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Microwave Assisted Synthesis, Characterizations and Antibacterial Activity of Some of Thiazole Derivatives.

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ABSTRACT

A series of substitution 2-amino thiazole compounds were synthesis by reaction of substitution acetophenone with thiourea and iodine in microwave oven. The synthesis compounds have been characterized by M.P., TLC, CHN, UV, FT-IR, ^{1}HNMR,^{13}CNMR and Mass spectra. The biological screening data of the synthesized compounds were also studied.

Keywords: Microwave, Thiazole, Anti-bacterial

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INTRODUCTION

Microwave irradiation has gained popularity in the past decade as a powerful tool for rapid and efficient synthesis of a variety of compounds because of selective absorption of microwave energy by polar molecules. The application of microwave irradiation to provide enhanced reaction rate and improved product field in chemical synthesis and it is providing quite successful in the formation of a variety of carbon-heteroatom bonds. [1, 2] During recent years, microwaves have been extensively used for carrying out chemical reactions and have become a useful non-conventional energy source for performing organic synthesis [3-5]. This is supported by a great number of publications in recent years, particularly in 2003, related to the application of microwaves as a consequence of a great availability of dedicated and reliable microwave instrumentation [6-10].

Heterocyclic compounds are highly attractive compounds in the research and development of materials for organic chemistry. The first synthesis of the thiazolic ring at the end of the nineteenth century by Rudolf Hantzch in 1887 [11].

Thiazole or 1,3 thiazole is a heterocyclic compound featuring both a nitrogen atom and sulphur atom have molecular formula C_3H_3NS as part of the aromatic five-membered ring [12]. Thiazole and related compounds are called 1,3-azoles [nitrogen and one other heteroatom in a five-membered ring]. The term thiazole refer to a large family of derivatives. They are isomeric with the 1, 2-azoles, the nitrogen and sulphur compound being called isothiazole [13].The numbering system was shown below Fig. 1, for naming derivatives of thiazole.

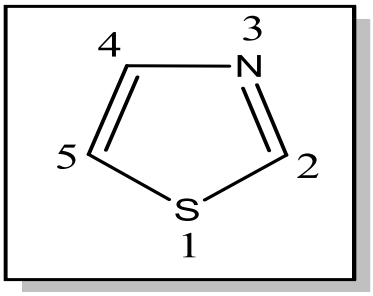

Figure 1: Numbering system of thiazole ring

Heterocyclic compounds containing thiazole and its derivatives are playing a vital role in nature. For example, the thaizolunim ring present in vitamin B_1 [Thiamine] [14] Fig. [2] Serves as an electron sink and its coenzyme form was important for the decarboxylation of α-keto acids. This heterocyclic system has found broad applications in drug development for the treatment allergies, inflammation, hypertension, schizophrenia, bacterial and HIV infections [15].

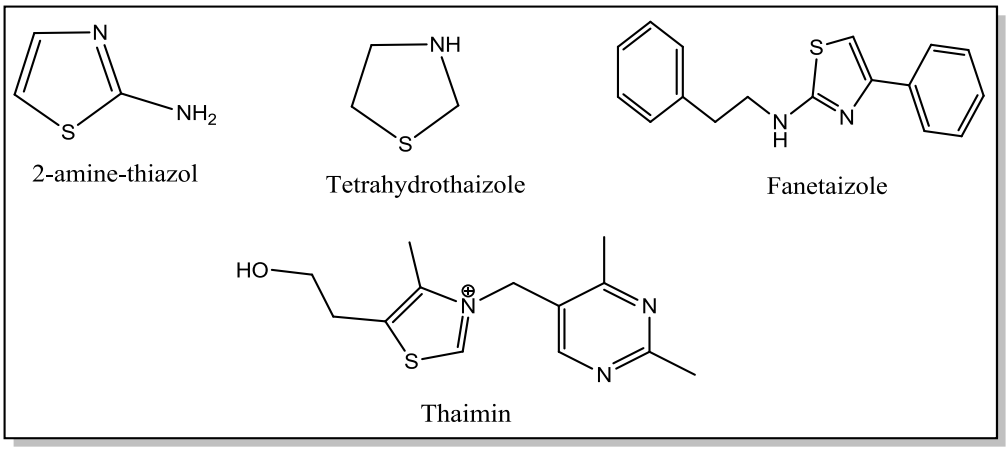

Figure 2: The structure of thiazole derivatives

A tetrahydrothiazole also appears in the skeleton of penicillin, which is one of the first and most important broad-spectrum antibiotics. Aminothiazoles are known to be ligands of oestrogen receptors as well as a novel class of adenosine receptor antagonists [16, 17]. Fanetaizole compound was a derivative of 2-aminthiazole is an anti- inflammatory agent, as shown in Fig. [2].

EXPERIMENTAL WORK

Melting point were determined in Buchi thermal point apparatus and were uncorrected, Elemental analysis [CHN] were recorded in EA300 Euro-Vector in University of Al-albyat in Jordon. FT-IR Spectra were recorded on Shimadzu FT-IR 8400 Fourier Transformer infrared as KBr disk in the range 40-4000cm^{-1}. Ultraviolet spectra were recorded in spectro scan 80 in the wavelength 200-800 nm. ^{1}HNMR and ^{13}CNMR spectra were recorded on Brucker spctrospin ultra shield magnets 400MHz instrument using tetramethyl silane [TMS] as an internal standard and DMSO-d_6 as a solvent in university of Tabriz-Iran. The GC-Mass spectra were obtained by using TQ8040 SHIMADZU [Japan]. The method used was electron impact [70ev] [Pharmaceutical Department, Faculty of Pharmacy, Tabriz University [Iran]]. The compounds were synthesized by microwave type Newal microwave instrument [Turkey] NWL101, compact 20L, power1200 Watt and frequency 2450 MHz, by using turntable system with different powers between 90-300W. Thin layer chromatography were performed on pre-coated sheets with 0.25 mm layer of Silica Gel GF254 of the Merck Company.

Synthesis Thiazole Derivatives

All thiazoles were synthesized by reaction acetophenones [0.05mole], iodine [0.1mole] and thaiurea [0.1mole]; they were mixed well with mortar-pestle and placed in small conical flask at room temperature. The mixture was then exposed to microwave irradiation for 2-4min. at 90W, then 100ml distilled water was added to, the mixture and heated in microwave for 5min. at 180W till the precipitate dissolve, the obtained was triturated with diethyl ether and separate the liquid layer and washed with hot water. Filter the yellow solution and alkaline it with ammonia solution. Separate out the product, washed in ether and recrystallization with ethanol followed by diethyl ether under reduce pressure. The purity of the synthesized compounds was tested with thin layer chromatography [TLC] by using eluent [hexane: ethyl acetate] ratio [3:7] respectively. Other thiazoles were synthesized in similar way; the products were obtained in 79-99%. Physical properties of thiazole compounds as shown in Table [1].

Synthesis Compounds

H: 4-phenyl-2-amino thiazole

CHN analysis that formula **$C_9H_8N_2S$** calculated C, 61.342 H, 4.582 N, 15.904 S, 18.195 ; Found C, 61.335 H, 4.578 N, 15.776 S, 18.150, Ultraviolet spectra λmax 210, 242 and 288nm. FT-IR spectra vmax 3242, 3294, 3113, 2924, 1621, 1603, 1314, 1072cm^{-1}. ^{1}HNMR spectra δppm, [6.75, 5H] and [3.93, 2H]. ^{13}CNMR spectra δppm 126, 123, 114, 128, 140, 112 and 183. MS Spectra m/s, 176, 134, 102, 77 and 51.

4-OH: 4-[4-hydroxyphenyl]-2-amino thiazole

CHN analysis that formula **$C_9H_8N_2OS$** calculated C, 56.238 H, 4.192 N, 15.904 S, 16.683 ; Found C, 56.234 H, 4.146 N, 14.555 S, 16.588. Ultraviolet spectra λmax 215, 238 and 280nm. FT-IR spectra vmax 3466, 3226, 3252, 3090, 1633, 1452, 1326, 1292, 1170 cm^{-1}. ^{1}HNMR spectra δppm [7.27, 5H], [9.4, 1H] and [4.3, 2H]. ^{13}CNMR spectra δppm 140, 113, 130, 127, 139, 103 and183. MS Spectra m/s, 192, 133, 101, 76 and 51.

4-Br: 4-[4-bromophenyl]-2-amino thiazole

CHN analysis that formula **$C_9H_7N_2BrS$** calculated C, 42.350 H, 2.772 N, 10.981 S, 12.577 ; Found C, 42.334 H, 2.699 N, 10.886 S, 12.532. Ultraviolet spectra λmax 210, 228 and 282nm. FT-IR spectra vmax 3311, 3353, 3122, 1633, 1587, 1266, 1091, 829cm-^{1}. ^{1}HNMR spectra δppm [6.32, 5H], and [3.97, 2H]. ^{13}CNMR spectra δppm, 119, 136, 128, 130, 140, 117, 183. MS Spectra m/s, 252, 177, 133, 101, 76, 51.

4-Cl: 4-[4-chlorophenyl]-2-amino thiazole

CHN analysis that formula **$C_9H_7N_2ClS$** calculated C, 51.310 H, 3.351 N, 16.830 S, 15.223 ; Found C, 51.294 H, 3.223 N, 16.312 S, 15.170. Ultraviolet spectra λmax 217, 234 and 280nm. FT-IR spectra vmax 3218, 3312, 2912, 1600. 1575, 1313, 1151, 813cm^{-1}. ^{1}HNMR spectra δppm [6.94, 5H], and [3.99, 2H]. ^{13}CNMR spectra δppm 134, 129, 132, 133, 135, 127,170. MS Spectra m/s, 210, 168, 133, 101, 76, 51.

3-NO_2: 4-[3-nitrophenyl]-2-amino thiazole

CHN analysis that formula **$C_9H_7N_3O_2S$** calculated C, 48,869 H, 3.192 N, 18.990 S, 14.494 ; Found C, 48.755 H, 3.164 N, 18.882 S, 14.376. Ultraviolet spectra λmax 210, 250 and 280nm. FT-IR spectra vmax 3283, 3430, 3112, 1634, 1534, 1395, 1037cm^{-1}. ^{1}HNMR spectra δppm [6.32, 5H], and [3.85, 2H]. ^{13}CNMR spectra δppm 131, 151, 135, 145, 136, 131, 166, 113, 182.

4-NO_2: 4-[4-nitrophenyl]-2-amino thiazole

CHN analysis that formula **$C_9H_7N_3O_2S$** calculated C, 48,869 H, 3.192 N, 18.990 S, 14.494 ; Found C, 48.763 H, 3.133 N, 18.873 S, 14.393. Ultraviolet spectra λmax 220, 240 and 280nm. FT-IR spectra vmax 3263, 3363, 3167, 1632, 1589, 1389, 1095cm^{-1}. ^{1}HNMR spectra δppm [6.69, 5H], and [3.93, 2H]. ^{13}CNMR spectra δppm 128, 119, 120, 121, 133, 117, 170. MS Spectra m/s, 221, 179, 133, 101, 76, 51.

4-CH_3: 4-[4-methylphenyl]-2-amino thiazole

CHN analysis that formula **$C_{10}H_{10}N_2S$** calculated C, 63.135 H, 5.305 N, 14.720 S, 16.857 ; Found C, 63.076 H, 5.278 N, 14.654 S, 16.693. Ultraviolet spectra λmax 218, 233 and 280nm. FT-IR spectra vmax 3232, 3273, 2977, 1623, 1480, 1380, 1057cm^{-1}. ^{1}HNMR spectra δppm [6.62, 5H], and [3.93, 2H]. ^{13}CNMR spectra δppm 129, 128, 127, 132, 164, 114, 183, 21. MS Spectra m/s, 190, 148, 133, 101, 76, 51.

4-OCH_3: 4-[4-methoxyphenyl]-2-amino thiazole

CHN analysis that formula **$C_{10}H_{10}N_2OS$** calculated C, 58.236 H, 4.894 N, 13.580 S, 15.556 ; Found C, 58.212 H, 4.775 N, 13.442 S, 15.493. Ultraviolet spectra λmax 212, 245 and 280nm. FT-IR spectra vmax 3247, 3372, 3055, 1630, 1501, 1330, 1254, 1101cm^{-1}. ^{1}HNMR spectra δppm [7.27, 5H], and [4.24, 2H]. ^{13}CNMR spectra δppm 158, 121, 129, 123, 130, 120, 169, 92. MS Spectra m/s, 206, 194, 133, 101, 76, 51.

4-F: 4-[4-fluorophenyl]-2-amino thiazole

CHN analysis that formula **$C_9H_7N_2FS$** calculated C, 55.563 H, 3.636 N, 14.420 S, 16.518; Found C, 55.553 H, 3.535 N, 14.237 S, 16.221. Ultraviolet spectra λmax 210, 226 and 285nm. FT-IR spectra vmax 3249, 3282, 3063, 1619, 1449, 1222, 1002,703 cm^{-1}. ^{1}HNMR spectra δppm [6.75, 5H], and [3.99, 2H] .^{13}CNMR spectra δppm 135, 129. MS Spectra m/s, 194, 152, 133, 101, 76, 51.

2-F: 4-[2-fluorophenyl]-2-amino thiazole

CHN analysis that formula **$C_9H_7N_2FS$** calculated C, 55.563 H, 3.636 N, 14.420 S, 16.518;; Found C, 55.534 H, 3.499 N, 14.198 S, 16.101. Ultraviolet spectra λmax 213, 236 and 285nm. FT-IR spectra vmax 3200, 3257, 3078, 2989, 1615, 1466, 1385, 1085, 690cm^{-1}. ^{1}HNMR spectra δppm [6.74, 5H], and [3.98, 2H]. ^{13}CNMR spectra δppm 127, 113, 164, 114, 125, 115, 151, 113,183.

2-OCH_3: 4-[2-methoxyphenyl]-2-amino thiazole

CHN analysis that formula **$C_{10}H_{10}N_2OS$** calculated C, 58.236 H, 4.894 N, 13.580 S, 15.556; Found C, 58.187 H, 4.845 N, 13.344 S, 15.502 . Ultraviolet spectra λmax 210, 245 and 285nm. FT-IR spectra vmax 3281, 3362, 3096, 2961, 1596, 1533, 1280, 1141, 1088cm^{-1}. ^{1}HNMR spectra δppm [6.62, 5H], and [4.08, 2H]. ^{13}CNMR spectra δppm 129, 118, 158, 120, 123, 129, 130, 114, 170, 92.

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2-OH: 4-[2-hydroxyphenyl]-2-amino thiazole

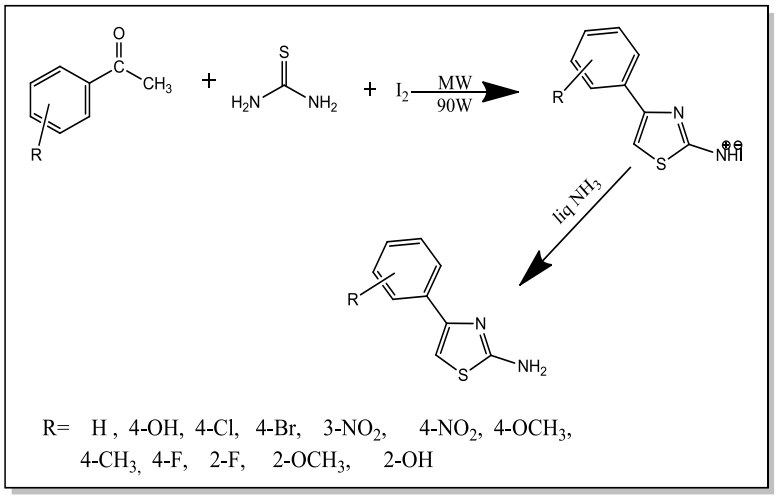
CHN analysis that formula **$C_9H_8N_2OS$** calculated C, 56.238 H, 4.192 N, 15.904 S, 16.683; Found C, 56.123 H, 4.009 N, 14.346, S, 16,528. Ultraviolet spectra λmax 214, 248 and 281nm. FT-IR spectra vmax 3488, 3268, 3362, 3098, 1623, 1484, 1307, 1162, 1099cm^{-1}. ^{1}HNMR spectra δppm [6.64, 5H], [3.93, 2H] and [9.15, 1H]. ^{13}CNMR spectra δppm 129, 125, 164, 128, 134, 128, 138, 118, 113, 183.

Table 1: Some physical data of thiazole compounds

Symbol of Thiazole	Name of the Thiazole	Colour	Melting Point[^{0}C]	Yield [%]	R_f
THI 1 [H]	4-phenyl-2-amino thiazole	white	145-146	88	0.93
THI 2 [4-OH]	4-[4-hydroxyphenyl]-2-amino thiazole	yellow	216-218	99	0.76
THI 3 [4-Br]	4-[4-bromophenyl]-2-amino thiazole	yellow	183-185	85	0.83
THI 4 [4-Cl]	4-[4-chlorophenyl]-2-amino thiazole	white	179-181	93	0.79
THI 5 [3-NO_2]	4-[3-nitrophenyl]-2-amino thiazole	Pale yellow	177-179	79	0.87
THI 6 [4-NO_2]	4-[4-nitrophenyl]-2-amino thiazole	Dark yellow	280-282	91	0.88
THI 7 [4-OCH_3]	4-[4-methoxyphenyl]-2-amino thiazole	Yellow	206-208	93	0.91
THI 8 [4-CH_3]	4-[4-methylphenyl]-2-amino thiazole	Yellow	132-136	87	0.78
THI 9 [4-F]	4-[4-fluorophenyl]-2-amino thiazole	Yellow	103-104	91	0.85
THI 10 [2-F]	4-[2-fluorophenyl]-2-amino thiazole	Yellow	107-108	84	0.82
THI 11 [2-OCH_3]	4-[2-methoxyphenyl]-2-amino thiazole	Pale yellow	178-180	97	0.81
THI 12 [2-OH]	4-[2-hydroxyphenyl]-2-amino thiazole	Yellow	213-215	81	0.82

RESULT AND DISCUSSION

Microwave dielectric heating uses the ability of some liquids and solids to transform electromagnetic radiation into heat to drive chemical reactions. The entry of microwave ovens possible to carry out many transformations with greater efficiency and ease of workup [18], the use of microwave has becomes very attractive in the field of medical sciences.



Scheme [1]

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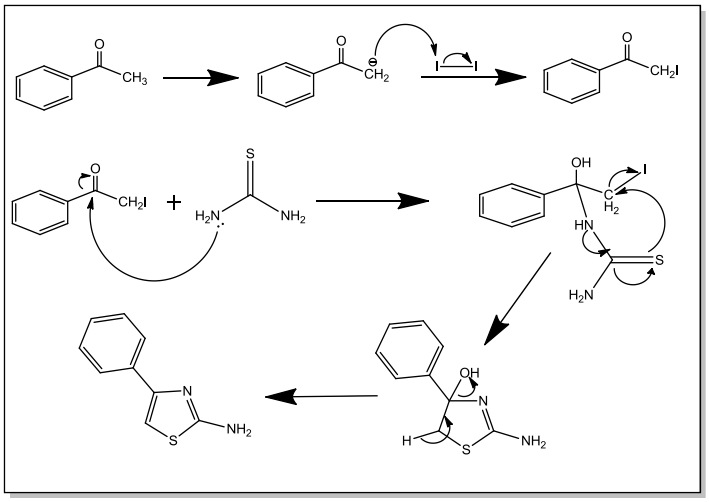
A series of substituted phenyl thiazole compounds TH1-TH12 were synthesized by reaction of substituted acetophenone with thiourea and iodine in microwave oven with 90W. All these reaction were monitored by TLC. The end of reaction was concentrated by liquid ammonia, as shown in scheme [1].

The synthesis substituted phenyl thiazole compounds showed high different yields because the acetophenones compounds contained electron donating or electron withdrawing groups on their structures. The electron-donating groups led to increasing the electron density at the carbon atom of carbonyl group so, their electrophilic properties were enhanced, while the electron withdrawing groups decrease the electron density at the carbon atom of carbonyl group, therefore, the yield was of product increased and decrease the reaction time when using microwave irradiation.

The Purification of thiazole compounds were tested first by thin layer chromatography [TLC] using different eluents. The best separation was obtained in mixture of [hexane: ethyl acetate] having ratio [7:3] respectively as eluent. Then, the products were purified by absolute ethanol.

The mechanism of reaction can be explained in scheme [2], which first showed the formation of phencyl iodide by nucleophilic attack of amine group of thaiurea at the carbon atom of carbonyl group, the second nucleophilic attack of sulpher of thiourea and the active carbon carrying iodide group, with the elimination of iodide at the end of reaction.



Scheme [2]

The structures of the synthesized substituent phenyl thiazole were confirmed by their elemental analysis, UV, IR, NMR and MS. CHN were situated within the range which confirmed the validity of the suggested structure of the prepared compounds. The spectra of substituents phenyl thiazole compounds were characterized by three bands in absolute ethanol, the first band, have the wave length and appeared in range [210-220] nm [ϵ=[720-1785] l. mole^{-1}. cm^{-1}] which was attributed to the [π-π*] transition of aromatic system. The second band appeared in the range [228-250] nm [ϵ= [638-2144] l.mole^{-1}. cm^{-1}] which was attributed to the [π-π*] transition of aromatic system. The third band in the range [280-290] nm [ϵ= [200-1138] l.mole^{-1}. cm^{-1}] which was attributed to the [π-π*] transition of [C=N-S] group.

The IR spectra of all substituent phenyl thiazole compounds were characterized by the disappearance of the absorption band that was attributed to the [C=O] stretching which appeared at [1700-1750] cm^{-1}. In addition, showed a strong infrared absorption band in the region between [3224-3430] cm^{-1} due to NH_2 stretching.

All ^{1}HNMR spectra showed a peak at the region [2.4-2.5] ppm, which was due to the DMSO solvent. The ^{1}HNMR spectra of [TH1-TH12] substituent phenyl thiazole compounds showed multiplet signal within the region [6.7-8] ppm due to aromatic ring system. While the proton of thiazole ring was interference with the protons of aromatic ring in the same region.

All these spectra showed a peak at the region [3.9-4.2] ppm, which was due to the two-proton equivalent of amino group.

All ^{13}CNMR spectra showed [7] peak, come back to THI-TH9 expect TH5 and [10] peak for TH1, TH10-TH12.

From the mass spectra, it was found that the peaks at [m/z = 176, 192, 255, 210, 221, 206, 190 and 194] represented the molecular ion [M^+] for [TH1-TH9] except TH5 compounds, respectively. These peaks indicated that the structures of the thiazoles compounds that were synthesis in our study were correct. All synthesized substituent phenyl thiazole compounds had similar fragment mechanisms.

Biological Activities

The antibacterial [19, 20] activities of the series [TH1-TH12] have been carried out against some strain of bacteria. The result [Table 2] showed that prepared compounds are toxic against the bacteria. The compounds TH3, TH4, TH5 and TH6 were found more active against the above microbes. The comparison of the antibacterial activity of these compounds with Streptomycin shows that these compounds have almost similar activity.

The bacterial cultures for S. aureus, and E. coli were obtained from Department of biology University of Basrah. Iraq. The bacterial cultures were incubated at 30 ^{o}C for 24 hours by inoculation into nutrient agar. Schiff bases and azetidinone were stored dry at room temperature and dissolved 20mg/ml in dimethyl sulfoxide [DMSO]. Antibacterial activities of each compound were evaluated by the agar disc-diffusion method. Mueller Hinton Agar Media [15 cm^3] kept at 45^{o}C was poured in the petridishes and allowed to solidify. Poured Petri plates [9 cm] were incubated with 50µL of normal saline solution of above culture media [105-106 bacteria per ml]. Discs injected with prepared Schiff bases and azetidinone [50µL] were applied on the solid agar medium by pressing tightly. The Petri plates were placed at 37^{o}C for 24 hours. At the end of period, the inhibition zones formed on media were measured with a zone reader in millimetres.

Table 2: The antibacterial activities of the compounds [a-c]

Antibacterial data in MIC[µg/ml]		
Compound	**Staphylococcus aurous[gram +ve]**	**E. Coli [gram –ve]**
TH1	**9**	**5**
TH2	**7**	**5**
TH3	**12**	**12**
TH4	**12**	**12**
TH5	**14**	**13**
TH6	**15**	**14**
TH7	**X**	**X**
TH8	**4**	**3**
TH9	**12**	**12**
TH10	**9**	**7**
TH11	**X**	**X**
TH12	**X**	**X**
Streptomycin standard	**9**	**12**

X= zero activity

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