

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** prove to be effective with MIC (mg ml^{-1}), among them **1c**, **1e**, **1g** showed excellent activity against a panel of microorganisms. The newly synthesized compounds were characterized using IR, $^1\text{H-NMR}$ and elemental analysis.

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-protozoals^[1], anticancer agents^[2], estrogen receptor modulators^[3], antimalarials^[4], cyclin-dependent kinase modulators^[5], and antimicrobials^[6]. Cyanuric chloride, an inexpensive, easily available reagent, of low toxicity and less corrosive than other similar reactants, has been widely used in organic reactions^[7]. In the present research, 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. An important class of compounds having anticancer, antitumor, antiviral and antifungal activity consists of substituted s-triazine

derivatives. These compounds have been used in the treatment of depression and hence gained considerable significance. These are valuable bases for estrogen receptor modulators^[8] and also used as bridging agents to synthesize herbicides and in the production of drugs or polymers^[9].

1,3,5-Triazine derivatives^[10] have displayed a broad range of biological activities including cytotoxic activities^[11-13], antiangiogenic activity by targeting either VEGF-R2 (KDR)^[14] or direct modulation of Tie-2 tyrosine kinase phosphorylation^[15], antiparasitic activities^[16,17], and glucocerebrosidase inhibition with potential as chemical chaperones for Gaucher disease^[18]. Cyanuric chloride derivatives have been studied for decades, especially its amino derivatives. It is generally accepted that the first chlorine of cyanuric chloride can be easily

substituted by NH₂-group at 0–5 °C, the second one at 30–50 °C, and the third one typically above 80 °C, which depends on the activity of amine nucleophiles^[19].

1,2,4 – Triazole have wide range of biological activities such as anti bacterial^[20], anti cancer^[21], anti tubercular^[22], anti HIV^[23] and anti depressant activity, anti tumor^[24] and anti viral^[24] activity, anti hypertensive^[25] activity, analgesic and anti inflammatory^[26] activity.

Thiourea derivatives possess antibacterial^[27], hypnotic antitubercular and possible anticonvulsant activities. It also represent a new class of human immuno deficiency virus type (HIV-1), non-nucleoside reverse transcriptase (NNRT) inhibitors^[28], found as antagonist^[29], and high density lipoprotein (HDL) elevating agents^[30]. Over the last few years, the thiourea moiety has been of interest to design molecules as receptor antagonists, as natural product mimics or as synthetic intermediates to amidines or guanidines.^[31] Thiourea not only confers antibacterial, antitubercular or antileprotic activity, but has also been reported to possess antifungal as well as antiviral properties.^[32]

Urea derivatives are reported to possess antibacterial^[33], antimicrobial antifungal, anticancer^[34] and anticonvulsant^[35] activities. Urea derivatives possess wide therapeutic activities such as antithyroidal^[36], hypnotic and anesthetic^[37], antibacterial^[38], diuretic^[39] and anthelmintics.

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-METHOXYPHENYL)THIOUREA: (A)

To a stirred solution of cyanuric chloride (0.1 mole, 18.4 g.) in acetone (100 ml) at 0-5⁰C, 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 0-5⁰C 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.

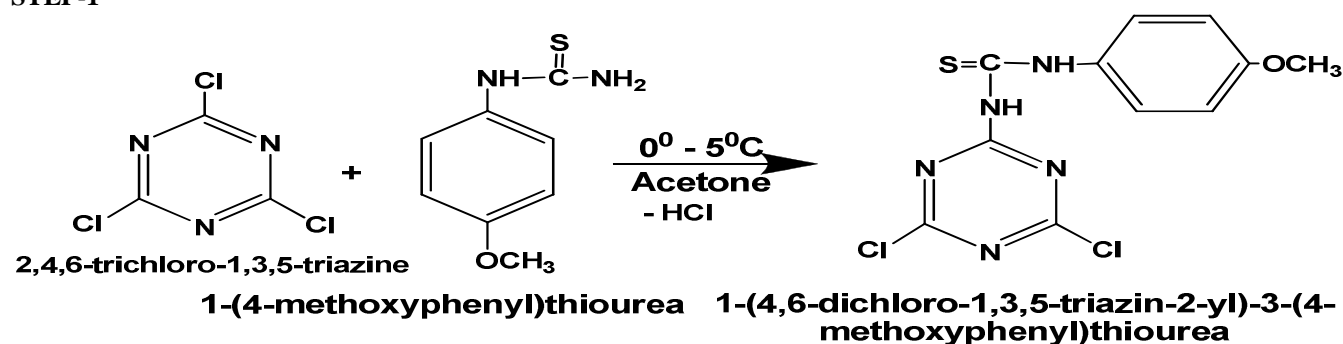
STEP-3

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.

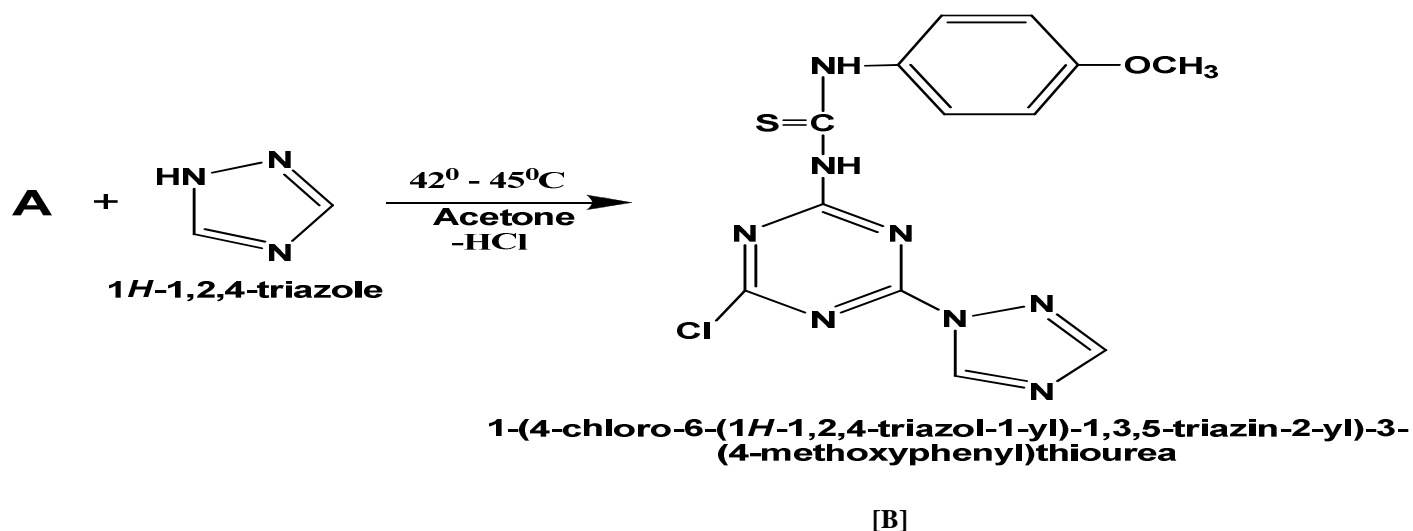
ROUTE OF SYNTHESIS :-

STEP-1

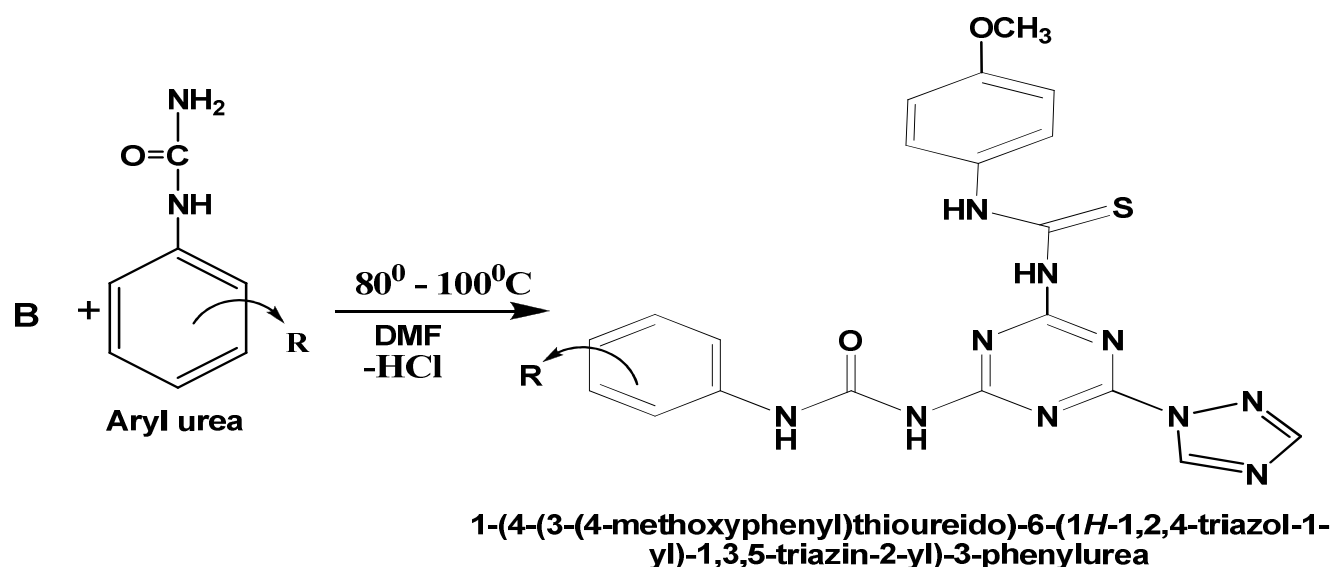


[A]

STEP-2



STEP-3



WHERE R = given in below table.

Table 1 Physical data of synthesized compounds:-

Sr. No.	R	Mol. Formula	Mol. Weight	M.P. °C	Yield %
1a	H	C ₂₀ H ₁₈ N ₁₀ O ₂ S	462.49	120 ⁰	60
1b	2-OCH ₃	C ₂₁ H ₂₀ N ₁₀ O ₃ S	492.51	122 ⁰	61
1c	4-CH ₃	C ₂₁ H ₂₀ N ₁₀ O ₂ S	476.51	190 ⁰	59
1d	4-Cl	C ₂₀ H ₁₇ ClN ₁₀ O ₂ S	496.93	220 ⁰	74
1e	4-OCH ₃	C ₂₁ H ₂₀ N ₁₀ O ₃ S	492.51	140 ⁰	59
1f	2-CH ₃	C ₂₁ H ₂₀ N ₁₀ O ₂ S	476.51	140 ⁰	58
1g	2-Cl	C ₂₀ H ₁₇ ClN ₁₀ O ₂ S	496.93	135 ⁰	62
1h	4-Br	C ₂₀ H ₁₇ BrN ₁₀ O ₂ S	541.38	180 ⁰	60
1i	4-F	C ₂₀ H ₁₇ FN ₁₀ O ₂ S	480.48	175 ⁰	65

Compound (1a): Yield: 60%; m.p. 120⁰C (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-,3⁰ 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) 1170.64 cm⁻¹(-C=S-)1023.14 cm⁻¹(-N-N-str) **¹H-NMR:δ** 8.90(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. 122⁰C (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-,3⁰ amine)1562.70cm⁻¹(-NH-def)1643.16 cm⁻¹(-C=O-) 3311.16 cm⁻¹
(-NH-str)2916.48 cm⁻¹(-OCH₃ str)1177.34cm⁻¹(-C=S-)1033.34 cm⁻¹(-N-N-str) **¹H-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. 190⁰C (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-,3⁰ amine) 1596.6 cm⁻¹(-NH-def)
1643.16cm⁻¹(-C=O-) 3311.16 cm⁻¹(-NH-str) 2916.48 cm⁻¹(-OCH₃ str) 1177.34 cm⁻¹(-C=S-)1308.20 cm⁻¹(-C-
CH₃ str) 1033.34 cm⁻¹(-N-N-str) **¹H-NMR:δ** 8.55(s,2H,-CONH) 10.10(s,2H,-CSNH),3.71(s,3H, -
OCH₃)3.74(s,3H,C-CH₃) 7.32-7.66 (m,10H, Ar-H).

Compound (1d): Yield: 74%; m.p. 220⁰C (dec.); **IR (KBr,cm⁻¹)** : 795 cm⁻¹
(-C=N- s-triazine) 816.34 cm⁻¹(1,4 Di sub. in benzene) 1418.09 cm⁻¹(>N-,3⁰ amine)1559.90 cm⁻¹(-NH-def)1638.80 cm⁻¹
(-C=O-) 3330.30 cm⁻¹(-NH-str)2890.50 cm⁻¹(-OCH₃ str)1180.80cm⁻¹(-C=S-)707 cm⁻¹(-C-Cl-str)1029.34 cm⁻¹
(-N-N-str) **¹H-NMR:δ** 8.64(s,2H,-CONH) 10.22(s,2H,-CSNH),3.69(s,3H, -OCH₃)7.40-7.78 (m,10H, Ar-H).

Compound (1e): Yield: 59%; m.p. 140⁰C (dec.); **IR (KBr,cm⁻¹)** : 804 cm⁻¹
(-C=N- s-triazine) 812.40 cm⁻¹(1,4 Di sub. in benzene) 1416.30 cm⁻¹(>N-,3⁰ amine)1569.70 cm⁻¹(-NH-def)1651.60 cm⁻¹
(-C=O-) 3334.11 cm⁻¹(-NH-str)2930.30 cm⁻¹(-OCH₃ str)1169.64cm⁻¹(-C=S-)1028.71 cm⁻¹(-N-N-str) **¹H-NMR:δ** 8.90(s,2H,-CONH)
10.90(s,2H,-CSNH),3.80(s,6H, -OCH₃)7.50-8.18 (m,10H, Ar-H).

Compound (1f): Yield: 58%; m.p. 140⁰C (dec.); **IR (KBr,cm⁻¹)** : 795.65 cm⁻¹
(-C=N- s-triazine) 819.40 cm⁻¹(1,4 Di sub. in benzene)1418.30 cm⁻¹(>N-,3⁰ amine) 1584.20 cm⁻¹(-NH-def) 1637.60cm⁻¹
(-C=O-) 3320.65 cm⁻¹(-NH-str) 2898.28 cm⁻¹(-OCH₃ str) 1169.70 cm⁻¹(-C=S-)1316.60 cm⁻¹(-C-CH₃ str) 1040.85 cm⁻¹
(-N-N-str) **¹H-NMR:δ** 8.60(s,2H,-CONH) 9.95(s,2H,-CSNH),3.66(s,3H, -OCH₃)3.60(s,3H,C-CH₃) 7.22-7.90 (m,10H, Ar-H).

Sr.No &	Minimum Inhibitory Concentration ($\mu\text{g/ml}$)
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Compound (1g): Yield: 62%; m.p. 135⁰C (dec.); **IR (KBr,cm⁻¹)** : 789.30 cm⁻¹ (-C=N- s-triazine) 825.30 cm⁻¹(1,4 Di sub. in benzene) 1430.10 cm⁻¹(>N-,3⁰ amine)1565.60 cm⁻¹(-NH-def)1650.70 cm⁻¹ (-C=O-) 3310.80 cm⁻¹(-NH-str)2900.50 cm⁻¹ (-OCH₃ str)1170.60cm⁻¹(-C=S-)717 cm⁻¹(-C-Cl-str)1036.74 cm⁻¹ (-N-N-str) **¹H-NMR:** δ 8.70(s,2H,-CONH) 10.29(s,2H,-CSNH),3.75(s,3H, -OCH₃)7.50-7.84 (m,10H, Ar-H).

Compound (1h): Yield: 60%; m.p. 180⁰C (dec.); **IR (KBr,cm⁻¹)** : 797.40 cm⁻¹ (-C=N- s-triazine) 829.90 cm⁻¹(1,4 Di sub. in benzene) 1420.10 cm⁻¹(>N-,3⁰ amine)1560.50cm⁻¹ (-NH-def)1654.90 cm⁻¹ (-C=O-) 33170.55 cm⁻¹(-NH-str)2920.45 cm⁻¹ (-OCH₃ str) 1162.70cm⁻¹(-C=S-)692 cm⁻¹(-C-Br-str) 1028.47 cm⁻¹ (-N-N-str) **¹H-NMR:** δ 8.67(s,2H,-CONH) 10.75(s,2H,-CSNH),3.66(s,3H,-OCH₃)7.42-7.74(m,10H, Ar-H).

Compound (1i): Yield: 65%; m.p. 175⁰C (dec.); **IR (KBr,cm⁻¹)** : 790.30 cm⁻¹ (-C=N- s-triazine) 820.40 cm⁻¹(1,4 Di sub. in benzene) 1435.10 cm⁻¹(>N-,3⁰ amine)1561.50 cm⁻¹(-NH-def)1642.60 cm⁻¹ (-C=O-) 3300.75 cm⁻¹(-NH-str)2914.50 cm⁻¹ (-OCH₃ str)1160.60cm⁻¹(-C=S-)1055 cm⁻¹(-C-F-str) 1040.10 cm⁻¹ (-N-N-str) **¹H-NMR:** δ 8.75(s,2H,-CONH) 10.40(s,2H,-CSNH),3.85(s,3H, -OCH₃)7.70-7.94 (m,10H, Ar-H).

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^[40].The antimicrobial activity of all the compounds was studied 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($\mu\text{g/ml}$).

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*.

		R	Gram positive bacteria		Gram negative bacteria		Fungus
			S. aureus	B. subtilis	E. coli	P. aeruginosa	C. albicans
1.	1a	H	125-250	250-500	125-250	125-250	125-250
2.	1b	2-OCH ₃	125-250	125-250	125-250	250-500	125-250
3.	1c	4-CH ₃	125-250	31.25-62.5	125-250	31.25-62.5	31.25-62.5
4.	1d	4-Cl	125-250	250-500	125-250	125-250	125-250
5.	1e	4-OCH ₃	62.5-125	125-250	125-250	125-250	125-250
6.	1f	2-CH ₃	125-250	125-250	125-250	125-250	125-250
7.	1g	2-Cl	62.5-125	125-250	125-250	125-250	250-500
8.	1h	4-Br	125-250	125-250	125-250	125-250	250-500
9.	1i	4-F	125-250	125-250	125-250	125-250	125-250
Ampicillin		-----	250	100	100	100	-----
Nystatin		-----	---	---	---	---	100

Note: The higher value in given range is MIC but practically we can find out exact value from the given range by using different dilutions.(by secondary screening).

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