

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF 2-(DIALKYLAMINO)-N-(5-(5-(ALKYLTHIO)-1,3,4-OXADIAZOL-2-YL)BENZOXAZOL-2-YL) ACETAMIDES

Nageshwara Rao Chilumula, Blessi Priyanka K*, Ravi J*, Kusuma B, Kalyani T.,
Gade Dayakar

¹Department of Chemistry, Kakatiya University, Warangal, Andhra Pradesh, India

²Department of Pharmacy, Kakatiya University, Warangal, Andhra Pradesh, India

Article Received on
18 May 2014,

Revised on 12 June 2014,
Accepted on 06 July 2014

*Correspondence for
Author

Gade Dayakar

Department of Chemistry,
Kakatiya University, Warangal,
Andhra Pradesh, India

ABSTRACT

A series of 2-(dialkylamino)-n-(5-(5-(alkylthio)-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamides were synthesized by taking 4-carbomethoxyphenol a starting material. The final resultant compounds were evaluated for antimicrobial activity by using disc fusion method. All *E.coli* and *S.typhi*, *B.subtilis* and *S.aureus* and *A.niger* and *C.albicans* were adopted as Gram negative, Gram positive and fungal organisms. Among all the compounds of 2-(dialkylamino)-N-(5-(5-(alkylthio)-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamides (XV), compound XVd was active against both Gram positive *B.subtilis* and *S.aureus* and Gram negative bacteria *E.coli* and *S.typhi*.

Compound XVd, XVk and XVp were active against the organisms *A.niger* and *C.albicans*.

KEY WORDS: Oxadiazole, Benzoxazole, antibacterial, antifungal.

INTRODUCTION

Oxadiazole, a heterocyclic nucleus has attracted a wide attention of the chemist in search for the new therapeutic molecules. Out of its four possible isomers, 1,3,4-oxadiazole is widely exploited for various applications. A number of therapeutic agents such as HIV-integrase inhibitor raltegravir, a nitrofurantoin antibacterial furazolidone, a potent PDGFR inhibitor BB-83698, antihypertensive agents tadalafil and nesipidil are based on 1,3,4-oxadiazole moiety. The 1,3,4-oxadiazole undergoes number of reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical. The present study is an attempt to synthesise new oxadiazoles coupled with benzoxazoles microbial evaluation of

them. 1, 3, 4-Oxadiazole, Chemistry, Reactions, Syntheses Oxadiazoles are well known for their antifungal, antibacterial and anticancer activities.¹⁻⁵ Chemistry: A series of 2-(dialkylamino)-n-(5-(5-(alkylthio)-1, 3, 4-oxadiazol-2-yl) benzoxazol-2-yl) acetamides were synthesized by taking 4-carbomethoxyphenol a starting material. This upon nitration with aluminium nitrate in acetic acid- acetic anhydride (1:1) mixture 4-Carbomethoxy-2-nitrophenol (II) was formed. This upon reduction with sodium dithionite 4-carbomethoxy-2-aminophenol (III) was obtained. This upon cyclization with cyanogen bromide we got methyl-2-aminobenzoxazole-5-carboxylate (IV). This upon treatment with chloroacetyl chloride we got methyl 2-(2-chloroacetamido) benzoxazole-5-carboxylate (V). This upon dialkylation we got methyl-2-((2-(dialkylamino) acetamido))-benzoxazole-5-carboxylates (XII). This upon treatment with hydrazine hydrate 2-(dialkylamino)-n-(5-(hydrazinecarbonyl) benzoxazole-2-yl) acetamides (XIII) was formed. This upon cyclization with carbon disulphide Oxadiazole ring formed at 2nd position. 2-(dialkyl amino)-n-(5-(5-mercapto-1, 3, 4-oxadiazol-2-yl) benzoxazol-2-yl) acetamides (XIV). 2-(dialkylamino)-n-(5-(5-(alkylthio)-1, 3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamides (XV) was formed by alkylation of thiol. IR spectra -NH showed characteristic absorption band at 3364, C=O stretching at 1683 (C=O), (C=N) band at 1588, C-O-C band at 1284, C-N band at 1126 cm⁻¹.

I. Synthesis of 4-Carbomethoxy-2-nitrophenol (II)

To a solution of aluminium nitrate (40 gm) in acetic acid- acetic anhydride (1:1) mixture (60 ml), was added an appropriate phenol (I, 40 gm) in small portions, while cooling and shaking occasionally. The reaction mixture was left at room temperature for 1.5 hours while shaking the contents intermittently to complete the nitration. The resulting brown solution was diluted to complete the nitration. The resulting brown solution was diluted with ice-cold water and acidified with concentrated nitric acid to get a bulky, yellow precipitate. It was filtered washed with small quantity of methanol and purified by recrystallization from alcohol to get a yellow crystalline solid (44 g, 85%), m.p. 73°C. ^[6] Compound (XIIb): IR (cm⁻¹) 3364 (NH), 1683 (C=O), 1588 (C=N), 1284 (COC), 1126 (CN). ¹H NMR (dmsod6): 8.6 (s, 1H, CONH), 8.1 (dd, 2H, ArH), 7.8 (d, 1H, ArH), 7.7 (s, 1H, ArH), 3.9 (s, 3H, CH₃), 3.2 (s, 2H, CH₂), 2.3 (s, 6H, (CH₃)₂).

II. Synthesis of 4-carbomethoxy-2-aminophenol (III)

4-carbomethoxy-2-nitrophenol (II, 10 grams) was dissolved in boiling alcohol (50%, 100 ml) and sodium dithionite was added to this boiling alcohol solution until it becomes almost

colourless. Then the alcohol was reduced to one-third of its volume by distillation and the residual liquid was triturated with crushed ice. The resulting colourless, shiny product was filtered, washed with cold water and dried in the air. Its purification was effected by recrystallization from benzene to get colourless, shiny scales (5.1 g; 60%) m.p 143°C.^[7]

III.Synthesis of methyl-2-aminobenzoxazole-5-carboxylate (IV)

4-Carbomethoxy-2-aminophenol (III, 1.3mol) was dissolved in 1lit. Methyl alcohol and cooled the solution to 5°C by adding chopped ice. A cold suspension of Cyanogen bromide (1.5 moles) in 1lit.of water was added over a period of 5min with rapid stirring.The reaction mixture was stirred for 0.75hrs at room temperature, solid Sodium bicarbonate (1.3 moles) in small portions over a period of 1.5 hrs was added to bring the pH 6.5 -7.0. Stirring was continued for another 1hour. The solid was separated by filtration, washed with cold water and on recrystallization from ethyl alcohol has resulted white solid, yield 70% and M.P is 238°C.

IV.synthesis of methyl2-(2-chloroacetamido) benzoxazole-5-carboxylate (V)

A mixture of methyl-2-aminobenzoxazole-5-carboxylate (IV, 0.01mol) and chloro acetyl chloride (0.01mol) was taken in 20 ml of dry benzene and the reaction mixture was refluxed for 5hrs on a water bath. The solvent was evaporated and the residue was washed first with benzene and then with Petroleum ether. The compound was recrystallized from suitable solvent(s). The compound was found to be containing yield 72% and m.p.177°C.

V.synthesis of methyl-2-((2-(dialkylamino) acetamido))-benzoxazole-5-carboxylates (XII)

To a solution of Methyl-2-(2-chloroacetamido) benzoxazole-5-carboxylate (V, 0.01mol) in 20 ml of dry Acetone, N, N-dialkylamine (0.01mol) was added and the reaction mixture was refluxed for 5hrs on a water bath. The colorless products formed were recrystallized by suitable solvents. The compounds were characterized as the methyl- 2-((2-dialkylamino)acetamido))benzoxazole-5-carboxylates (XII) by their spectral data. For instance, to a solution of Methyl-2-(2-chloroacetamido) benzoxazole-5-carboxylate (V, 0.01mol) in 20ml of dry Acetone, dimethylamine (0.01mol) was added and the reaction mixture was refluxed for 5hrs, the colorless product formed has been purified by recrystallization from alcohol resulted white solid, yield 65% m.p 164°C.

VI.Synthesis of 2-(dialkylamino)-n-(5-(hydrazinecarbonyl) benzoxazole-2-yl) acetamides (XIII)

A mixture of methyl-2-(2-(dialkylamino)acetamido)benzoxazole-5-carboxylate (XII,0.01mol) and hydrazine hydrate (99%) (0.02mol) were taken in 50ml of alcohol, heated under reflux on a water bath for 5hrs. The alcohol was reduced to half of its volume and cooled.The product separated was filtered and washed with small portions of cold alcohol first and then with cold water repeatedly and dried. The product was purified by recrystallization from suitable solvents. The compounds were characterized by spectral data. For example, the compound obtained on reaction of methyl-2-(2-(dimethylamino) acetamido) benzoxazole-5-carboxylate (0.01mol) with hydrazine hydrate (99%, 0.02mol) yielded a white solid. The product was purified by recrystallization from methanol. The compound was found to be containing yield 77% and m.p 258°C. Compound (XIIIa):IR (cm⁻¹) 3364(NH₂), 3150(NH), 1683(C=O), 1615(C=C), 1576(C=N),1223(COC).¹HNMR(dmsod6):9.3(s,1H,NH),8.8(s,1H,NH),7.8(s,1H,ArH),7.5(dd,1H,Ar-H),7.3(dd,1H,Ar-H)5.4(s,2H,NH₂),3.8(s,2H,NH₂),2.9(s,6H,(CH₃)₂).

VII.synthesis of 2-(dialkylamino)-n-(5-(5-mercapto-1,3 ,4-oxadiazol-2-yl)benzoxazol-2-yl) acetamides (XIV)

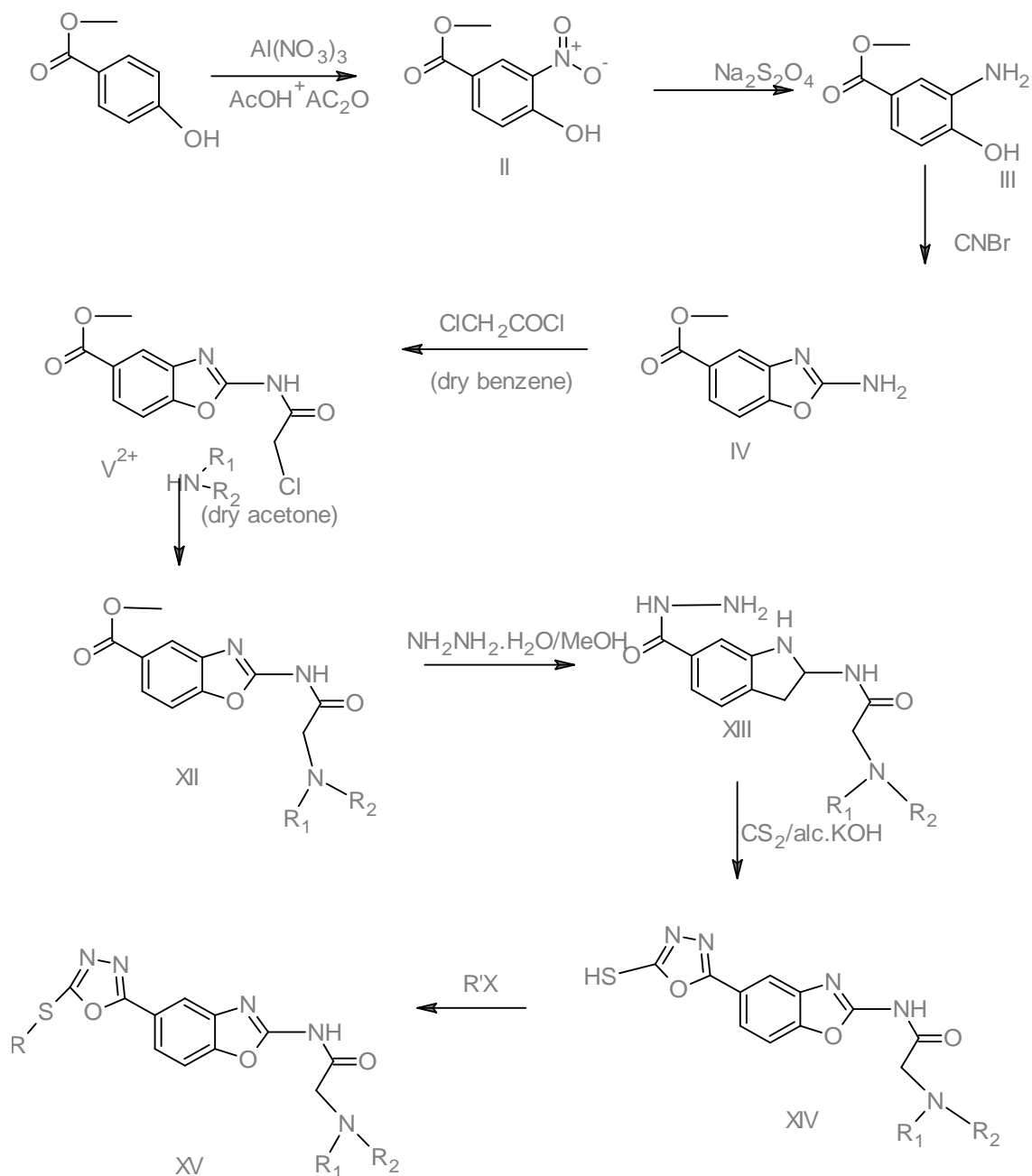
Each of the 2-(dialkylamino)-N-(5-hydrazinecarbonyl)benzoxazole-2-yl)acetamide was been subjected to a reaction with carbon-di-sulphide in alcoholic potassium hydroxide by heating under reflux for 3hrs , the resulted solid was acidified with 10% hydrochloric acid to get a colourless product. It was purified by alcohol and characterized as 2-(dialkylamino)-N-(5-(5-mercapto-1, 3, 4-oxadiazol-2-yl) benzoxazol-2-yl) acetamide (XIV) based on its analytical and spectral data. For instance, 2-(dimethylamino)-N-(5-hydrazinecarbonyl) benzoxazole-2-yl) acetamide (XIIIa) on heating with alcoholic potassium hydroxide and carbon-disulphide, for 3hrs, yielded a product (XIVa). The product on purification by recrystallization from alcohol yielded crystalline solid, m.p 302°C.Compound (XIVa):IR (cm⁻¹):3146(NH), 1708(C=O), 1626(C=C),1528(C=N),1428(SH).¹HNMR(dmsd6):8.8(s,1H,NH),8.2(s,1H,SH),8.0(s,1H,AR H), 7.9(d,1H,Ar-H),7.8(d,1H,Ar-H),4.2(s,2H,CH₂),2.7(s,6H,(CH₃)₂).

VIII.Synthesis of 2-(dialkylamino)-N-(5-(5-(alkylthio)-1, 3, 4-oxadiazol-2-yl)benzoxazol-2-yl) acetamides (XV)

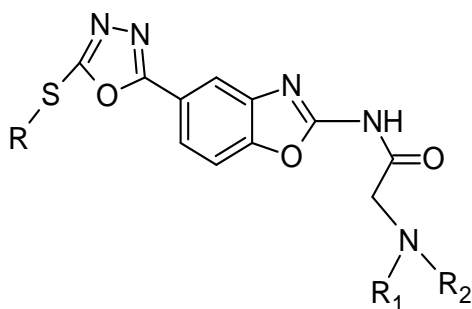
Each of the 2-(dialkylamino)-N-(5-(5-mercapto-1, 3, 4-oxadiazol-2-yl) benzoxazol-2-yl)acetamide (0.01m, XIV) was treated with 0.01mol of methyl iodide, ethylbromide and n-butylbromide. This reaction mixture was stirred in alcoholic potassium hydroxide (5%) for 4hrs. The product obtained on workout, in each case was purified by recrystallization from suitable solvent(s) and characterized as respective 2-(dialkylamino)-N-(5-(5-(alkylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)acetamides (XV), by its satisfactory physical and spectral data. For instance, 2-(dimethylamino)-N-(5-(5-mercapto-1, 3, 4-oxadiazol-2-yl) benzoxazol-2-yl)acetamide was treated with methyl iodide obtained a single product. This on purification by recrystallization from alcohol has resulted a crystalline solid, m.p 265C°. Compound (XVa):IR (cm⁻¹):3363(NH), 1682(C=O), 1575(C=C), 1565(C=N), 1442(SH), 1195(CS).¹HNMR(dmsod6):8.2(s,1H,NH),7.9(s,1H,ArH),7.7(d,1H,ArH),7.6(d,1H,ArH),4.0(s,2H,CH₂),2.8(s,6H,(CH₃)₂),2.4(s,3H,CH₃).Mass: Molecular ion peak was observed at 333.

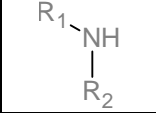
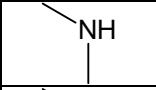
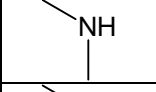
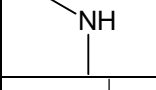
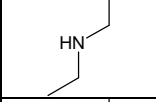
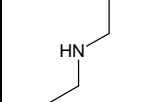
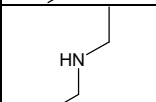
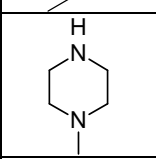
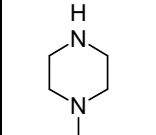
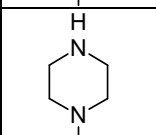
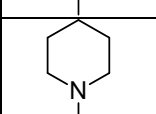
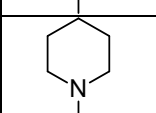
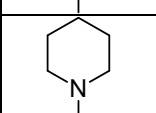
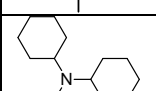
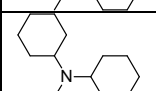
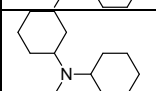
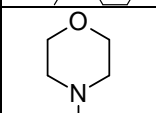
RESULTS AND DISCUSSION

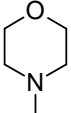
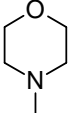
Among all the compounds of 2-(dialkylamino)-N-(5-(5-(alkylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)acetamides (XV, Table 2), compound XVd was active against both Gram positive organisms *B.subtilis* and *S.aureaus* and Gram negative bacteria *E.coli* and *S.typhi* with zone of inhibition of 23mm, 21mm, 19mm and 18mm respectively. Compound XVk was also active against both types of organism with zone of inhibition of 21mm, 20mm, 25mm and 20mm respectively. Rest of the compounds in this series was mild to moderate active against *B.subtilis*, *S.aureaus*, *E.coli* and *S.typhi*. Compounds XVn was not active against the test organisms. Compounds XVg, XVh and Xvi were not active against gram positive bacteria, where as compounds XVo and XVp were not active against gram negative bacteria. Among the compounds of 2-(dialkylamino)-N-(5-(5-(alkylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl) acetamides (XV, Table 2) compound XVp was more active against the organisms *A.niger* and *C. albicans* with the zone of inhibition of 21mm and 25mm respectively. Compounds XVd and XVk were also equipotent in the activity. Rest of the compounds was mild to moderately active against test organisms.



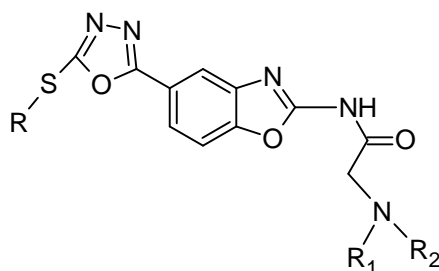
Physical data of 2-(dialkylamino)-n-(5-(5-(alkylthio)-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamides (XV)







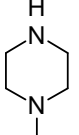
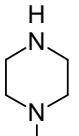


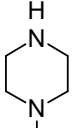
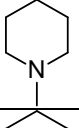
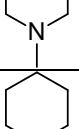
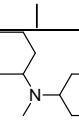
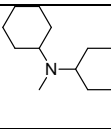
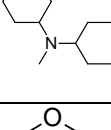
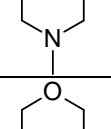
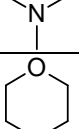
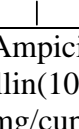
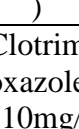
S.No.	Compound		R''	Chemical formula	Melting Point	Yield (%)
1	XVa		Methyl	C ₁₄ H ₁₅ N ₅ O ₃ S	265	75
2	XVb		Ethyl	C ₁₅ H ₁₇ N ₅ O ₃ S	322	74
3	XVc		n-butyl	C ₁₇ H ₂₁ N ₅ O ₃ S	305	74
4	XVd		Methyl	C ₁₆ H ₁₉ N ₅ O ₃ S	289	80
5	XVe		Ethyl	C ₁₇ H ₂₁ N ₅ O ₃ S	265	76
6	XVf		n-butyl	C ₁₉ H ₂₅ N ₅ O ₃ S	298	77
7	XVg		Methyl	C ₁₆ H ₁₈ N ₆ O ₃ S	248	78
8	XVh		Ethyl	C ₁₇ H ₂₀ N ₆ O ₃ S	301	78
9	XVi		n-butyl	C ₁₉ H ₂₄ N ₆ O ₃ S	297	60
10	XVj		Methyl	C ₁₇ H ₁₉ N ₅ O ₃ S	326	79
11	XVk		Ethyl	C ₁₈ H ₂₁ N ₅ O ₃ S	325	69
12	XVl		n-butyl	C ₂₀ H ₂₅ N ₅ O ₃ S	209	77
13	XVm		Methyl	C ₂₄ H ₃₁ N ₅ O ₃ S	218	62
14	XVn		Ethyl	C ₂₅ H ₃₅ N ₅ O ₃ S	226	76
15	XVo		n-butyl	C ₂₇ H ₃₇ N ₅ O ₃ S	232	51
16	XVp		Methyl	C ₁₆ H ₁₇ N ₅ O ₄ S	312	65

17	XVq		Ethyl	C ₁₇ H ₁₉ N ₅ O ₄ S	308	70
18	XVr		n-butyl	C ₁₉ H ₂₃ N ₅ O ₃ S	269	72

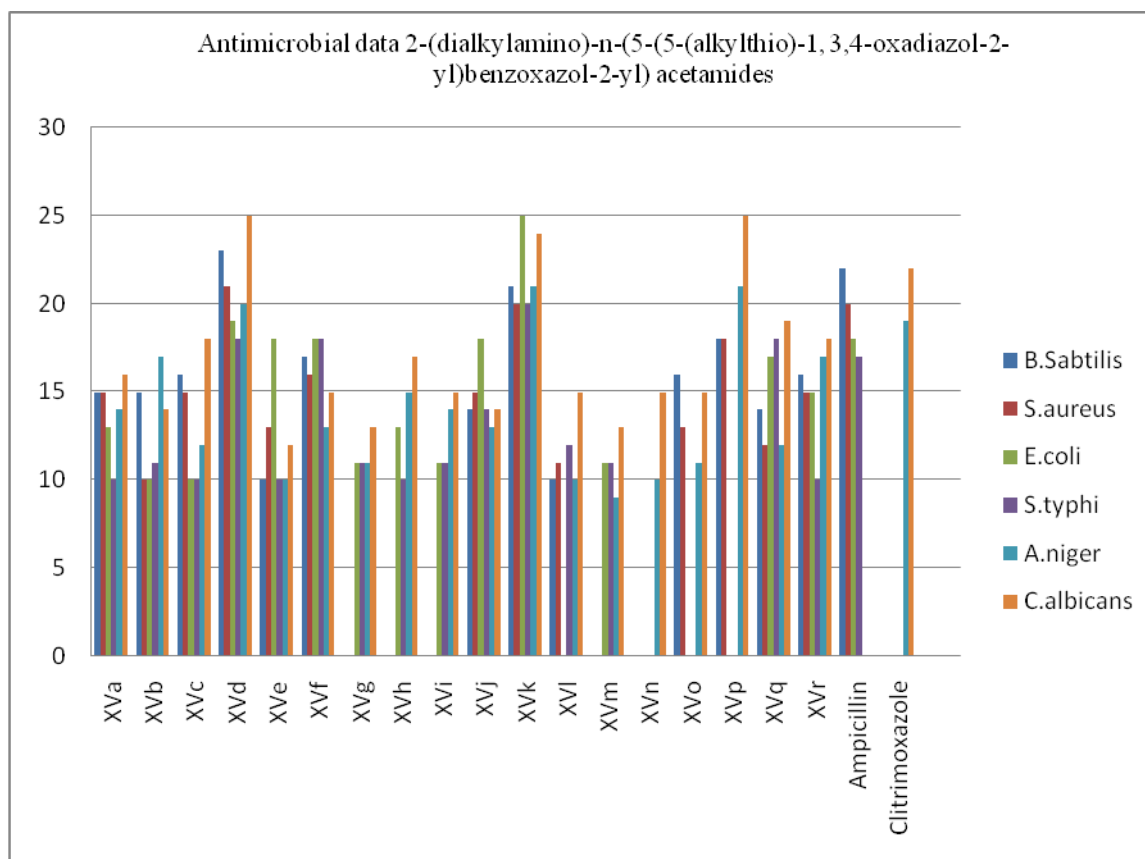
Antimicrobial data 2-(dialkylamino)-n-(5-(5-(alkylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl) acetamides (XV)



S. No	Compound	R ₁ -NH R ₂	R''	Zone of inhibition					
				B.Sabtilis	S.aureus	E.coli	S.typhi	A.niger	C.albicans
1	XVa		Methyl	15	15	13	10	14	16
2	XVb		Ethyl	15	10	10	11	17	14
3	XVc		n-butyl	16	15	10	10	12	18
4	XVd		Methyl	23	21	19	18	20	25
5	XVe		Ethyl	10	13	18	10	10	12
6	XVf		n-butyl	17	16	18	18	13	15
7	XVg		Methyl	--	--	11	11	11	13
8	XVh		Ethyl	--	--	13	10	15	17

9	XVi		n-butyl	--	--	11	11	14	15
10	XVj		Methyl	14	15	18	14	13	14
11	XVk		Ethyl	21	20	25	20	21	24
12	XVl		n-butyl	10	11	--	12	10	15
13	XVm		Methyl	--	--	11	11	9	13
14	XVn		Ethyl	--	--	--	--	10	15
15	XVo		n-butyl	16	13	--	--	11	15
16	XVp		Methyl	18	18	--	--	21	25
17	XVq		Ethyl	14	12	17	18	12	19
18	XVr		n-butyl	16	15	15	10	17	18
19	std	Ampicillin (10 mg/cup)		22	20	18	17	--	--
20	std	Clotrimazole (10mg/cup)		--	--	--	--	19	22

Concentration of the test compound: 100mg/cup.



CONCLUSION

Among all the compounds of 2-(dialkylamino)-N-(5-(5-(alkylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)acetamides (XV), compound XVd was active against both Gram positive B. subtilis and S. aureus and Gram negative bacteria E. coli and S. typhi. Compound XVd, XVk and XVp were active against the organisms A. niger and C. albicans.

REFERENCES

1. L.D.S. Yadav and Saigal, Indian Journal of Chemistry, (1995), 34B, 500-503.
2. K. Mogilaiah, K. Srinivas and R. Sudhakar, Indian Journal of Chemistry, (2004), 43B, 2014-2017.
3. H. Liszeiewicz, M. W. Kowalska, J. Weitryk and A. Opolski, Indian Journal of Chemistry, (2003), 42B, 2846-2852.
4. K. S. Bhat, M. S. Karthikeyan, B. S. Holla and N. S. Shetty, Indian Journal of Chemistry, (2004), 43B, 1765-1769.
5. K. Laya, P. Patel, P. Upadhyay and H. Parekh, Indian Journal of Chemistry, (1996), 35B, 1062-1066.

6. Gerard P.Moloney,James A.Angu,Alan D.Robertson,Martin J.Stormer,Michel Robinon,Christine E.Wright,Ken McRae,Arthur Christopoulo,European Journal of Medicinal Chemistry,(2008),43,513-539.
7. Ana Cristina Lima Leite,Renata Freitas Fisher Vieira,Diogo Rodrigo deM.Moreira,Dalci Jose Brondani,Rajendra .Srivastava,Veronica Freitada Silva,Marcos Antonio de Morais ,Junior mutation research,(2005),588,166-171.