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"SYNTHESIS AND ANTIBACTERIAL ASSAY OF NANOPARTICLES OF IMMIDAZOLE DERIVATIVES OF ARYL SUBSTITUTED 1,3-THIAZOLE"

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ABSTRACT
The synthesis, spectral analysis and biological activities of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-[4-(2-hydroxy-3,5-dichlorophenyl)-2-mercapto-imidazolo]-1,3-thiazole (D") have been carried out. In this case 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-amine-1,3-thiazole (D), 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-[(2-hydroxy-3,5-dichlorophenyl) ethanonylamino]-1,3-thiazole (D') & 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-[4-(2-hydroxy-3,5-dichlorophenyl)-2-mercapto-imidazolo]-1,3-thiazole (D'') have been screened. The compounds (D), and was synthesized from 1-(2'-hydroxy-3' ,5'-dichlor ophenyl)-2-bromo-3-(4"-nitrophenyl)-1,3 propanedione (a4) by the action of thiourea, while (D'') was synthesized from (D) by reaction with α-bromo,2-hydroxy-3,5 dichloroacetophenone to get 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-[(2-hydroxy-3,5-dichlorophenyl) ethanonylamino]-1,3-thiazole (D'). Further (D') on treatment with KSCN was dissolved in acetic acid gave (D''). The nanoparticles of the compounds D, D'and D'' have been prepared by using ultrasonic technique. The newly synthesized titled compound and it's nanoparticles were screened for their antibacterial activities against some Gram positive Staphylococcus aureus and Streptococcus sp. and Gram negative Pseudomonas sp. and Solmonella typhi pathogens. All the newly synthesized compounds were found to be active against test pathogens.

KEYWORDS: Chalcone, thiazine, thiourea, α-bromo,2-hydroxy-3,5 dichloroacetophenone, KSCN was dissolved in acetic, antibacterial assay.

INTRODUCTION
Heterocyclic nucleus plays an important role in medicinal chemistry and it is a key template for the growth of various therapeutic agents. Thiazole is a heterocyclic compound featuring both a nitrogen atom and sulfur atom as part of the aromatic five-membered ring. Thiazoles and re lated compounds are called1,3-azoles (nitrogen and one other hetero atom in a f ive-membered ring). They are isomeric with the 1,2- azoles, the nitrogen and sulphur containing compound being called isothiazoles. Thiazoles are found naturally in the essential vitamins. Molecules that possess sulfur atoms are important in living organisms. Chalcones and their analogues having α, β -unsaturated carbonyl system are very versatile substrates for the evolution of various reactions and physiologically active compounds. Plant Pathology or Phytopathology deals with the cause, etiology, resulting losses and control or management of the plant diseases.

It is the scientific study of diseases in plants caused by pathogens (infectious organisms) and environmental conditions (physiological factors). Organisms that cause infectious disease include fungi, oomycetes, bacteria, viruses, phytoplasmas, protozoa, nematodes and parasitic plants.

The researchers[1-6] have reported the synthesis of several thiazoles and also their potent biological activities such as antimicrobial[7], antibacterial[8], antifungal[9], fungicidal[10] and insecticidal agent.[11]

Now a days nanotechnology is a promising field of interdisciplinary research. It opens up a wide array of opportunities in various fields like medicine, pharmaceuticals, electronics and agriculture. Since the physiochemical properties of nanoforms vary greatly, it becomes important to examine the effect of nanoparticles on microorganisms to harness the benefit of this technology in the plant protection especially against phytopathogens. Previous studies confirmed that metal nanoparticles are effective against pathogens, insects and pests. Hence nanoparticles can be used in the preparation of new formulations like nanomedicines for the diseases like diagnosing & treating cancer[12], enhancing outer membrane of living cells[13], inhibiting tumour growth in

human being[14], brain cancer.[15] Nanotechnology has the potential to revolutionize the different sectors of agriculture and food industry with modern tools for the treatment of diseases by providing the medicines for rapid diseases like malaria[16], cancer & HIV[17], breast cancer[18], localized diseases.[19]

In the present study, the chlorosubstituted 1,3-thiazole & their imidazole derivatives (D") have been prepared along with their nanoparticles and. screened them for their antibacterial activities against some *Gram positive Staphylococcus aureus and Streptococcus sp*. and *Gram negative Pseudomonas sp.* and *Solmonella typhi* pathogens. All the newly synthesized compounds were found to be active against test pathogens.

EXPERIMENTAL

All the glasswares used in the present work were of pyrex quality. Melting points were determined in hot paraffin bath and are uncorrected. The purity of compounds was monitored on silica gel coated TLC plate. IR spectra were recorded on Perkin-Elmer spectrophotometer in KBr pelletes, H^1 NMR spectra on spectrophotometer in CDCl3 with TMS as internal standard. UV spectra were recorded in nujol med ium. The analytical data of the titled compounds was highly satisfactory. All the chemicals used were of analytical grade. All the solvents used were purified by standard methods. Physical characterisation data of all the compounds is given in Table 1.

2'-Hydroxy 3',5'-Dichloroacetophenone

2-Hydroxy- 5-chloroacetophenone was dissolved in acetic acid (5 ml), Sodium acetate (3g) was added to the reaction mixture and then chlorine in acetic acid reagent (40 ml; 7.5 w/v) was added dropwise with stirring. The temperature of the reaction mixture was maintained be low 20^0C. The mixture was allowed to stand for 30 minutes. It was poured into cold water with stirring. A pale yellow solid then obtained was filtered, dried and crystallized from ethanol to get the compound 2'-hydroxy 3',5'-dichloroacetophenone.

Preparation of 2'-hydroxy-3',5'-dichlorophenyl-4-(4''-nitrophenyl) chalcone (a)

To the boiling solution of the 2-hydroxy-3,5-dichloroacetophenone (0.01 mol) and p-nitrobenza ldehyde (0.01 mol) in ethanol (20 ml) a 40% solution of NaOH was added gradually. The reaction mixture was stirred mechanically at room temperature for 1 hour and kept steady for 6 to 8 hours, followed by decomposition with ice cold HCl (1:1). The yellow granules thus obtained were filtered, washed with 10% $NaHCO_3$ solution and then crystallized from ethanol-acetic acid mixture to obtain the compound (a).

Preparation of 1-(2'-hydroxy-3',5'-dichlorophenyl)-2,3-dibromo-3-(4"-nitrophenyl)-propan-1-one (a_1)

2'-Hydroxy- 3',5'- dichlorophenyl-4-(4"-nitrophenyl)chalcone (a) (0.001 M) was suspended in bromine -glacial acetic acid reagent (25% w/v) (6.4 ml).

The reagent was added dropwise with constant stirring and the reaction mixture was kept at room temperature for about 30 minutes. The solid product, thus separated, was filtered and washed with a little petroleum ether to get the compound (a_1).

Preparation of 2-(4"-nitrophenyl)-6,8-dichloroflavone (a_2)

1-(2'-Hydroxy- 3',5'-dichlorophenyl)-2,3-dibromo-3-(4"-nitrophenyl)-propan-1-one (a_1) (0.01 mol) was dissolved in ethanol (25ml). To this, aqueous KOH solution (25 ml) was added. The reaction mixture was refluxed for 1 hour, cooled and diluted with water. The product thus separated was filtered and crystallized from ethanol to get the compound (a_2).

Preparation of 1-(2'-hydroxy-3',5'-dichlorophenyl)-3-(4"-nitrophenyl)-1,3-propandione (a_3)

2-(4"-Nitrophenyl)-6,8-dichloro-flavone (a_2) (0.01 mol) was dissolved in ethanol (25ml). To this, aqueous solution of HCl (25 ml) was added. The reaction mixture was then refluxed for 1 hour, cooled, and diluted with water. The product, thus separated, was filtered, and crystallized from ethanol to get the compound (a_3).

Preparation of 1-(2'-hydroxy-3',5'-dichlorophenyl)-2-bromo-3-(4"-nitrophenyl)-1,3-propanedione (a_4)

1-(2'-Hydroxy-3',5'-dichlorophenyl)-3-(4"-nitrophenyl)-1,3-propandione (a_3) (0.01 mol) was dissolved in a mixture of ethanol and dioxane. To this, calculated amount of liquid bromine was added. The product was not separated even after standing for one hour. It was then diluted with water, washed with water several times and extracted with ether. The solvent was removed under reduced pressure to get the white solid of the compound (a_4).

Preparation of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-amine-1,3-thiazole (D)

1-(2'-Hydroxy- 3',5'-dichlorophenyl)-2-bromo- 3-(4"-nitrophenyl)-1,3-propandione (a_4) (0.01 mol) and thiourea (0.01 mol) was dissolved in ethanol (25 ml). To this, aqueous KOH solution (0.02 mol) was added. The reaction mixture was then ref luxed for 3 hours, cooled, diluted with water and acidified with conc. HCl. The product thus separated was filtered and crystallized from ethanol to get the compound (D).

Preparation of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-[(2-hydroxy-3,5-dichlorophenyl) ethanonylamino]-1,3-thiazole (D')

A stoichiometeric mixture of 5-(2'-hydroxy-3',5'-dichlorophenyl) -4-(4"-nitrobenzoyl)-2-amine-1,3-thiazole (D) and α-bromo,2-hydroxy-3,5 dichloroacetophenone was dissolved in ethanol and refluxed for one hour. It was then cooled, diluted with water and crystallized from ethanol to get the compound (D').

Preparation of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-[4-(2-hydroxy-3,5-dichlorophenyl)-2-mercapto-imidazolo]-1,3-thiazole (D")

A stoichiometeric mixture of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-[(2-hydroxy-3,5-dichlorophenyl)ethanonylamino]-1,3-thiazole (D') and KSCN was dissolved in acetic acid and refluxed for 4.5 hours, cooled and diluted with water. The product, thus separated, was crystallized from ethanol to get the compound (D")**.**

The UV, IR, and NMR spectral data

Compound (D)

UV: Spectrum No. 1

The UV-Vis spectrum of the compound D reported in dioxane showed λ_{max} value **475** nm corresponding to n→π* transition.

IR (KBr):- Spectrum No. 2

3335.23 cm^{-1} (-OH phenolic), 2923.23cm^{-1} (aliphatic -C-H stretching), 3074.22cm^{-1} (aromatic -C-H stretching), 3788.41 cm^{-1} (-NH_2 stretching), 1566. cm^{-1} (-C=N stretching), 1229 cm^{-1} [(C-N=) stretching], 740.23 cm^{-1} (C-Cl stretching in aliphatic), 1053.26 cm^{-1} (C-Cl) stretching in aromatic).

PMR:- Spectrum No. 3

∂ 3.4 (hump, 2H, -N-**H**); ∂ 6.7 (d, 1H, -CH=C-**H**); ∂ 6.8 (d, 1H, -C**H**=C-H); ∂ 7.1 to 8.3 (m, 6H, Ar-**H**); ∂ 12.6 (s, 1H, O-**H**)

Compound (D'')

UV: Spectrum No. 4

The UV-Vis spectrum of the compound D" reported in dioxane showed λ_{max} value 398 nm corresponding to n→π* transition.

IR (KBr):- Spectrum No. 5

1650. cm^{-1} (=C=O stretching), 3429 cm^{-1} (-OH phenolic), 2920.20 cm^{-1} (aliphatic -C-H stretching), 3068 cm^{-1} (aromatic -C-H stretching), 1435 cm^{-1} (-C=N stretching), 1365 cm^{-1} [(C-N) (C-NO_2) stretching], 738 cm^{-1} (C-Cl stretching in aliphatic), 2547.38 cm^{-1} (-S-H stretching).

PMR:- Spectrum No. 6

∂ 7.7 to 7.9 (m, 8H, Ar-**H**); ∂ 12.6 (s, 1H, O-**H**)

Preparation of Nanoparticles of the Titled Compound

Ultrasonic Processor Sonapros PR-250MP was used to produce nanoparticles of the test compound. The test compound was dissolved in dioxane to prepare 0.1 M solutions. This solution was taken in a beaker and the probe of the sonapras 250 MP was dipped in solution. These solution was exposed to sonopros MP 250 for 10 minutes separately. The test compound was converted to nanoparticles. The solvent dioxane was evaporated by conventional heating method. The size of nanoparticles of the test compound was confirmed by X-ray diffraction studies using Benchtop x-ray diffraction (XRD) instrument **(**Miniflex).

The thin film of the nanoparticles of the test compound was prepared on glass slide. This slide was introduced to the X-ray diffraction instrument to get graphical information which was used for the calculation of the crystal size of test compounds.

Characterisation of Size of Nanoparticles of the Test Compound

The crystal size of nanoparticles of the test compound is calculated by using Debye -Scherrer equation.

$$D = \frac{0.94\,\lambda}{\beta . \cos\theta}$$

Where,

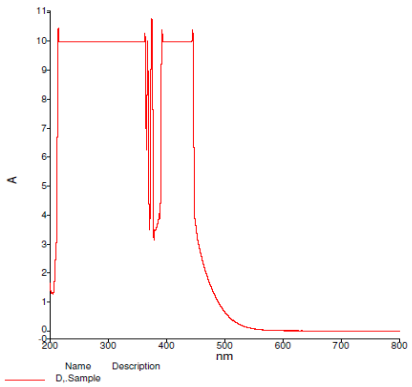
D = The average crystalline size.

0.94 = The particle shape factor which depends on the shape and size of the particle.

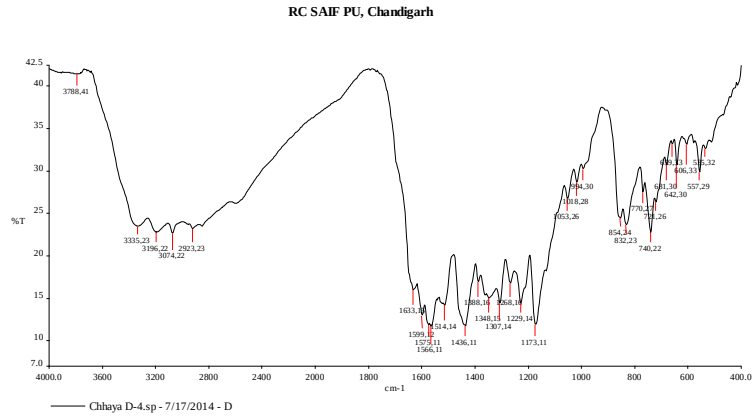
λ = is the wavelength.

□ = is the full width at half maximum [FWHM] of the selected diffraction peaks (β = 0.545)

□ = is the Bragg's angle obtained from 2θ values which was corresponding to the maximum intensity peak in XRD pattern (□ = 0.7501 rad).



Spectrum No. 01



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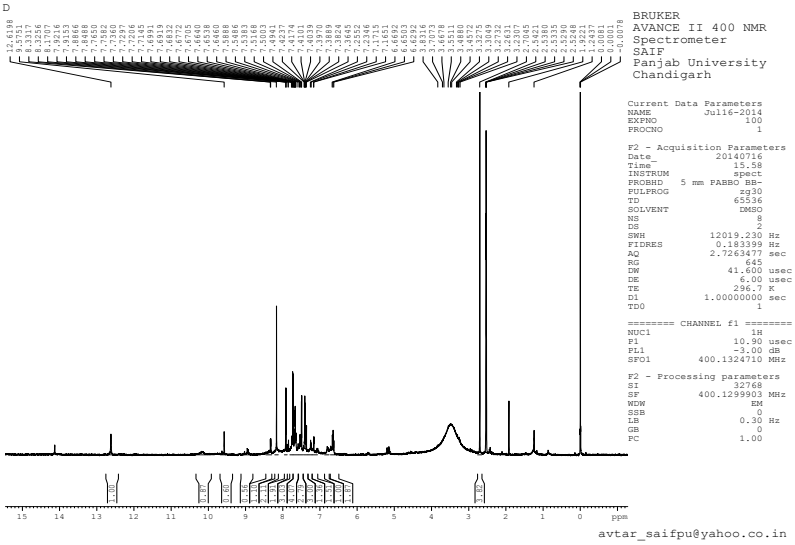

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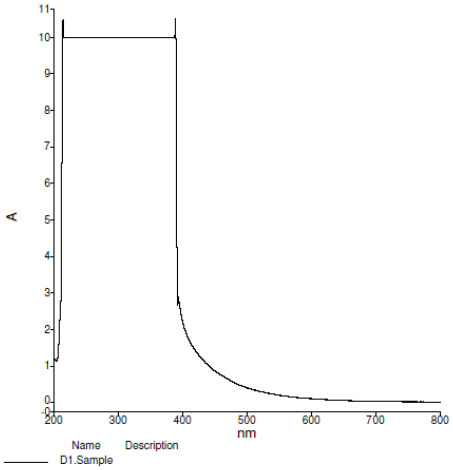

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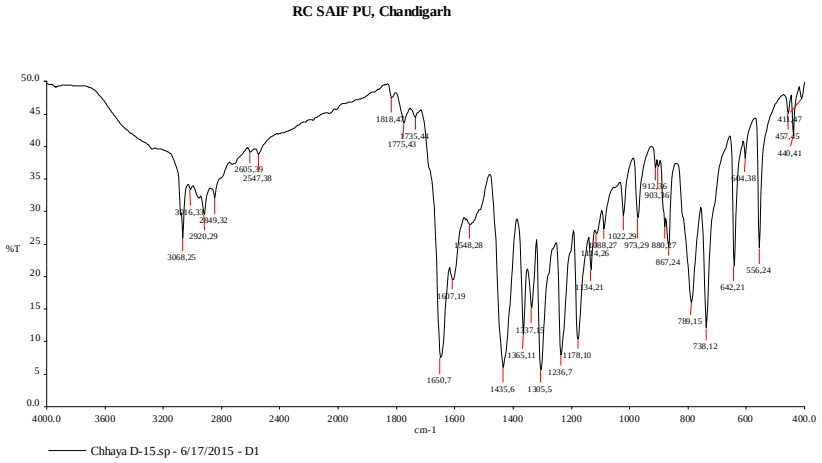

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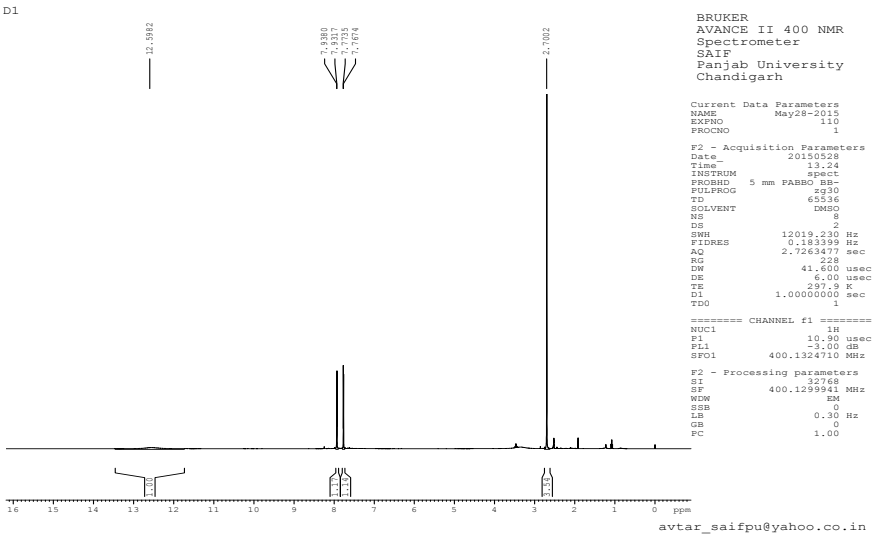
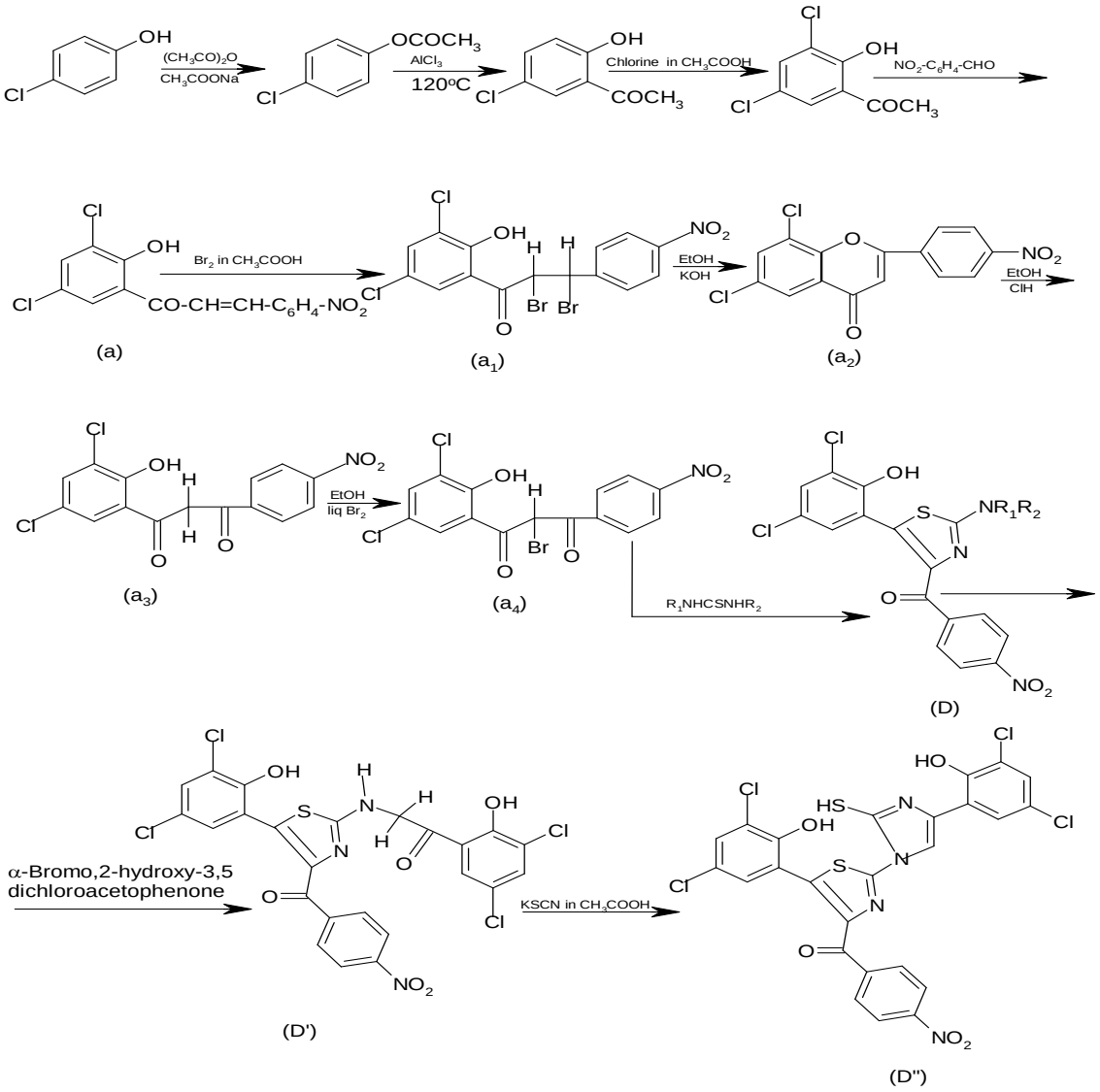


Spectrum No. 06

Table 1: Characterisation data of newly synthesized compounds.

Compounds	Molecular formula	M.P. in ^{0}C	% of yield	% of element					
				C	H	N	S	Cl	Br
	$C_8H_6O_2Cl_2$	54	80	47.90/48	2.95/3			34.15/34.58	
a	$C_{15}H_9O_4NCl_2$	250	70	53.10/53.25	2.40/2.66	3.98/4.18		21/21.77	
a_1	$C_{15}H_9O_4NCl_2Br_2$	72	70	36.01/36.14	1.78/1.80	2.78/2.81		14.20/14.25	32.08/32.12
a_2	$C_{15}H_7O_4NCl_2$	132	60	53.14/53.57	2.07/2.08	4.13/4.16		21.03/21.13	
a_3	$C_{15}H_9O_5NCl_2$	117	50	50.74/50.84	2.45/2.54	3.90/3.95		20.03/20.05	
a_4	$C_{15}H_8O_5NCl_2Br$	78	60	41.12/41.57	1.78/1.84	3.20/3.23		16.08/16.39	18.34/18.47
D	$C_{16}H_{11}O_4N_3Cl_2S$	170	70	46.50/46.60	2.56/2.66	10.05/10.19	7.67/7.76	17.20/17.23	
D’	$C_{24}H_{13}O_6N_3Cl_4S$	105	70	46.90/46.98	2.08/2.12	6.80/6.85	5.2/5.22	23.10/23.16	
D”	$C_{25}H_{12}O_5N_4Cl_4S_2$	115	70	51/51.47	2.00/2.05	9.56/9.60	10.9/10.97	12.00/12.17	

Scheme



Where:

1) R_1 = -H, -C_6H_5
2) R_2 = -H, -C_6H_5

EXPERIMENTAL DETAILS AND DISCUSSION OF RESULTS

All the newly synthesised compound (D") and it's nanoparticles were screened for their antibacterial activity against some *Gram positive* pathogens viz. *Staphylococcus aureus* and *Streptococcus sp.* and some *Gram negative* pathogens viz. *Pseudomonas sp.* and *Solmonella Typhi.* at conc. of 1000 µm gentamycine as a standard. DMF was used as solvent control using agar plate techniques. The zones of inhibition formed were measured in mm and are shown in table -2.

Table 2: Antibacterial Activities of Synthesised New Compounds.

Zones of inhibition (mm)

Compounds	Staphylococcus aureus	Streptococcus sp.	Pseudomonas sp.	Solmonella typhi
a	16	14	16	16
D"	16	17	17	16

RESULT AND DISCUSSION

The newly synthesized compound (D") and it's nanoparticles were found to be active against test pathogens. However a further detailed study in the light of Medical sciences is advised.

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REFERENCES

1. K. Anilkumar, P.K., K. Shrivastava Rao, Reddana P., *Ind. J. of chem.* sec., B, June 2007; 1033-1037.
2. Kakade B.S., *"Synthesis in heterocyclic compounds Ph.D. Thesis"*, Nagpur University, 1983.
3. Seiji Miwatashi, Yasayoshi Arikava, Shigonori Ohkawa, Keiko Ugo-*Chem., Pharm,* Bull., 2008; 56(8): 1126-1137.
4. Airody Vasudeva Adhikari, Karabasanagouda T., Ramgopal Dhanwad and G. Parameshwarappa, *Indian J. of Chem.*, Jan. 2008; 47 B: 144-152.
5. Yasuda, Nobuyuki, Karikome, Michinori, Toda, Takashi, *Chem., Lett.* (12), 1141-2-1995.
6. Bhavin Sutariya, Raziya S.K., S. Mohan and S.V. Sombassiva Rao, *Indian J. of Chem*., May 2007; 46 B: 884-887.
7. Airody Vasudeva Adhikari, Karabasanagouda T., Ramgopal Dhanwad and G. Parameshwarappa, *Indian J. of Chem.*, Jan. 2008; 47 B: 144-152.
8. Mr. Prakash Anil Castelina, Dr. Jagdish Prasad, Dr. Prasanntha Naik, Vol 4/ISSUE: 3/Mar. (2014)/ISSN-2249-555 x.
9. Khare, P.K., H. Singh, Shrivastava, *Indian J. Chem.*, Sec., May 2007; B: 875-879.
10. Pathan S.R., Dighe N. and S. Shinde, H.V. *Asian J. of Research chem*., 2(2), April-June 2009.
11. Suman Adhikari, S.B. Bari, A. Samanta, *Journal of Applied Research*, 2014; 8(1): 31-40.
12. Piotr Grodzinski, *American cancer society*, 3 Aug. (2012); DOI: 10.1002/CnCr. 27766.
13. Yue Yaun, Xijun Wang Bin Mei, *Dongxin Zhan Scientific Reports* 3, Article number: 3523, doi: 10.1038/srep 035 23; 29 November (2013).
14. Andrei L. Gartel, *Scientifica*, volume (2014) (2014), Article ID 59 658, http://dx. doi.org./10.1155/2014/596528.
15. Dr. Ho, Nanotech advancements, *Scientific hardness nanotechnology to better diagnose and tract cancer*, 120: 2781-2783; doi 10.1002/Cner.28982.
16. Patricia Urban and Zavier Fernandez Busquets, *Bentham science, Current Medicinal chemistry*, ISSN 1875-533 x. Volume 22, 38 Issues (2015).
17. Chun-Mao Lin and Tan-Yi Lu, *Bentham Science*, ISSN: 2212-4020.
18. Ming Wang, Mariana Holasia, Kasim Kabirov, Aryamitra Banerjee, *Cell Cycle*, 2012; *11:* 18.
19. Oriol Planas, Thibault Gallavardin and Santi Nonell, Institut Quimic de Sarria, Universitat Ramon L/ull Via Augusta, 390, 08017, DOI: 10.1039/C_4CC 09070 E ICommun, 2015; 51: 5586-5589.