Synthesis, Characterization and Antibacterial Activity of a New Series of *s*-Triazines Derived with Quinolines

J. J. VORA*, S. B. VASAVA, ASHA. D. PATEL,
K. C. PARMAR, S. K. CHAUHAN and S. S. SHARMA

Department of Chemistry,
Hemchandracharya North Gujarat University,
Patan-384265 (Gujarat), India.
jabali_vora@hotmail.com

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Abstract: 8-Hydroxy quinoline was synthesized using Skraup reaction. This was condensed with trichloro-*s*-triazine. The product of the above reaction was allowed to react with triazole derivative. Finally, urea derivatives were allowed to react and the products were characterized by conventional and instrumental methods. Their structures were determined and important biochemical properties were studied

Keywords: *s*-Triazine derivatives, 8-Hydroxy quinoline, Biochemical study.

Introduction

Nitrogen containing heterocycles play an important role, not only for life science industry but also in many other industrial fields related to special and fine chemistry. Among them 1,3,5-triazines represent a widely used lead structure with multitude of interesting applications in numerous fields¹. Several derivatives of *s*-triazine show antibacterial², antimicrobial³, and herbicidal activities⁴. The replacement of a chlorine atom in cyanuric chloride by basic group is greatly facilitated by the ring nitrogen atom of the symmetrically built *s*-triazine nucleus. 2,4,6-trichloro-*s*-triazine derivatives prepared^{5,6} by replacement of one chlorine atom at 0-5°C, second one at 35-45°C and third one at 80-100°C. Quinoline and their derivatives are receiving increasing importance due to their wide range of biological activities as antimalarial, antihypertensive, anti-inflammatory, antibacterial, antiasthmatic, antiplatelet activity and as tyrosinase inhibiting activity⁷⁻¹⁰. In addition, quinolines have also been employed in the study of bioorganic and

bioorganometallic processes¹¹. Benzotriazole (BT) is an anticorrosive agent well known for its use in antifreeze fluids. It is highly persistent in the environment; therefore, BT is frequently found in runoff emanating from large airports as well as in the surrounding groundwater. Its derivatives such as 5-chloro-1*H*-benzotriazole, 1-hydroxy benzotriazole and 5-Me-1*H*-benzotriazole could be used as nitrification inhibitors for fertilizers to increase their effectiveness and reduce the leaching of nitrate-N. Benzotriazole derivatives also are pharmaceutically important. *N*-Alkylated benzotriazole derivatives show antibacterial and antifungal activity¹². Their *N*-alkyl derivatives were tested in vitro against the protozoa *Acanthamoeba Castellanii*¹³. Among other urea derivatives, phenyl urea derivatives are widely used particularly in pharmaceutical chemistry. Urea derivatives possess wide therapeutic activities such as antithyroidal, hyponotic and anaesthetic¹⁴, anthelmintics, anti malarial¹⁵, anti HIV¹⁶ and analgesic activity, antibacterial and diuretic.

Experimental

The reagent grade chemicals were obtained from commercial sources and purified by either distillation or recrystallization before use. Purity of synthesized compounds has been checked by thin layer chromatography. Melting points were determined by open capillary method and are uncorrected. IR spectra are recorded on FT-IR Perkin-Elmer spectrophotometer RX1 using KBr disc. ¹H-NMR spectra are recorded in DMSO-*d*₆ on a Bruker DRX-400 MHz using TMS as internal standard. The chemical shifts are reported as parts per million (ppm) and mass spectra were determined on Jeol SX-102 (FAB) spectrometer.

Preparation of 8-[(4,6-dichloro-1,3,5- triazine-2-yl)oxy]quinoline(1)

To a stirred solution of cyanuric chloride (9.22 g, 0.05 mole) in acetone at low temperature, the solution of 8-hydroxy quinoline (7.25 g, 0.05 mole) in acetone was added and neutral pH was maintained by adding 10% NaHCO₃ solution. The stirring was continued at the same temperature for three hours. Then stirring was stopped and solution was mixed with crushed ice. The product obtained was filtered and dried. The crude product was purified by recrystallization from DMF to give 85% yield of the title compound. Melting point 245°C

*Preparation of 8-[(4-(1*H*-benzotriazole-1-yl))-6-chloro-1,3,5-triazin-2-yl]oxy}quinoline(2)*

To a stirred solution of (1) (14.60 g, 0.05 mole) in acetone at 35°C the solution of 1*H*-benzotriazole (5.95 g, 0.05 mole) in acetone was added drop wise and neutral pH was maintained by adding 10% NaHCO₃ solution. The temperature was gradually raised to 45°C during two hours. Then stirring was stopped and solution was poured into cold water. The solid product thus obtained was filtered and dried. The crude product was purified by recrystallization from DMF to give 75% yield of the title compound. Melting point >300°C

*Preparation of 1- {4-[quinoline-8-yl] oxy}-6-[(1*H*-benzotriazole-1-yl)]-1,3,5-triazin-2-yl}-3-phenyl uea(3a)*

To the mixture of (2) (3.75 g, 0.01 mole) and phenyl urea (1.36 g, 0.01 mole) in acetone was refluxed in a water bath for 2-3 h. The pH was adjusted to neutral by adding 10% NaHCO₃. After completion of reaction the content was added to cold water. The solid obtained was dried and crystallized from DMF to give 80% yield of the title compound. Melting point 270°C

Spectral study of N-[4-(1H-benzo triazol-yl)-6-(quinolin-8-yloxy)-1,3,5- triazin-2-yl]-N'-phenylurea(3a)

IR (KBr) cm^{-1} : 3400.3 and 1491.6 (N-H stretching of 2° amine), 3056 (Ar-H) str, 1653 (NH-CO-NH stretching), 821 (C_3N_3 stretching), 1569 (benzotriazole ring str), 1255 (C-O-C stretching), 1333 (C-N stretching).

$^1\text{H-NMR}$ (DMSO-d_6) δ (ppm): 7.80-7.82 (d, 1H, N-CH=CH), 7.85-7.87 (t, 1H, N-CH=CH-CH), 7.15-7.17 (d, 1H, N-CH=CH-CH=C), 8.07-8.09 (d, 1H, -O-C=CH-CH=CH-), 8.14-8.19 (t, 1H, -O-C=CH-CH=CH), 8.77-8.78 (d, 1H, -O-C=CH-CH=), 9.14 (s, 2H, NH-CO-NH), 7.30-7.50 (m, 5H, Ar-H), 8.45-8.47 (d, 1H, N=N-N-C=CH-CH), 6.58-6.62 (t, 1H, N=N-N-C=CH-CH=CH), 6.98-7.03 (t, 1H, N=N-N-C=CH-CH=CH-CH), 8.32-8.33 (d, 1H, N=N-N-C=CH-CH=CH-CH-C)

Mass Spectra (m/z): 476 [MH]⁺, 458, 223, 135, 118.

Results and Discussion

s-Triazine has three active chlorine atoms at position 2,4,6, which can be replaced by bases. Various *s*-triazine derivatives were prepared as shown in the scheme 1. O-H stretching peak at 3610 cm^{-1} disappeared in the product and characteristic C-O-C peak appeared at 1255 cm^{-1} . and final product was also confirmed by missing of C-Cl stretching peak at $750\text{--}700\text{ cm}^{-1}$. The major characteristic absorption bands are observed at 3400 cm^{-1} and 1491 cm^{-1} (broad, N-H stretching of secondary amine), 1653 cm^{-1} (NH-CO-NH stretching), 821 cm^{-1} (C_3N_3 stretching in *s*-triazine ring).

The ^1H NMR spectra of compound **3a** showed the following chemical shifts. The δ at 7.30-7.50 ppm is 5H of phenyl ring. A δ observed at 9.14 ppm is 2H of urea moiety (-NH-CO-NH-) appeared by the merge of two signals. More over the structure of compound **3a** has been assigned on the basis of elemental analysis (Table 1) supporting the gross formula $\text{C}_{25}\text{H}_{17}\text{N}_9\text{O}_2$. This was also confirmed by the mass spectrum, which gave a quasimolecular ion [MH]⁺ peak at m/z 476. Presence of 9-nitronen atoms (from elemental analysis) makes it must to have odd molecular weight. 458 peak is the base peak which is due to loss of H_2O from the 476 peak. 477 peak is 27.77% of 476 peak indicating the presence of 25 carbon atoms in the molecule (**3a**).

Antimicrobial activity

Antimicrobial activity testing was carried out by using broth dilution method. Each purified compound is dissolved in dimethyl sulfoxide (DMSO), sterilized by filtration using sintered glass filter and store at 4°C . All the synthesized compounds were screened for their antibacterial and antifungal activities (Table 2 & 3) against the *E. coli*, *P. auregenosa*, *S. aureus*, *S. pyogenus* and the fungi *C. albicans*, *A. niger*, and *A. clavatus*. The compounds were tested at 500, 250, 100 and $50\text{ }\mu\text{g/mL}$ concentration using nutrient agar tubes. The highest dilution showing at least 99% inhibition is taken as MBC (minimal bacterial concentration). Control experiment was carried out under similar condition by using gentamycin, ampicillin, chloramphenicol for antibacterial activity and nystatin, greseofulvin for antifungal activity as standard drugs.

Out of ten synthesized heterocyclic compounds, compound **3b** showed equal antibacterial activity as chloramphenicol (against *E. coli*) and compound **3f** (against *E. coli*) and **3j** (against *S. pyogenus*) showed equal antibacterial activity as ampicillin. Compound **3a**, **3b** and **3f** showed marginal higher antibacterial activity against *P. aeruginosa* compared to the other compounds. Against the organism *S. aureus*, compound **3f** and **3j** showed comparable antibacterial activity similar to standard drug.

Scheme 1. Synthetic route to *s*-triazine derivatives (**3**)**Table 1.** Physical and analytical data of title compound and its other substitute derivatives (**3a-3j**)

Compd	R	Molecular Formula	F.W.	% Yield (Color Final step)	m.p. °C (<i>R_f</i>)	% of Carbon Found, (Calcd.)	% of Hydrogen Found, (Calcd.)	% of Nitrogen Found, (Calcd.)
3a	-H	C ₂₅ H ₁₇ N ₉ O ₂	475.46	85 (White)	270 (0.90)	63.21 (63.15)	3.68 (3.60)	26.57 (26.51)
3b	<i>O</i> -NO ₂	C ₂₅ H ₁₆ N ₁₀ O ₄	520.45	89 (Yellow)	280 (0.84)	57.76 (57.69)	3.16 (3.10)	26.84 (26.91)
3c	<i>m</i> -NO ₂	C ₂₅ H ₁₆ N ₁₀ O ₃	520.45	86 (Yellow)	289 (0.85)	57.78 (57.69)	3.15 (3.10)	26.85 (26.91)
3d	<i>p</i> -NO ₂	C ₂₅ H ₁₆ N ₁₀ O ₃	520.45	79 (Yellow)	272 (0.92)	57.75 (57.69)	3.18 (3.10)	26.87 (26.91)
3e	<i>O</i> -CH ₃	C ₂₆ H ₁₉ N ₉ O ₂	489.48	84 (White)	275 (0.93)	63.86 (63.80)	3.97 (3.91)	25.81 (25.75)
3f	<i>m</i> -CH ₃	C ₂₆ H ₁₉ N ₉ O ₂	489.48	80 (Blue)	282 (0.95)	63.88 (63.80)	3.96 (3.91)	25.83 (25.75)
3g	<i>p</i> -CH ₃	C ₂₆ H ₁₉ N ₉ O ₂	489.48	82 (White)	286 (0.80)	63.85 (63.80)	3.99 (3.91)	25.82 (25.75)
3h	<i>O</i> -Cl	C ₂₅ H ₁₆ N ₉ O ₂ Cl	509.90	80 (White)	279 (0.76)	58.86 (58.89)	3.22 (3.16)	24.77 (24.72)
3i	<i>m</i> -Cl	C ₂₅ H ₁₆ N ₉ O ₂ Cl	509.90	82 (White)	285 (0.79)	58.84 (58.89)	3.25 (3.16)	24.79 (24.72)
3j	<i>p</i> -Cl	C ₂₅ H ₁₆ N ₉ O ₂ Cl	509.90	78 (White)	274 (0.82)	58.83 (58.89)	3.21 (3.16)	24.80 (24.72)

Out of ten synthesized compounds **3f** showed equal antifungal activity as greseofulvin (against *C. albicans*) and less activity against the two other organisms. Compound **3f** contains methyl group in *meta* position, Compound **3f** and **3i** showed marginal higher antifungal activity against *A. niger* compared to the other compounds, however less than the standard drugs. The ten compounds against *A. clavatus* seemed much less effective as antifungal.

Table 2. Antibacterial activity of synthesized compounds **3a** to **3j**

Comp	<i>R</i>	Minimal bactericidal concentration, µg/mL			
		<i>E.coli</i> MTCC 443	<i>P.aeruginosa</i> MTCC 1688	<i>S.aures</i> MTCC 96	<i>S.pyogenus</i> MTCC 442
3a	-H	500	200	200	500
3b	- <i>o</i> -NO ₂	50	200	500	500
3c	- <i>m</i> -NO ₂	500	250	500	200
3d	- <i>p</i> -NO ₂	500	500	500	200
3e	- <i>o</i> -CH ₃	250	250	200	250
3f	- <i>m</i> -CH ₃	100	200	100	500
3g	- <i>p</i> -CH ₃	500	500	500	500
3h	- <i>o</i> -Cl	500	500	200	500
3i	- <i>m</i> -Cl	250	250	500	500
3j	- <i>p</i> -Cl	500	500	100	100
Gentamycine		0.05	1	0.25	0.5
Ampicillin		100	100	250	100
Chloramphenicol		50	50	50	50

Table 3. Antifungal activity of synthesized compounds **3a** to **3j**

Comp	<i>R</i>	Minimal fungicidal Concentration, µg/mL		
		<i>C.albicans</i>	<i>A.niger</i>	<i>A.clavatus</i>
3a	-H	>1000	>1000	>1000
3b	- <i>o</i> -NO ₂	>1000	>1000	>1000
3c	- <i>m</i> -NO ₂	>1000	>1000	1000
3d	- <i>p</i> -NO ₂	>1000	>1000	1000
3e	- <i>o</i> -CH ₃	>1000	>1000	>1000
3f	- <i>m</i> -CH ₃	500	500	1000
3g	- <i>p</i> -CH ₃	>1000	>1000	>1000
3h	- <i>o</i> -Cl	>1000	>1000	>1000
3i	- <i>m</i> -Cl	>1000	500	>1000
3j	- <i>p</i> -Cl	>1000	>1000	>1000
Nystatin		100	100	100
Greseofulvin		500	100	100

Conclusion

Ten cyanuric chloride derivatives were synthesized and characterized for their structure elucidation. Various chemical and spectral data supported the structures thought of. Antibacterial and antifungal studies of these compounds indicated that compound **3b**, **3f**, **3j** were found to be equal active against some bacteria compared to standard antibiotic drugs. However, they could not exhibit appreciable antifungal action.

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