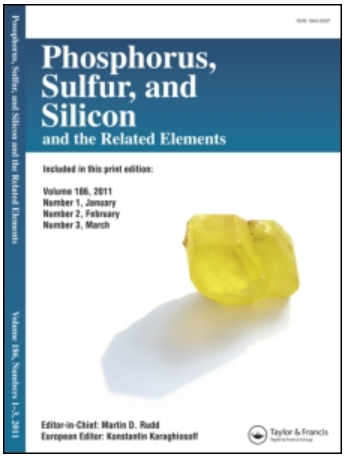


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# SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NEW HETEROCYCLIC QUINOLINE DERIVATIVES

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## *Communication*

# SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NEW HETEROCYCLIC QUINOLINE DERIVATIVES

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Alkylation of 2-mercapto-3-cyano-4-aryl-5,6,7,8-tetrahydroquinoline (**I**) gave compounds **II–IV**. Cyclization of **III** and **IV** afforded thienoquinolines **V** and **VI** respectively. On diazotization of **V** and **VI**, the corresponding triazinone derivatives **VII** and **VIII** were obtained. Also, reaction of **V** with benzoyl chloride yielded the tetracyclic compound **IX**. Structures of the new compounds were established by their elemental analyses and spectral data. Some of these compounds were screened in vitro for their antibacterial activities.

*Key words:* Mercaptoquinolines, cyanoquinolines, thienoquinolines, triazinones and pyrimidines.



In recent years, a number of reports concerning the synthesis of 2-mercapto-3-cyano-4-aryl-5,6,7,8-tetrahydroquinoline (**I**) have been appeared.[1–4] Since these compounds happen to be the starting materials for the syntheses of various heterocyclic compounds of biological interest, the synthesis of some new quinoline derivatives are presented here. Also, some representative compounds were screened in vitro for their antimicrobial activity.

The starting materials $\mathbf{I}_{a,b}$ were prepared by reaction of 2-arylidene-cyclohexanone with cyanothioacetamide in methanol containing sodium methoxide.[4]

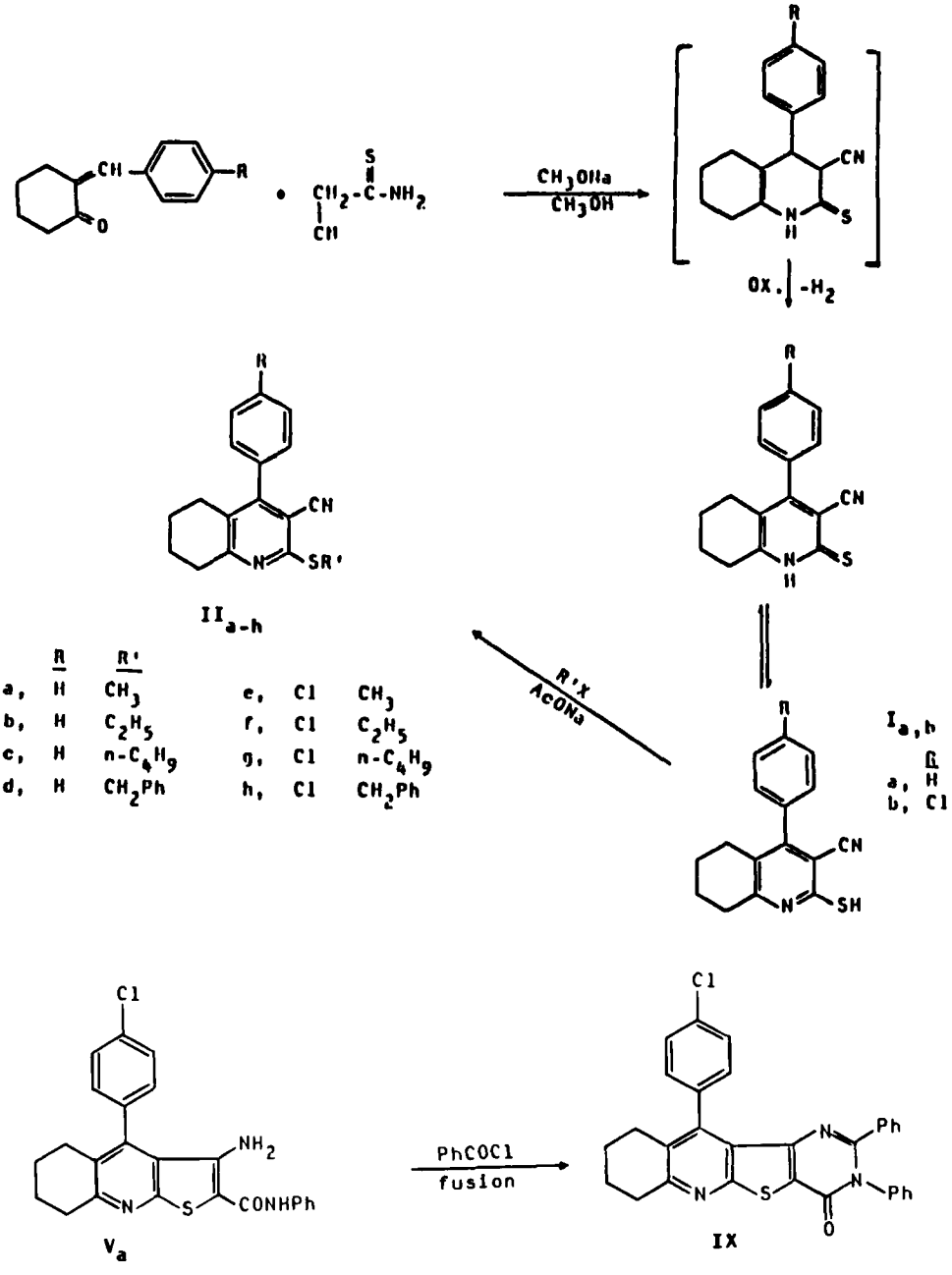
Reaction of $\mathbf{I}_{a,b}$ with alkyl/aralkyl halides in presence of sodium acetate gave 2-alkyl/aralkyl thio-3-cyano-4-aryl-5,6,7,8-tetrahydroquinolines ($\mathbf{II}_{a-h}$).

Similarly, compound $\mathbf{I}_b$ was reacted with the N-chloroacetyl derivative of *p*-substituted anilines and/or 2-amino-4-arylthiazoles to yield 2-(N-substituted)-carboxamidomethyl thio-3-cyano-4-*p*-chlorophenyl-5,6,7,8-tetrahydroquinolines ($\mathbf{III}_{a-c}$ and $\mathbf{IV}_{a-c}$ respectively).

Cyclization of $\mathbf{III}_{a-c}$ and $\mathbf{IV}_{a-c}$ by heating in ethanol containing sodium ethoxide furnished 2-(N-substituted)carboxamido-3-amino-4-*p*-chlorophenyl-5,6,7,8-tetrahydro-thieno[2,3-b]quinolines ($\mathbf{V}_{a-c}$ and $\mathbf{VI}_{a-c}$ respectively) in nearly quantitative yield. The latter compounds $\mathbf{V}_{a-c}$ and $\mathbf{VI}_{a-c}$ were also obtained through interaction of $\mathbf{I}_b$ with N-chloroacetyl derivative of *p*-substituted anilines and/or 2-amino-4-arylthiazoles in refluxing ethanol containing sodium ethoxide.

Treatment of $\mathbf{V}_{a-c}$ and $\mathbf{VI}_{a-c}$ in concentrated HCl-AcOH mixture with sodium nitrite solution at low temperature affording 3-substituted-11-*p*-chlorophenyl-7,8,9,10-tetrahydroquinolino[3′,2′:4,5]thieno[3,2-d]-1,2,3-triazin-4-ones ($\mathbf{VII}_{a-c}$ and $\mathbf{VIII}_{a-c}$) in excellent yield.

Moreover, fusion of $\mathbf{V}_a$ with an excess of benzoyl chloride gave 2,3-diphenyl-11-*p*-chlorophenyl-7,8,9,10-tetrahydroquinolino[3′,2′:4,5]-thieno[3,2-d]pyrimidin-4-one (**IX**).




| | R | R' | | R | R' |
|---|---|---|---|---|---|
| a, | H | $CH_3$ | e, | Cl | $CH_3$ |
| b, | H | $C_2H_5$ | f, | Cl | $C_2H_5$ |
| c, | H | $n\text{-}C_4H_9$ | g, | Cl | $n\text{-}C_4H_9$ |
| d, | H | $CH_2Ph$ | h, | Cl | $CH_2Ph$ |

| | R |
|---|---|
| a, | H |
| b, | Cl |

The structure of all newly synthesized compounds was confirmed by elemental analysis (Table I) and spectroscopic data (Tables II and III).

The biological activity of some representative compounds ($\mathbf{II}_{a,b,g}$, $\mathbf{III}_{a,b}$, $\mathbf{IV}_b$, $\mathbf{V}_{a,b}$, $\mathbf{VI}_b$, $\mathbf{VII}_{a-c}$, $\mathbf{VIII}_{a-c}$ and **IX**) were tested against five strains of bacteria. It was observed that cyclization of $\mathbf{III}_{a,b}$ increased the antibacterial activity whereas cyclization of $\mathbf{IV}_b$ decreased it.

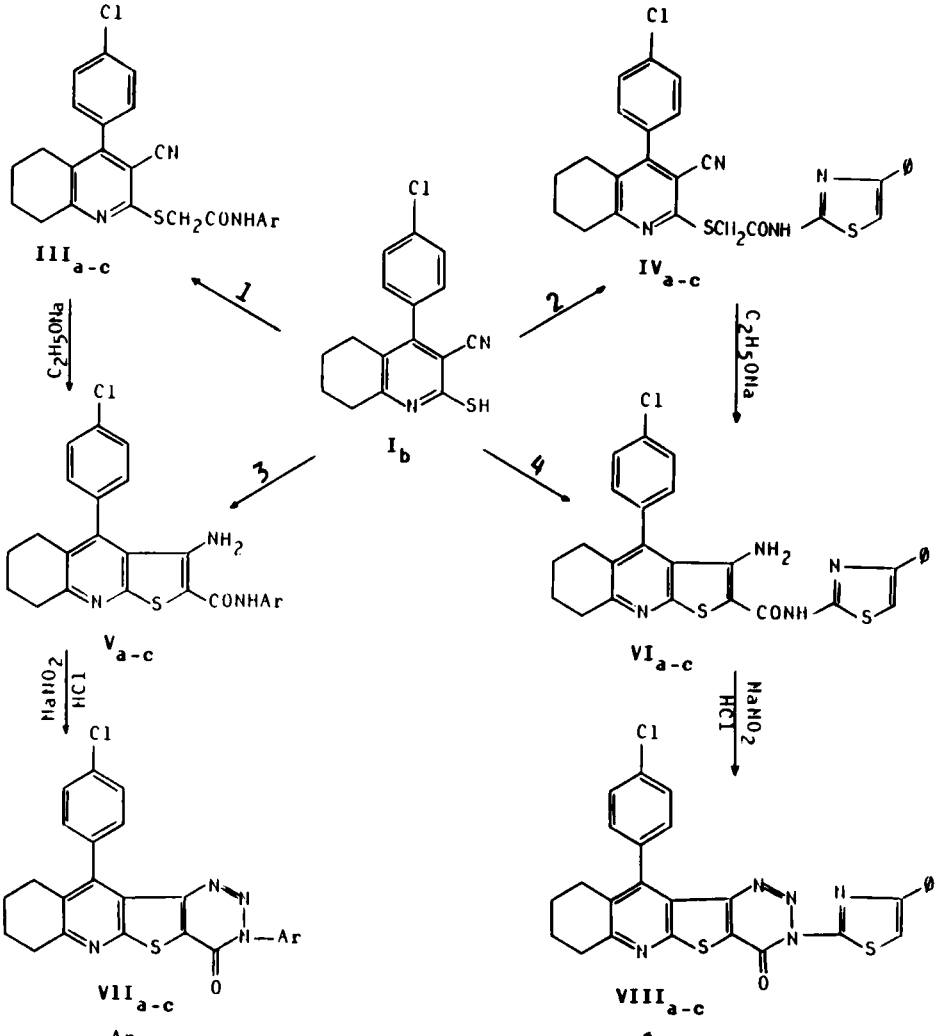


TABLE I

Physical and analytical data of all newly synthesized compounds

| Compound No. | M.P. °C | Yield % | Molecular formula | Analytical calcd./fou | | |
|---|---|---|---|---|---|---|
| | | | | C | H | N |
| $II_a$ | 104 | 91 | $C_{17}H_{16}N_2S$ | 72.82 | 5.75 | 9.99 |
| | | | | 72.71 | 5.75 | 9.58 |
| $II_b$ | 98 | 93 | $C_{18}H_{18}N_2S$ | 73.43 | 6.16 | 9.51 |
| | | | | 73.80 | 6.11 | 9.61 |
| $II_c$ | 99 | 95 | $C_{20}H_{22}N_2S$ | 74.49 | 6.88 | 8.69 |
| | | | | 74.73 | 7.15 | 9.01 |
| $II_d$ | 175 | 94 | $C_{23}H_{20}N_2S$ | 77.49 | 5.65 | 7.86 |
| | | | | 77.65 | 5.70 | 7.53 |
| $II_e$ | 139 | 90 | $C_{17}H_{15}ClN_2S$ | 64.86 | 4.80 | 8.90 |
| | | | | 64.86 | 4.60 | 8.84 |
| $II_f$ | 137 | 95 | $C_{18}H_{17}ClN_2S$ | 65.74 | 5.21 | 8.52 |
| | | | | 65.62 | 5.33 | 8.68 |
| $II_g$ | 115 | 96 | $C_{20}H_{21}ClN_2S$ | 67.31 | 5.93 | 7.85 |
| | | | | 67.50 | 5.99 | 7.90 |
| $II_h$ | 154 | 93 | $C_{23}H_{19}ClN_2S$ | 70.67 | 4.90 | 7.16 |
| | | | | 70.83 | 5.05 | 7.02 |
| $III_a$ | 150 | 91 | $C_{24}H_{20}ClN_3OS$ | 66.43 | 4.65 | 9.68 |
| | | | | 66.57 | 4.78 | 9.28 |

TABLE I (*Continued*)

| Compound No. | M.P. °C | Yield % | Molecular formula | Analyt calcd. C | H | |
|---|---|---|---|---|---|---|
| $III_b$ | 190 | 90 | $C_{25}H_{22}ClN_3O_2S$ | 64.72 | 4.78 | 9 |
| | | | | 65.00 | 4.76 | 8 |
| $III_c$ | 216 | 94 | $C_{26}H_{22}ClN_3O_2S$ | 65.61 | 4.66 | 8 |
| | | | | 65.37 | 4.42 | 8 |
| $IV_a$ | 178 | 85 | $C_{27}H_{21}ClN_4OS_2$ | 62.72 | 4.09 | 10 |
| | | | | 62.93 | 3.95 | 11 |
| $IV_b$ | 235 | 86 | $C_{28}H_{23}ClN_4OS_2$ | 63.32 | 4.36 | 10 |
| | | | | 63.50 | 4.25 | 10 |
| $IV_c$ | 218 | 83 | $C_{27}H_{20}Cl_2N_4OS_2$ | 58.80 | 3.66 | 10 |
| | | | | 58.54 | 3.69 | 10 |
| $V_a$ | 268-70 | 98 | $C_{24}H_{20}ClN_3OS$ | 66.43 | 4.65 | 9 |
| | | | | 66.15 | 4.46 | 9 |
| $V_b$ | 255-6 | 98 | $C_{25}H_{22}ClN_3O_2S$ | 64.72 | 4.78 | 9 |
| | | | | 65.07 | 4.72 | 9 |
| $V_c$ | 271-2 | 96 | $C_{26}H_{22}ClN_3O_2S$ | 65.61 | 4.66 | 8 |
| | | | | 65.51 | 4.60 | 8 |
| $VI_a$ | 184-6 | 95 | $C_{27}H_{21}ClN_4OS_2$ | 62.72 | 4.09 | 10 |
| | | | | 62.44 | 4.06 | 10 |

TABLE I (*Continued*)

| Compound No. | M.P. °C | Yield % | Molecular formula | Analytic calcd./f | | |
|---|---|---|---|---|---|---|
| | | | | C | H | N |
| $VI_b$ | 256-7 | 92 | $C_{28}H_{23}ClN_4OS_2$ | 63.32 | 4.36 | 10. |
| | | | | 63.27 | 4.38 | 10. |
| $VI_c$ | 264-5 | 97 | $C_{27}H_{20}Cl_2N_4OS_2$ | 58.80 | 3.66 | 10. |
| | | | | 58.54 | 3.91 | 9. |
| $VII_a$ | 257-9 | 90 | $C_{24}H_{17}ClN_4OS$ | 64.79 | 3.85 | 12. |
| | | | | 64.73 | 3.86 | 12. |
| $VII_b$ | 219-21 | 91 | $C_{25}H_{19}ClN_4O_2S$ | 63.22 | 4.03 | 11. |
| | | | | 63.56 | 4.11 | 11. |
| $VII_c$ | 206-8 | 98 | $C_{26}H_{19}ClN_4O_2S$ | 64.13 | 3.93 | 11. |
| | | | | 64.45 | 3.81 | 11. |
| $VIII_a$ | 235-6 | 87 | $C_{27}H_{18}ClN_5OS_2$ | 61.42 | 3.44 | 13. |
| | | | | 61.33 | 3.46 | 13. |
| $VIII_b$ | 225-7 | 82 | $C_{28}H_{20}ClN_5OS_2$ | 62.04 | 3.72 | 12. |
| | | | | 62.25 | 3.76 | 13. |
| $VIII_c$ | 213-15 | 80 | $C_{27}H_{17}Cl_2N_5OS_2$ | 57.65 | 3.05 | 12. |
| | | | | 57.67 | 3.12 | 12. |
| IX | 288-91 | 65 | $C_{31}H_{22}ClN_3OS$ | 71.60 | 4.26 | 8. |
| | | | | 71.43 | 4.24 | 8. |

TABLE II

Important IR bands of the synthesized compounds

| Assignment | $II_{a-h}$ | $III_{a-c}$ | $IV_{a-c}$ | $V_{a-c}$ | $VI_{a-c}$ | $VII_{a-c}$ | $VIII_{a-c}$ | IX |
|---|---|---|---|---|---|---|---|---|
| νNH | - | 3300-3250 | 3250-3200 | 3300-3200 | 3400 | - | - | - |
| $\nu NH_2$ | - | - | - | 3500,3360 | 3500,3360 | - | - | - |
| νCH ali. | 2940 | 2940 | 2940 | 2940 | 2940 | 2940 | 2940 | 2940 |
| νC≡N | 2240-2220 | 2230-2220 | 2230-2220 | - | - | - | - | - |
| νC=O | - | 1680-1660 | 1690-1670 | 1660-1640 | 1630 | 1690-1680 | 1670 | 1670 |
| νC=N | 1600 | 1600 | 1600 | 1600 | 1600 | 1600 | 1600 | 1600 |

TABLE III

$^1$H-NMR spectra of representative examples of the synthesized compounds (chemic

| Compound [solvent] | Aromatic protons (m) | $-CH_2-$ at C-8 (t) | $-CH_2-$ at C-5 (t) | $-(CH_2)_2-$ at C-6,7 (m) |
|---|---|---|---|---|
| $II_f$ [A] | 7.05-7.50(4H) | 2.80-3.05 | 2.25-2.50 | 1.50-2.15 |
| $III_b$ [A] | 6.70-7.50(8H) | 2.90-3.15 | 2.30-2.55 | 1.50-2.10 |
| $IV_a$ [A] | 7.10-7.90(9H) | 3.20-3.45 | 2.30-2.55 | 1.60-2.20 |
| $V_a$ [B] | 7.00-7.70(9H) | 2.85-3.05 | 2.25-2.45 | 1.55-1.85 |
| $V_b$ [B] | 6.70-7.50(8H) | 2.95-3.20 | 2.30-2.55 | 1.60-2.05 |
| $VI_a$ [A] | 7.00-7.80(12H: 9H aromatic, 1H of CH-thiazole and 1H of NH group) | 2.95-3.20 | 2.30-2.55 | 1.50-2.00 |
| $VII_b$ [A] | 6.90-7.60(8H) | (3.15-3.40)* | (2.50-2.75)** | (1.70-2.20)*** |
| IX [A] | 6.70-7.40(14H) | (3.05-3.30)* | (2.45-2.70)** | (1.60-2.00)*** |

A = $CDCl_3$, B = DMSO-$d_6$ *at C-7; **at C-10; ***at C-8,9

## EXPERIMENTAL

All melting points reported are uncorrected. IR spectra were run on a Pye Unicam SP3-100 Infrared Spectrophotometer using KBr disc technique. $^1$H-NMR spectra were recorded on a Varian EM-390 90 MHZ Spectrometer. Elemental analysis was carried out by Elemental Analyzer model 240 C. The physical and analytical data of all new compounds are given in Table I.

*2-Alkyl/Aralkyl thio-3-cyano-4-aryl-5,6,7,8-tetrahydroquinolines* (**$II_{a-h}$**). A mixture of **$I_{a,b}$** (0.01 mole), alkyl/or aralkyl halides 10% excess and anhydrous sodium acetate (2 g) in ethanol (50 ml) was refluxed for one hour. The reaction mixture was diluted with water. The white crystalline solid thus formed was collected and recrystallized from ethanol as colourless needles.

*2-(N-Aryl)carboxamidomethyl thio-3-cyano-4-(p-chlorophenyl)-5,6,7,8-tetrahydroquinolines* (**$III_{a-c}$**). To a suspension of **$I_b$** (0.01 mole) and anhydrous sodium acetate (2 g) in ethanol (50 ml) was added 0.01 mole of the N-chloroacetyl derivative of aniline or *p*-substituted aniline. The mixture was refluxed for 2 hrs. On cooling, the product precipitated was filtered and recrystallized from ethanol.

*2-[N-(4'-arylthiazol-2'-yl)]carboxamidomethyl thio-3-cyano-4-(p-chlorophenyl)-5,6,7,8-tetrahydroquinolines* (**$IV_{a-c}$**). These compounds were synthesized in analogy to the method above by reaction of **$I_b$** with N-chloroacetyl derivative of 2-amino-4-arylthiazoles. The products were recrystallized from ethanol.

*2-(N-Substituted)carboxamido-3-amino-4-(p-chlorophenyl)-5,6,7,8-tetrahydro-thieno[2,3-b]quinolines* (**$V_{a-c}$** *and* **$VI_{a-c}$**). **Method A:** 0.01 Mole of compounds **$III_{a-c}$** or **$V_{a-c}$** was suspended in sodium ethoxide solution (10 mg sodium in 50 ml ethanol) and refluxed for 15 min. The solid formed was collected and recrystallized from ethanol-chloroform mixture in the form of canarian yellow fine needles.

**Method B:** A mixture of compound **$I_b$** (0.01 mole) and N-chloroacetyl derivative of aniline or *p*-substituted aniline/or 2-amino-4-arylthiazole (0.01 mole) in sodium ethoxide solution (10 mg sodium in 50 ml ethanol) was refluxed for 30 min. The yellow product formed upon recrystallization was identical to that described in method A.

*3-Substituted-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]-thieno[3,2-d]-1,2,3-triazin-4-ones* (**$VII_{a-c}$** *and* **$VIII_{a-c}$**). Sodium nitrite solution (7 ml 10%, 0.01 mole) was added to a solution of **$V_{a-c}$**/or **$VI_{a-c}$** (0.009 mole) in concentrated hydrochloric acid (5 ml) and glacial acetic acid (5 ml) at 0°C during 5 minutes with stirring. The solid thus precipitated was collected and recrystallized from ethanol.

*2,3-Diphenyl-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]-thieno[3,2-d]pyrimidin-4-one* (**IX**). A mixture of **$V_a$** (0.01 mole) and excess benzoyl chloride (6 ml) was refluxed for 2 hrs. Excess benzoyl chloride was extracted several times with pet. ether (60–80) and the residue was recrystallized from ethanol-chloroform mixture into colourless plates.

*Biological screening.* Sixteen compounds were screened for their antibacterial activity *in vitro* against five microorganisms; *Bacillus cereus*, *Micrococcus roseus*, *Staphylococcus aureus*, *Escherichia coli* and *Serratia rhodnii* using paper disc diffusion method.[5]

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