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Synthesis and studies of antifungal activity of 2,4,6-trisubstituted 1,3,5-triazines

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ABSTRACT

A Series of 2,4,6-trisubstituted 1,3,5 triazines are synthesized. The synthesized compounds are evaluated for their in-vitro antifungal activity against Candida albicans. Out of 10 compounds, all of them showed antifungal activity in the range of 1000 µg/ml to 10 µg/ml. All the compounds are found active against the said fungus. The promising results are in support of the fact that the compounds are worth to be optimized for some novel drugs in future. The newly synthesized compounds were characterized using IR, ^{1}H-NMR.

Keywords: Benztriazole, Substituted urea/thiourea, Cyclohexyl amine, Cyanuric chloride and Antifungal activity.

INTRODUCTION

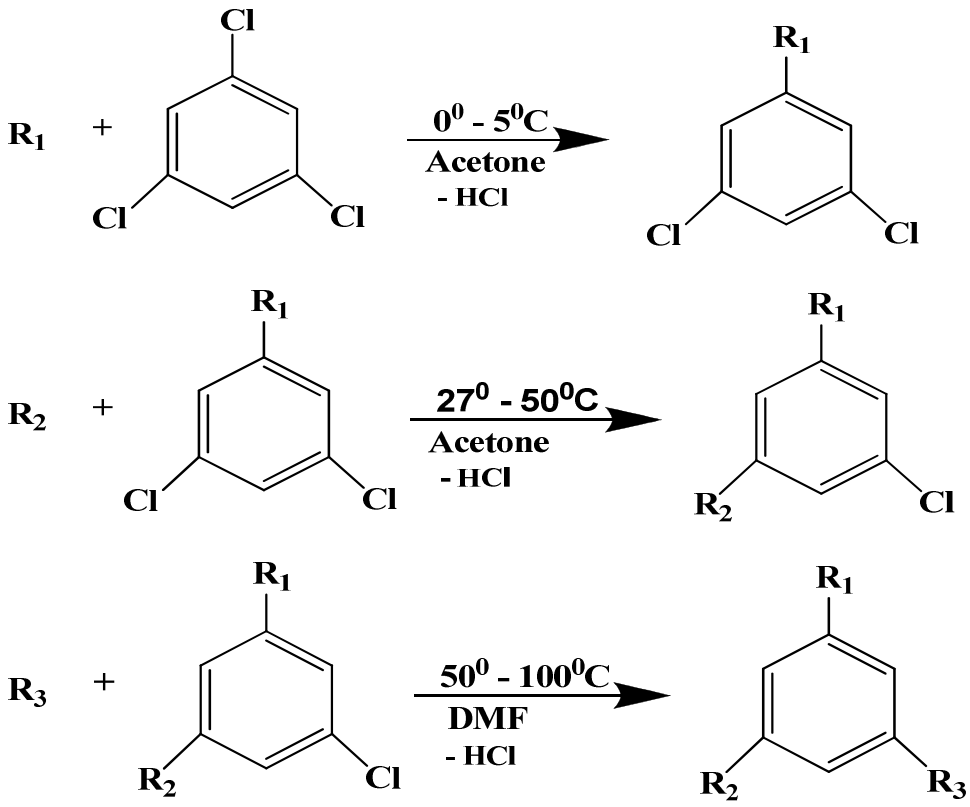
An important class of compounds having anticancer, antitumor, antiviral and antifungal activity consists of substituted s-triazine derivatives. These compounds have been used in the treatment of depression and hence gained considerable significance. These are valuable bases for estrogen receptor modulators**[1]** and also used as bridging agents to synthesize herbicides and in the production of drugs or polymers**[2].**s-Triazine derivatives represent an important class of compounds due to their potential to be biologically active. They are known to be anti-protozoals**[3]** anticancer agents**[4],** estrogen receptor modulators**[5]**, antimalarials**[6-7]**, cyclin-dependent kinase modulators**[8]**, and antimicrobials**[9]**. It has been reported that s-triazine derivatives are used as templates for molecular imprinting**[10]** and for the construction of three-helix bundle protein**[11]**.Triazines are a class of nitrogen containing cyclic compounds having remarkable thermal and chemical stabilities**[12].** Their unusual properties make them uniquely suitable for several specialized application in the field of Material and Biomedical sciences. The delocalization of electron in the ring has been utilized in the preparation of special polymer**[13-15],** herbicides,**[16-17]** and antiviral, antifungal and anticancer agents**[18]**. In particular, numerous 1,3,5-s-triazine derivatives still have unexplored pharmacological properties. Many s-triazine derivatives have attained significance in agriculture as herbicides and fungicides, including simazine (2-chloro-4,6-bis (ethyl amino)-s-triazine), Atrazine (2-chloro-4 ethyl amino-6-isopropyl amino-s-triazine), and others. In 1955, Gysin and co-workers discovered the phytotoxic and plant growth regulating properties of a series of amino derivatives of triazines (Gast et al., 1955,1956)**[19-20].** Urea**[21]** and thiourea**[22]** of different aryl amines are associated with a wide range of pharmacological activities**[23]** and anti-inflammatory**[24]**. In this paper we present the synthesis, characterization and antifungal activity of the tri-substituted-1,3,5-triazine derivatives.

MATERIALS AND METHODS

Melting points were determined by open glass capillary method and are uncorrected. The structures of these compounds have been confirmed from spectral analysis like FTIR, ^{1}H NMR (400 MHz).

The triazines described were synthesized starting from cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) and different nucleophiles . The chlorine atoms of cyanuric chloride can be replaced successively by substituted or non–substituted different amino groups. The nucleophiles can selectively displace the different chlorines by controlling the reaction temperature.

Scheme



*WHERE **R**$_1$,**R**$_2$ and **R**$_3$ are given in below table.*

Table 1: Various Substituted compound

Compound	R1	R2	R3
1a.	Benztriazole	Cyclohexyl amine	(Thiourea of m-Toludine)
1b	Benztriazole	Cyclohexyl amine	(Thiourea of o-Toludine)
1c	Benztriazole	Cyclohexyl amine	(Thiourea of p-Toludine)
1d	Benztriazole	Cyclohexyl amine	(Thiourea of p-chloro aniline)
1e	Benztriazole	Cyclohexyl amine	(Thiourea of p-anisidine)
1f	Benztriazole	Cyclohexyl amine	(Thiourea of p-bromo aniline)
2a	Benztriazole	Benzimidazole	(Urea of p-chloro aniline)
2b	Benztriazole	Benzimidazole	(Urea of p-fluoro aniline)
3a	Dicyclo hexyl amine	Mono ethanol amine	----------
3b	Dicyclo hexyl amine	N-methyl piperazine	----------

Step - 1 : Preparation of 2-substituted-4,6-dichloro-1,3,5-triazine: To a stirred solution of cyanuric chloride in acetone at 0-5^{0}C was added a solution of amine in acetone in drop wise fashion. After addition is complete, the reaction mixture was stirred for 2 hrs. Sodium bicarbonate (10% aq) solution was added to neutralize HCl evolved

during the reaction. Finally the contents were poured into crushed ice. The solid separated out was filtered, wash with water dried and recrystallised from suitable solvent.

Step - 2 : Preparation of 2,4-disubstituted-6-chloro-1,3,5-triazine:
Amine was added slowly to 2-substituted-4,6-dichloro-1,3,5-triazine in acetone with constant stirring within 2 hours at 27-50^{0}C temperature. Sodium bicarbonate (10%aq) solution was added to neutralize HCl evolved during the reaction. Finally the contents were poured in to crushed ice. The solid separated out was filtered, washed with water, dried and recrystallized from suitable solvent.

Step 3: Preparation of Trisubstituted-1,3,5-triaziene:
Amine was added slowly to 2,4-di-substituted-6-chloro-1,3,5-triazine in acetone with constant stirring within 4 hours at refluxed temperature. Sodium bicarbonate (10%aq) solution was added to neutralize HCl evolved during the reaction. Finally the reaction mixture was cooled and poured in to crushed ice. The solid separated out was filtered, washed with water, dried and recrystallized from methanolic and ethanolic water solution.

Table 2 : Analytical Data

Compound No	M.P.	Yield (%)	M.F.	IR (in KBr) cm^{-1}	1H NMR $CDCl_3$ (δ, ppm)
1a	92-94 ^{0}C	71.18	$C_{23}H_{25}N_9S$	1618 (C=N),1410 (C=S) 1320 (C-N) ,1290 (C-NH)	7.10-7.80 (m,Ar-H),3.69(Aryl NH),7.90,7.88 (Long NH),2.39(s,3H),1.30-1.50 (m,11H)
1b	110-112^{0}C	65.40	$C_{23}H_{25}N_9S$	1624 (C=N),1429 (C=S) 1310 (C-N), 1286 (C-NH)	7.19-7.78 (m,Ar-H),3.69(Aryl NH),8.10,7.95 (Long NH),2.41(s,3H),1.20-1.45 (m,11H)
1c	96-98 ^{0}C	70.25	$C_{23}H_{25}N_9S$	1616 (C=N), 1419 (C=S) 1329 (C-N), 1286 (C-NH)	7.05-7.76 (m,Ar-H),3.59(Aryl NH),8.25,7.98 (Long NH),2.45(s,3H),1.24-1.38 (m,11H)
1d	85-87^{0}C	72.20	$C_{22}H_{22}N_9SCl$	1610 (C=N), 1396 (C=S) 1300 (C-N), 1290 (C-NH)	7.15-7.60 (m,Ar-H),3.68(Aryl NH),7.96,8.18 (Long NH),2.38(s,3H),1.29-1.47 (m,11H)
1e	94-96 ^{0}C	70.10	$C_{23}H_{25}ON_9S$	1604 (C=N),1411 (C=S) 1320 (C-N), 1292 (C-NH)	6.98-7.75 (m,Ar-H),3.66(Aryl NH),8.14,8.25 (Long NH),2.30(s,3H),1.15-1.38 (m,11H)
1f	178-180 ^{0}C	68.80	$C_{22}H_{22}N_9SBr$	1612 (C=N), 1406 (C=S) 1303 (C-N), 1412 (C-NH), 585(C-Br)	7.02-7.85 (m,Ar-H),3.60(Aryl NH),8.28,8.18 (Long NH),2.45(s,3H),1.08-1.34 (m,11H)
2a	160-162 ^{0}C	67.20	$C_{23}H_{15}ON_{10}Cl$	1618 (C=N), 720 (Ar-Cl) 1313 (C-N),	6.92-7.73 (m,12H,Ar-H),7.98,8.54(Long NH)
2b	158-160^{0}C	67.40	$C_{23}H_{15}ON_{10}F$	1614 (C=N),1050 (Ar-F) 1309 (C-N)	6.98-7.75 (m,12H,Ar-H),8.28,8.44(Long NH)
3a	153-155^{0}C	68.35	$C_{17}H_{28}N_5OCl$	1578(C=N), 1340 (C-N) 3259 (-OH), 501.5(Ar-Cl) 1530 (C-NH)	1.02-1.36 (m,10H) , 1.57 -1.66(t,3H) ,4.21 (-OH) ,3.79-3.81(t,3H)
3b	166-167^{0}C	68.70	$C_{20}H_{33}N_6Cl$	1619 (C=N), 1327(C-N) 504.4 (Ar-Cl)	1.031.83(m,10H),2.75 (s,3H –CH_3) , 2.93-3.79 (m,4H) , 4.07-4.57(m,4H)

The antifungal activity of the above synthesized compounds were screened against *candida albicans*

Table 3 : Antifungal Screening of 2,4,6-trisubstituted-1,3,5-triazine

Compound	1000 µg/ml	100 µg/ml	10 µg/ml
1a	+	++	++
1b	+	++	++
1c	+	+	+
1d	+	+	++
1e	+	++	++
1f	+	+	++
2a	+	+	++
2b	+	+	+
3a	+	+	++
3b	-	+	+

\- *Highly active*
\+ *Active*
++ *Less active*
+++ *Least active*

RESULTS AND DISCUSSION:

In the series of ten compounds the compounds 2-N-(Dicyclohexyl amino)-4-N-(Methyl piperazine)-6-chloro-1,3,5-triazine is highly active which has the potential to be used as antifungal lead in future.

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