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Full Paper

Synthetic and Biological Studies of Ethyl-7-methyl-3-(naphthalen-2-yl)-5-phenyl-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate Derivatives

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Abstract: Novel series of ethyl-7-methyl-3-(naphthalen-2-yl)-5-phenyl-5*H*-thiazolo[3,2-a] pyrimidine-6-carboxylate (**4a–g**) heterocyclic compounds have been synthesized in a one-pot reaction under solvent-free conditions from 4-(naphthalen-2-yl)thiazol-2-amine (1), various aromatic benzaldehyde (2a–g) and ethylacetoacetate (3). All the synthesized compounds were duly characterized by physic chemical analysis and various spectrometric technique viz., NMR, CMR and FT–IR spectral features. Compounds **4a–g** were screened for their in vitro antibacterial activity against Gram-positive bacterial strains (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative bacterial strains (*Salmonella typhimurium* and *Escherichia coli*). Compounds **4a–g** were also examined for antifungal activity against different fungal strains, i.e. *Penicillium expansum*, *Botryodiplodia theobromae*, *Nigrospora sp*., and *Trichothesium sp.*

Keywords: antimicrobial activity; solvent-free; one-pot synthesis; thiazolo[3,2-a]pyrimidine

1. INTRODUCTION

The last few decades have seen a flurry of activity in the solvent free synthesis and development of heterocyclic compound because of their important biological properties [1–2]. 2-Aminothiazoles and their derivatives are well-known because of their wide spectrum of biological activity shown by the thiazole moiety [3–6]. Pyrimidine derivatives have been used for the structural modification to synthesize various heterocyclic compounds with different biological properties, among which, thiazole ring fused to pyrimidine ring resulting in thiazolopyrimidine is found to be more active [7–8]. Heterocyclic compounds containing thiazolo[3,2-a]pyrimidines have attracted much attention of chemists. Various researchers [9–28] have devoted their attention because of their biological and medicinal activities. These types of fused benzothiazole-pyrimidine compounds have been synthesized from 2-amino-benzothiazoles derivatives and β-haloesters [29–31], orthoesters [32–35], allenic [36] and acetylenic groups [37–38], β-ketosters [39–40], α-haloacids [41] and malonates [42]. Based on this concept, our main concern was to synthesize such heterocyclic compounds under solvent-free condition which possess enhance biological activity by introducing fused benzothiazole–pyrimidine, i.e. thiazolo[3,2-a]pyrimidines segments together. Figure 1 summarizes our synthetic approach to this work. All compounds 4a–g was evaluated for their antibacterial activity against Gram–positive and Gram–negative bacterial strains. Antifungal activity was also carried out against different fungal strains.

2. MATERIAL AND METHODS

All common analytical grade reagents and solvents were used without further purification. 4-(naphthalen-2-yl)thiazol-2-amine (1) was synthesized as per the method reported. Various aldehydes viz., benzaldehyde (2a), 4-methyl benzaldehyde (2b), 4-methoxy benzaldehyde (2c), 2-hydroxy benzaldehyde (2d), 4-hydroxy benzaldehyde (2e), 3,4-diethoxy benzaldehyde (2f), 4-hydroxy-3-methoxy benzaldehyde (2g) and ethyl aceto acetate (3) were

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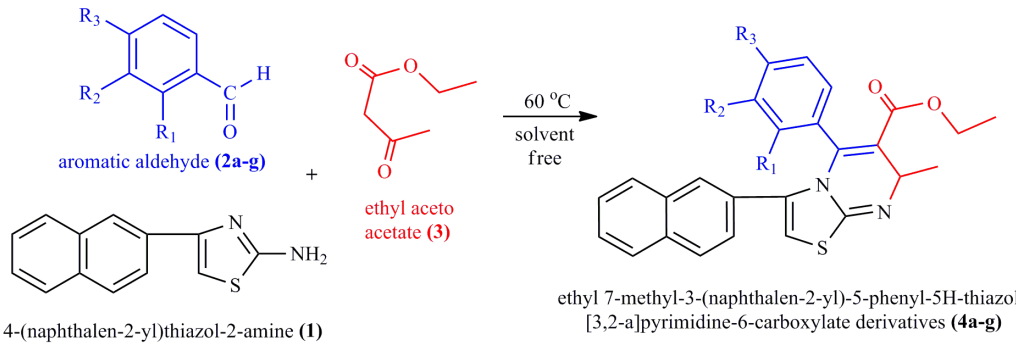
obtained from Sigma-Aldrich. Alumina supported pre-coated silica gel 60 F254 thin layer chromatography (TLC) plates were purchased from the E. Merck (India) Limited, Mumbai and were used to check purity of compounds and, to study the progress of the reaction whereby TLC plates were illuminated under Ultraviolet light (254 nm), evaluated in I_2 vapors and visualized by spraying with Draggendorff's reagent. Infrared spectra (FT–IR) were obtained from KBr pellets in the range of 4000–400 cm^{-1} with a Perkin Elmer spectrum GX spectrophotometer (FT–IR) instrument. ^1H NMR and ^{13}C NMR spectra were acquired at 400 MHz on a Bruker NMR spectrometer using DMSO–d_6 (residual peak at δ ~2.5 or ~ 39.5 ppm, 300 K) as a solvent as well as TMS an internal reference standard. Micro analytical (C, N, H) data was obtained by using a Perkin–Elmer 2400 CHN elemental analyzer. The melting point was checked by the standard open capillary method.



Aryl aldehyde 2a-g

R_1= -H, R_2= -H, R_3= -H = **2a**= benzaldehyde
R_1= -H, R_2= -H, R_3= $-CH_3$ = **2b**= 4-methylbenzaldehyde
R_1= -H, R_2= -H, R_3= $-OCH_3$ = **2c**= 4-methoxybenzaldehyde
R_1= -OH, R_2= -H, R_3= -H = **2d**= 2-hydroxybenzaldehyde
R_1= -H, R_2= -H, R_3= -OH = **2e**= 4-hydroxybenzaldehyde
R_1= -H, R_2= $-OC_2H_5$, R_3= $-OC_2H_5$ = **2f** = 3,4-diethoxybenzaldehyde
R_1= -H, R_2= $-OCH_3$, R_3= -OH = **2g**= 4-hydroxy-3-methoxybenzaldehyde

Scheme 1. Synthesis of compounds **4a-g**.

Synthesis of naphthalen-2-yl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate derivative: A mixture of 4-(naphthalen-2-yl)thiazol-2-amine (0.1 mol), various benzaldehyde (0.1 mol) and ethylacetoacetate (0.1 mol) were heated at 60 ˚C in the solvent free condition for 4–5 h. The resultant reaction mixture was allowed to stand for 3 h [43]. The precipitate formed was checked by TLC monitoring (petroleum ether : ethylacetate 1:4). Thus obtained products were filtered and washed 4 times with water and diethylether. The desired products were obtained with high purity.

*Ethyl-7-methyl-3-(naphthalen-2-yl)-5-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**4a**):* Yield 65%, M. Wt. 426.53 g, Mp > 250˚C (uncorrected). ^1H NMR (400 MHz, DMSO–*d6*): δppm = 1.88 (t, J=6.8Hz, 3H, CH_3–C11); 2.79 (s, 3H, CH_3–C8); 3.89 (q, J=6.8Hz, 2H, CH_2–C10); 6.23 (s, 1H, CH–C5); 6.87 (s, 1H, CH–C2); 6.94–7.48 (m, 5H, Ar.H–C13-17); 7.56–7.87 (m, 7H, Ar.H–C19-25). ^{13}C NMR: 34.2; 42.6; 47.0; 54.1; 114.5; 117.3; 119.4; 120.7; 123.3; 125.7; 128.0; 129.2; 131.4; 136.1; 137.2; 139.8; 140.7; 142.5; 147.2; 164.1; 173.0. FT–IR (KBr, cm^{-1}): 3062(C-H str, aromatic); 2884 (CH, str, aliphatic); 1596(C=C, asymmetric, str.); 1487, 1469(C=C, str. ring); 1224(C-N, str); 748(C-H def, aromatic); 1726(>C=O str,ester); 1223, 1041(C-O str, ester). Elemental analysis calculated for $C_{26}H_{22}N_2O_2S$ %: C 73.21; H 5.20; N 6.57; S 7.52; Found, %: C 73.13; H 5.08; N 6.50; S 7.44.

*Ethyl-7-methyl-3-(naphthalen-2-yl)-5-(p-tolyl)-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**4b**):* Yield 72%, M. Wt. 440.56 g, Mp > 250˚C (uncorrected). ^1H NMR (400 MHz, DMSO–*d6*): δppm = 1.91 (t, J=6.8Hz, 3H, CH_3–C11); 2.36 (s, 3H, CH_3–C15); 2.83 (s, 3H, CH_3–C8); 3.80 (q, J=6.8Hz, 2H, CH_2–C10); 6.20 (s, 1H, CH–C5); 6.92 (s, 1H, CH–C2); 7.09 (d, J=7.2Hz, 2H, Ar.H–C13,17); 7.19 (d, J=7.2Hz, 2H, Ar.H–C14,16); 7.47–7.78 (m, 7H, Ar.H–C18-25). ^{13}C NMR: 36.2; 40.4; 43.1; 49.7; 56.9; 114.2; 116.5; 119.2; 121.4; 122.6; 126.0; 128.1; 129.3; 130.2; 133.6; 136.0; 138.2; 140.5; 141.7; 145.8; 167.3; 171.4. FT–IR (KBr, cm^{-1}): 3070(C-H str, aromatic); 2878(CH, str, aliphatic); 1595(C=C, asymmetric, str.); 1483, 1471(C=C, str. ring); 1228(C-N, str); 742(C-H def,

aromatic); 1729(>C=O str,ester); 1220, 1047(C-O str, ester). Elemental analysis calculated for $C_{27}H_{24}N_2O_2S$ %: C 73.61; H 5.49; N 6.36; S 7.28; Found, %: C 73.52; H 5.40; N 6.28; S 7.19.

*Ethyl-5-(4-methoxyphenyl)-7-methyl-3-(naphthalen-2-yl)-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**4c**):* Yield 68%, M. Wt. 456.56 g, Mp > 250˚C (uncorrected). ^{1}H NMR (400 MHz, DMSO–*d6*): δppm = 1.89 (t, J=6.8Hz, 3H, CH_3–C11); 2.80 (s, 3H, CH_3–C8); 3.82 (s, 3H, OCH_3–C15); 3.72 (q, J=6.8Hz, 2H, CH_2–C10); 6.21 (s, 1H, CH–C5); 6.93 (s, 1H, CH–C2); 7.11 (d, J=7.2Hz, 2H, Ar.H–C13,17); 7.23 (d, J=7.2Hz, 2H, Ar.H–C14,16); 7.73–8.11 (m, 7H, Ar.H–C18-25). ^{13}C NMR: 30.7; 45.3; 47.1; 49.7; 54.2; 112.4; 115.7; 117.0; 119.0; 123.4; 124.6; 127.1; 129.5; 130.8; 132.2; 135.4; 138.6; 140.0; 141.5; 145.8; 166.2; 169.6. FT–IR (KBr, cm^{-1}): 3067(C-H str, aromatic); 2874(CH, str, aliphatic); 1592(C=C, asymmetric, str.); 1480, 1476(C=C, str. ring); 1230(C-N, str); 747(C-H def, aromatic); 1727(>C=O str, ester); 1220, 1049(C-O str, ester); 2832 (Ar-OCH_3). Elemental analysis calculated for $C_{27}H_{24}N_2O_3S$ %: C 71.03; H 5.30; N 6.14; S 7.02; Found, %: C 70.95; H 5.21; N 6.04; S 6.97.

*Ethyl-5-(2-hydroxyphenyl)-7-methyl-3-(naphthalen-2-yl)-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**4d**):* Yield 70%, M. Wt. 442.53 g, Mp > 250˚C (uncorrected). ^{1}H NMR (400 MHz, DMSO–*d6*): δppm = 1.82 (t, J=6.8Hz, 3H, CH_3–C11); 2.77 (s, 3H, CH_3–C8); 3.78 (q, J=6.8Hz, 2H, CH_2–C10); 6.23 (s, 1H, CH–C5); 6.97 (s, 1H, CH–C2); 7.06–7.22 (m, 4H, Ar.H–C13-16); 7.38–7.69 (m, 7H, Ar.H–C18-25); 9.65 (s, 1H, OH–C13). ^{13}C NMR: 37.5; 44.2; 46.9; 52.7; 111.8; 112.5; 115.3; 118.6; 121.7; 122.5; 127.0; 129.3; 130.1; 131.2; 133.0; 136.7; 138.5; 139.6; 141.4; 142.6; 146.8; 167.6; 171.2. FT–IR (KBr, cm^{-1}): 3072(C-H str, aromatic); 2874(CH, str, aliphatic); 1587(C=C, asymmetric, str.); 1478, 1493(C=C, str. ring); 1227(C-N, str); 744(C-H def, aromatic); 1730(>C=O str, ester); 1218, 1050(C-O str, ester); 3583(Ar-OH). Elemental analysis calculated for $C_{26}H_{22}N_2O_3S$ %: C 70.57; H 5.01; N 6.33; S 7.25; Found: C 70.51; H 4.92; N 6.25; S 7.20.

*Ethyl-5-(4-hydroxyphenyl)-7-methyl-3-(naphthalen-2-yl)-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**4e**):* Yield 68%, M. Wt. 442.53 g, Mp > 250˚C (uncorrected). ^{1}H NMR (400 MHz, DMSO–*d6*): δppm = 1.85 (t, J=6.8Hz, 3H, CH_3–C11); 2.73 (s, 3H, CH_3–C8); 3.76 (q, J=6.8Hz, 2H, CH_2–C10); 6.18 (s, 1H, CH–C5); 6.92 (s, 1H, CH–C2); 7.06 (d, J=7.2Hz, 2H, Ar.H–C13,17); 7.21 (d, J=7.2Hz, 2H, Ar.H–C14,16); 7.37–7.69 (m, 7H, Ar.H–C18-25); 9.65 (s, 1H, OH–C15). ^{13}C NMR: 38.3; 45.8; 48.4; 52.5; 112.9; 114.7; 117.6; 118.9; 120.3; 123.0; 128.3; 130.6; 132.7; 133.2; 136.9; 138.4; 140.2; 142.5; 146.1; 164.7; 170.2. FT–IR (KBr, cm^{-1}): 3070(C-H str, aromatic); 2874(CH, str, aliphatic); 1588(C=C, asymmetric, str.); 1476, 1493(C=C, str. ring); 1227(C-N, str); 743(C-H def, aromatic); 1729(>C=O str,ester); 1218, 1048(C-O str, ester); 3572(Ar-OH). Elemental analysis calculated for $C_{26}H_{22}N_2O_3S$ %: C 70.57; H 5.01; N 6.33; S 7.25; Found, %: C 70.52; H 4.91; N 6.28; S 7.18.

*Ethyl-5-(3,4-diethoxyphenyl)-7-methyl-3-(naphthalen-2-yl)-5H-thiazolo[3,2-a] pyrimidine -6-carboxylate (**4f**):* Yield 65%, M. Wt. 514.64 g, Mp > 250˚C (uncorrected). ^{1}H NMR (400 MHz, DMSO–*d6*): δppm = 1.68 (t, J=7.1Hz, 6H, -OCH_2CH_3); 1.87 (t, J=6.8Hz, 3H, CH_3–C11); 2.69 (s, 3H, CH_3–C8); 3.49 (q, J=7.1Hz, 4H, -OCH_2CH_3); 3.73 (q, J=6.8Hz, 2H, CH_2–C10); 6.89 (s, 1H, CH–C5); 7.02 (s, 1H, CH–C2); 7.18 (d, J=7.2Hz, 1H, Ar.H–C17); 7.23 (d, J=7.2Hz, 1H, Ar.H–C16); 7.36 (s, 1H, Ar.H–C13); 7.47–7.82 (m, 7H, Ar.H–C18-25); ^{13}C NMR: 30.7; 38.9; 41.5; 47.7; 49.3; 57.6; 112.1; 115.7; 116.4; 119.4; 121.5; 124.8; 128.4; 129.5; 130.7; 132.0; 136.1; 138.2; 140.5; 142.7; 145.7; 168.3; 172.1. FT–IR (KBr, cm^{-1}): 3074(C-H str, aromatic); 2869(CH, str, aliphatic); 1587(C=C, asymmetric, str.); 1471, 1496(C=C, str. ring); 1230(C-N, str); 749(C-H def, aromatic); 1732(>C=O str, ester); 1218, 1045(C-O str, ester). Elemental analysis calculated for $C_{30}H_{30}N_2O_4S$ %: C 70.01; H 5.88; N 5.44; S 6.23; Found, %: C 69.89; H 5.80; N 5.41; S 6.16.

*Ethyl-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-3-(naphthalen-2-yl)-5H-thiazolo[3,2-a] pyrimidine-6-carboxylate (**4g**):* Yield 63%, M. Wt. 472.56 g, Mp > 250˚C (uncorrected). ^{1}H NMR (400 MHz, DMSO–*d6*): δppm = 1.80 (t, J=6.8Hz, 3H, CH_3–C11); 2.78 (s, 3H, CH_3–C8); 3.42 (s, 3H, OCH_3); 3.78 (q, J=6.8Hz, 2H, CH_2–C10); 6.21 (s, 1H, CH–C5); 6.92 (s, 1H, CH–C2); 7.08 (d, J=7.2Hz, 1H, Ar.H–C17); 7.26 (d, J=7.2Hz, 1H, Ar.H–C16); 7.39 (s, 1H, Ar.H–C13); 7.56–7.82 (m, 7H, Ar.H–C18-25); 9.65 (s, 1H, OH). ^{13}C NMR: 42.8; 45.4; 48.6; 50.3; 56.0; 111.4; 113.7; 114.0; 118.5; 120.4; 124.9; 126.3; 129.4; 131.0; 132.2; 135.3; 137.3; 140.7; 142.3; 145.7; 168.3; 174.7. FT–IR (KBr, cm^{-1}): 3068(C-H str, aromatic); 2874(CH, str, aliphatic); 1578(C=C, asymmetric, str.); 1460, 1493(C=C, str. ring); 1236(C-N, str); 743(C-H def, aromatic); 1731(>C=O str, ester); 1217, 1051(C-O str, ester); 3524(Ar-OH). Elemental analysis calculated for $C_{27}H_{24}N_2O_4S$ %: C 68.62; H 5.12; N 5.93; S 6.79; Found, %: C 68.55; H 5.04; N 5.83; S 6.70.

Biological activity

Antibacterial activity (in vitro)

Compounds **4a–g** were screened for their in vitro antibacterial activity against Gram-positive bacterial strains (*Bacillus subtilis* [BS] and *Staphylococcus aureus* [SA]) and Gram-negative bacterial strains (*Salmonella typhimurium* [ST] and *Escherichia coli* [EC]) utilizing the agar diffusion assay [22, 44]. The method was described in our earlier paper [45]. In order to clarify any participating role of DMSO in the biological screening, separate studies were carried out with the solutions alone of DMSO and they showed no activity against any bacterial strains.

Antifungal activity (in vitro)

Compounds **4a–g** were also examined for antifungal activity against different fungal strains, i.e. *Penicillium expansum* [PE], *Botryodiplodia theobromae* [BT], *Nigrospora sp.* [NS], *Trichothesium sp.* [TS]. The antifungal drug, ketoconazole was used as a positive control. Antifungal screening for compounds 4a–g and positive control was performed at a recommended concentration. The fungal strains were grown and maintained on potato dextrose agar plates. The cultures of the fungi were purified by single spore isolation technique. Each compound 4a–g in DMSO solution was prepared for testing against spore germination of each fungus. The fungal culture plates were inoculated and incubated at 25± 2˚C for 48 h. The plates were then observed and diameters of the zone of inhibition (in mm) were measured. The percentage inhibition for fungi was calculated after five days using the formula given below:

$$\text{Percentage of inhibition} = \frac{100(X - Y)}{X}$$

where, X = Area of colony in control plate, and Y = Area of colony in test plate.

3. RESULTS AND DISCUSSION

Chemistry

A one pot solvent free synthesis have been successfully carried out using 4-(naphthalen-2-yl)thiazol-2-amine, various benzaldehyde and ethylacetoacetate and duly characterized. To the best of our knowledge, compounds **4a–g** has not been reported previously. The characterization of the reaction product provided the first unambiguous proof of the successful synthesis of naphthalen-2-yl-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives. Elemental analysis of all compounds was in good agreement with proposed structures. The predicted structures of analogs **4a–g** were consistent with their FT–IR, ^{1}H NMR and ^{13}C NMR values. The probable mechanism of the reaction is described as under (Scheme 2). In this mechanism carbonyl carbon of benzaldehyde act as an electrophile and β-ketoesters (ethyl aceto acetate) contains active methylene compounds which took part in the reaction hence, an alkene is primarily formed. 2-Aminobenzothiazole act as a donor which attacks on alkene during nucleophilic reaction, so an iminium ion is formed (**I**), subsequently with a proton transformation and an intramolecular cyclization, products **4a–g** are produced.

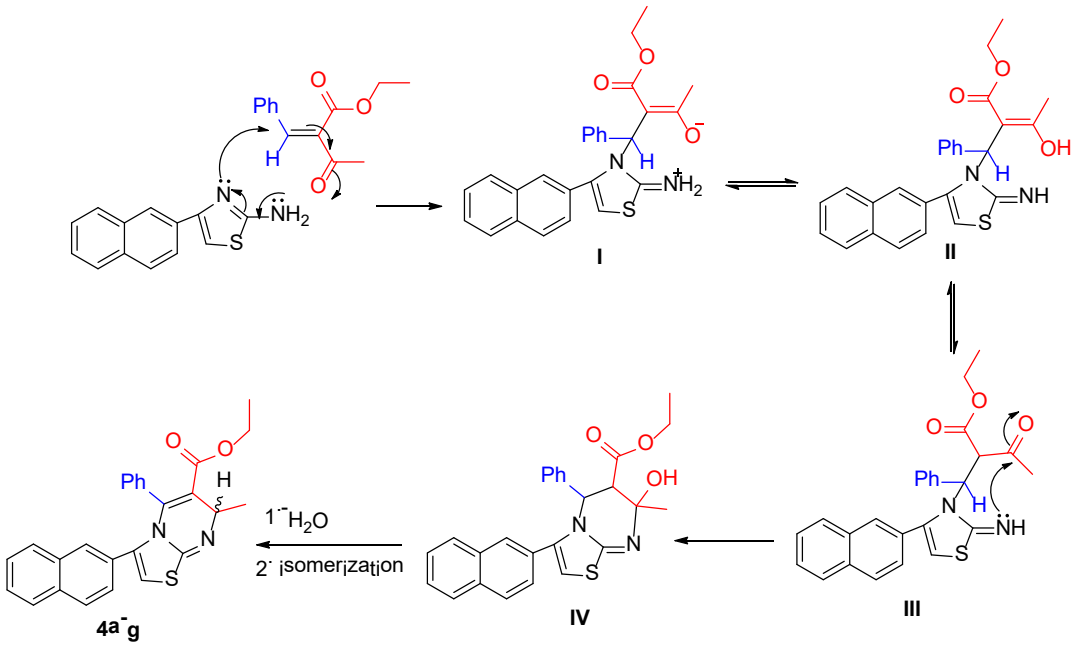
FT–IR Spectral features provide valuable information regarding the structures. The spectrum of **4a–g** showed the most relevant bands of naphthalene and aromatic ring, thiazole ring, carboxylate. One of the significance differences were to be observed is the formation of new pyrimidine ring. Bands at 1220 cm^{-1} and 1735 cm^{-1} were attributed to ester [22]. In the ^{1}H NMR spectroscopy, the signals in the range of 6.4–8.2 ppm were ascribed to the protons of the aromatic naphthalene, thiazole & benzene rings. The triplet-quartet pair at 1.80 and 3.70 ppm were ascribed to the protons of ester group, which was further confirmed by ^{13}C NMR value i.e. 169 attributed to carbonyl carbon. The expected structure was thus clearly verified by the spectroscopic analysis which indicated moreover the absence of any detectable impurity, particularly of the two reagents used to prepare 4a–g.

Biological activity

Antibacterial activity

Based on the data from the antibacterial studies against both Gram–positive and Gram–negative bacterial strains (Table 1), the following observations can be made. Compounds 4a–g exhibited antibacterial activity against both Gram–positive and Gram–negative bacterial strains with zones of inhibition (ZOI) ranging from 22 mm to 36 mm (Table 1). Among the compounds 4a–g, 4g ($ZOI_{[BS]}$ = 32 mm, $ZOI_{[SA]}$ = 31 mm, $ZOI_{[ST]}$ = 33 mm, $ZOI_{[EC]}$ = 34 mm) was identified as a potent antibacterial agent against all Gram-positive and Gram-negative bacterial strains. Compound 4f ($ZOI_{[BS]}$ = 29 mm, $ZOI_{[SA]}$ = 30 mm, $ZOI_{[ST]}$ = 31 mm, $ZOI_{[EC]}$ = 32 mm) had found good antibacterial activity against bacterial strains. Compound 4c ($ZOI_{[BS]}$ = 27 mm, $ZOI_{[SA]}$ = 28 mm,

$ZOI_{[ST]}$ = 28 mm, $ZOI_{[EC]}$ = 30 mm) and compound 4b ($ZOI_{[BS]}$ = 26 mm, $ZOI_{[SA]}$ = 26 mm, $ZOI_{[ST]}$ = 27 mm, $ZOI_{[EC]}$ = 28 mm) also had moderate antibacterial activity against bacterial strains. Compounds 4d, 4e and 4a exhibited less antibacterial activity. Compounds 4a–g exhibited less antibacterial activity as compare to standard antibiotic drug ciprofloxacin ($ZOI_{[BS]}$ = 35 mm, $ZOI_{[SA]}$ = 37 mm, $ZOI_{[ST]}$ = 38 mm, $ZOI_{[EC]}$ = 40 mm).



Scheme 2. Mechanism proposed for the synthesis of **4a-g**.

Table 1. Antimicrobial activity of compounds **4a–g**.

Compounds	Antibacterial Activity				Antifungal Activity			
	Zone of Inhibition				Zone of Inhibition			
	Gram +Ve		Gram –Ve					
	BS	***SA***	***ST***	***EC***	***PE***	***BT***	***NS***	***TS***
4a	22	23	24	24	26	20	21	22
4b	26	26	27	28	30	25	26	29
4c	27	28	28	30	32	28	29	32
4d	24	25	25	26	28	23	24	26
4e	24	25	26	25	28	24	23	26
4f	29	30	31	32	33	30	32	34
4g	32	31	33	34	34	31	34	35
Ciprofloxacin	35	37	38	40	---	---	---	---
Ketoconazole	---	---	---	---	35	33	39	41

BS: *Bacillus subtilis.* SA: *Staphylococcus aureus.* ST: *Salmonella typhi.* EC: *Escherichia coli.* PE: *Penicillium Expansum.* BT: *Botrydepladia Thiobromine.* NS: *Nigrospora Sp.* TS: *Trichothe-sium Sp.*

Antifungal activity

Based on the screening data from the antifungal studies (Table 1), the following observations can be made. All compounds (4a–g) exhibited antifungal activity against different fungal strains. Among the analogs 4a–g, Compound 4g ($ZOI_{[PE]}$ = 34 mm, $ZOI_{[BT]}$ = 31 mm, $ZOI_{[NS]}$ = 34 mm, $ZOI_{[TS]}$ = 35 mm) was found more active against all fungal strains. Compound 4f ($ZOI_{[PE]}$ = 33 mm, $ZOI_{[BT]}$ = 30 mm, $ZOI_{[NS]}$ = 32 mm, $ZOI_{[TS]}$ = 34 mm) and compound 4c ($ZOI_{[PE]}$ = 32 mm, $ZOI_{[BT]}$ = 28 mm, $ZOI_{[NS]}$ = 29 mm, $ZOI_{[TS]}$ = 32

mm) also had good antifungal activity against fungal strains. Compounds 4a, 4b, 4d and 4e exhibited moderate antifungal activity. Compounds 4a–g exhibited less antifungal activity as compare to standard antibiotic drug, ketoconazole ($ZOI_{[PE]}$ = 35 mm, $ZOI_{[BT]}$ = 33 mm, $ZOI_{[NS]}$ = 39 mm, $ZOI_{[TS]}$ = 41 mm).

4. CONCLUSION

Novel series of ethyl-7-methyl-3-(naphthalen-2-yl)-5-phenyl-5*H*-thiazolo[3,2-a] pyrimidine-6-carboxylate (**4a–g**) heterocyclic compounds have been successfully synthesized in a one-pot reaction under solvent-free conditions from 4-(naphthalen-2-yl)thiazol-2-amine and duly characterized.

5. REFERENCES AND NOTES

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