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IN-VITRO ANTIBACTERIAL AND CYTOTOXICITY EVALUATION OF SOME NOVEL TETRAZOLE DERIVATIVES

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Keywords:

Tetrazole derivatives, Dental plaque bacteria, Cytotoxicity screening

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ABSTRACT: A series of tetrazol derivatives 1(a-c) and 2(a-c) were synthesized by Mannich base reaction. Synthesized compounds 1(a-c) and 2(a-c) were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral, and elemental analysis. Synthesized compounds 1(a-c) and 2(a-c) were screened for dental plaque bacteria and cytotoxicity activity. The compound 1b was highly active against *Enterococcus feacalis* in antibacterial screening. The synthesized compounds have been screened for preliminary cytotoxicity against HepG2 (Liver), Hela (Cervical) and MCF-7 (Breast) cancer cells. The compound (1c) is highly active against MCF-7(Breast), and compound (2b) is highly active against HepG2 (Liver). Therefore, current study demonstrates the antibacterial and cytotoxicity activity potential of new tetrazole derivatives and provides future insights for developing dental plaque antibacterial drugs.

INTRODUTION: Azoles (imidazole, triazole and tetrazole) are presented in many effective anti-microbial activities and they are widely used for the treatment of topical or inner mycoses in particular AIDS-related mycotic pathologies [1]. Tetrazoles have been used as high energy compounds and some of the tetrazoles are used as drugs. A few examples are shown in **Fig. 1**. Losartan (1) is an angiotensin II antagonist and commonly used for treatment of hypertension. Tetrazole (2) has also been found to posses binding affinity to benzo-diazepine receptors [2].

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Mannose mimetics (3) have been reported to be inhibitors of α-mannosidase [3, 4]. 1,5-Disubstituted-1*H*-tetrazoles (4) is suitable bioisosteres of peptides [5], some of tetrazole derivatives are medicinally importance and it's have been reported to possess antibiotics [6] antifungal drugs [7], antinociceptive [8, 9], anti-mycobacterial [10], anti-inflammatory [11], anti-proliferative [12] and anticonvulsant activities [13].

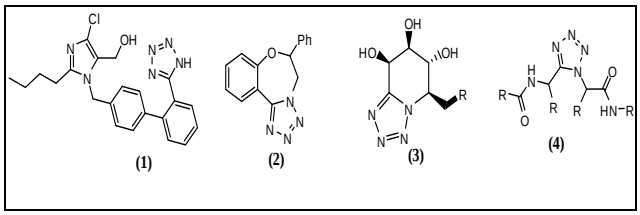

FIG. 1: BIOLOGICAL ACTIVE TETRAZOLES DERIVATIVES

Mannich reaction is of considerable importance for the synthesis of multidrug compounds and biologically important compounds [14 - 15]. Basically Mannich bases have several biological activities

such as antimicrobial [16, 17, 18], cytotoxic [19] and anticonvulsant activities [20]. Therefore, bearing in mind the above observation, we decided to synthesize new series of tetrazol derivatives and screening for dental plaque antibacterial and cytotoxicity activities.

MATERIALS AND METHODS:

Chemistry: Melting points were recorded in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr on an FT-IR spectrometer (Shimadzu 8201PC) in the range of 4000-400 cm^{-1}. The ^1H NMR spectra were recorded on a Bruker DRX-300 spectrometer at 300MHz. Elemental analysis (C, H, N and S) were performed using an elemental analyzer (Vario EL III). The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates.

Synthesis of 2-[phenyl(1*H*-tetrazol-1-yl)methyl] hydrazinecarbothioamide 1(a-c): A mixture of tetrazole (0.1 mol, 7.0 g), thiosemicarbazone (0.1 mol, 9.1g) and benzaldehyde (0.1 mol, 10mL) in ethanol (30 mL), the reaction mixture was taken in RB flask. The reaction mixture was refluxed and stirred for 2h with help of magnetic stirrer. Final product was purified by column chromatography.

2-[phenyl(1*H*-tetrazol-1-yl)methyl]hydrazinecarbothioamide 1(a): FT-IR (KBr, cm^{-1}): 3408 (NH_2), 3002 (NH), 2926 (CHstr), 1660 (C=S), 1512 (N=N), 1315 (C=N), 947(NH), 701(ArH). ^1H NMR (DMSO-d_6), δ_H (ppm): 9.60 (2H, s, NH_2), 8.72 (1H, s, 5C<u>H</u>-tetrazole), 7.30-7.26 (5*H*, m, Ph), 6.32 (1H, s, -CH-), 2.22(1H, s, NH). ^{13}C NMR (DMSO-d_6), δ_C (ppm): 182.86(C=S), 144.87 (5CH-tetrazole), 138.26-126.67 (Ph), 74.11(-CH-). EI-Ms, m/z (Relative intensity %): m/z 249.09 ($M,^+$ 10%).

2-[(4-chlorophenyl)(1*H*-tetrazol-1-yl) methyl] hydrazinecarbothioamide 1(b): FT-IR (KBr, cm^{-1}): 3377 (NH_2), 3023(NH), 2932 (CHstr), 1653(C=S), 1577(N=N), 936(NH), 646(Ar-Cl). ^1H NMR (DMSO-d_6) δ_H (ppm): 9.52(NH_2,s,2H), 8.82(5C<u>H</u>-teterzole, s,1H), 7.75(2H, dd, Ph, *J*=5.6Hz, *J*=6.2Hz), 7.44 (2H, dd, Ph, *J*=5.8Hz, *J*=6.4Hz), 6.43(1H, s, -CH-), 2.43(1H, s, NH), 2.14 (1H, s, NH). ^{13}C NMR (DMSO-d_6), δ(ppm): 181.12(C=S), 147.67 (5CH-tetrazole), 131.23 (C-Cl), 130.12-129.11 (Ph), 72.11 (-CH-). EI-Ms, m/z (Relative intensity %): *m*/*z* 283.65 ($M,^+$ 66%).

2-[(4-hydroxyphenyl)(1*H*-tetrazol- 1 -yl) methyl] hydrazinecarbothioamide 1(c): FT-IR (KBr, cm^{-1}): 3408 (NH_2), 2997(NH), 2909 (CHstr) 1560 (N=N), 1660 (C=S), 1315 (C=N), 942 (NH), 942 (Ar-OH) . ^1H NMR (DMSO-d_6), δ_H (ppm): 9.83 (1H, s, Ph-OH), 9.21 (2H, s, NH_2), 8.36 (1H, s, 5C<u>H</u>-tetrazole), 7.43(2H, dd, Ph, *J*=6.8Hz, *J*=7.2Hz), 7.22(2H, dd, Ph, *J*=6.7Hz, *J*=7.0Hz), 6.32(1H, s, -CH-), 2.43(1H, s, NH). ^{13}C NMR (DMSO-d_6), δ_C (ppm): 180.21 (C=S), 154.07(Ph-OH), 143.67 (5CH-tetrazole moiety), 138.26-126.67 (Ph), 72.08 (-CH-). EI-Ms, m/z (Relative intensity %): m/z 264.98($M,^+$ 26%); .

Synthesis of 1, 1-dimethyl-3-[phenyl (1*H*-tetrazol-1-yl) methyl] urea 2(a-c): A mixture of tetrazole (0.1mol, 7.0g), 1, 1-dimethylurea (0.1mol, 8.8g) and benzaldehyde (0.1 mol, 10mL) in ethanol (30 mL), the reaction mixture was taken in RB flask.

The reaction mixture was refluxed and stirred for 2h with help of magnetic stirrer. The reaction mixture cooled and poured into crushed ice. The resulting solid was filtered, dried and recrystallized from ethanol.

1,1-dimethyl-3-[phenyl(1*H*-tetrazol-1-yl) methyl] urea 2(a): FT-IR (KBr, cm^1): 2986 (NH), 2936 (CHstr), 1694 (C=O), 1512 (N=N), 1376 (C=N), 942 (NH), 919 (Ar). ^1H NMR (DMSO-d_6) δ_H (ppm): 9.52(2H, s, NH_2), 8.82 (2H, s, 5CH-tetrazole), 7.75-7.44 (5H, m, Ph), 6.43 (1H, s, -CH-), 6.12 (1H, s, NH), 2.14 (6H, s, -$NH(CH_3)_2$). ^{13}C NMR (DMSO-d_6), δ (ppm): 154.07 (C=O), 147.67 (5CH-tetrazole), 137.86-126.21 (Ph), 72.11(-CH-), 36.12 (-$N(CH_3)_2$). EI-Ms, m/z (Relative intensity %):*m*/*z* 246.88($M,^+$ 44%).

3-[(4-chlorophenyl)(1*H*-tetrazol-1-yl)methyl]-1,1-dimethylurea 2(b): FT-IR (KBr, cm^{-1}): 3240 (CH_3), 2934 (CHstr), 1683(-CONH), 1565(N=N), 1363 (C=N), 954(Ar), 646(Ar-Cl). ^1H NMR (DMSO-d_6) δ_H (ppm): 8.85 (1H, s, 5CH-teterzole), 7.47(2H, dd, Ph, *J*=5.9Hz, *J*=6.8Hz), 7.26 (2H, dd, Ph, *J*=5.7Hz, *J*=6.6Hz), 7.15(1H, s, -CH-), 6.13 (1H, s, NH), 2.83(6H, s, -$NH(CH_3)_2$). ^{13}C NMR (DMSO-d_6), δ (ppm): 156.67 (C=O), 143.30 (5CH-teterazole), 132.06(C-Cl), 131.01- 128.30 (Ph), 66.21 (-CH-), 36.12 (-$N(CH_3)_2$). EI-Ms, m/z (Relative intensity %): *m*/*z* 279.12($M,^+$ 38%).

3-[(4-hydroxyphenyl)(1*H*-tetrazol-1-yl) methyl] -1,1-dimethylurea 2(c): FT-IR(KBr, cm^{-1}): 3297 (CH_3), 2922 (CHstr), 1683 (-CONH), 1565 (N=N), 1377 (C=N), 942 (Ar), 942 (Ar-OH),. ^{1}H NMR (DMSO-d_6) δ_H (ppm): 9.83 (1H, s, Ph-OH), 8.84 (1H, s, 5CH-teterzole), 7.31(2H, dd, Ph, *J*=6.3Hz, *J*=5.7Hz), 7.22 (2H, dd, Ph, *J*=6.6Hz, *J*=5.8Hz), 7.14(1H, s, -CH-), 6.13 (1H, s, NH_2), 2.81(6H, s, -$NH(CH_3)_2$). ^{13}C NMR (DMSO-d_6), δ_C (ppm): 154.07 (Ph-OH), 156.43 (C=O), 143.12 (5CH-teterazole), 131.42-128.09 (Ph), 66.09 (-CH-), 36.01 (-$N(CH_3)_2$). EI-Ms, m/z (Relative intensity %): m/z 262.87 ($M,^+$ 21%).

***In-vitro* Dental Plaque Antibacterial Screening:** The compounds 1(a-c) and 2(a-c) were evaluated against *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus feacalis*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* (recultured) by disc diffusion method [21, 22] was performed using Mueller-Hinton agar (Hi-Media) medium. Each compound was tested at a concentration at 50 and 100 µg/mL in DMSO. The zone of inhibition was measured after 24h incubation at 37 ºC.

Determination of the Minimal Inhibitory Concentration (MIC): Compound was dissolved in dimethylsulphoxide at concentration of 64 µg/mL. The two fold dilutions of the solution were prepared (64, 32, 0.5 µg/mL). The microorganism suspensions at 106 CFU/mL (colony forming unit/mL) concentrations were inoculated to the corresponding wells. The plates were incubated at 36º C at 24 h.

Cytotoxic Activity: The newly synthesized compounds 1(a-c), and 2(a-c) were screened for their cytotoxicity activity according to the procedure suggested [23].

RESULTS AND DISCUSSION:

Chemistry: A series of compounds 1(a-c), and 2(a-c) were synthesized from condensation method and reactions are outline in **Fig. 2**, physicochemical data are given in **Table 1**.

TABLE 1: PHYSICAL CHARACTERIZATION OF COMPOUNDS 1(a-c), 2(a-c)

Com. no.	R	m. w.	Yield (%)	M. F	Elemental analysis	Calculated (Found) (%)	Elemental Analysis	Calculated (Found) (%)
					C	H	N	S
1a	-H	249.29	82	$C_9H_{11}N_7S$	43.36 (54.70)	4.45 (5.14)	39.33 (18.79)	12.86 (12.97)
1b	-Cl	265.29	79	$C_9H_{11}N_7OS$	40.75 (40.23)	4.18 (4.22)	36.96 (36.80)	12.09 (12.20)
1c	-OH	283.70	81	$C_9H_{10}N_7SCl$	38.10 (52.41)	3.55 (3.91)	34.56 (34.61)	11.30 (11.47)
2a	-H	233.23	78	$C_9H_{11}N_7O$	46.35 (46.34)	4.75 (4.71)	42.04 (42.06)	-
2b	-Cl	246.12	86	$C_{11}H_{14}N_6O$	53.65 (53.60)	5.73 (5.71)	34.13 (34.10)	-
2c	-OH	210.87	80	$C_{11}H_{14}N_6O_2$	50.38 (50.29)	5.38 (5.35)	32.04 (32.10)	-

The structures of compounds were characterized from IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis. IR spectra of the compounds (1a**)** shows that the absorption band at NH_2, C=S, C=N and N=N corresponding to 3408, 1660, 1315, and 1512 cm^{-1} respectively. ^{1}H NMR spectrum of the compound (1a) shows that signals obtained at δ 9.60, 6.32, and 2.22 corresponding to NH_2, -CH- and NH respectively.

The ^{13}C NMR spectrum of the compound (1a) shows that signals obtained at δ 182.86 and 74.11 corresponding to (C=S) and -CH- carbon group respectively. Mass spectra of the compound (1a) shows molecular ion peak at m/z 249.09 corresponding to expected molecule weight of the compound (1a). IR spectra of the compound (2a) shows that the absorption band at C=O, C=N, and NH corresponding to 1694, 1376, and 942 cm^{-1} respectively. ^{1}H NMR spectrum of the compound (2a) shows that the proton signals observed 6.43, 9.52, 6.12, and 2.14 corresponding to -CH-, NH_2, NH, and (-$NH(CH_3)_2$ protons respectively.

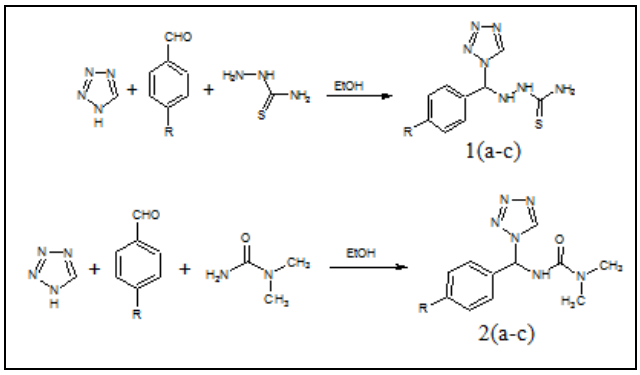

FIG. 2: SYNTHETIC ROUTE OF THE COMPOUNDS 1(a-c) AND 2(a-c)

The ^{13}C NMR spectrum of the compound (2a) shows that the carbon peaks obtained at 154.07, 72.11 and 36.12 corresponding to C=O, CH, and CH_2N respectively. Mass spectra of the compound (2a) shows molecular ion peak at m/z 246.88 corresponding to expected molecule weight of the compound (2a).

Biological Screnning:

Antibacterial Activity: The compounds 1(a-c), and 2(a-c) were screened for antibacterial activity. The compound (1b) was highly active (MIC: 8 µg/mL) against *E. faecalis* compared with standard and the compound (2b) has highly active (MIC: 8 µg/mL) against *E. coli* compared with other compounds completely remove this sentence. The compound (1c) was highly active against *S. aureus* (MIC: 4µ/mL) compound with other compounds but very low active compared with standard ciprofloxacin. The values are summarized in **Table 2**, antibacterial minimum inhibit concentration value are summarized in **Table 3**.

TABLE 2: ANTIBACTERIAL ACTIVITYOF COMPOUNDS 1(a-c), 2(a-c). ZONE OF INHIBITION IN mm

Com. no.	*S. aureus*	*E. coli*	*E. faecalis*	*P. aeruginosa*	*K. pneumoniae*
1a	10	12	-	-	14
1b	12	19	22	16	18
1c	20	10	17	10	8
2a	14	17	10	10	16
2b	17	22	10	12	18
2c	10	13	10	19	10
Standard	22	26	16	30	18

TABLE 3: THE MINIMAL INHIBITORY CONCENTRATIONS (MIC, µg/mL) OF COMPOUNDS 1(a-c), 2(a-c) AGAINST ORAL BACTERIAL SPECIES

Com. no.	SA	EC	EF	PA	KP
1a	64	64	-	-	32
1b	64	8	8	32	16
1c	4	32	16	64	>100
2a	64	64	>100	>100	64
2b	16	8	>100	64	16
2c	64	32	>100	16	>100
Ciprofloxacin	0.5	0.5	16	0.5	2

Oral bacterial species, zone of inhibition measured at (mm). The compounds were used at concentration 100 µg/mL. Ciprofloxacin used as a standard

Cytotoxicity: Compounds 1(a-c), 2(a-c) were found to be active in the preliminary cytotoxicity screening studies. The compounds were tested against the three cell lines of liver, cervical, breast cancer types. Their GI_{50}, TGI and LC_{50} values were determined. The result of the screening was expressed in terms of GI_{50} growth inhibitor concentration.

Table 4 shows that the compound (1c) has highly active against MCF_7 cancer cell line for the reason that low growth of inhibition (GI_{50}) at 8.2 µm compared to other and compounds (2b) is highly active against HepG2 for the reason that low Growth of inhibition (GI_{50}) at 5.4µm compared to other and compounds.

Structure Activity Relationship: From the results of antimicrobial and cytotoxicity activities, we are discussed in following structure activity relationships:

TABLE 4: CYTOTOXICITY ACTIVITY OF COMPOUNDS 1(a-c), 2(a-c)

Compounds	HepG2			MCF-7			HeLa		
	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}
1a	16.2	29.1	>100	22.9	46.8	>100	21.6	49.4	81.2
1b	23.3	54.8	81.2	20.1	45.1	>100	41.0	87.2	>100
1c	18.2	58.1	90.1	8.2	16.1	57.2	20.2	48.1	84.1
2a	6.3	15.3	51.2	5.2	20.1	>100	8.1	17.1	65.3
2b	5.4	12.5	62.5	13.5	26.9	83.5	16.8	34.7	92.8
2c	31.7	62.1	>100	22.6	52.5	88.4	29.8	52.6	>100

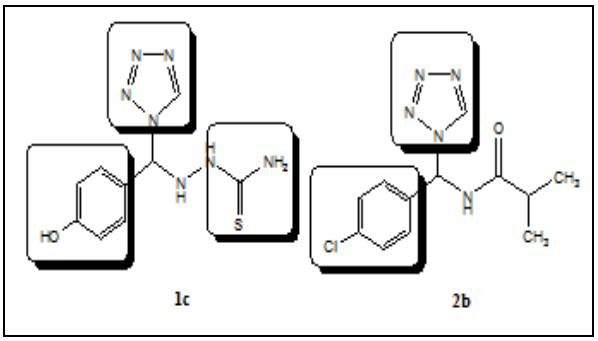

FIG. 2: STRUCTURE ACTIVE RELATIONSHIP ACTIVE COMPOUND

Fig. 2 indicates that highlighted that structure activity relationship. The compound (1c) is highly active against *S. aureus* (MIC, 4 µg/mL) as well as the compound response to MCF-7 cancer cell lines corresponding to TGI 16.1 due to presence of tetrazole ring with hydroxybenzene. The compound (2b) is highly active against *E.coli* (MIC, 8.µg/mL) as well as compound response to HepG2 (Liver) cancer cell line corresponding to TGI 12.5, due to presence of tetrazole ring with chlorophenzen.

CONCLUSION: In conclusion, we have found an efficient and practical procedure for the synthesis of tetrazole derivatives. The compound (1b) was highly active against *Enterococcus feacalis* in antibacterial screening. The most of compounds were active due to the para substitution of phenyl ring with tetrazole ring in antibacterial screening. The compound (1c) showed significant cytotoxicity properties against MCF7 cancer cell line and compound (2b) showed significant cytotoxicity properties against HepG2 cancer cell line with GC_{50} values in micromolar range.

Overall, this study demonstrates that antibacterial and cytotoxicity activity potential of new tretazole derivatives and provides future insights for developing dental plaque antibacterial drugs.

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CONFLICT OF INTEREST: The authors have declared no conflict of interest.

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