SYNTHESIS, CHARACTERIZATION, ANTIMICROBIAL STUDIES OF CERTAIN TRIAZOLE CONTAINING S-TRIAZINE DERIVED COMPOUND.

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Abstract

Some new substituted 1,3,5 triazine with 1,2,4 triazole and substituted urea/thiourea were synthesized and evaluated for their in vitro antimicrobial activity against Gram positive and Gram negative strains using a microdilution procedure. Synthesized compounds 1a to 1i proved to be effective with MIC (mg/ml), among them 1c, 1e, 1g showed excellent activity against a panel of microorganisms. The newly synthesized compounds were characterized using IR, H-NMR.

Keywords: - 1, 2, 4 Triazole, Substituted urea/thiourea, Cyanuric chloride and Antimicrobial activity.

Introduction:

S-Triazine derivatives represent an important class of compounds due to their potential to be biologically active. They are known to be anti-protozoals¹, antitumor agents², estrogen receptor modulators³, antimalariais⁴, cyclin-dependent kinase modulators⁵, and antimicrobials⁶. These are valuable bases for estrogen receptor modulators⁷ and also used as bridging agents to synthesize herbicides and in the production of drugs or polymers⁸.

1,2,4-Triazole have wide range of biological activities such as anti-bacterial⁹, anti cancer¹⁰, anti tubercular¹¹, anti HIV¹² and anti depressant activity, anti tumor¹³ and anti viral¹⁴ activity, anti hypertensive¹⁵ activity, analgesic and anti inflammatory¹⁶ activity.

Thiourea derivatives possess antibacterial¹⁷, hypnentic antitubercular and possible anticonvulsant activities. It also represent a new class of human immuno deficiency virus type (HIV-1), non-nucleoside reverse transcriptase (NNRT) inhibitors¹⁸, found as antagonist¹⁹, and high density lipoprotein (HDL) elevating agents²⁰. Urea derivatives are reported to possess antibacterial²¹, antimicrobial antifungal, anticancer²² and anticonvulsant²³ activities. Urea derivatives possess wide therapeutic activities such as antithyroidal, hypnotic and anesthetic, antibacterial, diuretic²⁴ and antihelmintics.

we wish to describe a simple and efficient protocol for the rapid preparation of 1-(4-(3-(4-METHOXYPHENYL)THIOUREIDO)-6-(1H-1,2,4-TRIAZOL-1-YL)-1,3,5-TRIAZINE-2-YL)-3-PHENYLUREA at different temperature conditions. To the best of our knowledge, there are no reports on three-component coupling of triazole, substituted urea and thiourea to produce a title compound. We planned to undertake the synthesis and characterization of some triazine derivatives carrying the above biodynamic heterocyclic systems with the hope to achieve enhanced biological activity.

Experimental: -

General

All the melting points were taken in open capillaries tube and are uncorrected. The purity of compounds was checked routinely by TLC (0.5 mm thickness) Using silica gel – G coated Al – plates (Merck) and spots were visualized by exposing the dry plates in iodine vapours. IR spectra were recorded on FTIR spectrophotometer using KBr or Nujol technique. 1H NMR spectra on a Varian 400 FT MHz NMR instrument at using CDCl₃ or DMSO-d₆ as solvent and TMS as internal reference.

Scheme: -

Step-1

Preparation Of 1-(4,6-Dichloro-1,3,5-Triazin-2-Yl)-3-(4-Methoxy Phenyl)Thiourea: (A)

To a stirred solution of cyanuric chloride (0.1 mole, 18.4 g.) in acetone (100 ml) at 0-5°C, the solution of 1-(4-methoxyphenyl)thiourea (0.1 mole,17.3g) in acetone (45 ml) was added and pH being maintained neutral by the addition of 10% sodium bi-carbonate solution from time to time as per requirement of reaction condition. The stirring was continued at 0-5°C for 2 hours. After the completion of reaction the stirring was stopped and the solution was treated with crushed ice. The solid product obtained was filtered and dried. The crude product was purified by crystallization from absolute alcohol to get title compound.
Step-2
Preparation Of 1-(4-Chloro-6-(1 H-1,2,4-Triazol-1-Yl)-1,3,5-Triazine-2-Yl)-3-(4-Methoxyphenyl) Thiourea : (B)
To a stirred solution of (A) (0.1 mole, 33.0 g) in acetone (100 ml) was added, the solution of 1,2,4 triazole (0.1 mole, 6.9 g) in acetone (25 ml) was added drop wise maintaining the temperature at 40°C, the pH being maintained neutral by the addition of 10% sodium bi-carbonate solution from time to time as per requirement of reaction condition. The temperature was gradually raised to 45°C during three hours. After the completion of reaction, the resultant content was poured into ice-cold water. The solid product obtained was filtered and dried. The crude product was purified by crystallization from absolute alcohol to get the title compound.

Step-3
Preparation Of Final Compound:
A mixture of (B) (0.01 mole, 3.62 g) and aryl urea (0.01 mole) in DMF (20ml) was refluxed in oil bath. The temperature was gradually raised to 80-100°C during four hours, the pH being maintained neutral by the addition of 10% sodium bi-carbonate solution from time to time as per requirement of reaction condition. After the completion of reaction, add little charcoal in R.B.F and then filter it into cold water. The solid product obtained was filtered and dried. The crude product was purified by recrystallization from absolute alcohol. Prepare all derivatives by this method. Analytical data are given below.

ROUTE OF SYNTHESIS :
STEP-1

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{N} & \quad \text{N} \\
\text{Cl} & \quad \text{Cl} \\
\text{2,4,6-trichloro-1,3,5-triazine} & \quad \text{OCH}_3 \\
+ & \quad \text{OCH}_3 \\
\text{1-phenyl-1H-triazole} & \quad \text{1-(4-methoxyphenyl)thiourea} \\
\end{align*}
\]

\[
\begin{align*}
\text{NH} & \quad \text{C} \quad \text{N} \\
\text{S} & \quad \text{C} \\
\text{1-(4-methoxyphenyl)thiourea} & \quad \text{1-(4,6-dichloro-1,3,5-triazin-2-yl)-3-(4-methoxyphenyl)thiourea} \\
\end{align*}
\]

[A]

STEP-2

\[
\begin{align*}
\text{A} & \quad \text{NH} \\
\text{1H-1,2,4-triazole} & \quad \text{S} \quad \text{C} \\
+ & \quad \text{1-(4-chloro-6-(1H-1,2,4-triazol-1-yl)-1,3,5-triazin-2-yl)-3-(4-methoxyphenyl)thiourea} \\
\end{align*}
\]

[B]
STEP-3

Where R = given in below table.

Table 1 Physical data of synthesized compounds:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>Mol. Formula</th>
<th>Mol. Weight</th>
<th>M.P. °C</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>H</td>
<td>C₂₀H₁₈N₁₀O₂S</td>
<td>462.49</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>1b</td>
<td>2-OCH₃</td>
<td>C₂₁H₂₀N₁₀O₂S</td>
<td>492.51</td>
<td>122</td>
<td>61</td>
</tr>
<tr>
<td>1c</td>
<td>4-CH₃</td>
<td>C₂₁H₂₀N₁₀O₂S</td>
<td>476.51</td>
<td>190</td>
<td>59</td>
</tr>
<tr>
<td>1d</td>
<td>4-Cl</td>
<td>C₂₁H₁₉ClN₁₀O₂S</td>
<td>496.93</td>
<td>220</td>
<td>74</td>
</tr>
<tr>
<td>1e</td>
<td>4-OCH₃</td>
<td>C₂₁H₂₀N₁₀O₂S</td>
<td>492.51</td>
<td>140</td>
<td>59</td>
</tr>
<tr>
<td>1f</td>
<td>2-CH₃</td>
<td>C₂₁H₂₀N₁₀O₂S</td>
<td>476.51</td>
<td>140</td>
<td>58</td>
</tr>
<tr>
<td>1g</td>
<td>2-Cl</td>
<td>C₂₁H₁₉ClN₁₀O₂S</td>
<td>496.93</td>
<td>135</td>
<td>62</td>
</tr>
<tr>
<td>1h</td>
<td>4-Br</td>
<td>C₂₁H₁₈BrN₁₀O₂S</td>
<td>541.38</td>
<td>180</td>
<td>60</td>
</tr>
<tr>
<td>1i</td>
<td>4-F</td>
<td>C₂₁H₁₈F₃N₁₀O₂S</td>
<td>480.48</td>
<td>175</td>
<td>65</td>
</tr>
</tbody>
</table>

**Compound (1a):** Yield: 60%; m.p. 120°C (dec.); IR (KBr, cm⁻¹): 798 cm⁻¹ (C=N- s-triazine) 818.47 cm⁻¹ (1,4 Di sub. in benzene) 1416.15 cm⁻¹ (>N-3° amine) 1548.50 cm⁻¹ (NH-def) 1656.15 cm⁻¹ (C=O-) 3290.15 cm⁻¹ (NH-str) 2800.50 cm⁻¹ (OCH₃ str) 1660.00 cm⁻¹ (C=S) 1170.64 cm⁻¹ (C=S) 1023.14 cm⁻¹ (N-N-str) H-NMR: δ 8.90 (s,2H, CONH), 10.30 (s,2H, CONH), 10.30 (s,2H, CSNH), 3.64 (s,3H, -OCH₃). 7.20-7.98 (m,11H, Ar-H).

**Compound (1b):** Yield: 61%; m.p. 122°C (dec.); IR (KBr, cm⁻¹): 801 cm⁻¹ (C=N- s-triazine) 819.25 cm⁻¹ (1,4 Di sub. in benzene) 1410.98 cm⁻¹ (>N-3° amine) 1562.70 cm⁻¹ (NH-def) 1643.16 cm⁻¹ (C=O-) 3311.16 cm⁻¹ (NH-str) 2916.48 cm⁻¹ (OCH₃ str) 1177.34 cm⁻¹ (C=S) 1033.34 cm⁻¹ (N-N-str) H-NMR: δ 8.64 (s,2H, CONH) 10.22 (s,2H, CSNH), 3.69 (s,6H, -OCH₃) 7.40-7.78 (m,10H, Ar-H).

**Compound (1c):** Yield: 59%; m.p. 190°C (dec.); IR (KBr, cm⁻¹): 783.07 cm⁻¹ (C=N- s-triazine) 821.07 cm⁻¹ (1,4 Di sub. in benzene) 1410.98 cm⁻¹ (>N-3° amine) 1596.6 cm⁻¹ (NH-def) 1643.16 cm⁻¹ (C=O-) 3311.10 cm⁻¹ (NH-str) 2916.48 cm⁻¹ (OCH₃ str) 1173.34 cm⁻¹ (C=S) 1308.20 cm⁻¹ (C=CH₂ str) 1033.34 cm⁻¹ (N-N-str) H-NMR: δ 8.71 (s,2H, CONH) 10.10 (s,2H, CSNH), 3.71 (s,3H, -OCH₃) 3.74 (s,3H, C=CH₂) 7.32-7.66 (m,10H, Ar-H).

**Compound (1d):** Yield: 74%; m.p. 220°C (dec.); IR (KBr, cm⁻¹): 795 cm⁻¹

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**Note:** The image contains chemical structures and reactions, which are not transcribed due to the limitations of text-based representation. For detailed chemical data and analysis, please refer to the original source or supplementary materials.
Antimicrobial Activity

For the testing antimicrobial activity various microorganism were used for the study. The broth dilution method was used for this study. Following general procedure is adopted\textsuperscript{24}. The antimicrobial activity of all the compounds was studies at 1000 ppm concentration in vitro. The different types of microorganism used were some gram negative bacteria [Escherichia coli, Pseudomonas aeruginosa], gram positive bacteria [Bacillus subtilis, Staphylococcus aureus] and fungus [Candida albicans].
80% DMSO are used as solvent to dissolve compound 1a to 1i to 10 (μg/ml).

Conclusions:-
A series of cyanuric chloride derivatives were prepared and tested for their in vitro antibacterial activity against the four strains of bacteria (gram +ve, gram –ve). Three compounds of the obtained series showed high in vitro antimicrobial activity. Compound (1c, 1e, 1g) showed excellent activity against Staphylococcus aureus. Whereas compound 1c has excellent activity against B. subtilis, P. aeruginosa, C. albicans.

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Reference:-
24. Dr. Hancock, www.cmdr.ubc.ca/bobh