
REACTIVITY OF 4-(4-METHOXYPHENYL)-1(2H)-PHTHALAZINONE TOWARDS SOME NUCLEOPHILES

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Abstract

The reactivity of 4-(4-methoxy)phenylphthalazinone (1) towards halogen and sulphur nucleophiles has been investigated. The influence of amino acids, hydrazines, acid hydrazides and sodium ethoxide on the products is discussed. The structures of the products have been assigned by elemental analyses and spectral data.

Key Words Convenient Synthesis of Functionally Substituted Phthalazines, Pyrazolophthalazine, Phthalazinopyridone and Triazolophthalazine Derivatives.

Introduction and Discussion

The promising biological activity of some phthalazines have stimulated recent interest in the syntheses of these ring system⁽¹⁾.

Thus, interaction of 4-[(4'-methoxy) phenyl] phthalazin-2-(1H) one (1)⁽²⁾ with phosphorous oxychloride/phosphorous pentachloride mixture afforded the corresponding 4-substituted-phenyl-1-chlorophthalazine derivative (2)⁽³⁾. i) The mass spectrum of (2) showed a molecular ion peak at m/z 270.5 (53%) which was in accordance with its structure, ii) IR spectrum showed bands at 1665 cm⁻¹ of γ C=N and at 1075 cm⁻¹ of γ C-Cl.

Treatment of (2) with glycine in boiling ethanol furnished a single product analyzed for the molecular formula C₁₇H₁₃O₂N₃. This product was 5-(4-methoxy phenyl)-phthalazino[1,2-b]imidazoline-3-one (3) i) IR spectrum of (3) devoid γ C-Cl and showed bands at 1670, 1600 cm⁻¹ due to γ C=N, C=C and at 1720 cm⁻¹ (γ N-C=O imidazoliny), ii) The mass spectrum of (3) showed a molecular ion peak at (m/z 353).

Similarly, the reaction of 2 with anthranilic acid in refluxing ethanol afforded the corresponding phthalazino [1,2-b] quinazolinone (4)⁽⁴⁾ in reasonable yield. The IR spectrum of (4) devoid γ C-Cl and showed absorption bands at 1675 cm⁻¹ of γ C=N

The applicability of compound (2) for the synthesis of heterocycles of expected bioresponse was investigated. Thus, compound (2) reacted with hydrazine hydrate and with 2- hydroxybenzoyl hydrazide afforded the corresponding hydrazine derivative (5) and the triazolo[4,3-b]phthalazine derivative (6)⁽⁵⁾, the structure of (5) was established by i) IR spectrum which showed strong absorption bands at 1675, 3250cm⁻¹ of (γ C=N, NH) and devoid of γ C-Cl also the structure of (6) was inferred

from i) $^1\text{H-NMR}$ δ 3.8 (s,3H, OCH_3), 9.1-10.1 (br,s,1H,OH) and 7.25-8.5 (m,12.Ar-H), ii) IR spectrum devoid $\gamma\text{C-Cl}$ and showed bands at 1625 cm^{-1} of $\gamma\text{C=N}$.

The reaction of 2 with sodium ethoxide in boiling ethanol provided the corresponding N- substituted -1-ethoxy phthalazine (7), IR spectrum showed absorption bands at 1675 cm^{-1} of $\gamma\text{C=N}$ and devoid $\gamma\text{C-Cl}$.

The reaction of 1 with monochloro acetic acid in the presence of sodium hydroxide solution, yielded 4-substituted phthalazine-2-glycolic acid (8)⁽⁶⁾, the structure of (8) was established by IR spectrum which showed strong absorption bands at 1710 cm^{-1} ($\gamma\text{C=O}$) of acid, 1630 cm^{-1} ($\gamma\text{C=N}$) and $3443\text{-}3280\text{ cm}^{-1}$ (γOH). Treatment of (8) with salicylaldehyde afforded the corresponding 4-[-substituted (-phthala-zine-2-yl)-3-hydroxy styrene] (9)⁽⁷⁾, its $^1\text{H-MNR}$ showed bands at δ 3.8 (s,3H, OCH_3), 6.8- 8.2 (m,12-Ar-H and olefinic H) and 10.5 (s,1H, OH). and its IR spectrum showed strong absorption bands at 1670 cm^{-1} ($\gamma\text{C=N}$) and at 1610 cm^{-1} of ($\gamma\text{C=C}$).

4-substituted-phthalazine-1-thione (10) was obtained by the action of phosphorus pentasulphide on (1), the IR spectrum showed absorption bands at 3320, 2850, 2555, 1615 and 1255 cm^{-1} corresponding to γ (NH,C-H, SH, C=N and $\gamma\text{C=S}$ respectively. The ethanolic solution of (10) with primary and / or secondary amines such as benzylamine and diphenylamine gave the corresponding 4- substituted-hydrazone derivatives (11a, b). IR spectrum of (11 a,b) showed strong absorption bands at 3300 and 1620 cm^{-1} attributable to γ (NH and C=N) and devoid ($\gamma\text{C=S}$). Hydrazinolysis of (10) with hydrazine hydrate afforded the corresponding 4-substituted-1-hydrazino-phthalazine 12⁽⁸⁾. i) $^1\text{H-NMR}$. δ 2.8(s,3H, OCH_3), at 5.3 (m.broad.3H,NH, NH_2) and 7.0-8.1 (m,8H,Ar-H) and 10.9 (br.s, 2H,NH). ii) IR spectrum showed stretching frequencies at 1930, 3300, 3200 cm^{-1} for $\gamma\text{C=N}$, γNH_2 and γNH functions respectively. The reaction of (12) with benzaldehyde in the presence of piperidine afforded the corresponding 1-(benzylideneamino-)-4-substituted phthalazine (13). IR spectrum of 13 reveals the presence of ($\gamma\text{C=N}$) at 1595 cm^{-1} and NH absorption vibration occurred at 3215 cm^{-1} .

Treatment of (10) with acrylonitrile afforded 4-(substituted)-1-(mercapto cyanoethyl) phthalazine (14)⁽⁹⁾.IR spectrum of 14 showed absorption bands at 2860, 2210 and 1600 cm^{-1} due to $\gamma\text{C-H}$, $\text{C}\equiv\text{N}$ and $\gamma\text{C=N}$ respectively .

Treatment of (10) with phenylisothiocyanate afforded the corresponding 4-(substituted)-1-(N-phenylthiocarbamoyl) mercapto phthala-zine (15). The IR spectrum showed absorption bands at 3320, 1615 and 1255 cm^{-1} corresponding to γ (NH,C=N) and ($\gamma\text{C=S}$) respectively. Similarly, Alkylation of (10) with ethyl bromoacetate in the presence of acetone and anhydrous potassium carbonate yielded 4-(substituted) -phthalazine-1-thioglycolic ester (16)⁽¹⁰⁾. The IR spectrum of 16

showed strong absorption bands at 1745 cm^{-1} ($\gamma\text{C=O}$ of ester) and 1630 cm^{-1} ($\gamma\text{C=N}$).

The reaction of (16) with anthranilic acid in boiling butanol gave the corresponding 2-(substituted)-4H-3, 1 benzoxazinone (17)⁽¹¹⁾. i) The mass spectrum of (17) showed a molecular ion peak at (m/z 427) which is in accordance with the proposed structure. ii) the IR spectrum exhibited bands at 1760 cm^{-1} (oxazinone $\gamma\text{C=O}$), 1635 ($\gamma\text{C=N}$) and 1605 ($\gamma\text{C=C}$). Hydrazinolysis of (16) with hydrazine hydrate gave the corresponding 2- substituted -1-(N-mercapto methyl hydrazide-4-substituted phthalazine (18)⁽¹²⁾. IR spectrum showed absorption bands at 3300 , 1670 and 1620 cm^{-1} to $\gamma(\text{NH}$, C=O and C=N) respectively.

The structure of these products were confirmed from their analytical data (c.f. Table 1).

Experimental Section

All melting points are uncorrected. IR spectra were recorded (KBr) on a PYE Unicam SP-1000 spectrophotometer $^1\text{H-NMR}$ spectra were recorded on a Gemini 200-MHZ spectrophotometer using TMS as an internal standard and DMSO-d₆ as a solvent.

Chemical shifts are expressed in δ ppm. Mass spectra were run on a Mat 112 instrument

Compounds 1 and 2 were prepared according to literature procedures^(2,3).

Reaction of 4-[4'(-methoxy) phenyl] Phthalazinone with a mixture of Phosphorus oxychloride phosphorus Pentachloride:Formation of 4-(substituted)-1- chloro Phthalazine 2.

A mixture of 1 (0.01mol) and phosphorus pentachloride (0.01mol) in 5 ml of phosphorus oxychloride was heated on steam-bath for 2hrs. it was then Poured into ice-water while stirring .the solid obtained was filtered off, washed well with cold water, dried and recrystallized from ethanol to give 2 as a gray crystals (Table 1).

Reaction of 2 with Amino-acids : Formation of 3 and 4

A mixture of 2 (0.01 mol) and amino acids namely glycin and/or anthranilic acid (0.01 mol)in 30 ml ethanol and little amount of water was heated under reflux for 8 hrs after cooling , it was poured into ice–water and the product that obtained was had washed and recrystallized from ethanol to give 3 as brownish red crystals and 4 as yellow crystals (Table 1).

Reaction of 2 with Hydrazine hydrate : formation of 5

Hydrazine hydrate (1 ml) was added to 2 (0.01mol) in ethanol (40 ml) and refluxed for 6.hrs. Left to cool. Then poured it in to ice dilute HCl. The solid product

was washed well and recrystallized from ethanol to give 5 as yellow crystals (Table 1).

Reaction of (2) with Acylhydrazine: Formation of 6.

A mixture of 2 (0.01mol) acylhydrazine namely p-hydroxy benzoyl hydrazine in (40ml) of butanol was heated under reflux for 18hrs. the solid separated after concentration and cooling was filtered off and recrystallized from ethanol to give 6 as white crystals (Table 1).

Reaction of (2) with Sodium ethoxide: Formation of (7)

A mixture of 2 (0.01mol) of sodium ethoxide (prepared by dissolving 1.1 g of sodium metal in 35ml of absolute ethanol), was heated under reflux for 3hrs. The reaction mixture was cooled, acidified with dilute HCl. and the solid that separated was filtered off, dried and recrystallised from ethanol to give 7 as beige crystals (Table 1).

Reaction of 1 with chloro acetic acid : formation of 8 .

A mixture of monochloro acetic acid (0.01 mol) and 1 (0.01mol) in (20 ml) of aqueous NaOH (10%) was heated under reflux for 4 hrs. after cooling it was diluted with water, extracted with ether, washed well and recrystallised from ethanol to give 8 as gray crystals (Table 1).

Condensation of 8 with salicylaldehyde : formation of 9.

To a well stirred suspension of the acid derivative 8 (0.01mol) in (25ml) of absolute ethanol containing sodium ethoxide (0.01mol) was added dropwise salicylaldehyde (0.01mol) and stirring was continued for 3 hrs. while cooling the reaction mixture was left overnight then diluted with water containing 10ml of NaOH (10%). The product separated was collected, washed and recrystallized from P.E (b.p 60-80°C) to give 9 as orange crystals (Table 1).

Thionation of 1 : formation of thiophthalazine 10

A mixture of 1 (0.01mol) and phosphorus pentasulphide (0.01 mol) in 30 ml of dry xylene was refluxed for 2 hrs. It was then filtered off while hot then left to cool. The solid product was recrystallized from ethanol to give 10 as yellow crystals (Table 1).

Reaction of 10 with Amines : Formation of 11a,b

A mixture of 10 (0.01 mol) and amines, namely benzylamine and/or diphenylamine (0.01 mol) in 30 ml of ethanol was refluxed for 6 hrs. After concentration and cooling the solid that separated was collected and recrystallized from ethanol to give 11a as beige crystals and 11b as yellow crystals (Table 1).

Reaction of 10 with Hydrazine hydrate : Formation of 12

A mixture of 10 (0.01 mol) and hydrazine hydrate (0.01 mol) in 30 ml of ethanol was heated under reflux for 8 hrs . After concentration and cooling the solid product collected and recrystallized from ethanol to give 12 as brownish red crystals

Reaction of (12) with Benzaldehyde : Formation of (13)

A solution of 12 (0.01 mol) in 30 ml ethanol was treated with benzaldehyde (0.01 mol) and one drop of piperidine, the mixture was heated under reflux for 3 hrs . The crystals separated on cooling were filtered off and recrystallized from ethanol to give 13 as yellow crystals (Table 1).

Reaction of 10 with Acrylonitrile : Formation of 14.

A mixture of 10 (0.01 mol) and acrylonitrile (0.01 mol) in 30 ml of pyridine was refluxed for 3 hrs . it was then poured into ice – dilute HCl and the product that separated was collected, washed well with water then recrystallized from ethanol to give 14 as brown crystals (Table 1).

Reaction of 10 with phenylisothiocyanate : Formation of 15

A mixture of 10 (0.01 mol) and phenylisothiocyanate (0.01 mol) in 30 ml of pyridine was heated under reflux for 6 hrs after cooling it was poured into ice – dilute HCl and the product separated was collected and washed with water and then recrystallized from ethanol to give 15 as yellow – brown crystals (Table 1).

Alkylation of (10) with Ethylbromoacetate: Formation of 16

A mixture of 10 (0.01 mol), ethylbromoacetate (0.01 mol) and anhydrous potassium carbonate (0.04 mol) in 50 ml of dry acetone was refluxed for 24 hrs. It was filtered off on hot and poured into water. The product that separated was collected, washed well and recrystallized from methanol to give 16 as white crystals (Table 1).

Reaction of 16 with Anthranilic acid : Formation of 17

A mixture of 16 (0.01 mol) and anthranilic acid (0.01 mol) in 30ml butanol was heated under reflux for 10 hrs. After concentration and cooling the solid that separated was recrystallized from ethanol to give 17 as yellow crystals (Table 1).

Action of Hydrazines on (16) :Formation of 18

A mixture of 16 (0.01 mol) and hydrazine hydrate (0.01 mol) in 30 ml ethanol was heated under reflux for 6 hrs. After cooling the solid that separated collected and recrystallized from ethanol to give 18 as yellowish white crystals (Table 1).

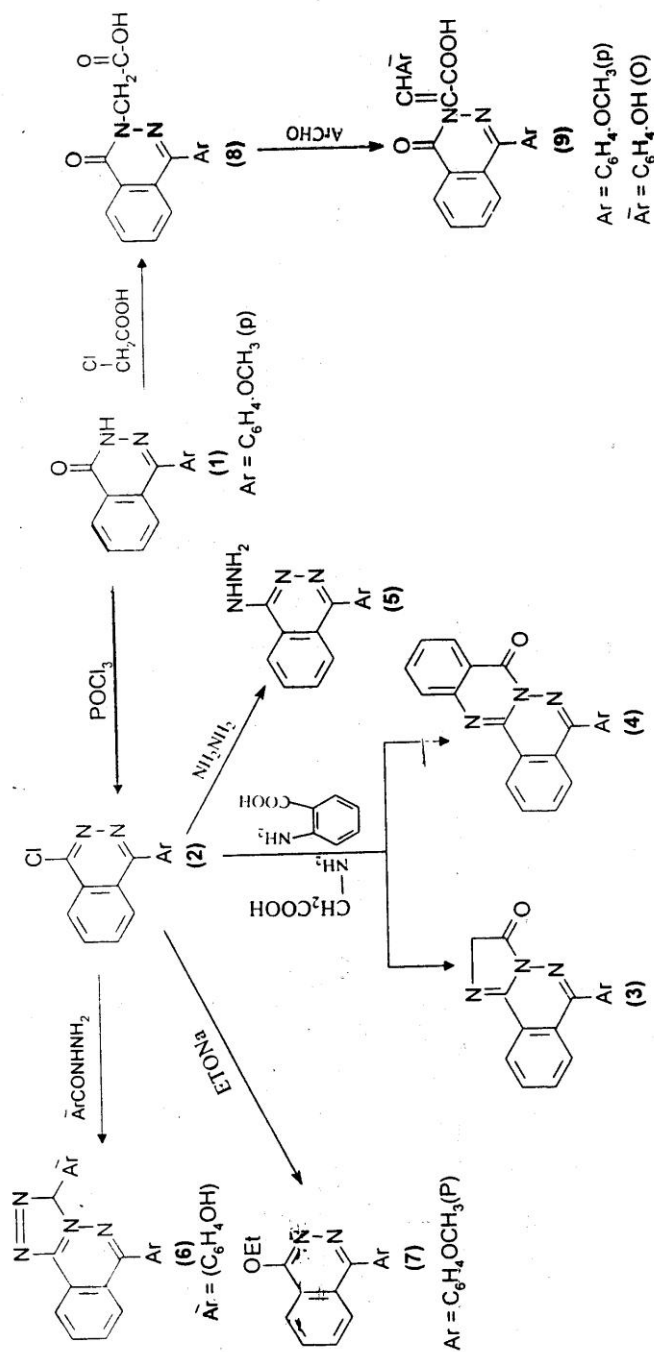
Table (1) : Physical and analysis data of the products

| Compound | M.P.(°C ^o) Solvent of crystallization | Yield % | Molecular Formula | Found (%) | | | | | Calcd (%) | | | | |
|----------|---|------------|---|-----------|-----|-------|------|------|-----------|------|-------|-------|------|
| | | | | C | H | N | S | Cl | C | H | N | S | Cl |
| 2 | 190 EtOH | 60 | C ₁₅ H ₁₁ ON ₂ Cl | 65.3 | 4.5 | 9.83 | | 12.5 | 65.4 | 4.0 | 10.5 | | 13.1 |
| 3 | 220 EtOH | 70 | C ₁₇ H ₁₃ O ₂ N ₃ | 69.0 | 4.5 | 13.8 | | | 70.1 | 4.46 | 14.4 | | |
| 4 | 195 EtOH | 60 | C ₂₂ H ₁₅ O ₂ N ₃ | 73.7 | 4.2 | 11.5 | | | 74.8 | 4.2 | 11.8 | | |
| 5 | 160 EtOH | 65 | C ₁₅ H ₁₇ ON ₄ | 65.8 | 5.8 | 19.9 | | | 66.9 | 6.3 | 20.8 | | |
| 6 | 210 EtOH | 60 | C ₁₇ H ₁₆ O ₂ N ₂ | 72.3 | 5.6 | 9.4 | | | 72.8 | 5.8 | 10.0 | | |
| 7 | 210 EtOH | 50 | C ₂₂ H ₁₆ O ₂ N ₄ | 70.3 | 4.1 | 16.9 | | | 71.7 | 4.3 | 17.3 | | |
| 8 | 190 EtOH | 75 | C ₁₇ H ₁₄ O ₄ N ₂ | 66.3 | 4.5 | 8.6 | | | 67.5 | 4.6 | 9.2 | | |
| 9 | 110 P.E (60-80) | 70 | C ₂₄ H ₁₈ O ₃ N ₂ | 69.0 | 4.4 | 6.1 | | | 69.5 | 4.4 | 6.7 | | |
| 10 | 220 EtOH | 60 | C ₁₇ H ₁₂ ON ₂ S | 66.7 | 4.1 | 10.3 | 10.9 | | 67.1 | 4.47 | 10.44 | 11.94 | |
| 11a | 160 EtOH | 70 | C ₂₂ H ₁₉ ON ₃ | 77.0 | 5.5 | 11.93 | | | 77.4 | 5.5 | 12.3 | | |
| 11b | 170 EtOH | 70 | C ₂₇ H ₂₂ ON ₃ | 79.0 | 5.4 | 10.1 | | | 80.1 | 5.4 | 10.39 | | |
| 12 | 150 EtOH | 50 | C ₁₅ H ₁₃ ON ₄ | 67.0 | 4.8 | 20.3 | | | 67.9 | 4.9 | 21.13 | | |
| 13 | 180 EtOH | 60 | C ₂₂ H ₁₈ ON ₄ | 74.3 | 4.9 | 14.93 | | | 74.57 | 5.0 | 15.8 | | |
| 14 | 160 EtOH | 65 | C ₁₈ H ₁₅ ON ₃ S | 67.0 | 4.3 | 13.0 | 8.89 | | 67.2 | 4.6 | 13.08 | 9.96 | |
| 15 | 220 EtOH | 70 | C ₂₂ H ₁₇ ON ₃ S ₂ | 65.0 | 4.1 | 10.0 | 14.9 | | 65.55 | 4.2 | 10.42 | 15.88 | |
| 16 | 120 MeOH | 40 | C ₁₉ H ₁₈ O ₃ N ₂ S | 64.1 | 5.0 | 7.4 | 8.8 | | 64.4 | 5.8 | 7.9 | 9.03 | |
| 17 | 140 EtOH | 50 | C ₁₇ H ₁₆ O ₂ N ₂ S | 64.3 | 5.0 | 8.2 | 9.6 | | 65.3 | 5.12 | 8.97 | 10.25 | |
| 18 | 180 EtOH | 50 | C ₂₄ H ₁₇ O ₃ N ₃ S | 67.1 | 3.5 | 9.5 | 7.3 | | 67.4 | 3.98 | 9.8 | 7.49 | |

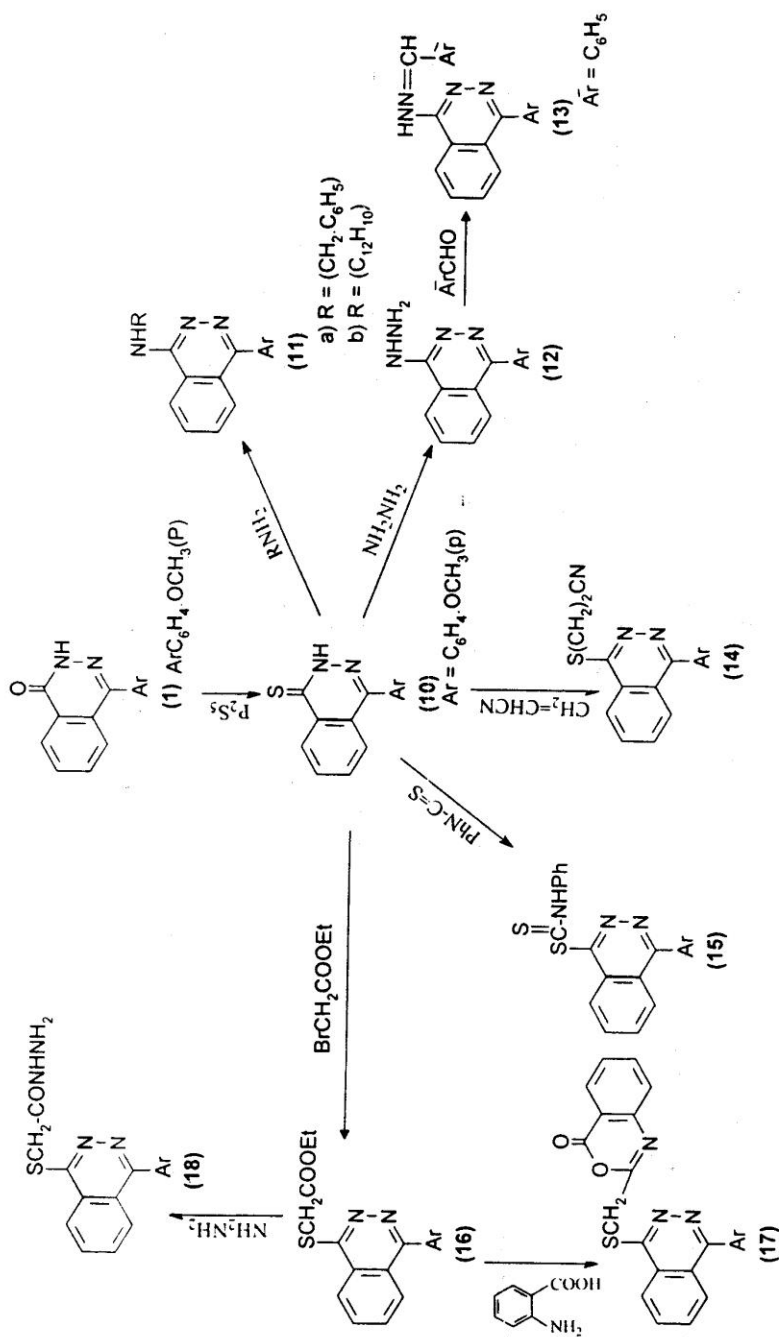
Table (2): Antimicrobial activity

| Samples | 1 | | 3 | | 4 | | 9 | | 13 | | 16 | | 17 | | 18 | | St | | |
|---------------------------------|-------|-----|---|----|-----|---|---|-----|----|---|-----|---|----|-----|----|---|-----|---|---|
| | 5 | 2.5 | 1 | 5 | 2.5 | 1 | 5 | 2.5 | 1 | 5 | 2.5 | 1 | 5 | 2.5 | 1 | 5 | 2.5 | 1 | |
| Concentration | mg/ml | | | | | | | | | | | | | | | | | | |
| <i>Aspergillus niger</i> | ++ | + | 0 | ++ | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| <i>Penicillium talicum</i> | ++ | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| <i>Syncephala trumracemosum</i> | ++ | + | 0 | ++ | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <i>Candida albicans</i> | ++ | + | 0 | ++ | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| <i>Staphylococcus aureus</i> | ++ | + | 0 | ++ | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| <i>Escherichia coli</i> | ++ | + | 0 | ++ | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Inhibition values = 0.1 - 0.5 cm beyond control = + ; inhibition values = 0.6 - 1.0 control = ++
 Inhibition values = 1.1-1.5 cm beyond control = +++ ; 0= not detected;



Scheme (1)



Scheme (2)

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