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SYNTHESIS, CHARACTERIZATION AND EVALUATION OF SOME NOVEL SUBSTITUTED 3-PROPYLBENZO[D]THIAZOL-2(3H)-ONES AND 3-PROPYLBENZO[D]OXAZOL-2(3H)-ONES FOR THEIR ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES

Sowjanya M.*, Vishwanath B. A. and Kumudha D.

Aditya Bangalore Institute of Pharmacy Education and Research, Bangalore, Karnataka, India – 560064.

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***Corresponding Author**
Sowjanya M.
Aditya Bangalore Institute of Pharmacy Education and Research, Bangalore, Karnataka, India - 560064.

ABSTRACT

A series of some novel benzo[d]thiazole-2(3H)ones **(7aA-7aD)** and benzo[d]oxazole-2(3H)ones **(7bA-7bD)** were synthesized and evaluated for antibacterial and antifungal activities. In the present work the thiazole and oxazole ring structures were synthesized by reacting with ortho thiophenol or ortho aminophenol with urea to yield benzo[d]thiazol-2(3H)-one **(3a)** or benzo[d]oxazol-2(3H)-one **(3b)** respectively. The then formed compounds **3a** and **3b** are alkylated using dibromopropane to yield 3-(3-bromopropyl)benzo[d]thiazol-2(3H)-one **(5a)** and 3-(3-bromopropyl)benzo[d]oxazol-2(3H)-one **(5b).** Titled compounds are synthesized by reacting **5a** and **5b** with various secondary amines **(A-D)** in presence of K_2CO_3 to yield **7aA-7aD** and **7bA-7bD**.

KEYWORDS: Benzthiazole, Benzoxazole, Antibacterial, Antifungal.

INTRODUCTION

Heterocyclic chemistry is gaining a renaissance as heterocyclic scaffolds as templates for combinatorial chemistry. The availability of simple synthetic procedures that enable the preparation of different heterocycles with functionally stable groups as substituents is an important task for organic and medicinal chemists. Due to excessive use of antimicrobials, the antibiotics resistance is also increasing. So there is a need to synthesize an effective antimicrobial drug. Thiazoles are five membered heteroaromatic with sulphur and nitrogen in the ring structure having varied biological activities like antibacterial[1], anti-

inflammatory[7,15], neuroprotective[6], anticancer[2,6,9,13,18], antioxidant[6], anticonvulsant[7,20], antimicrobial[7, 8, 10, 15], anthelmintic[7], H_2 receptor agonist[3], antitubercular.[14,19] Oxazole are five membered heteroaromatic with oxygen and nitrogen in the ring structure having varied biological activities like antimicrobials[5,17], antibacterial[4], antifungal[17], anticancer.[2] Taking these observations into account in the present work some novel thiazole and oxazole derivatives were synthesized **(Of Scheme-I)** and characterized. The physical data of the synthesized compounds **(7aA-7aD)** and **(7bA-7bD)** are given in **Table-1**. All the synthesized compounds were characterized on the basis of IR, ^{1}H NMR and Mass data. All the compounds were screened for their in-vitro antimicrobial activity against six bacterial strains *K.pneumoniae*, *E.coli*, *S.aureus*, *P.aeroginosa*, *S.epidermidis* and *B.subtilis* and five fungal strains *R.oryzae*, *A.niger*, *A.flavus*, *C.albicans*, *S.cerevisiae* and their Minimum Inhibitory Concentration(MIC) and Zone of Inhibition(ZOI) was determined respectively.

MATERIALS AND METHODS

All the chemicals were procured from Sigma-Aldrich and were of LR grade. Melting points of the synthesised compounds were recorded on Metler Fp-51 instrument and are uncorrected. Infra-Red spectra were recorded on Perkin Elmer Model 283B and Nicolet-740 FT-IR instruments and values are given in cm^{-1}. Proton Magnetic Resonance spectra were recorded on Varian Gemini-200, Varian Gemini-400, Avance 300 MHz and Ux-NMR instrument. The samples were made in CCl_4/Chloroform-d (1:1) or DMSO-d6 using tetramethylsilane (TMS) as the internal standard and are given in the δ scale. A mass spectrum is recorded on VG Micromass 7070H (ESI and EI) and was given in mass units (m/z). Analytical thin layer chromatography (TLC) is performed on precoated silica gel-60 F254 (0.5mm) glass plates. Visualisation of the spots on TLC plates is achieved either by exposure to iodine vapour or UV light. Moisture sensitive reactions were carried out by standard syringe septum techniques. All solvent extracts were washed with water, brine, dried over anhydrous sodium sulphate and concentrated at reduced pressures on Buchi-R-3000 rotary evaporator below 50°C. All solvents used for silica gel column chromatography were distilled prior to use. Silica gel used is 60-120 mesh size (ACME).

Chemistry

Synthesis of benzo[d]thiazol-2(3H)-one (3a) or benzo[d]oxazol-2(3H)-one (3b)

The synthesis of benzo[d]thiazol-2(3H)-one **(3a)** and benzo[d]oxazol-2(3H)-one **(3b)** which involves, the reaction between equimolar ratios of o-amino thiophenol **(1a)** or o-amino

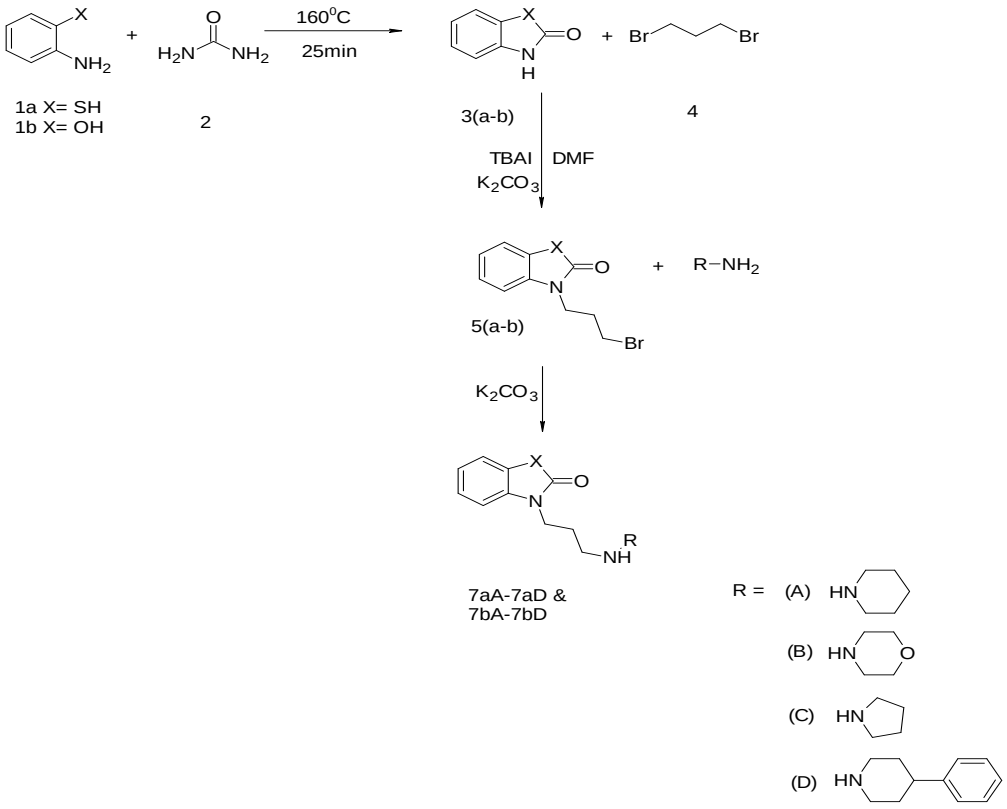
phenol **(1b)** and urea **(2),** which was heated at 160°C for 25min in an RB flask. The melt was allowed to cool and was extracted with 4M hydrochloric acid. This purple acidic solution was in turn extracted with adequate quantity of ether. The residue resulting from evaporation of dried ether layer was taken up in boiling methanol, decolourized and product was allowed to recrystallize using suitable solvents.

Synthesis of 3-(3-bromopropyl)benzo[d]thiazol-2(3H)-one (5a) or 3-(3-bromopropyl)benzo[d]oxazol-2(3H)-one (5b)

The compounds **3a** and **3b** (0.0445moles) were taken and alkylated by using dimethyl formamide of 15 ml, potassium carbonate (0.1335 moles) and tributyl ammonium bromide of (0.1335 moles) by continuous stirring for half an hour. Then dibromopropane (15 ml, 3 eq) was added and stirred for another 5 hours. Later the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water followed by brine and dried over sodium sulphate. The ethyl acetate layer was distilled under reduced pressures and the crude product obtained was purified.

Synthesis of 3-(3-bromopropyl)benzo[d]thiazol-2(3H)-one (7aA-7aD) and 3-(3-bromopropyl)benzo[d]oxazol-2(3H)-one (7bA-7bD) derivatives

3-(3-bromopropyl)benzo[d]thiazol-2(3H)-one **(5a)** of (0.0011 moles) and 3-(3-bromopropyl)benzo[d]oxazol-2(3H)-one **(5b)** of (0.0011 moles) was taken in a round bottom flask respectively and dissolved in anhydrous dimethyl formamide (4 ml), potassium carbonate (150 mg). To this mixture secondary amines **7(A-D)** of (0.1 ml, 0.0011 moles) were added by a syringe in nitrogen environment. The whole mass was heated at 60°C for 12 hours and cooled to room temperature. The reaction mixture was extracted with ethyl acetate and water followed by brine. The ethyl acetate layer was dried over anhydrous sodium sulphate, distilled under reduced pressures and the crude product obtained was purified.



Scheme: 1.

Table-1: Physicochemical characterization of synthesized compounds 7aA-7bD.

Compound Code	Molecular Formula	Molecular Weight	Melting Point	% Yield	R_f value
7aA	$C_{15}H_{20}N_2OS$	276	102-106	78.6	0.81
7aB	$C_{14}H_{18}N_2O_2S$	278	120-125	78.7	0.79
7aC	$C_{14}H_{18}N_2OS$	262	145-149	79.9	0.82
7aD	$C_{20}H_{23}N_3OS$	353	127-133	72.2	0.78
7bA	$C_{15}H_{20}N_2O_2$	260	119-123	86	0.79
7bB	$C_{14}H_{18}N_2O_3$	26	147-149	83	0.80
7bC	$C_{14}H_{18}N_2O_2$	246	132-136	85.4	0.82
7bD	$C_{20}H_{23}N_3O_2$	337	112-115	80.9	0.77

Spectral interpretation of all the synthesized compounds

Benzo[d]thiazol -2(3H)-one (3a)

IR (KBr, cm^{-1}) 1664cm^{-1} (C=O); 3155cm^{-1} (N-H); The ^{1}H NMR (DMSO-d_6): δ 10.1 (s, H, N-H, 7.1(m, 4H, Ar-H); $[M^+]$ m/z: 151.

3-(3-bromopropyl)benzo[d]thiazol -2(3H)-one (5a)

IR (KBr, cm^{-1}) 1763 cm^{-1} (C=O); 2947cm^{-1} (Aliphatic-H); The ^{1}H NMR (DMSO-d_6): δ 7.4, (d, H, Ar-H), 7.3 (t, H, Ar-H) 7.12 (q, 2H, Ar-H) 4.1(d, 2H, CH_2), 3.4 (t, H_A, CH_2), 3.2 (t, H_B, CH_2), 2.3 (m, 2H, -CH_2); [M+H; M+2H]$^+$m/z: 272 and 274.

3-(3-(piperidin-1-propyl)benzo[d]thiazol-2[3H]-one (7aA)

IR (KBr, cm^{-1}): 1678cm^{-1}(C=O), 2933cm^{-1} (Aliphatic-H); ^1H NMR (DMSO-d_6): δ 7.0(m, 4H, Ar-H), 3.8 (t, 2H, CH_2), 2.2 (t, 6H, 3 CH_2), 1.9 (m, 6H, CH_2), 1.5 (m, 2H, CH_2), 1.4 (s, 2H, CH_2); $[M+H]^+$ m/z : 277.

3-(3-morpholinopropyl)benzo[d]thiazol-2[3H]-one (7aB)

IR (KBr, cm^{-1}): 1677cm^{-1}(C=O), 2951cm^{-1} (Aliphatic-H); The ^1H NMR (DMSO-d_6): δ 7.4 (d, H, Ar-H), 7.2 (t, H, Ar-H), 3.9(t, 2H, CH_2), 3.5(t, 4H, 2CH_2), 2.3 (t, 6H, 3CH_2), 1.9 (m, 2H, CH_2); $[M+H]^+$ m/z: 279.

3-(3-(pyrrolidin-1-yl) propyl) benzo[d]thiazol-2[3H]-one (7aC)

IR (KBr, cm^{-1}): 1677cm^{-1} (C=O), 2930cm^{-1} (Aliphatic-H); The ^1H NMR (DMSO-d_6): δ 7.4 (d, H, Ar-H), 7.2 (t, H, Ar-H), 7.12(m, 2H, Ar-H), 4.0 (t, 2H, CH_2), 2.5 (t, 6H, 3 CH_2), 1.9 (m, 2H, CH_2), 1.7 (s, 4H, 2 CH_2); $[M+H]^+$ m/z: 263.

3-(3-(4-phenylpiperazin-1-yl)propyl)benzo[d]thiazol-2[3H]-one (7aD)

IR (KBr, cm^{-1}): 1674cm^{-1} (C=O); 2924cm^{-1} (Aliphatic-H). The ^1H NMR (DMSO-d_6): δ 7.4 (d, H, Ar-H), 7.1(m, 5H, Ar-H), 6.7 (m, 3H, Ar-H), 4.0 (t, H, CH_2), 4.1(d, H, CH_2), 3.1(t, 4H, 2CH_2), 2.4 (t, 2H, CH_2),1.9(q, 2H, CH_2); $[M+H]^+$ m/z 354.

Benzo[d]oxazole-2(3H)-one (3b)

IR (KBr, cm^{-1}): 1734cm^{-1} (C=O); 3219cm^{-1} (N-H); ^1H NMR (DMSO-d_6): δ 10.2 (s, H, N-H), 7.0 (m, 4H, Ar-H); [M-^{1}] m/z 135.

3-(3-(bromopropyl)benzo[d]oxazol-2(3H)-one (5B)

IR (KBr, cm^{-1}): 1763cm^{-1}(C=O); 2942cm^{-1} (Aliphatic-H)**;** ^1H NMR (DMSO-d_6): δ 7.7(s, H, Ar-H), 7.4 (d, H, Ar-H), 7.3(t, H, Ar-H), 7.1(m, H, Ar- H), 4.0 (dt, 2H, CH_2), 3.2 (t, H, CH_2), 3.4 (t, H, CH_2), 2.2 (m, 2H, CH_2`); [M+H;M+2H] m/z: 256 and 257.

3-(3-(piperidin-1-yl)propyl)benzo[d]oxazol-2[3H]-one (7bA)

IR (KBr, cm^{-1}): 1778cm^{-1} (C=O), 2853cm^{-1} f (Aliphatic-H); 1H NMR (DMSO-d6): δ 7.4 (d, H, Ar- H), 7.3(t, H, Ar- H), 7.0 (m, 2H, Ar- H), 4.0 (t, 2H, CH_2), 2.5 (s, 6H, 3 CH_2), 2.0 (m, 2H, CH_2), 1.7 (t, 4H, 2 CH_2), 1.4 (s, 2H, CH_2); [M+H]+ m/z : 262.

3-(3-morpholinopropyl)benzo[d]oxazol-2[3H]-one (7bB)

IR (KBr, cm^{-1}): 1765cm^{-1}(C=O), 2859cm^{-1} (Aliphatic-H); ^{1}H NMR (DMSO-d_6): δ 7.4 (d, H, Ar- H), 7.2 (t, H, Ar- H), 7.0 (m, 2H, Ar- H), 4.0 (t, 2H, CH_2), δ 3.7 (t, 4H, $2CH_2$), 2.4 (t, 6H, 3 CH_2), 1.9 (m, 2H, CH_2); [M+H] m/z : 263

3-(3-(pyrrolidin-1-yl)propyl)benzo[d]oxazol-2-[3H]-one (7bC)

IR (KBr, cm^{-1}): 1774cm^{-1} (C=O); 3425cm^{-1} (Aliphatic-H); ^{1}H NMR (DMSO-d_6): δ 7.3, (s, H, Ar- H), 7.1(t, H, Ar- H), 7.0 (m, 2H, Ar- H), 3.9 (t, 2H, CH_2), 2.6 (t, 6H, 3 CH_2), 2.0(t, 2H, CH_2), 1.8 (s, 4H, $2CH_2$); $[M+H]^+$ m/z: 247

3-(3-(4-phenylpiperazin-1-yl)propyl)benzo[d]oxazol-2[3H]-one (7bD)

IR (KBr, cm^{-1}): 1772cm^{-1}(C=O), 29321cm^{-1} (Aliphatic-H); ^{1}H NMR (DMSO-d_6): δ 7.0 (m, 6H, Ar- H), 6.7(m, 3H, Ar- H), 3.9(t, 2H, CH_2), 3.1(t, 4H, $2CH_2$), 2.5(t, 2H, CH_2), 1.9 (q, 2H, CH_2); [M+H]. m/z: 338

Antimicrobial Activity

All the compounds were screened for their in-vitro antimicrobial activity against *B.subtilis*, *S.aureus*, *S.epidermidis* (Gram-positive) and *E.coli*, *P.aeroginosa*, *K.pneumoniae* (Gram-negative) by serial dilution method; and antifungal activity against *R.oryzae*, *A.niger*, *A.flavus*, *C.albicans*, *S.cerevisiae* by cup plate method. The Minimum Inhibitory Concentration (MIC) was determined by using Streptomycin and Penicillin as standards for antibacterial activity. The Zone of Inhibition (ZOI) was determined by using Amphotericin-B as a standard for antifungal activity.

Antibacterial activity: The exact amount of nutrient broth or sabouraud dextrose was weighed and dissolves in 1L of distilled water. Then, 1ml of nutrient medium was transferred to each test tube. The test tubes having a nutrient medium were autoclaved at 120ºC for 30 min. the solution of test compound was prepared by adding 0.1 gm of synthesized compounds in 10ml DMSO. Then 1ml of this solution was diluted with DMSO upto 10ml to give a stock solution of 100 µgm/ ml. The solution of test compound was transferred into one test tube and serially diluted to give a concentration of 50, 25, 12.5, 6.25, 3.125 µgm/ml. to all the test tubes 0.1 ml of the suspension of bacteria in saline was added. The inoculation of the test strains was done with the help of micropippete with sterilized tips. The freshly cultured strain was transferred to the test tube and incubated at 37 ºC for 24 h. The potency of titled compounds was tested against the microbes and compared with standard drugs Streptomycin

and Penicillin. The MIC values were determined as the lowest concentration that completely inhibited visible growth of the microorganisms.

Antifungal activity: The exact amount of agar nutrient medium are placed in Pyrex bacteriological test tubes, autoclaved at 10 lb, for 10 min and stored in the refrigerator until required. just before the use the test tubes are heated in boiling water bath to melt the medium and then held in bath at 45 ºC, until needed the tubes are now inoculated with 1ml of suitable suspension of the organism; after thorough mixing by several inversions, the medium is poured into petri dishes and allowed to cool. Holes are cut with the help of a cork borer. The Synthesized compound and the standard (Amphotericin-B) are added into subsequent holes and incubated for 48h at 37ºC. The ZOI (Zone of Inhibition) values were determined as the lowest concentration that completely inhibited visible growth of the microorganisms.

RESULTS AND DISCUSSION

The structure of all the synthesized compounds was confirmed by IR, ^{1}H NMR and Mass spectra. Spectral analysis of the newly synthesized compounds **(7aA-7bD)** was in full agreement with the proposed structure. In the ^{1}H NMR spectra of **(3a-b)**. (N-H) of benzthiazole and benzoxazole shows a signal at δ 10.1 and 10.2 respectively. The IR spectrum **(3a-b)** of showed a characteristic absorption band at 1664 and 1734 cm^{-1} that was assigned to aromatic ring (C=O) stretching; characteristic absorption band at 1457 and 1478 cm^{-1} that was assigned to (N-H) stretching. In the ^{1}H NMR spectra of **(7aA-7bD)**. C-H (Aliphatic) of methylene groups displayed a signal around δ 4-1.4. The C-H (Ar) displayed signal around δ 7.7-6.7. The IR spectrum of **(7aA-7bD)** showed a characteristic absorption band around 1741-1778 cm^{-1} that was assigned to (C=O) stretching. The absorption band around 3448-2853 cm^{-1} that was assigned to C-H (Ar). The absorption band around 2947-2853 cm^{-1} was assigned to C-H (Aliphatic). The absorption band around 1114-800cm^{-1} was assigned to C-C stretching.

Antibacterial activity

The studies on antibacterial activity indicate that the compound **7bA** showed a very good anti-bacterial activity at 4.60 µg/mL against *S.aureus* and P.aeroginosa. Compounds **7aA** and **7aD** showed moderate activity at 9.35 µg/mL against *S.aureus*, *P.aeroginosa* and *S.epidermidis*. Compounds **7aA, 7bB** showed significant activity at 12.25 µg/mL against *K.pneumoniae, E.coli*. Compound **7aB** showed significant activity at 13.75µg/mL against *P.aeroginosa*. Compounds **7aA, 7aB, 7bC** showed significant activity at 15.75 µg/mL

against *E.coli*. *S.epidermidis* and *B.subtilis*. Compound **7bC** showed significant activity at 13.75 µg/mL against *K.pneumoniae*. Compound **7bB** showed significant activity at 16.75 µg/mL against *S.epidermidis*. The compounds **7aB, 7bA** showed significant activity at 18.65 µg/mL against *B.subtilis* and *K.pneumoniae*. The compound **7bB s**howed significant activity at 21.65 µg/mL against *B.subtilis*. The compound **7aD** showed significant activity at 24.58 µg/mL against *B.subtilis*. The compounds **7aB, 7aC** showed significant activity at 27.5 µg/mL against *S.aureus*. Compounds **7aA, 7aB, 7bB, 7bC, 7bD** showed significant activity at 75.0 µg/mL against *S.aureus*, *S.epidermidis* and *B.subtilis* **(Figure-1).**

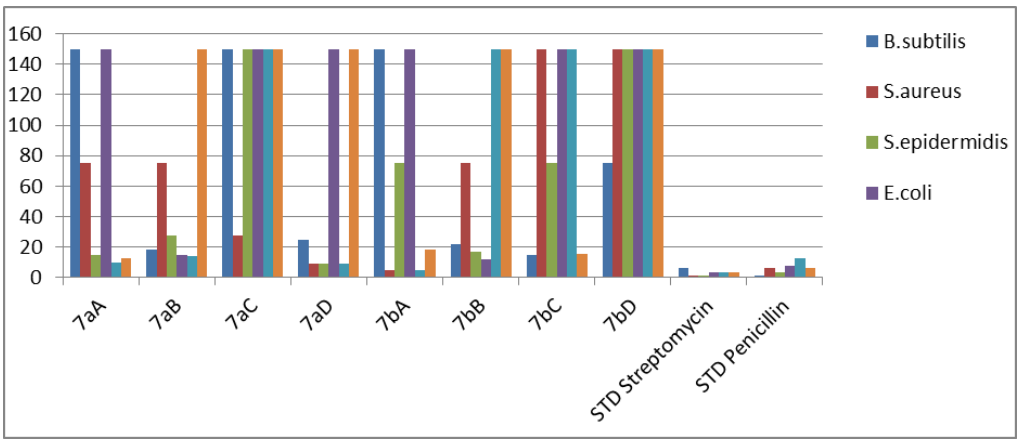


Figure 1: Graphical representation showing Antibacterial activity of synthesized compounds (µgm/L).

Antifungal activity

The compound **7aD** showed maximum ZOI of 26mm against *Rhizopus oryzae*. The compound **7bA** showed maximum ZOI of 26mm against *Aspergillus niger*. The compound **7aA** showed maximum ZOI of 26mm against *Aspergillus flavus*. The compound **7aD, 7bA** showed maximum ZOI of 26mm against *Candida albicans*. The compound **7bA** showed maximum ZOI of 26mm against *Saccharomyces cerevisiae*. **(Figure – 2).**

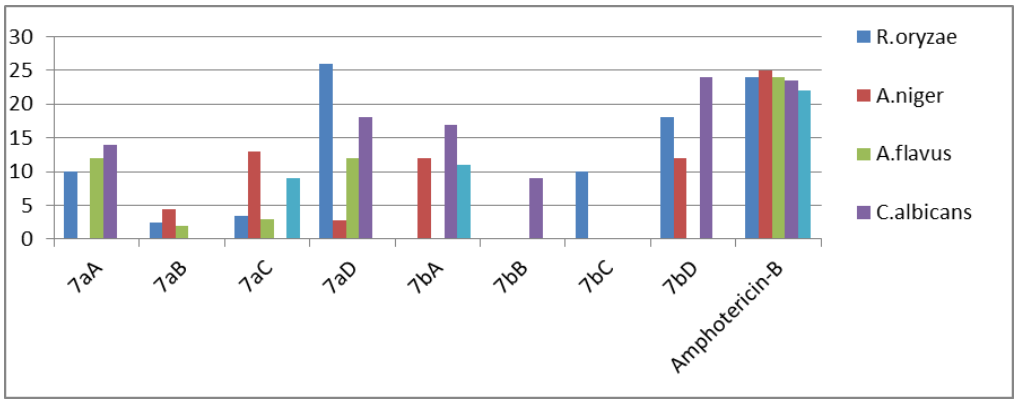


Figure 2: Graphical representation showing Antifungal activity of synthesized compounds (µgm/L).

CONCLUSION

To conclude, the strategy adopted for the synthesis of substituted benzothiazoles and benzoxazoles utilizes easily available commercial compounds as starting materials. The reactions are completed in shorter times with high purity and the yields are found to be good. All the synthesised compounds are purified by column chromatography and characterised by analytical and spectral (IR, ^{1}H, Mass) data. The compounds are evaluated for antibacterial and antifungal activity by serial dilution and cup-plate methods respectively. All compounds were found to have good anti-bacterial activity against both gram-positive and gram-negative bacteria and anti-fungal activities especially the compounds **7aA, 7aB, 7aD, 7bA, 7bB, 7bD** showed good anti-bacterial activity. Among which compounds ***7bA*** **(4.06 MIC)** showed the impressive anti-bacterial activity. The compound **7aD** showed impressive anti-fungal activity with maximum zone of inhibition **(26 mm)** against the *R. oryzae.* The work on anticancer is under investigation.

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