SYNTHESIS AND BIOLOGICAL APPLICATIONS OF 1, 2-BENZISIXAZOLYL GLUCURONIDES

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ABSTRACT

*A variety of 1-{3-methyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazol-5-yl}-ethan-1-ones (**4a-k**) were prepared by the condensation of hydroxylamine hydrochloride with various N-(5-acetyl-3-methyl-1,2-benzoxazol-7-yl)-3-arylprop-2-enamides (**3a-k**).Oxidation of (**4a-k**)with alkaline $KMnO_4$ solution afforded5-acetyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazole-3-carboxylic acids (**5a-k**). Glucuronidation of (**5a-k**)with free D-gluconic acid by using dry pyridine to afford β-D-glucuronosyl-5-acetyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazole-3-carboxylates (**6a-k**). The structure of these compounds has been characterized on the basis of their sophisticated instrumental analysis like FT-IR, ^{1}H-NMR, FAB-MS, elemental analysis and chemical properties. Some compounds showed significant antibacterial activity against E. coli and S. aureus and moderate to feeble antifungal activity against A. niger and C. albicans.*

Introduction

Continuing my studies about the synthesis of 1,2-benzisoxazoles,chalcones, isoxazoles and glucuronides, herein we describe the synthesis of 1,2-benzisoxazoles, chalcones,isoxazoles and their β-D-glucuronidederivatives. 1,2-Benzisoxazolederivatives have been used as potential anti-inflammatory, analgesic,sedative etc. agents.1,2-Benzisoxazoles have beenused like potentialtuberculostearicagents.Several derivatives of 1,2-benzisoxazole havebeen found to possess antidepressant,hypertensive, anticonvulsant and antifungalproperties[1-4].A large number of chalcones have displayed interesting antineoplastic, diuretic, choleretic andantidiabetic properties. Various derivatives show anti-inflammatory, antibacterial, antiviral and gastric protectant activities. It possesses insecticidal, antimicrobial and antipicorhenovirus activities. Chalcones find applications in industries and some of the chalcones are used as artificial sweeteners. Various chalcones find their applications in photosensitive polymers, produce nematic liquid crystals and as an antioxidant for oils[5-11].Isoxazoles are important class of five-membered heterocycles associated with biological activities. Naturally occurring isoxazoles are used as anti-tuberculosis drug. Isoxazole derivatives involve substances with analgesics and local anaesthetic activity. The activities of isoxazoles include main topics like remarkable antileprous,psychotherapy, anabolic, antibacterial, antiviral, anti-inflammatory, antifungal *etc*. properties[12-14].β-D-Glucuronides are the conjugation productsof compounds possessing a carboxylic acidfunctional group with free D-glucuronic acid.β-D-Glucuronides are polar and chemicallyreactive metabolites[15-16]. Prompted by above facts some β-D-glucuronide compounds have been synthesized with a view to studying their biological profile.

The desired compounds 1-{3-methyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazol-5-yl}-ethan-1-ones (**4a-k**) were prepared by condensing (**3a-k**) with hydroxylamine hydrochloride in 2% NaOH solution. Similarly,β-D-glucuronosyl-5-acetyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazole-3-carboxylates (**6a-k**) were synthesized by glucuronidation of5-acetyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazole-3-carboxylic acids (**5a-k**) with glucuronic acid.Their structures were established by the spectral studies.

Experimental
Material and Methods

All the starting materials and reagents were obtained from Merk, Aldrich (USA) and Rankem Pvt Ltd (India) and were used without further purification. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded as KBr pallets on Shimadzu-810 IA and Perkin Elmer FTIR spectrometer and only significant

absorption levels (cm^{-1})are listed. ^1H NMR spectra were recorded on Bruker AC-300F (300MHz) instrument with TMS as internal standard and the chemical shift are expressed in ppm values. Mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer using *m*-nitrobenzyl alcohol (NBA) matrix. Elemental analyses were quite comparable with their structures.

General procedure of synthesis

N-(5-Acetyl-3-methyl-1, 2-benzoxazol-7-yl)-acetamide (2a)

The starting compounds 1-(7-amino-3-methyl-1,2-benzoxazol-5-yl)-ethan-1-one**1** have been prepared according to the reported work[17].To a solution of **1** (0.1 mole, 19.01g) in dry benzene (50ml), acetyl chloride (0.1 mole) was added drop by drop at 0-5^{0}C. The reaction mixture was stirred for 1hr and kept over night. The excess of solvent was distilled off under reduced pressure and then cooled mixture poured onto ice. The solid thus obtained were crystallized by using appropriate solvents(12.0g, 63.1%), m.p. 112^{0}C. IR (KBr): 1715 (C=O str aryl ketone), 1652 (C=O of NHCO), 1360 (C-O), 3005 (Ar-H), 2930 (methyl C-H) cm^{-1}; ^1H NMR ($CDCl_3$): signal at δ2.8 (s, 3H, CH_3), 7.5-9.3 (m, aromatic protons), 6.0-6.8 (2H, d, CH=CH), 2.80 (s, 3H, $COCH_3$), 8.6 (s, 1H, NHCO); FAB-MS: M^+ 232, m/z 216, m/z 190, m/z 176, m/z 134 and m/z 132.

N-(5-Acetyl-3-methyl-1,2-benzoxazol-7-yl)-3-phenylprop-2-enamide (3a)

A solution of*N*-(5-acetyl-3-methyl-1,2-benzoxazol-7-yl)-acetamide **2a** (0.01 mole, 3.32g) in absolute ethanol (50ml) in 2% NaOH was refluxed for 7-12hrs, reaction mixture cooled and poured onto ice. The obtained solid was filtered, washed with water and crystallized from appropriate solvent (2.3g, 71.8%), m.p.114^{0}C. IR (KBr): 1730 (C=O str aryl ketone),1665(C=O of NHCO), 1620 (CH=CH), 3410 (N-H), 3007 (Ar-H), 2930 (methyl C-H) cm^{-1}; ^1H NMR ($CDCl_3$): signal at δ2.3 (s, 3H, CH_3), 7.4-8.7 (m, aromatic protons), 6.74 (d, 1H, COCH=), 8.5 (d, 1H, =CH-Ar), 8.6 (s, 1H, NHCO); FAB-MS: M^+320, m/z 232, m/z 190, m/z 175, m/z 134 and m/z 132.

In the same way, various *N*-(5-acetyl-3-methyl-1,2-benzoxazol-7-yl)-3-arylprop-2-enamides (**3a-k**) were synthesized.

1-{3-Methyl-7-[(5-phenyl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazol-5-yl}-ethan-1-one (4a)

A mixture of **3a** (0.01 mole, 3.20g) in methanol (50ml), hydroxylamine hydrochloride (0.01 mole) was added. The reaction mixture was refluxed for 10hrs in presence of 2% NaOH solution. The reaction mixture was cooled and poured onto ice. The obtained solid was filtered, wash with water and crystallized from appropriate solvent[18] (2.1g, 62.6%), m.p. 110^{0}C. IR (KBr): 1732 (C=Oketone), 1232 (-C-O-N of isoxazole), 1570 (C=N), 3412 (N-H), 3009 (Ar-H), 2930 (methyl C-H) cm^{-1}; ^1H NMR ($CDCl_3$): signal at δ2.8 (s, 3H, CH_3), 7.4-8.5 (m, aromatic protons), 2.63 (m, 2H, isoxazole CH_2), 6.5 (s, 1H for isoxazoles ringC_4-H), 8.6 (s, 1H, NH); FAB-MS: M^+ 335, m/z 259, m/z 190, m/z 175, m/z 133, m/z 132 and m/z 119.

Following the above procedure 1-{3-methyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazol-5-yl}-ethan-1-ones (**4a-k**)were prepared and compounds gave satisfactory C, H, and N analysis (**Table I**).

5-Acetyl-7-[(5-phenyl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazole-3-carboxylic acid (5a)

In 100ml round bottom flask a mixture of 1-{3-methyl-7-[(5-phenyl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazol-5-yl}-ethan-1-ones **4a** (0.01mol, 3.35g), sodium carbonate (1.5g), $KMnO_4$ (1.5g) and water (100ml) was refluxed under water bath for 4hrs, until the purple colour has disappeared. It was acidified with dil. H_2SO_4, the excess manganese dioxide was removed by sodium metabisulphite (0.1g), filtered, washed and crystallized with water (2.4g, 71.6%), m.p. 103^{0}C. IR (KBr): 3460 (OH peak), 1732 (C=O), 1232 (-C-O-N of isoxazole), 1365(C=N ter. amine), 3410 (N-H); ^1H-NMR signal at δ10.5 (s, COOH), 6.2-7.7 (m, aromatic protons), 2.62 (m, 2H, isoxazole CH_2), 8.5 (s, 1H, NH); FAB-MS: M^+ 365, m/z 289, m/z 220, m/z 205, m/z 175 and m/z 133, m/z 161, m/z 119.

In the same way, various carboxylic acids, 5-acetyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-

amino]-1,2-benzoxazole-3-carboxylic acids (**5a-k**) were synthesized.

β-D-Glucuronosyl-5-acetyl-7-[(5-phenyl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazole-3-carboxylate (6a).

To a solution of 5-acetyl-7-[(5-phenyl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazole-3-carboxylic acid **5a**(0.01 mol, 3.65g) in dry pyridine (5ml), which was kept at 0^0C, D-glucuronic acid (1.94g) was added in portion with constant stirring. The reaction mixture was left at room temperature for 18hrs and it was poured over crushed ice. The resulting white product was filtered and washed with ice-cold water (2.02g, 55.3%). FAB-MS: M^+ 541, the base peak appearing at m/z 365 (due toloss of D-glucuronic acid moiety), m/z 289, m/z220, m/z 205, m/z 175 and m/z 161.

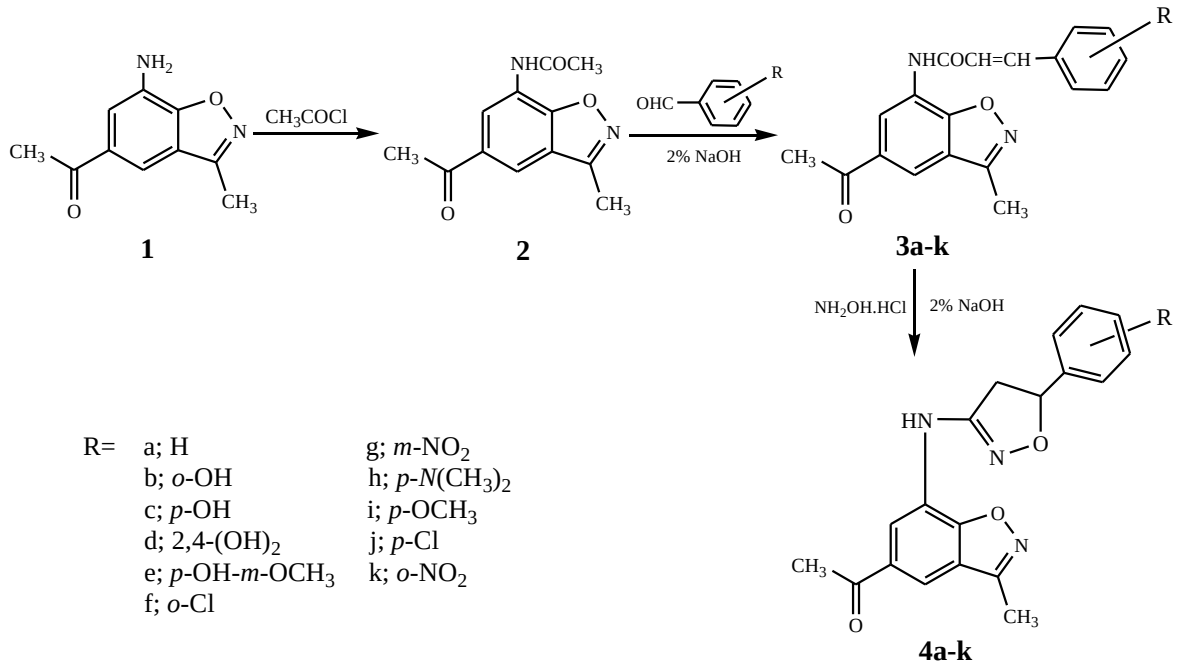
Following the above procedure, others β-D-Glucuronosyl-5-acetyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazole-3-carboxylates (**6a-k**)wereprepared starting from the appropriate carboxylicacids. Compounds gave satisfactory C, H, and Nanalysis (**Table 2**).

Microbial Activities

The synthesized compounds were tested for their antibacterial activities by the using the cup plate method against *S. aureus*(gram-positive) and *E. coli* (gram-negative) at concentration of 100µg/ml in DMF. Pure Norfloxacin was used as standard antibiotic for the comparison of the results. The sterilized Mullier-Hinton agar medium 50ml was inoculated with test organism and poured into petridishes. Then four holes of 6mm were completely filled with different test solution. Theplates were then incubated for 24hrs at 37^0C and zones of inhibitions were measured. Similar procedure was adopted for pure Norfloxacin and the corresponding zone diameters were compared. Screening results indicate that compounds **4a-o** showed to excellent bactericidal activities against both organisms (**Table 3**).The antifungal activity of synthesized compounds was evaluated by the using above same procedure (cup-plate) against *Aspergillus niger* and *Candida albicans* at a concentration100µm/mL in DMF. The plates were incubated for 8 days at 37^0C. The zones of inhibitions were measured. A commercial fungicide griseofulvin was also tested under similar condition with aview of comparing the results. The compounds showed significant fungi toxicity against both the fungi (**Table 3**).

Result and Discussion

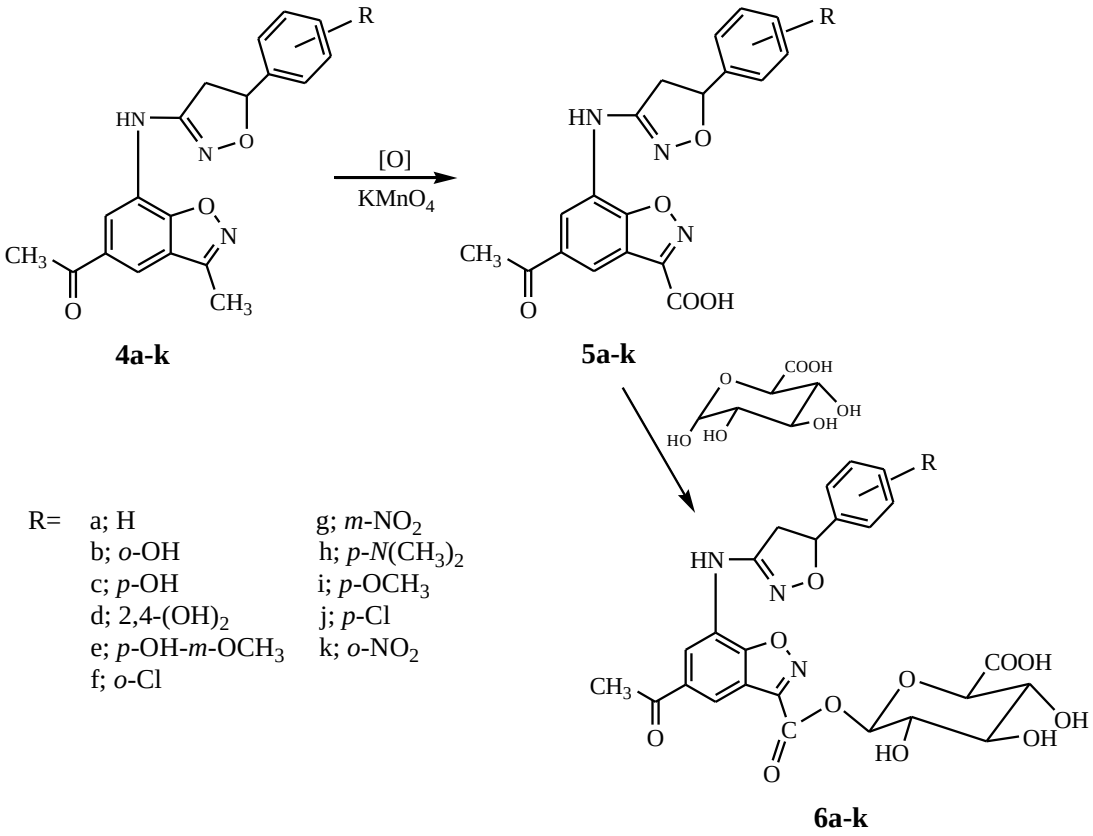
In view of pronounced biological applications of some β-D-glucuronosyl-5-acetyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazole-3-carboxylates**6a-k**have been prepared with a view of study their biological significance by the glucuronidation of 5-acetyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazole-3-carboxylic acids**5a-k** with free D-glucuronic acid using dry pyridine. The above acids were prepared by the oxidation of 1-{3-methyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazol-5-yl}-ethan-1-ones **4a-k**using alkaline $KMnO_4$solution and the products **4a-k**were prepared by cyclization of *N*-(5-acetyl-3-methyl-1,2-benzoxazol-7-yl)-3-aryl prop-2-enamides **3a-k** with $NH_2OH.HCl$ using NaOH. Compounds **3a-k**were obtained by thecondensation of *N*-(5-acetyl-3-methyl-1,2-benzoxazol-7-yl)-acetamide **2a**with different aldehydes using NaOH solution and product **2a** is obtained from the starting compound 1-(7-amino-3-methyl-1,2-benzoxazol-5-yl)-ethan-1-one**1** by using dry benzene and acetyl chloride.



Scheme I

Table 1.Characterization data of 1-{3-methyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazol-5-yl}-ethan-1-ones (**4a-k**)

Comp	R	Molecular Formula	Mol. Wt.	M.P. (^{0}C)	R_f Value	Calculated (Found) %		
						C	H	N
4a	H	$C_{19}H_{17}N_3O_3$	335.3	110	0.20	68.05 (68.00)	5.11 (5.10)	12.53 (12.53)
4b	*o*-OH	$C_{19}H_{17}N_3O_4$	351.3	102	0.19	64.95 (64.95)	4.88 (4.87)	11.96 (11.64)
4c	*p*-OH	$C_{19}H_{17}N_3O_4$	351.3	111	0.31	64.95 (64.93)	4.88 (4.87)	11.96 (11.95)
4d	2,4-$(OH)_2$	$C_{19}H_{17}N_3O_5$	367.3	98	0.25	62.12 (62.11)	4.66 (4.62)	11.44 (11.40)
4e	*p*-OH-*m*-OCH_3	$C_{20}H_{19}N_3O_5$	381.3	104	0.32	62.99 (62.97)	5.02 (5.01)	11.02 (10.98)
4f	*o*-Cl	$C_{19}H_{16}ClN_3O_3$	369.8	109	0.26	61.71 (61.69)	4.36 (4.35)	11.36 (11.34)
4g	*m*-NO_2	$C_{19}H_{16}N_4O_5$	380.3	108	0.28	60.00 (59.60)	4.24 (4.24)	14.73 (14.72)
4h	*p*-*N*$(CH_3)_2$	$C_{21}H_{22}N_4O_3$	378.4	107	0.30	66.65 (66.64)	5.86 (5.86)	14.81 (14.78)
4i	*p*-OCH_3	$C_{20}H_{19}N_3O_4$	365.3	109	0.32	65.74 (65.72)	5.24 (5.23)	11.50 (11.47)
4j	*p*-Cl	$C_{19}H_{16}ClN_3O_3$	369.8	99	0.30	61.71 (61.70)	4.36 (4.34)	11.36 (11.30)
4k	*o*-NO_2	$C_{19}H_{16}N_4O_5$	380.3	108	0.26	60.00 (59.58)	4.24 (4.23)	14.73 (14.71)



Scheme II

Table 2. Characterization data of β-D-Glucuronosyl-5-acetyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazole-3-carboxylates (**6a-k**)

Comp	R	Molecular Formula	Mol. Wt.	$[\alpha]_D^{25}$ (^{0})	R_f Value	Calculated (Found) %		
						C	H	N
6a	H	$C_{25}H_{23}N_3O_{11}$	541.4	+44.2	0.27	55.45 (55.44)	4.28 (4.25)	7.76 (7.75)
6b	*o*-OH	$C_{25}H_{23}N_3O_{12}$	557.4	+41.3	0.19	53.86 (53.84)	4.16 (4.15)	7.54 (7.54)
6c	*p*-OH	$C_{25}H_{23}N_3O_{12}$	557.4	+39.4	0.31	53.86 (53.80)	4.16 (4.13)	7.54 (7.52)
6d	2,4-$(OH)_2$	$C_{25}H_{23}N_3O_{13}$	573.4	+40.5	0.32	62.36 (62.35)	4.04 (4.02)	7.33 (7.32)
6e	*p*-OH-*m*-OCH_3	$C_{26}H_{25}N_3O_{13}$	587.4	+42.4	0.26	53.15 (53.15)	4.29 (4.27)	7.15 (7.16)
6f	*o*-Cl	$C_{25}H_{22}ClN_3O_{11}$	575.9	+34.6	0.28	52.14 (52.12)	3.85 (3.84)	7.30 (7.28)
6g	*m*-NO_2	$C_{25}H_{22}N_4O_{13}$	586.4	+40.2	0.32	51.20 (51.15)	3.78 (3.77)	9.55 (9.54)
6h	*p*-*N*$(CH_3)_2$	$C_{27}H_{28}N_4O_{11}$	584.5	+46.1	0.22	55.48 (55.45)	4.83 (4.80)	9.58 (9.57)
6i	*p*-OCH_3	$C_{26}H_{25}N_3O_{12}$	571.4	+38.6	0.32	54.64 (54.63)	4.41 (4.40)	7.35 (7.33)
6j	*p*-Cl	$C_{25}H_{22}ClN_3O_{11}$	575.9	+46.5	0.31	52.14 (52.13)	3.85 (3.83)	7.30 (7.29)
6k	*o*-NO_2	$C_{25}H_{22}N_4O_{13}$	586.4	+44.1	0.30	51.20 (51.18)	3.78 (3.75)	9.55 (9.52)

Table 3: Data for in vitro antibacterial and antifungal activities of compounds (**6a-k**)

Products	Diameter of Inhibition Zone (in mm) Against			
	Bacterial Strains		Fungal Strain	
	E. Coli	*S. aureus*	*A. niger*	*C. albicans*
6a	14	16	19	23
6b	13	12	17	24
6c	15	13	26	--
6d	--	11	22	18
6e	16	--	14	19
6f	11	14	18	14
6g	15	13	--	--
6h	--	15	--	18
6i	16	14	19	19
6j	14	13	20	20
6k	15	14	--	20

-- = No inhibition of growth.

Diameter of zone of inhibition from 13-16 (in mm) shows excellent activity and that of 9-12 (in mm) exhibit moderate activity for bacterial strains. Diameter of zone of inhibition from 22-28 (in mm) shows excellent activity, that of 15-21 (in mm) exhibits moderate activity and that of 11-14 (in mm) shows poor activity for fungal strains. Norfloxacin 100µg/mL used as standard against *E. coli* and *S. aureus*diameter of zone of inhibition is 20. Griseofulvin 100µm/mL used as standard against *A. niger* and *C. albicans* diameter of zone of inhibition is 32.

Conclusion

Novel compounds synthesized β-D-Glucuronosyl-5-acetyl-7-[(5-aryl-4,5-dihydro-1,2-oxazol-3-yl)-amino]-1,2-benzoxazole-3-carboxylates**6a-k**were evaluated for in vitro antibacterial activity against *E. coli* and *S. aureus*strains as well as for antifungal activity against *A. niger* and *C. albicans* strains using cup-plate technique. Some compounds gave excellent results against bacterial and fungal strain. All synthesized compounds are confirmed by FT-IR, ^{1}H-NMR, FAB-MS, optical activity and elemental analysis.

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