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SYNTHESIS AND EVALUATION OF SOME NEW ORTHO HYDROXY BENZYLIDINES DERIVATIVES OF HETEROCYCLIC COMPOUNDS FOR THEIR BIOLOGICAL ACTIVITIES

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Abstract

The thiazole / oxazole nucleus is also known to possess various biological activities viz. antidepressant, hypertrophy, cardiac, antimicrobial, anaesthetic and antifungal activity. The different substituted heterocyclic moieties were condensed with ortho hydroxy benzaldehyde which was converted into various ortho hydroxy benzylidine-4- substituted thiazol / oxazol-2-amine. The structures of the synthesized compounds were characterized on the basis of IR and HNMR spectral data. All the synthesized compounds were screened for their antimicrobial activity against Bacillus pumillus, Micrococcus luteus, Pseudomonas aeruginosa, Pseudomonas fluorescens, and Penicillium chrysogenum, Aspergillus Niger for antifungal activity.

Keywords:Thiazole;Oxazole;Ortho-hydroxy benzaldehyde;Antifungal;Antibacterial.

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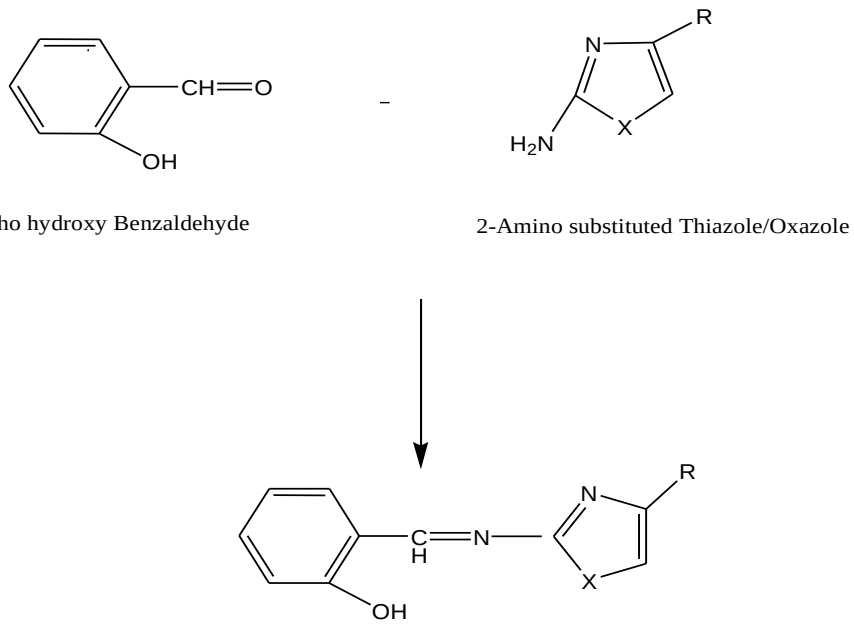
1. Introduction

The present investigating studies includes the chemistry and application of highly interesting and significantly useful sulphur and nitrogen molecules. Among the various branch of organic, sulphur and nitrogen chemistry, the chemistry of thiazole, pyrimidine, pyridine, thiadiazoles, oxadiazoles, tetralin occupy a position of importance. Thiazoles containing N=C-S moiety has been employed as an antipsychotic and antibacterial agent. Thiazole derivatives particularly amino thiazoles play vital role in pharmaceutical practice owing to their wide biological activities like fungicidal, antimicrobial, anti-tuberculosis, anticancer and anti-inflammatory. Several physiological activities of various thiazole derivatives have proved the efficiency and efficacy in combating various diseases and found to good antibacterial and antifungal activity and it has been seen that the thiazole analogues incorporated with different nuclei have shown variety of pharmacological profile such as anticancer etc.

Benzylidine /oxaquinazolin [1] phenyl semicarbazide & quinazolinone heterocyclic derivatives [2] shows antimicrobial and antifungal activities. Triazole derivatives of gallic acid [3] and 1,2,4 triazoles derivatives [4] found to possess antibacterial and antifungal activities. Pyrimidine containing furanose derivatives [5] and substituted pyrimidine derivatives [6] has been reported to possess various biological activities viz. antifungal, antioxidant, anticancer activities.

1,3,4 oxadiazoles [7], thiazolidinone derivatives [8], 2,4 di substituted thiazoles [9], thiazoles and 1,3,4 oxadiazoles [10] hybrid heterocycles has been known for antimicrobial and antifungal activities. Literature stud reveals that Pyrrole derivatives [11], tetrazoles derivatives [12], pyrano pyrazole derivatives [13], azoles and azine derivatives of tertiary butyl carbazate [14], Schiff base derivative [15], chalcones derivatives of heterocyclic compounds [16]-[17], heterocyclic based 6-chloro pyridazine thiones [18], substituted 3-indolylthiophene derivatives know for potential antimicrobial and antifungal activities [19].The present work describes the effect of ortho hydroxy group in the carbon phenyl nucleus on the course of reactions with substituted thiazole /oxazole nucleus and on the antibacterial, antifungal activities of the synthesized products.

Keeping all the view from the literature study and facts in mind the present work describes the condensation of ortho hydroxy benzaldehyde with 2-amino thiazole /4`-(p-subst/unsubst)-phenyl thiazole/ oxazole and evaluated for antibacterial & antifungal activity as given in scheme 1.



ortho hydroxy Benzaldehyde

2-Amino substituted Thiazole/Oxazole

ortho hydroxy benzylidene- 4-substituted thiazol/oxazol-2-amine

(1 - 14)

When X= S,Thiazole

Where 1. R= H
2. R= -C6H5
3. R= -C6H4Cl
4. R= -C6H4F
5. R= -C6H4NO2
6. R= -C6H4OCH3
7.R= -C6H4OH

When X= O,Oxazole

Where 8. R= H
9. R= -C6H5
10. R= -C6H4Cl
11. R= -C6H4F
12. R= -C6H4NO2
13. R= -C6H4OCH3
14. R= -C6H4OH

(Scheme-1)

2. Research Methods

All the melting points were determined in open capillary tubes. IR spectra were recorded in solid state using KBr pellet method. The spectra were recorded on Perkin Elmer FT-IR spectrophotometer (model RX-1). The PMR spectra were recorded in DMSO-d6 solvent at room

temperature using TMS as reference compound. The spectra were recorded on Perkin Elmer Model 32 NMR spectrometer at 300MHz at CDRI Lucknow. The reactions were monitored by TLC. The required 2-Amino-4-[p-subst/unsubst] phenyl thiazoles / oxazoles were prepared by know method. Procedure for one compound of each step has been described in sequel.

Synthesis of 2-Amino - Thiazole

A solution of 76 gm of thiourea in 200 ml of warm water is placed in 500ml three necked flask equipped with dropping funnel ,mechanical stirrer and reflux condenser.143 gm of α,β-dichloroethyl ether is added and the mixture is heated under gentle reflux with stirring for 2 hrs. As the reaction proceeds, the two layers gradually merge. To the cold solution, sufficient solid NaOH is added to liberate 2-Amino Thiazole from its salt. Ether is added to dissolve the product and ether is evaporated.2-Amino Thiazole is recrystallized from ethanol.

M.P.: 90- 91^{0}C.

IR (KBr): 1255 cm-^{1} (due to C-N), 694 cm-^{1} (due to C-S-C), 1615 & 1535 cm-^{1}(due to C=N)

PMR: δ 6.6 (s, 1H, due to -CH), δ 7.1 (s, 1H, due to -CH), δ 11.4 (d, 2H).

Synthesis of 2-Amino-4-phenyl Thiazole

A mixture of acetophenone (12.0gm, 0.1mol), thiourea (15.2gm, 0.2mol) and iodine (25.4gm, 0.1mol) was heated for 10 hours on a steam bath. The crude reaction mixture was cooled and repeatedly extracted with ether to remove unreacted acetophenone and iodine. The residue was then dissolved in hot water and filtered to remove sulphur and other impurities. The solution was then moderately cooled and made alkaline with conc. Ammonia.2-amino-4-phenyl thiazole, thus precipitated was collected and recrystallized from diluted ethanol as long colorless needles.

M.P.: 149^{0}C.

IR (KBr): 1255 cm-^{1} (due to C-N), 694 cm-^{1} (due to C-S-C), 1615 & 1535 cm-^{1}(due to C=N)

PMR: δ 6.6 (s, 1H, due to -CH), δ 7.5 (m, 5H, Aromatic), δ 11.35 (d, 2H,-NH_2).

Synthesis of 2-Amino – Oxazole

A solution of 60 gm of urea in 200 ml of warm water is placed in 500 ml three necked flask equipped with dropping funnel ,mechanical stirrer and reflux condenser.143 gm of α,β-dichloroethyl ether is added and the mixture is heated under gentle reflux with stirring for 2 hrs. As the reaction proceeds, the two layers gradually merge. To the cold solution, sufficient solid NaOH is added to liberate 2-Amino oxazole from its salt. Ether is added to dissolve the product and ether is evaporated.2-Amino oxazole is recrystallized from ethanol.

M.P.: 90- 95^{0}C.

IR (KBr): 1255 cm-^{1} (due to C-N), 1475 - 1453 cm-^{1}(due to C=N), 3065-3005 cm-^{1} (due to C-H), 1565-1558 cm-^{1} (due to N=C-O), 3300-3135 cm-^{1} (due to N-H),

PMR: δ 6.7 (s, 1H, due to -CH), δ 7.2 (s, 1H, due to -CH), δ 5.12 (br, s, 2H, due to NH_2).

Synthesis of 2-Amino-4-phenyl Oxazole:

A mixture of 2-bromo-1-phenylethanone (1.0 mmol), urea (1.0 mmol) and PEG (0.5mL) was stirred at room temperature until completion of the reaction (monitored by thin layer chromatography). The mixture was washed with water (4mL) extracted with ethyl acetate (3 X 15 ml); the organic phase was separated, dried over anhydrous sodium sulphate, and filtered. The solvent was removed under vacuum. The crude product was purified by silica gel column chromatography using ethyl acetate-petroleum ether (1:1).After extraction with ethyl acetate, the solution of H_2O and PEG 400 was concentrated.

B.P: 113-115^{0}C

IR (KBr): 1255 cm-^{1} (due to C-N), 1475 - 1453 cm-^{1}(due to C=N), 3065-3005 cm-^{1} (due to C-H), 1565-1558 cm-^{1} (due to N=C-O), 3300-3135 cm-^{1} (due to N-H), 1155-1103 cm-^{1} (due to C-O-C)

NMR: (300 MHz, CDCl3): δ 7.52–7.47 (m, 2H, ArH), 7.33–7.28 (m, 2H, ArH), 7.09 (m, 1H, ArH), 6.74 (s, 1H, oxazole), 5.17 (br s, 2H, NH2)

Similarly, 2-Amino-4-p-chloro/fluoro/nitro/methoxy/hydroxyl phenyl thiazoles /oxazoles were prepared.

Synthesis of ortho hydroxy benzylidine- 4- substituted thiazol -2- amine

Ortho hydroxy benzaldehyde (0.1 mol) and 2-amino-4-phenyl thiazole (0.1mol) were taken in benzene (100ml) in a R.B flask (250ml) fitted with Dean & Stark apparatus. The mixture was refluxed till water (0.1mol) was separate out. The mixture was then cooled to obtained the crude product which was recrystallize from ethanol to get white crystals of ortho hydroxy benzylidine- 4- substituted thiazol / oxazol-2- amine

Yield: 65%, M.P 125-127°C.

IR (KBr): 685cm^{-1} (due to C-S-C), 1605 cm^{-1} & 1250 cm^{-1} (due to C=N & C-N), 1600-1575cm^{-1} (due to azomethine proton), 1280-1270 cm^{-1} (due to C-O, due to phenolic)

PMR: δ 5.1 (1H, due to phenolic protons), δ 8.1 (singlet, due to azomethine proton), 2H), δ 9.85, δ 6.8 – 7.9 (m, 6H, Ar-H).

Synthesis of ortho hydroxy benzylidine- 4- substituted oxazol -2- amine.

Similarly ortho hydroxy benzylidine- 4- substituted oxazol -2- amine were prepared as per above method**.**

Yield: 67%, M.P 130-132°C.

IR (KBr): 685cm^{-1} (due to C-S-C), 1140-1100 cm-^{1} (due to C-O-C), 1605 cm^{-1} & 1250 cm^{-1} (due to C=N & C-N), 1600-1575cm^{-1} (due to azomethine proton), 1280-1270 cm^{-1} (due to C-O, due to phenolic)

PMR: δ 5.0 (1H, due to phenolic protons), δ 8.1 (singlet, due to azomethine proton), 2H), δ 9.85, δ 6.8 – 7.9 (m, 6H, Ar-H).

Similarly, ortho hydroxy benzylidine- 4- subst / unsubst thiazol / oxazol-2- amine were prepared.

Physical Data of Synthesized Compounds (Table-1)

Comp'd No.	Nature of R	Molecular Formula	MP°C	Yield (%)
1.	2-Amino- Thiazole	$C_{10}H_8N_2S$	125 – 127	65
2.	2-Amino-4-phenyl Thiazole	$C_{16}H_{12}N_2S$	138 – 140	62

3.	2-Amino-4-(p-chloro) phenyl Thiazole	$C_{16}H_{11}N_2SCl$	145 -147	58
4.	2-Amino-4-(p-fluoro) phenyl Thiazole	$C_{16}H_{11}N_2SF$	150-152	55
5.	2-Amino-4-(p-nitro) phenyl Thiazole	$C_{16}H_{11}N_3SO_2$	166-168	60
6.	2-Amino-4-(p-methoxy) phenyl Thiazole	$C_{17}H_{14}N_2SO$	164-166	55
7.	2-Amino-4-(p-Hydroxy) phenyl Thiazole	$C_{16}H_{12}N_2SO$	172-174	50
8.	2-Amino- oxazole	$C_{10}H_8N_2O$	130-132	67
9.	2-Amino-4-phenyl oxazole	$C_{16}H_{12}N_2O$	139-141	63
10.	2-Amino-4-(p-chloro) phenyl oxazole	$C_{16}H_{11}N_2Ocl$	151-153	58
11.	2-Amino-4-(p-fluoro) phenyl oxazole	$C_{16}H_{11}N_2OF$	165-167	62
12.	2-Amino-4-(p-nitro) phenyl oxazole	$C_{16}H_{11}N_3O_3$	173-175	65
13.	2-Amino-4-(p-methoxy) phenyl oxazole	$C_{17}H_{14}N_2O_2$	187-189	53
14.	2-Amino-4-(p-Hydroxy) phenyl oxazole	$C_{16}H_{12}N_2O_2$	184-186	52

3. Results and Analysis

Antibacterial & Antifungal Screening

The synthesized compounds were screened for their Antibacterial properties against Bacillus pumillus, Micrococcus luteus (gram positive bacteria), Pseudomonas aeruginosa, Pseudomonas fluorescens (gram negative bacteria) & Antifungal Properties against Penicillium chrysogenum, Aspergillus Niger. The activities of the synthesized compounds were tested by cup plate method, using a sterile cork borer of about 5 mm diameters. Wells were made in each petri dish using sterile syringe injected 0.1 ml of standard control and test into the cups. After injection the petri dishes were kept at room temperature for 24 hrs. For uniform diffusion of the agent to occur in seeded in agar medium. The petry dishes Incubated at 37±0.5 °C for 24 hrs. After 24 hrs. diameter of inhibition in millimeter was compared with standard drug. Norfloxacin (100 µgm/ml) used as standard for bacteria and Fluconazole (100 µgm/ml) used as standard for fungi. The zone of inhibition was measured in mm to estimate the potency of synthesized compounds as given in Table 2.

Table 2: Antibacterial & Antifungal Screenings of synthesized compounds

Inhibition Zone (in mm)						
Comp'd no.	**Gram + ve Bacteria**		**Gram – ve Bacteria**		**Fungi**	
	Bp	**Ml**	**Pa**	**Pf**	**Pc**	**An**
1	5	4	8	7	10	9
2	11	6	5	13	8	9
3	16	15	17	16	18	16
4	18	19	19	17	17	15
5	14	12	13	14	16	16
6	15	16	16	16	12	10
7	17	15	20	16	10	11
8	6	11	10	9	12	13
9	8	10	13	9	13	11
10	17	16	18	15	12	14
11	18	17	13	15	13	11
12	13	14	11	13	16	17
13	18	16	19	15	11	12
14	16	17	18	16	10	9
Norfloxacin	**20**	**22**	**24**	**18**	**-**	**-**
Fluconazole	**-**	**-**	**-**	**-**	**20**	**18**

Where Bp: Bacillus pumillus, Ml: Micrococcus luteus, Pa: Pseudomonas aeruginosa, Pf: Pseudomonas fluorescens, Pc: Penicillium chrysogenum, An: Aspergillus Niger

Zone of inhibition measured in mm (for Antibacterial compounds)

1. 11-15 mm: moderate activity
2. >15 mm: strong activity

Zone of inhibition measured in mm (for Antifungal compounds)

1. 11-15 mm: moderate activity

2. >15 mm: strong activity

From the activity Data (Table 2), we concluded that compound No 3, 4, 6, 7, 10, 11, 13 & 14 showed maximum inhibition against all the four strains Bacillus pumillus, Micrococcus luteus (gram positive bacteria), Pseudomonas aeruginosa, Pseudomonas fluorescens (gram negative bacteria) & compound No 2, 5 & 12 showed moderate activity against Bacillus pumillus, compound No 5 & 8 showed moderate activity against Micrococcus luteus. Compound No 5, 9, 11 & 12 showed moderate activity against Pseudomonas aeruginosa. Compound No 2, 5 & 12showed moderate activity against Pseudomonas fluorescens. From the above antibacterial screening data the compounds containing fluoro, methoxy & hydroxyl groups at para positions exhibited very good activity against both the strains.The synthesized compounds were also evaluated for Antifungal activity against Penicillium chrysogenum, Aspergillus Niger and found that Compound number 3, 4, 5, 12 showed maximum inhibitions against Penicillium chrysogenum & Aspergillus Niger. Compound number 6, 8, 9, 10, 11, 13 showed moderate inhibitions against Aspergillus Niger.

4. Conclusions

The antibacterial & antifungal screening data the synthesized compounds exhibit nitro group & fluoro at para positions exhibited strong activity against both the strains i.e. electron withdrawing group showed maximum inhibition in both the strains i.e. gram positive & gram negative.

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6. References

[1] Saravanan, G., Alagarsamy V. and Prakash, C.R. “Synthesis, Characterization and In Vitro Antimicrobial Activity of Some 1-(Substitutedbenzylidene)-4-(4-(2-(Methyl/Phenyl)-4-Oxoquinazolin-3(4H)-Yl) Phenyl) Semicarbazide Derivatives,” *J Saudi Chem Soc*, vol. 19, pp. 3–11, 2015.

[2] Singh, T., Sharma, S., Srivastava, V.K. and Kumar, A., "Synthesis, Insecticidal and Antimicrobial Activity of Some Heterocyclic Derivatives of Quinazolinone," *I J Chem*, vol. 45B, pp. 2558- 5, 2006.

[3] Mandal, S., Saha, D., Jain, V.K. and Jain, B., **"**Synthesis, Characterization and Evaluation of Antibacterial and Antifungal Activity of Triazole Derivatives Of Gallic Acid," *IJABPT*, vol. I, pp. 1300-11, 2010.

[4] Kotla, V.V. and Chunduri, V.R., "Synthesis and Antimicrobial Activity of Novel 1,2,4-Triazole Derivatives," *Der Pharmacia Sinica*, vol. 4, pp. 103-8 2013.

[5] Dudhe, R., Sharma, P.K. and Verma, P.K., "Pyrimidine Containing Furanose Derivative having Antifungal, Antioxidant, and Anticancer Activity," *Org Med Chem Letters*, vol. 4, pp. 2-18, 2014.

[6] Eatedal, H., All, A.E., Osman, N.A., Mahmoudy, A.M. and Hassan, A.N., "Synthesis of New Pyrimidine Derivatives and Evaluation of Their Anticancer and Antimicrobial Activities," *Asian J Pharm Clin Res*, vol. 9, pp. 306-13, 2016.

[7] Ramaprasad, G.C., Kalluraya. B., Kumar. B.S. and Mallya. S., "Synthesis, Antibacterial and Antifungal Activities of Some Novel 1, 3, 4-Oxadiazole Analogues," *Int J Pharm Pharm Sci*, vol. 4, pp. 210-3, 2012.

[8] Sharma, R. and Vijay, V., "Synthesis and Antimicrobial Activity of Thiazolidinone Derivatives," *IJRPS*, vol. 1, pp. 57-6, 2012.

[9] Arora, P., Narang, R., Bhatia, S., Nayak, S.K., Singh, S.K. and Narasimhan, B., "Synthesis, Molecular Docking and QSAR Studies of 2, 4-Disubstituted Thiazoles as Antimicrobial Agents," *J Appl Pharm Sci*, vol. 5, pp. 28-42, 2015.

[10] Desai, N.C., Bhatt, N.B., Somani, H.C. and Bhatt, K.A., "Synthesis and Antimicrobial Activity of Some Thiazole and 1,3,4-Oxadiazole Hybrid Heterocycles," *Ind J Chem*, vol. 55B, pp. 94-101, 2016.

[11] Idhayadhulla, A., Kumar, R.S. and Nasser, A.J.A., "Synthesis, Characterization and Antimicrobial Activity of New Pyrrole Derivatives," *J Mex Chem Soc*, vol. 55, pp. 218-223, 2011.

[12] Ali, O.M., "Synthesis and Antimicrobial Activity of New Tetrazole Derivatives from1(1H-tetrazol-5-yl) methyl)-1H-benzo[d][1,2,3] triazole as synthon," *I J Chem*, vol. 2, 2012,

[13] Amin, B.N., Parikh, A.R., Parikh, H. and Gudaparthi, V., "Synthesis and Screening of Antibacterial and Antifungal Activity of 6-Amino-4-(Aryl/Heteroaryl)Phenyl-3-Methyl-2,4-Dihydropyrano[2,3-*c*]Pyrazole-5- Carboxamide Derivatives," *Sch Acad J Pharm*, vol. 3, pp. 208-212, 2014.

[14] Ghoneim, A.A. and Assy, M.G., "Synthesis and Characterization of Antimicrobial Activity of Azoles and Azines Derivatives from Tertiary Butyl Carbazatel," *Organic Chem Curr Res*, vol. 4, 2015.

[15] Azab, M.E., Rizk, S.A. and Amr A.GE., "Synthesis of Some Novel Heterocyclic and Schiff Base Derivatives as Antimicrobial Agents," *Molecules*, vol. 20, pp. 18201-18, 2015.

[16] Mowlana, M.Y., Nasser, A.J.A. and Karthikeyan, R., "Synthesis, Characterization and biological activity of some Heterocyclic Chalcone Derivatives," *I J B Res*, vol. 5, 2014.

[17] Tran, D.T., Nguyen, T.N., Do, T.H., Huynh, T.N.P., Tran, C.D. and Thai, K.M., "Synthesis and Antibacterial Activity of Some Heterocyclic Chalcone Analogues Alone and in Combination with Antibiotics," *Molecules*, vol. 17, pp. 6684-6696, 2012.

[18] Nasser, M., Abd El-Salam, N.M., Mostafa, M.S., Ahmed, G.A., Alothman O.Y., "Synthesis and Antimicrobial Activities of Some New Heterocyclic Compounds Based on 6-Chloropyridazine-3(2*H*)-thione," *J of Chem*, pp. 1-8, 2013.

[19] Heba, M., Abo-Salem, Eslam, R., El-Sawy, Ahmed, Fathy. and Mandour, A.H., "Synthesis, Antifungal Activity, and Molecular Docking Study of Some Novel Highly Substituted 3-Indolylthiophene Derivatives," *Egyptian Pharmaceutical Journal*, vol. 13, pp. 71–86, 2014.