



Convergent One Pot Synthesis of Novel Thiazolo Pyrimidine and Their Antimicrobial Activities

KEYWORDS

2-amino thiazole, Thiazolo pyrimidines, synthesis, antimicrobial study

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ABSTRACT One pot three component cyclocondensation of 2-amino-4-phenyl thiazole, ethyl benzoyl acetate and aromatic aldehydes produces Thiazolo Pyrimidine in moderate to good yields. Some of the compounds were screened for anti-bacterial (*Staphylococcus aureus*, *Staphylococcus aureus* (MRSA), *Streptococcus pyogenes*) and antifungal (*Aspergillus niger*) studies by Agar Diffusion method. Compounds show moderate to good antifungal activity but low antibacterial activity.

INTRODUCTION

Various 2-amino thiazole derivatives are of great importance to chemists as well as biologists as they exhibit a variety of biological activities like antibacterial¹, antiviral², anti-inflammatory³, anti-allergies⁴ and antihypertensive⁵. The high scientific interest attracted by 3,4-dihydropyrimidines is due to broad spectrum of biological activities exhibited by these compounds like antihypertensive⁶, antioxidant agents⁷, anti-tumor activity⁸ and calcium channel modulation⁹. In 1893, Italian Chemist Pietro Bignelli¹⁰ synthesized 3,4-dihydropyrimidin-2(1H)-ones by heating a mixture of aldehyde, β -ketoester and urea in ethanol containing a catalytic amount of HCl. However, this procedure suffers from harsh reaction conditions, long reaction time and frequently low yield. Later on subsequent multistep synthesis furnished some what higher yield but these do not have the simplicity of original one pot protocol¹¹.

This paper reports a novel approach to the synthesis of thiazolo-pyrimidines. As thiazolo pyrimidines are classes of fused heterocycles that are of considerable interest because of their wide range of biological activities like anti cancer¹², phosphate inhibitors¹³, antimicrobial¹⁴ and acetylcholinesterase inhibitors¹⁵.

Various methods have been reported for the synthesis of thiazolo pyrimidine in literature¹⁶ which are associated with many drawbacks like multistep synthetic route, longer reaction time with drastic conditions, difficult workup, unsatisfactory yields and use of expensive & hazardous chemicals. Hence, here we report herein a general, single step and efficient approach towards the synthesis of thiazolo pyrimidines.

Prompted by the observed biological activities of the above mentioned derivatives and in continuation of our research for thiazolo pyrimidines¹⁷, a rapid and efficient synthesis of a series of novel thiazolo pyrimidines and evaluation of their antimicrobial potency is being reported.

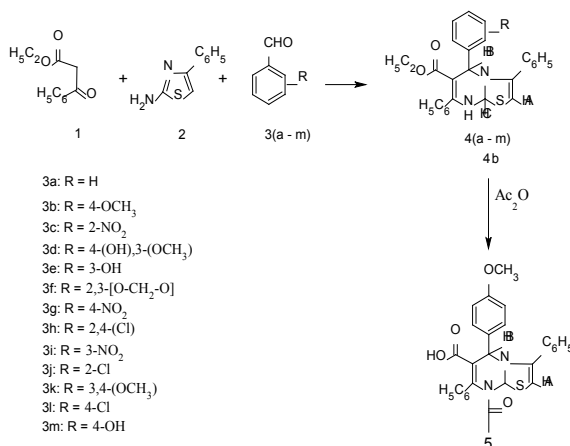
RESULTS AND DISCUSSION

Synthesis and characterization

In view of the recent emphasis aimed at developing simple, highly efficient and one pot methodologies for the preparation of organic compounds, herein we report convergent one pot cyclocondensation of ethyl benzoyl acetate **1** (0.01 mole), thiazole **2** (0.01 mole), various substituted aromatic

aldehydes **3** (0.01 mole) which give thiazolo pyrimidines **4** (Scheme 1). A variety of aromatic aldehydes carrying either electron donating or electron withdrawing substituents reacted very well, giving products in high purity.

Scheme 1: synthesis of thiazolo pyrimidine



The structure of the purified compounds (4a-m) was characterized by elemental analysis, IR, ¹H NMR and mass spectral studies. Formation of 4b was confirmed from its spectral data. IR spectra of the compound 4b showed absorption bands at 3282.1 cm⁻¹, 1628 cm⁻¹ and 1537 cm⁻¹ due to NH, C=O and C=N stretching vibrations. The ¹H NMR showed broad singlet at δ 8.12 corresponding to NH proton that got exchanged with D₂O, multiplet at δ 6.87 - δ 7.27 was observed for aromatic and HA protons. 3 protons of -OCH₃ group appeared as singlet at δ 3.75. Also singlet at δ 5.61 was observed for HB proton which confirms the ring closing in the compound. Another singlet at δ 2.51 for HC proton, quartet for -OCH₂CH₃ protons at δ 3.47 and triplet for -OCH₂CH₃ at δ 1.06 confirms the structure of 4b. The mass spectra of compound 4b showed molecular ion peak M⁺ at m/z 470 which corresponds to the molecular formula C₂₈H₂₆N₂O₃S which further give the evidence for the formation of compound 4b. The elemental analysis of compounds (4a-m) was found to be in good agreement with the calculated values (\pm 0.4%). The characterization data of ethyl-3,7-biphenyl-5-[substituted

phenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4a-m) are given in experimental section. The structure of 4b was further established via acetylation of compound 4b with acetic anhydride under reflux led to the formation of 8-acetyl-5-(4-methoxyphenyl)-3,7-diphenyl-8,8a-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid 5.

Where the usual acetylation took place at secondary NH group (position 8) and ester group at position 6 got hydrolysed to acid group which is established by the downfield appearance of the acid hydrogen at position δ 11.67 and further the compound gave brisk effervescence on treatment with aq. NaHCO₃. Disappearance of quartet because of CH₂ group of ethyl at δ 3.47 and a triplet because of CH₃ group of ethyl at δ 1.06 further proves its structure.

ANTIMICROBIAL STUDIES

Some of the compounds were screened for anti-bacterial (*Staphylococcus aureus*, *Staphylococcus aureus* (MRSA), *Streptococcus pyogenes*) and antifungal (*Aspergillus niger*, *Neurospora crassa*) studies by Agar Diffusion method. For evaluating antimicrobial activity Gentamycin and Amphotericin were used as the standard drug. The observed minimum inhibitory concentration (MIC) and zone of inhibition at a concentration of 800 μ g/ml of some newly synthesized compounds were measured against various strains (Table 1).

Table 1: Antimicrobial screening of different compounds against different strains

Tested Samples	S. Au-reus		MRSA		S. Pyo-gens		A. Niger		N. Crassa	
	A*	MIC (μ g)	A*	MIC (μ g)	A*	MIC (μ g)	A*	MIC (μ g)	A*	MIC (μ g)
4b	--	>800	--	>800	--	>800	--	>800	--	>800
4d	--	>800	7	400	9	400	5	200	13	100
4g	3	800	--	>800	--	>800	--	>800	--	>800
4h	2	800	--	>800	--	>800	3	800	--	>800
4i	2	800	--	>800	--	>800	--	>800	--	>800
4m	4	400	7	100	10	400	5	400	12	100
Genta-mycin	34	<25	34	<25	33	<25	--	--	--	--
Ampho-tericin	--	--	--	--	--	--	7	100	9	400

* A = Zone of inhibition in mm. at a concentration of 800 μ g/ml

(--) showing no activity.

The compounds '4d' and '4m' show maximum activities against this bacterial and fungal strain. For strain N. Crassa, they show MIC value even less than the standard drug. So compounds '4d' and '4m', having hydroxy group at the para position of the aryl moiety are more active than the compounds bearing other substituents on the aryl moiety. In

general compounds exert very low antibacterial activity but moderate to good antifungal activity.

EXPERIMENTAL

Instrumentation

Melting points were taken in open end capillaries and were uncorrected. The purity of the synthesized compounds was checked by thin layer chromatography on Silica gel G (Merck) plates and spots were located by iodine vapours. ¹H NMR spectra were recorded on BRUKER ADVANCE II 400 (400 MHz) NMR Spectrometer using tetramethyl silane (TMS) as internal standard. All chemical shifts were reported as δ (ppm) values. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System using KBr pellets. The mass spectra were obtained on a JEOL 5 x 102/DA-6000 mass spectrometer. The elemental analyses were recorded on VARIO MICRO CHNS ANALYZER. All the compounds gave satisfactory results within \pm 0.4% of theoretical values.

General Procedure for the synthesis of 2-amino-4-phenyl thiazole(2): 2-amino-4-phenyl thiazole was prepared as per method reported in literature [18]: m.p. 146°C; IR (KBr, cm⁻¹): 3251.9(NH), 1599.3, 1533(aromatic stretching), 1460(C=N); PMR(400MHz, CDCl₃, δ , ppm): 5.20(s, 2H, NH₂), 6.71(s, 1H, CH), 7.75-7.25(m, 5H, C₆H₅)

General Procedure for the synthesis of ethyl-3,7-biphenyl-5-[substituted phenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate(4a-m): A mixture of ethyl benzoyl acetate **1** (0.01 mole), thiazole **2** (0.01 mole), various substituted aromatic aldehydes **3** (0.01 mole) in absolute ethanol(10ml) with 4-5 drops of hydrochloric acid was heated under reflux for 2-6 hour (Scheme 1). After completion of the reaction (followed by TLC), Removal of the solvent under reduced pressure yielded the product which was recrystallized from ethanol. The structure of the prepared compounds was characterized on the basis of melting point, IR, NMR, Mass and elemental analysis spectra. The spectral data of the prepared compounds are given below:

Ethyl-3,7-biphenyl-5-[phenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4a):

This compound was obtained as off white solid; yield 53%; m.p. 235-237°C; IR (KBr,cm⁻¹): 3276.1, 3103.3, 2975.5, 1631.8, 1537.3, 1492.6; ¹H NMR (DMSO-d₆- δ , ppm): 8.17(s, 1H, NH), 6.72-7.54(m, 16H, Ar-H & HA), 5.60(s, 1H, HB), 3.56(q, 2H, -OCH₂CH₃), 2.49(s, 1H, HC), 1.05(t, 3H, OCH₂CH₃); MS: m/z (M⁺) 440; Anal. Calcd. for C₂₇H₂₄N₂O₃S: C 73.55, H 5.45, N 6.36; Found: C 73.81, H 5.46, N 6.33.

Ethyl-3,7-biphenyl-5-[4-methoxyphenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4b):

This compound was obtained as off white solid; yield 40%; m.p. 242-244°C; IR (KBr,cm⁻¹): 3282.1, 3125.1, 2962, 1628, 1537.7; ¹H NMR (DMSO-d₆- δ , ppm): 8.12(s, 1H, NH), 6.87-7.27(m, 15H, Ar-H & HA), 5.61(s, 1H, HB), 3.75(s, 3H, OCH₃), 3.47(q, 2H, -OCH₂CH₃), 2.51(s, 1H, HC), 1.06(t, 3H, OCH₂CH₃); MS: m/z (M⁺) 470; Anal. Calcd. for C₂₈H₂₆N₂O₃S: C 71.41, H 5.53, N 5.95 Found: C 71.58, H 5.52, N 5.94.

Ethyl-3,7-biphenyl-5-[2-nitrophenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4c):

This compound was obtained as yellow solid, yield 39%; m.p. 182-184°C; IR (KBr,cm⁻¹): 3284, 2922.4, 1640, 1592; ¹H NMR (DMSO-d₆- δ , ppm): 9.10(s, 1H, NH), 6.82-7.65(m, 15H, Ar-H & HA), 5.63(s, 1H, HB), 3.78(q, 2H, -OCH₂CH₃), 2.50(s, 1H, HC), 1.10(t, 3H, OCH₂CH₃); MS: m/z (M⁺) 485; Anal. Calcd. for C₂₇H₂₃N₃O₄S: C 66.74, H 4.74, N 8.65; Found: C 66.90, H 4.72, N 8.64.

Ethyl-3,7-biphenyl-5-[4-hydroxy-3-methoxyphenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4d):

This compound was obtained as green solid, yield 44%; m.p. 215-217°C; IR (KBr, cm⁻¹): 3438.6, 3266.4, 3063.8, 2946.7,

1635.3, 1519.2; ¹H NMR (DMSO-d₆-δ, ppm): 9.49 (s, 2H, OH, NH), 6.69-7.42 (m, 14H, Ar-H & HA), 5.60 (s, 1H, HB), 3.82 (s, 3H, OCH₃), 3.58 (q, 2H, -OCH₂CH₃), 2.58 (s, 1H, HC), 1.15 (t, 3H, OCH₂CH₃); MS: m/z (M⁺) 486; Anal. Calcd. for C₂₈H₂₆N₂O₄S: C 69.07, H 5.34, N 5.75; Found: C 69.28, H 5.33, N 5.74.

Ethyl-3,7-biphenyl-5-[3-hydroxyphenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4e):

This compound was obtained as green solid, yield 52% ; m.p. 210-212°C; IR (KBr,cm⁻¹): 3356.6; 3215, 3085.3; 2924.3, 1627.2, 1559.1; ¹H NMR (DMSO-d₆-δ, ppm): 9.18 (s, 1H, OH), 8.10 (s, 1H, NH), 6.69-7.35 (m, 15H, Ar-H & HA), 5.62 (s, 1H, HB), 3.56 (q, 2H, -OCH₂CH₃), 2.57 (s, 1H, HC), 1.25 (t, 3H, OCH₂CH₃); MS: m/z (M⁺) 456; Anal. Calcd. for C₂₇H₂₄N₂O₃S: C 70.97, H 5.25, N 6.13; Found: C 71.21, H 5.27, N 6.11.

Ethyl-3,7-biphenyl-5-[2,3-methylenedioxyphenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4f):

This compound was obtained as brown solid, yield 50% ; m.p. 185-187°C; IR (KBr,cm⁻¹): 3282.3, 3083.5, 2909.4, 1630.3, 1534.7, 1485.8; ¹H NMR (DMSO-d₆-δ, ppm): 8.09 (s, 1H, NH), 6.73-7.93 (m, 14H, Ar-H & HA), 6.01 (s, 2H, O-CH₂-O), 5.61 (s, 1H, HB), 4.18 (q, 2H, -OCH₂CH₃), 2.53 (s, 1H, HC), 1.15 (t, 3H, OCH₂CH₃); MS: m/z (M⁺) 484; Anal. Calcd. for C₂₇H₂₄N₂O₄S: C 69.35, H 4.95, N 5.78; Found: C 69.12, H 4.97, N 5.76.

Ethyl-3,7-biphenyl-5-[4-nitrophenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4g):

This compound was obtained as light green solid, yield 68% ; m.p. 251-252°C; IR (KBr,cm⁻¹): 3281, 3122.6, 2925, 1632.9, 1539.9, 1349.8; ¹H NMR (DMSO-d₆-δ, ppm): 8.20 (s, 1H, NH), 7.14-7.50 (m, 15H, Ar-H & HA), 5.78 (s, 1H, HB), 3.52 (q, 2H, -OCH₂CH₃), 2.50 (s, 1H, HC), 1.09 (t, 3H, OCH₂CH₃); MS: m/z (M⁺) 485; Anal. Calcd. for C₂₇H₂₃N₃O₄S: C 66.74, H 4.74, N 8.65; Found: C 66.98, H 4.72, N 8.62.

Ethyl-3,7-biphenyl-5-[2,4-dichlorophenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4h):

This compound was obtained as off white solid, yield 32% ; m.p. 240-241°C; IR (KBr,cm⁻¹): 3283.6; 3118.4; 2924.4; 1630.6; 1539; ¹H NMR (DMSO-d₆-δ, ppm): 7.59 (s, 1H, NH), 7.10-7.49 (m, 14H, Ar-H & HA), 5.72 (s, 1H, HB), 3.50 (q, 2H, -OCH₂CH₃), 2.56 (s, 1H, HC), 1.12 (t, 3H, OCH₂CH₃); MS: m/z (M⁺) 510; Anal. Calcd. for C₂₇H₂₂Cl₂N₂O₂S: C 63.60; H 4.32; N 5.50. Found: C 63.41; H 4.33; N 5.52.

Ethyl-3,7-biphenyl-5-[3-nitrophenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4i):

This compound was obtained as yellow solid, yield 36% ; m.p. 188-190°C; IR (KBr,cm⁻¹): 3274.6, 3177.7, 2996.8, 1643.8, 1526.2, 1493.1; ¹H NMR (DMSO-d₆-δ, ppm): 9.55 (s, 1H, NH), 7.17-8.25 (m, 15H, Ar-H & HA), 5.88 (s, 1H, HB), 3.85 (q, 2H, -OCH₂CH₃), 2.52 (s, 1H, HC), 1.14 (t, 3H, OCH₂CH₃); MS: m/z (M⁺) 485; Anal. Calcd. for C₂₇H₂₃N₃O₄S: C 66.74, H 4.74, N 8.65; Found: C 66.93, H 4.72, N 8.62.

Ethyl-3,7-biphenyl-5-[2-chlorophenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4j):

This compound was obtained as white solid, yield 50% ; m.p. 255-256°C; IR (KBr,cm⁻¹): 3278.4, 2930.4, 1640.4, 1585.2, 1488.2; ¹H NMR (DMSO-d₆-δ, ppm): 9.10 (s, 1H, NH), 6.75-7.35 (m, 15H, Ar-H & HA), 5.70 (s, 1H, HB), 3.80 (q, 2H, -OCH₂CH₃), 2.54 (s, 1H, HC), 1.20 (t, 3H, OCH₂CH₃); MS: m/z (M⁺) 475; Anal. Calcd. for C₂₇H₂₃ClN₂O₂S: C 69.05, H 4.84, N 5.90; Found: C 69.12, H 4.86, N 5.91.

Ethyl-3,7-biphenyl-5-[3,4-dimethoxyphenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4k):

This compound was obtained as grey solid, yield 71% ; m.p. 211-213°C; IR (KBr,cm⁻¹): 3274.6, 3080.1, 2946.7, 1628.4, 1514.8, 1265.8; ¹H NMR (DMSO-d₆-δ, ppm): 8.35 (s, 1H, NH), 6.73-7.62 (m, 14H, Ar-H & HA), 5.65 (s, 1H, HB), 4.24 (q,

2H, -OCH₂CH₃), 3.86 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 2.51 (s, 1H, HC), 1.25 (t, 3H, OCH₂CH₃); MS: m/z (M⁺) 500; Anal. Calcd. for C₂₉H₂₈N₂O₄S: C 69.52, H 5.60, N 5.59; Found: C 69.55, H 5.61, N 5.61.

Ethyl-3,7-biphenyl-5-[4-chlorophenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4l):

This compound was obtained as light brown solid, yield 37% ; m.p. 243-244°C; IR (KBr,cm⁻¹): 3275.4, 3056.7, 2940, 1639.4, 1530.1, 1260.7; ¹H NMR (DMSO-d₆-δ, ppm): 8.01 (s, 1H, NH), 7.12-7.34 (m, 15H, Ar-H & HA), 5.65 (s, 1H, HB), 3.46 (q, 2H, -OCH₂CH₃), 2.49 (s, 1H, HC), 1.07 (t, 3H, OCH₂CH₃); MS: m/z (M⁺) 475; Anal. Calcd. for C₂₇H₂₃ClN₂O₂S: C 68.21, H 4.84, N 5.89; Found: C 67.98, H 4.86, N 5.91.

Ethyl-3,7-biphenyl-5-[4-hydroxyphenyl]-8,8a-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate (4m):

This compound was obtained as light brown solid, yield 42% ; m.p. 190-192°C; IR (KBr,cm⁻¹): 3450.2, 3272.4, 3060.5, 2935.2, 1638, 1525.8; ¹H NMR (DMSO-d₆-δ, ppm): 9.10 (s, 1H, OH), 8.14 (s, 1H, NH), 6.80-7.51 (m, 15H, Ar-H & HA), 5.58 (s, 1H, HB), 3.65 (q, 2H, -OCH₂CH₃), 2.57 (s, 1H, HC), 1.15 (t, 3H, OCH₂CH₃); MS: m/z (M⁺) 456; Anal. Calcd. for C₂₇H₂₄N₂O₃S: C 70.96, H 5.26, N 6.13; Found: C 71.12, H 5.24, N 6.12.

General Procedure for the synthesis of 8-acetyl-5-(4-methoxyphenyl)-3,7-diphenyl-8,8a-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid (5) (acetylation of compound 4b):

A mixture of compound 4b and acetic anhydride was heated on a steam bath until a clear solution was obtained. The reaction mixture was cooled to room temperature and poured into crushed ice. Precipitate of acetylated product thus obtained was filtered and recrystallized from ethanol (scheme-1). The yield of the product varied between 85 and 89%. This compound was obtained as white solid, m.p. 202.5-204°C, IR (KBr,cm⁻¹): 3292.1, 3061.1, 2938, 1694.4, 1608.58, 1543.17, 1524.86 ; ¹H NMR (400 MHz, DMSO-d₆-δ, ppm): 11.67 (s, 1H, OH), 6.87-7.51 (m, 15H, Ar-H & HA), 5.81 (s, 1H, HB), 3.73 (s, 3H, OCH₃), 2.45 (s, 1H, HC), 2.06 (s, 3H, CH₃); MS: m/z (M⁺) 484; Anal. Calcd. for C₂₈H₂₄N₂O₄S: C 69.42, H 4.95, N 5.78 Found: C 69.31, H 4.96, N 5.80.

ANTIMICROBIAL STUDIES

Antibacterial studies: Some of the synthesized compounds were screened for their antibacterial activity against Staphylococcus aureus, Staphylococcus aureus (MRSA), Streptococcus pyogenes according to the Agar Diffusion Method using dimethylsulfoxide as solvent. The stock cultures of bacteria were revived by inoculating in broth media and grown at 37°C for 18 hrs. The agar plates of the above media were prepared and wells were made in the plate. Each plate was inoculated with 18 h old cultures (100 µl, 10⁴ cfu) and spread evenly on the plate. After 20 min, the wells were filled with compounds at different concentrations. The control wells with Gentamycin were also prepared. All the plates were incubated at 37°C for 24 h and the diameter of inhibition zone were recorded in Table-1.

Antifungal studies: The antifungal screening studies of some compounds were performed by the standard Agar diffusion Method. Aspergillus niger, Neurospora crassa were used as test organisms.

Media Used: Potato Dextrose Agar (PDA). 250 g of peeled potato were boiled for 20 min and squeezed and filtered. To this filtrate 20 g of dextrose was added and the volume was made up to 1000ml by distilled water. Initially, the stock cultures were revived by inoculating in broth media and grown at 27°C for 48 hrs. The agar plates of the above media were prepared and wells were made in the plate. Each plate was inoculated with 48 h old cultures (100 µl 10⁴ CFU) and spread evenly on the plate. After 20 min, the wells were filled with compounds at different concentrations. The control plates

with antibiotic were also prepared. All the plates were incubated at 27°C for 48 h and the diameter of inhibition zone were recorded in Table-1.

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