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Cycloaddition involving activated isothiocyanate: Synthesis and antimicrobial activities of thiazine, pyrimidine and pyridine derivatives

Amira A.Ghoneim*, Mohamed G.Assy, Enaiat K.Mohamed, Islam Ragab

Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt

A B S T R A C T

Aniline was added to acylisothiocyante [1] to produce 1,3-thiourea derivative [2]. Allowing compound [2] to react with sodium ethoxide, at room temperature resulted in thiazine cyclization affofding [3]. Refluxing 2 in sodium ethoxide afforded the pyrimidine derivative [4]. Cyclization of heteroallene [1] using phenylenediamine [5] afforded benzimidazolo pyrimidine derivative [7]. enaminones of type [8] and compound undergo [3+3] cycloaddition producing pyridine derivative [9]. While enaminone of type [12] afforded acetyl pyrimidine derivatives [13]. Finally the reaction of compound 1 was allowed to react with aminoesrer producing thiophene derivative [16]. The structures of the synthesized compounds have been deduced from their elemental analysis and spectral data. The synthesized compounds were screened for antibacterial and antifungal activities.

Keywords: Acylisothhiocyanate, thiazine, benzimidazole, thiophene, antifungal activities.

A R T I C L E I N F O

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***Corresponding Author**
Amira A.Ghoneim
Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt
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1. Introduction

Importance of uracil and its derivatives annulated is well known by Synthetic as well as biological chemists [l-8]. With anti-evolution of cancer clinically useful and antiviral drugs [9-12], there has recently a significant interest in the synthetic manipulations of uracils [13-16] Pyrimidines and condensed pyrimidines have received considerable attention over the past years due to a range of broad biological activities, which include antitumor [17], antibacterial [18], anti-inflammatory [19], antifungal [20], and also serves as cyclin-dependent Kinase 4 inhibitors [21]. As part of our current studies on the developments of new methods for heterocyclization here in described a facile synthesis of fused barbituric acid as anticancer agents.

2. Matirials and Methods

Chemistry

Melting points are uncorrected and were recorded on Buchi 510 apparatus. IR spectra were recorded as KBr disks on a perkin-Elmer 383 spectrometer and FTIR-spectrometer Nicolet, impact 400.^{1}H -NMR spectra was recorded on a Varian Mercury Plus-400 or Bruer-300 in DMSO-d_6 with TMS as an internal standard. The types of signals are indicated by the following letters: s = singlet, d = doublet, t = triplet, q = quartat. Elemental analysis was carried out LECO-Analyser CHNS-932. Microanalytical were carried out at microanalytical center and Cairo University, Egypt.

1-((Z)-3-(3-Nitrophenyl)-2-phenylacryloyl)-3-arylthiourea (2)

A mixture of compound **1** (0.01 mol) and aniline (0.01 mol) in dry acetone (20 ml) was stirred for 7 hrs. The separated solid formed after dilution with water was filtered, dried and crystallized from ethanol to give light brown crystals of **2**, yield 90.5 %; mp 175 °C. IR spectrum (υ_{max}, cm^{-1}): 3380 (NH) and 1673 (C=O). Anal. Calcd. For $C_{22}H_{17}N_3O_3S$: C, 65.49; H, 4.25; N, 10.42. Found: C, 65.47; H, 4.22; N, 10.39.

5, 6-Dihydro-6(3-nitrophenyl)-5-phenyl-2(phenyl amino) -1,3-thiazin-4-one (3)

A mixture of compound **2** (0.01 mol) and sodium ethoxide (0.01 mol) in ethanol (20 ml) was stirred for 7 hrs. The separated solid formed upon acidification with HCl (10 ml, 20%) and dilution with water was filtered, dried and crystallized from ethanol to give light brown crystals of **3**, light brown solid, yield 91.6%; mp 238-240 °C. IR spectrum (υ_{max}, cm^{-1}): 3320 (NH) and 1742(C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 12.53 (s, 1H, NH), 12.06 (s, 1H, NH), 7.29-8.12 (m, 14H, ArH's), 5.80 (d, 1H, CH), 4.32 (d, 1H, CH), 3.92(d, 1H, CH), and 3.82 (d, 1H, CH). Anal. Calcd. For $C_{22}H_{17}N_3O_3S$: C, 65.49; H, 4.25; N, 10.42. Found C 65.45, H 4.23, N 10.40.

2,3-Dihydro-6-(3-nitrophenyl)-1,5-diphenyl-2-thioxo pyrimidin -4(1H)-one (4)

A mixture of compound **2** (0.01 mol) and sodium ethoxide (0.01 mol) in ethanol (20 ml) was refluxed for 7 hrs. The separated solid was formed upon acidification with HCl (10 ml, 20%) and dilution with water was filtered, dried and was crystallized from ethanol yielded dark brown crystals of **4**, yield 89.8%; mp >360 °C. IR spectrum (υ_{max}, cm^{-1}): 3379 (NH), 1742 (C=O) and 1594(C=S). ^{1}H NMR (DMSO-d6, δ, ppm): 12.52 (s, 1H, NH) and 7.26-8.03 (m, 14H, ArH's). Anal. Calcd. For $C_{22}H_{15}N_3O_3S$: C, 65.82; H, 3.77; N, 10.47. Found: C, 65.79; H, 3.74; N, 10.42.

5,6-Dihydro-5-(3-nitrophenyl)-6-(phenyl)-pyrido[1,2-a] benzimidazole-7(1H)-one (7)

A mixture of compound **1** (0.01 mol) and O-phenylendiamine **5** (0.01 mol) in dry acetone (20 ml) was refluxed for 6 hrs. The separated solid that was formed upon dilution with water was filtered, dried and crystallized from toluene to give dark brown crystals of **7**, yield 83.8%; mp >360 °C. IR spectrum (υmax, cm^{-1}): 3381(NH) and 1675(C=O). ^{1}H NMR (DMSO-d6, δ, ppm): 8.33 (s, 1H, NH) and 7.65-8.23 (m, 13H, ArH's). Anal. Calcd. For $C_{22}H_{14}N_4O_3$: C, 69.10; H, 3.69; N, 14.65. Found: C, 69.7; H 3.65; N, 4.62.

1-(2-Mercapto-6-((Z)-2-(3-nitrophenyl)-1-phenylvinyl)-4-(phenyl-amino) pyridin-3-yl)ethanone(9)

A mixture of compound **1** (0.01 mol), enaminone **8** (0.01 mol) in dry acetone (20 ml) is was stirred for 7 hours at room temperature. The separated solid formed after dilution with water was filtered, dried and crystallized from ethanol to give dark brown crystals of **9,** yellow solid, yield 80.8%; mp 136-139 °C. IR spectrum (υ_{max}, cm^{-1}): 3383 and 3242 (NH) and 1678 (C=O). ^{1}H NMR (DMSO-d6, δ, ppm) :12.06 (s, 1H, SH) ,10.93 (s, 1H, NH), 2.53 (s, 3H, CH_3), 7.28-8.03 (m, 14H, ArH's). Anal. Calcd. For $C_{27}H_{21}N_3O_3S$: C, 69.36; H, 4.53; N, 8.99. Found: C, 69.33; H, 4.50; N, 8.95.

1-(4-Mercapto-6-methyl-2-((Z)-2-(3-nitrophenyl)-1-phenylvinyl)-pyrimidin-5-yl)ethanone (13)

A mixture of compound **1** (0.01 mol) and enaminone **12** (0.01 mol) in dry acetone (20 ml) was stirred for two hrs at room temperature, then was boiled in NaOH for half hour, The separated solid was formed upon acidification with HCl (10 ml, 20%) and dilution with water was filtered, dried and recrystallized from ethanol to give yellow crystals of **13**, yellow solid, yield 85.8%; mp 210 °C. IR spectrum (υmax, cm^{-1}): 3373(NH) and 1706 (C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 13.95 (s, 1H, SH), 7.63-8.21(m, 9H, ArH's), 2.85 (s, 3H, CH_3), 2.45 (s, 3H, CH_3). Anal. Calcd. For $C_{21}H_{17}N_3O_3S$: C, 64.43; H 4.38; N, 10.73. Found: C, 64.41; H, 4.32; N, 10.70.

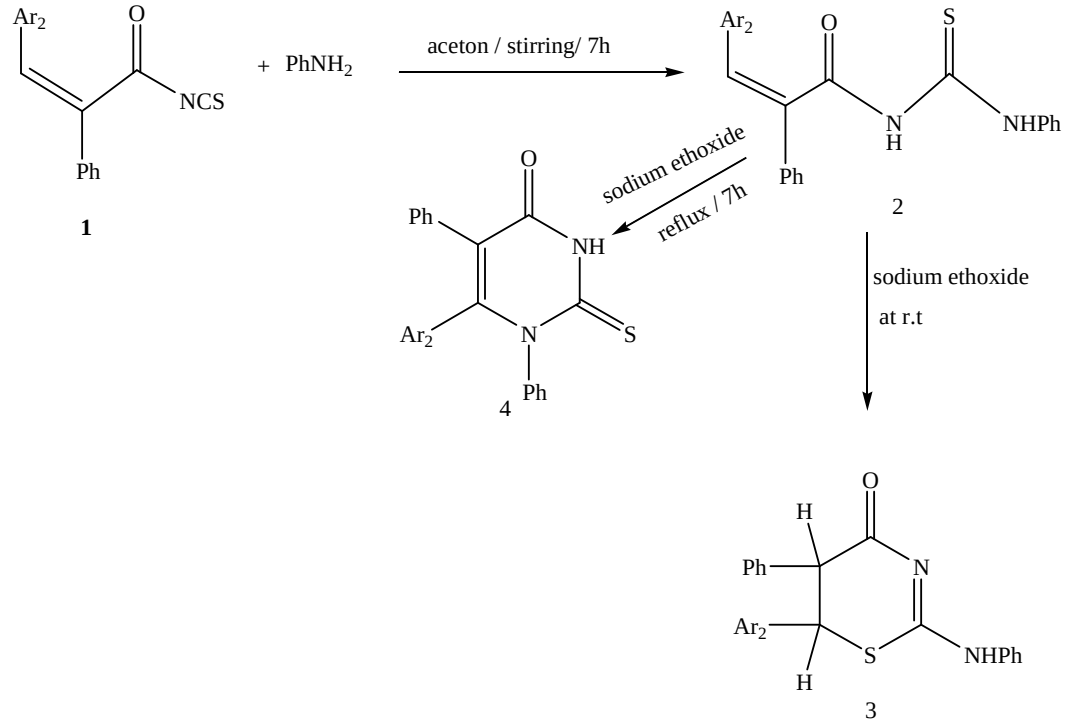
Ethyl4,5,6,7-tetrahydro-2-(3-((Z)-3-(3-nitrophenyl)-2-phenylacryloyl)-thioureido)benzo[b]thiophene-3-carboxylate (15): A mixture of compound **1** (0.01 mol) and aminthiophene derivative **14** (0.01 mol) in dry acetone (20 ml) was stirred for 7 hrs. The separated solid was formed upon dilution with water was filtered, dried and recrystallized from ethanol afforded yellow crystals of **15**, yield 90.5%; mp 220 °C. Anal. Calcd. For $C_{27}H_{25}N_3O_5S_2$: C, 60.54; H, 4.70; N, 7.84. Found: C, 60.52; H, 4.86; N 7.82. IR spectrum (υ_{max}, cm^{-1}): 3368 (NH), 2934 (CH) and 1678 (C=O).

Ethyl4,5,6,7-tetrahydro-2-(3,4-dihydro-6(3-nitrophenyl) -4-oxo-5-phenyl-2-thioxopyrimidin-1(2H)-yl)-benzo[b] thiophene-3-carboxylate (16)

A mixture of compound **15** (0.01 mol) and sodium ethoxide (0.01 mol) in ethanol (20 ml) was refluxed for half hour. The separated solid was formed upon acidification with HCl (10 ml, 20%) and dilution with water was filtered, dried and recrystallized from ethanol to give brown crystals of **16,** yield 83.8%; m.p 190 °C. IR spectrum (υ_{max}, cm^{-1}): 2924 (CH), 1706 (C=O). ^{1}H NMR (DMSO, d_6, δ, ppm): 12.63 (s, 1H, SH), 7.63-8.02(m, 9H, ArH's), 3.94 (q, 2H, CH_2), 1.62-2.45 (m, 8H, cyclohexane), 1.23 (t, 3H, CH_3), and. Anal. Calcd. For $C_{27}H_{23}N_3O_5S_2$: C, 60.77; H, 4.34; N, 7.87. Found: C, 60.75; H, 4.31; N, 7.85.

3. Result and Discussion

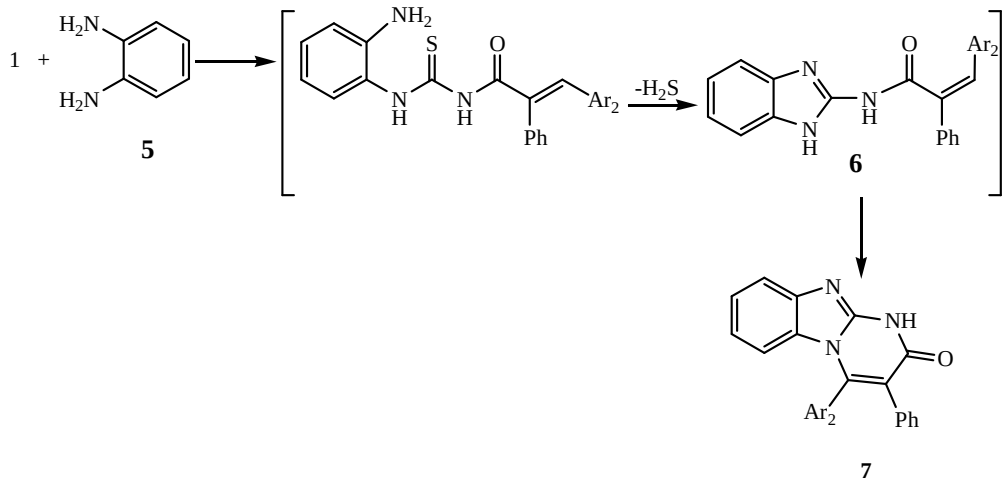
Cycloaddition have gained increasing popularity in the last two decades. Owing to their versatility in construction of heterocycles [22-25]. Among them intramolecular thiourea moiety cycloaddition to the polarized double bond giving rise to interesting structures in which 1,3 thiazine or pyrimidine ring constitutes the main feature of the whole system [26-27]. On pursuing our research line in this field [28]. We report here the synthesis of 1,3-thiazine, pyrimidine, imidazole-pyrimidine and pyridine derivatives. The synthesis of acylthiourea **2** was performed via an aniline Michael addition to heteroallene **1** (scheme 1). The IR spectrum of compound **2** showed medium band at 3380 cm^{-1} arising from N-H stretching in addition to sharp strong band at 1673 cm^{-1} due to the carbonyl stretching frequency. Treatment of thiourea derivative **2** with catalytic amount of sodium ethoxide at room temperature provided a way to thiazinone **3** as kinetic product in the Cis and Trans mixture presumably *via* Michael intramolecular cycloaddition involving the addition of thiolate anion ion to the polarized ethenylic group. The structure of compound **3** was assigned by IR and HNMR spectral data .In its IR spectrum, there were two stretching bands assignable to NH, C=O groups at 3320 cm^{-1} and 1742 cm^{-1} respectively. In the HNMR of **3**, the chemical shift for NH protons were observed at 12.53, 12.06 ppm. The aryl structure showed multiplet that observed at in the interval 7.29-8.12 ppm. The cis and trans methyl protons were also clearly observed at 5.8, 4.32, 3.92 and 3.8 ppm. Compound **2** was treated with base in order to accomplished hetero cyclization. Thus, the pyrimidine cyclization was obtained upon refluxing in sodium ethoxide to produce pyrimidine derivative **4** Scheme1. The IR spectrum of thiouracil derivative **4,** a medium band at 3379 cm^{-1} was observed corresponding to valiancy oscillation of the N-H two stretching bands assignable to C=O, C=S groups were also observed at 1751 cm^{-1} and 1594 cm^{-1} respectively.



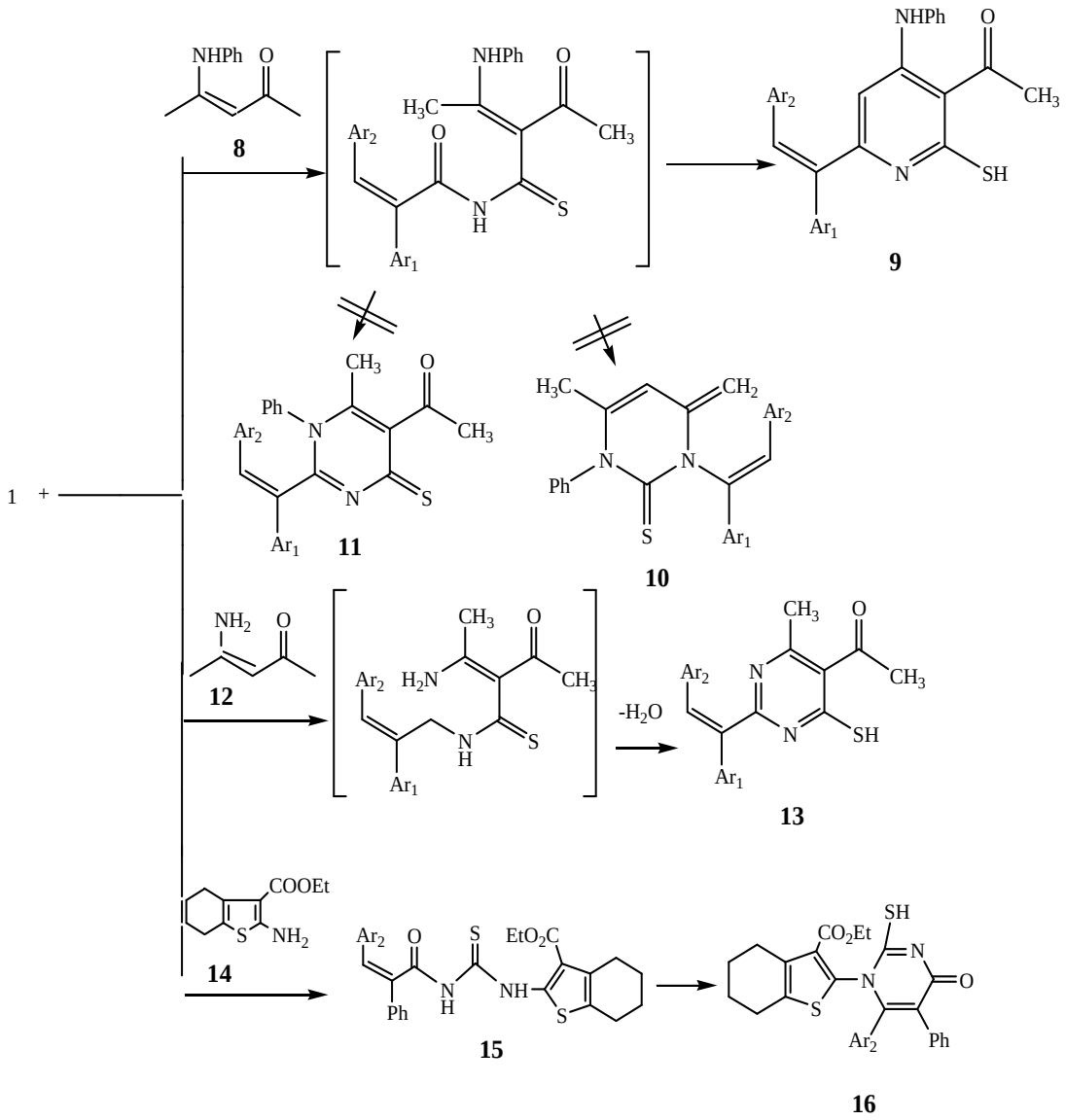
Scheme1

Treatment of the activated isothiocyanate **1** with phenylenediamine **5** led to the formation of condensed pyrimidine derivative **7** through the intermediacy of benzimidazole **6** followed by intramolecular cycloaddition and subsequent dehydrogenation Scheme 2. The structure of this product was proved by its spectroscopic data. Thus, the IR spectrum of condensed pyrimidine **7** exhibit characteristic absorption bands of NH and carbonyl: ν (NH) 3381cm^{-1} and ν (C=O) 1675 cm^{-1} respectively. ^{1}H-NMR spectrum of **7** display signal at lowest field at δ 8.38 ppm

ascribed to two NH proton. The compound possess signals of aromatic protons whose position and multiplicity corresponding to aryl structure at δ7.15-7.26 ppm.



Scheme 2



Scheme 3

The synthesis of pyridine derivative 9 was performed via a heteroallene 1 cycloaddition reaction with enaminone 8, none of the expected pyrimidines 10 and 11 were obtained. The IR spectrum of compound 9 showed a strong absorption at 3383-3241 cm^{-1} due to NH and CO absorption band at 1678 cm^{-1}. The ^{1}H-NMR spectrum assignment was made by considering compound 9 represent compound. However the mercapto and imino protons appeared at 12.06 ppm and 10.9 ppm respectively. The aromatic and ethylenic structure was identified by the multiplet signal at δ region 8.03-7.23 ppm. The acetyl protons was observed at 2.50 ppm as a singlet. The formation of 9 may be proceed through the formation of adduct followed by cyclization involving the enamine nucleophilic carbon to avoid the steric factor of the less nucleophilic nitrogen. The currently accepted mechanism of pyridine cyclization involves a reaction sequences of Michael addition and intramolecular cycloaddition of methyl carbanion to amidic carbonyl cyclization. First, the Michael addition reaction of enaminic nucleophilic carbon of enaminone 8 to electrophilic carbon of activated isothiocyanate 1 give intermediate A, which on intermolecular cycloaddition of nucleophilic carbon to carbonyl group gave rise 9. [Nitrogen nucleophile not involved in the pyrimidine cyclization may be due to the steric effect in addition to the involvement of lone pair in resonance].

The reaction between Enaminone 12 and acylisothiocyanate 1 is convenient and versatile mothed for the preparation of pyrimidine derivative 13. So the addition of nucleophilic enaminic carbon to electrophilic carbon of heteroallene results Michael adduct, that underwent intramolecular cyclocondensation to yield 5-acetylpyrimidine 13. In the IR bands spectrum of pyrimidine derivative 13 a medium bands around 3373cm^{-1} was observed due to stretching frequency of NH and the carbonyl stretching frequency was observed at 1720 cm^{-1} as a strong band. The lowest field of SH signal was observed at δ 13.92. ppm. The aromatic signals resonated at 8.01-7.82 ppm. The aliphatic protons were also observed at up field regions. When isothiocyantate 1 was allowed to react with ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*] thiophene-3-carboxylate 14 under reflux thiourea derivative 15 was produced while in the presence of sodium ethoxide afforded thiouracil 16. In the IR spectrum of compound 15 there are absorption bands of medium intensity at 3368 cm^{-1} due to NH stretching frequency in addition to the strong stretching frequency observed at 1678 cm^{-1} due to carbonyl group. The IR spectrum of compound 1 showed strong absorption bands at 2924 cm^{-1}, 1706 cm^{-1} and 1532 cm^{-1} due to SH, CH aliphatic, CO respectively. The *in vitro* antimicrobial activity of the synthesized compounds was investigated against pathogenic Gram-positive bacteria *(Bacillus subtilis)*, Gram-negative *(Escherichia coli)* and two fungus by using the disk diffusion method. Generally, as showed in Table (1). Compound (3) and (7) showed moderate activity against *(B. subtilis)*, *(E. coli)* and (*F. oxysporum*), while they showed no activity against *(A. oryzae)*.

Table 1: Antibacterial activities and Antifungal activities of synthesized compounds

Inhibition Zone (mm)				
Comp. No.	**Bacteria**	**fungi**		
	Gram (+ve)	**Gram (-ve)**	***Fusarium oxysporum***	***Aspergillus oryzae***
	Bacillus subtilis	***Escherichia Coli***		
3	26	-ve	13	-ve
4	15	9	16	-ve
7	20	15	16	9
13	25	5	12	-ve
16	15	10	10	-ve
Tetracycline	23	22	15	12
Amphotericin B	13	17	12	17

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