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# Synthesis of 3-[3-(Benzothiazol-2-yl)-4-oxo-thiazolidin-2-yl]chromones as Antifungal Agents

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Antifungal activities associated with chromones and thiazolidones prompted us to synthesize 3-[3-(benzothiazol-2-yl)-4-oxo-thiazolidin-2-yl]chromones through the intermediacy of Schiff bases. Structures of new compounds have been assigned by the interpretation of their IR and PMR spectral data and are supported by elemental analysis. One of the Schiff base adduct has shown high antifungal activity (90.93 % inhibition of growth) against *Aspergillus niger i.e.*, the fungus responsible for food poisoning and aspergillosis. It is worth mentioning as the isolation and purification of Schiff bases was not easy due to 1,4-adduct formation. Hence, a one pot synthesis of title compounds was designed by refluxing a mixture of 3-formylchromone, 2-aminobenzothiazole and thioglycollic acid (TGA) in benzene in presence of zinc chloride instead of reacting Schiff base with thioglycollic acid.

**Key Words: Synthesis, Chromones, Antifungal.**

## INTRODUCTION

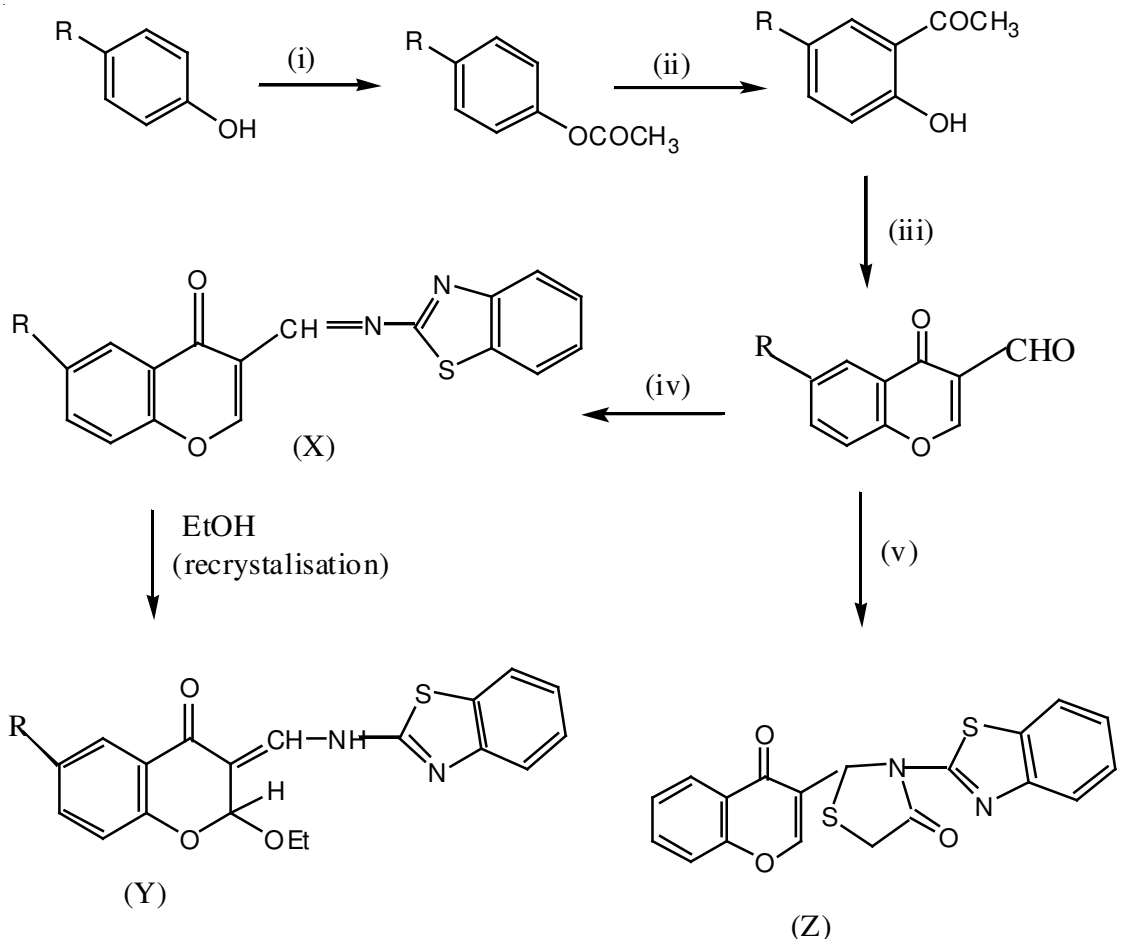
Microbial infections are haunting the society since the time immortal. They attack the men, animals and plants without any discrimination. Methods to counter them varied from time to time and synthetic medicines are one of them. Antimicrobial activities are found in chromones[1-6], benzothiazoles[7-16], Schiff bases[17-20] and thiazolidin-4-ones[21-30]. Therefore, it was thought to bring all these active scaffolds in one molecule in a quest to synthesize strong and safer anti fungal agents. Synthesis of 3-[3-(benzothiazol-2-yl)-4-oxo-thiazolidin-2-yl]chromones was tried through the intermediacy of Schiff bases. As the isolation and purification of Schiff bases was not easy due to 1,4-adduct formation a one pot synthesis of title compounds was designed by refluxing a mixture of 3- formylchromone, 2-aminobenzothiazole and thioglycollic acid in benzene in presence of zinc chloride instead of reacting Schiff base with thioglycollic acid (**Scheme-I**).

## EXPERIMENTAL

All the melting points and boiling points are uncorrected. IR-spectra were recorded on SPECTRUM BX SERIES in KBr. Absorption frequencies were recorded in $cm^{-1}$. PMR-spectra were recorded on BRUKER AVANCE II 400 NMR spectrometer. Chemical shifts are recorded in ppm unit (δ) downfield from internal TMS standard. Solvents and starting materials were purified using standard procedures. Purity of the compounds was checked on TLC plates coated with silica gel.

**General procedure for the synthesis of 3-(2-benzothiazolyl imino methyl)chromones [Y] (Schiff bases):** A solution of 3-formylchromone (10 mmol) in toluene was added to solution of 2-amino benzothiazole (10 mmol) in toluene in presence of *p*-toluene sulphonic acid (0.1 g) and reaction mixture was refluxed on oil bath for about 7 h. The reaction mixture was then cooled to room temperature and solid separated was filtered, washed with toluene and re-crystallized from ethanol. Structures of the compounds were assigned on the basis of elemental analysis, IR and PMR-spectral data.

**Synthesis of 3-(2-benzothiazolyl imino methyl)-6-methylchromone [Ya]:** To a solution of 6-methyl-3-formylchromone (1.0 g) and 2-amino benzothiazole (0.724 g) in dry toluene was added 0.1 g of *p*-toluene sulphonic acid and reaction mixture was refluxed on oil bath using Dean and Stark apparatus for 6.0 h. Reaction mixture was then worked up as given in general procedure and was re-crystallized from ethanol which yielded its 1,4-adduct. m.p. 168 ºC; yield 65 %; found (%): C = 65.22, H = 4.62, N = 7.32, S = 8.72, $C_{20}H_{18}O_3N_2S$ requires: C = 65.57, H = 4.92, N = 7.65 and S = 8.74. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3120 (-NH stretching), 2976 (=C-H str., aromatic), 1638(s) [-C=O str., chromone], 1608 [C=C str., aromatic], 1560 (s) [C=N str.], 1491 [C-H def, aromatic], 1268 [C-N str.], 1209 [N-C-S str.], 995 (s) [aromatic str.,




**Scheme-I**

*p*-substituted], 820 (s) [aromatic str.], 741 [aromatic stretching, *m*- substitution ].

PMR [$CDCl_3$] (δ): 1.20 [3H, t, -$OCH_2CH_3$], 2.15 [3H, s, C6-$CH_3$], 3.85 [2H, q, -$OCH_2CH_3$], 5.82 [1H, s, C3=CH (chromone)], 6.98 [1H, dd, C8-H (chromone)], 7.31-7.45 [4H, m, C4-H, C5-H, C6-H and C7-H (benzothiazole)], 7.73 [1H, dd, C7-H (chromone)], 7.78 [1H, s, C2-H (chromone)], 8.04 [1H, dd, C5-H (chromone)], 12.23 [1H, s, -NH proton of C3 = CH-NH-].

**Synthesis of 3-(2-benzothiazolyl imino methyl)-6-chloro chromone [Yb]:** To a solution of 6-chloro-3-formylchromone (1.004 g) and 2-amino benzothiazole (0.798 g) in dry toluene was added 0.1 g of *p*-toluene sulphonic acid and reaction mixture was refluxed on oil bath using Dean and Stark apparatus for 8.5 h. Reaction mixture was then worked up as given in general procedure. Re-crystallization was done with ethanol. m.p. 185 ºC; yield = 60 %; found (%): C = 58.96, H = 3.82, N = 7.22, S = 8.20 $C_{19}H_{15}O_3N_2SCl$ requires: C = 59.25, H = 3.88, N = 7.24, S = 8.28. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3160 (b) [= CH aromatic str. and N-H str.], 1649 [C=O str. (chromone)], 1606 [C=C str. (aromatic)], 1549 [C=N str.], 1470 [CH def.], 1303 [C-N str.], 1227 [C-O str.], 1041 [N-C-S str.], 903 (m) [aromatic str., *p*-substituted], 855 [aromatic str.], 751 C-Cl str.], 723 (m) [m-substitution ].

**Synthesis of 3-(2-benzothiazolyl imino methyl) chromone [Yc]:** To a solution of 3-formylchromone (1.740 g) and 2-amino benzothiazole (1.360 g) in dry toluene was added 0.1 g of *p*-toluene sulphonic acid and reaction mixture as refluxed on oil bath using Dean and Stark apparatus for 7 h. Reaction mixture was then worked up as given in general procedure. Re-crystallization was done with ethanol. m.p. 132 ºC; yield = 52 %; found (%): C = 64.72, H = 4.43, N = 7.90, S = 9.00 required: C = 64.77, H = 4.55, N = 7.95, S = 9.09. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3290 (-NH stretching), 2970 (= C-H str., aromatic), 1640 (s) [-C=O str., chromone], 1600 [C=C str., aromatic], 1545 (s) [C=N str.], 1465 [C-H def, aromatic], 1300 [C-N str.], 1250 [N-C-S str.], 1195 [C-O str.], 820 (s) [aromatic str.].

**Synthesis of 3- [ 3-(benzothiazol-2-yl)-4-oxo-thiazolidin -2-yl] chromone [Z]:** To equimolar solution of 3-formyl chromone (1.740 g) and 2-aminothiazole (1.360 g) in dry benzene was added 0.92 mL of thioglycollic acid and 0.2 g of anhydrous $ZnCl_2$. Reaction mixture was refluxed on water bath for 17 h. Then reaction mixture was cooled and solid separated was filtered, washed with $NaHCO_3$ solution followed by 2N-HCl to remove unreacted acid. The compound obtained was re-crystallized from 95 % ethanol. m.p. 248 ºC, yield = 30 %. Found (%): C = 60.25, H = 3.12, N = 7.32, S = 10.54 $C_{19}H_{12}O_3N_2S_2$ requires C = 60.00, H = 3.16, N = 7.73, S = 10.69. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3083 [-CH str. (aromatic)], 2929 [-CH str. (aliphatic)], 1691 [C= O str. (thiazolidone)], 1674 [- C=O str. (chromone)], 1569 [C=N str. (benzothiazole)], 1465 [-CH def. (aromatic)], 1347 [C-N str.], 1247 [-N-C-S-str.], 1176 [C-O str.]. PMR (DMSO-$d_6$) δ: 3.87 [1H, d, -CH proton of

thiazolidone near S-atom of the ring], 4.49 [1H, d, -CH proton of thiazolidone ring near C=O group of the ring], 6.63 [1H, s, C2-H of thiazolidone], 7.34-7.83 [7H, m, C6-H, C7-H, C8-H of chromone and C4-H, C5-H, C6-H and C8-H of benzothiazole], 8.09 [1H, dd, C5-H (chromone) and 8.39 [1H, s, C2-H (chromone)].

**Antifungal testing:** Anti-fungal activity was tested by filter paper disc method using DMF as solvent. Fungal growth was measured after every 24 h on both x as well as y axis. Linear growth was calculated by following formula[31]:

Linear growth = [Growth on x axis + Growth on y axis – 2 (diameter of disc)]/4

Percentage of inhibition was calculated by the formula

Inhibition (%) = 100 × [Linear growth in conrol – Linear growth in experiment]/Linear grwoth in control

% inhibition by compound [**Ya**] at various concentrations in DMF in shown in Table-1 given below:

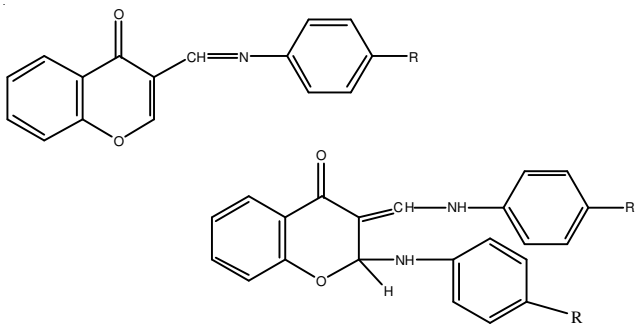
TABLE-1
EXPERIMENTAL CONCENTRATIONS

| S. No. | No. of days | 0.25 % | 0.50 % | 0.75 % |
|---|---|---|---|---|
| 1 | 2 | 24.00 | 50.93 | 77.06 |
| 2 | 4 | 34.85 | 61.90 | 77.14 |
| 3 | 6 | 54.06 | 72.38 | 82.97 |
| 4 | 8 | 71.10 | 84.00 | 90.93 |

## RESULTS AND DISCUSSION

Phenols were esterified with acetic anhydride in basic medium and esters thus formed were subjected to Fries migration to give *o*-hydroxyacetophenones which upon treatment with dimethyl formamide (DMF) and phosphorus oxychloride at low temperature yielded 3-formyl chromones. 3-Formyl chromones were condensed with 2-aminobenzothiazole in dry toluene in presence of *p*-toluene sulphonic acid using Dean and Stark apparatus. The products of this reaction were probably Schiff bases of 3-formyl chromones which upon re-crystallization might have produced 1,4 - adduct which is evident by spectral studies.

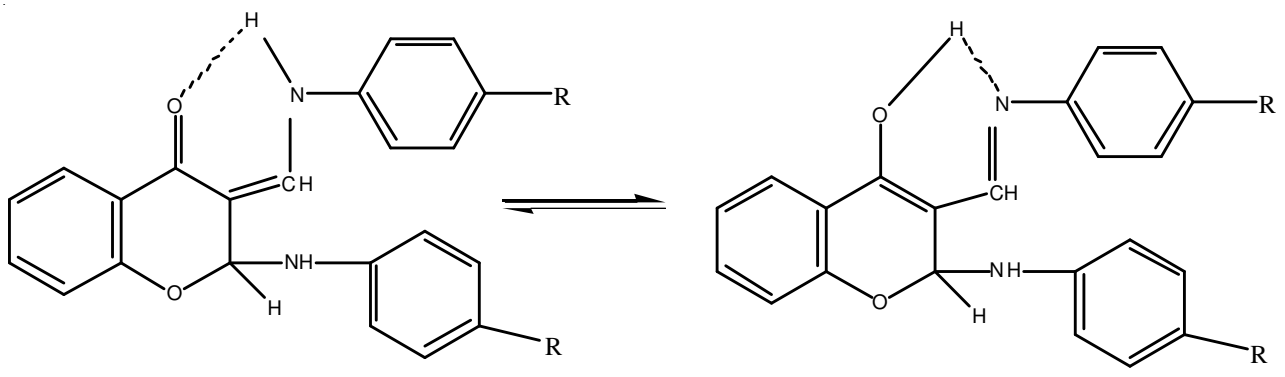
It is important to note that chromone ring usually opens by the attack of nucleophile at C-2 position[32]. But presence of iminomethyl group alters the reactivity of system towards nucleophile and facilitates nucleophilic ring addition over ring opening. Thus upon reaction with anilines a mixture Schiff bases and 2-amino-3-(anilino methylene) chroman-4-one is obtained[33,34.]



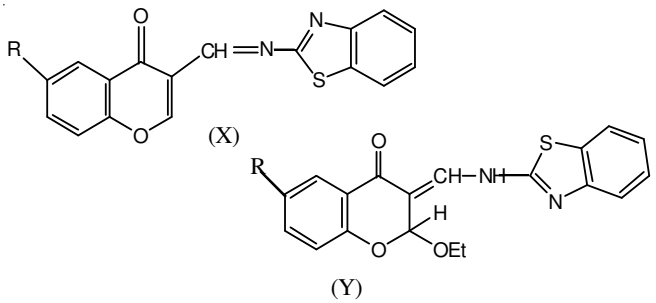
Reason for addition reaction over fission may be formation of stable hydrogen bonded keto-amine system:

Adduct formation takes place by the addition of amines, alcohols and thiophenols to Schiff bases. When 1:1 molar ratio of 3-formyl chromones and primary amines is allowed to react[34] mixture of Schiff bases and 1,4-adduct is obtained which is difficult to separate. Even during chromatographic separations traces of moisture on column hydrolyse Schiff base and amines thus again form adduct. However in presence of *p*-toluene sulphonic acid good yield of anils (Schiff bases) is formed.

Structures of compounds formed are supported by their IR and PMR spectral data. IR spectrum of **Ya**, a typical compound of the series, exhibited characteristic absorption bands at 3491, 2976, 1649, 1606, 1470, 1227, 1198 $cm^{-1}$. Most important peaks of these was at 1649 $cm^{-1}$ (C=O stretching of chroman-4-one). This spectrum was used as an indirect evidence of formation of **Ya** as -CH=O vibration of formyl group and -NH vibrations (two peaks) of 2-amino benzothiazole were absent in it. However vibration at 3491 $cm^{-1}$ (-NH str.) was there in spectrum indicating adduct formation. Peaks at 1690 and 2900-2800 (C=O and C-H stretching of -CHO group) were absent which further support this fact. N-C-S stretching at 1227 is indicative of thiazole ring in the compound. PMR spectrum [$CDCl_3$] also indicated that compound formed was [Y] and not [X]. It exhibited signals for all the protons which should be present in 1,4-adduct with ethanol. Starting from the highest field to appear was three proton triplet due to C2-$OCH_2$ $CH_3$ methyl group centered at 1.20 ppm. C6-$CH_3$ of chroman-4-one moiety was present as three proton singlet at δ 2.15 which was followed by two proton quartet centered at δ 3.85 (-$OCH_2CH_3$). C3=CH was visible as a singlet at δ 5.82 (integral area one proton). C8-H of chroman-4-one is assignable to doublet centered at δ 6.98. Four protons of benzothiazole nucleus showed their appearance as a multiplet in the region



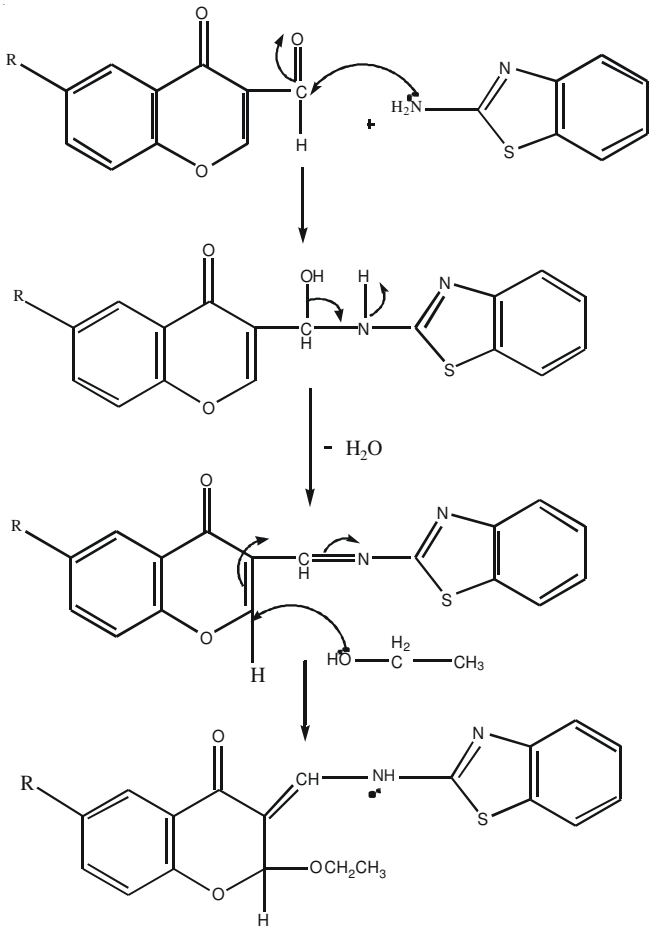
7.31-7.45. δ 7.73 doublet is assignable to C7-H of chroman-4-one where as C2-H of this system may have exhibited its presence as a singlet at δ 7.78. Last doublet at δ 8.04 may be safely assigned to C5-H of chroman-4-one and -NH proton might have been at δ 12.23.



(X)

(Y)

Following mechanism may be assigned to the formation of [Y] from [X] (**Scheme-II**):

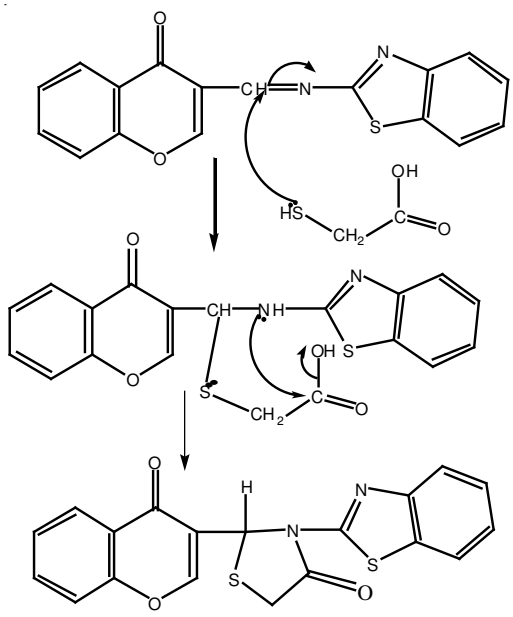


**Scheme-II**

As isolation of Schiff base from the reaction mixture was not easy even through chromatography proposed compound [**Z**] was synthesized from 3-formyl chromone by one pot synthesis which involved condensation of 2-aminobenzothiazole and thioglycollic acid with 3-formyl chromone in presence of anhydride $ZnCl_2$ in one step. Structure of compound [**Z**] is supported by the interpretation of its IR and PMR-spectral data.

IR spectrum of [**Z**] was used as an indirect evidence for its formation. It showed additional C=O stretching vibrational band at 1691 $cm^{-1}$ besides C=O stretching of chromone at 1641 $cm^{-1}$. All other stretching and bending vibrations were present in the spectrum. For example, aromatic =C-H stretching and bending, C=N, C-N, C-O, -S-C-N stretchings. PMR spectrum of this compound completely revealed the structure assigned to it. 400 MHz PMR spectrum of this compound run in DMSO-$d_6$ showed signals for all the twelve protons. First to appear were $CH_2$ protons of thiazolidone nucleus which appeared as doublets centered at δ 3.87 and 4.49. At 3.87 appeared CH proton in neighborhood of S as a doublet, whereas CH proton of this $CH_2$ in neighborhood of C=O group appeared downfield as doublet centered at δ 4.49. C2-H of thiazolidone was visible at δ 6.63 as a singlet. C6-H, C7-H and C8-H of chromone and C4-H, C5-H, C6-H and C7-H of benzothiazole moiety appeared as multiplet from δ 7.34-7.83. C5-H of chromone showed up as doublet of doublet at δ 8.09. Last and most downfield signal present at δ 8.39 as singlet may be assigned to C2-H of chromone ring.

It is thought first Schiff base might have formed *in situ* which upon reaction with thioglycollic acid might have given [**Z**]. A plausible mechanism may be as given in **Scheme-III**:



**Scheme-III**

Compound [**Ya**} was screened for antifungal activity against *Aspergillus niger* (Table-1). Observations show 90 % inhibition of growth at 0.75 % concentration, hence it is good antifungal which is also visible in following Fig. 1.

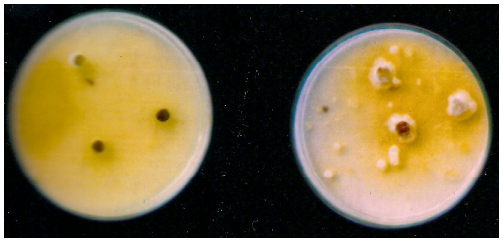


Fig. 1. Left:sample [**Ya**] (0.75 % concentration); right:control

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