International Journal of Technical Research and Applications e-ISSN: 2320-8163,
www.ijtra.com Volume 8, Issue 3 (MAY-JUNE 2020), PP. 36-41

AN INVESTIGATION LEADING TO THE SYNTHESIS AND BIOEVALUATION OF OXADIAZOLOTRIAZINES

Soniya Singh[1], V.K. Pandey[2],
Department of Chemistry
[1,2]University of Lucknow-226007
Uttar Pradesh, India

***Abstract*— Condensation of 2-amino-5-aryl-[1,3,4] oxadiazoles (I) with aromatic aldehyde in ethanol afforded 2-arylidenoamino-5-aryl [1,3,4] oxadiazoles (II) in excellent yields. Heating under reflux of (II) with ammonium thiocyanate in dioxane resulted in 6,7-dihydro-2,7-diaryl-[1,3,4]oxadiazolo[3,2-a][1,3,5]triazine-5-thiones (III) in moderate yields. Treatment of the compounds (III) with N-(hydroxyalkyl)-phthalimide in concentrated H2SO4 yielded the target compounds named as 2-[(2,7-diaryl-5-thioxo-5H-[1,3,4]oxadiazolo [3,2-a][1,3,5]triazine-6(7H) -yl)alkyl] isoindolin-1,3-diones (IV) in the yields ranging from 57 to 68%. The compounds (IV) were screened for their antimicrobial activity in vitro. (SCHEME)**

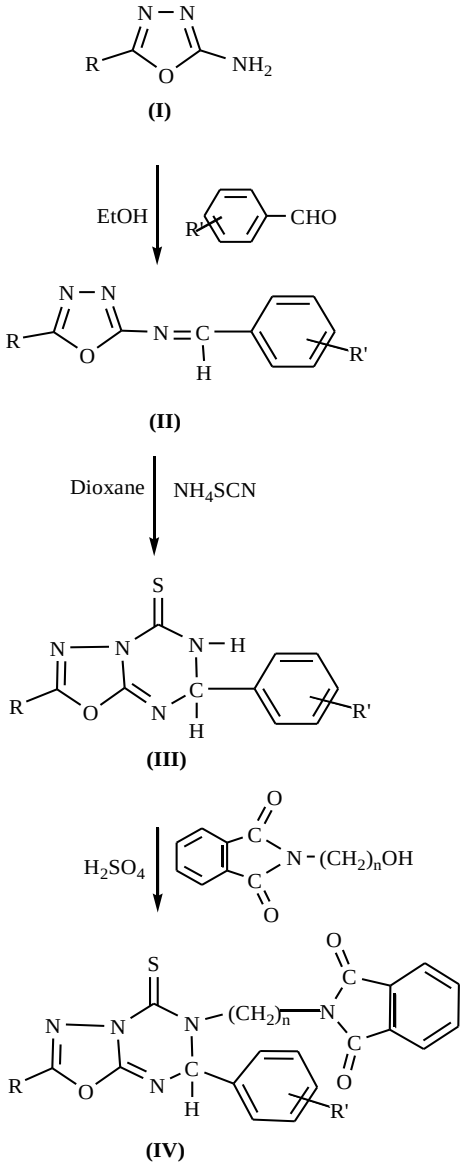
***Index Terms*— Oxadiazolotriazines, Antimicrobial Activity.**

I. INTRODUCTION

Several triazines have been considered as potential drugs for treating common cold infections caused by rhino-viruses with strong in vivo activity observed by many rhino-virus strains[1-4] and moderate effect reported following administration to experimentally infected chimpanzees[5-6.] These compounds also reportedly have activity in vitro against a number of other RNA and DNA viruses as well as inhibiting vaccinia virus infection in mice. The mechanism of antiviral action of these compounds has not been described.

In recent past, emphasis has been laid down on the synthesis of 1,3,5-trisubstituted s-triazines for studying their antiviral activity against several RNA and DNA viruses. In order to find relationship between structure and activity as well as toxicity, several compounds with a symmetrical triazine nucleus in an experimental type of influenza virus were studied in detail. Such triazines were found to suppress splenomegaly (enlargement of spleen) in Rouscher virus leukemia and increased the survival time of mice with Moloney virus leukemia[7-8]. A literature survey reveals the fact that the triazine derivatives also have greater clinical applications in other health areas particularly as anticancer agents and as diuretics.[9-13]

The diverse pharmacological properties exhibited by triazine compounds prompted the author to plan a protocol for undertaking the synthesis of some novel[(2,7 diaryl-5-thioxo-5H[1,3,4]oxadiazolo[3,2-a][1,3,5]triazin-7H) yl)alkyl] isoindole-1,3-diones for their antimicrobial potentials.



(SCHEME)

II. EXPERIMENTAL

The melting points were determined in open glass capillary tubes in a Toshniwal Electric Apparatus (Japan) and therefore, the values reported are uncorrected. The infra red (i.r.) nuclear magnetic resonance (NMR) spectra, mass spectra and biological activity data recorded were obtained from Central Drug Research Institute (CDRI), Lucknow.

2-Arylidenoamino-5-aryl [1,3,4] oxadiazoles (II)

The method of Zehra, T.[14] was followed for the synthesis of (II).

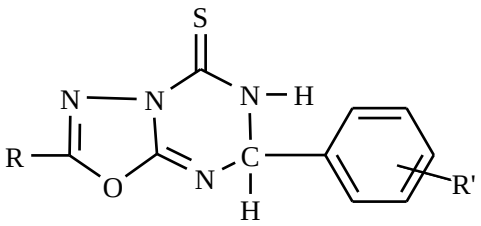
6,7-Dihydro-2,7-diaryl-[1,3,4]oxadiazolo[3,2-a][1,3,5] triazine-5-thiones (III)

A mixture consisting of 2-arylidenoamino-5-aryl [1,3,4]oxadiazole (II) (0.025mol) and ammonium thiocyanate (0.025mol) in dioxane (100mL) was heated under reflux for five hours in such a manner that the moisture could not pass in the reaction mixture. Dioxane was removed by distillation under reduced pressure. The solid thus obtained was filtered off, washed repeatedly with cold water, dried in vacuum and recrystallized from diluted ethanol. The compounds of this category are presented in Table I. along with their certain physical data.

2-[(2,7-Diaryl-5-thioxo-5H-[1,3,4]oxadiazolo[3,2-a][1,3,5] triazine-6(7H) -yl)alkyl] isoindolin-1,3-diones (IV)

A mixture of 6,7-dihydro-2,7-diaryl-[1,3,4] oxadiazolo [3,2-a][1,3,5] triazine-5-thiones (III) (0.01mole) and N-(hydroxyalkyl)-phthalimide (0.01mole) was dissolved in minimum quantity of conc. H_2SO_4 with constant shaking. While dissolving, the contents were cooled in order to prevent the exothermic reaction. When the dissolution was complete, the resultant reaction mixture was stirred mechanically for three hours. It was cooled and subsequently poured into crushed ice in installments with stirring. A precipitate was obtained which was allowed to settle down for half an hour. It was filtered off, washed several times with cold water in order to remove the sulphonated products, if any and air dried. The crude products thus obtained, were recrystallized from ethanol. The target compounds, thus isolated, are presented in Table II along with their some physical data.

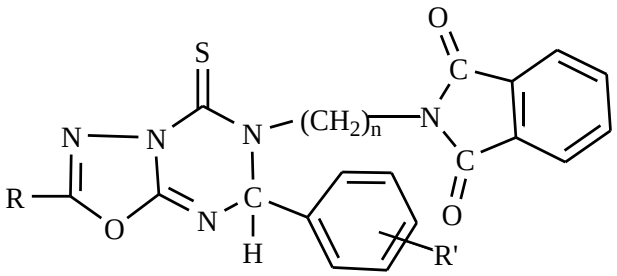
TABLE-I



Physical data of 6,7-dihydro-2,7-diaryl-[1,3,4] oxadiazolo [3,2-a] triazine-5-thiones (II)

Compd. No.	R	R'	m.p. (°C)	Yield (%)	Colour	Molecular formula	Molecular Weight	Nitrogen %	
								Calcd.	Found
1	C_6H_5 –	H	190	57	Grey	$C_{16}H_{12}N_4OS$	308	18.18	18.16
2	C_6H_5 –	4-OH	175	68	White	$C_{16}H_{12}N_4O_2S$	324	17.28	17.16
3	C_6H_5CH=CH–	H	206	61	Yellow	$C_{18}H_{14}N_4OS$	334	16.76	16.70
4	C_6H_5CH=CH–	4-OH	240	59	Brown	$C_{18}H_{14}N_4O_2S$	350	12.00	11.93

TABLE II

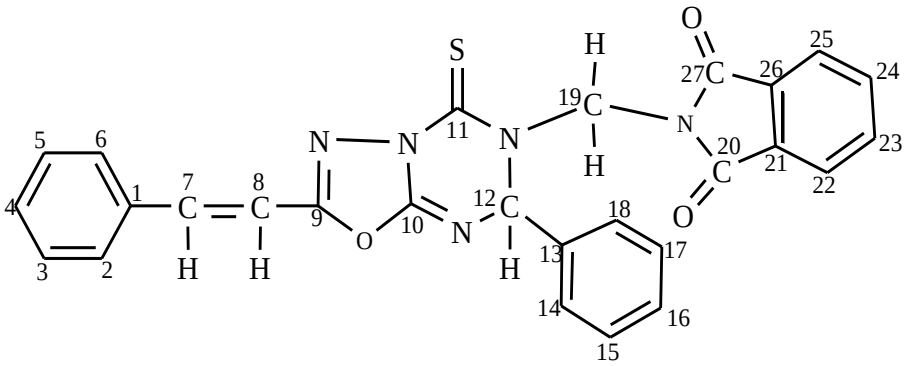


Physical data of 2-[(2,7-diaryl-5-thioxo-5*H*-[1,3,4]oxadiazolo[3,2-a] triazine-6(7*H*)-yl)alkyl]isoindolin-1,3- diones (IV)

Compd. No.	R	R'	n	m.p. (°C)	Yield (%)	Colour	Molecular formula	Molecular Weight	Nitrogen %	
									Calcd.	Found
1	C_6H_5 –	H	2	102	67	Brown	$C_{26}H_{19}N_5O_3S$	481	14.55	14.54
2	C_6H_5 –	4-OH	1	60	64	Yellows	$C_{25}H_{17}N_5O_4S$	483	14.49	14.40
3	C_6H_5CH=CH–	H	1	120	65	White	$C_{27}H_{19}N_5O_3S$	493	14.19	14.09
4	C_6H_5CH=CH–	4-OH	2	75	58	Grey	$C_{28}H_{21}N_5O_4S$	523	13.38	13.25

IR, ^{1}H NMR and ^{13}C NMR spectral data of 2-[(2-styryl-7-phenyl-5-thioxo-5*H*[1,3,4]oxadiazolo[3,2-a][1,3,5]triazin-6(7*H*)-yl)methyl]-isoindoline-1,3-dione.

(compound no.3 of the Table-II)



IR (KBr) cm^{-1}: 1716.0 (imi de C=O),1614.1(C=N), 3020.6 (RCH=CH-, trans, C–H stret.), 955.8 (RCH=CH, trans, C–H,defor.), 1215.9 (C–O–C, cyclic).

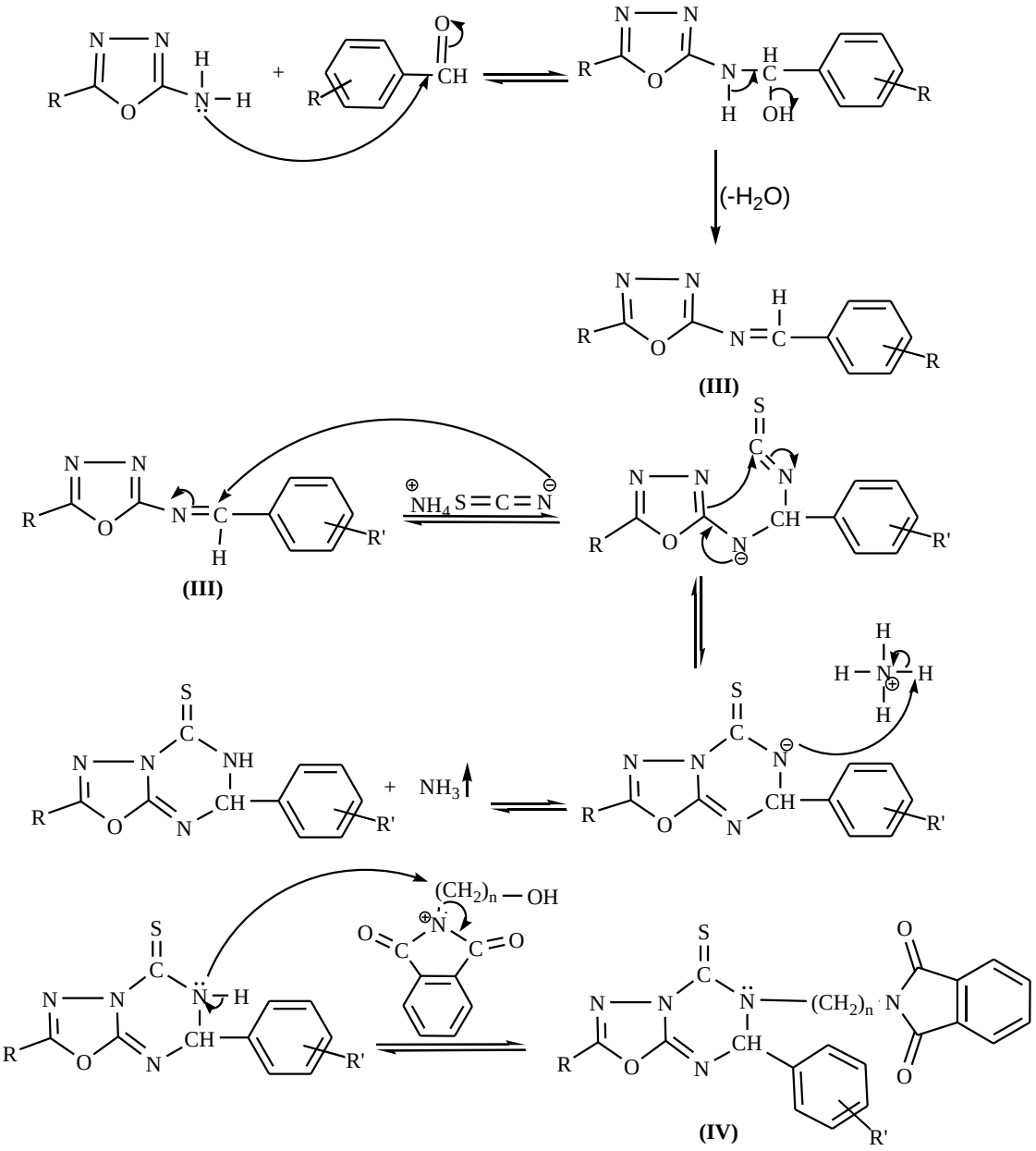
^{1}H NMR ($CDCl_3$) δ ppm: 7.26-7.91 (m, 14H, ArH), 5.64 (d, HC=CH–C=N, J=15.8), 5.25 (d, C–CH=CH, J=15.8), 4.86 (s, 1H, N–CH–N), 4.92 (s, 2H, N–CH2–N)

. **^{13}C NMR ($CDCl_3$) δ ppm**: 37.50 (C-7, C-8), 80.25 (C-12, C-19), 117.25, 119.50, 120.31, 125.52, 127.25, 129.15 133.34, 133.86, 137.45, 139.21, 141.25 (C-22 to C-26), 152.20 (C-11), 163.75 (C-9, C-10) 168.25 (C-20, C-27)

Mass (FAB): M^+ was not observed, Base peak appeared at m/z 160. Other peaks were at m/z 107, 236, 314, 342, 386 and 449

.

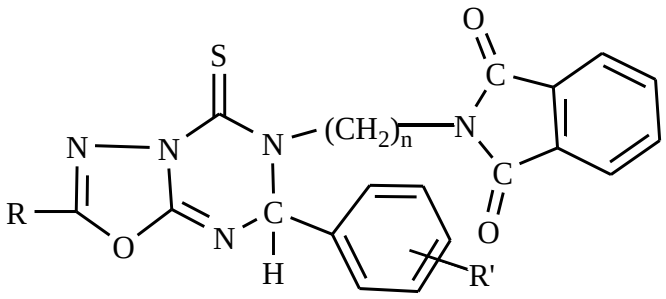
An attempt has been made to explain the formation of (IV) mechanistically.



III. BIOASSAY

All the four oxadiazolo-triazines were bioevaluated for their antifungal activity against five strains of fungi, viz., Candida albicans (Ca), Cryptococcus neoformans (Cn), Trichophyton mentagrophytes (Tm), Aspergillus fumigatus (Af) and Candida parapsilosis (Cp), in vitro. Fluconazole was taken as a standard drug having minimum inhibitory concentration (MIC) values of 0.5, 1.0, 1.0, 2.0 and 1.0µg/mL against Ca, Cn, Tm, Af and Cp respectively. These compound were also bioassayed for their antibacterial activity against human pathogenic bacteria viz., Escherichia coli (ATCC-9637) (Ec), Pseudomonas aeruginosa (ATCCBAA-427) (Pa), Staphylococcus aureus (ATCC-25923) (Sa) and Klebsiella pneumoniae (ATCC-27736) (Kp). Gentamycin was taken as a standard drug having minimum inhibitory concentration (MIC) values of 0.18, 25, 6.25 and 0.18µg/mL against Ec, Pa, Sa and Kp respectively. In order to screen these compounds for their antifungal and antibacterial activity, two Fold Serial Dilution Technique was employed as recommended by the National Committee for Clinical Laboratory Standards (NCCLS). The antimicrobial data are incorporated in Table-III.

TABLE III



Antimicrobial **Data of Compounds (IV)**

Compd. No.	**R**	**R'**	**n**	**A**ntifungal activity (MIC in µg/ml)					**A**ntibacterial activity (MIC in µg/ml)			
				Ca	**Cn**	**Tm**	**Af**	**Cp**	**Ec**	**Pa**	**Sa**	**Kp**
1	C_6H_5 –	H	2	50	50	6.25	>50	>50	25	25	6.25	3.12
2	C_6H_5 –	4-OH	1	>50	>50	25	>50	>50	25	12.5	6.25	3.12
3	C_6H_5CH=CH–	H	1	>50	>50	>50	>50	>50	>50	25	25	>50
4	C_6H_5CH=CH–	4-OH	2	>50	>50	>50	>50	>50	>50	>50	>50	>50

IV. RESULT AND DISCUSSION

Regarding the antifungal activity of these four oxadiazolo-triazines the data incorporated in Table III are indicative of less significant activity of such compounds since only one compound (compound no.1) having R= C6H5, R'=H and n=2 shows measurable degree of antifungal activity only against Tm (MIC value of 6.25) and no observable level of antifungal activity against four other fungal strains. The compound no. 2 structurally similar to the compound no. 1, only differing at 4-position of one of the phenyl groups and having a 4-OH group has MIC value of 25 other two compounds (compound no.3 and 4) having R= C6H5CH=CH- substituent were completely devoid of any antifungal activity. More such compounds with other pharmacophoric groups are required in order to probe their antifungal potentials.

The antibacterial activity data recorded in Table III are indicative of highly satisfactory inhibitory properties of the compound nos. 1 and 2 against all the four bacterial strains. These two compounds were found most active against Kp with a MIC value of 3.12 each, however less active than the reference standard , the gentamycin with a MIC value of 0.18. The compound no.1 was found antibacterially active equal to gentamycin against Pa and Sa (MIC values of 25 and 6.25, respectively, equal to gentamycin). The compound no.2 was more active than gentamycin against Pa and equal to gentamycin against Sa. This compound also showed promising antibacterial activity against Kp with a MIC value of 3.12, however, less than the standard drug gentamycin with a MIC value of 0.18. Other two compounds (3 and 4) could not provoke any measurable level of antibacterial activity against all the four bacterial strains.

V. CONCLUSION

On the basis of the antifungal and antibacterial activity data recorded in Table III it is obvious that oxadiazolo-triazines are potential candidate molecules against bacterial strains since two out of four such compounds investigated exhibited highly promising activity against two pathogenic bacteria viz., Pa and Sa. These two compounds showed comparable activity with the standard drug gentamycin and in one case even better than the standard drug.

VI. ACKNOWLEDGEMENT

The authors are grateful to the Head, Chemistry Department, Lucknow University, Lucknow for providing necessary laboratory facilities and the Director Central Drug Research Institute (CDRI), Lucknow for providing the elemental, spectral and biological activity data reported in the manuscript.

REFERENCES

[1] Gladych, J.M.Z., Hunt, Z.H., Jack, D., Haff, R.F., Boyle, J.J., Steward, R.C. and Ferlando, R.J., Nature, 221, 286(1968).

[2] Boyle, J.J., Raupp, W.G., Stanfield, F.J., Haff, R.F., Dick, E.C., D'Allesio, D. and Dick, C.R., Ann. N.Y. Acad. Sci., 173, 477(1970).

[3] Gwaltney, T.M., Proc. Soc. Exp. Biol. Med., 133, 448(1970).

[4] Haff, R.F., Flagg, W.B., Gallo, J.J., Hoover, J.R.F., Miller, J.A., Pinto, C.A. and Pegano, J.F., Proc. Soc. Exp. Biol., 144, 457(1972).

[5] Angeluci, R., Giorn. Mnl. Infect. Parasit., 13, 309(1961).

[6] Tokeo, V., and Shigerue, E., Japan Pat., 11984(1962).

[7] Chirigos, M.A., Proc. Am. Assoc. Cancer, Res., 3, 310(1962).

[8] Chirigos, M.A., Moloney, J.B., Humphreys, S.R., Mantel, N. and Goldin, A., Cancer Res., 21, 803(1961).

[9] Elion, G.B., Biekur, S., Nathan, H. and Hitchings, G.H., Cancer Res., 18, 802(1958).

[10] Hakala, M.T., Law, I.W. and Welch, A.D., Proc. Am. Assoc. Cancer Res., 2, 113(1956).

[11] Handschumacher, R.E., J. Biol. Chem., 235, 764(1960).

[12] Lipschitz, W.L. and Andidian, Z., J. Pharmacol Exp. Therap., 81, 84(1944).

[13] Ludwig, H., Schweiz Med. Wochenschr, 76, 822(1946).

[14] Zehra. T., "Synthesis of Fused Ring Systems Containing Amidoalkyl and other Pharmacophoric Groups for Studying their Biological Activities", A Ph.D. Thesis, Chemistry Department, Lucknow University, Lucknow, p.88(2002).