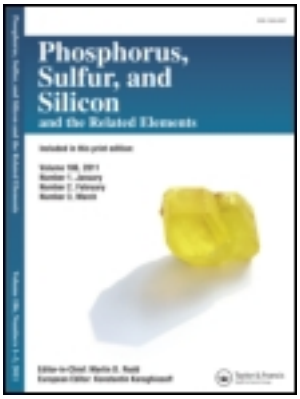

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Reactions of Cyanothioformamide and Thiohydantoin Derivatives With Some Arylidenes of Cyanothioacetamide and Other Elecetrophilic and Nucleophilic Reagents

A. M. Sh. El-Sharief [a] , F. F. Mahmoud [b] , N. M. Taha [b] & E. M. Ahmed [b]

[a] Chemistry Department , Faculty of Science, Al-Azhar University (for Boys) , Cairo, Egypt

[b] Chemistry Department , Faculty of Science, Al-Azhar University (for Girls) , Cairo, Egypt

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Reactions of Cyanothioformamide and Thiohydantoin Derivatives With Some Arylidenes of Cyanothioacetamide and Other Elecetrophilic and Nucleophilic Reagents

A. M. Sh. El-Sharief
Chemistry Department, Faculty of Science, Al-Azhar University (for Boys), Cairo, Egypt

F. F. Mahmoud
N. M. Taha
E. M. Ahmed
Chemistry Department, Faculty of Science, Al-Azhar University (for Girls), Cairo, Egypt

N-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)cyanothioformamide was synthesized from the corresponding 4-amino-pyrazole. Various cyanothioformamides were reacted with different arylidenes of cyanothioacetamide to produce either 4-imino-5-thioxo-3-(pyrroline & pyrrolidine)carbonitrile or pyrrolo[3,2-d]thiazole. Interaction of thiohydantoin with the arylidenes of either malononitrile or cyanothioacetamide furnished the same 5-aminothiopyrano[2,3-d]-imidazole-6-carbonitriles. Also, thiohydantoin reacted with the anilide of chloroacetic acid and with anthranilic acid to produce thieno[2,3-d]-imidazole-2-one and imidazo[4,5-b]quinoline-2,9-dione, respectively.

INTRODUCTION

A variety of heterocyclic ring closure reactions with cyanothioformamides[1–3] give rise to imidazoles,[4] oxazoles[5] thiazoles[6,7] and other

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Address correspondence to A. M. Sh. El-Sharief, Chemistry Department, Faculty of Science, Al-Azhar University (for Boys), Cairo, Egypt. E-mail: hmadian@hotmail.com

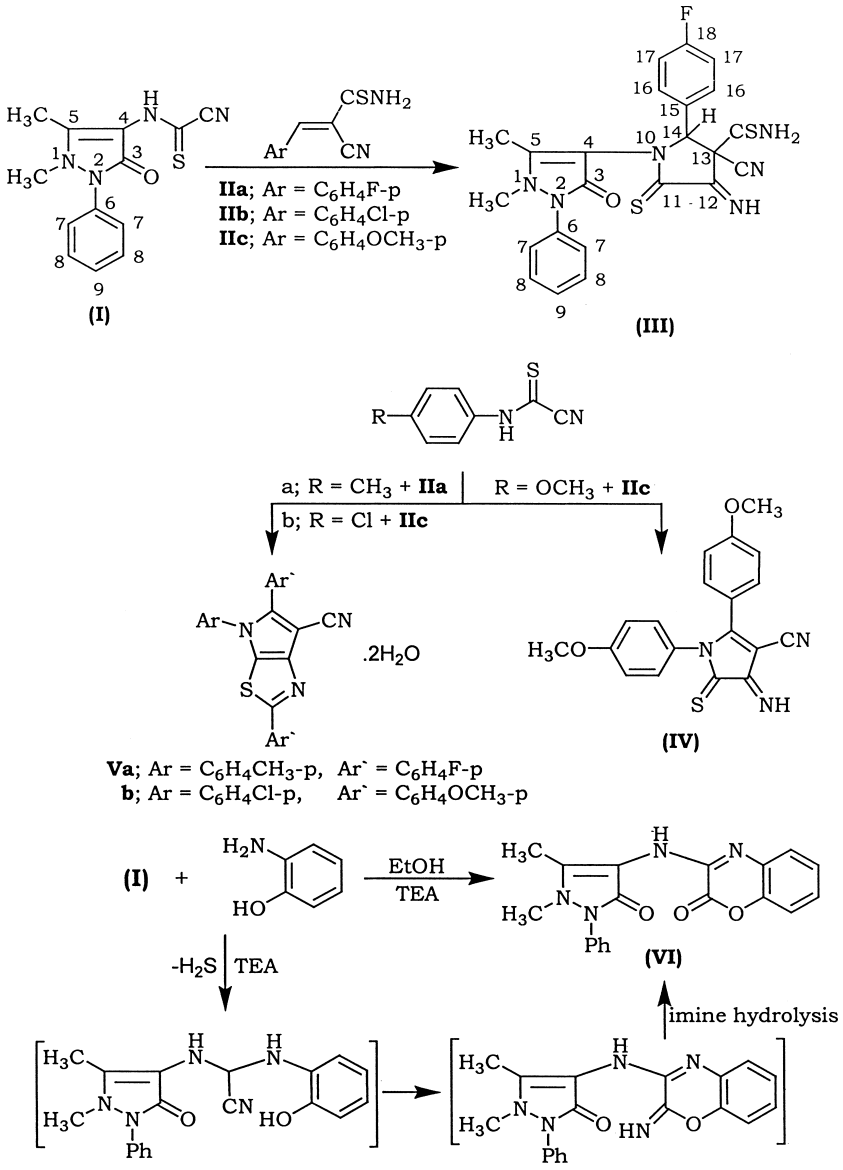
heterocycles.[8,9] Our interest in activated nitriles[10,11] and the chemistry of cyanothioformamide[12–22] led us to synthesize a new cyanothioformamide which contain a heterocyclic ring (pyrazole) and reacted it with different types of activated nitriles.

Thus, N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-cyanothioformamide **I** (Scheme 1) was prepared by the same procedure reported in Ref. (23). Its structure was demonstrated by IR, ^{1}HNMR, ^{13}CNMR, mass spectra and elemental analyses. Reaction of **I** with p-fluorobenzylidene cyanothioacetamide **IIa** in EtOH/TEA (TEA = triethylamine), furnished a product for which its elemental and spectral data (IR, ^{1}HNMR, ^{13}CNMR, and mass spectra) were compatible with structure **III** (Scheme 1) viz., l-(l,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-lH-4-pyrazolyl)-4-imino-2-(p-fluorophenyl)-5-thioxo-3-thioamido-3-pyrrolidinecarbonitrile. This product **III** could easily lose one molecule of thioformamide $H.CS.NH_2$ to give the 2-pyrroline 3-carbonitrile derivative which appeared as the first fragment in its mass spectrum and also could be isolated with other derivatives.

Similarly, reaction of N(p-anisyl)cyanothioformamide with p-anisylidinecyanothioacetamide **IIc** yielded the 4-imino-l,2-di (p-anisyl)-5-thioxo-4,5-dihydro-lH-2-pyrroline-3-carbonitrile, **IV** (Scheme 1). Its structure was confirmed by IR, ^{1}HNMR, mass spectra and elemental analyses. Also, reaction of N(p-tolyl) and (p-chlorophenyl)cyanothioformamide with arylidene **II** (a & c) produced in each case one product in which its IR, ^{1}HNMR, mass spectra and elemental analyses were compatible with structure **V** as 1-(p-tolyl)-2,5-di-(p-fluorophenyl)-pyrrolo[3,2-d]thiazole-3-carbonitrile dihydrate (**Va**) and l-(p-chlorophenyl)-2,5-di(p-anisyl)pyrrolo[3,2-d]thiazole-3-carbonitrile dihydrate **Vb** (Scheme 1). The mechanism of formation of **V** can be rationalized as described in Scheme 2. This pyrrolo[3,2-d]thiazole structure was obtained by the authors[15] through interaction of pyrrolidineimino- thione with p-chlorobenzoyl chloride.

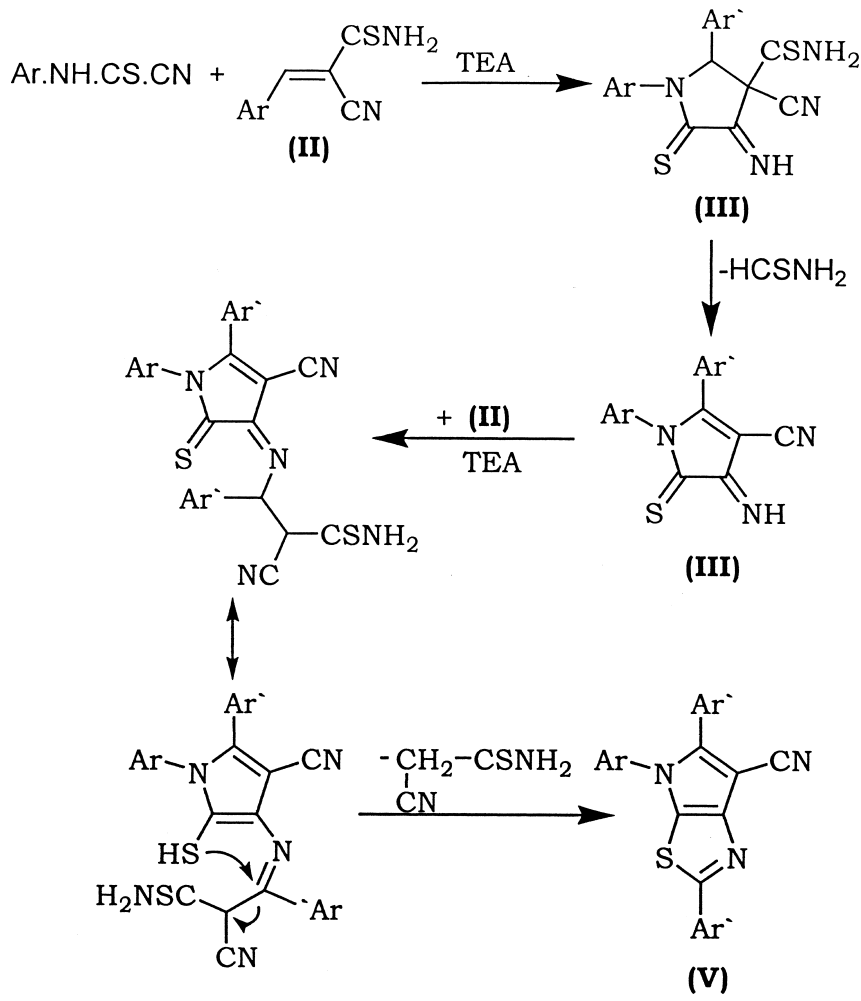
Cyanothioformamide **I** was also reacted with o-amino phenol as a nucleophilic reagent to produce a product with elemental and spectral data compatible with the 3-(l,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-lH-4-pyrazolylamino)benzo[l,4]-oxazin-2-one **VI** (Scheme 1).

The known higher activity of thiohydantoin that contains adjacent active methylene and thione groups influenced us to couple it with different reagents to produce various fused heterocyclic systems having potential biological interest. Thus 5-iminoimidazolidine-4-thiones which were prepared by the reaction of the corresponding cyanothioformamides with phenyl isocyanate, were reacted with H_2S/TEA[4] to produce the respective thiohydantoin derivatives **VIIa–f** (Scheme 3).



SCHEME 1

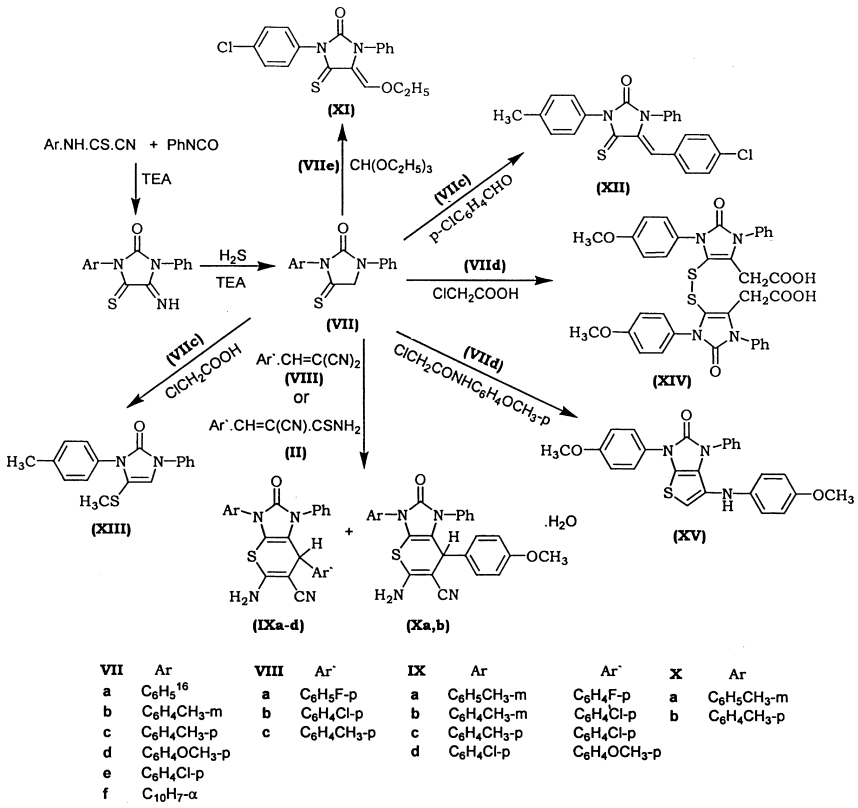
Reaction of **VII** with various arylidenes of malononitrile **VIII** furnished the corresponding 5-amino-3,7-diaryl-2-oxo-1-phenyl-1,2,3,4-tetrahy-drothiopyrano[2,3-d]imidazole-6-carbonitriles, **IXa–d** (Scheme 3). There is a point of interest with respect to compounds



SCHEME 2

IXa,**b** & **c**: The base peak in all of them is M-l which sheds some light on the stability of these compounds. Another important observation is the ratio between M: M + 2 in **IXb–d** which is about 3:1 due to the presence of the chlorine atom.

Reaction of **VIIb**,**c** with **VIII** (Ar′-$C_6H_4OCH_3$-p) furnished in each case one product wherein its elemental and spectral data were consistent with the monohydrate of 5-amino-3-[m-tolyl **Xa** and p-tolyl **Xb**]-7-(p-methoxyphenyl)-2-oxo-1-phenyl-1,2,3,4-tetrahydrothiopyrano-[2,3-d]imidazole-6-carbonitrile (Scheme 3). Mass spectra of **Xb** showed a



VII	Ar
a	C_6H_5[16]
b	$C_6H_4CH_3$-m
c	$C_6H_4CH_3$-p
d	$C_6H_4OCH_3$-p
e	C_6H_4Cl-p
f	$C_{10}H_7$-α

VIII	Ar`
a	C_6H_5F-p
b	C_6H_4Cl-p
c	$C_6H_4CH_3$-p

IX	Ar	Ar`
a	$C_6H_5CH_3$-m	C_6H_4F-p
b	$C_6H_4CH_3$-m	C_6H_4Cl-p
c	$C_6H_4CH_3$-p	C_6H_4Cl-p
d	C_6H_4Cl-p	$C_6H_4OCH_3$-p

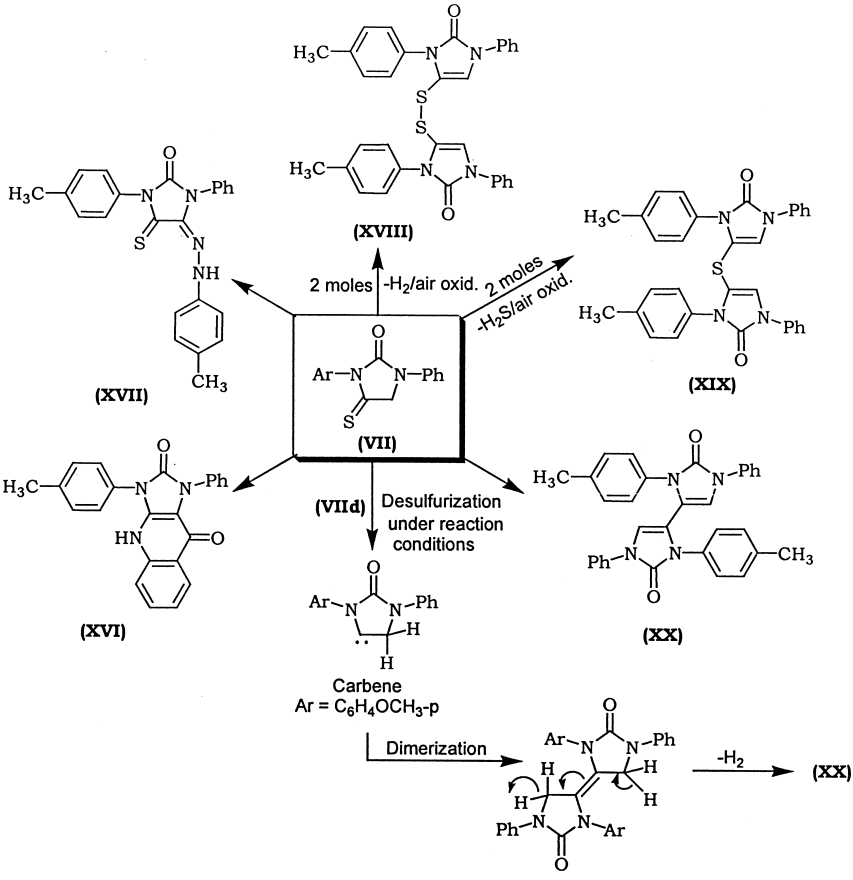
X	Ar
a	$C_6H_5CH_3$-m
b	$C_6H_4CH_3$-p

SCHEME 3

peak at m/z 484 corresponding to ($M + H_2O$. 65%) that then lost water to give a molecular ion peak at m/z 466 (43%) and a base peak at m/z 464 (100%, M-2). On using the arylidenes of cyanothioacetamide **IIa–c** instead of the arylidene derivatives of malononitrile **VIII** to react with **VII**, H_2S was liberated during the reaction period and the same products were obtained (if they have the same Ar & Ar′ groups) (m.p., mixed m.p and TLC) which were in complete agreement with our previous finding.[17]

Reaction of **VIIe** with triethyl orthoformate gave the 1-(p-chlorophenyl)-4-(1-ethoxymethylidene)-3-phenyl-5-thioxoperhydro-2-imidazolone **XI** (Scheme 3). Also **VIIc** was reacted with p-chlorobenzaldehyde to yield the 4-(p-chlorobenzylidene)-1-(p-tolyl)-3-phenyl-5-thioxoperhydro-2-imidazol one **XII**, (Scheme 3). Reaction of **VIIc** with chloroacetic acid gave imidazole derivative **XIII**, (Scheme 3) which could be obtained by alkylation followed by decarboxylation. Repetition of

this reaction using **VIId** furnished a product for which its elemental and spectral data were compatible with structure **XIV** (Scheme 3) viz., 2-[5-carboxy-methyl-3-(p-methoxyphenyl)-2-oxo-1-phenyl-2,3-dihydro-1H-4-imida-zolyldisulphanyl]-1-(p-methoxypheny1)-2-oxo-3-phenyl-2,3-dihydro- lH-4-imidazolylacetic acid. The formation of **XIV** can be attributed to air oxidation of the thiohydantion to give diimidazolyl disulphide which then reacted with chloroacetic acid to give **XIV**. On using a chloroacetic acid derivative such as its p-methoxyanilide to react with thiohydantoin **VIId** we produced the 3-(p-methoxyphenyl)-6-(p-methoxyphenyl-amino)-1-phenyl-2,3-dihydro-lH-thieno[2,3-d]imidazol-2-one **XV**, (Scheme 3). Thiohydantoin **VIIc** was reacted with anthranilic acid through elimination of H_2S and H_2O to produce **XVI** (Scheme 4) as 1-phenyl-3-(p-tolyl)-l,4-dihydro-



SCHEME 4

3H-imidazo[4,5-b]quinoline-2,9-dione, and it was also coupled with p-toluenediazonium chloride to give the 5-(p-tolylazo)-4-thiohydantoin **XVII**, (Scheme 4). Some by-products could be isolated from the reactions of thiohydantoin which can be attributed to facile air oxidation of thiohydantoin under the reaction conditions. These by-products are the disulphides **XVIII**, the monosulphide **XIX** and the diimidazolone **XX** derivatives (Scheme 4). The mechanism of formation of **XX** can be rationalized as described in Scheme 4 and these are in complete agreement with the previous findings obtained by Katcham et al.[4]

EXPERIMENTAL

Melting points were taken on a Stuart apparatus and are uncorrected. IR spectra were determined with a Jasco FT/IR 5300 spectrophotometer using the KBr technique. ^{1}HNMR spectra were measured using a Jeol FX-100 spectrometer 60 MHz and a Varian Gemini 200 instrument 200 MHz (Cairo University) and 250 & 300 MHz with TMS as an internal reference. Mass spectra were obtained by use of a Schimadzu-GC MS-QP 1000 EX instrument using the direct inlet system (Cairo University). Microanalyses were performed by the microanalytical unit at Cairo University. All compounds gave satisfactory elemental analyses.

N-(l,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-*1H*-pyrazol-4-yl)-cyano-thioformamide (I)

This compound was prepared by the same procedure reported in ref. 23. The obtained product was recrystallized from ethanol to give **I** (Table IV). The ^{1}HNMR spectrum of **I** ($CDCl_3$) exhibited signals at: $\delta = 2.20$ (3H, s, CH_3-C), 3.35 (3H, s, CH_3-N), 7.45 (6H, m, Ar—H + NH which disappeared following the addition of D_2O). ^{13}CNMR spectroscopy exhibited the following signals: 13.4 (Me-C); 34.8 (Me-N), 106.9 (—C≡N), 113.5 (C-4), 126.1 and 126.3 (2C-8), 128.7 (C-9), 129.6 and 129.7 (2C-7), 133.1 (C-5), 148.7 (C=S), 160.4 (C-6) and 164.8 (C=O). Mass spectrum of **I** ($C_{13}H_{12}N_4OS$, 272) showed a molecular ion peak at m/z 272 (2.07%) with a base peak at m/z 56 (100%) other significant peaks were observed at m/z 245 (95.09%), 203 (3%), 187 (1.7%), 171 (6.0%) and 119 (2.6%).

General Procedure for the Preparation of Compounds (III–VI)

A mixture of the requisite cyanothioformamide (0.01 mol), arylidene of cyanothioacetamide (in case of **III–V**) or o-aminophenol (in case of

VI) (0.001 mol) and 0.1 ml piperidine in absolute ethanol (30 ml) was refluxed for 4 hrs. The reaction mixture was then cooled, poured into crushed ice (50 gm), neutralized with dil. HCl (5 molar) and the obtained product was recrystallized from ethanol to give (**III**, **IV**, **Va**,**b** & **VI**) (Table IV).

l-(l,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-4-pyrazolyl)-4-imi-no-2-(p-fluorophenyl)-5-thioxo-3-thioamido-3-pyrrolidinecarbonitrile (III)

^{1}H NMR; $\delta = 2.0$ (3H, s, CH_3-C), 3.35 (3H, s, CH_3-N), 5.0 (1H, s, CH), 7.05–7.70 (10H, m, Ar-H + NH, disappeared following the addition of D_2O) and 8.30 ppm (2H, hump, NH_2, disappeared following the addition of D_2O). ^{13}CNMR; at $\delta = 10.3$ (Me-C); 34.8 (Me-N); 83.6 (C-13); 103.2 (C≡N); 106.4 (C-14); 114.9 (C-4); 115.5, 115.9 (2C-16); 117.9 (C-15); 119.4 (C-9); 123.6, 123.7 (2C-17); 125.3, 125.4 (2C-8); 128.3 (C-5); 130.5, 130.7 (2C-7); 134 (C-18); 149 (CS-NH_2); 152.7 (C=S; pyrrole); 158.1 (C=NH) and 162.9 (C=O). The mass spectrum of **III** ($C_{23}H_{19}N_6S_2OF$) showed a peak at m/z 417 (3.8%) corresponding to [M-(H.CS.NH_2)] with a base at m/z 56 (100%). Other significant beaks were apparent at m/z 272 (2.4%), 245 (1.7%), 213 (1.1%). 187 (1.0%) and 145 (2.5%).

4-Imino-l,2-di-(p-anisyl)-5-thioxo-4,5-dihydro-1*H*-2-pyrroline-3-carbonitrile (IV)

^{1}HNMR; at $\delta = 3.69$ (3H, s, CH_3-O—C_6H_4-C—p), 3.77 (3H, s, CH_3-O—C_6H_4-N-p), 4.11(1H, a broad signal which disappeared following the addition of D_2O, NH), 6.79–7.00 ppm (8H, 2 A-B q, 2 p-substituted). Mass spectrum of **IV** ($C_{19}H_{15}N_3O_2S$) exhibited a molecular ion peak at m/z (349, 8.2%) with a base peak (350, M + 1, 100%). Other significant peaks appeared at 351 (M + 2, 81%) and 352 (M + 3, 34.4%).

Vb

^{1}HNMR in (DMSO-d_6 + D_2O); at $\delta = 3.74$ & 3.75 (6H, 2s, 2-OCH_3) and 6.6–7.3 ppm (12H, m, Ar-H). Mass spectrum of **Vb** ($C_{26}H_{22}N_3O_4SCl$) showed a molecular ion peak (base peak) at m/z 508 (100%). **Va**; Mass spectrum ($C_{25}H_{19}N_3O_2SF_2$) revealed a molecular ion peak at m/z 463 (72.6%) with a base peak at m/z 292 (100%) and other significant peaks were appeared at m/z 322 (58%), 307 (34%), 306 (20%), 297 (10.5%), 250 (9%) and 211 (5.1%).

3-(l,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-*1H*-4-pyrazolylamino)-benzo[l,4]oxazin-2-one (Vl)

Mass spectrum ($C_{19}H_{16}N_4O_3$) exhibited a molecular ion peak at m/z 348 (21.5%), a base peak at m/z 56 (100%), 203 (11.9%), 149 (19.7%), 146 (9.3%), 119 (17.3%), 103 (13.5%) and 77 (62.8%). ^{1}HNMR spectra of **VI** revealed the following signals at $\delta = 2.1$ (3H, s, CH_3-C), 3.4 (3H, s, CH_3-N), 4.1 (1H, a broad signal which disappeared following the addition of D_2O, NH) and 6.2–7.8 ppm (9H, m, Ar—H).

Synthesis of Thiohydantoin Derivatives (Vlla–f)

To a solution of 3-aryl-l-phenyl-2-oxo-5-iminoimidazolidine-4-thione (0.001 mol) in ethanol or benzene (30 ml), triethylamine (3 drops) was added. A stream of H_2S was bubbled into the solution with stirring. The obtained products were recrystallized from the proper solvent to give **VIIa–f**, (Table IV). The ^{1}HNMR spectrum of compound **VIIc** exhibited the following signals at $\delta = 2.4$ (3H, s, CH_3-Ar), 4.9 (2H, s, $CSCH_2N$), 7.0–7.6 ppm (9H, m, Ar—H). Mass spectrum of **Vlld** ($C_{16}H_{14}N_2O_2S$) showed a molecular ion peak at m/z 298 (100%), 149 (80.6%; $H_3COC_6H_4NCO$-p); 133 (3% H_3CO-C_6H_4NC-p) and 103 (5.5% Ph NC).Mass spectrum of **VIIe** ($C_{15}H_{11}N_2SOCl$) exhibited a molecular ion peak at m/z 302 (18.8%), a base peak 139 (100%), 303 (18.8%), 286 (41.7%), 111 (25%) and 77 (36.8%).

Synthesis of Thiopyrano[2,3-d]imidazole Derivatives IXa–d & Xa,b: Method (A)

A mixture of substituted thiohydantoin (**VII**; 0.001 mol), substituted arylidene derivatives of malononitrile (0.001 mol) and piperidine (0.1 ml) in absolute ethanol (30 ml) was refluxed for 4 h. The reaction mixture was then cooled, poured in to crushed ice (50 gm), neutralized with dil. HC1 (5 molar) and the obtained product was recrystallized from the proper solvent to give **IXa–d** and **Xa**,**b** (Table IV).

Method (B)

A mixture of substituted thiohydantoin (**Vll**; 0.001 mol), arylidene of cyanothioacetamide (0.001 mol) and piperidine (0.1 ml) in ethanol (30 ml) was refluxed for 4 h. The reaction mixture was worked as above to give **IXa–d** and **Xa**,**b**. ^{1}HNMR spectrum of **IXb** exhibited the following signals at $\delta = 2.15$ (3H, s, CH_3), 3,52 (2H, hump, NH_2, disappeared following the addition of D_2O), 4.37 (1H, s, CH),

6.65–7.75 ppm (8H, m, Ar—H). Mass spectrum of **IXb** ($C_{26}H_{19}N_4OSCl$) exhibited a molecular ion peak at m/z 470 (44%) with a base peak at 469 (100%, M − 1), 471 (39.5% M + 1), 472 (12.4% M + 2), 187 [33%, p—Cl—C_6H_4-CH=C$(CN)_2$-1], 119 (4.2%, C_6H_5NCO), 117 (2.6%, m—CH_3-C_6H_4NC) and 111 (2.3%; p—ClC_6H_4—). Mass spectrum of **IXa** ($C_{26}H_{19}N_4OSF$) showed a molecular ion peak at m/z 454 (33.7%) with a base peak at 453 (M − l; 100%). Other significant peaks were appeared at 421 (3.8%), 376 (4.3%). 333 (6.2%), 300 (4.9%), 119 (5.2%), 117 (27%), 105 (2.7%) and 95 (1.4%). Mass spectrum of **IXc** ($C_{26}H_{19}N_40SCl$) showed a molecular ion peak at 470 (40.4%) with a base peak 469 (M − 1; 100%). Other significant peaks 472 (14.8%, M + 2), 282 (5.3%), 250 (3.3%), 188 [2.3%, p—Cl-C_6H_4-CH=C(CN)$CSNH_2$], 149 (4.2%, p—$CH_3C_6H_4NCS$), 119 (14.0% C_6H_5NCO), 113 (2.0%, Cl—C_6H_5) and 91 (43.3%. p—$CH_3C_6H_4$). Mass spectrum of **IXd** ($C_{26}H_{19}N_40_2SCl$) assigned a molecular ion peak at 486(43%) with a base peak at 484 (100%, M − 2), 487 (36.8%, M + 1),488 (10%, M + 2), 302 (30%), 184 [5.3%, p—CH_3-O-C_6H_4CH=C:(CN)$CSNH_2$], 150 [1.7% p—CH_3-O—C_6H_4-CH=C:$(CN)_2$], 169 (2.1%, p-Cl— C_6H_4NCS) and 119 (1.8%, PhNCO). Mass spectrum of **Xb** ($C_{27}H_{24}N_4O_3S$) exhibited peaks at m/z 484 (M + H_2O, 65%), a molecular ion peak at 466 (43%) base peak at 464 (100%, M − 2), 465 (M − l, 84.8%), 463(M − 3, 57.6%), 184 [9.1%, p—CH_3-OC_6H_4-CH:C $(CN)_2$], 119 (8.4%, C_6H_5NCO) and 117 (6.7%, p—CH_3-C_6H_4NC) (Scheme 5).

Formation of l-(p-Chlorophenyl)-4-(1-ethoxymethylidene)-3-phenyl-5-thioxoperhydro-2-imidazolone (Xl)

A mixture of substituted thiohydantoin **VIId**; (0.001 mol; 0.3 gm) and triethylorthoformate (0.002 mol; 0.3 gm) in acetic anhydride (10 ml) was refluxed for 1 h. The obtained solid was recrystallized from petroleum ether 60/80 to give **XI** (Table IV). ^{1}HNMR spectrum of **XI** exhibited the following signals: $\delta = 1.18$ (3H, t, CH_3), 4.09 (2H, q, CH_2), 6.97–7.53 ppm (10H, m, Ar—H + CH). Mass spectrum of (**XI**; $C_{18}H_{15}N_2O_2SCl$) exhibited a molecular ion peak at m/z 358 (53.7%), a base peak at 315 (100%), 359 (33.4%, M + l) and 360 (20%, M + 2).

Synthesis of 4-[(p-Chlorophenyl)methylidene]-l-(p-tolyl)-3-phenyl-5-thioxoperhydro-2-imidazolone XII

A mixture of substituted thiohydantoin **VIId** (0.001 mol; 0.3 gm) p-chlorobenzaldehyde (0.001 mol; 0.14 gm) and fused sod. acetate (0.1 gm) in Ac_2O/AcOH mixture (10:20 ml) was refluxed for 2 h. The obtained product was recrystallized from ethanol to give **XII** (Table IV). Mass spectrum of **XII** ($C_{23}H_{17}N_2OSCl$) exhibited a peak at 405 (2.18%,

referred to M + l), a base peak at 91 (100%, p—CH_3-C_6H_4—), 285 (3.3%), 275 (2.4%) and 209 (2.6%).

Formation of Imidazole Derivative (XIII)

A mixture of substituted thiohydantoin **VIIb** (0.001 mol; 0.3 gm) chloroacetic acid (0.001 mol; 0.1 gm) and sodium ethoxide (0.001 mol; 0.07 gm) in absolute ethanol (30 ml) was refluxed for 7 h. The obtained solid was recrystallized from ethanol to give **XIII** (Table IV). ^{1}HNMR spectrum exhibited the following signals at $\delta = 2.21$ (3H, s, CH_3-Ar), 2.5 (3H, s, S—CH_3), 6.6 (1H, s, CH), and 6.8–7.58 ppm (9H, m, Ar—H).

Synthesis of (XIV)

A mixture of thiohydantoin **VIId** (0.001 mol; 0.3 gm), chloroacetic acid (0.001 mol; 0.1 gm) and sodium ethoxide (0.001 mol; 0.07 gm) in absolute ethanol (30 ml) was reacted as above to give **XIV** (Table IV). Mass spectrum of **XIV** ($C_{36}H_{30}N_8S_2$) exhibited a molecular ion peak-2H (M-H_2, 708, 1.3%) also a molecular ion peak-water (M—H_2O) was observed at m/z 692 (3.6%). Other significant peaks were appeared at m/z 648 (2%), 620 (1%), 588 (7.7%), 574 (7.8%), 542 (9.6%) and 528 (100%, base peak). (Scheme 6).

Formation of 3-(p-Methoxyphenyl)-6-(p-methoxyphenyl Amino)-l-phenyl-2,3-dihydro-1H-thieno[2,3-d]imidazol-2-one (XV)

A mixture of substituted thiohydantoin **VII-d** (0.001 mol; 0.3 gm), p-methoxy- γ-chloroacetanilide (0.001 mol; 0.2 gm) and sodium ethoxide (0.001 mol; 0.07 gm) in absolute ethanol (30 ml) was refluxed for 6h. The obtained solid was recrystallized from ethanol to give **XV** (Table IV). ^{1}HNMR spectra of **XV** exhibited the following signals at $\delta = 3.7$ (6H, s, $2CH_3OC_6H_5$), and 6.4–7.3 ppm (14H, m, Ar—H). The NH proton was appeared underneath the Ar—H. Mass spectrum of **XV** exhibited a molecular ion peak at 443 (7%) a base peak at (77, 100%), 445 (27%), 187 (10%), 179 (66%), 165 (36%), 149 (20%), 133 (4%) and 119(20%).

Synthesis of l-Phenyl-3-(p-tolyl)-l,4-dihydro-3-H-imidazo[4,5-b]-quinoline-2,9-dione (XVI)

A mixture of the thiohydantoin **VIIc** (0.001 mol; 0.28 gm) anthranilic acid (0.001 mol; 0.14 gm) and sodium ethoxide (0.001 mol; 0.07 gm) in absolute ethanol (20 ml) was refluxed for 12 h. The reaction mixture was then cooled poured into crushed ice (50 gm), neutralized with dil. HCl

(5 molar) and the obtained product was recrystallized from ethanol to give **XVI** (Table IV). Mass spectrum of **XVI** ($C_{23}H_{17}N_3O_2$, 367) exhibited peaks at 368 (M + 1, 2.64%), 266 (100%), 263 (3.9%), 133 (24.6%), 119 (73.5%), 117 (6%) and 105 (66.3%).

Synthesis of 5-(p-Tolylazo)-4-thiohydantion Derivative (XVII)

p-Toluidine (0.01 mol; 1.1 gm) was dissolved in a mixture of HCl (4 ml; 10 molar) and H_2O (5 ml) then cooled to 0°C. To this a cold aqueous solution of sodium nitrite (0.69 g) was then added. The diazonium salt so obtained was added dropwise to a cold mixture of sodium acetate (1 g)

TABLE I Antibacterial Activity of Synthesized Compounds

Compd. no.	*Staphylococcus aureus (NCTC-7447)*	*Bacillus cereus (ATCC-14579)*	*Serratia Marcescens (IMRU-70)*	*Proteus mirabilis (NTCC-289)*
I	++	+++	++	+++
III	++	+++	++	++
IV	+++	++	++	++
Va	++	+++	++	++
Vb	++	++	++	+++
VI	+++	++	+++	+++
VIIb	++	++	+	+++
VIIc	++	++	++	+++
IXa	++	+++	+++	+++
IXb	+++	+++	++	++
IXc	++	+++	++	+
IXd	++	+	+++	+++
Xa	++	+++	++	++
Xb	++	++	+	+++
XI	+++	+++	++	++
XII	++	+++	++	+++
XIV	+++	++	+++	+++
XV	+++	++	++	+++
XVI	+++	++	++	+++
XVII	+++	++	++	++
XVIII	++	+++	+++	++
XIX	+	++	++	+++
Ampicillin (25 μg)	++++	++++	++++	++++

+: Less active (0.2–0.5 cm).
++: Moderately active (0.6–1.4 cm).
+++: Highly active (1.5–3.0 cm).
++++: Very highly active (over 3.0 cm).
Standard for Gram positive and gram negative bacteria: Ampicillin 25 μg.

and substituted thiohydantoin **VIIb** (0.01 mol; 2.8 gm) in ethanol. The resulting solid was washed with water and recrystallized from ethanol to give **XVII** (Table IV). Mass spectrum of **XVII** ($C_{23}H_{20}N_4OS$, 400) showed a molecular ion peak at 400 (35%) with a base peak at 91 (100%) and other significant at m/z 401 (M + 1, 43%), 402 (M + 2, 15%), 385 (M-CH_3,17%),149 (20%), 133 (23%), 119 (33%), 105 (22%) and 91 (79%).

Antimicrobial Activity

1-Antibacterial Activity

The newly synthesized compounds were screened for their antibacterial activity against two species of Gram positive bacteria, namely

TABLE II Antifungal Activity of Synthesized Compounds

Compd. no.	*Aspergillus ochraceus Wilhelm (AUCC-230)*	*Penicillium chrysogenum Thom (AUCC-530)*
I	++	+
III	++	++
IV	++	+
Va	+	+
Vb	+++	++
VI	+	+++
VIIb	+	+
VIIc	+++	+++
IXa	++	+++
IXb	+	+
IXc	+++	+
IXd	++	++
Xa	+	+
Xb	++	++
XI	+	+++
XII	++	+++
XIV	++	+
XV	+	+
XVI	++	+
XVII	+++	++
XVIII	++	++
XIX	+	++
Mycostatin (30 μg)	++++	++++

+: Less active (0.2–0.5 cm).
++: Moderately active (0.6–1.4 cm).
+++: Highly active (1.5–3.0 cm).
++++: Very highly active (over 3.0 cm).
Standard: for fungi: Mycostatin.

Staphylococcus aureus (NCTC-7447), *Bacillus cereus* (ATCC-14579) and two species of Gram negative bacteria *Serratia marcescens* (IMRU-70) and *Proteus mirabilis* (NTCC-289) using Ampicillin (25 μg) as the reference compound. Table I Shows the effect of compounds **I**, **III**, **IV**, **Va**, **Vb**, **VI**, **VIIb,c**, **IXa–d**, **Xa,b**, **XI**, **XII**, **XIV–XVIII**, and **XIX** on the microorganisms tested. It was found that all compounds were shown to exhibit an activity pattern which suggests that they may have a broad spectrum antibacterial effect with a sustained high degree of inhibition, giving almost + + + ratings against all of the test organisms.

2-Antifungal Activity

The newly synthesized compounds were screened for their antifungal activity against two species of fungi, *Aspergillius ochraceus Wilhelm*

TABLE III IR Spectra of Synthesized Compounds

Compd. no.	ν_{max} (cm^{-1})
I	3150 (NH), 2950 (CH-aliph.), 2207 (C≡N), 1690 (C=O), 1490, 1120 (S=C–N).
III	3270–3109 (NH), 3030 (CH-arom.), 2922, 2860 (CH-aliph.), 2214 (C≡N), 1684 (C=O), 1630 (C=N), 1421, 1124 (S=C–N).
IV	3248 (NH), 2933, 2837 (CH-aliph.), 2216 (C≡N), 1412, 1149 (S=C–N).
Vb	3030 (CH-arom), 2922, 2854 (CH-aliph.), 2214 (C≡N), 1612 (C=N), 1530 (C=C).
VI	3250(NH), 2950 (CH-aliph.), 1710 (C=O).
VIIb	2927 (CH-aliph.), 1757 (C=O), 1490, 1150 (S=C–N).
IXa	3330, 3150 (NH_2), 3050 (CH-arom.), 2927 (CH-aliph.), 2218 (C≡N), 1743 (C=O).
IXb	3317, 3197 (NH_2), 3034 (CH-arom.), 2931 (CH-aliph.), 2213 (C≡N), 1741 (C=O).
IXc	3325, 3190 (NH_2), 3050 (CH-arom.), 2218 (C≡N), 743 (C=O).
IXd	3323, 3140 (NH_2), 3063 (CH-arom.), 2931 (CH-aliph), 2217 (C≡N), 1745 (C=O).
Xb	3400, 3200 (NH_2), 3067, 3026 (CH-arom.), 2930, 2836 (CH-aliph), 2218 (C≡N), 1745 (C=O).
XI	3060 (CH-arom.), 2923, 2852 (CH-aliph), 1712 (C=O), 1595 (C=C), 1490, 1130 (S=C–N).
XII	3050 (CH-arom.), 1712 (C=O), 1560 (C=C), 1492, 1150 (S=C–N).
XIII	2990 (CH-aliph.), 1709 (C=O), 1595 (C=C).
XIV	3200–2500 (OH), 1708, 1670 (C=O).
XV	3300 (NH), 3050 (CH-arom.), 2930 (CH-aliph.), 1680 (C=O).
XVI	3200 (NH), 3030 (CH-arom.), 2950 (CH-aliph.), 1710 (C=O).
XVII	3400 (NH), 3033 (CH-arom.), 2918, 2827 (CH-aliph.), 1717 (C=O), 1615 (C=N), 1498, 1124 (S=C–N).

TABLE IV Physical Data of the Synthesized Compounds

Compd. no.	Yield (%)	M.p. [°C]	Cryst. solvent	Mol. formula (Mol. Wt)	Elemental analyses calcd./found [%]			
					c	*h*	*n*	*s*
I	85	175	Ethanol	$C_{13}H_{12}N_4OS$	57.34	4.44	20.57	11.77
				272.33	57.40	4.40	20.60	11.80
III	65	218	Ethanol	$C_{23}H_{19}N_6OS_2$	57.73	4.00	17.56	13.40
				478.57	57.90	4.00	17.30	13.20
IV	70	218	Benzene	$C_{19}H_{15}N_3O_2S$	65..31	4.33	12.03	9.18
				349.42	65.20	4.30	12.00	9.00
Va	75	220	Ethanol	$C_{25}H_{19}N_3O_2SF_2$	64.78	4.13	9.07	6.92
				462.51	64.50	4.10	9.10	7.00
Vb	80	300	Benzene	$C_{26}H_{22}N_3O_4SCl$	61.47	4.37	8.27	6.31
				508	61.70	4.20	8.10	6.20
VI	75	180	Ethanol	$C_{19}H_{16}N_4O_3$	65.51	4.63	16.08	—
				348.37	65.70	4.60	16.10	—
VIIb	70	153	Ethanol	$C_{16}H_{14}N_2OS$	68.06	4.99	9.92	11.36
				282.37	68.10	5.00	9.90	11.40
VIIc	85	160	Ethanol	$C_{16}H_{14}N_2OS$	68.06	4.99	9.92	11.36
				282.37	68.10	5.00	9.90	11.50
VIId	65	136	Ethanol	$C_{16}H_{14}N_2O_2S$	64.41	4.73	9.39	10.75
				298.37	64.40	4.70	9.40	10.95
VIIe	70	170	Ethanol	$C_{15}H_{11}N_2OSCl$	59.50	3.66	9.25	10.59
				302.78	59.60	3.60	9.20	11.70
VIIf	75	180	Ethanol	$C_{19}H_{14}N_2SO$	71.68	4.43	8.79	10.07
				318.39	71.70	4.40	8.80	10.00
IXa	65	210	Ethanol	$C_{26}H_{19}N_4OSF$	68.71	4.21	12.33	7.05
				454.53	68.90	4.20	12.30	7.00
IXb	70	313	Benzene	$C_{26}H_{19}N_4OSCl$	66.31	4.07	11.90	6.81
				470.98	66.50	4.00	11.90	6.70
IXc	80	200	Benzene	$C_{26}H_{19}N_4OSCl$	66.31	4.07	11.90	6.81
				470.98	66.60	4.10	12.00	6.90
IXd	80	232	Ethanol	$C_{26}H_{19}N_4O_2SCl$	64.13	3.93	11.51	6.58
				486.98	64.20	3.90	11.50	6.40
Xa	75	153	Ethanol	$C_{27}H_{24}N_4O_3S$	66.92	4.99	11.56	6.62
				484.58	67.10	4.70	11.50	6.50
Xb	80	170	Ethanol	$C_{27}H_{24}N_4O_3S$	66.92	4.99	11.56	6.62
				484.58	67.00	4.90	11.70	6.40
XI	70	78	Pet.ether 60/80	$C_{18}H_{15}N_2O_2SCl$	60.25	4.21	7.81	8.94
				358.85	60.30	4.20	7.80	9.00
XII	85	160	Ethanol	$C_{23}H_{17}N_2OSCl$	68.22	4.23	6.92	7.92
				404.92	68.10	4.20	6.90	8.00
XIII	60	200	Ethanol	$C_{17}H_{16}N_2OS$	68.89	5.44	9.45	10.82
				296.39	69.00	5.30	9.50	10.70
XIV	85	206	Ethanol	$C_{36}H_{30}N_4O_8S_2$	60.83	4.25	8.00	9.02
				710.79	60.90	4.20	7.89	9.00
XV	85	200	Ethanol	$C_{25}H_{21}N_3O_3S$	67.70	4.77	9.47	7.23
				443.53	67.40	4.70	9.40	7.10

(Continued on next page)

TABLE IV Physical Data of the Synthesized Compounds *(continued)*

Compd. no.	Yield %	M.p. [°C]	Cryst. solvent	Mol. formula (Mol. Wt)	Elemental analyses Calcd./found [%]			
					c	*h*	*n*	*s*
XVI	75	162	Ethanol	$C_{23}H_{17}N_3O_2$	75.19	4.66	11.44	—
				367.41	75.00	4.70	11.50	—
XVII	85	180	Ethanol	$C_{23}H_{20}N_4O$	68.98	5.03	13.99	8.01
				400.5	68.80	5.00	13.90	8.00
XVIII	65	200	Ethanol	$C_{32}H_{26}N_4O_2S_2$	68.30	4.66	9.96	11.40
				562.72	68.40	4.60	9.90	11.30
XIX	60	160	Ethanol	$C_{32}H_{26}N_4O_2S$	72.43	4.94	10.56	6.04
				530.66	72.60	4.90	10.30	6.00
XX	75	200	Ethanol	$C_{32}H_{26}N_4O_4$	72.44	4.94	10.56	—
				530.59	72.50	5.00	10.70	—

(AUCC-230) and *Penicillium chrysogemim Thorn* (AUCC-530) using the Mycostatin (30 ug) as the reference compound. Table II Showed the effect of compounds **I**, **III**, **IV**, **Va**, **Vb**, **VI**, **VIIb**,**c**, **IXa–d**, **Xa**,**b**, **XI**, **XII**, **XIV–XVIII**, and **XIX** on the microorganisms tested. It was found that all compounds were shown to exhibit an activity pattern which suggested that they may have broad spectrum antifungal action with a sustained high degree of inhibition, giving almost ++ ratings against all of the test organisms.

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