Thiazolo[3,2-*a*] Pyrimidones as a Novel Anti-TB Agents

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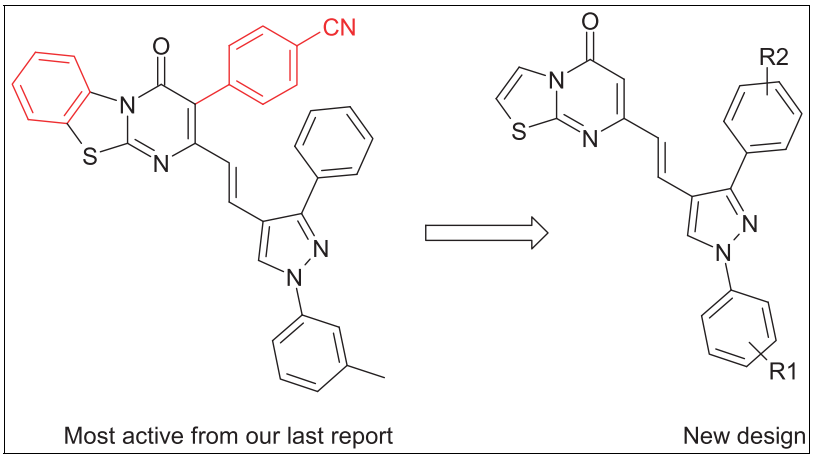

A series of novel thiazolo pyrimidine derivatives were designed, synthesized, and assessed for their *in vitro* anti-mycobacterial activities. All hybrids displayed considerable antitubercular activities against primary *Mycobacterium smegmatis* mc^2 155 screening and successive *Mycobacterium tuberculosis* H37Rv. In particular, the hybrid entities **13** and **14** (minimum inhibitory concentration: 47 and 39 µg/mL) were found to be equipotent candidates with first-line antitubercular agent rifampicin, which could act as a lead for further optimization.

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INTRODUCTION

It is a bigger global challenge to tackle the increasing population of tuberculosis (TB) due to emergence multidrug-resistant TB and extensively drug-resistant TB. World Health Organization reports TB as a second leading reason for mortality from an infective disease. Current document records about 9 million new patients and 1.5 million deaths owing to this infection, including 360,000 deaths among HIV-positive people [1]. It is also mentioned that one-third of the world's people is infected with latent TB and 10% of which is expected to develop active TB at some point in their lives [1]. The strategy of vaccination and current antibiotic therapy to treat the disease is not effective in current scenario due to multidrug resistance strains of *Mycobacterium tuberculosis* [2]. In the early 1950s, there was a gradual decline in the number of cases of TB, but there has been resurgence since 1984 [3]. This growth of TB, all the way through the recent years, was mainly due to HIV-1 infection, immigration, increased trade, and globalization [4]. Due to multidrug-resistant and extensively drug-resistant TB occurrence, in 1993, World Health Organization declared TB a global emergency [5]. The market is lack of new anti-TB agent from the last 40 years except Bedaquiline, which was approved in the year 2012 by USFDA [6]. Hence, advancement in anti-TB drugs is a clinical need to reduce toxicity as well as treatment time.

Pyrazole and its derivatives are considered a pharmacologically important active scaffold that possesses almost all types of pharmacological activities. Pyrazole in pharmacological agents of various therapeutic areas, such as celecoxib, a potent anti-inflammatory; the antipsychotic CDPPB; the anti-obesity drug rimonabant; difenamizole, an analgesic; betazole, an H_2-receptor agonist; and the antidepressant agent fezolamide, has proved the pharmacological potential of the pyrazole nucleus [7]. Pyrazoles are also documented for their anti-TB activity [8–10]. Our previous results showed that hybrid pyrazole derivatives were endowed with potential anti-TB property, wherein most active hybrid derivative (compound **10**) demonstrated minimum inhibitory concentration (MIC) 1.9 µg/mL in *M. tuberculosis* H37Rv screening [11] (Fig. 1). Further, compound **10** also showed very good synergism with the first-line and second-line antibiotics used in the screening. Hence, pyrazole derivatives are a reasonable choice to develop new anti-TB agents.

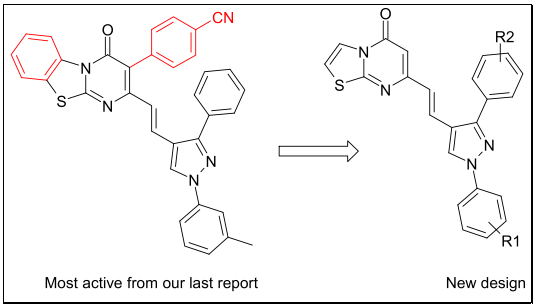


Figure 1. Molecular designing for compounds **1–17**. [Color figure can be viewed at wileyonlinelibrary.com]

As an ongoing research program and to continue our efforts to develop new anti-TB agents, a series of pyrazole derivatives were designed, wherein our primary objective was to remove benzene rings from our previously synthesized series (Fig. 1) to bring down the molecular bulk. Hence, novel derivatives **1–17** were synthesized and were explored for their anti-TB potential.

RESULTS AND DISCUSSIONS

Chemistry. The synthetic program starts with preparation of different pyrazole aldehydes **D** as shown in Scheme 1. Here, as per the literature [12], commercially available different substituted acetophenones **A** when treated with commercially available various phenylhydrazines **B** in acidic medium in refluxing ethanol gave imine as an intermediate **C**. This intermediate **C** upon reaction with $POCl_3$ in DMF underwent cyclization to give different pyrazole aldehydes **D** in good yield as key precursors. Another important precursor **F** was prepared as outlined in Scheme 1. 2-Amino thiazole **E** on treatment with ethyl acetoacetate at reflux temperature in acetic acid affords 7-methyl-thiazolo[3,2-*a*]pyrimidin-5-one **F**. Here, different aldehydes **D** were condensed with 7-methyl-thiazolo[3,2-*a*]pyrimidin-5-one **F** using sodium ethoxide at refluxed temperature in ethanol to give targeted compounds **1–17** (Table 1).

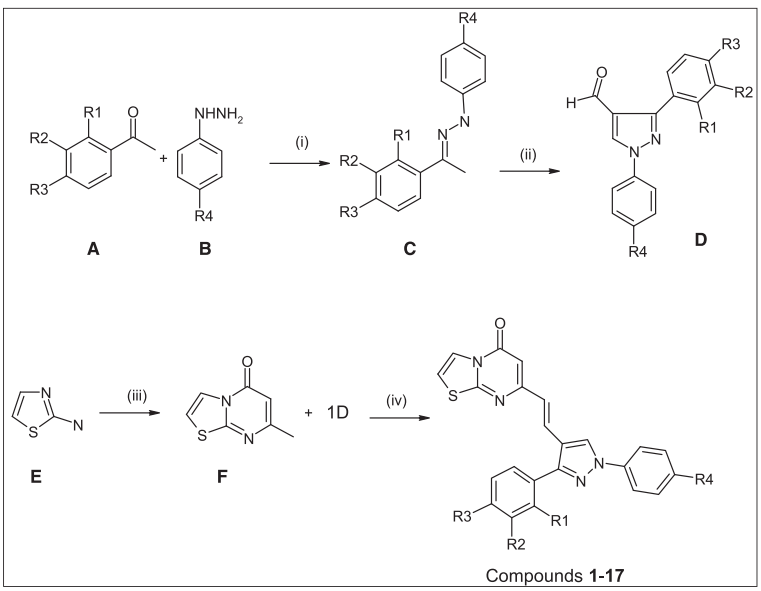
The progresses of all reactions were monitored by TLC. All the newly synthesized compounds were isolated in

Table 1

Substitution strategy for the compounds **1–17**.

ID	R1	R2	R3	R4
1	H	H	H	H
2	H	H	H	Cl
3	H	H	H	F
4	H	H	H	CH_3
5	H	H	Cl	H
6	H	H	F	H
7	H	H	OCH_3	H
8	H	H	CF_3	H
9	H	H	CH_3	H
10	H	H	OCF_3	H
11	OCH_3	H	H	H
12	H	OCH_3	H	H
13	CH_3	H	H	H
14	H	CH_3	H	H
15	OCH_3	CH_3	H	H
16	CH_3	OCH_3	H	H
17	CH_3	CH_3	H	H

Scheme 1. Reagents and conditions: (i) AcOH/EtOH, reflux, 30 min; (ii) DMF/$POCl_3$, 0–30°C, 12–14 h; (iii) ethyl acetoacetate, AcOH, 12- to 14-h reflux; and (iv) NaOEt, EtOH, reflux, room temperature, 12–14 h.



moderate to good yields and were characterized by ES-MS, ^{1}H NMR (400 MHz), ^{13}C NMR spectral data, and elemental analysis.

Figure 2 represents probable mechanistic pathway of thiazo[3,2-*a*]pyrimidinone. Acetic acid provides initial proton for triggering this reaction, wherein nitrogen and oxygen uses their lone pair of electrons for bond formations. The reaction completes when quenched with proton donor producing ethanol and water as by product.

Biology. ***Growth inhibitory potential against Mycobacterium smegmatis mc^2 155 stains and cell cytotoxicity for compounds 1–17.*** Synthesized compounds from this series were initially tested for their ability to inhibit the growth of *Mycobacterium smegmatis* mc^2 155 (Table 2). In the beginning, compound **1** was synthesized and tested. As a result, it was inferior (MIC = 85 μg/mL) compared with standard. But, for the satisfaction, we were happy with the result obtained. In the next step, H at R_4 position was replaced by chloro, fluoro, and methyl groups (compounds **2–4**). In screening, we found that there is a massive drop in *M. smegmatis* mc^2 155 growth inhibition compared with compound **1**. We concluded that the substitution at R_4 position may not be favorable for the mentioned growth inhibition activity.

In the next level, chloro, fluoro, methoxy, trifluoromethyl, methyl, and trifluoromethoxy groups were employed at R_3 position (**5–10**). In the screening results, no significant improvements have been noticed except compounds **9** and **7**. Compound **9** showed MIC = 69 μg/mL; in addition, compound **7** displayed MIC = 87 μg/mL. Based on these findings, we synthesized **11** and **12**, wherein methoxy group was introduced at R_1 and R_2 positions, and activity was screened. Both these compounds were inactive, hinted us that methoxy group at these positions does not help. Further, methyl group was introduced at R_1 and R_2. Surprisingly, the resulted **13** and **14** were superior compared with the compound prepared so far. Compound **13** displayed MIC = 42 μg/mL and that of **14** showed MIC = 39 μg/mL. Further, **15–17** disubstitution by methoxy and methyl groups was introduced at R_1 and R_2 positions. In the screening results, the growth inhibitory potentials of all these compounds were poor, hinted us that the disubstitutions at R_1 and R_2 positions are not tolerated.

Table 2

Antitubercular activity of **1–17** against *Mycobacterium smegmatis* mc^2 155 and their toxicity index towards human monocyte derived macrophages.

ID	*Mycobacterium smegmatis* mc^2 155		IC_{50} (μg/mL)
	MIC (μg/mL)	REF ± SD	
1	85	1.1 ± 0.03*	ND
2	110	0.19 ± 0.01	ND
3	121	0.74 ± 0.03	ND
4	139	0.71 ± 0.01	ND
5	201	0.25 ± 0.07	ND
6	367	0.86 ± 0.09	ND
7	87	0.70 ± 0.084	ND
8	151	0.85 ± 0.05	ND
9	69	0.34 ± 0.02	ND
10	191	1.9 ± 0.08*	ND
11	342	1.7 ± 0.03*	ND
12	312	0.61 ± 0.05	ND
13	47	0.34 ± 0.09	377
14	39	0.61 ± 0.07	369
15	211	0.61 ± 0.05	ND
16	209	0.34 ± 0.09	ND
17	312	0.67 ± 0.05	ND
Rifampicin	32	1.67 ± 0.09*	400

MIC, minimum inhibitory concentration; ND, no data.
*$P < 0.05$.

Cell cytotoxicity. Compounds **13** and **14** were taken for cell cytotoxicity study. Here, **13** (IC_{50} = 377 μg/mL) and **14** (IC_{50} = 369 μg/mL) were found to be a safe compound like rifampicin (400 μg/mL) (Table 2). Hence, **13** and **14** were taken ahead for growth inhibition study against *M. tuberculosis* H37Rv.

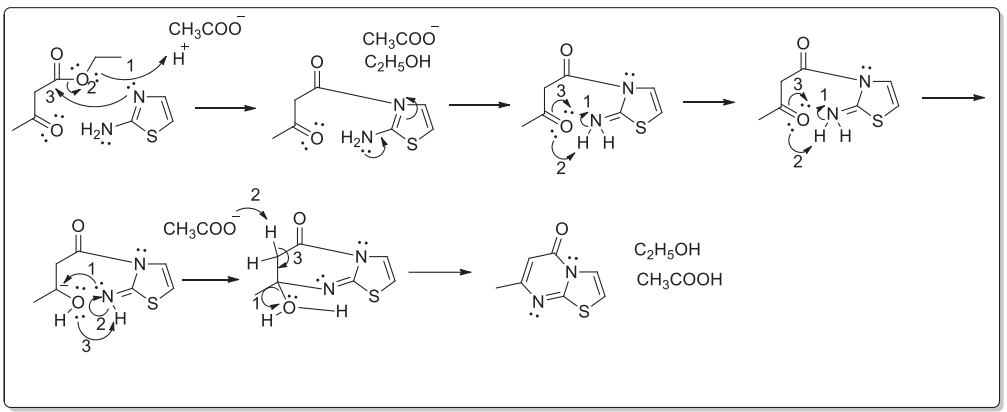


Figure 2. Reaction mechanism of thiazo[3,2-*a*]pyrimidinone.

Growth inhibitory potential of compounds 13 and 14 against Mycobacterium tuberculosis H37Rv. Based on MIC and cell cytotoxicity results obtained from the primary screenings, compounds **13** and **14** were selected for establishing their *M. tuberculosis* growth inhibition study (Table 3). Herein, **13** and **14** were found equipotent (MIC = 3.12 μg/mL and MIC = 3.05 μg/mL) when compared with standard rifampicin (2.80 μg/mL). Consequently, **13**, **14**, and rifampicin were found to be almost similar in potency; therefore, these compounds were taken ahead for further synergistic evaluation study (Table 3).

Synergism. After screening growth inhibition against *M. tuberculosis* H37Rv, in the next level, **13** and **14** were taken ahead for synergistic study with first-line rifampicin (RIF) and isoniazide (INH) and second-line ofloxacin (OFX) and amikacin (AMK) antitubercular drugs. The MICs of RIF, INH, OFX, and AMK were calculated in the absence and in the presence of various concentrations of compounds **13** and **14** against *M. tuberculosis* H37Rv (Table 4).

Compounds **13** and **14** were tested at their ½ MIC followed by two-dimensional broth micro dilution checkerboard assay, which is used to calculate the magnitude of synergism. Compound **13** does not show effective synergism with INH and RIF, whereas it demonstrated good synergism with OFX and AMK. On the other hand, **14** showed synergism everywhere. Hence, **14** was found to be a good potent compound among the series.

Table 3

Growth inhibitory potential of compounds **13** and **14** against *Mycobacterium tuberculosis* H37Rv.

	Mycobacterium tuberculosis H37Rv	
ID	MIC (μg/mL)	REF ± SD
13	3.12	1.1 ± 0.10*
14	3.05	2.3 ± 0.03*
Rifampicin	2.80	1.35 ± 0.04*

Results are presented as an average of three independent assays plus standard deviation (±SD). MIC, minimum inhibitory concentration.
*$P < 0.05$.

Table 4

Synergistic effect and modulation factor for compounds **13** and **14** with first-line and second-line drugs against *Mycobacterium tuberculosis* H37Rv.

ID	Test conc.	INH	RIF	OFX	AMK
Standalone MIC		1.2	1.7	2.4	2.9
13	9.60	0.47	0.51	0.032 (35)	0.023 (127)
	4.80	0.99	0.71	0.91	0.57
	2.40	1.2	0.81	1.4	1.12
	1.20	1.2	1.29	2.4	2.9
	0.60	1.2	1.7	2.4	2.9
	0.30	1.2	1.7	2.4	2.9
14	9.60	0.029 (16)	0.021 (81)	0.04 (60)	0.06 (49)
	4.80	0.071 (17)	0.19 (9)	0.29	0.69
	2.40	1.2	1.7	2.4	1.01
	1.20	1.2	1.7	2.4	2.9
	0.60	1.2	1.7	2.4	2.9
	0.30	1.2	1.7	2.4	2.9

INH, isoniazid; RIF, rifampin; OFX, ofloxacin; AMK, amikacin; MIC, minimum inhibitory concentration.

EXPERIMENTAL PROTOCOLS

Chemistry. ***Synthesis of 3-(substituted-phenyl)-1-(substituted-phenyl)-1H-pyrazole-4-carbaldehyde (D).*** Synthesis of these aldehydes was carried using Vilsmeier–Haack reaction condition. A mixture of substituted acetophenone (**A**, 1 mol) and substituted phenyl hydrazine (**B**, 1 mol) was heated in ethanol (20 mL) using AcOH as a catalyst at reflux temperature for 30 min. Solid precipitated from the reaction was separated by the filtration. This product **C** was washed by cold ethanol (7 mL) and was dried under vacuum.

A mixture of *N,N*-dimethylformamide (2.5 mol) and $POCl_3$ (2.5 mol) was stirred together at 0°C for 30 min. To this reaction mixture, above solid product **C** was added at 0°C with constant stirring. The reaction mixture was then slowly allowed to warm up to room temperature and stirred for 12 h. After completion of reaction on TLC and mass, the reaction mixture was poured on crushed ice where upon the solid was separated. It was filtered and washed by saturated aq. $NaHCO_3$ solution followed by water. The solid was crystallized from ethanol to get a white crystalline product **D** in an average 70% yield. The conversion was monitored by TLC only, so mass and ^1H NMR analysis was not performed at this stage of chemistry.

Synthesis of 7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (F). Ethyl acetoacetate (39 g, 0.3 mol) was added to a stirred mixture of 2-aminothiazole **E** (20 g, 0.2 mol) and acetic acid (200 mL). The mixture was refluxed for 15 h. The reaction mixture was cooled to room temperature, and acetic acid was removed to afford dark brown crude solid. It was then dissolved in ethyl acetate (250 mL) and washed with saturated $NaHCO_3$ solution (200 mL × 2) followed by saturated brine (200 mL). Organic layer was dried over anhydrous Na_2SO_4, and solvent was concentrated under vacuum to afford the crude product. The crude was purified by column chromatography using silica (60–120) to give 11.5 g (35%) of white solid of 7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**F**). ^1H NMR

(400 MHz, DMSO-d_6) δ ppm:2.35 (s, 3H, pyrimidone ring C<u>H</u>$_3$), 6.21 (s, 1H, pyrimidone ring <u>H</u>), 6.91 (d, J = 5.4 Hz, thiazole ring <u>H</u> near to sulfur), 7.99 (d, J = 5.2 Hz, thiazole ring <u>H</u> near to nitrogen); ES-MS *m/z* 167.4 [M + 1].

Condensation of 3-(substituted-phenyl)-1-(substituted-phenyl)-1*H*-pyrazole-4-carbaldehyde (D) and 7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (F) to yield compounds 1–17. A mixture of 3-(substituted-phenyl)-1-(substituted-phenyl)-1*H*-pyrazole-4-carbaldehyde (**D**) (1.2 mol), 7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**F**) (1.0 mol), and sodium ethoxide (2 mol) was refluxed together in ethanol for 13 h (overnight). Heating was ceased, and the reaction mixture was allowed to cool to room temperature. On cooling, yellow solid was separated. It was filtered and washed with cold ethanol. The solid was then dissolved in ethyl acetate and adsorbed on silica gel (60–120). Product was then column purified, solvent was evaporated, and product was then dried to obtain product (**1**–**17**) in 50–75% yield.

7-[2-(1,3-Diphenyl-1H-pyrazol-4-yl)-vinyl]-thiazolo[3,2-a] pyrimidin-5-one (1). Yield 59%, M.P. 211–213°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 6.20 (s, 1H, pyrimidinone ring <u>H</u>), 7.10 (d, 1H, J = 16 Hz, olefinic <u>H</u> close to pyrazole ring), 7.38 (d, 1H, J = 4.3 Hz, thiazole ring <u>H</u> near to sulfur), 7.40 (t, 2H, Ar<u>H</u>), 7.50–7.70 (m, 7H, olefinic <u>H</u> near to pyrimidinone ring and Ar<u>H</u>), 7.80 (t, 2H, Ar<u>H</u>), 8.00 (d, 1H, J = 4 Hz, thiazole ring <u>H</u> near to bridge head nitrogen), 9.20 (s, 1H, pyrazole ring <u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6): 102.8 (thiazole ring <u>C</u> near to sulfur), 105.9 (pyrazole ring <u>C</u> attached to olefin), 118.2, 120.1, 121.4, 122.1, 122.4, 123.4, 124.3, 129.7, 132.3 (olfine <u>C</u> near to pyrazole), 135.1 (olefin <u>C</u> near to pyrimidinone), 138.0 (phenyl <u>C</u> attached to N), 144 (pyrimidinone ring <u>C</u> near to N), 147.9 (pyrazole ring <u>C</u> attached to phenyl), 161.9 (thiazole ring <u>C</u> near to sulfur and nitrogen), 162.8 (<u>C</u>═O); ES-MS (*m/z*) 397.1 (M + 1), *Anal*. Calcd for **$C_{23}H_{16}N_4OS$** (396.47): C, 69.68; H, 4.07; N, 14.23; found C, 68.99; H, 4.59; N, 13.91.

7-{2-[1-(4-Chloro-phenyl)-3-phenyl-1H-pyrazol-4-yl}-thiazolo[3,2-a]pyrimidin-5-one (2). Yield 64%, M.P. 223–225°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 6.19 (s, 1H, pyrimidinone ring <u>H</u>), 7.05 (d, 1H, J = 16 Hz, olefinic <u>H</u> close to pyrazole ring), 7.37 (d, 1H, J = 4.1 Hz, thiazole ring <u>H</u> near to sulfur), 7.41 (t, 2H, Ar<u>H</u>), 7.43–7.67 (m, 6H, olefinic H near to pyrazole ring and Ar<u>H</u>), 7.88 (t, 2H, Ar<u>H</u>), 8.01 (d, 1H, J = 4 Hz, thiazole ring <u>H</u> near to bridge head nitrogen), 9.21 (s, 1H, pyrazole ring <u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6): 103.2 (thiazole ring <u>C</u> near to sulfur), 106.3 (pyrazole ring <u>C</u> attached to olefin), 119.2, 120.6, 121.5, 121.9, 124.3, 126.9, 129.4, 132.2 (olefinic <u>C</u> near to pyrazole), 135.8 (olefinic <u>C</u> near to pyrimidinone), 138.2 (phenyl <u>C</u> attached to N), 145.3 (pyrimidinone ring <u>C</u> near to N), 148.1 (pyrazole ring <u>C</u> attached to phenyl), 161.2 (thiazole ring <u>C</u> near to sulfur and nitrogen), 162.5 (<u>C</u>═O); ES-MS (*m/z*) 431.1 (M + 1), *Anal*. Calcd for **$C_{23}H_{15}ClN_4OS$** (430.92): C, 64.11; H, 3.51; N, 13.00; found C, 64.23; H, 4.01; N, 13.41.

7-{2-[1-(4-Fluoro-phenyl)-3-phenyl-1H-pyrazol-4-yl}-thiazolo[3,2-a]pyrimidin-5-one (3). Yield 61%, M.P. 227–229°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 6.12 (s, 1H, pyrimidinone ring <u>H</u>), 7.11 (d, 1H, J = 16 Hz, olefinic <u>H</u> close to pyrazole ring), 7.31 (d, 1H, J = 4.0 Hz, thiazole ring <u>H</u> near to sulfur), 7.45 (t, 2H, Ar<u>H</u>), 7.41–7.77 (m, 8H, olefinic H near to pyrazole ring and Ar<u>H</u>), 7.99 (d, 1H, J = 4.1 Hz, thiazole ring <u>H</u> near to bridge head nitrogen), 9.21(s, 1H, pyrazole ring <u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6): 103.6 (thiazole ring <u>C</u> near to sulfur), 107.1 (pyrazole ring <u>C</u> attached to olefin), 119.6, 120.4, 121.1, 121.9, 123.6, 124.3, 126.8, 131.4, 133.6 (olfine <u>C</u> near to pyrazole), 135.1 (olefin <u>C</u> near to pyrimidinone), 138.7 (phenyl <u>C</u> attached to N), 141.1 (phenyl <u>C</u> attached to fluoro), 145.8 (pyrimidinone ring <u>C</u> near to N), 149.2 (pyrazole ring <u>C</u> attached to phenyl), 161.0 (thiazole ring <u>C</u> near to sulfur and nitrogen), 162.1 (<u>C</u>═O); ES-MS (*m/z*) 415.1 (M + 1), *Anal*. Calcd for **$C_{23}H_{15}FN_4OS$** (414.46): C, 66.65; H, 3.65; N, 13.52; found C, 66.89; H, 4.03; N, 13.21.

7-[2-[1-(3-Phenyl-1-p-tolyl-1H-pyrazol-4-yl}-thiazolo[3,2-a] pyrimidin-5-one (4). Yield 67%, M.P. 232–234°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 2.38 (s, 3H, ArC<u>H</u>$_3$), 6.22 (s, 1H, pyrimidinone ring <u>H</u>), 7.06 (d, 1H, J = 16.2 Hz, olefinic <u>H</u> close to pyrazole ring), 7.21 (d, 1H, J = 4.3 Hz, thiazole ring <u>H</u> near to sulfur), 7.38 (d, 1H, J = 8.1 Hz, Ar<u>H</u>), 7.41–7.67 (m, 6H, olefinic <u>H</u> near to pyrimidinone ring and Ar<u>H</u>), 7.78–7.80 (m, 3H, Ar<u>H</u>), 8.07 (d, 1H, J = 4.1 Hz, thiazole ring <u>H</u> near to bridge head nitrogen), 9.11 (s, 1H, pyrazole ring <u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6): 103.1 (thiazole ring <u>C</u> near to sulfur), 105.8 (pyrazole ring <u>C</u> attached to olefin), 120.3, 121.2, 121.9, 123.4, 129.4, 132.1 (olfine <u>C</u> near to pyrazole), 136.1 (olefin <u>C</u> near to pyrimidinone), 138.4 (phenyl <u>C</u> attached to N), 145.2 (pyrimidinone ring <u>C</u> near to N), 149.5 (pyrazole ring <u>C</u> attached to phenyl), 161.9 (thiazole ring <u>C</u> near to sulfur and nitrogen), 163.1 (<u>C</u>═O); ES-MS (*m/z*) 411.3 (M + 1), *Anal*. Calcd for **$C_{24}H_{18}N_4OS$** (410.50): C, 70.22; H, 4.42; N, 13.62; found C, 71.00; H, 4.32; N, 13.67.

7-{2-[3-(4-Chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-thiazolo[3,2-a]pyrimidin-5-one (5). Yield 63.5%, M.P. 227–229°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 6.17 (s, 1H, pyrimidinone ring <u>H</u>), 6.98 (d, 1H, J = 16.0 Hz, olefinic <u>H</u> close to pyrazole ring), 7.14 (d, 1H, J = 4.3 Hz, thiazole ring <u>H</u> near to sulfur), 7.41 (t, 2H, Ar<u>H</u>), 7.45–7.70 (m, 6H, olefinic <u>H</u> near to pyrimidinone ring and Ar<u>H</u>), 7.89 (d, 2H, J = 8.2 Hz, Ar<u>H</u>), 8.07 (d, 1H, J = 4.1 Hz, thiazole ring <u>H</u> near to bridge head nitrogen), 9.18 (s, 1H, pyrazole ring <u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6): 103.2 (thiazole ring <u>C</u> near to

sulfur), 107.2 (pyrazole ring C attached to olefin), 114.7, 119.6, 120.4, 120.8, 121.9, 123.6, 126.3, 130.1, 131.4, 133.2 (olfine C near to pyrazole), 135.1 (olefin C near to pyrimidinone), 137.2 (phenyl C attached to N), 144.3 (phenyl C attached to chloro), 145.1 (pyrimidinone ring C near to N), 149.0 (pyrazole ring C attached to phenyl), 161.1 (thiazole ring C near to sulfur and nitrogen), 163.0 (C=O); ES-MS (*m/z*) 431.3 (M + 1), *Anal*. Calcd for **$C_{23}H_{15}ClN_4OS$** (430.92): C, 64.11; H, 3.51; N, 13.00; found C, 64.29; H, 3.89; N, 13.47.

7-{2-[3-(4-Fluoro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-thiazolo[3,2-a]pyrimidin-5-one (6). Yield 59%, M.P. 209–211°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 6.19 (s, 1H, pyrimidinone ring H), 6.96 (d, 1H, *J* = 16.7 Hz, olefinic H close to pyrazole ring), 7.20 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to sulfur), 7.35 (d, 1H, *J* = 8.3 Hz, ArH), 7.39–7.65 (m, 7H, olefinic H near to pyrimidinone ring and ArH), 7.80 (t, 2H, ArH), 8.07 (d, 1H, *J* = 4.0 Hz, thiazole ring H near to bridge head nitrogen), 9.07 (s, 1H, pyrazole ring H); ^{13}C NMR (100 MHz, DMSO-d_6): 103.2 (thiazole ring C near to sulfur), 106.1 (pyrazole ring C attached to olefin), 120.3, 121.2, 123.4, 126.8, 129.4, 132.8 (olfine C near to pyrazole), 136.1 (olefin C near to pyrimidinone), 138.3 (phenyl C attached to N), 141.3 (phenyl C attached to fluoro), 145.7 (pyrimidinone ring C near to N), 149.2 (pyrazole ring C attached to phenyl), 161.8 (thiazole ring C near to sulfur and nitrogen), 163.5 (C=O); ES-MS (*m/z*) 415.1 (M + 1), *Anal*. Calcd for **$C_{23}H_{15}FN_4OS$** (414.16): C, 66.65; H, 3.65; N, 13.52; found C, 66.98; H, 4.51; N, 13.04.

7-{2-[3-(4-Methoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-thiazolo[3,2-a]pyrimidin-5-one (7). Yield 69.7%, M. P. 229–231°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 3.89 (s, 3H, Ar–OCH$_3$), 6.19 (s, 1H, pyrimidinone ring H), 7.01 (d, 1H, *J* = 16.7 Hz, olefinic H close to pyrimidone ring), 7.19 (d, 2H, *J* = 4.0 Hz, thiazole ring H near to sulfur and ArH), 7.39 (t, 1H, ArH), 7.51–7.68 (m, 6H, olefinic H near to pyrazole ring and ArH), 7.91 (m, 2H, ArH), 8.00 (d, 1H, *J* = 4.3 Hz, thiazole ring H near to bridge head nitrogen), 9.07 (s, 1H, pyrazole ring H); ^{13}C NMR (100 MHz, DMSO-d_6): 102.9 (thiazole ring C near to sulfur), 107.1 (pyrazole ring C attached to olefin), 120.4, 121.1, 123.6, 124.3, 126.3, 126.8, 130.1, 131.4, 133.8 (olfine C near to pyrazole), 135.2 (olefin C near to pyrimidinone), 138.5 (phenyl C attached to N), 141.8 (phenyl C attached to methoxy group), 144.9 (pyrimidinone ring C near to N), 149.7 (pyrazole ring C attached to phenyl), 161.7 (thiazole ring C near to sulfur and nitrogen), 164.0 (C=O); ES-MS (*m/z*) 427.1 (M + 1), *Anal*. Calcd for **$C_{24}H_{18}N_4O_2S$** (426.50): C, 67.60; H, 4.25; N, 13.14; found C, 66.94; H, 4.45; N, 13.47.

7-{2-[3-(4-Trifluoromethyl-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-thiazolo[3,2-a]pyrimidin-5-one (8). Yield 64%, M. P. 224–226°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 6.31 (s, 1H, pyrimidinone ring H), 7.03 (d, 1H, *J* = 16.7 Hz, olefinic H close to pyrazole ring), 7.21 (d, 1H, *J* = 4.8 Hz, thiazole ring H near to sulfur), 7.31 (d, 2H, *J* = 8.2 Hz, ArH), 7.43–7.75 (m, 7H, olefinic H near to pyrimidinone ring and ArH), 7.87 (d, 1H, *J* = 8.0 Hz, ArH), 8.07 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to bridge head nitrogen), 9.09 (s, 1H, pyrazole ring H); ^{13}C NMR (100 MHz, DMSO-d_6): 102.8 (thiazole ring C near to sulfur), 105.1 (pyrazole ring C attached to olefin), 120.3, 121.1, 122.3, 122.8, 124.3, 129.1, 132.0 (olfine C near to pyrazole), 135.1 (olefin C near to pyrimidinone), 139.2 (phenyl C attached to N), 141.2 (phenyl C attached to trifluoro methyl), 145.2 (pyrimidinone ring C near to N), 149.0 (pyrazole ring C attached to phenyl), 162.2 (thiazole ring C near to sulfur and nitrogen), 162.8 (C=O); E-MS (*m/z*) 465.3 (M + 1), *Anal*. Calcd for **$C_{24}H_{15}F_3N_4OS$** (464.4): C, 62.05; H, 3.26; N, 12.06; found C, 61.98; H, 3.51; N, 12.10.

7-{2-[3-(4-Methyl-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-thiazolo[3,2-a]pyrimidin-5-one (9). Yield 66.3%, M.P. 220–222°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 2.38 (s, 3H, Ar–CH$_3$), 6.29 (s, 1H, pyrimidinone ring H), 7.09 (d, 1H, *J* = 16.0 Hz, olefinic H close to pyrazole ring), 7.23 (d, 1H, *J* = −4.1 Hz, thiazole ring H near to sulfur), 7.31 (d, 2H, *J* = 8.0 Hz, ArH), 7.43–7.79 (m, 6H, olefinic H near to pyrimidinone ring and ArH), 7.84 (d, 1H, *J* = 8.0 Hz, ArH), 8.07 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to bridge head nitrogen), 9.11 (s, 1H, pyrazole ring H); ^{13}C NMR (100 MHz, DMSO-d_6): 101.9 (thiazole ring C near to sulfur), 106.0 (pyrazole ring C attached to olefin), 120.9, 121.4, 122.6, 124.5, 129.7, 133.0 (olfine C near to pyrazole), 135.2 (olefin C near to pyrimidinone), 138.0 (phenyl C attached to N), 145.0 (pyrimidinone ring C near to N), 149.2 (pyrazole ring C attached to phenyl), 162.8 (thiazole ring C near to sulfur and nitrogen), 163.1 (C=O); ES-MS (*m/z*) 411.3 (M + 1), *Anal*. Calcd for **$C_{24}H_{18}F_3N_4OS$** (410.50): C, 70.22; H, 4.42; N, 13.65; found C, 71.01; H, 4.21; N, 13.81.

7-{2-[3-(4-Trifluoromethoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-thiazolo[3,2-a]pyrimidin-5-one (10). Yield 61%, M.P. 226–228°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 6.37 (s, 1H, pyrimidinone ring H), 7.12 (d, 1H, *J* = 16.0 Hz, olefinic H close to pyrazole ring), 7.29 (d, 1H, *J* = 4.0 Hz, thiazole ring H near to sulfur), 7.38 (d, 2H, *J* = 8.0 Hz, ArH), 7.46–7.68 (m, 7H, olefinic H near to pyrimidinone ring and ArH), 7.90 (d, 1H, *J* = 8.0 Hz, ArH), 8.10 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to bridge head nitrogen), 9.13 (s, 1H, pyrazole ring H); ^{13}C NMR (100 MHz, DMSO-d_6): 101.9 (thiazole ring C near to sulfur), 107.2 (pyrazole ring C attached to olefin), 120.4, 121.1, 121.8, 122.9, 124.3, 129.7, 133.1 (olfine C near to pyrazole), 134.1 (olefin C near to pyrimidinone), 139.7 (phenyl C attached to N), 145.2 (pyrimidinone ring C near to N), 149.0 (pyrazole ring C attached to phenyl), 161.9 (thiazole

ring C near to sulfur and nitrogen), 163.1 (C═O); ^{13}C NMR (100 MHz, DMSO-d_6): 103.1 (thiazole ring C near to sulfur), 104.2 (pyrazole ring C attached to olefin), 120.1, 120.5, 121.2, 122.5, 124.2, 129.2, 133.5 (olfine C near to pyrazole), 137.2 (olefin C near to pyrimidinone), 139.1 (phenyl C attached to N), 144.2 (pyrimidinone ring C near to N), 147.3 (pyrazole ring C attached to phenyl), 162.4 (thiazole ring C near to sulfur and nitrogen), 162.8 (C═O); ES-MS (*m/z*) 481.4 (M + 1), *Anal*. Calcd for **$C_{24}H_{15}F_3N_4O_2S$** (480.47): calculated C, 60.00; H, 3.15; N, 11.66; observed C, 60.89; H, 3.27; N, 12.00.

7-{2-[3-(2-Methoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-thiazolo[3,2-a]pyrimidin-5-one (11). Yield 67.88%, M.P. 221–223°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 3.79 (s, 3H, Ar–OCH_3), 6.37 (s, 1H, pyrimidinone ring H), 7.19 (d, 1H, *J* = 16.1 Hz, olefinic H close to pyrazole ring), 7.20 (d, 1H, *J* = 4.0 Hz, thiazole ring H near to sulfur), 7.40 (d, 1H, *J* = 7.90 Hz, ArH), 7.43–7.76 (m, 8H, olefinic H near to pyrimidinone ring and ArH), 7.84 (d, 1H, *J* = 8.0 Hz, ArH), 8.01 (d, 1H, *J* = 4.7 Hz, thiazole ring H near to bridge head nitrogen), 9.09 (s, 1H, pyrazole ring H); ^{13}C NMR (100 MHz, DMSO-d_6): 102.8 (thiazole ring C near to sulfur), 103.8 (pyrazole ring C attached to olefin), 119.9, 121.2, 122.3, 122.9, 124.9, 129.5, 133.1 (olfine C near to pyrazole), 134.2 (olefin C near to pyrimidinone), 139.5 (phenyl C attached to N), 145.2 (pyrimidinone ring C near to N), 149.0 (pyrazole ring C attached to phenyl), 157.0 (phenyl C attached to OCH_3), 161.9 (thiazole ring C near to sulfur and nitrogen), 162.2 (C═O); ES-MS (*m/z*) 427.3 (M + 1), *Anal*. Calcd for **$C_{24}H_{18}N_4O_2S$** (426.50): found C, 67.60; H, 4.25; N, 13.14; observed C, 66.84; H, 4.41; N, 13.40.

7-{2-[3-(3-Methoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-thiazolo[3,2-a]pyrimidin-5-one (12). Yield 58%, M. P. 224–226°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 3.84 (s, 3H, Ar–OCH_3), 6.40 (s, 1H, pyrimidinone ring H), 7.20 (d, 1H, *J* = 16.0 Hz, olefinic H close to pyrazole ring), 7.21 (d, 1H, *J* = 4.0 Hz, thiazole ring H near to sulfur), 7.42–7.46 (m, 5H,, ArH), 7.51–7.67 (m, 4H, olefinic H near to pyrimidinone ring and ArH), 7.80 (d, 1H, *J* = 8.29 Hz, ArH), 8.00 (d, 1H, *J* = 4.0 Hz, thiazole ring H near to bridge head nitrogen), 9.10 (s, 1H, pyrazole ring H); ^{13}C NMR (100 MHz, DMSO-d_6): 102.0 (thiazole ring C near to sulfur), 103.1 (pyrazole ring C attached to olefin), 119.1, 120.1, 121.7, 122.2, 124.3, 129.5, 133.3 (olfine C near to pyrazole), 134.4 (olefin C near to pyrimidinone), 139.2 (phenyl C attached to N), 143.2 (pyrimidinone ring C near to N), 149.6 (pyrazole ring C attached to phenyl), 157.6 (phenyl C attached to OCH_3), 161.9 (thiazole ring C near to sulfur and nitrogen), 162.9 (C═O); ES-MS (*m/z*) 427.3 (M + 1), *Anal*. Calcd for **$C_{24}H_{18}N_4O_2S$** (426.50): C, 67.60; H, 4.25; N, 13.14; found C, 67.04; H, 4.91; N, 13.42.

7-{2-[3-(2-Methyl-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-thiazolo[3,2-a]pyrimidin-5-one (13). Yield 66.3%, M.P. 220–222°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 2.39 (s, 3H, Ar–CH_3), 6.60 (s, 1H, pyrimidinone ring H), 7.12 (d, 1H, *J* = 16.2 Hz, olefinic H close to pyrazole ring), 7.25 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to sulfur), 7.38 (t, 2H, ArH), 7.44–7.46 (m, 3H, ArH), 7.48–7.71 (m, 4H, olefinic H near to pyrimidinone ring and ArH), 7.94 (d, 1H, *J* = 8.2 Hz, ArH), 8.00 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to bridge head nitrogen), 9.08 (s, 1H, pyrazole ring H); ^{13}C NMR (100 MHz, DMSO-d_6): 103.3 (thiazole ring C near to sulfur), 104.6 (pyrazole ring C attached to olefin), 119.9, 121.4, 121.7, 122.2, 122.9, 129.5, 134.4 (olfine C near to pyrazole), 136.3 (olefin C near to pyrimidinone), 141.4 (phenyl C attached to N), 145.5 (pyrimidinone ring C near to N), 149.0 (pyrazole ring C attached to phenyl), 162.5 (thiazole ring C near to sulfur and nitrogen), 163.1 (C═O); ES-MS (*m/z*) 411.3 (M + 1), *Anal*. Calcd for **$C_{24}H_{18}N_4OS$** (410.50): C, 70.22; H, 4.42; N, 13.65; found C, 71.11; H, 4.49; N, 13.81.

7-{2-[3-(3-Methyl-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-thiazolo[3,2-a]pyrimidin-5-one (14). Yield 63.2%, M.P. 219−221°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 2.41 (s, 3H, Ar–CH_3), 6.68 (s, 1H, pyrimidinone ring H), 7.22 (d, 1H, *J* = 16.2 Hz, olefinic H close to pyrazole ring), 7.27 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to sulfur), 7.40–7.44 (m, 3H, ArH), 7.50–7.57 (m, 2H, ArH), 7.48–7.71 (m, 4H, olefinic H near to pyrimidinone ring and ArH), 7.90 (d, 1H, *J* = 8.2 Hz, ArH), 8.05 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to bridge head nitrogen), 9.12 (s, 1H, pyrazole ring H); ^{13}C NMR (100 MHz, DMSO-d_6): 102.3 (thiazole ring C near to sulfur), 104.4 (pyrazole ring C attached to olefin), 119.1, 120.7, 121.1, 122.2, 124.1, 129.3, 133.6 (olfine C near to pyrazole), 134.8 (olefin C near to pyrimidinone), 139.2 (phenyl C attached to N), 145.1 (pyrimidinone ring C near to N), 149.2 (pyrazole ring C attached to phenyl), 162.8 (thiazole ring C near to sulfur and nitrogen), 163.7 (C═O); ES-MS (*m/z*) 411.3 (M + 1), *Anal*. Calcd for **$C_{24}H_{18}N_4OS$** (410.50): C, 70.22; H, 4.42; N, 13.65; found C, 71.11; H, 4.49; N, 13.88.

7-{2-[3-(2-Methoxy-3-methyl-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-thiazolo[3,2-a]pyrimidin-5-one (15). Yield 51%, M.P. 212–214°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 2.31 (s, 3H, Ar–CH_3), 3.49 (s, 3H, Ar–OCH_3), 6.79 (s, 1H, pyrimidinone ring H), 7.10 (d, 1H, *J* = 16.0 Hz, olefinic H close to pyrazole ring), 7.19 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to sulfur), 7.38–7.49 (m, 4H, ArH), 7.51–7.75 (m, 4H, olefinic H near to pyrimidinone ring and ArH), 7.91 (d, 1H, *J* = 8.0 Hz, ArH), 8.07 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to bridge head nitrogen), 9.00 (s, 1H, pyrazole ring H); ^{13}C NMR (100 MHz, DMSO-d_6): 102.2 (thiazole ring C near to sulfur), 104.5

(pyrazole ring C attached to olefin), 120.3, 121.2, 121.7, 122.7, 124.1, 129.7, 133.9 (olefin C near to pyrazole), 134.8 (olefin C near to pyrimidinone), 139.3 (phenyl C attached to N), 145.1 (pyrimidinone ring C near to N), 149.0 (pyrazole ring C attached to phenyl), 161.6 (thiazole ring C near to sulfur and nitrogen), 163.8 (C=O); ES-MS (*m/z*) 441.4 (M + 1), *Anal*. Calcd for **$C_{25}H_{20}N_4O_2S$** (440.53): C, 68.16; H, 4.58; N, 12.72; found C, 68.11; H, 4.41; N, 12.67.

7-{2-[3-(2-Methyl-3-methoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-thiazolo[3,2-a]pyrimidin-5-one (16). Yield 57%, M.P. 217–219°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 2.33 (s, 3H, Ar–CH_3), 3.59 (s, 3H, Ar–OCH_3), 6.82 (s, 1H, pyrimidinone ring H), 7.17 (d, 1H, *J* = 16.1 Hz, olefinic H close to pyrazole ring), 7.21 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to sulfur), 7.40 (t, 1H, ArH), 7.42–7.49 (m, 3H, ArH), 7.51–7.71 (m, 4H, olefinic H near to pyrimidinone ring and ArH), 7.82 (d, 1H, *J* = 8.0 Hz, ArH), 8.11 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to bridge head nitrogen), 9.03 (s, 1H, pyrazole ring H); ^{13}C NMR (100 MHz, DMSO-d_6): 103.0 (thiazole ring C near to sulfur), 104.1 (pyrazole ring C attached to olefin), 120.4, 121.2, 121.7, 122.2, 122.9, 124.3, 129.5, 133.2 (olfine C near to pyrazole), 133.9 (olefin C near to pyrimidinone), 139.7 (phenyl C attached to N), 144.9 (pyrimidinone ring C near to N), 149.7 (pyrazole ring C attached to phenyl), 162.2 (thiazole ring C near to sulfur and nitrogen), 163.6 (C=O); ES-MS (*m/z*) 441.38 (M + 1), *Anal*. Calcd for **$C_{25}H_{20}N_4O_2S$** (440.53): C, 68.16; H, 4.58; N, 12.72; found C, 68.77; H, 4.55; N, 12.98.

7-{2-[3-(2,3-Dimethyl-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-thiazolo[3,2-a]pyrimidin-5-one (17). Yield 57%, M. P. 217–219°C, ^{1}H NMR (400, DMSO-d_6), δ ppm: 2.33 (s, 3H, Ar–CH_3), 2.34 (s, 3H, CH_3), 6.80 (s, 1H, pyrimidinone ring H), 7.20 (d, 1H, *J* = 16.1 Hz, olefinic H close to pyrazole ring), 7.29 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to sulfur), 7.42 (t, 1H, ArH), 7.42–7.48 (d, 1H, *J* = 8.23 Hz, ArH), 7.51–7.71 (m, 6H, olefinic H near to pyrimidinone ring and ArH), 7.84 (d, 1H, *J* = 8.0 Hz, ArH), 8.11 (d, 1H, *J* = 4.1 Hz, thiazole ring H near to bridge head nitrogen), 9.09 (s, 1H, pyrazole ring H); ES-MS (*m/z*) 425.4 (M + 1), *Anal*. Calcd for **$C_{25}H_{20}N_4OS$** (424.53): C, 70.73; H, 4.74; N, 13.20; found C, 69.79; H, 4.65; N, 12.92.

CONCLUSION

Present communication reports novel pyrazole analogues and their growth inhibition study against *M. smegmatis* mc^2 155 strain. The design of these novel derivatives was based on our previous report. Selected compounds from preliminary screening (*M. smegmatis* mc^2 155 strain) were exposed for *M. tuberculosis* H37Rv growth inhibition studies as well as synergistic studies with first-line and second-line antibiotics. Compounds **13** and **14** (MIC: 47 and 39 μg/mL) were found to be equipotent candidates with first-line antitubercular agent rifampicin, which could act as a lead for further optimization.

REFERENCES AND NOTES

[1] Dixit, P.; Dixit, P.; Thore, S. Eur J Med Chem 2016, 107, 38.
[2] Boogaard, J.; Kibiki, G. S.; Kisanga, E. R. Antimicrob Chemother 2009, 53, 849.
[3] Ryan F., Brown: Boston, MA, 1993.
[4] World Health Organization. The World Health Organization Global Tuberculosis Program, 2003.
[5] Biava, M.; Porretta, G. C.; Poce, G.; Supino, S.; Deidda, D.; Pompei, R.; Manetti, P. M. F.; Botta, M. J Med Chem 2006, 49, 4946.
[6] Field, S. K. Ther Adv Chronic Dis 2015, 6, 170.
[7] Karrouchi K, Radi S, Ramli Y, Taoufik J, Mabkhot YN, Al-Aizari FA, Ansar M; Synthesis and pharmacological activities of pyrazole derivatives: a review. Molecules; 2018 doi:https://doi.org/10.3390/molecules23010134.
[8] Xu, Z.; Gao, C.; Ren, Q. C.; Song, X. F.; Feng, L. S.; Lv, Z. S. Eur J Med Chem 2017, 139, 429. https://doi.org/10.1016/j.ejmech.2017.07.059.
[9] Radi, S.; Ramli, Y.; Taoufik, J.; Mabkhot, Y. N.; Al-aizari, F. A.; Ansar, M. Molecules 2018, 23. https://doi.org/10.3390/molecules23010134.
[10] Pathak, R. B.; Chovatia, P. T.; Parekh, H. H. Bioorg Med Chem Lett 2012, 22, 15, 22, 5129.
[11] Jadhav, S. B.; Fatema, S.; Sanap, G.; Farooqui, M. J Heterocyclic Chem 2018, 55, 1634. https://doi.org/10.1002/jhet.3198.
[12] Chaudhari S.S., Thomas A., Kadam A.B., Dhone S.V., Kadam S.M., Khairatkar-Joshi N., Kattige V.G.; Fused imidazole carboxamides as TRPV3 modulators; 2010, US 2010/0152192A$_1$.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.