, 137.58, 140.12, 141.04, 141.99, 145.15, 150.48, 154.10, 155.19, 161.15, 161.29, 164.14, 172.21, 175.91, 178.17LC-MS: 644.6 $(M)^+$; Anal.Calc. For$C_{35}H_{25}FN_6O_4S$: C, 65.21; H, 3.91; N, 13.04; Observed C, 65.22; H, 3.89; N, 13.01 %.

(*Z*)-2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-5-((3-methyl-5-(2-nitrophenoxy)-1-phenyl-1*H*-pyrazol-4-yl)methylene)thiazol-4(5*H*)-one (7m)

Yellow solid; yield: mp 243-246 ºC; IR (KBr, *v*max, cm^{-1}) = 2960 (Ar-C-H), 1696 (C=O str.);1382 (-CH_3, Observed str.), 1221 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.24 (s, 3H, CH_3) 3.25 (dd, 1H, C_4 of pyrazoline) 3.80 (dd, 1H, C_4 of pyrazoline) 5.82 (dd, 1H, C_5 of pyrazoline) 6.63-8.51 („Ar-H + -C-H)^{13}C NMR (100 MHz DMSO-*d*6) δ : 13.02, 43.10, 63.19, 106.40, 115.22, 116.96, 119.64, 121.95, 123.97, 126.28, 127.09, 128.68, 131.93, 136.00, 137.67, 140.17, 140.89, 142.79, 144.19, 150.60, 153.90, 155.08, 160.03, 161.24, 163.96, 171.26, 175.92, 177.98LC-MS: 644.6 $(M)^+$; Anal.Calc. for $C_{35}H_{25}FN_6O_4S$: C, 65.21; H, 3.91; N, 13.04; Observed C, 65.22; H, 3.89; N, 13.01 %.

(*Z*)-2-(5-(4-fluorophenyl)-3-phenyl-4, 5-dihydro-1*H*-pyrazol-1-yl)-5-((3-methyl-5-phenoxy-1-phenyl-1*H*-pyrazol-4-yl) methylene) thiazol-4(5*H*)-one (7n)

Yellow solid; yield: mp 238-240 ºC; IR (KBr, *v*max, cm^{-1}) = 2945 (Ar-C-H), 1699 (C=O str.);1373 (-CH_3, Observed str.), 1225 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.35 (s, 3H, CH_3 3.60 (dd, 1H, C_4 of pyrazoline) 3.90 (dd, 1H, C_4 of pyrazoline) 5.75 (dd, 1H, C_5 of pyrazoline) 6.80-7.60 („Ar-H + -C-H)^{13}C NMR (100 MHz DMSO-d_6) δ : 12.85, 44.12, 61.80, 105.06, 115.84, 115.96, 119.69, 122.18, 127.10, 127.52, 127.83,128.18, 128.23, 129.35, 130.42, 131.59, 133.51, 135.12, 137.90, 145.49, 150.18, 154.56, 161.32, 161.45, 163.56, 172.76, 177.15. LC-MS: 599.6 $(M)^+$; Anal.Calc. For C, 70.10; H, 4.37; N, 11.68; Observed C, 70.08; H, 4.38; N, 11.65 %.

CONCLUSIONS:

The aim of the study was to synthesize and study the antituberculosis and antimalarial activities of pyrazole incorporated thiazolone and pyrazoline compound. Amongst the tested compounds **7a**, **7b**, **7e and 7h** showed more potent antituberculosis activities against *M. tuberculosis* H_{37}Rv **7a, 7b, 7g and 7j** showed highly antimalarial activities. From all new

synthesised heterocyclic compound **7a** have superior antituberculosis and antimalarial activity.

ACKNOWLEDGMENT:
The authors are thankful to the Head, Department of Chemistry, Sardar Patel University for providing ^{1}H NMR and ^{13}C NMR spectroscopy and research facilities. We are also thankful to the DST-Purse, Vallabh Vidyanagar for providing mass spectrometry facilities. Authors are also thankful to Hon. Director, Sophisticated Instrumentation Centre for Applied Research and Training (SICART), Vallabh Vidyanagar- 388 120, India for FT-IR analysis at concessional rate. We are also thankful to Dhanji P. Rajani, Microcare Laboratory, Surat for antituberculosis and antimalarial screening of the compounds reported here. TRP wishes to acknowledge the UGC, New Delhi, India for basic science research fellowship for meritorious for the year 2015-17.

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Received on February 25, 2017.