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Original Article

Design, Synthesis and Biological Evaluation of 1, 2, 4- Triazolothienopyrimidines and its Derivatives

Sri Venkateswarlu Rayudu[1, 3]*, Dr. Dipankar Karmakar[2], Dr. Pramod Kumar[3]

*[1]Department of Research and Development, Seutic Pharma Private Limited, Plot No.42/A, Sy. No.308, S.V. Co-Operative Industrial Estate, IDA, Jeedimetla, Hyderabad-500055, Telangana, India.

[2]Director-Chemistry Services, Novick Biosciences, Private Limited, Balanagar, Hyderabad 500037, Telangana, India.

[3]Centre for Chemical Sciences and Technology, Institute of Science and Technology, JNT University Hyderabad, 500085, Telangana, India

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ABSTRACT

***A** series of 8-methyl-2-phenyl-thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine and its derivatives (6a-f) have been synthesized from 2-amino-5-methylthiophene-3-carbonitrile (1) as raw material and N-(3-cyano-5-methyl-thiophen-2-yl)-formimidic acid ethyl ester (2), N-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide (3), benzoic acid N'-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazides (4a-f) and N-(4-imino-6-methyl-4H-thieno[2,3-d]pyrimidin-3-yl)-benzamides (5a-f) as intermediates. All the target compounds after structure elucidation have been used to find their antimicrobial ability against different microorganisms.*

Keywords: *1,2,4-Triazolo pyrimidines, Synthesis, Antimicrobial activity*

1. INTRODUCTION:

1,2,4-Triazoles and their derivatives are important group of heterocyclic compounds. The biological activity of 1,2,4-triazoles have been demonstrated by various studies [1]. For instance, data came from previous investigations showed that 1,2,4-triazole nucleus posses a wide range of pharmacological activities such as analgesic [3], antibacterial [4], antifungal [5], anti-inflammatory [6] and antioxidant [7] properties. Therefore, there is a continuing need for new antimicrobial agents with more selectivity and lower side effect. Pyrimidines are the most important six membered heterocyclic compounds and occur in living systems in the form of nucleic acids and vitamins. It is the basic nucleus in DNA and RNA and possesses diverse biological activities such as analgesic [8], anti-inflammatory [9], antitumor [10], antimicrobial [11], antibacterial [12], antifungal [13], antiplatelet [14] and antitubercular [15] activities. Triazolothienopyrimidines also emerged as important derivatives in medicinal chemistry [16-18].

***Corresponding Author**:

Sri Venkateswarlu Rayudu,

Department of Research and Development, Seutic Pharma Private Limited, Plot No.42/A, Sy. No.308, S.V. Co-Operative Industrial Estate, IDA, Jeedimetla, Hyderabad-500055, Telangana, India.

Email: rayuduchem123@gmail.com

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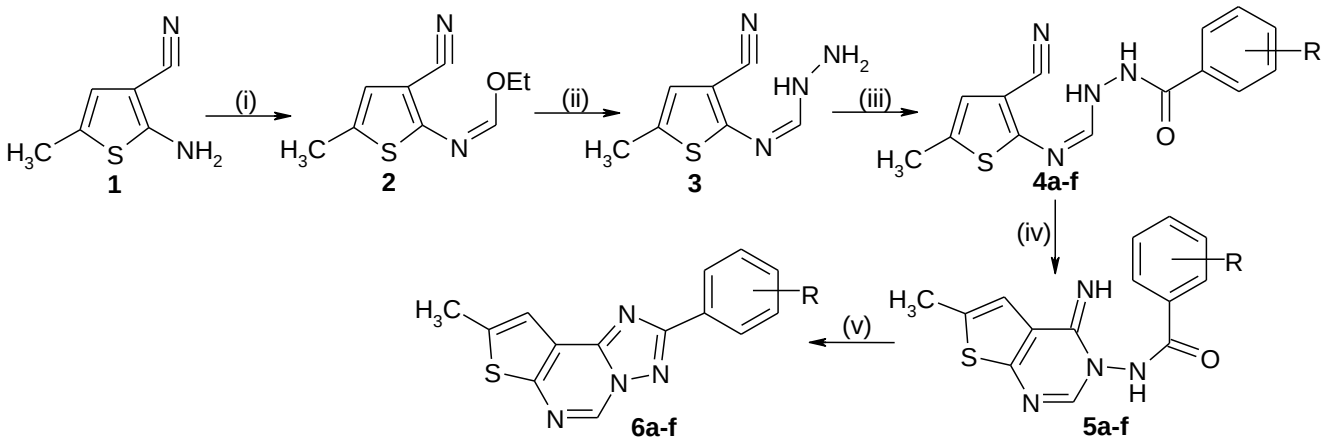
2. RESULTS AND DISCUSSION

Keeping these observations in view and in continuation of our study on the synthesis of biologically active heterocycles, we have reported the synthetic route to a series of 8-methyl-2-phenyl-thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives (6a-f). The synthesis of title compounds commenced from commercially available 2-amino-5-methylthiophene-3-carbonitrile (1) and by involving N-(3-cyano-5-methyl-thiophen-2-yl)-formimidic acid ethyl ester (2), N-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide (3), benzoic acid N'-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide and its derivatives (4a-f) and N-(4-imino-6-methyl-4H-thieno[2,3-d]pyrimidin-3-yl)-benzamide and its derivatives (5a-f) as intermediates (Scheme 1). Thus the initial intermediate 2 was prepared from the condensation reaction between compound 1 and triethyl orthoformate under reflux for 9 h with constant stirring. Then compound 2 is turned into the next intermediate 3 when reacts with hydrazine hydrate at reflux temperature in ethanol on uniform stirring for 8 h. Then compound 4a-f is achieved from compound 3 and different aromatic carbonyl chloride in dioxane solvent on steady stirring under reflux for 6-7 h. Further compound 4a-f on cyclization in dimethyl formamide

at reflux temperature on stable stirring for 10-12 h is converted into the final intermediate 5a-f. Finally the title compounds 6a-f have been synthesized on cyclization in chloroform solvent on equable stirring under reflux for 13-14 h. The chemical structures of all newly discovered compounds were established by IR, 1H & 13C-NMR, mass spectral data and elemental analysis. Further, the target compounds were used to find their antimicrobial ability against different microorganisms.



Scheme 1: (i) CH(OEt)3, reflux, 9 h, (ii) NH2NH2.H2O, EtOH, reflux, 8 h, (iii) ArCOCl, dioxane, reflux, 6-7 h, (iv) DMF, reflux, 10-12 h, (v) CHCl3, reflux, 12-14 h.

4/5/6R = (a) -H; (b) 2-Cl; (c) 2-NO2; (d) 4-Cl; (e) 4-Br; (f) 4-NO2.

Table 1: Antimicrobial activity of compounds 6a-f (Zones of inhibition in mm)

Compound	Antibacterial activity				Antifungal activity
	S. aureus	*S. pyogenes*	*P. aureginosa*	*E. coli*	*C. albicans*
6a	13.2	11.6	10.2	15.2	10.1
6b	12.8	12.1	12.3	11.0	12.6
6c	16.8	13.4	13.1	15.0	17.4
6d	14.0	13.2	10.6	14.9	12.3
6e	17.1	13.0	13.0	12.3	11.4
6f	16.6	12.6	13.2	15.3	17.6
Ampicilline	18	14	14	16	–
Fluoconazole	–	–	–	–	18

3. ANTIMICROBIAL ACTIVITY

The antimicrobial activity of the newly prepared 8-methyl-2-phenyl-thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine and derivatives (6a-f) has been carried out with cup plate method [19] using nutrient agar medium against four bacterial stains such as Stapylococcus aureous, Streptococcus pyogenes, Escherichia coli and Pseudomonas aureginosa and towards one fungal organism like Candida albicans. Ampicilline and Fluoconazole were used as reference drugs for antibacterial and antifungal study respectively. The DMSO was used as sample solution and the size of sample of all compounds was fixed at 0.1 mL and the concentration is restricted at 100 µg/mL. The test compound solution (0.1 mL) was added in the cups and the petri dishes were subsequently incubated at 37 oC for 48 hrs. Zone of inhibition produced by each compound was measured in mm and the results are listed in Table 1. According to the results, compounds 6c, 6e and 6f are highly active against all types of tested bacteria. Compounds like 6c and 6f are also highly active against C. albicans. Compounds 6a and 6d are highly active against S. pyogenes and E. coli while compound 6b is highly active against S. pyogenes and P. aeruginosa. The rest of products were found to be moderately active against the tested organisms. It is interesting to note that, none of the compound is inactive towards any microorganism and this outstanding property may be obtained to the target compound by incorporating triazole and pyrimidine rings into thiazole moiety.

4. EXPERIMETAL

All the reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60-120 mesh. IR spectra were obtained on a Perkin-Elmer BX serried FTIR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for 1H-NMR and 75 MHz for 13C-NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

Synthesis of N-(3-cyano-5-methyl-thiophen-2-yl)-formimidic acid ethyl ester (2)

A mixture of 2-amino-5-methylthiophene-3-carbonitrile (1) (0.01 mol) and suitable ortho formate (0.01 mol) was boiled under reflux for 9 h. After completion of the reaction (monitored by TLC), cooled the reaction mixture and solvent was removed under reduced pressure and the residue obtained was triturated with ethanol. The solid product obtained was collected by filtration and recrystallized from ethanol to give compound 2.

Synthesis of N-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide (3)

A solution of hydrazine hydrate (0.05 ml) in ethanol (5 mL) was added to a solution of N-(3-cyano-5-methyl-thiophen-2-yl)-formimidic acid ethyl ester (2) in ethanol (5 mL). The mixture was refluxed with constant stirring for 8 h. After realization of the reaction (observed by TLC), the resulted solution was poured in ice-cold water (20 mL) and the obtained precipitate was filtered off, washed and recrystallized from ethanol to get compound 3 in pure form.

Synthesis of benzoic acid N'-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazides (4a-f)

To the solution of N-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide (3) (0.01 mol) in dioxane (10 mL), aromatic carbonyl chloride (0.01 mol) was added. The mixture was refluxed for 6-7 h with constant stirring. After accomplishment of the reaction (watched by TLC), the mixture was poured into ice-cold water. Crude product was collected by filtration, washed, dried and recrystallized from ethanol to get pure corresponding benzoic acid N'-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide (4a-f).

Synthesis of N-(4-imino-6-methyl-4H-thieno[2,3-d]pyrimidin-3-yl)-benzamides (5a-f)

A suspension of N'-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide (4a-f) in DMF (5 mL) was heated at reflux temperature on uniform stirring for 10-12 h. After achievement of the reaction (examined by TLC), the mixture is precipitated after poured in ice-cold water. The crude product was filtered off and washed with hexane and recrystallized from ethyl acetate to get corresponding pure N-(4-imino-6-methyl-4H-thieno[2,3-d]pyrimidin-3-yl)-benzamides (5a-f).

Synthesis of 8-methyl-2-phenyl-thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines (6a-f)

A solution of N-(4-imino-6-methyl-4H-thieno[2,3-d]pyrimidin-3-yl)-benzamides (5a-f) in chloroform (5 mL) was heated for 12-14 h under reflux with stable stirring. After execution of the reaction (scanned by TLC), the mixture was cooled and the obtained solid was filtered off, dried and recrystallized from ethanol to obtain pure 8-methyl-2-phenyl-thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines (6a-f)..

5. PHYSICAL AND SPECTRAL DATA

N-(3-cyano-5-methyl-thiophen-2-yl)-formimidic acid ethyl ester (2)

Yield: 74 %, mp: 122-124 0C, IR (KBr): 3058 (C-H, Ar), 2945 (C-H, CH3), 2240 (C≡N), 1575 (C=C), 1436 (C=N), 1271 (C-S), 1145 (C-O) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.81 (s, 1H, N=CH), 6.89 (s, 1H, thiazole CH), 4.12 (q, 2H, J = 5.4 Hz, CH2), 2.36 (s, 3H, CH3), 1.24 (t, 3H, J = 5.4 Hz, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 162.3, 148.7, 132.2, 126.5, 115.7, 109.7, 61.4, 16.5, 14.7, MS: 194 m/z (M+); Elemental analysis: Calculated for C9H10N2OS: C-55.65, H-5.19, N-14.42, O-8.24, S-16.51. Found: C-55.42, H-5.11, N-14.31, O-8.20, S-16.42.

N-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide (3)

Yield: 71 %, mp: 141-143 0C, IR (KBr): 3320 (N-H), 3158 (N-H, NH2), 3047 (C-H, Ar), 2938 (C-H, CH3), 2247 (C≡N), 1592 (C=C), 1441 (C=N), 1261 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.78 (s, 1H, N=CH), 7.68 (s, 1H, NH), 6.92 (s, 1H, thiazole CH), 4.42 (s, 2H, NH2), 2.41 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 165.7, 144.7, 130.2, 128.4, 118.3, 112.4, 16.7; MS: 180 m/z (M+); Elemental analysis: Calculated for C7H8N4S: C-46.65, H-4.47, N-31.09, S-17.79. Found: C-46.36, H-4.41, N-30.98, S-17.69.

Benzoic acid N'-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide (4a)

Yield: 75 %, mp: 133-135 0C, IR (KBr): 3343 (N-H), 3052 (C-H, Ar), 2932 (C-H, CH3), 2239 (C≡N), 1673 (C=O), 1594 (C=C, Ar), 1456 (C=N), 1267 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.84 (s, 1H, N=CH), 7.62 (s, 1H, NH), 7.58-7.23 (m, 5H, Ar-H), 6.84 (s, 1H, thiazole CH), 4.47 (s, 1H, NH), 2.36 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 168.3, 162.3, 148.1, 134.2, 132.0, 131.0, 128.6, 126.3, 124.1, 120.1, 116.3, 18.7; MS: 284 m/z (M+); Elemental analysis: Calculated for C14H12N4OS: C-59.14, H-4.25, N-19.70, O-5.63, S-11.28. Found: C-59.01, H-4.22, N-19.47, O-5.52, S-11.01.

2-Chloro-benzoic acid N'-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide (4b)

Yield: 70 %, mp: 151-153 0C, IR (KBr): 3356 (N-H), 3060 (C-H, Ar), 2941 (C-H, CH3), 2232 (C≡N), 1665 (C=O), 1574 (C=C, Ar), 1426 (C=N), 1250 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.77 (s, 1H, N=CH), 7.51 (s, 1H, NH), 7.48-7.32 (m, 4H, Ar-H), 6.78 (s, 1H, thiazole CH), 4.51 (s, 1H, NH), 2.32 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 167.1, 161.8, 143.5, 138.4, 136.2, 133.1, 129.7, 128.6, 126.8, 125.1, 122.4, 121.0, 114.7, 17.6; MS: 318 m/z (M+); Elemental analysis: Calculated for C14H11ClN4OS: C-52.75, H-3.48, Cl-11.12, N-17.58, O-5.02, S-10.06. Found: C-52.36, H-3.41, Cl-11.02, N-17.48, O-4.95, S-9.99.

2-Nitro-benzoic acid N'-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide (4c)

Yield: 69 %, mp: 132-134 0C, IR (KBr): 3369 (N-H), 3048 (C-H, Ar), 2948 (C-H, CH3), 2246 (C≡N), 1654 (C=O), 1567 (C=C, Ar), 1434 (C=N), 1242 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.92 (s, 1H, N=CH), 7.60 (s, 1H, NH), 7.57-7.36 (m, 4H, Ar-H), 6.71 (s, 1H, thiazole CH), 4.54 (s, 1H, NH), 2.38 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 166.3, 162.7, 146.3, 142.6, 136.9, 135.7, 130.2, 129.6, 125.4, 123.7, 120.2, 119.7, 116.5, 16.8; MS: 329 m/z (M+); Elemental analysis: Calculated for C14H11N5O3S: C-51.06, H-3.37, N-21.27, O-14.57, S-9.74. Found: C-50.84, H-3.32, N-21.06, O-14.41, S-9.62.

4-Chloro-benzoic acid N'-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide (4d)

Yield: 77 %, mp: 118-120 0C, IR (KBr): 3360 (N-H), 3057 (C-H, Ar), 2955 (C-H, CH3), 2237 (C≡N), 1665 (C=O), 1571 (C=C, Ar), 1445 (C=N), 1247 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.82 (s, 1H, N=CH), 7.54 (s, 1H, NH), 7.52 (d, 2H, J = 7.4 Hz, Ar-H), 7.31 (d, 2H, J = 7.4 Hz, Ar-H), 6.67 (s, 1H, thiazole CH), 4.59 (s, 1H, NH), 2.31 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 165.8, 161.0, 148.7, 133.7, 133.3, 128.1, 126.4, 125.7, 123.2, 121.0, 118.7, 17.4; MS: 318 m/z (M+); Elemental analysis: Calculated for C14H11ClN4OS: C-52.75, H-3.48, Cl-11.12, N-17.58, O-5.02, S-10.06. Found: C-52.48, H-3.44, Cl-11.08, N-17.42, O-4.99, S-9.98.

4-Bromo-benzoic acid N'-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide (4e)

Yield: 76 %, mp: 145-147 0C, IR (KBr): 3352 (N-H), 3060 (C-H, Ar), 2947 (C-H, CH3), 2249 (C≡N), 1660 (C=O), 1565 (C=C, Ar), 1439 (C=N), 1241 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.63 (s, 1H, NH), 7.58 (s, 1H, N=CH), 7.57 (d, 2H, J = 7.2 Hz, Ar-H), 7.37 (d, 2H, J = 7.2 Hz, Ar-H), 6.70 (s, 1H, thiazole CH), 4.65 (s, 1H, NH), 2.37 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 168.6, 164.2, 146.3, 131.0, 130.1, 129.5, 127.4, 124.2, 122.1, 119.7, 116.3, 15.8; MS: 363 m/z (M+); Elemental analysis: Calculated for C14H11BrN4OS: C-46.29, H-3.05, Br-22.00, N-15.42, O-4.40, S-8.83. Found: C-46.08, H-2.98, Br-21.88, N-15.31, O-4.34, S-8.75.

4-Nitro-benzoic acid N'-[(3-cyano-5-methyl-thiophen-2-ylimino)-methyl]-hydrazide (4f)

Yield: 72 %, mp: 160-162 0C, IR (KBr): 3373 (N-H), 3053 (C-H, Ar), 2955 (C-H, CH3), 2253 (C≡N), 1664 (C=O), 1571 (C=C, Ar), 1445 (C=N), 1238 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.95 (s, 1H, N=CH), 7.65 (s, 1H, NH), 7.59 (d, 2H, J = 7.0 Hz, Ar-H), 7.39 (d, 2H, J = 7.0 Hz, Ar-H), 6.77 (s, 1H, thiazole CH), 4.63 (s, 1H, NH), 2.41 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 169.5, 165.2, 144.1, 133.2, 131.7, 128.5, 17.26, 123.4, 121.0, 117.4, 115.3, 19.6; MS: 329 m/z (M+); Elemental analysis: Calculated for C14H11N5O3S: C-51.06, H-3.37, N-21.27, O-14.57, S-9.74. Found: C-50.84, H-3.30, N-21.03, O-14.38, S-9.66.

N-(4-Imino-6-methyl-4H-thieno[2,3-d]pyrimidin-3-yl)-benzamide (5a)

Yield: 71 %, mp: 133-135 0C, IR (KBr): 3361 (N-H), 3062 (C-H, Ar), 2948 (C-H, CH3), 1672 (C=O), 1561 (C=C, Ar), 1452 (C=N), 1241 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.88 (s, 1H, N=CH), 7.59-7.26 (m, 5H, Ar-H), 7.21 (s, 1H, NH), 6.70 (s, 1H, thiazole CH), 3.85 (s, 1H, =NH), 2.47 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 168.4, 164.7, 161.0, 141.0, 136.2, 132.0, 128.4, 127.9, 126.3, 125.3, 124.7, 16.5; MS: 284 m/z (M+); Elemental analysis: Calculated for C14H12N4OS: C-59.14, H-4.25, N-19.70, O-5.63, S-11.28. Found: C-58.88, H-4.20, N-19.56, O-5.51, S-11.02.

2-Chloro-N-(4-imino-6-methyl-4H-thieno[2,3-d]pyrimidin-3-yl)-benzamide (5b)

Yield: 70 %, mp: 129-131 0C, IR (KBr): 3350 (N-H), 3059 (C-H, Ar), 2962 (C-H, CH3), 1662 (C=O), 1571 (C=C, Ar), 1460 (C=N), 1238 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.68 (s, 1H, N=CH), 7.60-7.32 (m, 4H, Ar-H), 7.28 (s, 1H, NH), 6.74 (s, 1H, thiazole CH), 3.81 (s, 1H, =NH), 2.51 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 166.3, 163.2, 162.7, 144.2, 139.5, 135.1, 129.7, 127.4, 126.1, 125.4, 124.8, 123.1, 122.0, 17.6; MS: 318 m/z (M+); Elemental analysis: Calculated for C14H11ClN4OS: C-52.75, H-3.48, Cl-11.12, N-17.58, O-5.02, S-10.06. Found: C-52.05, H-3.41, Cl-11.00, N-17.39, O-4.98, S-9.97.

2-Nitro-N-(4-Imino-6-methyl-4H-thieno[2,3-d]pyrimidin-3-yl)-benzamide (5c)

Yield: 74 %, mp: 143-145 0C, IR (KBr): 3326 (N-H), 3069 (C-H, Ar), 2954 (C-H, CH3), 1671 (C=O), 1558 (C=C, Ar), 1447 (C=N), 1233 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.71 (s, 1H, N=CH), 7.55-7.30 (m, 4H, Ar-H), 7.26 (s, 1H, NH), 6.81 (s, 1H, thiazole CH), 3.88 (s, 1H, =NH), 2.56 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 167.1, 164.3, 163.1, 142.1, 137.4, 136.2, 130.8, 129.3, 125.4, 123.2, 122.1, 121.0, 120.7, 18.4; MS: 329 m/z (M+); Elemental analysis: Calculated for C14H11N5O3S:

C-51.06, H-3.37, N-21.27, O-14.57, S-9.74. Found: C-50.85, H-3.31, N-21.00, O-14.47, S-9.68.

4-Chloro-N-(4-Imino-6-methyl-4H-thieno[2,3-d]pyrimidin-3-yl)-benzamide (5d)

Yield: 75 %, mp: 110-112 0C, IR (KBr): 3362 (N-H), 3061 (C-H, Ar), 2948 (C-H, CH3), 1663 (C=O), 1571 (C=C, Ar), 1470 (C=N), 1250 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.75 (s, 1H, N=CH), 7.54 (d, 2H, J = 7.4 Hz, Ar-H), 7.38 (d, 2H, J = 7.4 Hz, Ar-H), 7.30 (s, 1H, NH), 6.76 (s, 1H, thiazole CH), 3.81 (s, 1H, =NH), 2.61 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 165.1, 163.2, 160.7, 144.6, 136.3, 134.7, 127.4, 125.4, 123.2, 122.1, 121.4, 19.2; MS: 318 m/z (M+); Elemental analysis: Calculated for C14H11ClN4OS: C-52.75, H-3.48, Cl-11.12, N-17.58, O-5.02, S-10.06. Found: C-52.12, H-3.38, Cl-11.00, N-17.24, O-4.98, S-9.87.

4-Bromo-N-(4-Imino-6-methyl-4H-thieno[2,3-d]pyrimidin-3-yl)-benzamide (5e)

Yield: 78 %, mp: 118-120 0C, IR (KBr): 3352 (N-H), 3065 (C-H, Ar), 2951 (C-H, CH3), 1658 (C=O), 1564 (C=C, Ar), 1481 (C=N), 1241 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.65 (s, 1H, N=CH), 7.62 (d, 2H, J = 7.2 Hz, Ar-H), 7.41 (d, 2H, J = 7.2 Hz, Ar-H), 7.36 (s, 1H, NH), 6.68 (s, 1H, thiazole CH), 3.74 (s, 1H, =NH), 2.60 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 166.3, 164.1, 162.6, 146.7, 134.5, 133.1, 129.4, 126.4, 124.7, 121.2, 120.8, 21.0; MS: 361 m/z (M+); Elemental analysis: Calculated for C14H11BrN4OS: C-46.29, H-3.05, Br-22.00, N-15.42, O-4.40, S-8.83. Found: C-45.98, H-2.98, Br-21.87, N-15.31, O-4.31, S-8.68.

4-Nitro-N-(4-Imino-6-methyl-4H-thieno[2,3-d]pyrimidin-3-yl)-benzamide (5f)

Yield: 71 %, mp: 147-149 0C, IR (KBr): 3344 (N-H), 3061 (C-H, Ar), 2966 (C-H, CH3), 1663 (C=O), 1551 (C=C, Ar), 1474 (C=N), 1249 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.62 (s, 1H, N=CH), 7.59 (d, 2H, J = 7.0 Hz, Ar-H), 7.46 (d, 2H, J = 7.0 Hz, Ar-H), 7.33 (s, 1H, NH), 6.61 (s, 1H, thiazole CH), 3.71 (s, 1H, =NH), 2.58 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 165.7, 163.2, 160.1, 148.4, 136.7, 134.7, 128.5, 125.4, 123.2, 122.1, 121.0, 20.8; MS: 329 m/z (M+); Elemental analysis: Calculated for C14H11N5O3S: C-51.06, H-3.37, N-21.27, O-14.57, S-9.74. Found: C-50.65, H-3.28, N-21.14, O-14.33, S-9.68.

8-Methyl-2-phenyl-thieno[3,2-e][1,2,4] triazolo[1,5-c]pyrimidine (6a)

Yield: 73 %, mp: 139-141 0C, IR (KBr): 3066 (C-H, Ar), 2973 (C-H, CH3), 1565 (C=C, Ar), 1468 (C=N), 1253 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.61 (s, 1H, N=CH), 7.55-7.26 (m, 5H, Ar-H), 6.67 (s, 1H, thiazole CH), 2.48 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 156.3, 147.4, 146.3, 138.5, 135.4, 128.5, 127.4, 126.3, 125.3, 124.7, 122.4, 15.2; MS: 266 m/z (M+); Elemental analysis: Calculated for C14H10N4S: C-63.14, H-3.78, N-21.04, S-12.04. Found: C-62.64, H-3.69, N-20.89, S-11.87.

2-(2-Chloro-phenyl)-8-methyl-thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (6b)

Yield: 72 %, mp: 151-153 0C, IR (KBr): 3078 (C-H, Ar), 2967 (C-H, CH3), 1560 (C=C, Ar), 1474 (C=N), 1258 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.67 (s, 1H, N=CH), 7.60-7.30 (m, 4H, Ar-H), 6.71 (s, 1H, thiazole CH), 2.51 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 158.3, 149.4, 144.6, 140.1, 138.7, 135.6, 133.2, 130.2, 126.4, 124.2, 123.1, 122.0, 120.7, 16.8; MS: 300 m/z (M+); Elemental analysis: Calculated for C14H9ClN4S: C-55.91, H-3.02, Cl-11.79, N-18.63, S-10.66. Found: C-54.99, H-2.98, Cl-11.67, N-18.08, S-10.12.

2-(2-Nitro-phenyl)-8-methyl-thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (6c)

Yield: 70 %, mp: 140-142 0C, IR (KBr): 3071 (C-H, Ar), 2962 (C-H, CH3), 1571 (C=C, Ar), 1479 (C=N), 1264 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.74 (s, 1H, N=CH), 7.57-7.33 (m, 4H, Ar-H), 6.68 (s, 1H, thiazole CH), 2.64 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 156.7, 151.8, 146.3, 139.7, 137.2, 134.1, 132.3, 131.0, 128.7, 126.4, 123.7, 121.2, 119.7, 18.7; MS: 311 m/z (M+); Elemental analysis: Calculated for C14H9N5O2S: C-54.01, H-2.91, N-22.50, O-10.28, S-10.30. Found: C-53.78, H-2.79, N-21.98, O-10.12, S-10.01.

2-(4-Chloro-phenyl)-8-methyl-thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (6d)

Yield: 78 %, mp: 162-164 0C, IR (KBr): 3064 (C-H, Ar), 2967 (C-H, CH3), 1569 (C=C, Ar), 1471 (C=N), 1274 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.82 (s, 1H, N=CH), 7.61 (d, 2H, J = 7.0 Hz, Ar-H), 7.45 (d, 2H, J = 7.0 Hz, Ar-H), 6.71 (s, 1H, thiazole CH), 2.76 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 154.1, 148.4, 143.6, 140.1, 138.7, 130.1, 126.4, 124.7, 122.3, 121.7, 120.7, 16.8; MS: 300 m/z (M+); Elemental analysis: Calculated for C14H9ClN4S: C-55.91, H-3.02, Cl-11.79, N-18.63, S-10.66. Found: C-54.87, H-2.96, Cl-11.69, N-18.48, S-10.04.

2-(4-Bromo-phenyl)-8-methyl-thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (6e)

Yield: 77 %, mp: 152-154 0C, IR (KBr): 3058 (C-H, Ar), 2961 (C-H, CH3), 1552 (C=C, Ar), 1484 (C=N), 1282 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.69 (s, 1H,N=CH), 7.65 (d, 2H, J = 7.2 Hz, Ar-H), 7.40 (d, 2H, J = 7.2 Hz, Ar-H), 6.65 (s, 1H, thiazole CH), 2.70 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 153.5, 150.7, 146.7, 144.1, 140.8, 134.5, 129.7, 126.7, 124.7, 123.6, 121.7, 18.9; MS: 345 m/z (M+); Elemental analysis: Calculated for C14H9BrN4S: C-48.71, H-2.63, Br-23.15, N-16.23, S-9.29. Found: C-48.12, H-2.58, Br-22.87, N-16.09, S-9.05.

2-(4-Nitro-phenyl)-8-methyl-thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (6f)

Yield: 75 %, mp: 133-135 0C, IR (KBr): 3069 (C-H, Ar), 2957 (C-H, CH3), 1575 (C=C, Ar), 1479 (C=N), 1270 (C-S) cm-1; 1H NMR (300 MHz, DMSO-d6): δ 7.66 (s, 1H, N=CH), 7.59 (d, 2H, J = 7.4 Hz, Ar-H), 7.44 (d, 2H, J = 7.4 Hz, Ar-H), 6.60 (s, 1H, thiazole CH), 2.74 (s, 3H, CH3); 13 C NMR (75 MHz, DMSO-d6): δ 155.4, 152.6, 148.7, 142.6, 141.2, 136.5, 127.4, 124.3, 122.1, 121.7, 120.4, 17.9; MS: 311 m/z (M+); Elemental analysis: Calculated for C14H9N5O2S: C-54.01, H-2.91, N-22.50, O-10.28, S-10.30. Found: C-53.56, H-2.84, N-21.98, O-10.12, S-9.94.

6. CONCLUSION

In conclusion, a series of novel 8-methyl-2-phenyl-thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines (6a-f) have been designed and synthesized. The antimicrobial activity of these compounds was evaluated against various microorganisms. Among the synthesized compounds, almost all compounds showed good activity and emerged as potential molecules for further development

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