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Synthesis and Antimicrobial Evaluation of A Novel Series of Some S- Triazine Moiety

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ABSTRACT

Some new substituted 1,3,5 triazine with cyclohexyl amine and substituted thiourea N-(3,4,5-trimethoxy-benzylidino)-4-amino benzoyl hydrazone were synthesized and evaluated for their in vitro antimicrobial activity against Gram positive and Gram negative strains using a micro dilution procedure. Synthesized compounds NKSD 36 to 47 prove to be effective with MIC (mg ml^{-1}), among them NKSD 36,43,46,47 showed excellent activity against a panel of microorganisms. The newly synthesized compounds were characterized using IR,^{1}H-NMR.

Keywords: N-(3,4,5-trimethoxy-benzylidino)-4-amino benzoyl hydrazone, cyclohexyl amine Substituted thiourea, Cyanuric chloride and Antimicrobial activity.

INTRODUCTION

During the past decade, there has been a substantial rise in the number of antibiotic-resistant infectious organisms. Antimicrobial resistance is important because of its effect on the success and cost of antimicrobial treatment and on the treatment of patients in both the hospital and the community. There are few new antimicrobial compounds on the horizon, because many major pharmaceutical companies are no longer involved in the discovery of antimicrobial drugs. To that end, the principles of and programs for reducing the spread of resistant pathogens and of optimizing the efficacy of currently available antimicrobial agents are of interest to many clinicians and medicinal chemists[1].

S-Triazine derivatives represent an important class of compounds due to their potential to be biologically active. They are known to be anti-protozoals[2], anticancer agents[3], estrogen receptor modulators[4], antimalarials[5], cyclindependent kinase modulators[6], and antimicrobials[7]. Cyanuric chloride, an inexpensive, easily available reagent, of low toxicity and less corrosive than other similar reactants, has been widely used in organic reactions[8]. 1,3,5-triazines (or s-triazine) are a class of compounds well known for a long time and still continue the object of considerable interest mainly due to their application in different fields, including the production of herbicides and polymer photostabilizers[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] . Thiourea derivatives have been suggested for potential therapeutic agents by several investigators. They have used as antibacterial [19], anticancer [20,21], antimalarial [22], antitubercular [23], antiviral [24], anti- HIV [25] and anti-nociceptive [26], Looking to the large amount of work has been carried out so far; the field is wide open and need extensive investigation to understand the biological activities. Attention has been devoted to the development of safe and effective heterocycles that display noticeable medicinal activities. New challenging problems are multi-drug resistant microorganisms, which pose to the medicinal chemist. Based on this background and continuation of our research program on the synthesis new compounds with cyanuric chloride derivatives; we have decided to explore new biologically active compounds.

We have already reported some of our work on the synthesis and biological properties of various cyanuric chloride derivatives[27-31]. These compounds were screened for their antibacterial and antifungal activities and it was found that some of them have moderate to good biological properties. The biological significance of this class of compounds impelled us to continue working on the synthesis of new cyanuric chloride derivatives.

MATERIALS AND METHODS

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.^{1}H NMR spectra on a Varian 400 FT MHz NMR instrument at using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal reference.Antimicrobial activity was performed at Micro Care Laboratory, Surat according to the protocol mentioned in the Section 2.3 antimicrobial screening using broth dilution method [32].

Chemistry

Step 1: Preparation of 2-[N-(3,4,5-trimethoxy-benzylidino)-benzoyl hydrazonyl]-[amino-4- yl]-4,6-di chloro-1,3,5-triazine :

Preparation of the Schiff Base N-(3,4,5-trimethoxy-benzylidino)–4– amino benzoyl hydrazone **(Comp A)**:

1. Preparation of methyl-4-aminobezoate: In a round bottomed (RB) flask of 500 mL 13.7 (or 0.1M) gram of 4-aminobenzoic acid is mixed with methanol (100 mL) and 10 mL conc. HCl and heated at reflux for around 3 h till the completion of esterification. The mixture is cooled to room temperature and kept overnight.

2. Preparation of 4-amino benzoic acid hydrazide: To the separated solid white product around 10 mL (or 0.2M) of hydrazine hydrate is added and the resulting mixture is again heated at reflux temperature for another four to 5 h. The progress of the reaction is monitored through TLC at times. After cooling the product is poured into water and filtered at the pump. This prepared compound is purified and is now ready for the next step.

3. Preparation of the Schiff Base N - (3,4,5-trimethoxy-benzylidino) – 4– amino benzoyl hydrazone: From the above compound 1.51g (or 0.01M) of it is mixed with 0.01 mol of different aromatic aldehydes. Every resulting mixture in methanol is refluxed for 6 to 8 h till the condensation completes and the Schiff base is formed. The resulting mixture is poured into water and the product separates. The compounds obtained for each and every aldehydes under consideration are purified and these different Schiff bases are now ready for the final step.

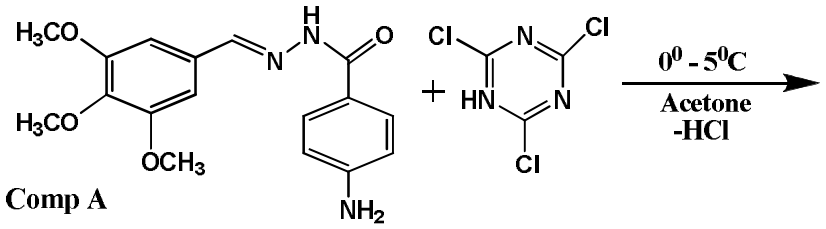
Now prepared the title compound as described: In a conical flask 0.1M of s-triazine in acetone is mixed with 0.1M of N-(3,4,5-trimethoxy-benzylidino)-4-amino benzoyl hydrazone(**Comp A**) and stirred continuously for 5 to 6 h at a temperature range of 0-5^{o}C. During the process 10% solution of $NaHCO_3$ is added drop wise at times to keep the medium neutral. The progress of the reaction is monitored by using

TLC at suitable intervals. After the completion of the reaction the reaction mixture is poured into crushed ice and after sometime filtered at the pump to get the above titled product. The product is purified by recrystallisation from absolute alcohol. It is now ready for the next step of reaction.

Step 2: Preparation of 2-[N-(3,4,5-trimethoxy benzylidino)-benzoyl hydrazonyl]-(amino-4-yl)-4-(cyclohexyl amino)-6-chloro-1,3,5-triazine: In a conical flask of 250 mL 0.1M of 2-[N-(3,4,5-trimethoxy-benzylidino)-benzoyl hydrazonyl]-[amino-4-yl]-4,6-dichloro-1,3,5-triazine is mixed with cyclohexyl amine in acetone. The mixture is stirred well and heated for 5-6 h maintaining the temperature between 45-55^{o}C. To keep the solution neutral, 10% solution of $NaHCO_3$ is added drop wise at times along with the checking of the progress of the reaction. After the completion of the reaction, the reaction mixture is put into ice-cold water with stirring. The product separated is filtered at the pump, dried and purified from absolute alcohol to get the above titled product. Melting point and yield are noted. The product is now ready for the third step of reactions.

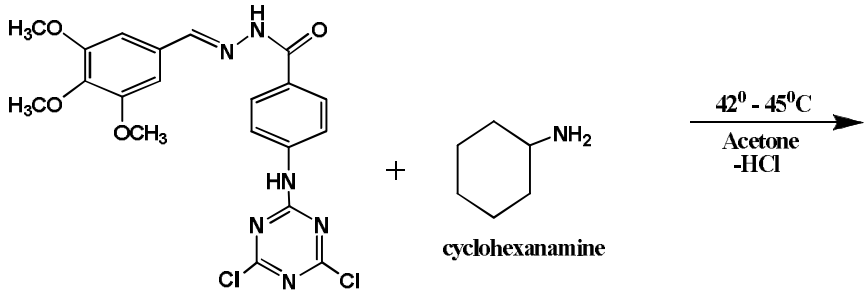
Step 3: Preparation of 2-[N-(3,4,5-trimethoxybenzylidino) –(benzoylhydrazinoyl)-amino- 4-yl]-4-(4-cyclohexylamino)-6-(arylthioureido)-1,3,5-triazine : 0.001M of the above product obtained in step-2 is mixed with 0.001 mol of different thioureas in different round bottom flasks in 1,4-dioxane as solvent. (Different thioureas are already prepared whose preparation procedure is given earlier to this series). The fluxes are heated at reflux temperature achieved gradually. Reflux is done for 7 to 8 h as per convenience so that the reactions almost complete. A 10% solution of $NaHCO_3$ is added drop wise intermittently to keep the reaction mixture neutral. The progress of the reactions is monitored at times. After the completion of the reaction, the reaction mixtures are cooled and poured into ice-cold water and the product of above title in this step separates out from every individual R.B flask. Different products are obtained from different thioureas, and these are dried and purified by recrystallisation from absolute alcohol.

Route of Synthesis



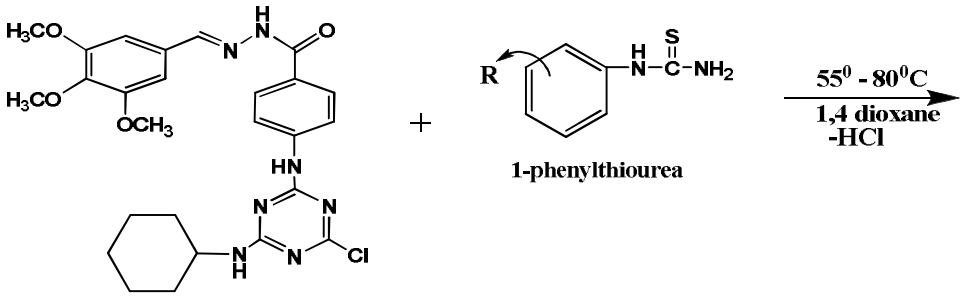
Comp A **2,4,6-trichloro-1,3,5-triazin-1-ium**

(*E*)-4-amino-*N*'-(3,4,5-trimethoxybenzylidene)benzohydrazide

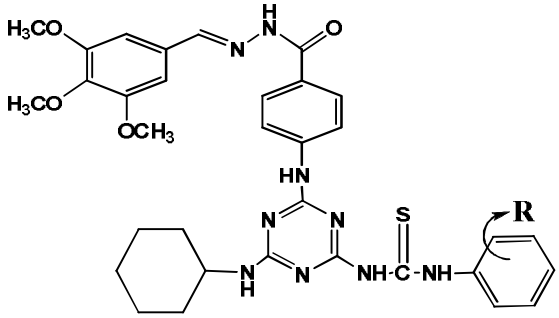


cyclohexanamine

2-[N-(3,4,5-trimethoxy-benzylidino)-benzoyl hydrazonyl]-[amino-4- yl]-4,6-dichloro-1,3,5-triazine



2-[N-(3,4,5-trimethoxy benzylidino)-benzoyl hydrazonyl]-(amino-4-yl)-4-(cyclohexyl amino)-6-chloro-1,3,5-triazine



(*E*)-1-(4-(cyclohexylamino)-6-(4-(2-(3,4,5-trimethoxybenzylidene)hydrazinecarbonyl)phenylamino)-1,3,5-triazin-2-yl)-3-phenylthiourea

Various R = 2-Methoxy --$NKSD_{35}$,3-Methoxy -- $NKSD_{36}$,2-Methyl --$NKSD_{37}$,3-Methyl --$NKSD_{38}$, 4-Methyl --$NKSD_{39}$,2-Chloro --$NKSD_{40}$,3-Chloro --$NKSD_{41}$,4-Chloro --$NKSD_{42}$,2-Nitro -- $NKSD_{43}$, 3-Nitro -- $NKSD_{44}$,4-Nitro -- $NKSD_{45}$, 2,4-Dinitro -- $NKSD_{46}$,2-Chloro-4-nitro --$NKSD_{47}$.

RESULTS AND DISCUSSION

The Properties of the prepared compounds are studied and given below.

Compound NKSD35 : Yield: 72%; m.p. 211^{0}C (dec.); **IR (KBr,cm^{-1}) :** 1128.27, 1415.13 cm^{-1} (C=S of thiourea), 1244.10 cm^{-1}(Aryl C-O str of (Ar-O-R)),1340 cm^{-1}(Ar-N< stre),1460.25 cm^{-1}(C- H clycloalkane bending), 1527.99 cm^{-1}(N-H 2^{o}amide,deforming), 1583.39 cm^{-1}(C=N),1618 cm^{-1}(C=O 2^{o}Amide),2932.64 cm^{-1}(Aldehyde-ammonia),3002.69 cm^{-1}(C-H Ar),3114.39 cm^{-1}(N-H 2^{o}Amide).**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 3.84(s,12H,-OCH_3),7.27(db,2H,-CH at Ar ring),3.87(s,1H, -CH=N),7.09(s,3H,-C-NH), 7.92(db,2H,-C=CH),6.94(db,2H,-C=CH),3.96(S,2H,-NH-C=), 1.25(S,10H, -CH_2 in cyclo hexane ring), 1.38(t,1H,-CH-CH_2), 7.27 (db,1H,CH=CH),Elem.Anal. for $C_{34}H_{39}O_5N_9S$: cal.C,59.51%, H 5.65%,N 18.40% and found C 59.56%, H 5.69%, N 18.39%.

Compound NKSD36 : Yield: 72%; m.p. 211^{0}C (dec.); **IR (KBr,cm^{-1}) :** 1135, 1410.23 cm^{-1} (C=S of thiourea), 1240.11 cm^{-1}(Aryl C-O str of (Ar-O-R)),1344 cm^{-1}(Ar-N< str),1466 cm^{-1}(C- H clycloalkane bending), 1530 cm^{-1}(N-H 2^{o}amide,deforming), 1580 cm^{-1}(C=N),1620 cm^{-1}(C=O 2^{o}Amide),2938.44 cm^{-1}(Aldehyde-ammonia), 3012.55 cm^{-1}(C-H Ar),3104.19 cm^{-1} (N-H 2^{o}Amide). **^{1}H NMR (400 MHz,DMSO-d$_6$) δ (ppm):** 3.82(s,12H,-OCH_3),7.48(db,2H,-CH at Ar ring),3.84(s,1H, -CH=N),7.10(s,3H,-C-NH), 7.92 (db,2H,-C=CH),6.91(db,2H,-C=CH), 3.95(S,2H,-NH-C=), 1.26 (S,10H,-CH_2 in cyclohexane ring), 1.44 (t,1H,-CH-CH_2), 7.50 (db,2H,CH=CH),6.90(db,2H,-O-C-CH),Elem.Anal. for $C_{34}H_{39}O_5N_9S$: cal. C, 59.50%, H 5.65%, N 18.41% and found C 59.56%, H 5.69%, N 18.39%.

Compound NKSD37 : Yield: 81%; m.p. 189^{0}C (dec.); **IR (KBr,cm^{-1}) :** 1127, 1366.40 cm^{-1} (C=S of thiourea), 1240.42 cm^{-1}(Aryl C-O str of (Ar-O-R)),1336 cm^{-1}(Ar-N< stre),1454.37 cm^{-1}(C- H clycloalkane bending), 1515.34 cm^{-1}(N-H 2^{o}amide,deforming), 1582.97 cm^{-1}(C=N),1616.58 cm^{-1} (C=O 2^{o}Amide),3339 cm^{-1}(Aldehyde-ammonia),3070 cm^{-1}(C-H Ar),3259.23 cm^{-1} (N-H 2^{o}Amide), 2933.63cm^{-1}(-CH_2 str of alkane). **^{1}H NMR (400 MHz,DMSO-d_6) δ (ppm):** 3.86(s,9H,-OCH_3), 7.50(s,2H,-CH at Ar ring), 3.86 (s,1H,-CH=N),7.09(s,3H,-C-NH),7.99(db,2H,-C=CH), 7.10 (db,2H,-C=CH), 3.88 (S,2H,-NH-C=), 1.43 (S,10H,-CH_2 in cyclohexane ring), 1.25(t,1H,-CH-CH_2), 7.54 (db,1H,CH=CH),2.41(s,3H,-C-CH_3). Elem.Anal. for $C_{34}H_{39}O_4N_9S$: cal.C,60.93%, H 5.81%, N 18.86%, and found C 60.98%, H 5.83%, N 18.83%.

Compound NKSD38 : Yield: 69%; m.p. 179^{0}C (dec.); **IR (KBr,cm^{-1}) :** 1126.47, 1340.41 cm^{-1} (C=S of thiourea), 1239.95 cm^{-1}(Aryl C-O str of (Ar-O-R)),1340.41 cm^{-1}(Ar-N< stre),1450 cm^{-1}(C- H clycloalkane bending), 1514.33 cm^{-1}(N-H 2^{o}amide,deforming), 1584.63 cm^{-1}(C=N),1694.00 cm^{-1}(C=O 2^{o}Amide), 326 0.98 cm^{-1}(Aldehyde-ammonia),3009.63 cm^{-1}(C-H Ar),3260.98 cm^{-1} (N-H 2^{o}Amide). 2933.63cm^{-1}(-CH_2 str of alkane). **^{1}H NMR (400 MHz,DMSO-d_6) δ (ppm):** 3.80 (s,9H,-OCH_3), 7.30(db,2H,-CH at Ar ring),3.90(s,1H, -CH=N),7.13(s,3H,-C-NH),7.87(db,2H,-C=CH), 6.89 (db,2H,-C=CH), 3.90(S,2H,-NH-C=), 1.32(S,10H,-CH_2 in cyclohexane ring), 1.42 (t,1H,-CH-CH_2), 7.35 (db,1H,CH=CH), 2.37 (s,3H,-C-CH_3).Elem.Anal. for $C_{34}H_{39}O_4N_9S$: cal. C 60.92%, H 5.81%, N 18.80%, and found C 60.98%, H 5.83%, N 18.83%.

Compound NKSD39 : Yield: 80%; m.p. 190^{0}C (dec.); **IR (KBr,cm^{-1}) :** 1128.27, 1415.13 cm^{-1} (C=S of thiourea), 1244.10 cm^{-1}(Aryl C-O str of (Ar-O-R)),1340 cm^{-1}(Ar-N< stre),1460.25 cm^{-1}(C- H clycloalkane bending), 1534.79 cm^{-1}(N-H 2^{o}amide,deforming), 1573.90 cm^{-1}(C=N),1610.20 cm^{-1}(C=O 2^{o}Amide) , 2972.44 cm^{-1}(Aldehyde-ammonia),3001.09 cm^{-1}(C-H Ar),3104.39 cm^{-1} (N-H 2^{o}Amide), 2973.53cm^{-1}(-CH_2 str of alkane). **^{1}H NMR (400 MHz,DMSO-d_6) δ (ppm):** 3.85 (s,9H,-OCH_3), 7.44(db,2H,-CH at Ar ring), 3.85(s,1H, -CH=N),7.24(s,3H,-C-NH),7.93(db,2H,-C=CH),7.10(db,2H,-C=CH), 3.91(S,2H,-NH-C=), 1.43(S,10H,-CH_2 in cyclohexane ring), 1.25(t,1H,-CH-CH_2), 7.57 (db,1H,CH=CH), 2.34(s,3H,-C-CH_3).Elem.Anal. for $C_{33}H_{39}O_4N_9S$: cal.C,60.94%, H 5.81%,N 18.85%, and found C 60.98%, H 5.83%, N 18.83%.

Compound NKSD40 : Yield: 58%; m.p. 186^{0}C (dec.); **IR (KBr,cm^{-1}) :** 717.86 cm^{-1}(-C-Cl- str in Ar ring),1130.47, 1410.43 cm^{-1} (C=S of thiourea), 1250.58 cm^{-1}(Aryl C-O str of (Ar-O-R)),1345.11 cm^{-1}(Ar-N< stre),1480.59 cm^{-1}(C-H clycloalkane bending),1544.54 cm^{-1}(N-H 2^{o}amide,deforming), 1600.09 cm^{-1}(C=N), 1620.35 cm^{-1} (C=O 2^{o}Amide),2942.84 cm^{-1}(Aldehyde-ammonia),3012.88 cm^{-1}(C-H Ar),3125.42 cm^{-1} (N-H 2^{o}Amide). **^{1}H NMR (400 MHz,DMSO-d_6) δ (ppm):** 3.80(s,9H,-OCH_3),7.15(db,2H,-CH at Ar ring), 3.92(s,1H, -CH=N),7.15(s,3H,-C-NH),7.85(db,2H,-C=CH),6.80(db,2H,-C=CH), 3.99(S,2H,-NH-C=), 1.30(S,10H,-CH_2 in cyclohexane ring), 1.30(t,1H,-CH-CH_2), 7.35 (db,1H,CH=CH),Elem.Anal. for $C_{33}H_{39}O_4N_9SCl$: cal. C 56.01%, H 5.48%, N 17.80%, and found C 56.05%, H 5.52%, N 17.83%.

Compound NKSD41 : Yield: 55%; m.p. 169^{0}C (dec.); **IR (KBr,cm^{-1}) :** 725.55 cm^{-1}(-C-Cl- str in Ar ring),1120.41, 1436.25 cm^{-1} (C=S of thiourea), 1259.54 cm^{-1}(Aryl C-O str of (Ar-O-R)),1370.32 cm^{-1}(Ar-N< stre),1485.32 cm^{-1}(C- H clycloalkane bending), 1550.44cm^{-1} (N-H 2^{o}amide,deforming), 1590.99 cm^{-1}(C=N),1645.45cm^{-1} (C=O 2^{o}Amide), 2992.51 cm^{-1}(Aldehyde-ammonia),3015.54 cm^{-1}(C-H Ar), 3140.11 cm^{-1} (N-H 2^{o}Amide). **^{1}H NMR (400 MHz,DMSO-d_6) δ (ppm):** 3.81(s,9H,-OCH_3), 7.20 (db,2H,-CH at Ar ring),3.94(s,1H,-CH=N),7.01(s,3H,-C-NH),7.99(db,2H,-C=CH),6.99(db,2H,-C=CH), 3.98(S,2H,-NH-C=), 1.20 (S,10H,-CH_2 in cyclohexane ring), 1.32(t,1H,-CH-CH_2), 7.36 (db,1H,CH=CH),Elem.Anal. for $C_{33}H_{39}O_4N_9SCl$: cal. C 56.01%, H 5.49%, N 17.79%, and found C 56.05%, H 5.52%, N 17.83%.

Compound NKSD42 : Yield: 63%; m.p. 180^{0}C (dec.); **IR (KBr,cm^{-1}) :** 710.46 cm^{-1}(-C-Cl- str in Ar ring),1137.87, 1422.36 cm^{-1} (C=S of thiourea), 1251.16 cm^{-1}(Aryl C-O str of (Ar-O-R)),1344 cm^{-1}(Ar-N< stre),1466.35 cm^{-1}(C- H clycloalkane bending), 1539.64 cm^{-1}(N-H 2^{o}amide,deforming), 1589.44 cm^{-1}

^{1}(C=N),1622.25 cm^{-1}(C=O 2^{o}Amide),2940.12 cm^{-1}(Aldehyde-ammonia),3016.19 cm^{-1}(C-H Ar),3121.21 cm^{-1} (N-H 2^{o}Amide). **^{1}H NMR (400 MHz,DMSO-d_6) δ (ppm):** 3.78(s,9H,-OCH_3),7.10(db,2H,-CH at Ar ring), 3.79(s,1H, -CH=N),7.15(s,3H,-C-NH),7.96(db,2H,-C=CH),6.90(db,2H,-C=CH), 3.99(S,2H,-NH-C=), 1.33(S,10H,-CH_2 in cyclohexane ring), 1.30 (t,1H,-CH-CH_2), 7.39 (db,1H,CH=CH),Elem.Anal. for $C_{33}H_{39}O_4N_9SCl$: cal. C 56.2%, H 5.50%, N 17.80%, and found C 56.05%, H 5.52%, N 17.83%.

Compound NKSD43 : Yield: 71%; m.p. 203^{0}C (dec.); **IR (KBr,cm^{-1}) :** 1127.32, 1416.93 cm^{-1} (C=S of thiourea), 1240.11 cm^{-1}(Aryl C-O str of (Ar-O-R)),1345 cm^{-1}(Ar-N< stre),1466.65 cm^{-1}(C- H clycloalkane bending),1536.52 cm^{-1}(N-H 2^{o}amide,deforming),1555.55cm^{-1}(-NO_2-str),1583.39 cm^{-1}(C=N), 1623.25 cm^{-1}(C=O 2^{o}Amide),2935.36 cm^{-1}(Aldehyde-ammonia),3021.21 cm^{-1}(C-H Ar),3122.41 cm^{-1} (N-H 2^{o}Amide). **^{1}H NMR (400 MHz,DMSO-d_6) δ (ppm):** 3.75(s,9H,-OCH_3), 7.40 (db,2H,-CH at Ar ring), 3.79(s,1H, -CH=N),7.14(s,3H,-C-NH),7.94(db,2H,-C=CH),6.90(db,2H,-C=CH), 3.90(S,2H,-NH-C=), 1.33(S,10H,-CH_2 in cyclohexane ring), 1.42(t,1H,-CH-CH_2), 7.31 (db,1H,CH=CH),Elem.Anal. for $C_{33}H_{39}O_6N_{10}S$: cal. C 56.30%, H 5.51%, N 19.87% and found C 56.33%, H 5.55%, N 19.91%.

Compound NKSD44 : Yield: 61%; m.p. 191^{0}C (dec.); **IR (KBr,cm^{-1}) :** 1144.88, 1434.33 cm^{-1} (C=S of thiourea), 1255.99 cm^{-1}(Aryl C-O str of (Ar-O-R)),1360.21 cm^{-1}(Ar-N< stre),1472.54 cm^{-1}(C- H clycloalkane bending), 1556.87 cm^{-1}(N-H 2^{o}amide,deforming),1564.48 cm^{-1}(-NO_2-str),1580.45 cm^{-1}(C=N),1623.24 cm^{-1}(C=O 2^{o}Amide),2942.14 cm^{-1}(Aldehyde-ammonia),2997.69 cm^{-1}(C-H Ar),3127.39 cm^{-1} (N-H 2^{o}Amide). **^{1}H NMR (400 MHz,DMSO-d_6) δ (ppm):** 3.77(s,9H,-OCH_3),7.38(db,2H,-CH at Ar ring), 3.92(s,1H, -CH=N),7.21(s,3H,-C-NH),7.82(db,2H,-C=CH),6.84(db,2H,-C=CH), 3.90(S,2H,-NH-C=), 1.31(S,10H,-CH_2 in cyclohexane ring), 1.44(t,1H,-CH-CH_2), 7.35 (db,1H,CH=CH),Elem.Anal. for $C_{33}H_{39}O_6N_{10}S$: cal. C 56.30%, H 5.53%, N 19.89% and found C 56.33%, H 5.55%, N 19.91%.

Compound NKSD45 : Yield: 74%; m.p. 208^{0}C (dec.); **IR (KBr,cm^{-1}) :** 1131.23, 1420.39 cm^{-1} (C=S of thiourea), 1261.14 cm^{-1}(Aryl C-O str of (Ar-O-R)),1347.69 cm^{-1}(Ar-N< stre),1461.95 cm^{-1}(C- H clycloalkane bending), 1544.71 cm^{-1}(N-H 2^{o}amide,deforming),1547.36 cm^{-1}(-NO_2-str),1590.39 cm^{-1}(C=N),1610.01 cm^{-1}(C=O 2^{o}Amide),2912.14 cm^{-1}(Aldehyde-ammonia),3011.12 cm^{-1}(C-H Ar),3121.39 cm^{-1} (N-H 2^{o}Amide). **^{1}H NMR (400 MHz,DMSO-d_6) δ (ppm):** 3.80(s,9H,-OCH_3),7.31(db,2H,-CH at Ar ring), 3.91(s,1H, -CH=N),7.11(s,3H,-C-NH),7.90(db,2H,-C=CH),6.90(db,2H,-C=CH), 3.90(S,2H,-NH-C=), 1.24(S,10H,-CH_2 in cyclohexane ring), 1.37(t,1H,-CH-CH_2), 7.36 (db,1H,CH=CH),Elem.Anal. for $C_{33}H_{39}O_6N_{10}S$: cal. C 56.31%, H 5.56%, N 19.90% and found C 56.33%, H 5.55%, N 19.91%.

Compound NKSD46 : Yield: 77%; m.p. 194^{0}C (dec.); **IR (KBr,cm^{-1}) :** 1133.47, 1419.11 cm^{-1} (C=S of thiourea), 1235.14 cm^{-1}(Aryl C-O str of (Ar-O-R)),1330.11 cm^{-1}(Ar-N< stre),1450.25 cm^{-1}(C- H clycloalkane bending),1520.99 cm^{-1}(N-H 2^{o}amide,deforming),1541 cm^{-1}(-NO_2-str), 1575.59 cm^{-1}(C=N), 1612.24 cm^{-1}(C=O 2^{o}Amide),2929.74 cm^{-1}(Aldehyde-ammonia),2990.49 cm^{-1}(C-H Ar),3101.54 cm^{-1} (N-H 2^{o}Amide). **^{1}H NMR (400 MHz,DMSO-d_6) δ (ppm):** 3.81(s,9H,-OCH_3),7.35(db,2H,-CH at Ar ring), 3.90(s,1H, -CH=N),7.11(s,3H,-C-NH),7.91(db,2H,-C=CH),6.94(db,2H,-C=CH), 3.96(S,2H,-NH-C=), 1.29(S,10H,-CH_2 in cyclohexane ring), 1.37(t,1H,-CH-CH_2), 7.29 (db,1H,CH=CH),Elem.Anal. for $C_{33}H_{38}O_8N_{11}S$: cal. C 52.82%, H 5.02%, N 20.53% and found C 52.87%, H 5.07%, N 20.56%.

Compound NKSD47 : Yield: 62%; m.p. 201^{0}C (dec.); **IR (KBr,cm^{-1}) :** 708.76 cm^{-1}(-C-Cl- str in Ar ring),1119.59, 1415.13 cm^{-1} (C=S of thiourea), 1237.16 cm^{-1}(Aryl C-O str of (Ar-O-R)),1330.35 cm^{-1}(Ar-N< stre),1450.15 cm^{-1}(C- H clycloalkane bending),1521.24 cm^{-1}(N-H 2^{o}amide,deforming),1542.26 cm^{-1}(-NO_2-str),1573.39 cm^{-1}(C=N),1622.25 cm^{-1}(C=O 2^{o}Amide),2933.54 cm^{-1}(Aldehyde-ammonia),3012.40 cm^{-1}(C-H Ar),3109.39 cm^{-1} (N-H 2^{o}Amide). **^{1}H NMR (400 MHz,DMSO-d_6) δ (ppm):** 3.80(s,9H,-OCH_3) ,7.31(db,2H,-CH at Ar ring),3.91(s,1H,-CH=N),7.13(s,3H,-C-NH),7.96(db,2H,-C=CH),6.90(db,2H,-C=CH),3.90(S,2H,-NH-C=),1.33(S,10H,-CH_2 in cyclohexane ring),1.44(t,1H,-CH-CH_2), 7.39 (db,1H, CH=CH),Elem.Anal.for $C_{33}H_{38}O_6N_{10}SCl$: cal. C 53.64%, H 5.14%,N 18.94% and found C 53.69%, H 5.15%, N 18.98%.

Antimicrobial screening: The in-vitro antibacterial study is carried out against randomly chosen four different bacterial strains containing both gram positive and gram negative types. The different strains chosen are: Escherichia coli, Streptococcus paratyphi-B, Staphylococcus aureus and Bacillus subtilis. The methodology adopted is-

The test compound is first dissolved in suitable media or solvent. DMF has been used in all the cases for present work to keep uniformity. Also, most of the compounds synthesized are water insoluble. 10 mg of the test compound is dissolved in DMF so as to make necessary dilutions as 400, 200, 100, 50, 20, 10, 5, 2 μg ml^{-1} from the stock solutions of the compounds to be tested. In the second phase, three types of controls are ensured to allow the organism to grow in the petridishes.

Antifungal Screening: In vitro antifungal screening is carried out taking Candida albicans(CA), Trichosporon beigelii(TB), Aspergillus fumigatus(AF) and Absidia corymbifera(AC) by using the microdilution broth test. The studies are performed with all the compounds NKSD35 to NKSD47. Among all these the compounds, the compound NKSD39 and NKSD45 is found to be the strongest of all whose MIC is 50 μg ml^{-1} for AF. The standard used here is potassium iodide.

Table 1. Antimicrobial activity

No.	Sr.Nos.	R	Antibacterial activity μg / ml				Antifungal activity	
			E.Coli	S.p.typhi-B	S. aureus	B.subtilis	C.albicans	A.fumigatus
1.	$NKSD_{35}$	2-methoxy	10	200	400	5	200	300
2.	$NKSD_{36}$	4-methoxy	100	500	nil	100	200	200
3.	$NKSD_{37}$	2-methyl	20	200	500	5	300	100
4.	$NKSD_{38}$	3-methyl	20	400	nil	20	300	300
5.	$NKSD_{39}$	4-methyl	200	nil	nil	400	100	50
6.	$NKSD_{40}$	2-chloro	200	400	200	400	200	100
7.	$NKSD_{41}$	3-chloro	200	400	400	nil	50	200
8.	$NKSD_{42}$	4-chloro	500	400	nil	nil	100	300
9.	$NKSD_{43}$	2-nitro	20	50	10	100	40	200
10.	$NKSD_{44}$	3-nitro	20	100	50	200	40	100
11.	$NKSD_{45}$	4-nitro	200	400	200	nil	40	50
12.	$NKSD_{46}$	2,4-dinitro	20	50	20	100	50	100
13.	$NKSD_{47}$	2 chloro 4-nitro	10	20	100	50	50	200
14.	Standard	Benzathine penicillin	Nil	12.5	25	25	*	*
15.	Standard	Potassium Iodide	*	*	*	*	10	10

APPLICATIONS

The newly synthesized Cyanuric chloride derivatives were screened for their antibacterial and antifungal activity and the results revealed that most of the compound showed mild to good activity. Thus, a further structured modification of this scaffold may lead to a promising antibacterial and fungal pharmacophore.

CONCLUSIONS

From the table it is seen that the compound $NKSD_{45}$ is the best compound to be optimized. Comparing NKSD40, NKSD46 and NKSD47 it can be safely concluded that the single chloro- group substitution at any position of phenyl ring almost no effect, but with other substitution like nitro-, it has a role of enhancing inhibitory potency effect. Methoxy group at ortho position has a stronger inhibitory effect

towards E. coli and B. subtilis which is higher than the standard. Safe conclusion from here is that chloro is an auxophore while nitro is a definite pharmacophore. Methyl group at ortho and meta position may be harmful to some strains but mostly less effective.

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