Synthesis and antimicrobial screening of novel azetidinone s-triazine derivatives

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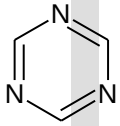
Abstract: Some new confined and synthesized heterocyclic framework, for example Schiff base, azetidinone derivatives and some related compounds have been synthesized by treatment of the s-triazine derivatives with the different substituted aldehyde to form Schiff base derivatives, then chloro acetyl chloride reacted with the Schiff base to synthesis differently substituted azetidinone derivatives. After the synthesis of desired compounds, they were characterized using spectroscopy methods NMR and elemental analysis. Then the antimicrobial activity performed using (MHA) disc diffusion method.

Key words: S-triazine derivatives, Schiff base, Azetidinone derivative, Antimicrobial activity, Disc diffusion method, Characterization by NMR, Elemental analysis.

1. Introduction:

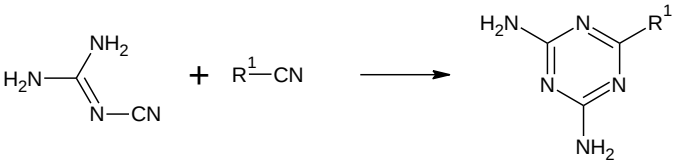
1,3,5-triazine, likewise called s-triazine, is a natural substance compound with the chemical formula (HCN)3[1]. It is a 6-membered heterocyclic as well aromatic compound, one of a few isomeric triazines. S-triazine and its subsidiaries are helpful in an assortment of utilizations.



1,3,5-Triazine (S-Triazine)

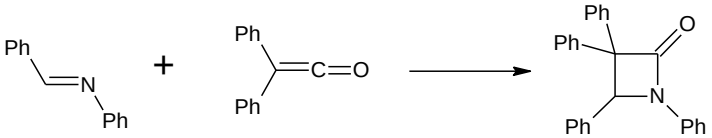
1,3,5-triazines are synthesised by trimerization of specific nitriles, for example, cyanogen chloride (cyanamide).
Benzonitrile and dicyandiamide reacted together to give Benzoguanamine containing 2-amino with 1-phenyl substituents [2]. Adolf pinner reacted alkyl/aryl amide with phosgene known as Pinner triazine amalgamation [3] [4]. The synthesis of 1,3,5 triazine depicted below in scheme-1

Scheme-1

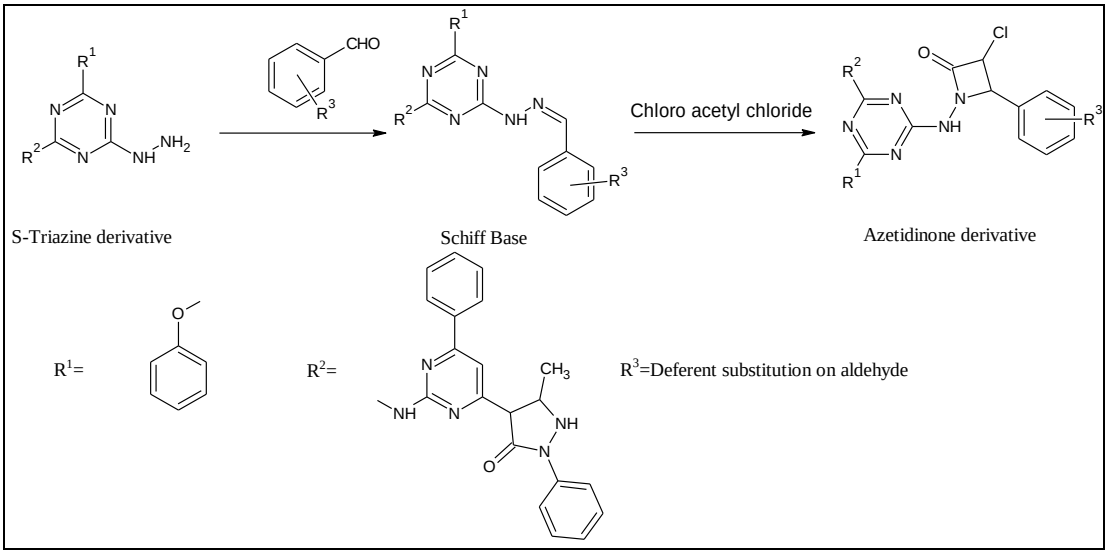


S-triazine derivative

Moreover, our nature provides favourable conditions for microbes to grow rapidly and some of them cause illness which may lead to fatality [5].These micro-organisms are developing resistance day by day, to antimicrobial drugs presently available in the market [6]. Therefore there is need to develop new chemical entities to fight against these fatal microbes. Till date the heterocyclic compounds are proved to be the best choice to fight against these microbial agents Thus it became the first choice for researchers to look upon the heterocyclic nuclear compounds as antimicrobial drugs [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17].
In the present invention we synthesised such s-triazine derivatives and characterised them using spectroscopic techniques i.e. Mass NMR and IR. After that the confirmed compounds were checked for their potentials to fight against both gram positive as well as gram negative bacteria/fungi via Mueller Hinton Agar (MHA) method [18].
S-triazine when treat with substituted aldehydes they give Schiff base which on treatment with chloroacetylchloride in presence of base such as triethlyamine gives Azetidinone ring.
It is four membered beta lactam ring containing nitrogen atom directly attached to carbonyl carbon [19].
Hermann Staudinger in 1907 worked on Schiff base of aniline and benzaldehyde with diphenylketene in a [2+2] cycloaddition depicted in scheme-2[20].
Scheme-2



2. Research Design:



3. Experimental work

3.1 Sep-I: Preparation of Schiff base derivatives

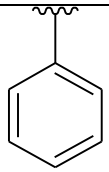
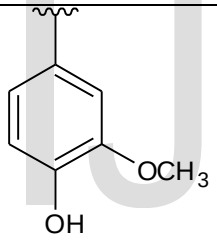
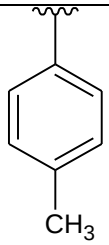
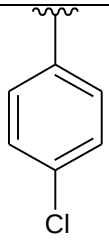
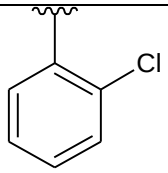
Tri-substituted S-triazine derivative was synthesized via reacting with substituted Aldehyde derivative in denatured alcohol. This mixture was stirred at room temperature. This will gives Schiff base derivative. These derivatives were filtered and washed with hot water and purified in ethyl alcohol.

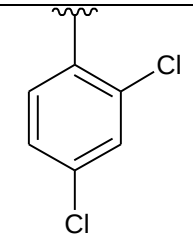
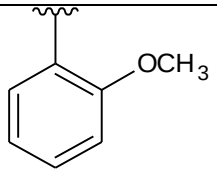
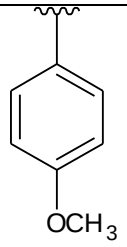
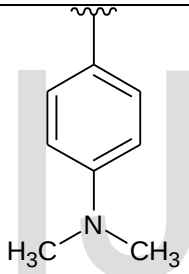
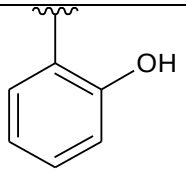
3.2 Step-II: Preparation of azetidinone derivatives.

The Schiff base which were obtained from step-I then reacted with required moles of triethyl amine and chloroacetylchloride in proportionate amount of DMP in solvent 1,4 dioxane. The mixture was refluxed for 4-5 hours into the oil bath to yield azetidinone substituted compounds. The resulted compounds were recrystallized using denatured alcohol or column chromatography.

Following table shows different azetidinone derivatives synthesised by using above method

TABLE: 1: SHOWING DIFFERENT AZETIDINONE DERIVATIVES.

No	Compound	Structure	Molecular formula	C%	H%	O%	N%	Cl%
1	-H		C38H31ClN10O3	64.18	4.39	6.75	19.70	4.99
2	-3-OCH3-4-OH		C39H33ClN10O5	61.86	4.39	10.56	18.50	4.68
3	-4-CH3		C39H33ClN10O3	64.59	4.59	6.62	19.31	4.89
4	-4-Cl		C38H30Cl2N10O3	61.21	4.06	6.44	18.79	9.51
5	-2-Cl		C38H30Cl2N10O3	61.21	4.06	6.44	18.79	9.51

6	**-2-Cl-4-Cl**		**C38H29Cl3N10O3**	**58.51**	**3.75**	**6.15**	**17.96**	**13.63**
7	**-2-OCH3**		**C39H33ClN10O4**	**63.20**	**4.49**	**8.63**	**18.90**	**4.78**
8	**-4-OCH3**		**C39H33ClN10O4**	**63.20**	**4.49**	**8.63**	**18.90**	**4.78**
9	**-4-N(CH3)2**		**C40H36ClN11O3**	**63.70**	**4.81**	**6.36**	**20.43**	**4.70**
10	**-2-OH**		**C38H31ClN10O4**	**62.76**	**4.30**	**8.80**	**19.26**	**4.88**

4. Antimicrobial Activity:

The above synthesized compounds (1-10) screened for their antimicrobial activity via Mueller Hinton Agar (MHA) disc diffusion method. DMSO was used as solvent to dissolve all the compounds. The stock solution was made 20mg/100ml in concentration of drug and checked for their activity at minimum inhibitory concentration (MIC). The activity testes were carried out on both the microbes i.e. (A) bacteria as well as (B) fungi.

A. Bacteria:

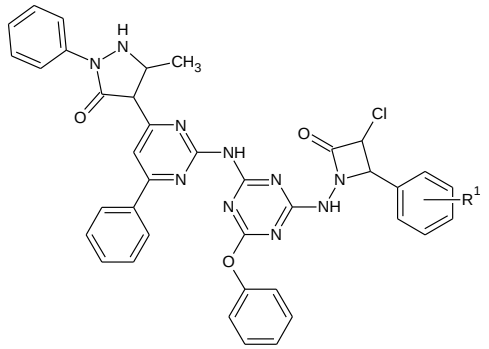
A1.)Staphylococcus aureus MTCC-96 (gram positive),
A2.)Escherichia coli MTCC-442 (gram-negative)
Standard used: Norfloxacin
B. Fungi:
B1.) Aspergillus flavus MTCC-9390 (gram-positive) and
B2.)Aspergillus niger MTCC-282(gram-negative).
Standard used: Amphotericin-B
The resultant data shown in table-2.

TABLE-2: SHOWING ANTIMICROBIAL ACTIVITY OF COMPOUND SYNTHESIZED ABOVE (1-10).

Compound as per table no.-1	Antibacterial activity Inhibition zone (mm)		Antifungal activity Inhibition zone (mm)	
	Staphylococcus aureus MTCC-96	Escherichia coli MTCC-442	Aspergillusflavus MTCC-9390	Aspergillus niger MTCC-282
1	9.2	2.1	3.3	1.2
2	2.7	2.4	3.9	1.2
3	-	-	-	-
4	-	1.2	7.2	9.3
5	8.9	8.6	0.6	0.1
6	11.2	13.6	2.1	2.4
7	7.9	6.4	-	-
8	9.6	9.5	3.1	1.1
9	13.6	12.2	-	-
10	10.9	12.1	-	-
Norfloxacin	18.0	15.0	-	-
Amphotericin-B	-	-	12.9	16.6

5. Characterization by NMR:

NMR Data of the synthesized compounds:



Azetidinone derivative

1. R1= Hydrogen : 1H NMR:

δ 7.3325 (2H, dd), 7.375 (1H, t), 7.303, (2H, dd), 7.215 (1H, t), 7.321 (2H, dd), 7.314 (1H, s), 7.1925 (2H, dd), 5.3 (1H, d), 3.519 (1H, q), 5.571 (1H, d), 7.606 (2H, dd), 7.227 (2H, dd), 7.444 (2H, dd), 7.282 (1H, dd), 4.606 (1H, d), 1.131(3H, d), 7.319 (1H, t), 7.836 (2H, dd).

2. R1= 3-OCH3-4-OH : 1H NMR :
δ 6.794 (1H, dd), 7.332 (2H, dd), 7.375 (1H, t), 7.314 (1H, s), 7.192 (2H, dd), 5.444 (1H, d), 3.519 (1H, q), 5.502 (1H, d), 7.606 (2H, dd), 7.227 (2H, t), 7.444 (2H, dd), 7.282 (1H, t), 4.606 (1H, d), 1.131 (3H, d), 6.785 (1H, dd), 6.654 (1H, dd), 3.792 (3H, s), 7.319 (1H, t), 7.836 (2H, dd).
3. R1= 4-CH3 : 1H NMR :
δ 7.332 (2H, dd), 7.375 (1H, t), 6.754 (2H, dd), 7.314 (1H, s), 7.192 (2H, dd), 5.357 (1H, d), 3.519 (1H, q), 5.550 (1H, d), 7.606 (2H, dd), 7.227 (2H, dd), 7.444 (2H, dd), 7.282 (1H, t), 2.263 (3H, s), 7.120 (2H, dd), 4.606 (1H, d), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd).
4. R1= 4-Cl : 1H NMR :
δ 7.332 (2H, dd), 7.375 (1H, t), 7.664 (2H, dd), 7.314 (1H, s), 7.192 (2H, dd), 5.299 (1H, d), 3.519 (1H, q), 5.554 (1H, d), 7.606 (2H, dd), 7.227 (2H, dd), 7.444 (2H, dd), 7.282 (1H, t), 7.523 (2H, dd), 4.606 (1H, d), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd).
5. R1= 2-Cl : 1H NMR :
δ 7.332 (2H, dd), 7.375 (1H, t), 7.314 (1H, s), 7.192 (2H, dd), 3.519 (1H, q), 5.307 (1H, d), 5.582 (1H, d), 7.606 (2H, dd), 7.227 (2H, dd), 7.444 (2H, dd), 7.282 (1H, t), 7.371 (1H, dd), 7.528 (1H, dd), 7.269 (1H, dd), 7.668 (1H, dd), 4.606 (1H, d), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd).
6. R1= 2-Cl-4-Cl : 1H NMR :
δ 7.332 (2H, dd), 7.375 (1H, t), 7.314 (1H, s), 7.192 (2H, dd), 3.519 (1H, q), 5.307 (1H, d), 7.211 (1H, dd), 7.172 (1H, dd), 5.567 (1H, d), 7.606 (2H, dd), 7.574 (1H, dd), 7.227 (2H, dd), 7.444 (2H, dd), 7.282 (1H, t), 4.606 (1H, d), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd).
7. R1= 2-OCH3: 1H NMR :
δ 7.332 (2H, dd), 7.375 (1H, t), 7.314 (1H, s), 7.192 (2H, dd), 3.519 (1H, q), 5.282 (1H, d), 7.040 (1H, dd), 3.801 (3H, s), 7.270 (1H, dd), 5.467 (1H, d), 7.606 (2H, dd), 6.947 (1H, dd), 7.051 (1H, dd), 7.227 (2H, dd), 7.444 (2H, dd), 7.282 (1H, t), 4.606 (1H, d), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd).
8. R1= 4-OCH3 : 1H NMR :
δ 7.332 (2H, dd), 7.375 (1H, t), 7.222 (2H, dd), 7.314 (1H, s), 7.192 (2H, dd), 5.232 (1H, d), 3.519 (1H, q), 6.886 (2H, dd), 3.741 (3H, s), 5.413 (1H, d), 7.606 (2H, dd), 7.227 (2H, dd), 7.444 (2H, dd), 7.282 (1H, t), 4.606 (1H, d), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd).
9. R1= 4-N(CH3)2: 1H NMR :
δ 7.332 (2H, dd), 7.375 (1H, t), 6.751 (2H, dd), 7.314 (1H, s), 6.647 (2H, dd), 7.192 (2H, dd), 5.312 (1H, d), 3.519 (1H, q), 2.784 (6H, s), 5.425 (1H, d), 7.606 (2H, dd), 7.227 (2H, dd), 7.444 (2H, dd), 7.282 (1H, t), 4.606 (1H, d), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd).
10. R1= 2-OH : 1H NMR :
δ 7.332 (2H, dd), 7.375 (1H, t), 7.314 (1H, s), 7.192 (2H, dd), 3.519 (1H, q), 5.285 (1H, d), 5.521 (1H, d), 7.606 (2H, dd), 7.227 (2H, dd), 7.444 (2H, dd), 7.282 (1H, t), 6.947 (1H, dd), 6.648 (1H, dd), 7.267 (1H, dd), 7.054 (1H, dd), 4.606 (1H, d), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd)

6. Conclusion:

It is concluded that the derivatization of s-triazine to give its azetidinone detivatives resulted in formation of new chemical entity which further can be used to inhibit the growth of bacterial and fungi. The compounds (1-10) almost all showed antimicrobial effects.

7. Acknowledgment:

This work was supported by the Department of Chemistry, Shri Jagdishprasad Jhabarmal Tibrewala University, Vidyanagari, Jhunjhunu, Rajasthan – 333001.

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