Synthesis, anti-microbial activity and docking studies of 3-(2-(phenylamino)thiazol-4-yl)-2H-chromen-2-ones and ethyl 2-(2-(phenylamino)thiazol-4-yl)acetates

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Received 4 April 2016; accepted (revised) 10 October 2016

Different approaches for the synthesis of a series of 3-(2-(phenylamino)thiazol-4-yl)-2H-chromen-2-ones 5a-h is described. Also, 5a-h can be prepared by the reaction of salicylaldehyde with ethyl 2-(2-(phenylamino)thiazol-4-yl)acetates 6a-h which in turn are prepared by the reaction of ethyl 4-chloroacetoacetate with phenylthioureas. All the compounds 5a-h and intermediates 6a-h prepared in this work have been screened for their antimicrobial activities such as anti-bacterial and anti-fungal. Compounds 6e, 6g and 6h show good anti-bacterial activity. The molecular interaction of the synthesized compounds 6a-h with S. aureus FtsZ protein is supported by molecular docking studies.

Keywords: 3-(2-Bromoacetyl)-2H-chromen-2-ones, ethyl 2-(2-(phenylamino)thiazol-4-yl)acetates, thiazoles, anti-microbial activity, docking studies

Coumarin derivatives are known to possess antibacterial, antitubercular, antioxidant and antipsychotic activities. Thiazole derivatives are also reported to possess a range of interesting biological properties such as antimicrobial, anti-inflammatory and antiviral.

Mitsunori et al. reported the reaction of 2-bromo-1-phenylethanones with potassium thiocyanate in refluxing ethanol for 3 h giving 1-phenyl-2-thiocyanatoethanones. Sohail and Jafar reported the condensation of 2-bromo-1-phenylethanones with potassium thiocyanate in water using tetrabutylammonium bromide (TBAB) as a phase transfer catalyst, at RT for 25-30 minutes yielding the corresponding 1-phenyl-2-thiocyanatoethanones. Lenin et al. reported the thiocyanation of ketones using ammonium thiocyanate in water using tetrabutylammonium bromide (TBAB) as a phase transfer catalyst, at RT for 25-30 minutes yielding the corresponding 1-phenyl-2-thiocyanatoethanones. Len in et al. reported the thiocyanation of ketones using ammonium thiocyanate catalyzed by the polystyrene resin i.e., Amberlyst-15, at RT for 4-6 h.

One-pot synthesis of 2-aminothiazoles was reported by Aoyama et al. by treating α-haloketones with the supported-reagent system - KSCN/SiO2–RNH3OAc/Al2O3 - in refluxing benzene for 6 h. Aerschot et al. reported the synthesis of substituted 2-aminothiazoles in a one-pot method by treating α-haloketones with potassium thiocyanate and subsequent addition of respective aniline under refluxing conditions for over 12 h.

Zhuravel et al. reported the reaction of 3-(2-bromoacetyl)-2H-chromen-2-one with thiourea and 4-oxo-4-thioureidobutanoic acid in boiling ethanol for 2 h yielding the corresponding thiazole derivatives. The condensation of 3-(2-bromoacetyl)-8-ethoxy-2H-chromen-2-one with o-phenylenediamine in boiling methanol for 3 h affording 8-ethoxy-3-(quinazolin-4-yl)-2H-chromen-2-one was reported by Mohammed et al. The latter also reported the reaction of 3-(2-bromoacetyl)-8-ethoxy-2H-chromen-2-one with thiourea, phenylthiourea and cyanothioacetamide in refluxing methanol resulting in the respective thiazole derivatives.

In recent years, the use of polyethylene glycol (PEG) as reaction media has attracted the attention of chemists in the context of green synthesis. PEG has been used as efficient and green solvent in substitution reactions, oxidation reactions and reduction reactions. Also, PEG has been used as an attractive green solvent for alkylations, one-pot-three-component reactions, Michael additions, etc. Apart from all these, the most advantageous application of PEG is that it can also act as phase transfer catalyst. Furthermore, PEG is an inexpensive, recoverable, easily bio-degradable and non-toxic hydrophilic solvent.
Based on the above observations and in continuation of our earlier work\textsuperscript{24,25} on synthesis of oxygen containing heterocycles of potential biological interest, herein we wish to report a simple and efficient one-pot method for the synthesis of 3-(2-(phenylamino)thiazol-4-yl)-2\textsubscript{H}-chromen-2-one in good yields, using the environmentally friendly polyethylene glycol (PEG) as the condensation medium.

**Results and Discussion**

As shown in Scheme I, commercially available salicylaldehyde 1 was treated with ethyl acetoacetate in triethanolamine containing catalytic amount of L-proline at RT for 30 min, using our earlier procedure\textsuperscript{26}, to yield 3-acetyl-2\textsubscript{H}-chromen-2-one 2. The latter, on bromination, using tetrabutylammonium tribromide (TBATB)\textsuperscript{27} in acetic acid, at RT for 2-3 h afforded 3-(2-bromoacetyl)-2\textsubscript{H}-chromen-2-one 3, also known in literature\textsuperscript{28}.

3 on reaction with potassium thiocyanate in PEG-600 at RT for 1 h led to 3-(2-thiocyanatoacetyl)-2\textsubscript{H}-chromen-2-one 4. Earlier reports\textsuperscript{29,30} showed that the reaction of simple \(\alpha\)-haloketones with potassium thiocyanate yielded the corresponding thiocyanatoacetyl derivatives using either phase transfer catalysts or by refluxation in suitable solvents for several hours for the reaction to complete. However, in the present case, reaction of 3 with KSCN in PEG-600, at RT alone, afforded 3-(2-thiocyanatoacetyl)-2\textsubscript{H}-chromen-2-one 4, smoothly, in just 1 h, in an yield of 73%. Alternatively, 4 itself was obtained from 2 by treatment with iodine and KSCN in PEG-600 at RT for 3 h in 59% yield. 4, on condensation with anilines in PEG-600 at RT for 2-3 h, resulted in the formation of the title compounds \(i.e.,\) 3-(2-(phenylamino)thiazol-4-yl)-2\textsubscript{H}-chromen-2-ones 5. The latter were also obtained in a one-pot reaction by treating equimolar amounts of 3-(2-bromoacetyl)-2\textsubscript{H}-chromen-2-one (3), potassium thiocyanate and respective aniline in PEG-600 at RT for 3-4 h and were found to be identical with the ones obtained earlier in the step-wise route \((i.e., 2\rightarrow 3\rightarrow 4\rightarrow 5)\).

The mechanism for the formation of 5 from 4 seems to be as follows (Scheme II).

In an yet another alternative approach, 3 was treated with different phenylthioureas in PEG-600 at RT for 1-2 h yielding 5 and were found to be identical with the ones obtained in the earlier routes. Phenylthioureas required in this condensation were prepared by refluxing the respective anilines with equimolar amount of ammonium thiocyanate in aq. HCl. A possible mechanism for the formation of 5 from 3 is shown in Scheme III.

Encouraged by the above results it was thought of interest to prepare the title compound 5 in a different
route starting from ethyl 4-chloroacetoacetate. Thus, commercially available ethyl 4-chloroacetoacetate was treated with phenylthiourea in PEG-600 at RT for 4-5 h to obtain ethyl 2-(2-(phenylamino)thiazol-4-yl) acetates 6 which on Knoevenagel condensation with salicylaldehyde in PEG-600 using piperidine as a catalyst at RT for 3-4 h yielded the title compounds in good yields (Scheme IV). 5, thus obtained were found to be identical with the same compounds prepared in the earlier routes, in all respects (m.p., m.m.p., and co-TLC).

All the products have been well characterized by spectral data. For details, please see the Experimental Section.

**Antimicrobial Activity**

All the compounds, 3-(2-(phenylamino)thiazol-4-yl)-2H-chromen-2-ones 5a–h, ethyl 2-(2-(phenylamino)thiazol-4-yl) acetates 6a-h were screened for their antimicrobial activity.

**Anti-bacterial activity**

Among 5a–h series, compounds 5e, 5g and 5h have showed very mild activity against Staphylococcus aureus and Escherichia coli and were found to be inactive against Streptococcus and Pseudomonas aeruginosa. In 6a-h series, the compounds 6e, 6f, 6g and 6h showed good activity against Staphylococcus aureus and Escherichia coli.
Scheme IV — Alternative route for the synthesis of title compounds

Table I — Anti-bacterial activity data of the synthesized compounds 5a-h and 6a-h

<table>
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<th>S.No</th>
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<th>Gram positive bacteria</th>
<th>Gram negative bacteria</th>
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<tr>
<td>1</td>
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<td>5g</td>
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<tr>
<td>17</td>
<td>Streptomycin</td>
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</tbody>
</table>

Zone of inhibition (in mm): - = <3 (no activity); + = 3-6 (mild activity); ++ = 6-9 (moderate activity); +++ = 9-12 (good activity); ++++ = 12-15 (excellent activity).

and remaining compounds showed moderate activity. They have shown mild to moderate activity against *Streptococcus* and *Pseudomonas aeruginosa*. The results were recorded in Table I.

**Anti-fungal activity**

All the synthesized compounds 5a-h and 6a-h were subjected to antifungal activity against *Aspergillus niger* and the results showed that the mycelial growth could not be prevented and indicated the absence of anti-fungal activity by the compounds.

**Molecular Docking studies**

The active compounds 6a-h from antibacterial studies further supported by molecular docking studies through molecular interaction with *S. aureus* Filamentous temperature sensitive protein Z (FtsZ), as an essential cell-division protein conserved in virtually all eubacteria, archeae and chloroplasts. Molecular docking studies revealed that compounds 6e, 6f, 6g and 6h showed better docking scores than remaining molecules. Though the docking scores are not more than that of the standard co-crystal ligand (PC190723) all the molecules showed required hydrogen bond (Gly205, Val207, Asn293) and hydrophobic interactions (Leu200, Val 203, Val 297) as that of standard ligand. Docking scores of ligands have been shown in Table II.

The compound 6h showed the best docking score of −7.283. Thus, the 2D interaction diagram of ligand 6h with the complex protein is shown in Figure 1. Representative diagram of interactions of compound 6h and co-crystal ligand were displayed in Figure 2. Nitro (-NO$_2$) group of compound 6h showed hydrogen bond interaction with Gly205 in distance of 2.58 Å and hydrophobic interactions with Val297, Leu200 and Ile 311.
Experimental Section

Melting points are uncorrected and were determined in open capillary tubes using hot sulphuric acid bath. TLC analyses were done on silica gel-G coated plastic sheets supplied by Merck Company and visualization was done using UV lam.p. and iodine chamber. ¹H NMR spectra were recorded in DMSO-d₆ using TMS as an internal standard using 400 MHz spectrometer. Mass spectra were recorded on an Agilent-LCMS instrument. Starting materials – Salicylaldehydes, ethyl acetoacetate and ethyl 4-chloroacetoacetate - and the green solvent - PEG-600 - were obtained from commercial suppliers and were used as such.

Preparation of 3 from 2

A mixture of 2 (1.88 g, 10 mmol), tetrabutylammonium tribromide (TBATB) (4.82 g, 10 mmol) and acetic acid (30 mL) was stirred at RT for 2 h. After completion of reaction, as indicated by TLC, the mixture was poured into ice-cold water (100 mL). The separated solid was filtered, washed with water (2×30 mL) and air-dried at RT. The crude product was recrystallized from ethanol to obtain pure 3. Yield 2.45 g (92%). m.p. 164-66°C.

Preparation of 4 from 3

A mixture of 3 (2.67 g, 10 mmol), potassium thiocyanate (0.97 g, 10 mmol) and PEG-600 (20 mL) was stirred at RT for 1 h. The reaction was monitored by TLC. After completion of reaction, as indicated by TLC, the mixture was poured into ice-cold water (100 mL). The separated solid was filtered, washed with water (2×30 mL) and air-dried at RT. The crude product was recrystallized from methanol to obtain pure 4. Yield 1.73 g (73%). m.p.132–34°C. IR(KBr): 1698 (strong, sharp, -CO of -COCH₃), 1720 (strong, sharp, -CO of coumarin ring), 2156 cm⁻¹ (strong, sharp, -SCN); ¹H NMR (DMSO-d₆/TMS): δ 4.91 (s, 2H, -CH₂), 7.46-8.02 (m, 4H,Ar-H), 8.90 (s, 1H, Ar-H); LCMS (CI): m/z 246 [M⁺+1].

Preparation of 4 from 2

A mixture of 2 (1.88 g, 10 mmol), iodine crystals (2.50 g, 10 mmol), potassium thiocyanate (0.97 g, 10 mmol) and PEG-600 (20 mL) was stirred at RT for 3 h. The reaction was checked by TLC. After completion of reaction, as indicated by TLC, the mixture was poured into ice-cold water (100 mL) and unreacted iodine were neutralized with aqueous sodium thiosulphate (10%). The separated solid was filtered under vacuum, washed with water (2×30 mL) and air-dried at RT. The crude product was recrystallized from methanol to obtain pure 4. Yield 1.39 g (59%). m.p.132–34°C.

General procedure for the synthesis of 5 from 4

A mixture of 4 (5 mmol), respective aniline (5 mmol) and PEG-600 (20 mL) was stirred at RT for 2.3 h. The reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice-cold water (100 mL). The separated solid was filtered, washed with water (2×30 mL) and air-dried at RT. The crude product was recrystallized from a suitable solvent to obtain pure 5.

<table>
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</tr>
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</tr>
<tr>
<td>3</td>
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</tr>
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<td>6</td>
<td>6f</td>
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<td>8</td>
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<tr>
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<td>Standard / Co-crystal ligand</td>
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</table>

Figure 1 — 2D interaction diagram for the ligand 6h with S. aureus FtsZ.

Green dotted lines: hydrophobic interaction, Yellow dotted lines: Hydrogen bond interaction.

Table II — Docking Scores of the synthesized compounds 6a-h
3-(2-(Phenylamino)thiazol-4-yl)-2H-chromen-2-one, 5a: Yellow solid. Yield 1.23 g (77%). m.p. 244–46°C (MeOH). IR(KBr): 1728 (strong, sharp, -CO of coumarin ring), 3390-3430 cm⁻¹ (broad, medium, -NH group); ¹H NMR (400 MHz, DMSO-d₆/ TMS): δ 6.98 (d, 2H, Ar-H) 7.39-7.68 (complex, m, 6H, Ar-H), 7.72 (s, 1H, Ar-H), 7.96 (d, 1H, Ar-H); ¹³C NMR (100 MHz, DMSO-d₆): 110.366, 116.336, 117.570, 119.754, 120.792, 121.925, 125.162, 129.470, 129.601, 130.792, 134.400, 141.440, 144.088, 152.775, 159.291, 162.993; HRMS Calcd for C₁₈H₁₂O₂N₂S [M+H]^+: m/z 321.0697. Found: 321.0707.

3-(2-((4-Chlorophenyl)amino)thiazol-4-yl)-2H-chromen-2-one, 5b: Yellow solid. Yield 1.24 g (71%). m.p.> 250°C (Ethanol). IR(KBr): 1701 (strong, sharp, -CO of coumarin ring), 3380-3460 cm⁻¹ (broad, medium, -NH group); ¹H NMR (400 MHz, DMSO-d₆/ TMS): δ 7.13 (t, 1H, Ar-H), 7.36-7.66 (m, 5H, Ar-H), 7.82 (s, 1H, Ar-H), 7.92 (d, 1H, Ar-H), 8.48 (d, 1H, Ar-H), 8.71 (s, 1H, Ar-H) and 9.79 (s, 1H, -NH); ¹³C NMR (100 MHz, DMSO-d₆): 115.035, 115.334, 115.823, 118.820, 118.984, 119.276, 120.624, 124.213, 127.952, 130.844, 136.960, 138.273, 143.706, 152.363, 156.010, 159.196, 159.341, 163.057; HRMS Calcd for C₁₈H₁₁O₂N₂SCl [M+H]^+: m/z 355.0321. Found: 355.0321.

3-(2-((2-Chlorophenyl)amino)thiazol-4-yl)-2H-chromen-2-one, 5c: Yellow solid. Yield 1.30 g (74%). m.p. 1720 (strong, sharp, -CO of coumarin ring), 3390-3450 cm⁻¹ (broad, medium, -NH group); ¹H NMR (400 MHz, DMSO-d₆/ TMS): δ 7.11 (t, 1H, Ar-H), 7.37-7.65 (complex, m, 5H, Ar-H), 7.82 (s, 1H, Ar-H), 7.91 (d, 1H, Ar-H), 8.48 (d, 1H, Ar-H), 8.71 (s, 1H, Ar-H) and 9.81 (s, 1H, -NH); ¹³C NMR (100 MHz, DMSO-d₆): 109.473, 115.574, 118.147, 118.984, 119.276, 120.624, 124.213, 127.952, 130.844, 136.960, 138.273, 143.706, 152.363, 156.010, 159.196, 159.341, 163.057; HRMS Calcd for C₁₈H₁₁O₂N₂SCl [M+H]^+: m/z 355.0321. Found: 355.0321.

3-((2-Chloro-4-fluorophenyl)amino)thiazol-4-yl)-2H-chromen-2-one, 5d: Yellow solid. Yield 1.39 g (80%). m.p.192-94°C (Acetonitrile). IR(KBr): 1716 cm\(^{-1}\) (broad, medium, -NH group); 1H NMR (400 MHz, DMSO-d\(_6\) TMS): \(\delta\) 6.98 (d, 2H, Ar-H), 7.40 (t, 1H, Ar-H), 7.47 (s, 1H, Ar-H), 7.61-7.68 (complex, m, 3H, Ar-H), 7.72 (s, 1H, Ar-H), 8.67 (s, 1H, Ar-H) and 10.15 (s, 1H, -NH); \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\))): 117.731, 118.595, 119.698, 120.685, 125.219, 129.245, 132.189, 136.627, 139.653, 139.850, 143.921, 151.210, 152.773, 153.600, 159.189, 162.633; HRMS Calcd for C_{18}H_{10}ClN_{2}O_{2}S [M+H]^+: m/z 353.0213. Found: 373.0402.

3-((2-Fluorophenyl)amino)thiazol-4-yl)-2H-chromen-2-one, 5e: Yellow solid. Yield 1.39 g (80%). m.p.212-24°C (Ethanol). IR(KBr): 1716 cm\(^{-1}\) (broad, medium, -NH group); 1H NMR (400 MHz, DMSO-d\(_6\) TMS): \(\delta\) 6.98 (d, 2H, Ar-H), 7.40 (t, 1H, Ar-H), 7.47 (s, 1H, Ar-H), 7.61-7.68 (complex, m, 3H, Ar-H), 7.72 (s, 1H, Ar-H), 7.72 (s, 1H, Ar-H) and 10.15 (s, 1H, -NH); \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\))): 117.731, 118.595, 119.698, 120.685, 125.219, 129.245, 132.189, 136.627, 139.653, 139.850, 143.921, 151.210, 152.773, 153.600, 159.189, 162.633; HRMS Calcd for C_{18}H_{10}ClN_{2}O_{2}S [M+H]^+: m/z 353.0213. Found: 373.0402.

General procedure for the one-pot preparation of 5 from 3

A mixture of 3 (5 mmol), potassium thiocyanate (5 mmol), respectively aniline (5 mmol) and PEG-600 (20 mL) was stirred at RT for 34 h. Progress of the reaction was monitored on TLC. After completion of the reaction, the mixture was poured into ice-cold water (100 mL). The separated solid was filtered, washed with water (2×30 mL) and dried. The crude product was recrystallized from a suitable solvent to obtain pure 5.

5a: Yield 1.39 g (87%); 5b: Yield 1.39 g (79%); 5c: Yield 1.60 g (91%); 5d: Yield 1.48 g (80%); 5e: Yield 1.36 g (82%); 5f: Yield 1.57 g (79%); 5g: Yield 1.53 g (88%); 5h: Yield 1.66 g (92%).

General procedure for the synthesis of 5 from 3 by reaction with phenylthioureas

A mixture of 3 (5 mmol), respective phenylthioureas (5 mmol) and PEG-600 (20 mL) was stirred at RT for 1-2 h. The reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice-cold water (100 mL). The separated solid was filtered, washed with water (2×30 mL) and air-dried at RT. The crude product...
was recrystallized from a suitable solvent to obtain pure 5.

5a: Yield 1.46 g (90%); 5b: Yield 1.49 g (85%); 5c: Yield 1.63 g (93%); 5d: Yield 1.67 g (90%); 5e: Yield 1.47 g (89%); 5f: Yield 1.78 g (90%); 5g: Yield 1.61 g (93%); 5h: Yield 1.66 g (92%).

**General procedure for the synthesis of 6**

A mixture of ethyl 4-chloroacetooctoate (5 mmol), respective phenylthioiourea (5 mmol) and PEG-600 (20 mL) was stirred at RT for 4-5 h. After completion of the reaction, as indicated by the disappearance of starting materials on TLC, the mixture was poured into ice-cold water (100 mL). The separated solid was filtered, washed with water (2×30 mL) and air-dried at RT. The crude product was recrystallized from a suitable solvent to obtain pure 6.

**Ethyl 2-(2-(phenylamino)thiazol-4-yl)acetate, 6a:** White solid. Yield 1.16 g (87%). m.p.68–70°C (Methanol). IR(KBr): 1723 (strong, sharp, -CO of ester group), 3390-3460 cm⁻¹ (broad, medium, -NH group); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 1.20 (t, 3H, -CH₃), 3.60 (s, 2H, -CH₂), 4.10 (q, 2H, -OCH₂), 6.60 (s, 1H, Ar-H), 7.08-7.72 (m, 5H, Ar-H); ¹³C NMR (100 MHz, DMSO-d₆): 14.064, 36.977, 60.193, 106.825, 121.048, 128.839, 141.151, 144.643, 163.093, 170.000; HRMS Calcd for C₁₅H₁₄NO₃S [M-H⁺]: m/z 263.0854. Found: 263.0851.

**Ethyl 2-(2-(4-chlorophenyl)amino)thiazol-4-yl)acetate, 6b:** White solid. Yield 0.79 g (86%). m.p.100–102°C (Ethanol). IR(KBr): 1718 (strong, sharp, -CO of ester group), 3390-3430 cm⁻¹ (broad, medium, -NH group); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 1.18 (t, 3H, -CH₃), 3.64 (s, 2H, -CH₂), 4.10 (q, 2H, -OCH₂), 6.60 (s, 1H, Ar-H), 7.10-7.74 (m, 4H, Ar-H); ¹³C NMR (100 MHz, DMSO-d₆): 14.166, 37.233, 61.063, 105.047, 119.455, 127.334, 129.341, 138.872, 144.809, 164.334, 170.423; HRMS Calcd for C₁₅H₁₄ClN₂O₃S [M+H⁺]: m/z 277.04645. Found: 277.04605.

**Ethyl 2-(2-(4-chlorophenyl)amino)thiazol-4-yl)acetate, 6c:** White solid. Yield 1.25 g (85%). m.p.121–123°C (Chloroform). IR(KBr): 1727 (strong, sharp, -CO of ester group), 3400-3460 cm⁻¹ (broad, medium, -NH group); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 1.18 (t, 3H, -CH₃), 3.62 (s, 2H, -CH₂), 4.06 (q, 2H, -OCH₂), 6.65 (s, 1H, Ar-H), 7.10-7.72 (m, 4H, Ar-H); ¹³C NMR (100 MHz, DMSO-d₆): 14.061, 36.929, 60.225, 105.371, 118.100, 124.331, 128.640, 140.068, 144.665, 162.706, 169.948; LC/MS (CI): m/z 297 [M+H⁺].

**Ethyl 2-(2-(4-chloro-4-fluorophenyl)amino)thiazol-4-yl)acetate, 6d:** White solid. Yield 1.33 g (85%). m.p.114-116°C (Methanol). IR(KBr): 1716 (strong, sharp, -CO of ester group), 3340-3390 cm⁻¹ (broad, medium, -NH group); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 1.21 (t, 3H, -CH₃), 3.64 (s, 2H, -CH₂), 4.11 (q, 2H, -OCH₂), 6.72 (s, 1H, Ar-H), 7.31-7.43 (d, 2H, Ar-H), 7.99 (s, 1H, Ar-H), 10.36 (s, 1H, -NH); ¹³C NMR (100 MHz, DMSO-d₆): 14.170, 35.673, 60.821, 106.127, 116.457, 117.128, 117.888, 119.095, 137.254, 143.324, 150.333, 152.844, 161.419, 168.543; HRMS Calcd for C₁₅H₁₂ClFN₂O₂S [M+H⁺]: m/z 277.0107. Found: 277.01053.

**Ethyl 2-(2-(p-tolylamino)thiazol-4-yl)acetate, 6e:** White solid. Yield 1.10 g (80%). m.p.74–76°C (Methanol). IR(KBr): 1724 (strong, sharp, -CO of ester group), 3300-3340 cm⁻¹ (broad, medium, -NH group); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 1.20 (t, 3H, -CH₃), 2.34 (s, 3H, -CH₃), 3.60 (s, 2H, -CH₂), 4.10 (q, 2H, -OCH₂), 6.60 (s, 1H, Ar-H), 7.08-7.68 (m, 4H, Ar-H), 10.21 (s, 1H, -NH); ¹³C NMR (100 MHz, DMSO-d₆): 14.143, 20.342, 35.673, 60.821, 106.127, 116.457, 117.128, 117.888, 119.095, 137.254, 143.324, 150.333, 152.844, 161.419, 168.543; HRMS Calcd for C₁₅H₁₆NO₂S [M+H⁺]: m/z 281.0760. Found: 281.0756.

**Ethyl 2-(2-(4-fluoroaryl)amino)thiazol-4-yl)acetate, 6f:** White solid. Yield 1.10 g (79%). m.p.36–38°C (Ethanol). IR(KBr): 1718 (strong, sharp, -CO of ester group), 3320-3370 cm⁻¹ (broad, medium, -NH group); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 1.15 (t, 3H, -CH₃), 3.62 (s, 2H, -CH₂), 4.08 (q, 2H, -OCH₂), 6.60 (s, 1H, Ar-H), 7.10-7.72 (m, 4H, Ar-H), 10.16 (s, 1H, -NH); ¹³C NMR (100 MHz, DMSO-d₆): 14.123, 36.242, 61.343, 106.845, 119.354, 126.244, 130.241, 138.772, 145.419, 163.234, 169.713; HRMS Calcd for C₁₅H₁₆FNO₂S [M+H⁺]: m/z 281.0760. Found: 281.0756.
140.038, 145.765, 161.546, 170.518; LCMS (CI): m/z 293 [M’+1].

**Ethyl 2-(2-((4-nitrophenyl)amino)thiazol-4-yl)acetate, 6h:** White solid. Yield 0.79 g (81%). m.p.126–28°C (Acetonitrile), IR(KBr); 1701 (strong, sharp, -CO of ester group), 3390-3450 cm⁻¹ (broad, medium, -NH group); ¹H NMR (400 MHz, DMSO-d₆): δ 1.18 (t, 3H, -CH₃), 3.60 (s, 2H, -CH₂), 4.08 (q, 2H, -OCH₂), 6.62 (s, 1H, Ar-H), 7.10-7.60 (m, 4H, Ar-H), 9.78 (s, 1H, -NH); ¹³C NMR (100 MHz, DMSO-d₆): 14.062, 36.937, 60.221, 105.577, 116.357, 117.028, 117.584, 119.095, 138.393, 144.624, 150.463, 152.844, 162.609, 169.919; HRMS Calcd for C₁₃H₁₃N₃O₂S [M+H]+: m/z 308.07050. Found: 308.07043.

**Antimicrobial Activity**

All the compounds, 3-(2-(phenylamino)thiazol-4-yl)-2H-chromen-2-ones 5a–h, ethyl 2-(2-(phenylamino)thiazol-4-yl)acetates 6a–h were screened for their antimicrobial activity using agar well diffusion method.

**Anti-bacterial activity**

Antibacterial activity of these synthesized compounds was carried out against Gram-positive bacteria such as *Staphylococcus aureus* (MTCC 737), *Streptococcus* (isolated from the lab samples) and gram negative organisms such as *E. coli* (MTCC 1089), *Pseudomonas aeruginosa* (MTCC 1688) at concentration of 200 µg/mL. Streptomycin was used as a reference standard.

Briefly, the Nutrient agar medium was prepared by mixing 0.5 g of peptone, 3.0 g of beef extract, and 5.0 g of sodium chloride (NaCl) in 1000 mL distilled water, and the pH was adjusted to 7.0. Finally, 15.0 g of agar was added to the solution. The agar medium was sterilized in a conical flask at a pressure of 15 lbs for 15 min. This agar was transferred into sterilized petri dishes in a laminar air flow. After solidification the nutrient agar plates were inoculated with 0.1 mL of the culture and spread plating was carried out. The wells were bored on the plate after inoculation to incorporate the samples 5a–h and 6a–h. The plates were incubated at 37°C for 24 h. The results were recorded and zone of inhibition was measured in diameter of mm which is indicated by zone of clearance.

**Anti-fungal activity**

For determining the antifungal activity, the same methodology (as in the case of anti-bacterial activity) was used taking Saborauds medium for culturing the fungal organisms.

**Molecular Modeling studies**

The crystal co-ordinates of *Staphylococcus aureus* FtsZ were taken from protein data bank (PDB ID: 3VOB) and binding site has been identified within 10 Å distance from co-crystal ligand. The multi-step Schrodinger's (Schrodinger L.L.C., USA.) Protein preparation tool (PPrep) has been used for final preparation of receptor model. PPrep neutralizes side chains and residues which are not involving in salt bridges. This step is then followed by restrained minimization using the OPLS 2005 force field to RMSD of 0.3 Å. The synthesized compounds 6a–h were sketched by using 2D sketcher and prepared for docking using Ligprep, module of Schrödinger. A total of 10 conformations were generated for all compounds. Active site pocket of co-crystal ligand has been considered for grid generation with coordinates of X: 0.81; Y: 11.76; Z: 22.09. GLIDE (Friesner et al. 2006) SP (Standard Precision) flexible program was used for docking.

**Conclusion**

In conclusion, we have demonstrated simple, efficient and environmental friendly methods for the preparation of 3-(2-(phenylamino)thiazol-4-yl)-2H-chromen-2-ones in different methods starting from salicylaldehyde 1. The use of PEG-600 as reaction media avoids the involvement of additional catalyst and higher temperatures and found to be of great value as mild and efficient solvent for the preparation of 5a–h and 6a–h. In addition, we have synthesized the title compound in another, new and alternative method, starting from ethyl 4-chloroacetoacetate which...
avoids the use of reagents like TBATB and KSCN. All the compounds 5a-h and 6a-h have been screened for their anti-bacterial and antifungal activities. Compounds 6a-h showed moderate to good anti-bacterial activity. The activity of the compounds 6a-h was further supported by Molecular Docking studies.

Acknowledgements
The authors are thankful to the authorities of Jawaharlal Nehru Technological University Hyderabad for providing laboratory facilities. They are grateful to the Department of Science and Technology, Govt. of India, New Delhi, for the financial support to one of them (DS) in the form of INSPIRE Fellowship. The authors are indebted to the Department of Microbiology, St. Francis College, Hyderabad for the anti-microbial activity evaluation studies.

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