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Short communication

Facile water promoted synthesis of 1,2,3-triazolyl dihydropyrimidine-2-thione hybrids – Highly potent antibacterial agents

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ABSTRACT

An elegant and efficient synthesis of hitherto novel 1,2,3-triazolyl dihydropyrimidine-2-thione hybrids has been accomplished for the first time in a green solvent *viz.* water. The hybrid molecules exhibit significant antibacterial activity when screened against four human pathogens *viz. Streptococcus pneumonia*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella typhi*. In comparison to the commercially marketed tetracycline, some of them were equally potent and a few more potent.

1. Introduction

Infectious diseases are the world's leading cause of premature deaths, killing almost 50,000 people every day [1]. The reason for this, is mainly attributed to the drug resistance to human pathogenic bacteria all over the world [2]. In recent years, the multi drug resistance (MDR) is alarming and the major public health concern worldwide [3]. Many strains causing infectious diseases that seemed to be in control are causing deaths each year due to the absence of an appropriate antibiotic [4].

For instance, *Streptococcus pneumonia*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella typhi* are important pathogens causing invasive diseases such as sepsis, meningitis, pneumonia [5], nosocomial pneumonia [6], cystic fibrosis, acute leukemia, organ transplants, and intravenous-drug addiction [7]. Some of these pathogens have been reported to develop resistance [8] to the well known commercially available drug *viz.* tetracycline. In view of this, the current study was undertaken to synthesize and investigate the antimicrobial activities of a series of 1,2,3-triazolyl dihydropyrimidine-2-thione hybrids against the above said human pathogenic bacteria.

The heterocycles *viz.* thiazine [9], imidazole [10], pyrimidine [11], pyrimidine-2-thione [12,13], 1,2,3-triazoles [14,15] and 1,2,4-triazole [16] have been reported as potential inhibitors of one or more of the above said pathogens. In view of these bioactivities of the individual heterocycles, it was envisaged that the synthesis and antibacterial study of hitherto novel hybrid molecules containing two of the above said moieties in a single frame is worth the attempt.

In continuation of our recent work on the environment friendly, solvent-free synthesis of amides [17–19], thioamides [20], thioazolidones [21], spirothiazolidones [22], 1,2,3-triazoles [23], and synthesis of 1,2,3-triazolyl chalcone [24] in water as solvent, we herein report an elegant water promoted synthesis of hitherto novel 1,2,3-triazolyl dihydropyrimidine-2-thione hybrids and screened their bioactivity against the above mentioned pathogens. Many of the compounds thus synthesized were found to be equally potent or more potent than the reference compound *viz.* tetracycline, the details of which are presented vide infra.

2. Results and discussion

2.1. Chemistry

Owing to the significant features of dihydropyrimidine-2-thiones, a number of protocols for their synthesis have been developed. These known methodologies involve the usage of organic solvents [25,26] which take long reaction time (5–10 h or even

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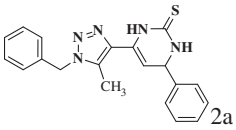
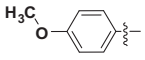
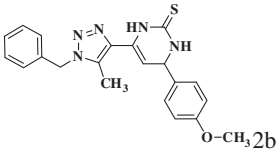
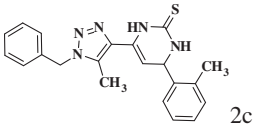
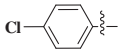
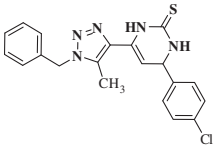
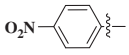
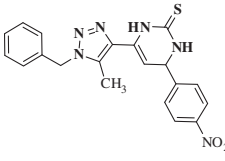
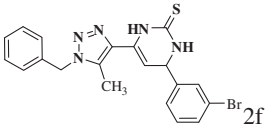
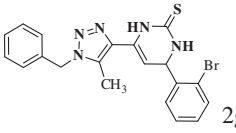
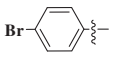
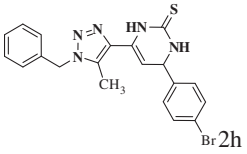
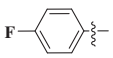
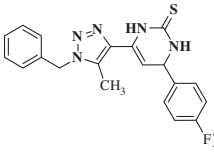
more) [27] or microwave as the energy source [12]. These organic solvents are hazardous to human health and cause environmental pollution due to their volatile nature. Hence, organic reactions under solvent-free conditions and in water medium, being eco-friendly have attained much importance and are of current interest.

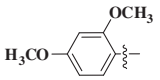
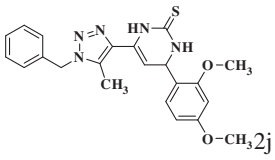
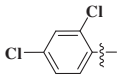
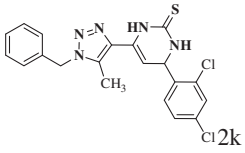
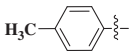
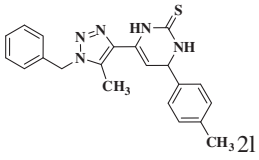
Herein we submit the first report on the synthesis of 1,2,3-triazolyl dihydropyrimidine-2-thione hybrids in water. It is pertinent to note that, the yield of the hybrids in the organic solvent *viz.* ethanol and in water medium is comparable, the details of which are presented in Table 1.

Table 1
Synthesis of 1,2,3-triazolyl dihydropyrimidine-2-thione hybrids (**2a**–**l**)[b] in ethanol and water.

S. No	Triazolyl chalcone	R	Product	Ethanol		Water	
				Yield[a] (%)	Time (min)	Yield[a] (%)	Time (min)
1	**1a**			85	30	89	40
2	**1b**			93	30	95	40
3	**1c**			83	30	85	40
4	**1d**			81	30	87	40
5	**1e**			74	30	81	40
6	**1f**			80	30	83	40
7	**1g**			76	30	80	40
8	**1h**			81	30	88	40
9	**1i**			87	30	91	40

(*continued on next page*)

Table 1 (*continued*)

S. No	Triazolyl chalcone	R	Product	Ethanol		Water	
				Yield[a] (%)	Time (min)	Yield[a] (%)	Time (min)
10	**1j**			86	30	86	40
11	**1k**			75	30	79	40
12	**1l**			95	30	93	40

[a] Yield of the isolated product.
[b] The synthesized compounds were characterized by NMR (1D & 2D).

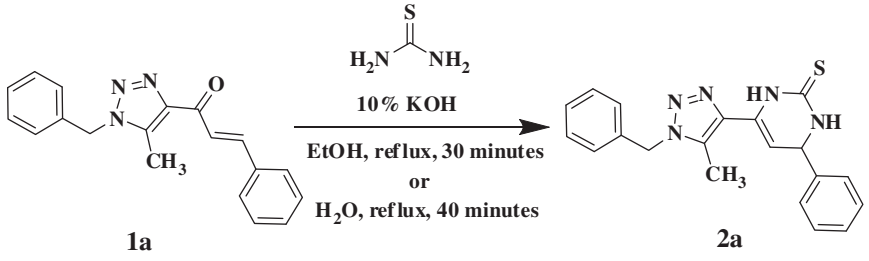
At the outset, a mixture of 1,2,3-triazolyl chalcone (**1a**, 1.0 equiv.), thiourea (1.1 equiv.) and 10% KOH in ethanol was refluxed (Scheme 1). The reaction was completed in 30 min affording 1,2,3-triazolyl dihydropyrimidine-2-thione hybrid (**2a**) in 85% yield. On the other hand, in water, the reaction was completed in 40 min affording comparable yield (89%) of **2a**. The later protocol avoiding the organic solvent *viz*. ethanol is greener (Scheme 1).

The broad scope of the greener methodology involving water as media was established *via* the synthesis of a library of 1,2,3-triazolyl dihydropyrimidine-2-thione hybrids (**2a**–**l**, Scheme 2) in good to excellent yields (79–95%, Table 1).

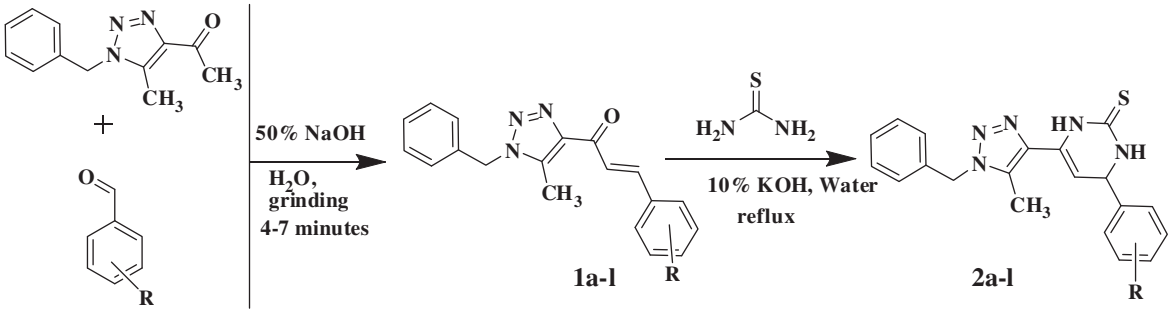
2.2. Biology

2.2.1. Antibacterial activity of compounds against human pathogens

The cultures of human pathogenic bacteria *S. aureus*, *S. pneumonia*, *P. aeruginosa* and *S. typhi* used in this study were obtained from the Department of Microbial Technology, School of Biological Sciences, Madurai Kamaraj University and maintained on Nutrient Agar (NA), consisting of the following [(g/L) Beef extract 1.0; Yeast extract 2.0; Peptone 5.0; NaCl 5.0; Agar 15.0; Distilled H_2O 1 L; pH 7.2.] in slants or Petriplates at room temperature (28 ± 2 °C). Originally the above said



Scheme 1. Optimization for the synthesis of triazolyl dihydropyrimidine-2-thione hybrid (**2a**).



Scheme 2. Synthesis of 1,2,3-triazolyl dihydropyrimidine-2-thione hybrids.

bacteria were collected from Bose Clinical Laboratory and X-ray (Madurai, Tamilnadu, India) [28]. All strains were identified by standard biochemical methods [29,30]. The antibacterial activity of the compounds against human pathogens was evaluated by the agar well diffusion method. About 1 mL of inoculums of each test pathogen was added to the molten Nutrient Agar (NA) medium and poured into sterile Petriplates under aseptic conditions. After solidification, a 5-mm well was made in the center of each plate using a sterile cork borer. Each compound was dissolved in 10% DMSO [31] to get different concentrations and filter was sterilized using 0.25 μL filter paper. Each well received 50 μL solution of each compound and the plates were incubated at room temperature. Sterile DMSO (10%) was used as control. After 48 h, the appearance of inhibition zone around the well was observed (Table 2).

All the twelve compounds (**2a**–**l**) exhibited different levels of inhibitory effects (Table 2) against the tested human pathogenic bacteria (*S. pneumonia*, *S. aureus*, *P. aeruginosa* and *S. typhi*). Compounds with the minimum inhibitory concentration (MIC) in the range of 8–20 μg mL^{-1} are reported as active, MIC in the range of 22–120 μg mL^{-1} are reported as moderate to low inhibition and those which showed no significant activity are reported as NI (No Inhibition). The hybrid molecule (**2a**) with **R** as the unsubstituted phenyl ring was a potent inhibitor for all the tested pathogens in the dosage level (10–19 μg mL^{-1}) comparable with that of the reference drug *viz*. tetracycline (Table 2). Subsequently, various substituents were introduced in either of the ortho, meta or para position of the phenyl ring to evaluate their effect on biological activities. The ortho and meta substituted hybrids (**2c**, **2g**, **2f**) showed moderate to low inhibition irrespective of whether they are electron releasing or withdrawing. Similar observations could be recognized in the case of the para substituted compounds with electron withdrawing groups such as nitro or fluoro or bromo (**2e**, **2i**, **2h**) functional groups. However, one of the para substituted compounds with electron withdrawing chloro function (**2d**) and electron releasing substituent *viz*. methyl group (**2l**) exhibited high inhibition against all the tested pathogens. On the other hand, compound with para substituted electron releasing methoxy substituent (**2b**) showed inhibition against *P. aeruginosa* selectively. Further, two ortho, para disubstituted compounds with two electron releasing methoxy substituents (**2j**) or two electron withdrawing chloro substituents (**2k**) showed moderate selective inhibition against two of the tested pathogens. All the results of the biological activities are shown in Table 2.

Table 2
In vitro antibacterial activity[b] of the 1,2,3-triazolyl dihydropyrimidine-2-thione hybrids (**2a**–**l**) and tetracycline with MIC[a] (μg mL^{-1}) values against four human pathogens.

Compounds	*S. aureus*	*S. pneumonia*	*P. aeruginosa*	*S. typhi*
2a	**10**	**19**	**12**	**18**
2b	NI	40	**10**	NI
2c	37	**19**	18	25
2d	**10**	**10**	**9**	20
2e	20	**20**	20	80
2f	22	35	24	90
2g	NI	33	NI	NI
2h	95	44	100	120
2i	85	100	130	NI
2j	NI	42	NI	32
2k	43	25	NI	NI
2l	**8**	**16**	**10**	**13**
Tetracycline	10	20	10	15
Control	NI	NI	NI	NI

NI – No Inhibition.
[a] The MIC is defined as the minimum concentration of the compound required to inhibit 99% of bacterial growth.
[b] Values in bold show significant activity compared to tetracycline.

3. Conclusion

An elegant water promoted synthesis of hybrid molecules *viz*. triazolyl dihydropyrimidine-2-thiones has been accomplished for the first time. Many of them exhibited potential antibacterial activity. Some of them were equally potent to or even of higher potency than the commercially marketed tetracycline. This study could be useful as a template for future development through modification or derivatization to design more potent biologically active compounds.

4. Experimental

All chemicals, reagents and solvents were of commercially high purity grade purchased from Avra Synthesis Pvt. Ltd. and Merck Ltd., India. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on Bruker Avance 300 MHz spectrometer and the chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane, with *J* values in Hertz. The splitting patterns in ^{1}H NMR spectra are reported as follows: s = singlet; d = doublet; br s = broad singlet; br d = broad doublet; m = multiplet. ^{13}C NMR data are reported with the solvent peak ($CDCl_3$ = 77.0 MHz) as the internal standard. Elemental analyses were in agreement with the calculated values i.e. error within ±0.4%. Electrospray Ionization Mass Spectrometry (ESI-MS) analyses of some representative compounds were recorded in LCQ Fleet, Thermo Fisher Instruments Limited, US.

4.1. General procedure for the synthesis of triazolyl dihydropyrimidine-2-thione (*2a*–*l*)

A mixture of (*E*)-1-(1-benzyl-5-methyl-1*H*-1,2,3-triazol-4-yl)-3-arylprop-2-en-1-one [24] (1.0 equiv.), thiourea (1.5 equiv.) and 10% aq. KOH in water or ethanol (10 mL) was refluxed for 30–40 min and poured onto excess of crushed ice and neutralized with dilute hydrochloric acid. The precipitated triazolyl dihydropyrimidine-2-thione derivatives (**2a**–**l**) were filtered and recrystallized from ethanol.

4.1.1. 6-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-phenyl-3,4-dihydropyrimidine-2(1H)-thione (*2a*)

White solid; m.p. 158 °C; Yield: 89%. IR (KBr): *v* 3411, 3192, 1677, 1552, 1462, 1355, 1181, 834, 729, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12–7.35 (m, 10H, Ar*H*), 5.51 (m, 2H, –CH_2), 5.25 (d, 1H, *J* = 3.6 Hz, –C*H*), 5.09 (d, 1H, *J* = 3.9 Hz, olefinic –C*H*), 2.2 (s, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.33, 142.42, 137.39, 134.15, 130.47, 129.12, 128.61, 127.11, 126.85, 126.18, 99.55, 56.80, 52.15, 9.48; MS (ESI): *m*/*z* (%) 362.26 (M + H); Anal. Calcd. for $C_{20}H_{19}N_5S$: C, 66.46; H, 5.30; N, 19.37; S, 8.87. Found: C, 66.50; H, 5.28; N, 19.39; S, 8.86.

4.1.2. 6-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-(4-methoxyphenyl)-3,4-dihydropyrimidine-2(1H)-thione (*2b*)

White solid; m.p. 198 °C; Yield: 95%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (bs, 1H, N*H*), 7.33–6.90 (m, 9H, Ar*H*), 6.79 (bs, 1H, N*H*), 5.52 (m, 2H, –CH_2), 5.22 (bs, 1H, –C*H*), 5.07 (bs, 1H, olefinic –C*H*), 3.79 (s, 3H, –OCH_3), 2.22 (s, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.21, 159.95, 134.65, 134.15, 129.10, 128.54, 128.17, 127.09, 126.11, 140.55, 99.71, 56.31, 55.33, 52.14, 9.45; MS (ESI): *m*/*z* (%) 391.42; Anal. Calcd. for $C_{21}H_{21}N_5OS$: C, 64.43; H, 5.41; N, 17.89; S, 8.19. Found: C, 64.46; H, 5.40; N, 17.90; S, 8.20.

4.1.3. 6-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-o-tolyl-3,4-dihydropyrimidine-2(1H)-thione (*2c*)

White solid, m.p. 201 °C; Yield: 85%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (bs, 1H, N*H*), 7.41–7.12 (m, 9H, Ar*H*), 6.54 (bs, 1H, N*H*), 5.54–

5.51 (m, 3H, merged with $-CH_2$ & $-CH$), 5.07 (bs, 1H, olefinic $-CH$), 2.39 (s, 3H, $-CH_3$), 2.21 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.80, 140.25, 133.99, 133.81, 130.36, 130.14, 128.52, 127.92, 127.51, 127.24, 126.60, 126.34, 126.68, 98.52, 52.86, 51.44, 18.43, 8.89; Anal. Calcd. for $C_{21}H_{21}N_5S$: C, 67.17; H, 5.64; N, 18.65; S, 8.54. Found: C, 67.20; H, 5.65; N, 18.63; S, 8.52.

*4.1.4. 6-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-(4-chlorophenyl)-3,4-dihydropyrimidine-2(1H)-thione (**2d**)*

White solid; m.p. 189 °C; Yield: 87%; IR (KBr): *ν* 3302, 3220, 1563, 1506, 1470, 1250, 1179, 1031, 826, 734 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.21 (bs, 1H, N*H*), 9.03 (bs, 1H, N*H*), 7.17–7.40 (m, 9H, Ar*H*), 5.58 (m, 2H, $-CH_2$), 5.28 (bs, 1H, $-CH$), 5.17 (bs, 1H, olefinic $-CH$), 2.26 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.97, 140.70, 135.59, 133.32, 130.83, 129.67, 126.97, 126.84, 126.48, 126.20, 125.82, 125.43, 124.55, 98.57, 52.50, 49.30, 7.09; MS (ESI): *m*/*z* (%) 396.17 (M + H); Anal. Calcd. for $C_{20}H_{18}ClN_5S$: C, 60.67; H, 4.58; N, 17.69; S, 8.10. Found: C, 60.68; H, 4.557; N, 17.68; S, 8.11.

*4.1.5. 6-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-(4-nitrophenyl)-3,4-dihydropyrimidine-2(1H)-thione (**2e**)*

White solid; m.p. 195 °C; Yield: 81%; ^1H NMR (300 MHz, DMSO-d_6): δ 7.51–7.16 (m, 9H, Ar*H*), 5.53 (m, 2H, $-CH_2$), 5.23 (bs, 1H, $-CH$), 5.19 (bs, 1H, olefinic $-CH$), 2.29 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 182.46, 149.75, 139.77, 137.72, 131.35, 130.36, 128.39, 127.98, 127.70, 126.36, 125.37, 122.23, 98.63, 55.73, 52.24, 8.90; Anal. Calcd. for $C_{20}H_{18}N_6O_2S$: C, 59.10; H, 4.46; N, 20.68; S, 7.89. Found: C, 59.14; H, 4.47; N, 20.67; S, 7.88.

*4.1.6. 6-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-(3-bromophenyl)-3,4-dihydropyrimidine-2(1H)-thione (**2f**)*

White solid, m.p. 185 °C; Yield: 83%; ^1H NMR (300 MHz, $CDCl_3$): δ 7.61–6.98 (m, 9H, Ar*H*), 5.55 (m, 2H, $-CH_2$), 5.20 (bs, 1H, $-CH$); 5.18 (bs, 1H, olefinic $-CH$), 2.27 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.35, 144.81, 134.03, 131.55, 130.65, 130.50, 129.84, 129.05, 128.50, 127.03, 126.53, 125.42, 98.58, 56.06, 52.07, 9.43; Anal. Calcd. for $C_{20}H_{18}BrN_5S$: C, 54.55; H, 4.12; N, 15.90; S, 7.28. Found: C, 54.58; H, 4.11; N, 15.91; S, 7.27.

*4.1.7. 6-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-(2-bromophenyl)-3,4-dihydropyrimidine-2(1H)-thione (**2g**)*

White solid; m.p. 179 °C; Yield: 83%; ^1H NMR (300 MHz, $CDCl_3$): 7.56–7.16 (m, 9H, Ar*H*), 5.69 (bs, 1H, $-CH$), 5.58 (m, 2H, $-CH_2$), 5.28 (bs, 1H, olefinic $-CH$), 2.25 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.92, 40.79, 137.26, 134.11, 133.12, 130.56, 129.87, 129.10, 128.93, 128.60, 128.55, 127.12, 126.96, 121.38, 97.54, 55.50, 52.15, 9.49; Anal. Calcd. for $C_{20}H_{18}BrN_5S$: C, 54.55; H, 4.12; 15; N, 15.90; S, 7.28. Found: C, 54.57; H, 4.13; N, 15.91; S, 7.26.

*4.1.8. 6-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-(4-bromophenyl)-3,4-dihydropyrimidine-2(1H)-thione (**2h**)*

White solid; m.p. 185 °C; Yield: 88%; ^1H NMR (300 MHz, $CDCl_3$): δ 8.68 (bs, 1H, N*H*), 8.62 (bs, 1H, N*H*), 7.51–7.16 (m, 9H, Ar*H*), 5.53 (m, 2H, $-CH_2$), 5.19 (bs, 1H, $-CH$), 5.14 (bs, 1H, olefinic $-CH$), 2.25 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.41, 141.71, 136.72, 133.70, 131.24, 130.21, 128.35, 127.94, 127.74, 126.46, 125.77, 121.22, 98.60, 54.74, 51.23, 8.70; Anal. Calcd. for $C_{20}H_{18}BrN_5S$: C, 54.55; H, 4.12; N, 15.90; S, 7.28. Found: C, 54.60; H, 4.14; N, 15.91; S, 7.30.

*4.1.9. 6-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-(4-fluorophenyl)-3,4-dihydropyrimidine-2(1H)-thione (**2i**)*

White solid; m.p. 330 °C; Yield: 91%; ^1H NMR (300 MHz, $CDCl_3$): δ 8.87 (bs, 1H, N*H*), 8.61 (bs, 1H, N*H*), 7.65–7.02 (m, 9H, Ar*H*), 5.52(m, 2H, $-CH_2$), 5.17 (m, 2H, merged, -olefinic C*H*, $-CH$), 2.34 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.51, 142.24, 136.01, 133.74, 133.54, 133.43, 133.06, 132.02, 131.07, 120.46, 120.17, 104.86, 59.63, 56.42, 14.04; MS (ESI): *m*/*z* (%) 380.27 (M + H); Anal. Calcd. for $C_{20}H_{18}FN_5S$: C, 63.31; H, 4.78; N, 18.46; S, 8.45. Found: C, 63.35; H, 4.80; N, 18.44; S, 8.43.

*4.1.10. 6-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-(2,4-dimethoxyphenyl)-3,4-dihydropyrimidine-2(1H)-thione (**2j**)*

White solid; m.p. 179 °C; Yield: 86%; ^1H NMR (300 MHz, $CDCl_3$): δ 8.57 (bs, 1H, N*H*), 7.33–6.84 (m, 8H, Ar*H*), 6.80 (bs, 1H, N*H*), 5.50 (m, 2H, $-CH_2$), 5.21 (bs, 1H, $-CH$), 5.05 (bs, 1H, olefinic $-CH$), 3.85 (bs, 6H, $-OCH_3$), 2.21 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.25, 149.77, 149.52, 137.41, 135.01, 134.11, 130.37, 129.11, 128.56, 127.10, 126.18, 119.29, 111.59, 110.17, 99.61, 56.67, 56.10, 56.01, 52.15, 9.47; Anal. Calcd. for $C_{22}H_{23}N_5O_2S$: C, 62.69; H, 5.50; N, 16.61; S, 7.61. Found: C, 62.72; H, 5.51; N, 16.63; S, 7.59.

*4.1.11. 6-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-(2,4-dichlorophenyl)-3,4-dihydropyrimidine-2(1H)-thione (**2k**)*

White solid; m.p. 205 °C; Yield: 79%; ^1H NMR (300 MHz, DMSO-d_6): δ 9.12 (bs, 2H, N*H*), 7.42–7.09 (m, 8H, Ar*H*), 5.50 (m, 2H, $-CH_2$), 5.42 (bs, 1H, $-CH$), 5.24 (bs, 1H, olefinic $-CH$), 2.12 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.74, 137.62, 133.08, 131.35, 129.58, 129.41, 127.59, 127.17, 126.83, 126.08, 126.03, 125.27, 124.99, 96.33, 76.36, 50.32, 49.21, 6.93; Anal. Calcd. for $C_{20}H_{17}Cl_2N_5S$: C, 55.82; H, 3.98; N, 16.27; S, 7.45. Found: C, 55.86; H, 3.96; N, 16.25; S, 7.46.

*4.1.12. 6-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-p-tolyl-3,4-dihydropyrimidine-2(1H)-thione (**2l**)*

White solid; m.p. 168 °C; Yield: 93%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.57 (bs, 1H, N*H*), 7.31–7.14 (m, 9H, Ar*H*), 6.92 (bs, 1H, N*H*), 5.51 (m, 2H, $-CH_2$), 5.22 (bs, 1H, $-CH$), 5.07 (bs, 1H, olefinic $-CH$), 2.32 (s, 3H, $-CH_3$), 2.23 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.25, 139.53, 138.52, 137.42, 134.16, 130.38, 129.78, 129.90, 128.54, 127.08, 126.78, 126.07, 99.69, 56.55, 52.13, 21.04, 9.47; MS (ESI): *m*/*z* (%) 376.30 (M + H); Anal. Calcd. for $C_{21}H_{21}N_5S$, 67.17; H, 5.64; N, 18.65; S, 8.54. Found: C, 67.21; H, 5.62; N, 18.63; S, 8.53.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2012.10.029.

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