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

Anis Ahamed<sup>1</sup>, Ibrahim A. Arif<sup>1</sup>, Meera Moydeen<sup>2</sup>, Radhakrishnan Surendra Kumar<sup>3</sup> and Akbar Idhayadhulla<sup>\*3</sup>

Department of Botany and Microbiology<sup>1</sup>, Prince Sultan Research Chair for Environment and Wildlife, Department of Chemistry<sup>2</sup>, College of Sciences, King Saud University (KSU), Riyadh, Saudi Arabia. Department of Chemistry<sup>3</sup>, Nehru Memorial College (Affiliated to Bharathidasan University), Puthanampatti, Tiruchirappalli - 621007, Tamil Nadu, India.

### Keywords:

Tetrazole derivatives, Dental plaque bacteria, Cytotoxicity screening

### Correspondence to Author:

**Dr. Akbar Idhayadhulla**

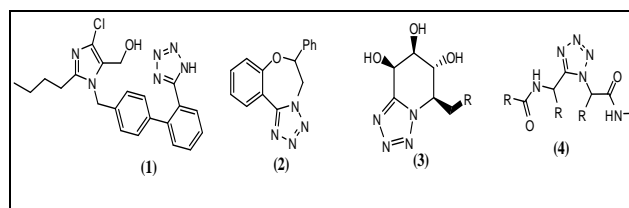
Assistant Professor,  
Department of Chemistry, Nehru  
Memorial College, Puthanampatti,  
Tiruchirappalli - 621007, Tamil Nadu,  
India.

**E-mail:** a.idhayadhulla@gmail.com

**ABSTRACT:** A series of tetrazole 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, <sup>1</sup>H NMR, <sup>13</sup>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 faecalis* 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.

**INTRODUCTION:** Azoles (imidazole, triazole and tetrazole) are presented in many effective antimicrobial activities and they are widely used for the treatment of topical or inner mycoses in particular AIDS-related mycotic pathologies<sup>1</sup>. 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 possess binding affinity to benzodiazepine receptors<sup>2</sup>.

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



**FIG. 1: BIOLOGICAL ACTIVE TETRAZOLES DERIVATIVES**

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

such as antimicrobial<sup>16, 17, 18</sup>, cytotoxic<sup>19</sup> and anticonvulsant activities<sup>20</sup>. 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  $\text{cm}^{-1}$ . The  $^1\text{H}$  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(1H-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(1H-tetrazol-1-yl)methyl]hydrazinecarbothioamide 1(a):** FT-IR (KBr,  $\text{cm}^{-1}$ ): 3408 ( $\text{NH}_2$ ), 3002 (NH), 2926 (CHstr), 1660 (C=S), 1512 (N=N), 1315 (C=N), 947(NH), 701(ArH).  $^1\text{H}$  NMR (DMSO- $d_6$ ),  $\delta_{\text{H}}$  (ppm): 9.60 (2H, s,  $\text{NH}_2$ ), 8.72 (1H, s, 5CH-tetrazole), 7.30-7.26 (5H, m, Ph), 6.32 (1H, s, -CH-), 2.22(1H, s, NH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ),  $\delta_{\text{C}}$  (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 ( $\text{M}^+$ , 10%).

**2-[(4-chlorophenyl)(1H-tetrazol-1-yl) methyl] hydrazinecarbothioamide 1(b):** FT-IR (KBr,  $\text{cm}^{-1}$ ): 3377 ( $\text{NH}_2$ ), 3023(NH), 2932 (CHstr), 1653(C=S), 1577(N=N), 936(NH), 646(Ar-Cl).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta_{\text{H}}$  (ppm): 9.52( $\text{NH}_2$ ,s,2H), 8.82(5CH-tetrazole, s,1H), 7.75(2H, dd, Ph,  $J=5.6\text{Hz}$ ,  $J=6.2\text{Hz}$ ), 7.44 (2H, dd, Ph,  $J=5.8\text{Hz}$ ,  $J=6.4\text{Hz}$ ), 6.43(1H, s, -CH-), 2.43(1H, s, NH), 2.14 (1H, s, NH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ),  $\delta$ (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 ( $\text{M}^+$ , 66%).

**2-[(4-hydroxyphenyl)(1H-tetrazol-1-yl) methyl] hydrazinecarbothioamide 1(c):** FT-IR (KBr,  $\text{cm}^{-1}$ ): 3408 ( $\text{NH}_2$ ), 2997(NH), 2909 (CHstr) 1560 (N=N), 1660 (C=S), 1315 (C=N), 942 (NH), 942 (Ar-OH) .  $^1\text{H}$  NMR (DMSO- $d_6$ ),  $\delta_{\text{H}}$  (ppm): 9.83 (1H, s, Ph-OH), 9.21 (2H, s,  $\text{NH}_2$ ), 8.36 (1H, s, 5CH-tetrazole), 7.43(2H, dd, Ph,  $J=6.8\text{Hz}$ ,  $J=7.2\text{Hz}$ ), 7.22(2H, dd, Ph,  $J=6.7\text{Hz}$ ,  $J=7.0\text{Hz}$ ), 6.32(1H, s, -CH-), 2.43(1H, s, NH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ),  $\delta_{\text{C}}$  (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( $\text{M}^+$ , 26%); .

**Synthesis of 1, 1-dimethyl-3-[phenyl (1H-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(1H-tetrazol-1-yl) methyl] urea 2(a):** FT-IR (KBr,  $\text{cm}^{-1}$ ): 2986 (NH), 2936 (CHstr), 1694 (C=O), 1512 (N=N), 1376 (C=N), 942 (NH), 919 (Ar).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta_{\text{H}}$  (ppm): 9.52(2H, s,  $\text{NH}_2$ ), 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, - $\text{NH}(\text{CH}_3)_2$ ).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ),  $\delta$  (ppm): 154.07 (C=O), 147.67 (5CH-tetrazole), 137.86-126.21 (Ph), 72.11(-CH-), 36.12 (- $\text{N}(\text{CH}_3)_2$ ). EI-MS, m/z (Relative intensity %):m/z 246.88( $\text{M}^+$ , 44%).

**3-[(4-chlorophenyl)(1H-tetrazol-1-yl)methyl]-1,1-dimethylurea 2(b):** FT-IR (KBr,  $\text{cm}^{-1}$ ): 3240 ( $\text{CH}_3$ ), 2934 (CHstr), 1683(-CONH), 1565(N=N), 1363 (C=N), 954(Ar), 646(Ar-Cl).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta_{\text{H}}$  (ppm): 8.85 (1H, s, 5CH-tetrazole), 7.47(2H, dd, Ph,  $J=5.9\text{Hz}$ ,  $J=6.8\text{Hz}$ ), 7.26 (2H, dd, Ph,  $J=5.7\text{Hz}$ ,  $J=6.6\text{Hz}$ ), 7.15(1H, s, -CH-), 6.13 (1H, s, NH), 2.83(6H, s, - $\text{NH}(\text{CH}_3)_2$ ).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ),  $\delta$  (ppm): 156.67 (C=O), 143.30 (5CH-tetrazole), 132.06(C-Cl), 131.01- 128.30 (Ph), 66.21 (-CH-), 36.12 (- $\text{N}(\text{CH}_3)_2$ ). EI-MS, m/z (Relative intensity %): m/z 279.12( $\text{M}^+$ , 38%).

**3-[(4-hydroxyphenyl)(1H-tetrazol-1-yl) methyl] -1,1-dimethylurea 2(c):** FT-IR(KBr,  $\text{cm}^{-1}$ ): 3297 ( $\text{CH}_3$ ), 2922 ( $\text{CH}_{\text{str}}$ ), 1683 ( $-\text{CONH}$ ), 1565 ( $\text{N}=\text{N}$ ), 1377 ( $\text{C}=\text{N}$ ), 942 (Ar), 942 (Ar-OH),.  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta_{\text{H}}$  (ppm): 9.83 (1H, s, Ph-OH), 8.84 (1H, s, 5CH-tetrazole), 7.31(2H, dd, Ph,  $J=6.3\text{Hz}$ ,  $J=5.7\text{Hz}$ ), 7.22 (2H, dd, Ph,  $J=6.6\text{Hz}$ ,  $J=5.8\text{Hz}$ ), 7.14(1H, s,  $-\text{CH}-$ ), 6.13 (1H, s,  $\text{NH}_2$ ), 2.81(6H, s,  $-\text{NH}(\text{CH}_3)_2$ ).  $^{13}\text{C}$  NMR ( $\text{DMSO-d}_6$ )  $\delta_{\text{C}}$  (ppm): 154.07 (Ph-OH), 156.43 ( $\text{C}=\text{O}$ ), 143.12 (5CH-tetrazole), 131.42-128.09 (Ph), 66.09 ( $-\text{CH}-$ ), 36.01 ( $-\text{N}(\text{CH}_3)_2$ ). EI-MS,  $m/z$  (Relative intensity %):  $m/z$  262.87 ( $\text{M}^+$ , 21%).

#### **In-vitro Dental Plaque Antibacterial Screening:**

The compounds 1(a-c) and 2(a-c) were evaluated against *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* (recultured) by disc diffusion method<sup>21, 22</sup> was performed using Mueller-Hinton agar (Hi-Media) medium. Each compound was tested at a concentration at 50 and

100  $\mu\text{g/mL}$  in DMSO. The zone of inhibition was measured after 24h incubation at 37 °C.

#### **Determination of the Minimal Inhibitory Concentration (MIC):**

Compound was dissolved in dimethylsulphoxide at concentration of 64  $\mu\text{g/mL}$ . The two fold dilutions of the solution were prepared (64, 32, 0.5  $\mu\text{g/mL}$ ). The microorganism suspensions at 106 CFU/mL (colony forming unit/mL) concentrations were inoculated to the corresponding wells. The plates were incubated at 36° 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<sup>23</sup>.

#### **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.

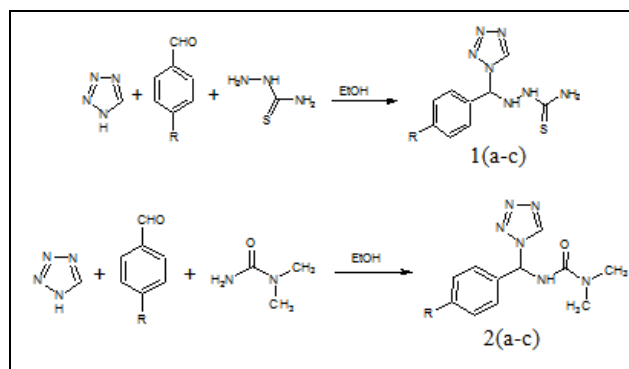
**TABLE 1: PHYSICAL CHARACTERIZATION OF COMPOUNDS 1(a-c), 2(a-c)**

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	$\text{C}_9\text{H}_{11}\text{N}_7\text{S}$	43.36 (54.70)	4.45 (5.14)	39.33 (18.79)	12.86 (12.97)
1b	-Cl	265.29	79	$\text{C}_9\text{H}_{11}\text{N}_7\text{OS}$	40.75 (40.23)	4.18 (4.22)	36.96 (36.80)	12.09 (12.20)
1c	-OH	283.70	81	$\text{C}_9\text{H}_{10}\text{N}_7\text{SCl}$	38.10 (52.41)	3.55 (3.91)	34.56 (34.61)	11.30 (11.47)
2a	-H	233.23	78	$\text{C}_9\text{H}_{11}\text{N}_7\text{O}$	46.35 (46.34)	4.75 (4.71)	42.04 (42.06)	-
2b	-Cl	246.12	86	$\text{C}_{11}\text{H}_{14}\text{N}_6\text{O}$	53.65 (53.60)	5.73 (5.71)	34.13 (34.10)	-
2c	-OH	210.87	80	$\text{C}_{11}\text{H}_{14}\text{N}_6\text{O}_2$	50.38 (50.29)	5.38 (5.35)	32.04 (32.10)	-

The structures of compounds were characterized from IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and Mass spectral analysis. IR spectra of the compounds (1a) shows that the absorption band at  $\text{NH}_2$ ,  $\text{C}=\text{S}$ ,  $\text{C}=\text{N}$  and  $\text{N}=\text{N}$  corresponding to 3408, 1660, 1315, and 1512  $\text{cm}^{-1}$  respectively.  $^1\text{H}$  NMR spectrum of the compound (1a) shows that signals obtained at  $\delta$  9.60, 6.32, and 2.22 corresponding to  $\text{NH}_2$ ,  $-\text{CH}-$  and  $\text{NH}$  respectively.

The  $^{13}\text{C}$  NMR spectrum of the compound (1a) shows that signals obtained at  $\delta$  182.86 and 74.11 corresponding to ( $\text{C}=\text{S}$ ) and  $-\text{CH}-$  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  $\text{C}=\text{O}$ ,  $\text{C}=\text{N}$ , and

$\text{NH}$  corresponding to 1694, 1376, and 942  $\text{cm}^{-1}$  respectively.  $^1\text{H}$  NMR spectrum of the compound (2a) shows that the proton signals observed 6.43, 9.52, 6.12, and 2.14 corresponding to  $-\text{CH}-$ ,  $\text{NH}_2$ ,  $\text{NH}$ , and ( $-\text{NH}(\text{CH}_3)_2$ ) protons respectively.



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

The  $^{13}\text{C}$  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  $\text{CH}_2\text{N}$  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 Screening:

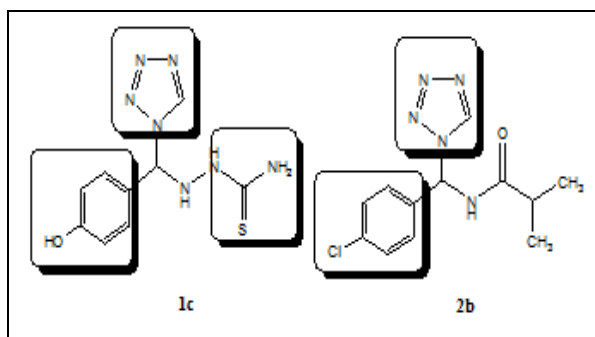
**Antibacterial Activity:** The compounds 1(a-c), and 2(a-c) were screened for antibacterial activity. The compound (1b) was highly active (MIC: 8  $\mu\text{g/mL}$ ) against *E. faecalis* compared with standard and the compound (2b) has highly active (MIC: 8  $\mu\text{g/mL}$ ) against *E. coli* compared with other compounds completely remove this sentence. The compound (1c) was highly active against *S. aureus* (MIC: 4 $\mu\text{g/mL}$ ) 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 ACTIVITY OF COMPOUNDS 1(a-c), 2(a-c). ZONE OF INHIBITION IN mm**

Com. no.	<i>S. aureus</i>	<i>E. coli</i>	<i>E. faecalis</i>	<i>P. aeruginosa</i>	<i>K. pneumoniae</i>
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 4: CYTOTOXICITY ACTIVITY OF COMPOUNDS 1(a-c), 2(a-c)**

Compounds	HepG2			MCF-7			HeLa		
	GI <sub>50</sub>	TGI	LC <sub>50</sub>	GI <sub>50</sub>	TGI	LC <sub>50</sub>	GI <sub>50</sub>	TGI	LC <sub>50</sub>
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**

**TABLE 3: THE MINIMAL INHIBITORY CONCENTRATIONS (MIC,  $\mu\text{g/mL}$ ) 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  $\mu\text{g/mL}$ . 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<sub>50</sub>, TGI and LC<sub>50</sub> values were determined. The result of the screening was expressed in terms of GI<sub>50</sub> growth inhibitor concentration.

**Table 4** shows that the compound (1c) has highly active against MCF<sub>7</sub> cancer cell line for the reason that low growth of inhibition (GI<sub>50</sub>) at 8.2  $\mu\text{m}$  compared to other and compounds (2b) is highly active against HepG2 for the reason that low Growth of inhibition (GI<sub>50</sub>) at 5.4 $\mu\text{m}$  compared to other and compounds.

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

**Fig. 2** indicates that highlighted that structure activity relationship. The compound (1c) is highly active against *S. aureus* (MIC, 4  $\mu\text{g/mL}$ ) 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.  $\mu\text{g/mL}$ ) 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 faecalis* 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<sub>50</sub> values in micromolar range.

Overall, this study demonstrates that antibacterial and cytotoxicity activity potential of new tetrazole 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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