الخلاصة

يهدف العلاج الكيمياوي لدراسة تحطيم الكائنات الامراضية ضمن الحد الادنى من الجوانب الثانوية للكائن تحت العلاج وهذه الكائنات قد تكون بكتريا او فايروس او فطر او خلايا سرطانية .

تم في هذه الدراسة تخليق مشتقات جديدة من الازوال ومشتقات من البريميدين والحاوية على حلقة خماسية تحتوي على ذرتي نتروجين وذات الفعالية البايولوجية العالية ضد الامراض الجلدية .

تم الحصول على مركب ١- استيتايل -٤-[٤-[[٢-(٢و٤- واي كلورفينل)-٢- (١H –اميدازول -١-Y١ –ميثايل) -3,1 - داكسولين-٤-Y١) ميثوكسي] فينل] بابرازين (1G) من تفاعل مركب (1F) مع مول واحد من مركب (2) .

تم الحصول على مركب اثيل -٤- امينو بنزين (2a) من تفاعل مركب -٤- امينو بنزوك اسد مع حامض الهيدروكلوريك .

تم الحصول على مركب ٦- ميثايل -٤-اوكسو -١و٢و٣و٤و-تيترا هايدرو -٢-بريميدين (4G) من تفاعل 0.1 مول من ثايويورل مع 0.1 مول من اثيل اسيتو استين .

تم الحصول على مركب ٢- هايدرازينو -٦- ميثايل بريميدين -٤- (H3) اون من تفاعل هايدرازين هايدريد مع مركب (4G) .

تم قياس نقاوه المركبات المحضرة باستخدام طيف الاشعة تحت الحمراء (FTIR)
تم دراسة تاثير المركبات الجديدة المحضرة (1G,2E,3G,4G,5G) على فعالية نمو المستعمرات الفطرية باستخدام طريقة الزراعة النسيجية في معالجة الاماض الجلدية بالاعتماد على فترات الحضن لمدة ٢٤ساعة , ٤٨ساعة , ٩٦ساعة .

الخلاصة

اجريت دراسة خارجية جسم الكائن الحي (invitro) باستخدام الانواع الفطرية (Trichopgyton rubrum) و (Geotrichum candidum) وباستخدام الاوساط الغذائية (potato dextrose agar) و (sabouraud agar)

وفي جزء اخر من هذه الدراسة بين تاثير مزيج من مركب كيتوكنزول (Ketoconazole) مع الكافيين (caffeine) على نمو الفطريات الامراضية وتم استنتاج بان المزيج (6G) المتكون من مزج المركب (Ketoconazole) مع الكافيين كان اكثر تثبيطا لنمو الفطريات وفيما اذا استخدم المركب كيتوكنزول لوحدة ضمن فئران حضن مختلفة .

ان المركب (4G) غير فعال لتثبيط نمو الفطريات في مختلف التراكيز وكان المركب (2e) ذو فعالية عالية في تثبيط مستعمرات الفطريات المستخدمة بغض النظر عن فترات الحضن .

Acknowledgment

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My special affection is extended to all my colleagues with whom I shared our common problems and ambitions.

Finally I would like to express my utmost respect to my family and wife who gave me all their love and support during my study.

Firas

1-1 Chemotherapy :

Chemotherapy is the science of selective toxicity the goal of chemotherapeutic treatment is to selectively attenuate or destroy pathogenic microorganisms or cells with minimal side effects to the host . These targeted cells or organisms may be bacteria , viruses , protozoans , fungi , helminths , or tumor cells . In order to achieve selective toxicity , the target for chemotherapeutic may be unique to the target population , may be structurally different in the target population from the form in the host population , or may be more essential in the target population than in the host population [(1)] .

The very term chemotherapy was invented by Ehrlich and expressed his belief that infectious disease could be combated by treatment with synthetic chemicals . Ehrlich postulated that cells possess chemical receptors which are concerned with the uptake of nutrients. Drugs that affect the cell must bind to one or other of these receptors . The toxicity of a drug is determined firstly by its distribution in the body . However , in the treatment of an infection it is the binding to the parasite relative to the host cell that determines the effectiveness of the compound . Thus Ehrlich recognized the importance of quantitative measurement of the relationship between the dose of a compound required to produce a therapeutic effect and the dose that will cause toxice reactions . Ehrlich's view of cell receptors also has its counterpart in modern views of membrane transport . [(1)]

The diversity of fungal pathogens which attack man and his domesticated animals is considerably smaller than that of bacteria .

neverless the fungi cause infections ranging from the trivial and inconvenient to those causing major illness and death . Fungal infections have assumed greater importance in recent years because of The increased number of medical conditions in which host immunity is

compromised . cytotoxic drugs, used to combat cancer , organ graft rejection and AIDS damage the immune system and increase susceptibility to infection by opportunist pathogens that rarely cause illness in healthy individuals .

Fungi as eukaryotes have much more biochemistry in common with mammalan cells than bacteria and, therefore, pose a serious challenge to chemotherapy . Specificity of action is more difficult to achieve . few antibiotics are useful against fungal infections and attention has concentrated on devising synthetic agents .Advantage has been taken of progress in devising compounds for the treatment of fungal infections of plants to produce reasonably safe and effective drugs of the azole type for human fungal infections . [3]

1-2 Principles of Antifungal Therapy :

Early in the development of an antifungal agents , susceptibility testing offers important clues as to the spectrum of activity . However , agents may appear resistant invitro and still have useful clinical activity [4,5,6]. Both fluconazole and flucytosine were initially considered inactive invitro but were developed because of their chemotherapeutic effect in mice infected with candida albicaus . [7,8].

Subsequently , noninhibitory culture media were found , permitting demonstration of in vitro activity .

Other compounds have been active in vitro and inactive clinically . most importantly . There has been no correlation between clinical response and susceptibility within a given species. For example Ketoconazole susceptibility did not correlate with clinical response of patients with blastomycosis , coccidioidomycosis,or histoplasmosis . [9,10,11,12] .

New drugs should be compared with standard regimens known to be effective in the particular animal . If both the standard drug and the new drug were in effective , it would suggest a problem in the model . If both drugs are effective , one should be cautions about concluding that one drug is superior to the other unless the optimum dose of each drug is compared .[13,14] . All too commonly , only one or two doses of each drug are used and no effort is made to show that the dose of either is optimum [15,16] .

For animal infections , the optimum dose is that which gives the best therapeutic effect without toxicity changing the end point [17,18].

1-3 Azole Antifungals :

Antifungal effect is critically dependent upon the conjugated double bonds . this hydrophobic part of the molecule complexes to certain sterols, including ergosterol , the principal sterol in fungal cytoplasmic membrances . [19,20]

Azole antifungal include imidazoles compounds , with a five – member edring containing two nitrogens , and triazoles , with three nitrogens in the ring Figure (1-1) [21,22] . Newer systemic drugs are in the second class , which has been found to be more stable within the human body . Compounds of the azoles have (azole ring N-linked) to a short aliphatic chain in which the second carbon is linked to a halogenated phenyl group.[23]

Beyond that point, a considerable variability exists in structure. clotrimazole and itraconazole are insoluble in water . ketoconazole is soluble at PH3 or less .(21). Fluconazole is water soluble at neutral PH [24].

Azole compounds have a broad antifungal spectrum *in vitro* , though the concentration of drug required varies enormously with the

assay conditions .With various compounds in this class, activity has been demonstrated in experimental animals or patients with candidiasis , cryptococcosis , coccidiodomycosis , blastomycosis , histoplasmosis ,pseudallescheriasis , tinea versicolor , and ringworm, . [25,26,27].

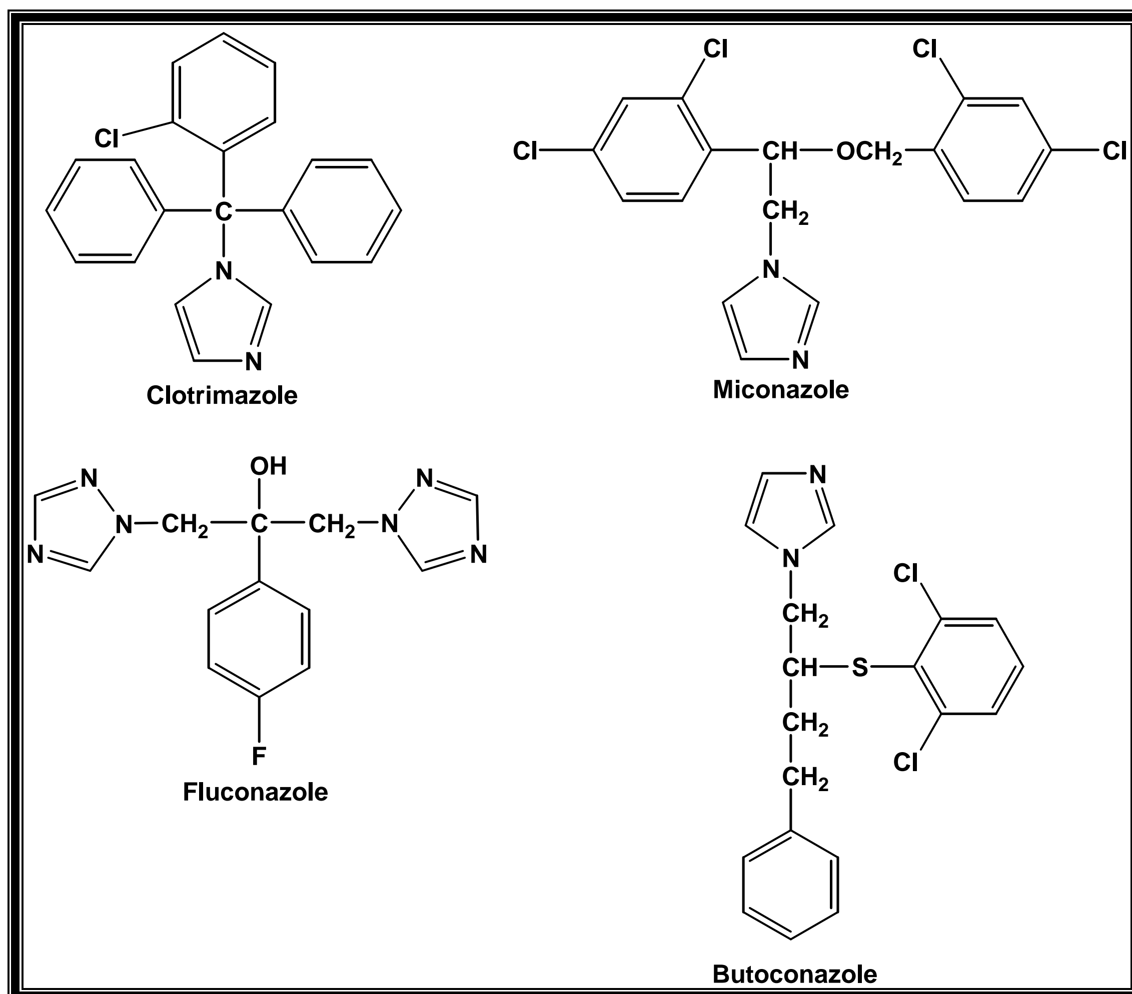


Figure (1.1) : A zole compounds

1-3-1 Mechanism of Action :

Azole antifungal bind to the heme moiety of cytochrome P_{450} and interfere with certain mixed oxidase functions [28]. Fungal α-14 demethylation of lanosterol is inhibited , blocking formation of ergosterol and leading to the accumulation of α -14 methyl sterols [29]. Both effects are deleterious to function of the cytoplasmic membrane and inhibit fungal growth . with higher concertrations that might be obtained topically fungicidal effects are also observed . [30,31,32].

1-3-2 Ergostererol Biosythesis :

Several groups of compounds are effective antifungal agents throught their actions on the biosynthesis of ergosterol. Ergosterol plays a similar role in fungal membranes to that taken by cholesterol in mammals .[33,34]. An outline of the biosynthetic pathway from squalene to ergosterol is shown in Figure (1-2) which indicates the points of inhibition of several types of antifungal agents . [35,36].

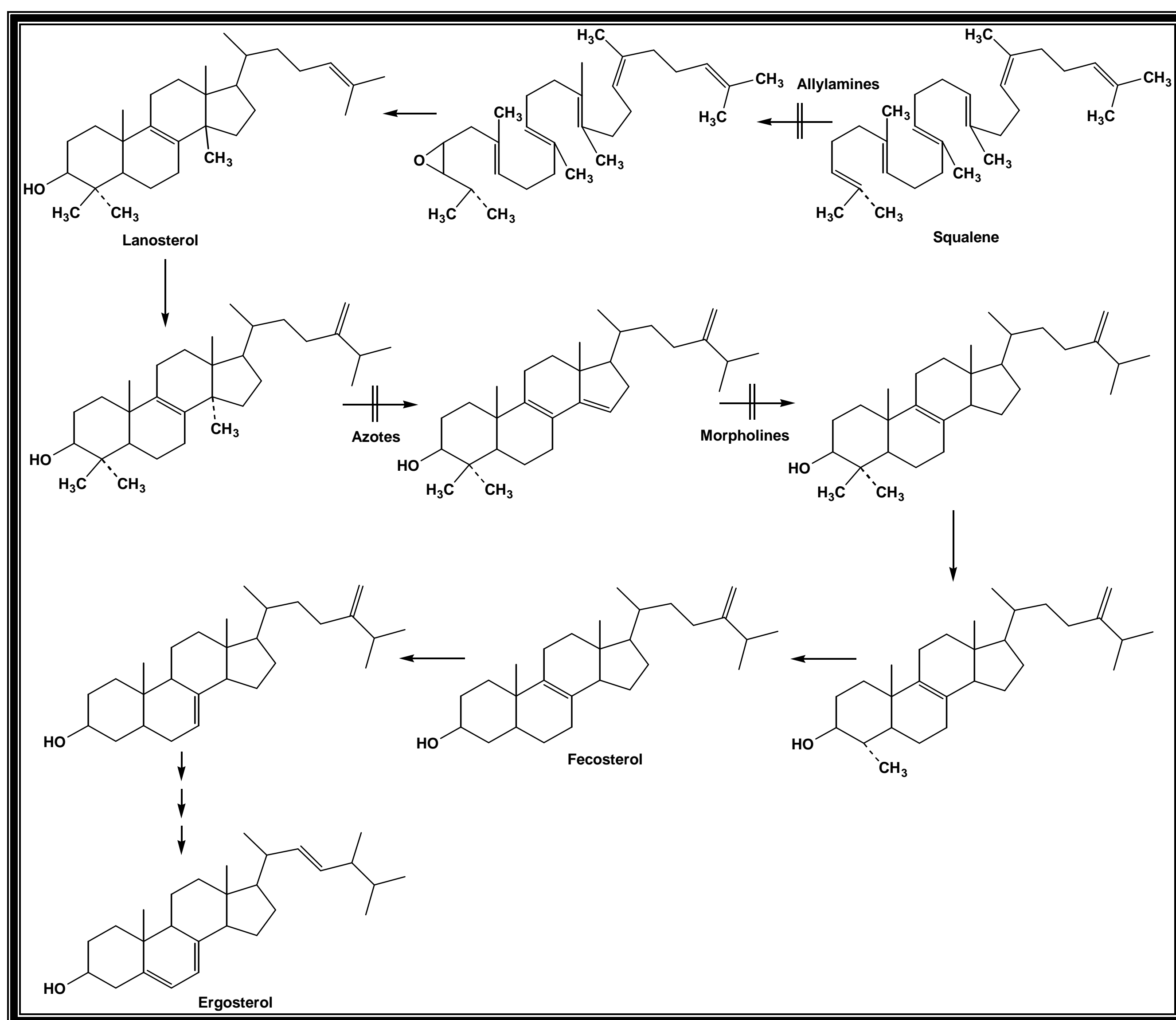


Figure (1-2) An outline scheme for the biosynthesis of ergosterol from squalene , showing the points of inhibition of several types of antifungal agents [37].

A group of compounds in common use includes those which inhibit at the stage of C-14. demethylation , These are generally referred to as the azole antifungals , by virtue of their nitrogen-containing herterocycle. Typical examples are the topically active agent miconazole Figure (1-3) , which is effective against thrush and dermatophyte infections , [38,39] and ketoconazole Figure (1-3) , which is orally active and was used to treat a wide range of fungal infections particularly deep-seated mycoses . [25,39,40]

However , ketoconazole is no longer much used for trivial infections because of the danger of toxic affects on the liver and on steroid hormone biosynthesis [41,42].

Azole –containing compounds have also been used in agriculture for treating various fungal infestations of plant e.g diclobutrazole and fenarimol Figure (1-3).[43].

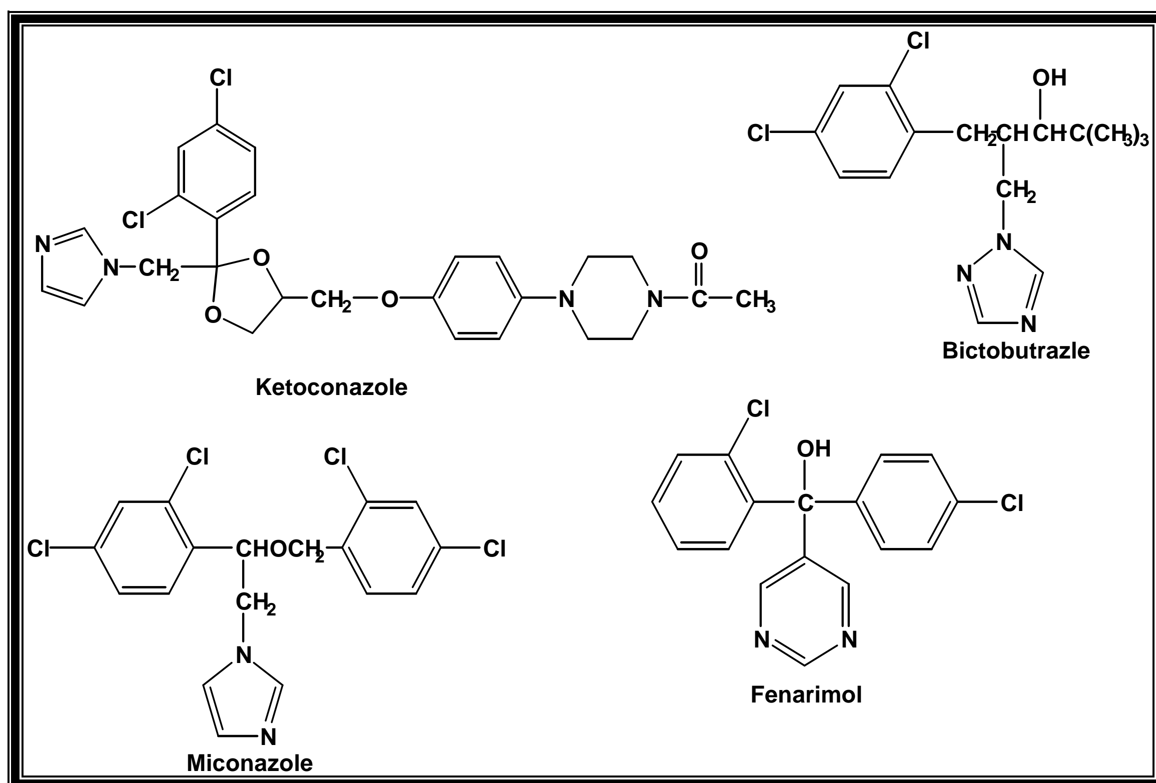


Figure (1.3): A zole antifungal agents

The Azoles have a common mode of action involving the interaction of the lone pair of electrons on the ring nitrogen with the haem group of the cytochrome P_{450} of the enzyme catalyzing the C-14 demethlation reaction. This interaction , stabilized at the binding site by the hydrophobic parts of the molecule , prevents the oxidation of the methyl group and hence its subsequent removal. The inhibition is non-competitive for the substrate and leads to a greater net production in flow through the metabolic pathway than competitive inhibition .

The result is an accumulation of methylated sterols in the cell , with a reduction of the ergosterol content .Methylated sterols are more bulky than ergsterol and donot easily fil into a normal membrane enzymes structure . This interference in the membraue structure is thought to have adverse effects on membrane –bound enzymes , either directly on their activity or their control . (44,45,46).

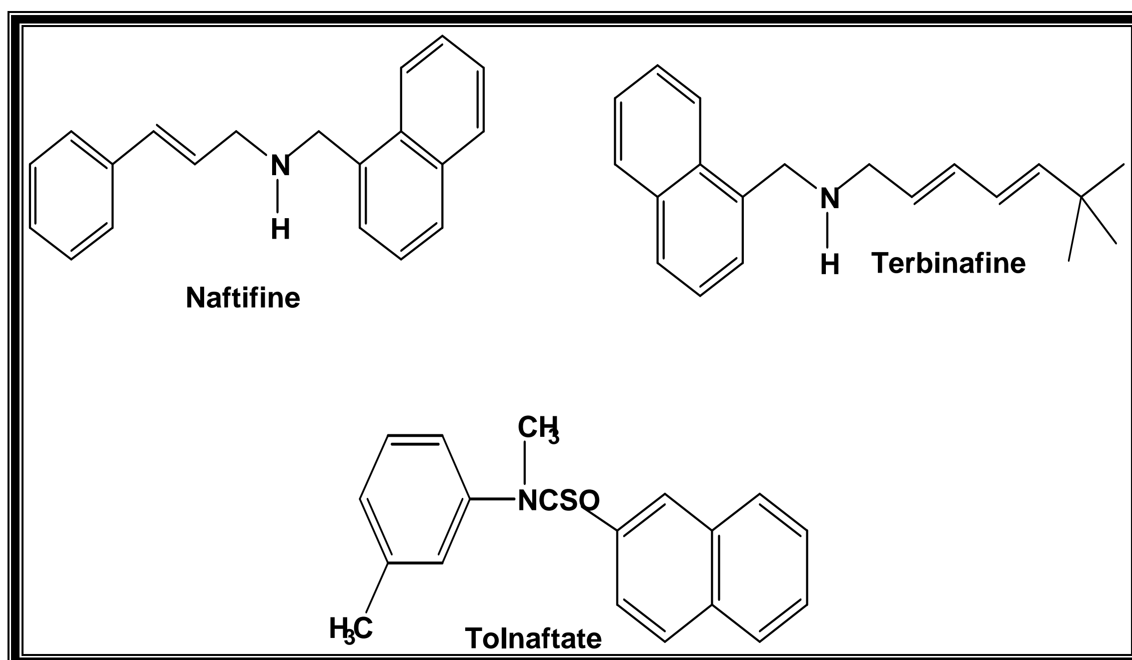


Figure (1.4): Antifungal agents that inhibit squalene expoxidation

These compounds Figure (1-4) used clinically in the treatment of dermatophyte infections which affect ergosterol biosynthesis at an earlier stage.[47,48].

The allylamine antifungal agents , naftifiue (fig.4), atopical agent , and terbinafine (fig.4) on orally active agent , inhibit the epoxidation of squalene. Recently, tolnaftate a topical antidermatophyte compound which has been in use for many years, has been shown to have the same mode of action [49,50] .

Squalene accumulates in the cell with a reduction in cellular ergosterol content and growth inhibition could result from either action . These compounds are much less active against yeasts although in broken cell preparations of candida albicans squalene epoxidation can be inhibited. The enzymes are less susceptible or perhaps yeasts have a lower sensitivity to the consequent build –up of squalene .[51]

Antifungals which inhibit ergosterol biosynthesis show a marked selectivity for fungal systems.

The Azole antifungals are several hundred times more potent against lanosterol demethylation in fungi than the corresponding reaction in mammals . Similarly , naftifine is several hundred times more potent against fungal epoxidase . This species selectivity is critical in making the ergosterol biosynthesis inhibitors such good antifungal agents . [52,53]

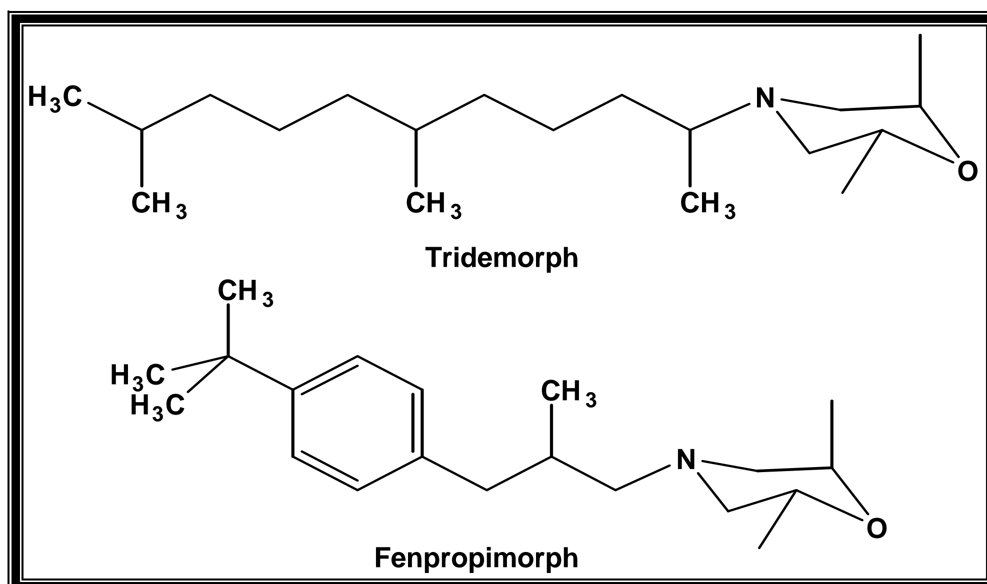


Figure (1-5) :Morpholine derivatives that are antifungal agents

.

These compounds which are used as agricultural fungicides , but only experimently by tridemorph and fenpropimorph (Figure 5) (54) . These compounds interfere with two stages of the ergosterol biosynthetic pathway :

The first target is the reduction of the double bond at the carbon 14-15 position which is formed after the removal of the carbon -14- methyl group [55].

The second target is the isomerization of the double bond between carbon atom 8 and 9 of fecosterol to a position between carbons 8 and 7 [56].

The balance between these two inhibitory activities varies from fungus to fungus and probably reflects subtle differences in the enzymes involved[57]. Tridemorph inhibits (ustilagomaydis) mainly at the C-14 reduction step whereas (Botrytis cinerea) is inhibited mainly at the C-8 and C-7 isomerization [58,59].

1-3-3 Ketoconazole compound:

In vitro studies suggest that the antifungal properties of ketoconazole may be related to its ability to impair the synthesis of ergosterol , a component of fungal and yeast cell membranes .[60].

Whithout the availability of this essential sterol , there are morphological alterations of the fungal and yeast cell membranes manifested as abnormal membranous inclusions between the cell wall and the plasma membrane .[61,62].

Ketoconazole requires an acidic environment for absorption. Drugs that alkalinize the stomach (for example , antacids , H2-recepter antagonists, proton pump inhibitors , and didanosine) may decrease the absorption of ketoconazole .It is often suggested that this interaction can be avoided if ketoconazole is administered 2 hours before the other drugs [63] .However , it is important to remember that some of these drugs especially the proton pump inhibitors may have long lasting effects and keep the stomach alkaline for 24 hours , therefor making the interaction impossible to avoid .[27]

Ketoconazole may decrease the clearance of corticosteroids and increase cortisol suppression , therefore , the corticosteroid dosage may have to be reduced when patients receive the antifungal.[29].

Ketoconazole may increase the plasma concentration of indinavir , an adjustment in the indinavir dosage may be necessary . Finally , patients who are taking ketoconazole can have a disufiram like reaction (including nausea and vomiting) if alcohol is consumed [25]

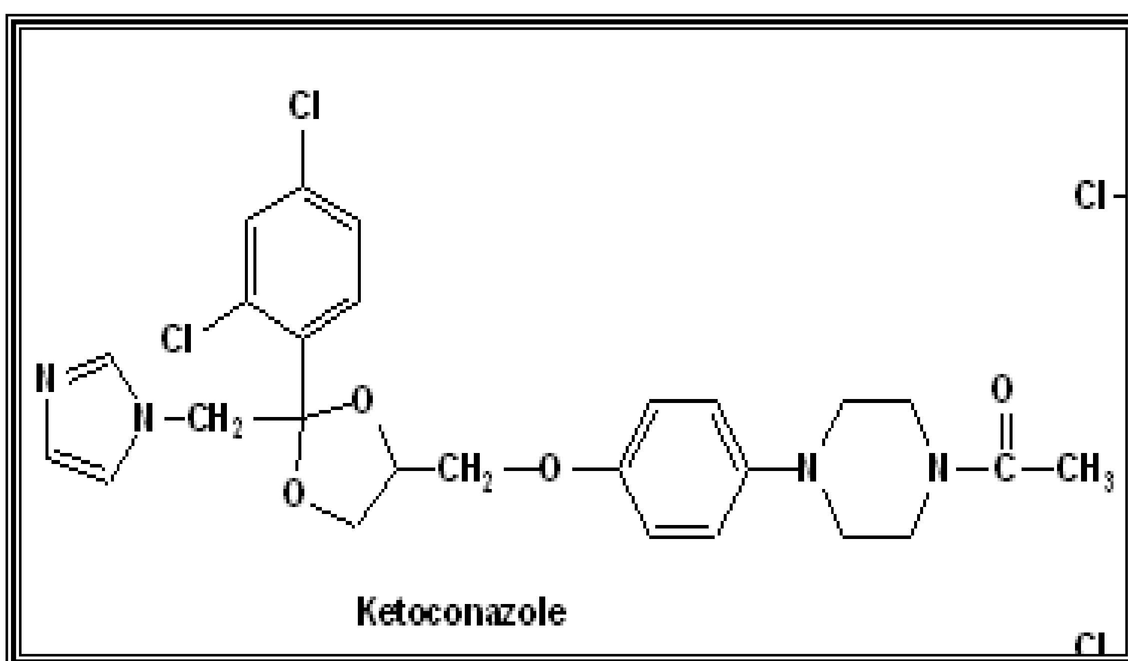


Figure (1.6): Ketoconazole compound as antifungal agents

1-3-3-1 Spectrum of Activity :

Ketoconazole is the drug of choice for chronic mucocutaneous candidiasis and the more indolent case of extrameningeal blastomycosis , histoplasmosis and paracoccidiodomycosis of immuno competent patients

. [11] .Tinea versicolor , tinea corporis and candida vaginitia respond to ketoconazole , but other drugs are preferred. Nonmeningeal chronic disseminated coccidioidomycosis and pseudallescheriasis often improve with ketoconazole the rapy . [64] Smaller lesions of chromomycosis and mycetoma due to madurella mycotomatis may also improve [61].

Although there has alleged to be some activity in pulmonary cytococcosis , ketoconazole does not prevent or treat the morbid complication of this infection , which spreads to the meninges . cutaneous sporotrichosis occasionally responds to ketoconazole .[65]

1-3-3-2 pharmacokinetics:

Oral bioavailability is critically dependent upon gastric acidity and is reduced in patients taking H_2- blocking agents , omeprazine or simultaneous antacids . Acquired immunodeficiency syndrome (AIDS) .patients with gastropathy have also reduced absorption [66] .

Ingestion of food has noeffect on bioavability . peak serum levels after 200,400, and 800my once daily are approximately 4,8 and 20 µg/ml.

Initial half –life increases from 90 min after 200 mg to 3 or 4 hours after 800mg . Several hours after dosing , elimination slows to ahalf –life of 8 to 9 hours . [69,70,71].

Ketoconazole is extensively metabolized , with inactive products appearing in feces and , to a lesser extent , in urine . Only insignificant amounts of bioactive drug appear in urine [72,73,74,75].

1-3-3-3 Hormonal effects:

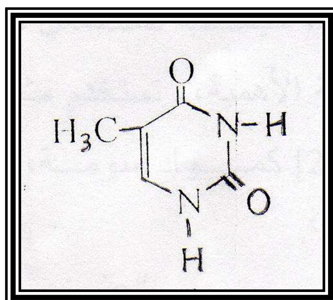
Ketocoazole exerts a dose and time dependent suppression on cortisol and testosterone secretion .The effect can be seen in cell culture experimental animals , and humans .[76] Clinically evident hormonal suppression is usually difficult to discern in adults given the usual dose of 400 mg daily , even through decreased plasma testosterone and cortisol are demonstrable [77,78]. There are report that clinical Addisons disease can be attributed to ketoconazole but the role of mycosis in depressing adrenal function and the variable documentation of symptomatic hypoadrenalism in these cases leave the matter unsettied .[79.80].

As far as ketoconazole is known , the testicular or adrenal suppression , as well as the gynecomastia , goes away after treatment is ended .[81,82,88] .

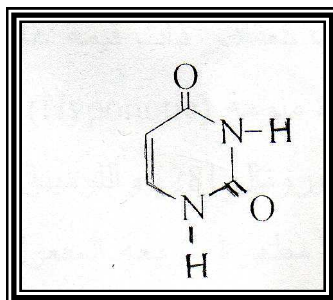
Ketocoazole , 800 to1200 mg daily , has been used to suppress testosterone in prostatic carcinoma , to suppress hyperadrenocorticism in cushing's disease , and to suppress aldosterone secretion in adenal hyperplasia [84,85]

1-4 Biological activity of pyrimidine derivatives:

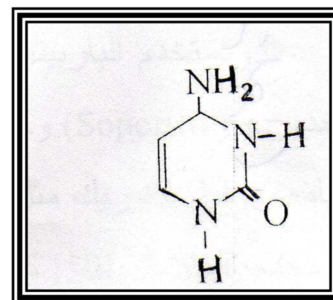
The pyrimidine compounds are stable compounds, colorless, some of them dissolved in water, and some of them have a high boiling point because being the polarization is important in biologinate Thymine (A), Uracil (B), and cytosine (C).[30].



(A)

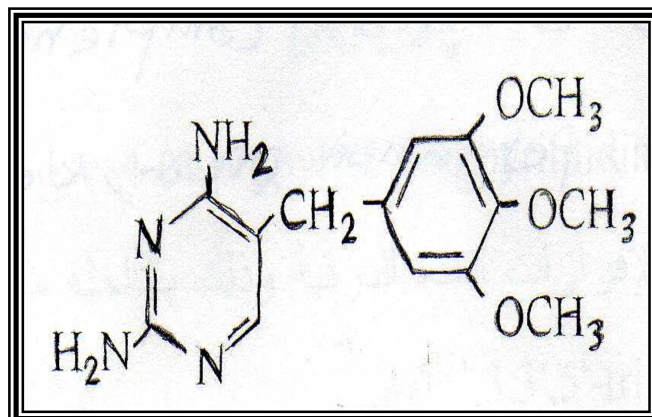


(B)



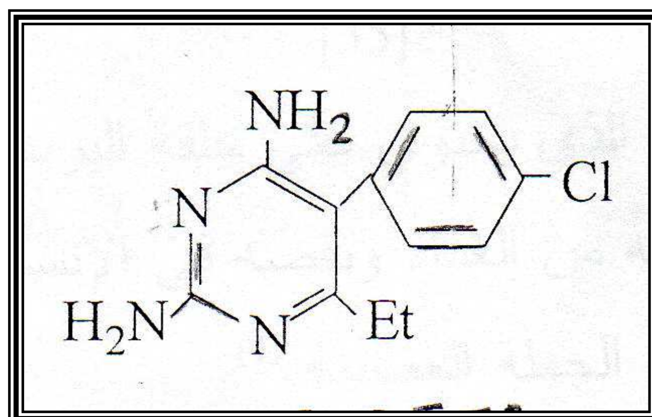
(C)

The Trimethoprin compounds have a biological activity as antibacterial.[42]



(D)

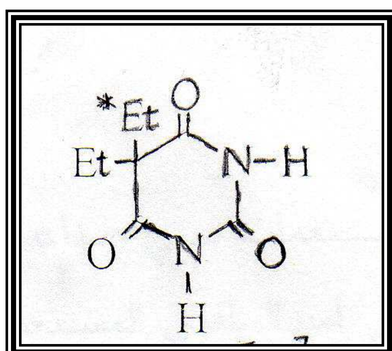
The pyrimidine derivatives that contain chloro group in the structure have been used as antivirus, and atifungi, such as compound 2,4-diamino-6-ethyl-5-(P-chloro phenyl) pyrimidine (E)[55].

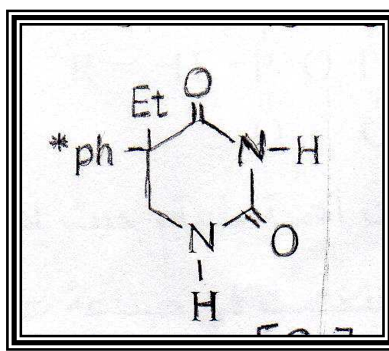


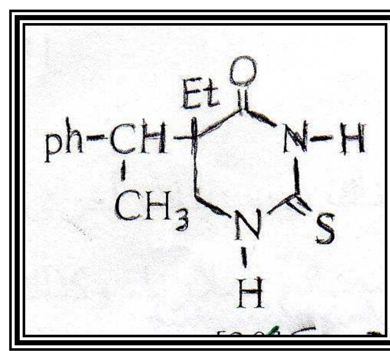
(E)

The compounds

The pyrimidine derivatives (F,G,H) are used as (Hyponotic).

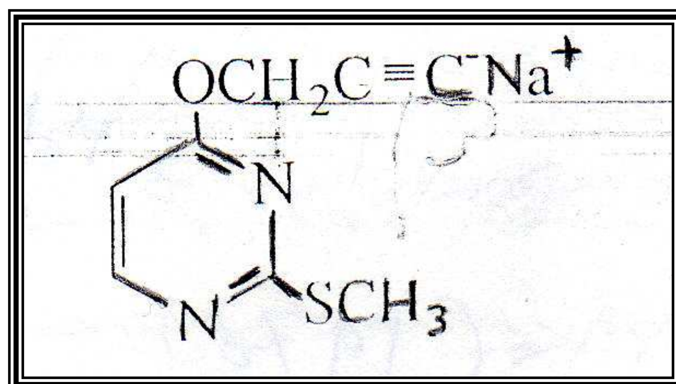






(F) **(G)** **(H)**

The compound (I) has a biological activity as antifungal, and antibacterial.[70]



(I)

1-5 Fungi :

Most people are familliar with infections and diseases caused by bacteria and viruses , but many are unaware that there is a whole set of disorders related to infections by fungi (singular :fungus). [86,87].

Many of these fungal infections affect the skin.Doctors give some fungal infections of the skin the general name "tinea". Superficial fungal infections are found in the top layers of the skin and mucous membranes , the hair , and the nails [89]. Examples of fungal infections of the skin and other external surfaces include athlete's foot , jock itch, ringworm , and candida . These can affect the hair and nails as well . Deep fungal infections invade deeper layers of the skin and hair follicles and can spread to the blood or internal organs [90,91]. Fungi are a uniqe group of organisms that have some plant-like characteristics . Examples of fungi include mushrooms , mold , and yeast . Fungi differ from plants , however , in two major ways :

1- Their cell walls are made of chitin , rather than cellulose .[92]
2- They lack the ability to make their own on food by photosynthesis , thus they grow directly on their food source [93].

Some fungi are simple one-celled organisms . others are relatively complex , exhibiting specialized cell functions . They grow in soil, on living and dead plants trees , as well as on animals and humans . The reproductive cell , or spore of a fungus can be spread by direct contact , air , and water. [94,95,96].

Fungi are multicellular eukaryotes that are heterotrophic by absorption . After external digestion , they absorb the resulting nutrient molecules.[86].Most fungi act as saprotrophic decomposers that aid the cycling of chemicals in ecosystems. Some fungi are parasitic , especially on plants , and others are symbiotic with roots and algae.[97].

Fungi cells are quite different from plant cells not only by lacking chloroplasts but also by having a cell wall that contains chitin and not cellulose . chitin , like cellulose , is a polymer of glucose organized into microfibrils .[98,99].

In chitin , however each glucose molecule has a nitrogen containing amino group attached to it . Chitin is also found in the external skeleton of insects and all arthropods .

The energy reserve of fungi is not starch but glycogen , as in animals , fungi are nonmotile , they lack basal bodies and do not have flagella at any stage in their life cycle [100,101].

The body of a fungus is composed of thin filaments called hyphae , which collectively are termed a mycelium .[96].

Fungi require moisture to grow and reproduce .Fungal infection are more prevalent in warm , moist areas of the body , such as the mouth and vagina . Also , sweaty clothes and shoes can enhance fungus growth on the skin .Exposure to fungi is more frequent in communal areas with moisture , such as locker rooms and showers [97].

1-5-1 Pathogenic fungi :

During the past five decades , there has been a significant increase in studies concerning fungal infections in both human and lower animals [102,103]

Historically , adermatophyte –Trichophyton schoenleinii was the first microorganism that was proven to cause an infections disease of humans .Although fungal infections of the skin were (and still are) regarded as the most common and relatively beginning of disease , their profile has taken a new and direr aspect reflected in new pathological conditions [19].

Dermatophytes are capable of infecting nails and the skin from almost any body sites [48].

Dermatophytes are infections of keratinized tissue , that is , the epidermis , hair and nails , caused by a group of specialized fungi .In general , the dermatophytes donot invade subcutaneous or deep tissues. [104,105,106].

Dermatophytoses refer to infections of the skin , nails or hairs that are caused by fungi classified as dermatophytes .Normally ,it is not considered that dermatophytic fungi can cause systemic disease , with only one minor exception , none of these fungi can grow at 37°C .[107,108]

The dermatophytic fungi include numerous species of fungi which contained in three major general [109]. These organisms occur world wide , mainly in soil and on certain animals [20].

Fungal infections of skin can be classified according to their sites of infection , into the following three group: [110,111]

1- superficial infection caused by fungi capable of utilizing keratin for their nutrition and invading such keratinized tissue as the stratum corneum of the skin , nails hair [112].

2- Cutaneous and subcutaneous infections produced by various moulds and yeasts which are usually acquired through traumatic implantation .[113].

3- Cutaneous manifestations of lif –threatening visceral or systemic fungal infection in immunologically competent or immuno compromised patients caused by dimorphic fungi and other opportunistic fungal pathogens [114].

The dermatophytes species can be categorized on an ecological basic as being geophilic, zoophilic or anthrophilic [115,116].The geophilic species are those natural habitats in the soil . Natural habitats of the zoophilic dermatopytes are domestic and wild animals [117]. The anthrophilic dermatophytes are those species of Epidermophyton , microsporum , and trichopgyton that cannot survive in soil , don't infect lower animals and whose natural habitat is the ketatinous tissues of the human body [118,119,120] .

1-5-2 Trichophyton rubrum :

Trichophyton rubrum occurs world wide because of the severity and longevity of the disease and its refractactivity to therapy . This organisms causes many problem [97].

Very often Trichophyton rubrum is the cause long –established foot and nail infections . Trichophyton rubrum may also cause tinea corporis .[94].

Skin lesions caused by Trichophyton rubrum often have a red margin , the central portion may appear to be relatively clear , although scaling may be apparent . on rare occasions , this organisum may cause tinea capitis . Infected hairs do not fluoresce and hair invasion is endothrix .primarily , these organisms are antropophilic [121]. Because cultures of Trichophyton rubrum are quite variable , identification can be

frustrating . This fungus is white and very fluffy and exhibits many aerial hyphae , this downy form is most commonly isolated from cases of chronic tinea pedis and tinea corporis [122]. This white colony is very flat , lacks aerial hyphae and has a pronounced granular appearance [20].

Trichophyton rubrum is the most common isolated from all regions except the scalp . Tinea pedis usually of the moccasin type is the most frequently seen form of disease .[123]

1-5-3 Geotrichum candidum :

Geotrichum candidum produces a rapidly growing , white to cream and smooth or hairy colong on sabouraud agar at 25°C .[24]

Geotrichosis has traditionally been defined as an infection caused by geotrichum candidum . The geotrichosis cases are based merely upon the isolation of the fungus from sputum and the etiologic relationship of geotrichum candidum to this disease has not been documented .

Because geotrichum candidum is ubiquitous in man's environment and on his food , more isolation of the fungus from the sputum or stool does not establish the diagnosis .In some bronchitis or tracheitis cases, white or patches were seen lining the trachea and bronchi by tronchoscopy and only geotrichum candidum grew from the blood – tinged sputum or from the scrapings of the patches [125]. These appear to be a growth of geotrichum candidum on a previously damaged mucosal surface .There are a few case reports of fungemia due to geotrichum , but whether the fungus geotrichum candidum is doubtful.[126].

Fungemia by geotrichum candidum has been reported following bronchoscopy in a patient with bronchogenic carcinoma [127].

Geotrichum candidum is belived to be part of the normal flora of human skin and gastrointestinal tract. Geotrichum candidum is frequently

isolated from milk and is recorded as a spoilage organism on dairy products . The fungus is found on a variety of fruits and vegetables [125].

Geotrichum candidum is a significant pathogen of citrus fruits during post tharvest storage ,causing sourrots . It occurs in fruit weakened by over maturity and long storage .Lemons and grape fruits are particularly susceptible , but a variety of other fruit can also be affected . Initial infection is mainly through injuries . Geotrichum candidum causes spoilage of tomatoes , dried capsicums and sapodillas intropical countries.A wide variety of vegetables including carrots , cucmbers , onions and potatoes are also susceptible [129].

1.6 Aims of the work :

The present work aims at the following:

1- synthesizing of 1- acety -4-[4-[[2-(2,4- dichloro pheny) -2- (1H – imidazole -1- methyl) -1,3-dioxolan -4-yl] methoxy]phenyl] piperazine(1G) .

2- synthesizing of ethyl -4- amino benzoate (2a) .

3- synthesizing of 2- Thioacetic -5- (4- amino phenyl)1,3,4-oxadiazole (2E).

4- synthesizing of 6-methyl -4- oxo-1,2,3,4- tetrahydro-2- thiopyrimidine (4G) .

5- synthesizing of 2- hydrazine -6-methy pyrimidine -4- (3H) one (5G) .

6- studying the effect of compounds (1G,6G,2a, 4G, and 5G) on the growth of Trichophyton rubrum in potato dextrose agar.

7- studying the effect of compounds (1G,6G,2a,4G and 5G) on the growth of geotrichum candidum in sabouraud agar.

8- determining the qualitative differences of colonial diameter between Trichopyton rubrum and geotrichum candidum in the different time of incubation .

9- carrying out astatistical calculation of standard error of colonial diameter of fungi affected by new compounds (1G,6G,2a,4G, and 5G).

Chapter Two

Experimental

2.1 Chemicals:

The following chemicals have been used directly from their mentioned suppliers without any further purification :

Table 2.1 chemicals and their manufactures .

Material	Supplied from
2,4 dichloracetophenone	BDH
Glycerine	BDH
P-amino benzoic acid	BDH
Ethanol	BDH
Hydrazine hydrate	BDH
Sodium hydroxide	Fluka
Pyridine	Merch
h-butanol	BDH
$MgSO_4$	Fluka
HCL	Fluka
Benzene	Fluka
Potassium hydroxide	Merch
Carbon disulfide	BDH
Chloro acetic acid	BDH
Benzoyl chloride	Fluka
P-toluene sulfonic acid	BDH
Chloroform	Hopkin and williams
Methanesulfonyl chloride	Fluka
Dioxane	BDH
Ethyl acetoacetate	Fluka
Hydrochloric acid	Merk
Imidazole	BDH
Agar	Oxoid
Peptone	Oxoid
Glucose	BDH
Sucrose	Sigma

2.2 Instruments:

All instruments used in this study are listed in table (2.2) .

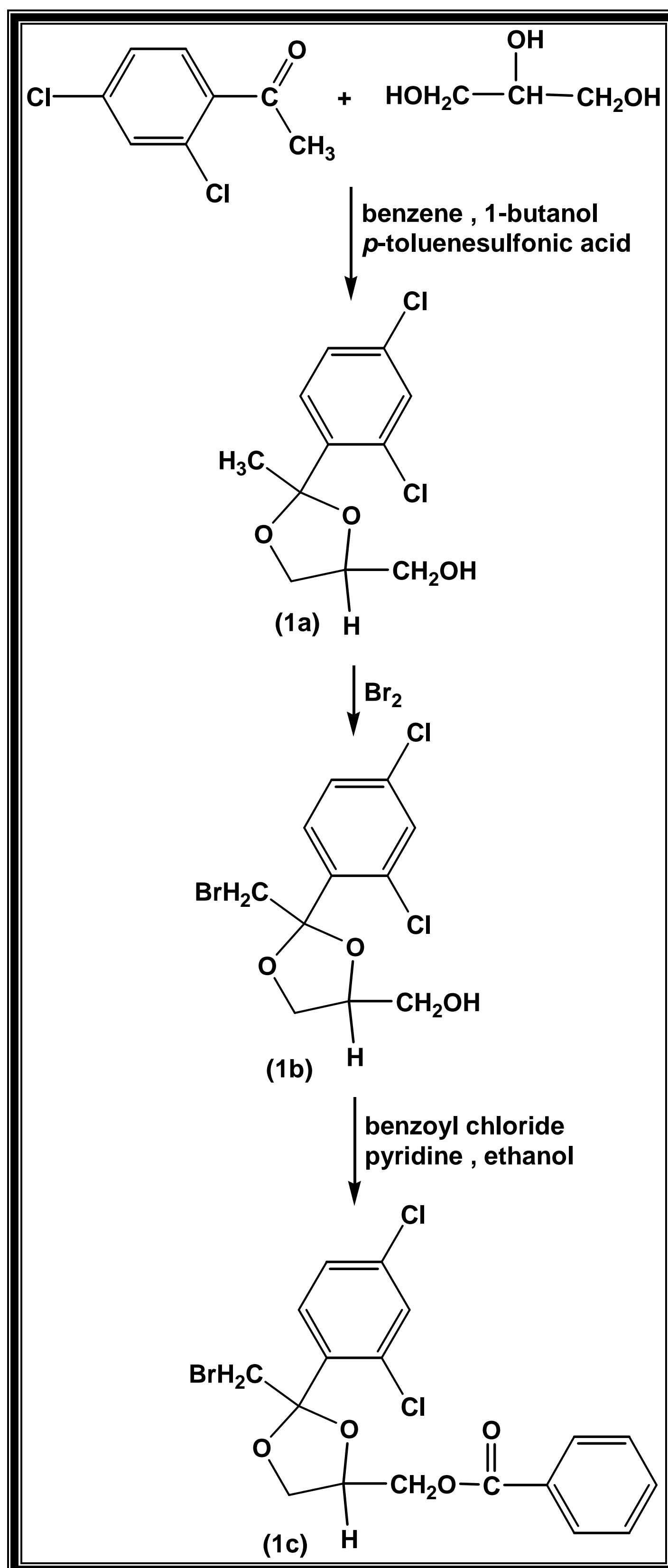
Table 2.2 Instruments and their manufacturer company .

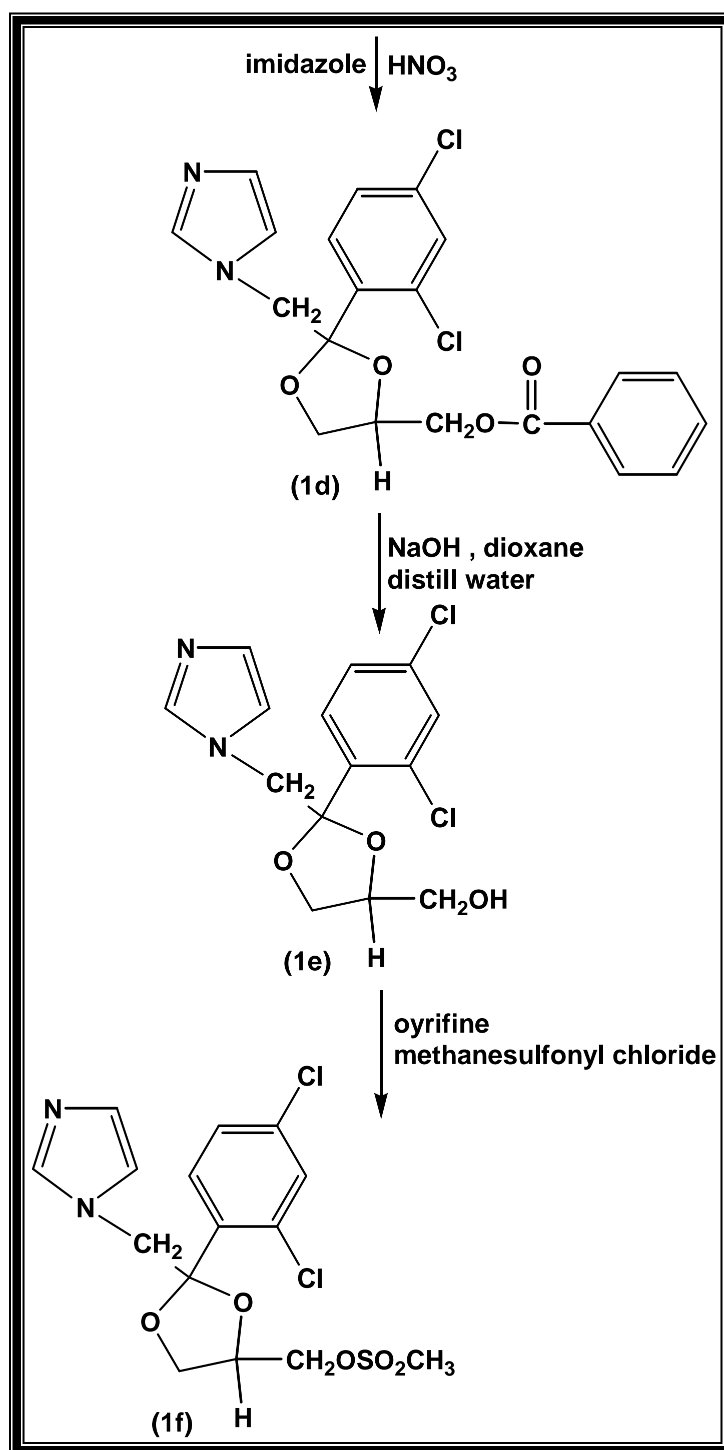
Instruments	Company
Fourier transform infrared spectrophotometer (FTIR)	**Shimadzu**
Melting points	**Gallen kamp melting point apparatus (U.K.)**
PH meter	**Pye unicam**
Cooling centerfuge, with a maximum speed 5000 r.p.m	**MSE**
Memmert water bath memmert incubator	**Gallen kamp**
SM- Shaker	**Branson**
Vaccum pump	**Edwards , 50 Hz (England)**
Rotary evaporator	**Buchi 461**
Autoclave	**Gallen kamp**
Electric balance	**Mettler (Switzer land)**
Electric oven	**Gallen kamp**
Personal computer PIII	**Gallen kamp**
Matlab V5.3 sftware	**Microsoft**

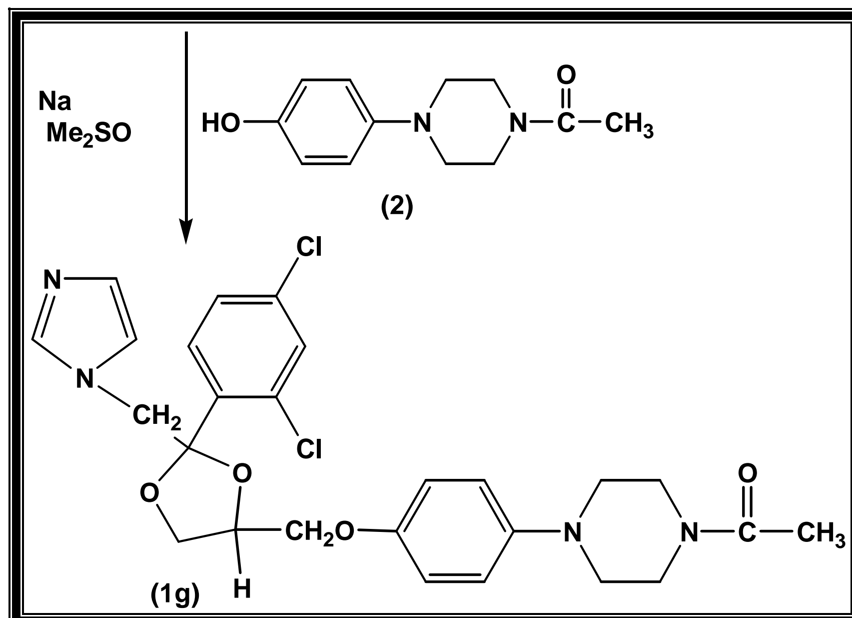
2.3. Preparations:

2.3.1 Perparation of compound 1- acetyl -4- {4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazole-1-yl-methyl)-1,3-dioxolan-4-yl] methoxy]phenyl]piperazine (1_G):

This compound was prepared as shown in the following scheme and as described below :


O
OH
Cl
C
+
HOH2C—CH—CH2OH
CH3
Cl
benzene , 1-butanol
p-toluenesulfonic acid
Cl
H3C
Cl
O
O
CH2OH
(1a)
H
Br2
Cl
BrH2C
Cl
O
O
CH2OH
(1b)
H
benzoyl chloride
pyridine , ethanol
Cl
BrH2C
Cl
O
O
O
CH2O—C
(1c)
H


imidazole
HNO3
Cl
N
N
CH2
Cl
O
O
O
CH2O—C
(1d)
H
NaOH , dioxane
distill water
Cl
N
N
CH2
Cl
O
O
CH2OH
(1e)
H
oyrifine
methanesulfonyl chloride
Cl
N
N
CH2
Cl
O
O
CH2OSO2CH3
(1f)
H



Scheme (2.1): Perparation of compound 1- acetyl -4- {4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazole-1-yl-methyl)-1,3-dioxolan-4-yl] methoxy]phenyl]piperazine (1_G)[132]

2.3.1.1 2- (Bromomethyl)-2-(2,4-dichloro phenyl) 1,3- dioxolane-4-methanol (1_b):

Glycerine (110g ,1.2ml) and 2,4-dichoroacetophenone (189g,1mol) in 400ml of benzene and 200ml of n-BuoH were refluxed in the presence of p-toluenesulfonic acid monohydrate (6g) for 24hrs.After cooling the mixture to 40°C , bromine (192g,1.2mol) was added dropwise over a period of 2hours . The mixture was stirred for 0.5 hour then evaporated in vaccum .The residue was dissolved in CH_2CL_2 washed with NaOH solution (200ml) , dried (MgS04) , and evaporated a gain in vaccum to give compound (1_b) (91% yield).

2.3.1.2 [2-(Bromomethyl) -2- (2,4-dichlorophenyl) 1,3-dioxolan -4-yl] methyl Benzoate (1_C)

Benzoyl chloride (140.5g,1mol) was added dropwise at 5°C to solution of (1_b) (311.2g, 0.91mol) in 600ml of pyridine over a period of 1 hour .The mixture was stirred for 2.5 hour and diluted with water .After the extraction of the mixture with chloroform, the organic layer was washed with HCL , dried (MgS04) and evaporated in vaccum to leave an oily residue with solidified on stirring methanol , giving (1_C) (50% yield) (m.p.=118.3°C).

2.3.1.3. [2-(2,4-dichlorophenyl) -2- (1H-imidazole -1-yl methyl)1,3 – dioxolan -4-yl] methyl Benzoate Nitrate (1_D):

A solution of (1_C) (220g,0.492 mol) was refluxed with excess of imidazole (100g,1.476 mol) for 4days . The reaction mixture was cooled , diluted with water , and extracted with ether . The organic layer was dried (Mg504) and treated with HNO_3 65%
Filtration of the precipitate gives (1_C) (55% yield)(m.p.=172°C).

2.3.1.4 2-(2,4-Dichloropheyl) -2- (1H-imidazole -1- ylmethyl)-1,3-dioxolane -4- methanol (1_E):

A solution of (1_D) (131g,0.264mol)in 1000ml of dioxane and 200ml of H_2O was refluxed with 200ml of 50% NaOH for 0.5hr . Then the reaction mixture was cooled. The product crystallized on dilution with H_2O , and the precipitate was filtered and taken up in chloroform . The solution was evaporated in vaccum to give (1_E) (96%yield) (m.P.=140°C).

2.3.1.5 [2-(2,4-dichlorophenyl)-2-(1H-imidazole -1-ylmethyl) -1,3-dioxolan -4-yl] methyl methanesulfonate (1_F).

To a solution (1_E) (10g,o.03 mol) in pyridine (50ml) methanesulfonyte chloride (5g) was added dropwise over a period of 20 min while cooling in ice.The reaction mixture was stirred for 5 hour .Then H_2O was added and the product crystallized out ,The solid was filtered to give compound (1_F) (87% yield) (m.p.=111.7°C).

2.3.1.6 1- acetyl -4- [4-[[2-(2,4-dichlorophyenyl)-2-(1H-imidazole -1-ylmethyl)-1,3-dioxolan -4-yl]methoxy phenyl] piperazine (1_G):

To a suspension of NaH (50%) dispersion (0.6g) in (Me_2SO), solution (1_F) (2.4g) was added .After stirring the suspension for 1 hours , compound (2) (4.1g) was added and stirring was continued for 5 hours at 80°C. The reaction mixture was cooled and water added . After extraction of mixture with CH_2CL_2 , the organic layer was dried ($MgSO_4$) and evaporated to afford an oil residue , to give compound (1_G) (59%yield)(m.p.=146C°).

2.3.2 preparation of ethyl -4-aminbenenzoate (2_a).

This compound was prepared according to the method described in literature [133], as follows :

Dry hydrogen chloride was passed , (which was prepared by the reaction of conc. H_2SO_4 with fused ammonium chloride in a kipps apparatus), through 80 ml of absolute ethanol in a 250ml conical flask equipped a two –holed cork and wash –bottle tubes until saturated , the increase in weight was about 20g . The solution was transferred to a 250ml round bottomed flask , 12g of p-amin benzoic acid (o.o8 mol) introduced , and the mixture was refluxed for 2hrs. The hot solution was poured into excess of water and sodium carbonate was added to the clear solution

until it is neutral to litmus . The precipitated ester was filtered off at the pump and dried . The yield of ethyle –p-amino benzoate , (m.p.=89-91°C) was 70%

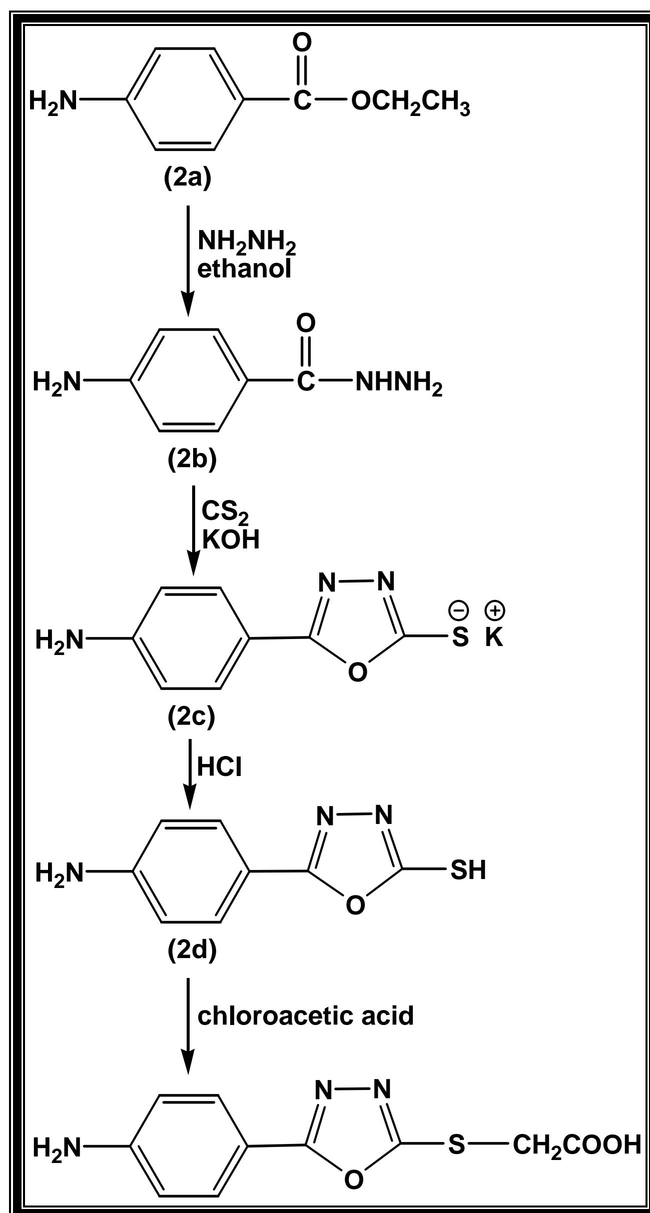
2.3.3 Preparation of 2-thioaceticacid -5- (4-amino phenyl) 1,3,4-oxadiazole (2_E). [133]

A mixture of ethyl -4- amino benzoate (0.1mol) and hydrazine hydrate (0.1mol) was refluxed for 2 hours , ethanol (50ml) was added and refluxed for 5 hours .

The precipitate benzoyl hydrazine which separated on cooling was filtered and washed with cold methanol. To a solution of benzoyl hydrazine (0.02 mol) in ethanol (100ml) at (0°C) carbon disulfide (0.04 mol) and potassium hydroxide (0.02mol) were added , the mixture was refluxed for 7 hours .The solvent was evaporated and the residue dissolved in water and acidified with dilute hydrochloric acid .

The precipitate was filtered and crystallized from (ethanol –water) to give 2- mercapto -5- (4-amino phyenyl) 1,3,4-oxadiazole which react with one equivalent of chlooracetic acid in the presence of KOH as a basic media to give 2- thioactic acid -5- (4-amino phenyl) 1,3,4-oxadiazole (m.p.=102-104°C).

The steps of the preparation of 2-thiocacetic acid -5-(4-amino phenyl) 1,3,4 oxadiazole can be shown in scheme (2.2).



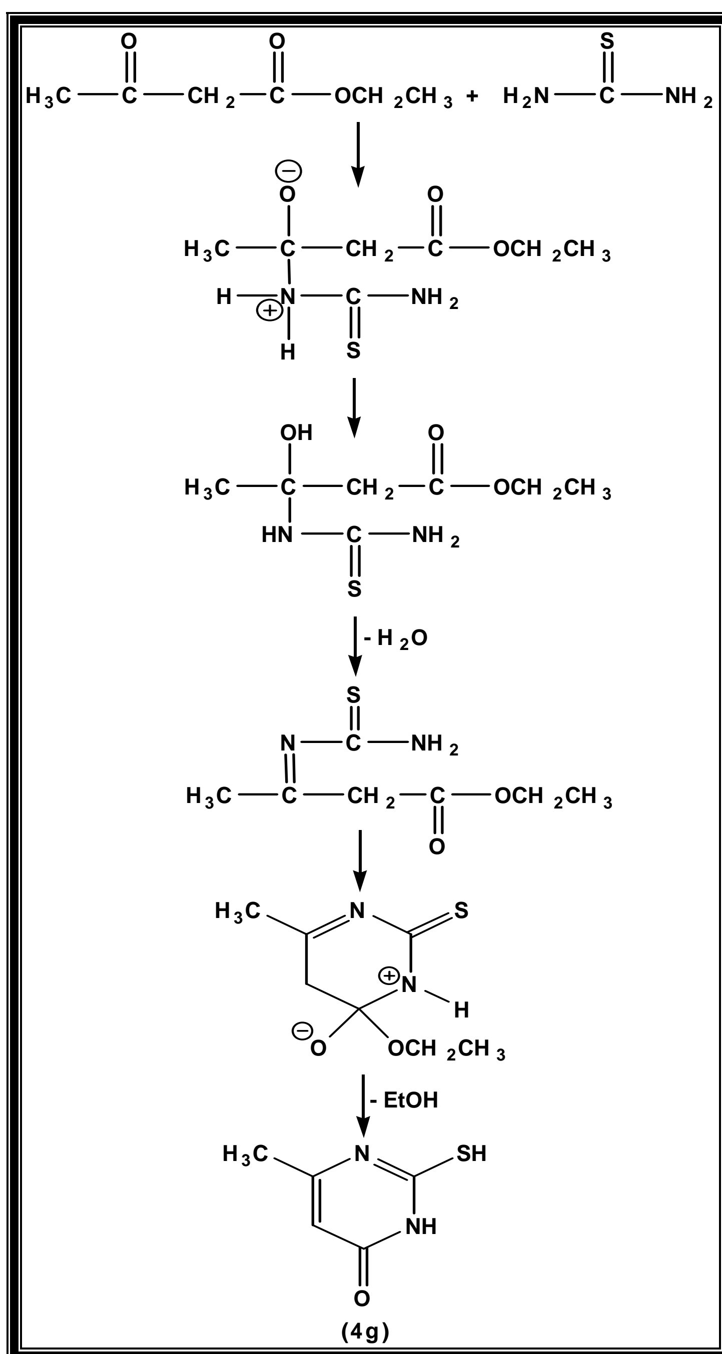
Scheme (2.2): Preparation of compound 2- thioactic acid -5- (4-amino phenyl) 1,3,4-oxadiazole (2_E)

2.3.4 Preparation of 6-methyl -4- oxo-1,2,3,4-tetrahydro -2-thiopyrimidine (4_G).[134].

Addition of sodium hydroxide (0.16mol,6.5g) with water (4ml and stirred gradually with a mixture of thiouria (0.1mol, 7.6g) and ethylacetoacetate (0.1mol,15.2g) in ethanol (10ml).

The mixture was refluxed for 2 hours , the residue was acidified by adding the hot solution of hydrochloricacid (20ml) , finally cooling the residue.The white precipitate was filtered to give 6- methyl -4-oxo-1,2,3,4 –tetrahydro-2- thiopyrimidine (93% yield) (m.p.=298-300C°).

The steps of the preparation of 6- methyl -4- oxo-1,2,3,4-tetrahydro-2- thiopyrimide can be shown in scheme (2.3).

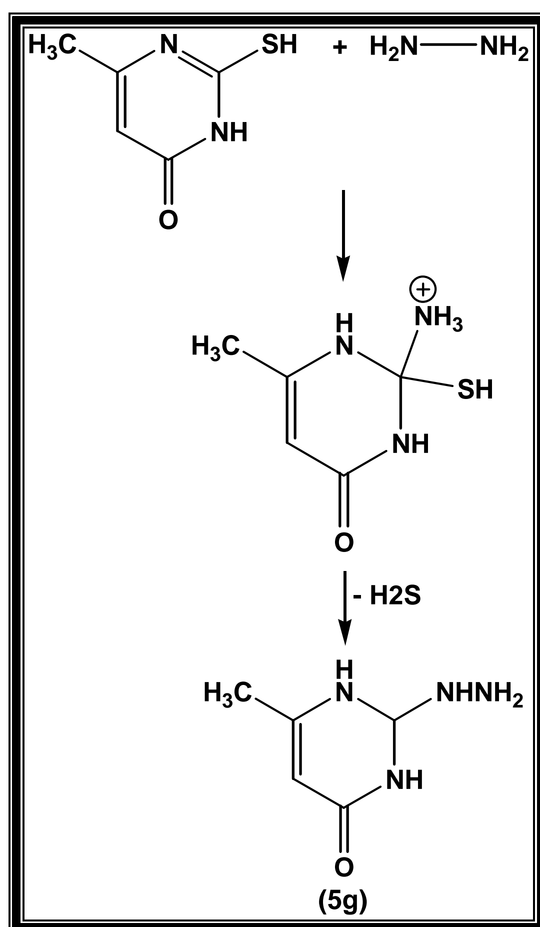


Scheme (2.3): Preparation of 6-methyl -4- oxo-1,2,3,4-tetrahydro -2-thiopyrimidine (4_G).[135]

2.3.5 preparation of 2- hydrazine -6-methyl pyrimidine -4- (3H) one (5_G) [136].

Compound (4_G) was mixed with hydrazine hydrate (99%) , the mixture was refluxed for 3 hours .The mixture was cooled by adding the water .Filtered the precipitate filtered and washed the residue washed by cold water , to give 2- hydrazine -6-methyl pyrimidine -4- (3H) one (5_G) (71%yield) (m.p.=212-215C°).

The steps of the preparation of 2-hydrazino -6-methyl pyrimidine -4-(3H) one can be shown in scheme (2.4).



Scheme (2.4): preparation of 2- hydrazine -6-methyl pyrimidine -4- (3H) one (5_G) [136].

2.4 Mixture of ketoconazole (1_G) with caffeine :

Caffeine is much more soluble in acetone , and ketoconazole in (DMSO).[135].Mix the caffeine that dissolved in acetone with ketoconazole compound (1_G) at the 1.5:1.5 ml .

This mixture (6_G) was prepared at different concentrations in two types of fungals .

2.5 *In vitro* study ;

In this study two types of fungal colonies were used (**Trichophyton rubrum ,Geotrichum candidum**), and two types of culture media used (sabouraud agar and Potato dextrose agar PDA) .

To each flask (50ml of media), except the sixth flask for control , 250µl 500µl, 750µl , 1000µl and 1500µL of the examined compounds (1_G,6_G,2_a,2_E,4_G, and 5_G) were added to give the final concentration 0.005mg/ml, 0.01mg/ml, 0.015mg/ml, 0.02mg/ml and 0.03mg/ml, respectively .For each concentration , duplicate plates were made .A suspension of fungal spores (Trichophyton and geotrichum spores) was made by dissolving 0.01 g of agar in (5ml) of distilled water , autoclaved and a loopful of spores was added to it .A loopful of spore suspension was taken and put at the middle of each plate , incubated at 30C° for 48 hrs ., 72hrs ., and 96hrs .

After each incubation period these plates were checked for fungal growth by determining the diameter of fungal colonies , then the inhibition percent was calculated according to the equation [137]:

$$\text{Inhibitio percentage \%} = \frac{\text{Average of fungal growth in control plate - plates}}{\text{Average of fungal growth in control plate}} \times 100$$

2.6Study of the Antimicrobial Activities :

The microorganisms used for antimicrobial activity include :

No.	Microorganisms	Origin
1-	Geotrichum candidum	Biotechnology Dep., Nahrain university
2-	Trichophyton rubrum	Baghdad Teaching Hospital

2.7 Biological study :

In the current study two types of fungi were tested (Trichophyton rubrum and geotrichum candidum). These fungi were chosen because of their importance in Dermatophyte diseases .

2.8 Procedures:

2.8.1 Sterilization methods [138]:

1- culture media were sterilized by autoclaving at 121°C , 15 pound /in ^{2} for 15 minutes .

2- Glasswares were sterilized in the electric oven 180-200 C° for 2 hours .

2.8.2 Preparation of culture media :

The following culture media were used routinely in our study :

2.8.2.1 Modified sabouraud dextrose agar:

Fungal (Geotrichum candidum) was cultured on modified sabouraud dextrose agar prepared by mixing the following ingredients [139]:

Peptone 10g

Glucose	20g
Agar	20g
Cycloheximide	500mg
Cephalexin	500mg
Distilled water	1000ml

Cephalexin was added to prevent the growth of bacteria , while cycloheximide was added to prevent the growth of saprophytic fungi [140].

2.8.2.1Potato dextrose agar (PDA):

Fungal (Trichopyton rubrum) was cultured on potato dextrose agar (PDA) prepared by mixing the following ingredients [141]

potato	200g
sucrose	20g
agar	15g
cyclohexmide	500m
cephalexin	500mg
distilled water	1000ml

1- two hundered gms of potato were weighted , boiled with 500ml of D.W. and then filtered with gauze .
2- ingredients were added to the potato filterate and the volume completed to 1 Liter with D.W.
3- fifty ml of this media were dispensed into (12) flasks of 250ml and autoclaved at 121C°, pound/in^2 for 15 min .

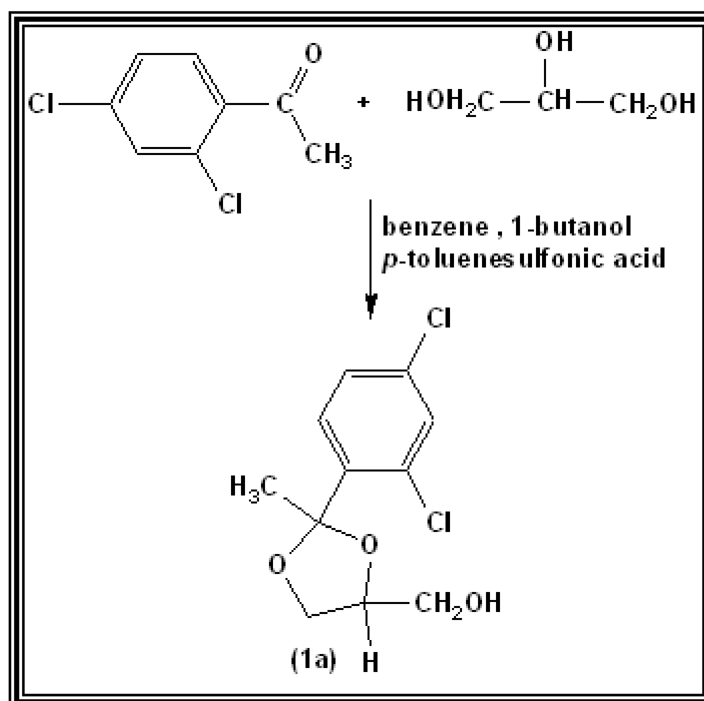
Chapter Three

Results and discussion

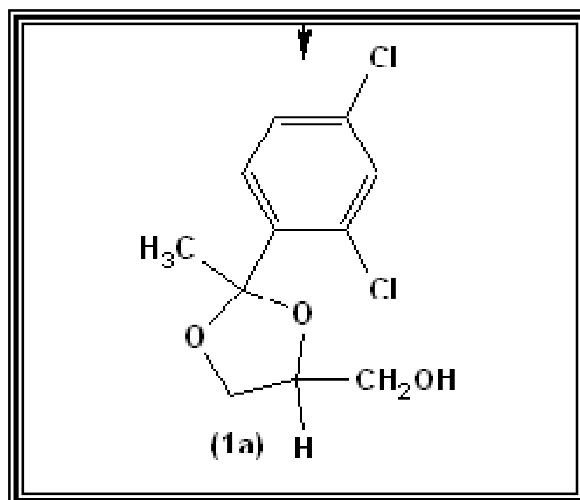
3.1 synthesis and characterization of compound

1-acetyl-4- [4-[[2-(2,4-dichlorophenyl)-2- (1H-imidazole -1- yl-methyl)-1,3-dioxolan -4- yl]methoxy] phenyl]piperazine (1G) [ketoconazole] :

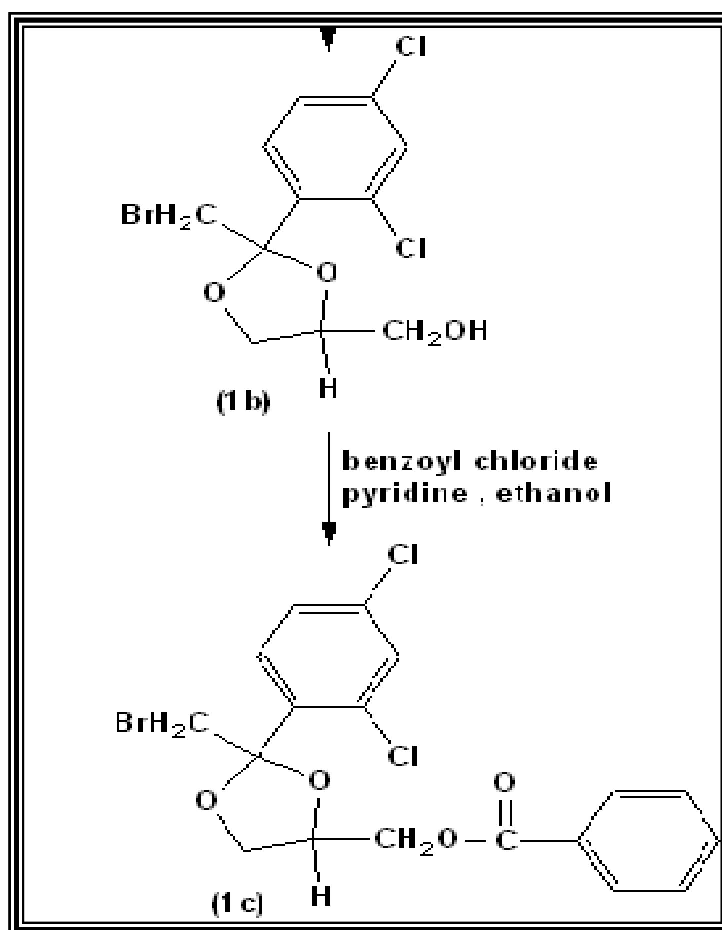
The compound (1_G)was prepared as previously shown in scheme (2.1).
Cis and trans -2- (Bromomethyl)-2- (2,4-dichlorophenyl) 1,3 –dixolane -4- methanol (1_a) was prepared by reflux the glycerine and 2,4 –dichloacetophenone with benzene and butanol in the prescence of p-toluene sulfonic acid monohydrate



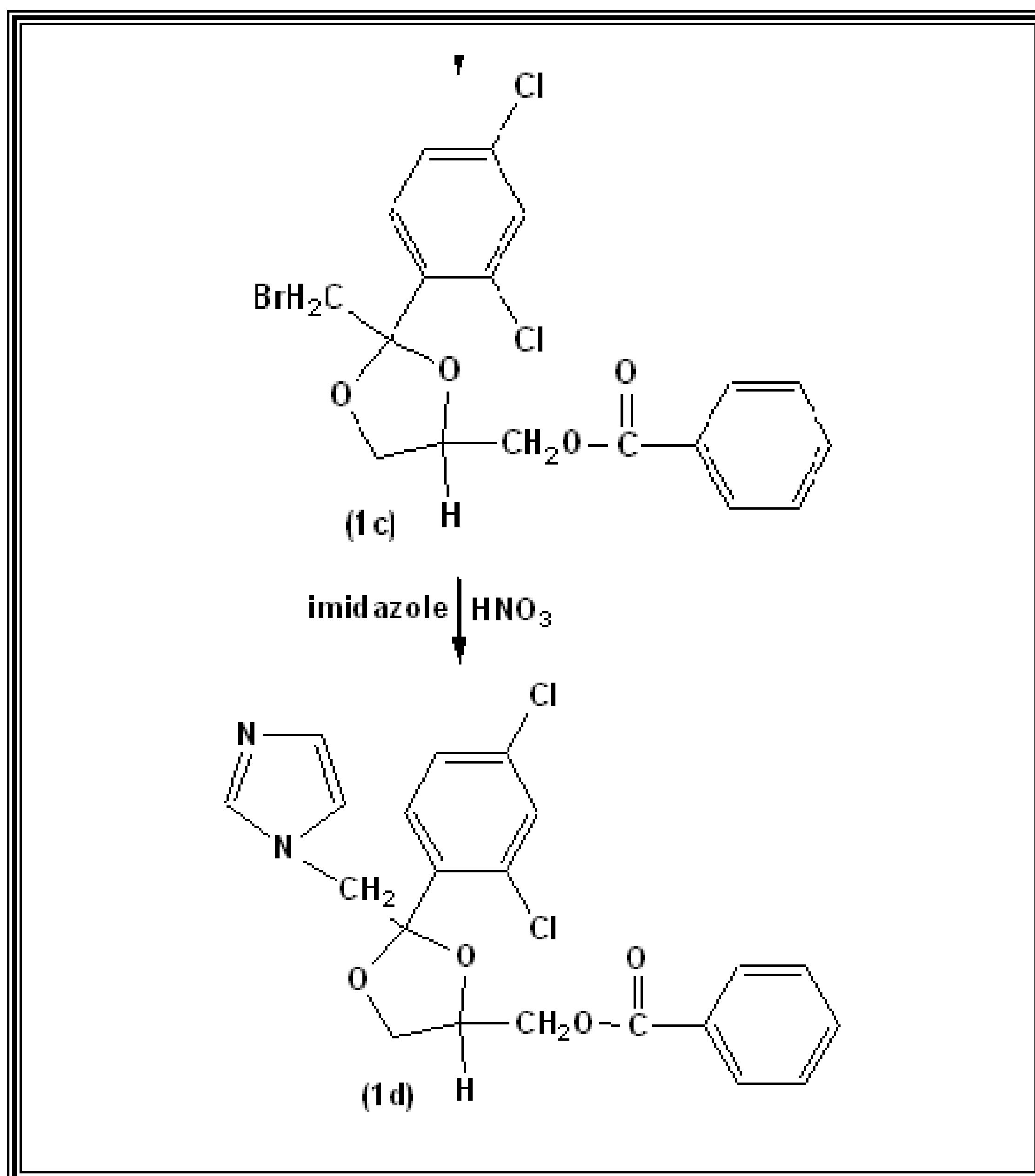
Compound (1_b) was prepared by adding the bromine to compound (1_a)



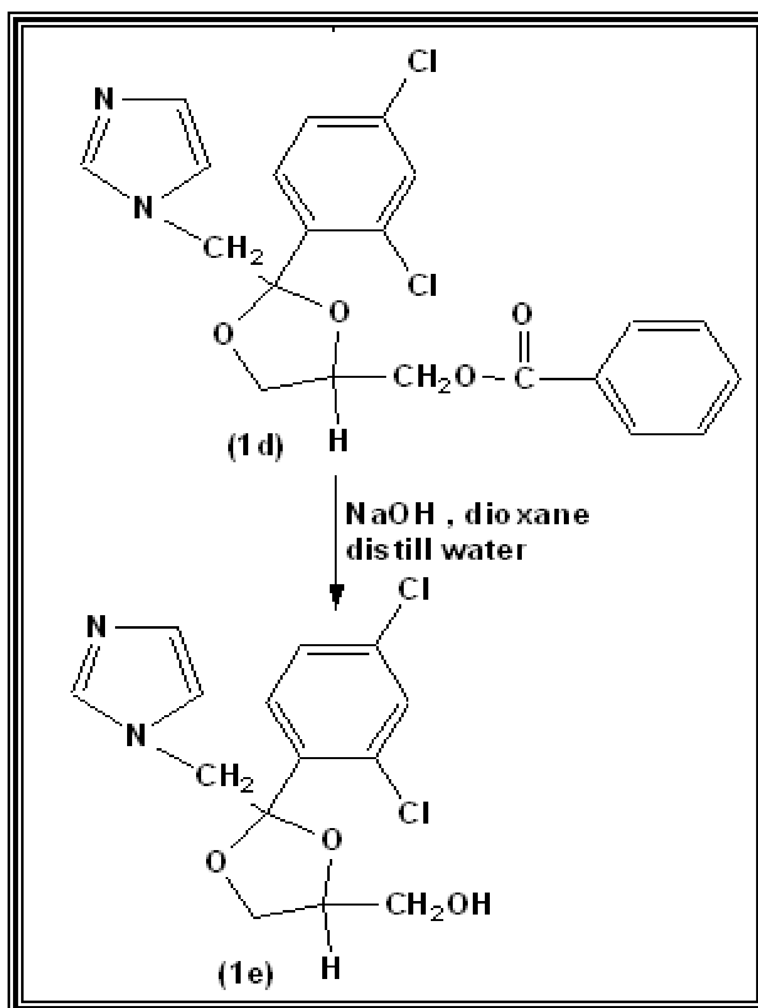
Cis-[2-(Bromomethyl) -2- (2,4-dichlorophenyl)-1,3-dioxolan -4-yl)methyl benzoate (1_c) was prepared by reaction benzoyl chloride and pyridine with compound (1_b) in the presence of ethanol as solvent :



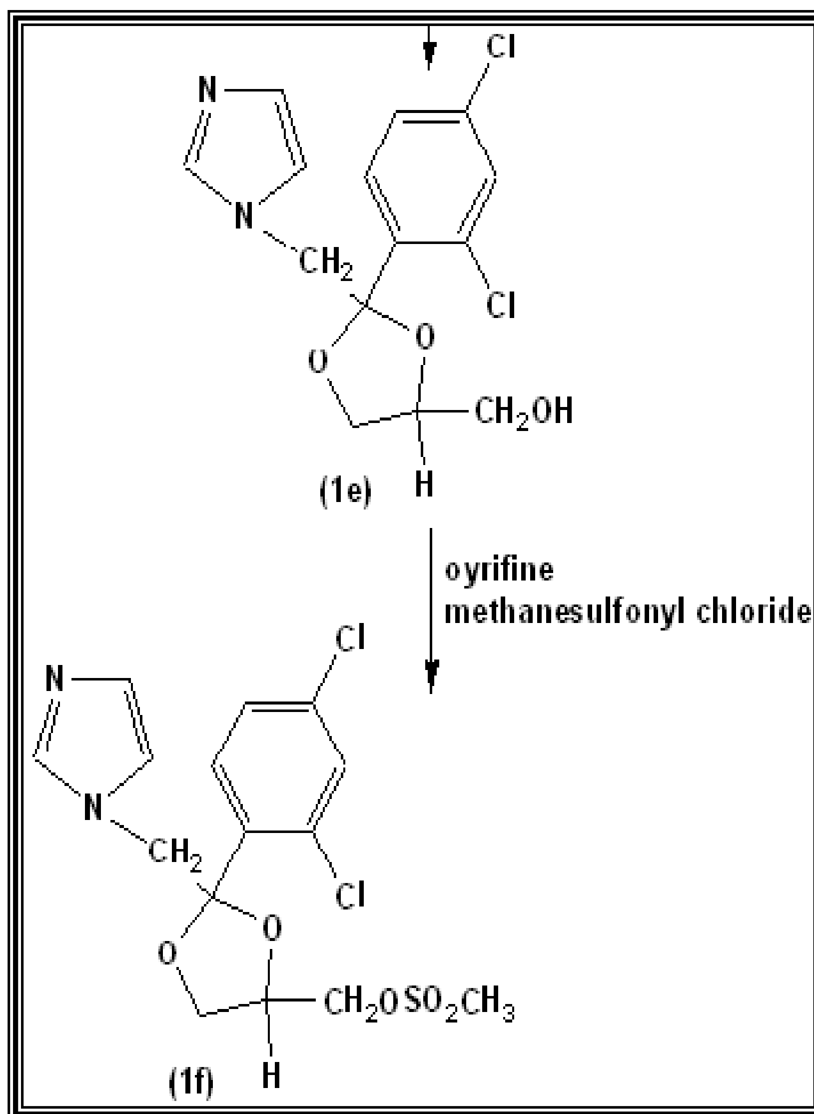
Compound cis –[2- (2,4-dichlorophenyl)-2-(1H-imidazole -1-ylmethyl)-1,3 dioxolan -4-yl] methyl benzoate Nitrate (1_D) was prepared by the reaction of compound (1_c) with imidazole in the presence of 65% HNO_3:



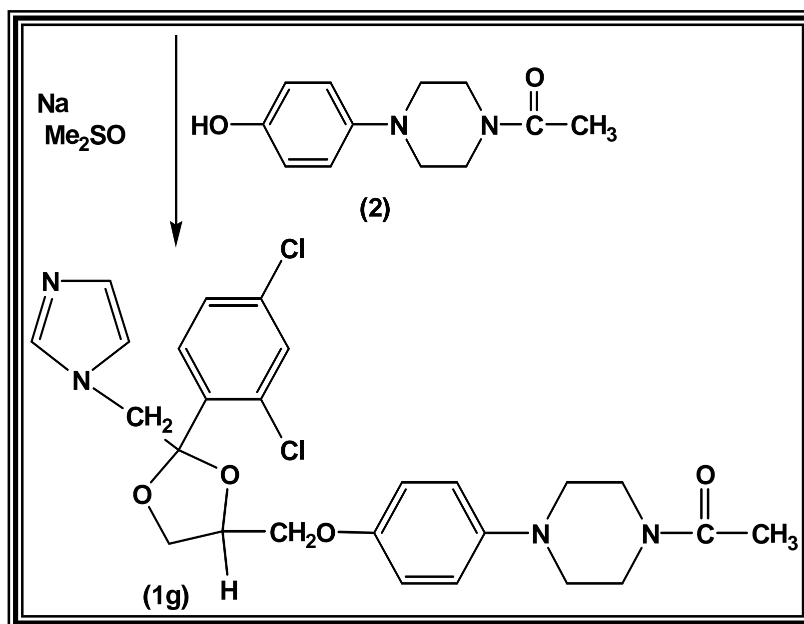
Compound cis -2-(2,4-dichlorophenyl) -2- (1H-imidazole -1-yl methyl)-1,3 –dioxolane - 4 - methanol (1_E) was synthesized by refluxing compound (1_D) with dioxolane and distill water in the presence of 50% NaOH :



The reaction of (1_E) with methanesulfonyl chloride and pyridine yielded cis –[2-(2,4-dichlorophenyl)-2- (1H –imidazole –l-yl methyl)-1,3 –dioxolan -4-yl) methyl methanesulfonate (1_F) as shown below :



Compound cis -1- acetyl-4- [[2-(2,4-dichlorophenyl) -2- (1H-imidazole - 1- yl methyl_ -1,3- dioxolan -4- yl] methoxy] phenyl] piperazine (1_G) was prepared by reaction compound (1_F) with compound (2) and Me_2SO compound :



The melting point of the compound was (142-144C°) , the reported melting point 146C° [135] . It was also identified by FITR spectroscopy . Figure (3.1) showed the FITR spectrum of compound (1_G) using KBr disc which showed the following characteristic absorption bands :Stretching band appeared at 1573cm^{-1} which could be attributed to (C=N) , 1670 cm^{-1} for (C=O) , 2931 cm-1 for (C-H aliphatie) , 821.6 cm^{-1} for (C-CL), 1573cm^{-1} for (C-H) aromatic .

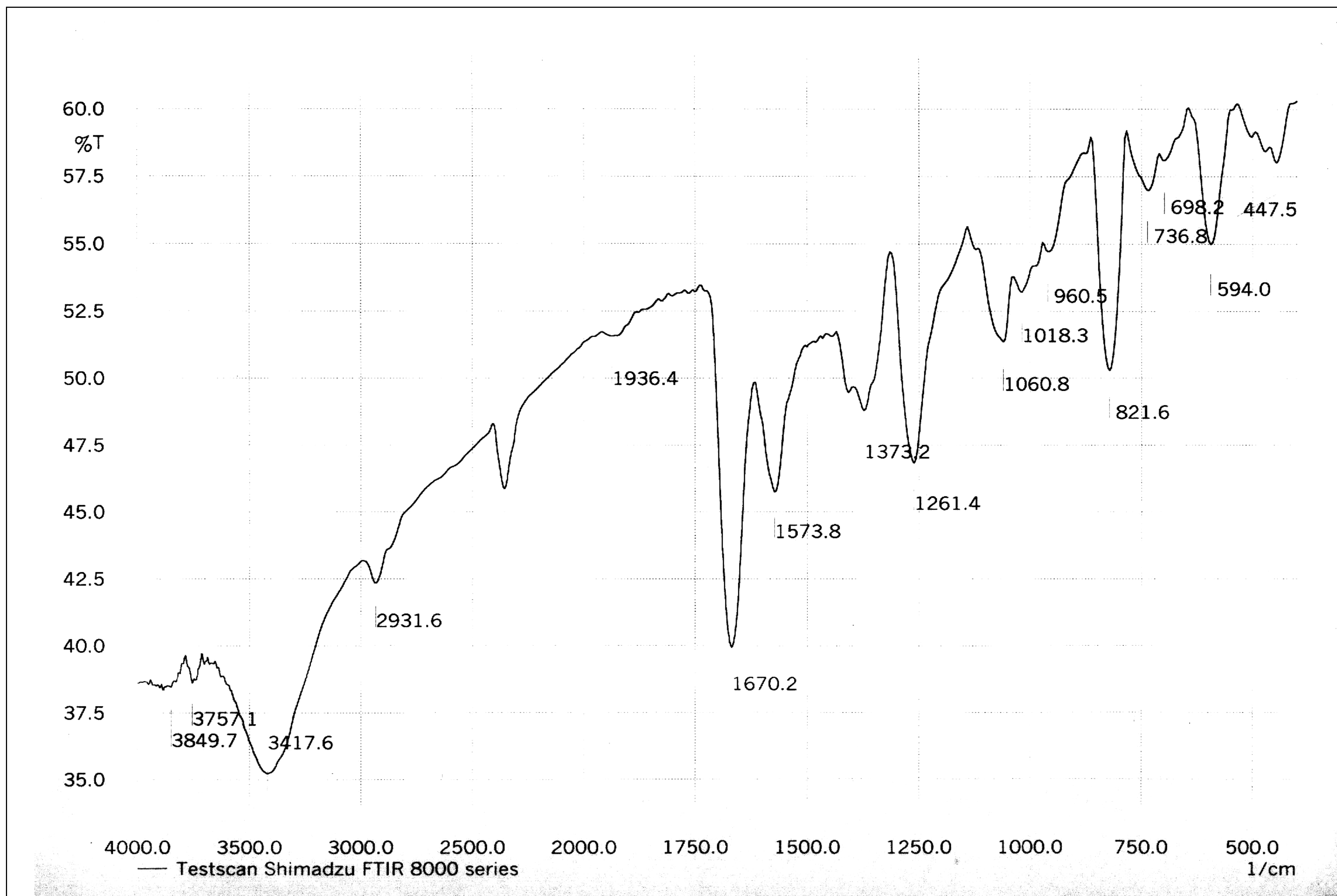
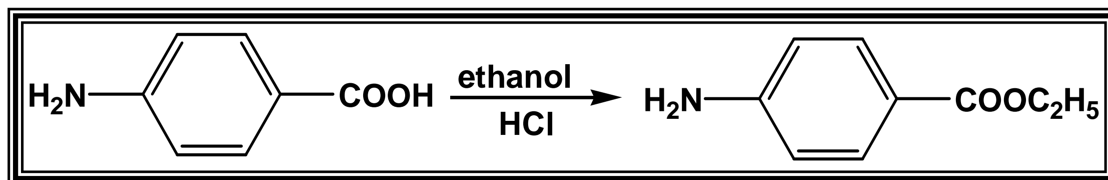


Figure (3-1):F.T.IR spectrum of cis-1-acetyl-4-[4-[[2-,4-dichlorophenyl)-2-(1H-imidazole-1-yl methyl)-1,3-dioxolan-4-yl] methoxy]phenyl]piprazine(1G).

3.2 synthesis and characterization of ethyl -4- amino benzoate (2_G):

Ethyl -4- amino benzoate (2_G) was obtained by condensation reaction of -4- amino benzoic acid with HCL saturated ethanol :



The melting point of the compound 2_G was 89-91C° .

Compound 2_G was characterized by its melting point 89-91C° (142)

This compound has been verified using FTIR , as shown in figure (3.2) the following characteristic absorption bands (KBr dis cm^{-1}) : 3413 and 3334 that could be attributed to NH_2 asymmetrical and symmetrical stretching , respectively , and bands at 2975 ,2891 due to aliphatic C-H stretching , the carbonyl of the ester at 1683 .

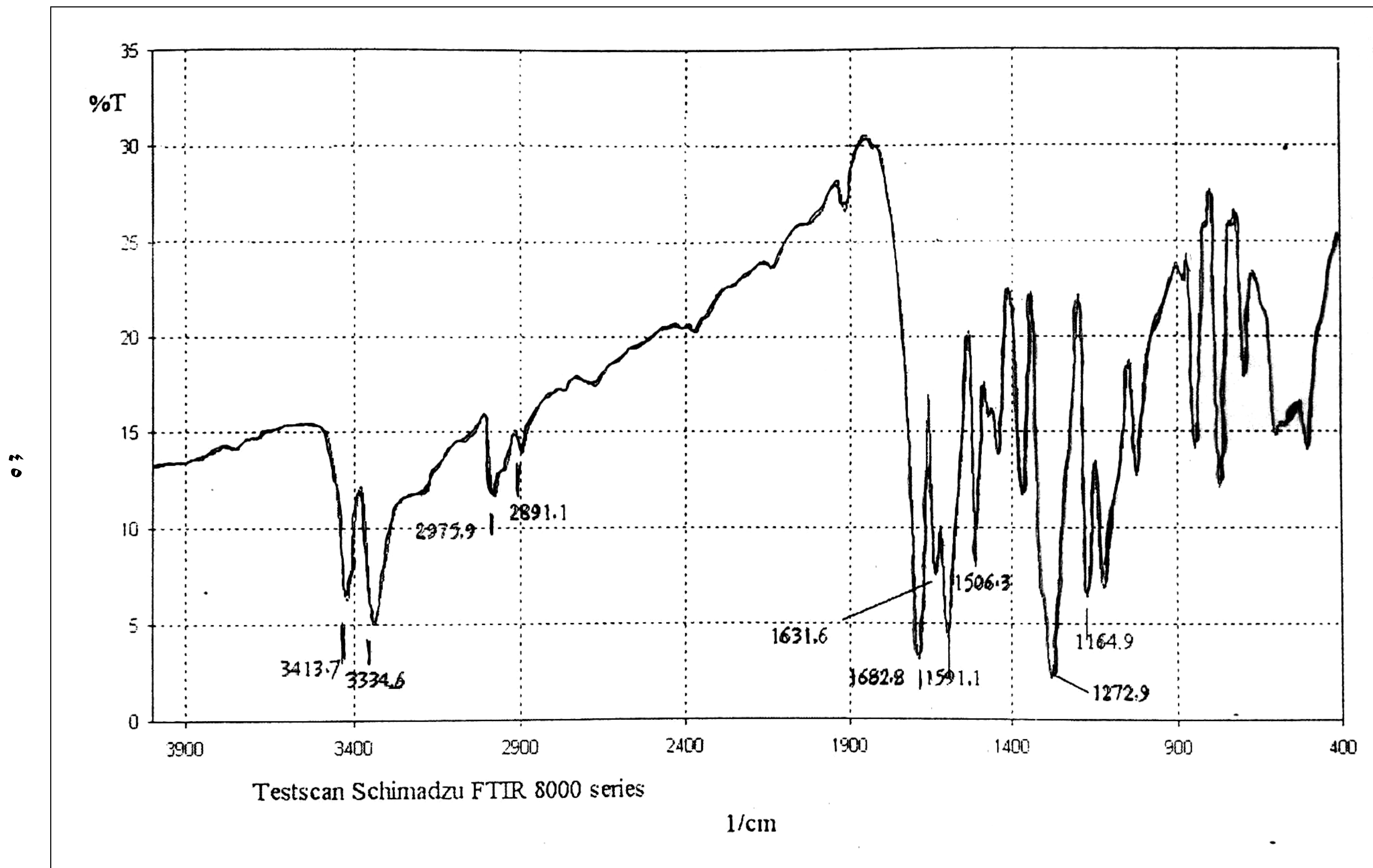
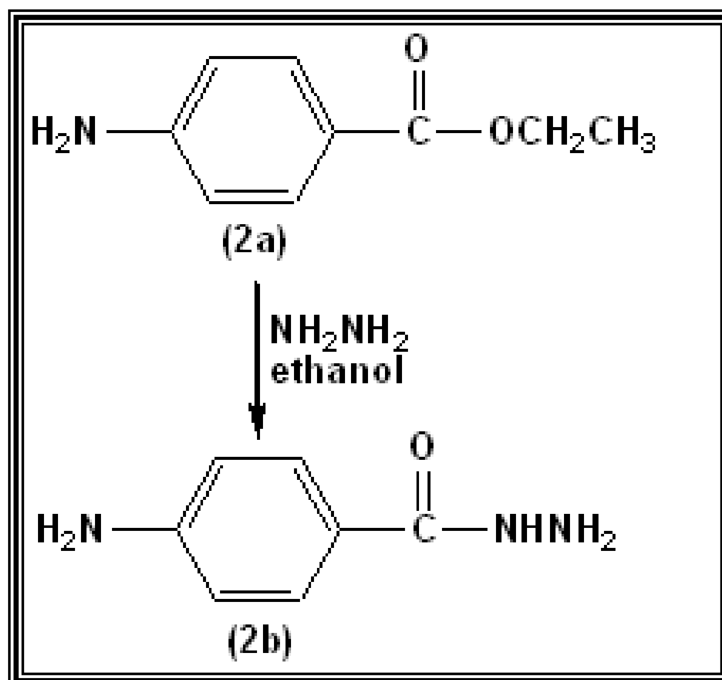


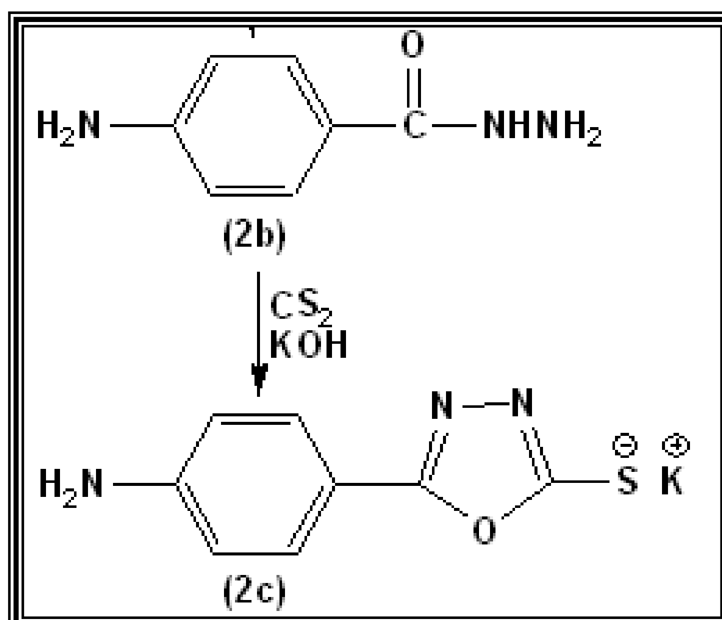
Figure (3-2):F.T.IR spectrum of ethyl-4-amino benzoate (2a).

3.3 synthesis and characterization of compound 2- thioacetic acid -5- (4- amino phenyl) 1,3,4- oxadiazole (2_E) :

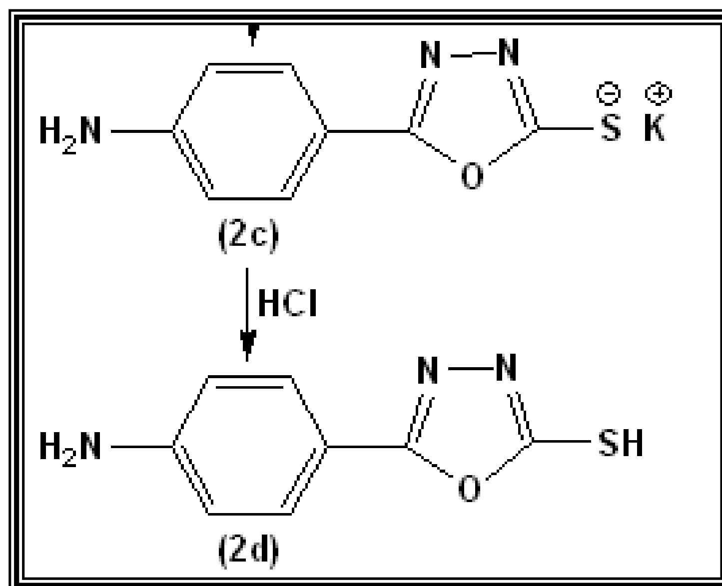
The compound (2_E) was prepared as previously shown in scheme (2.2) . Compound (2_b) was synthesized by refluxing (2_a) with hydrazine hydrate and ethanol :



Compound (2_C)has been prepared by refluxing the compound (2_b) with carbon disulfide in the presence of potassium hydroxide :



Compound (2_D) was obtained by adding the HCL to compound (2_c) .



Compound (2_E) was prepared by the reaction of compound (2_D) with chloroacetic acid :

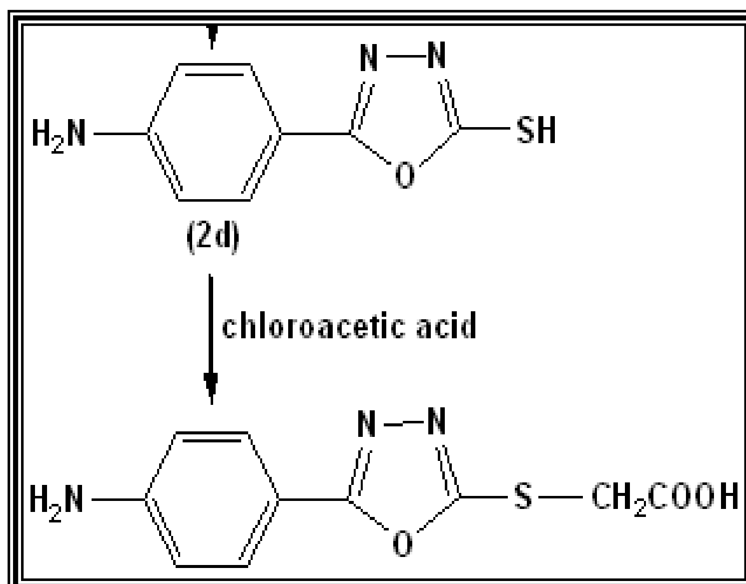


Figure (3.3) show the FTIR spectrum of compound (2E) using KBr disc which showed the appearance of band at 2740 cm^{-1} for (S-H) and appearance of band at 1350 cm-1 for (C=S) stretching .

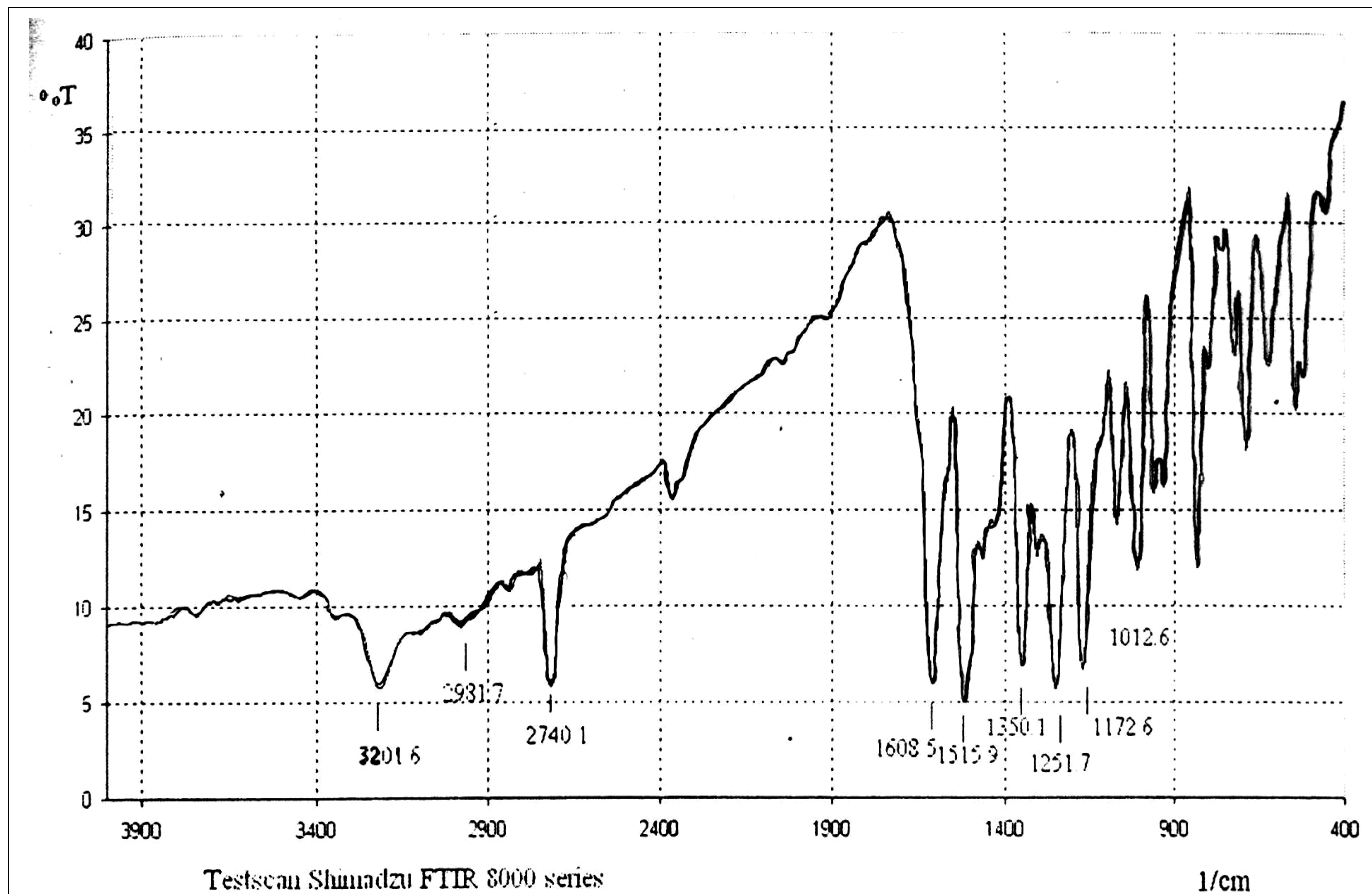
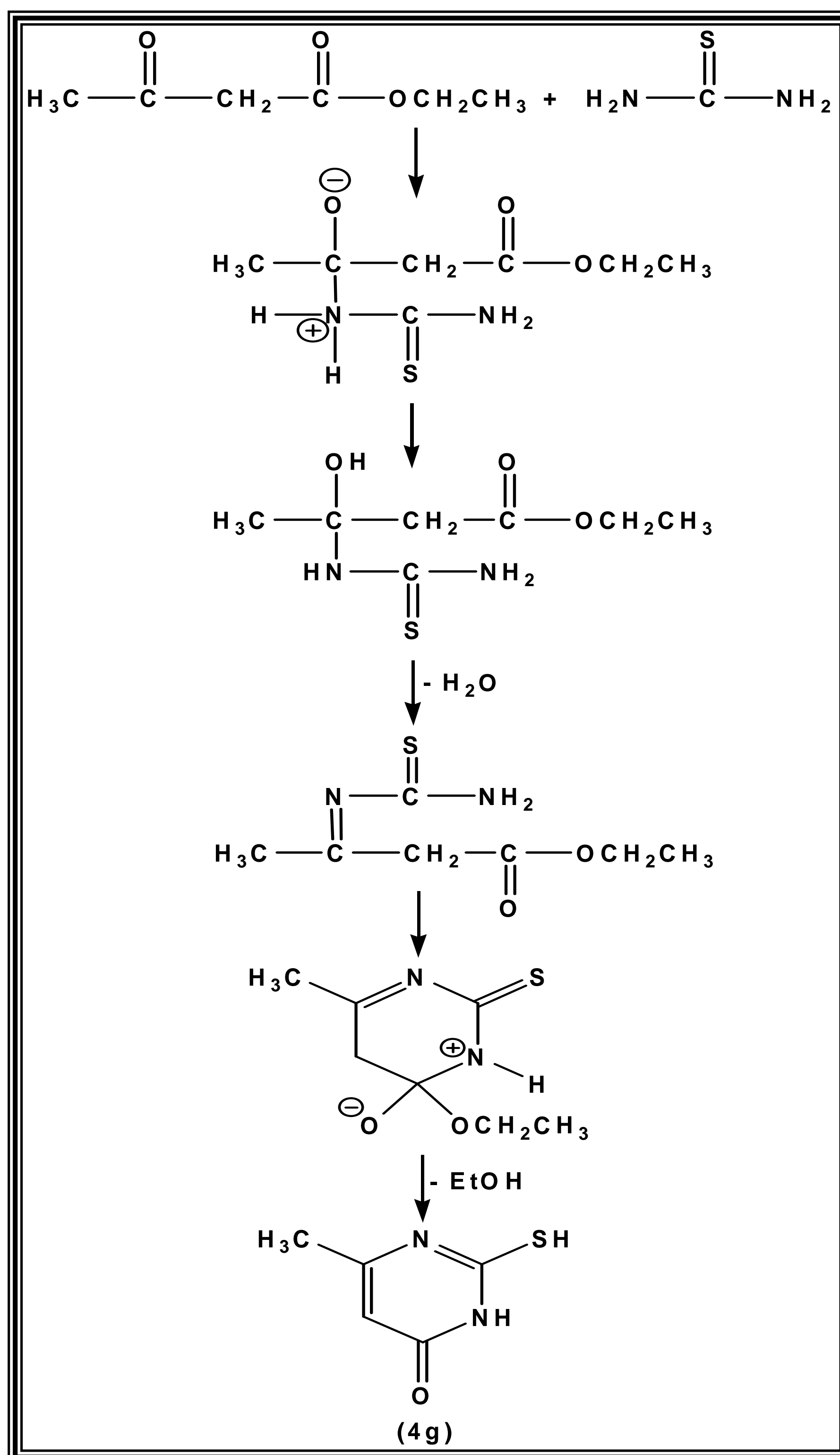


Figure (3-3):F.T.IR spectrum of 2-thioacetic acid-5-(4-aminophenyl)-1,3,4-oxadiazole (2E).

3.4 synthesis and characterization of compound 6- methyl -4- oxo -1,2,3,4 –tetrahydro -2- thiopyrimidine (4_G) :

The compound (4_G) was prepared as previously shown in scheme (2.3) Compound (4_G) has been obtained by refluxing ethylacetoacetate with sodium hydroxide and thiouria in prescence of hydrochloric acid :



The synthesized compound was characterized by FTIR . The characteristic (KBr cm^{-1}) as shown in figure (3.4). A stretching band appeared at 2582 ,2337 which could be attributed to (S-H) ,1240 and 1197 (C=S) stretching 731 of (C-S) , 2889 of (C-H) alphatic , 1633 for (C=O) , and 1556 (C=N) . [143] .

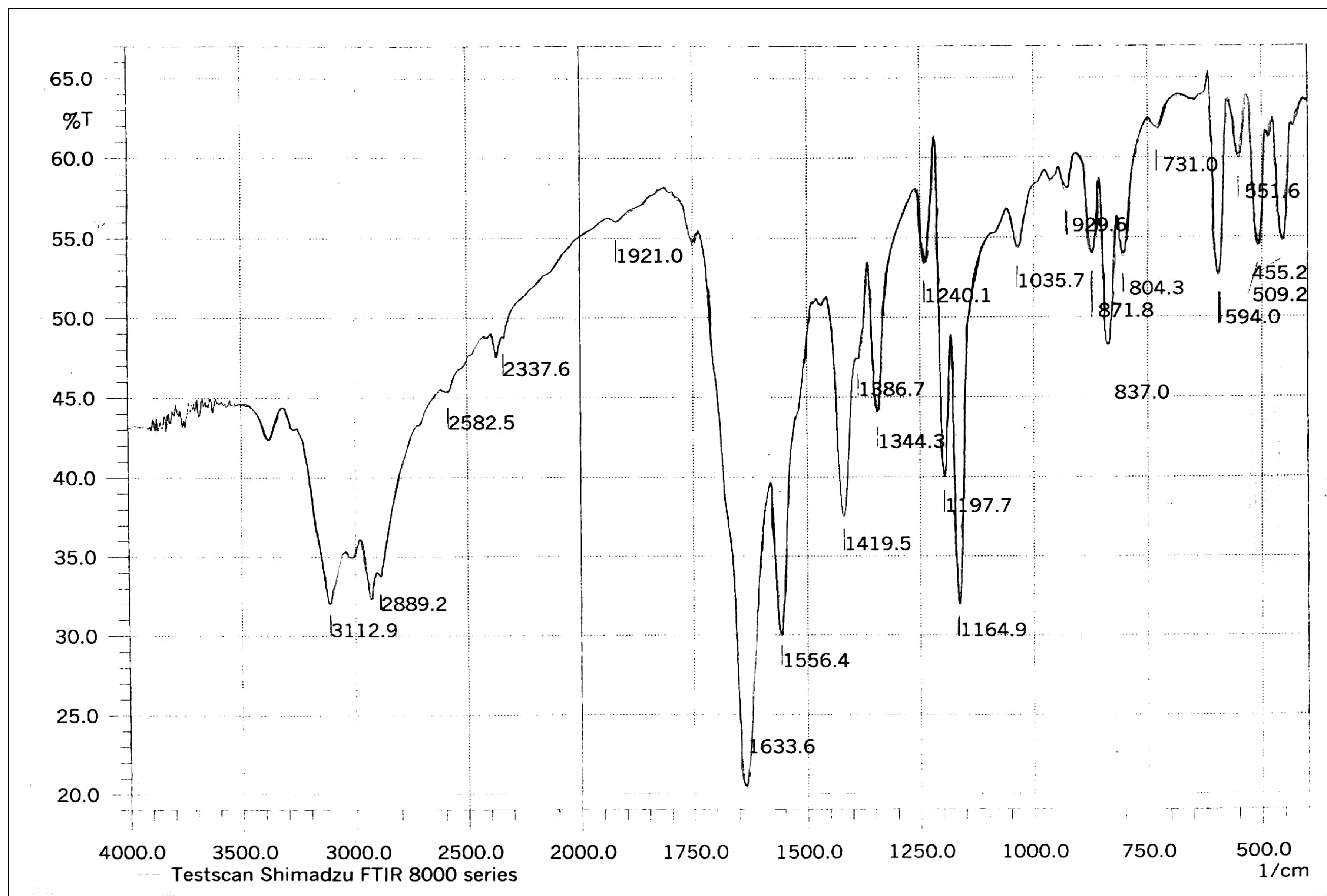
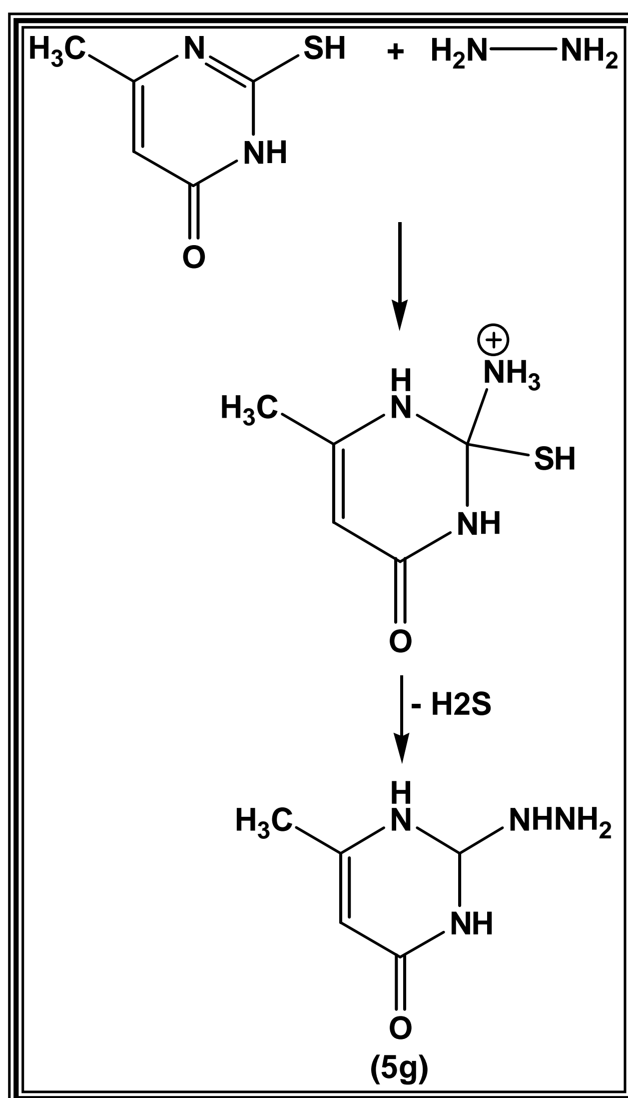


Figure (3-4):F.T.IR spectrum of 6-methyl-4-oxo-1,2,3,4-tetrahydro-2-thiopyrimidine (4G).

3.5 synthesis and characterization of compound 2- hydrazino- -6- methyl pyrimidine -4- (3H) one (5_G) :

Compound (5_G) was synthesized by refluxing compound (4_G) with hydrazine hydrate 99% :



The synthesized compound was characterized by FTIR .FTIR spectrum has showed the disappearance of (S-H) and (C=S) bands , and appearance of bands at 3300,3210 for NH_2 and N-H stretching [144] , as shown in figure (3.5).

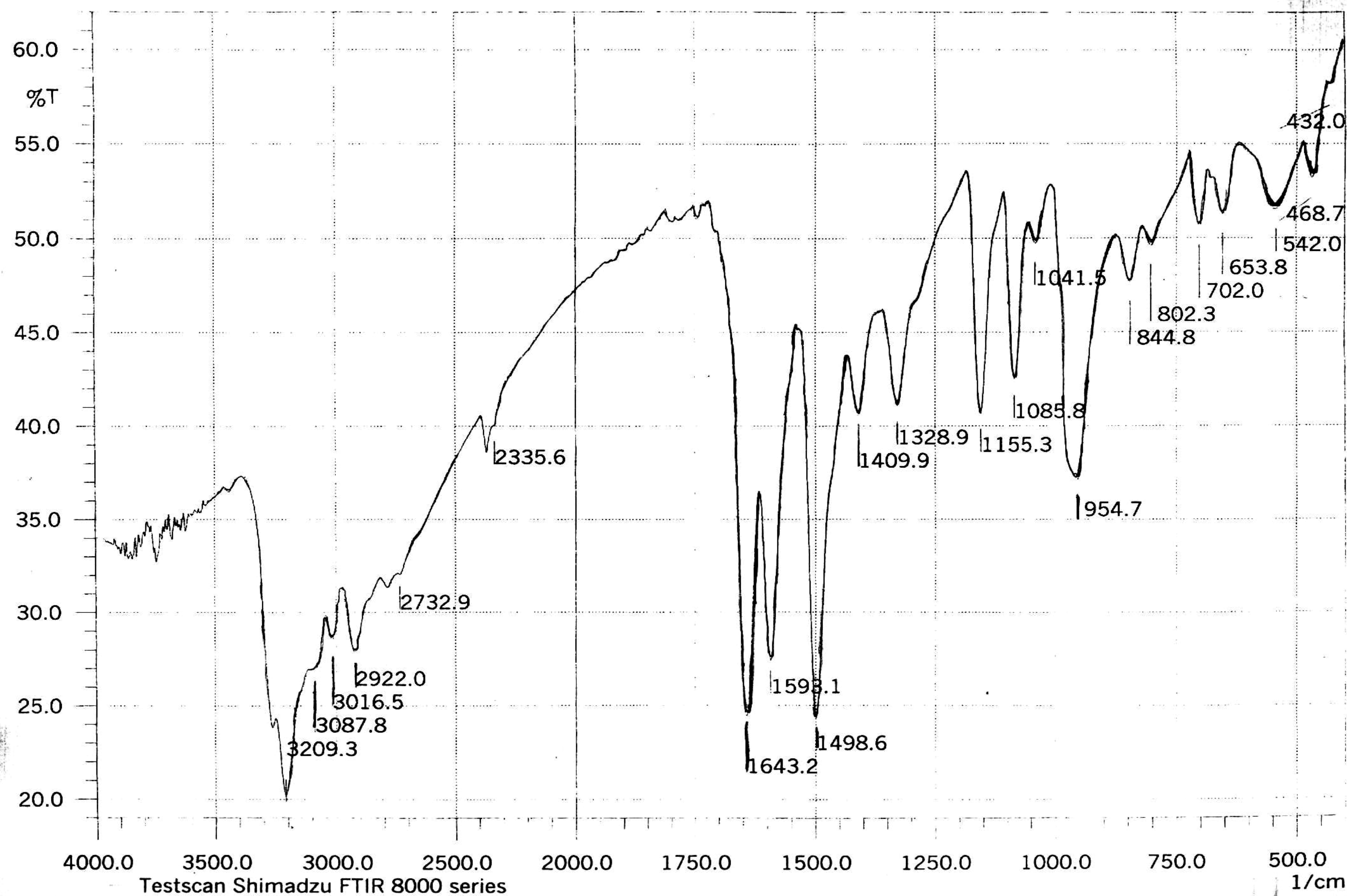


Figure (3-5):F.T.IR spectrum of 2-hydrazino-6-methyl pyrimidine-4-(3H) one.

3.6 *In vitro* study :

The results of our study indicated some variations in the ability of different compounds to inhibit fungal growth , these results depends on the type of compounds , the concentration used , type of media , and the type of microorganisms .

The New compounds (1_G, 6_G,4_G,2_E and 5_G) were found to have inhibition effect on growth of fungal . The effect of these new compounds were calculated at different concentrations .The inhibitiory effect was found to increase as the the concentration of compounds increase

3.6.1. Effects of ketoconazole compounds (1_G) on the growth of fungi:

The ketoconazole compound showed an inhibitory effect on the growth of Trichophyton rubrum and Geotrichum candidum .

Throughout 48 hrs. of incubation , the percentage of inhibition of Trichophyton rubrum at concentration 0.005 mg/ml, 0.01 mg/ml ,0.015mg/ml ,0.02mg/ml , and 0.03 mg/ml were (21.8,34.37,100,100,100%) respectively .

The percentage of inhibition of Geotrichum candidum in these concentrations were (42.5,50,100,100, and 100%) respectively , indicating that the best concentration of ketoconazole compound 1_G to inhibit the growth of Trichophyton rubrum and geotrichum candidum were 0.015 mg/ml , 0.02 mg/ml , and 0.03 mg/ml as shown in Table (3-1) and figures (3-6) and (3-7) .

Throughout 72 hrs . of incubation , the percentage of inhibition of Trichophyton rubrum at concentration 0.005 mg/ml , 0.01mg/ml , 0.015mg/ml , 0.02mg/ml ,and 0.03 mg/ml were (9.09,21.2,

100,100,100%) respectively , and the diameter of colonies were (33,30,26,0,0,0) respectively .

The inhibitory effect was found to increase as the concentration of ketoconazole compound increase , decrease the diameters of colonies of fungi with increase the concentrations and also increase the inhibitory effect of ketoconzole compound

The percentage of inhibition of geotrichum candidum in these concentrations were (13.51,24.32,100,100,and 100%) respectively , and the average of colonial diameters were (37,32,28,0,0,0) respectively as shown in Table (3-2) and Figures (3-8) and (3-9) .

Throughout 96 hrs . of incubation , the growth of Trichophyton rubrum was inhibited by different concentration of the ketoconazole compound used . The percentage of inhibition at concentration 0.005mg/ml , 0.01mg/ml , 0.015mg/ml and 0.03mg/ml were (6.66,42.66,100,100%) respectively , and the average of colonial diameters were (75,70,43,0,0) as in the table (3-3) and figure of (3-10) and (3-11) .
The percentage of the inhibition of geotrichum candidum by the same concentrations for the ketoconazole compound reached to (5.88,52.9,100,100%) respectively .

Increase the incubation time of fungi colonies will be increase the average of colonial diameters , the best inhibitory effect of ketoconazole compound after 48 hrs. of incubation.

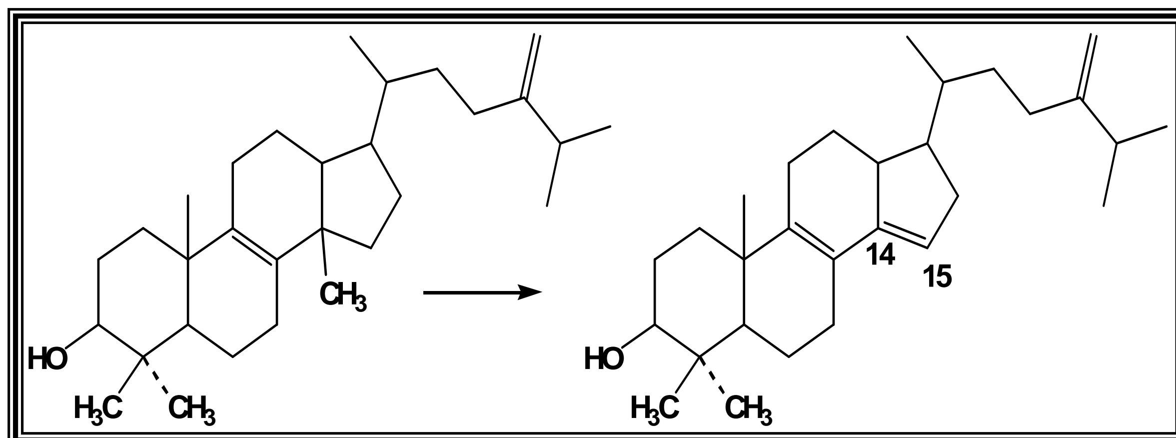
Incubation time is inversely proportional with the treatment of dermatophytes by ketoconazole compound . [145] .

In our present work , ketoconazole showed complete inhibition of growth at the concentration (0.015mg/ml , 0.02mg/ml , and 0.03mg/ml) indicated against of fungi colonies .Dermatophyte inhibition was read after 48 hours of incubation at 30 C ° [146,147].The outer wall of the fungal cell is a complex multilayered structure where amorphous , granular and fibrillar structures interact with one another to give the cell a rigid shape and to confer osmotic stability .The cell walls of fungi do not contain peptidoglycan so that the B- lactam antibiotics have no effect . In recent years research to discover agents that affect the fungal cell wall has been intense but although several compounds emerged none has so for demonstrated clinical effectiveness [148].

Thomas novinson , Roland K. Robins , and Thomas R. matthews (1978)[147]. Refers to the azoles compounds have a common mode of action involving the interaction of the lone pair of electrons on the ring nitrogen with the haem group of the cytochrome P 450 of the enzyme catalysing the C-14 demethylation reaction . The interaction ,stabilized at the binding site by the hydrophobic parts of the molecule ,prevents the oxidation of the methyl group and hence its subsequent removal . The result is an accumulation of methylated sterols in the cell , with a reduction of the ergosterol content . Methylated sterols are more bulky than ergosterol and do not easily fit into a normal membrane structure[149].

Betiana (1983) [150] refer to the ketoconazole compound is effective antifungal agent throught their action on the biosyntesis of ergosterol.
Ergosterol plays a simslar role in fungal membranes to that taken by cholesterol in mammals .

A goup of compounds in common use includes those which inhibit at the stage of C-14 demethylation these are generally referred to as the A zole antifungals , by virtue of their .nigtrgen- containing heterocyle [151].



Antifungal which inhibit ergosterol biosyn thesis show marked selectivily for fungal systems . The azole antifungals are several hundred times more potent against lanosterol demethylation in fungi than the corresponding reaction in mammals [152].

Sheinerman , Norel , and Honing (2000) [55] refers to that invitro ketoconazole compound is show high activity after treatment against experimental Trichophyton rubrum. Ketoconazole which is orally active and was used to treat a wide range of fungal infections particularly deep-seated mycoceses [153].In sabouraud agar , the antifungal activity of ketoconazole was markedly enhanced ([154].

Table (3-1): Effects of compound (1G) on the diameter of fungal colonies throughout 48 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	32	0	40	0
0.005 mg/ml	25	21.8	23	42.5
0.01 mg/ml	21	34.37	20	50
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

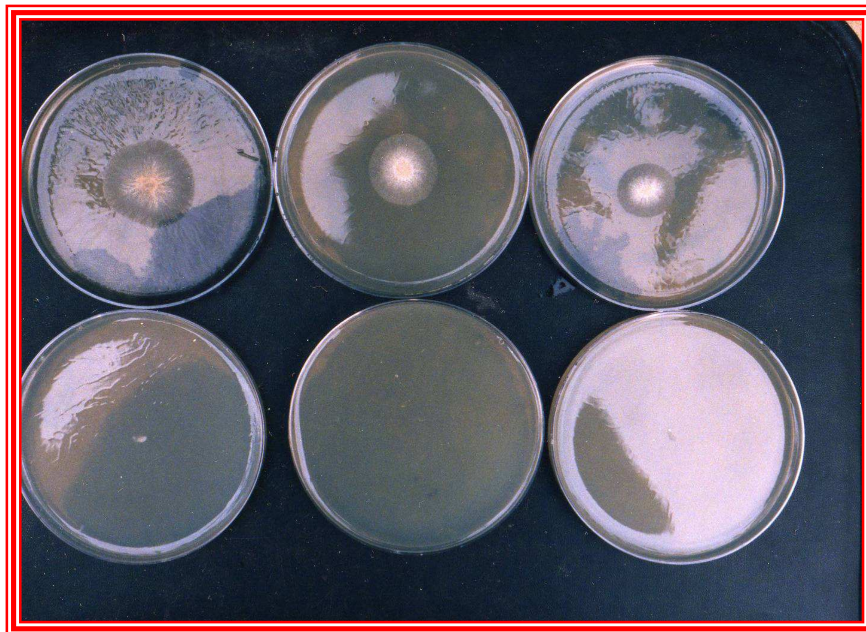


Figure (3-6): Effect of Ketoconazole compound (1_G) on the growth of Trichophyton rubrum after 48 hrs. of incubation

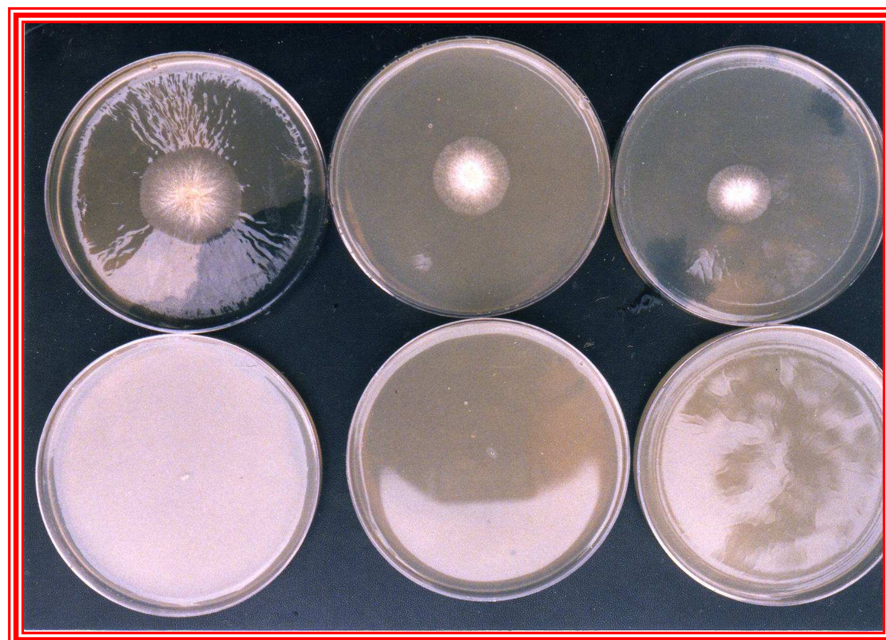


Figure (3-7): Effect of Ketoconazole compound (1_G) on the growth of Geotrichum Candidum after 48 hrs. of incubation

Table (3-2): Effects of compound (1G) on the diameter of fungal colonies throughout 72 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	33	0	37	0
0.005 mg/ml	30	9.09	32	13.51
0.01 mg/ml	26	21.2	28	24.32
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

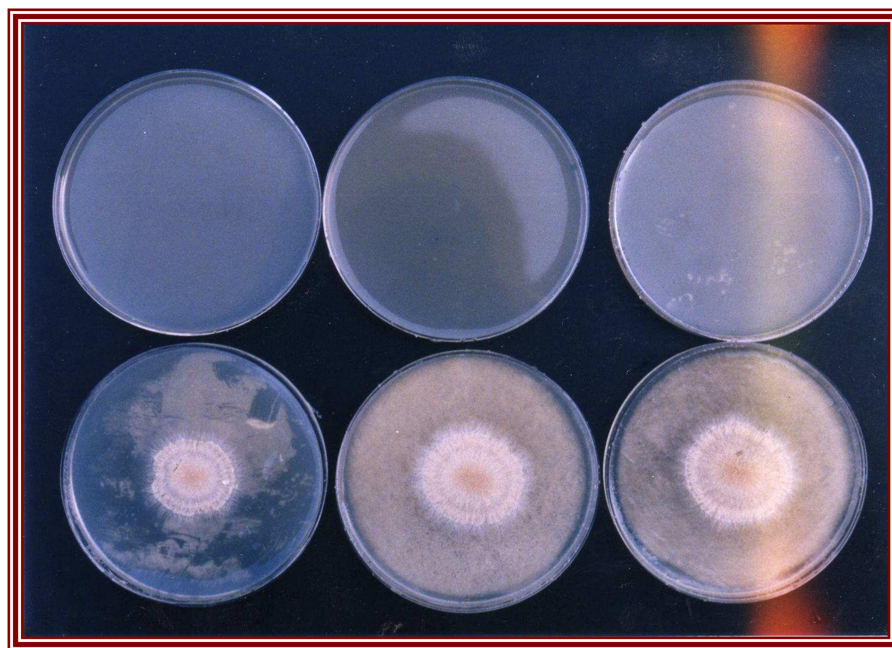


Figure (3-8): Effect of Ketoconazole compound (1_G) on the growth of Trichophyton rubrum after 72 hrs. of incubation

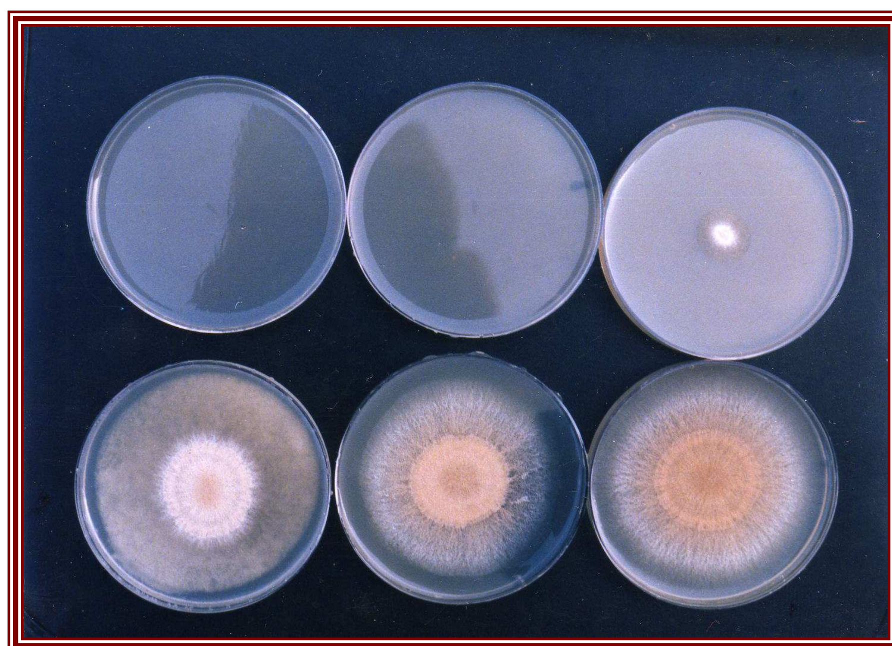


Figure (3-9): Effect of Ketoconazole compound (1_G) on the growth of Geotrichum Candidum after 72 hrs. of incubation

Table (3-3): Effects of compound (1G) on the diameter of fungal colonies throughout 96 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	75	0	85	0
0.005 mg/ml	70	6.66	80	5.88
0.01 mg/ml	43	42.66	40	52.9
0.015 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

Figure (3-10): Effect of Ketoconazole compound (1_G) on the growth of Trichophyton rubrum after 96 hrs. of incubation

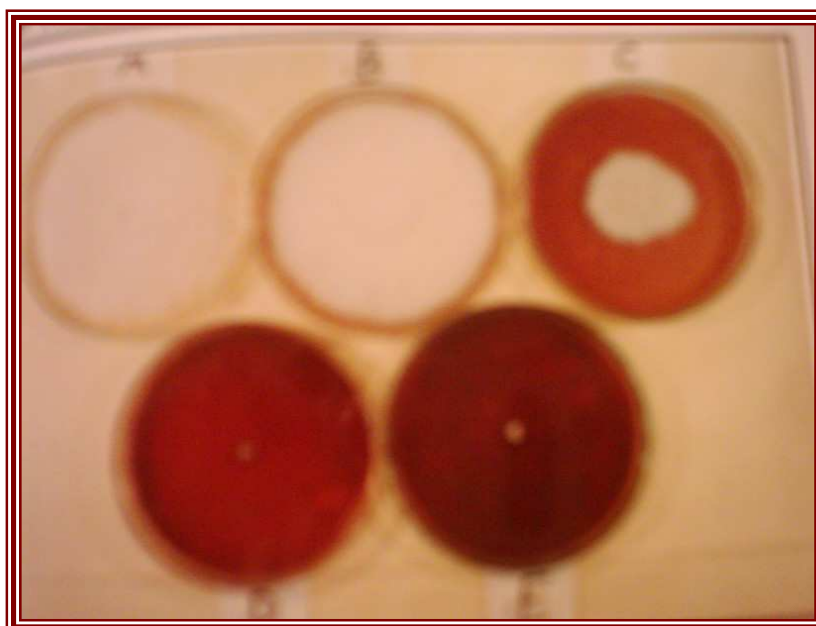


Figure (3-11): Effect of Ketoconazole compound (1_G) on the growth of Geotrichum Candidum after 96 hrs. of incubation

3.6.2 Mixture of ketoconazole with caffeine (6G) :

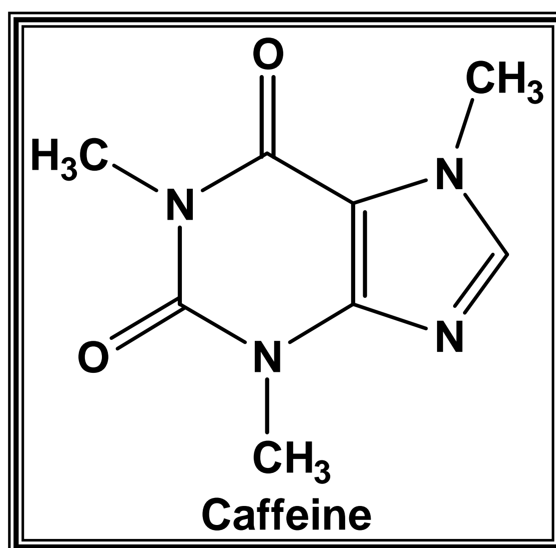
Throughout 48 hrs . of incubation , The growth of Trichophyton rubrum was inhibited by different concentration of the mixture (6_G) used .
The percentage of inhibition was 100% as in table (3-4)and figure (3-12) and (3-13). While the percentage of the inhibition of geotrichum candidum by the same mixture (6G) reached to 80% only in the concentration of 0.005 mg/ml , but other concentrations give same percentage of Trichophyton rubrum .

Throughout 72 hrs . of incubation , The mixture (6G) showed an inhibitory effect on the growth of both species . The percentage of inhibition of Trichophyton rumrum at concentrations 0.005 mg/ml ,0.01mg/ml ,0.015mg/ml ,0.02mg/ml & 0.03 mg/ml were (71.4,100,100,100,&100%) respectively , and the average of colonial diameters were (14,4,0,0,0,0) respectively .
The percentage of inhibition of geotrichum candidum in these concentrations were (76.1,100,100,100,& 100%) respectively , the average of colonial diameters were (21,5,0,0,0) respectively .

The best concentration of mixture (6G) to inhibit the growth of trichophy rubrum and geotrichum candidum were (0.01mg/ml , 0.015mg/ml, 0.02mg/ml , and 0.03mg/ml) only concentration 0.005 mg/ml appeared little inhibitory effect on the growth of both species , as shown in table (3-5) and figures (3-14) and (3-15) .
Throughout 96 hrs .of incubation , the inhibitory effect of mixture (6G) similar of inhibitory effect after 72 hrs . of incubation , as in table (3-6) and figures (3-16) and (3-17) .

Todd,orengo , and thornton (2001) [30] refers to that the effect of A zole compound (ketoconazole) was increased by mixture with alkaloids compounds .

Caffeine is a member of alarge class of organic compounds known as alkaloids . alkaloids are nitrogen- containing ring compounds of vegetable origin that usually have a bitter taste, , have some of pharmacological activity and sensitive against dermatophyte diseases [155].



Caffeine

Table (3-4): Effects of mixture (6G) on the diameter of fungal colonies throughout 48 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	10	0	20	0
0.005 mg/ml	0	100	4	80
0.01 mg/ml	0	100	0	100
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

Figure (3-12): Effect of mixture compound (6_G) on the growth of Trichophyton rubrum after 48 hrs. of incubation

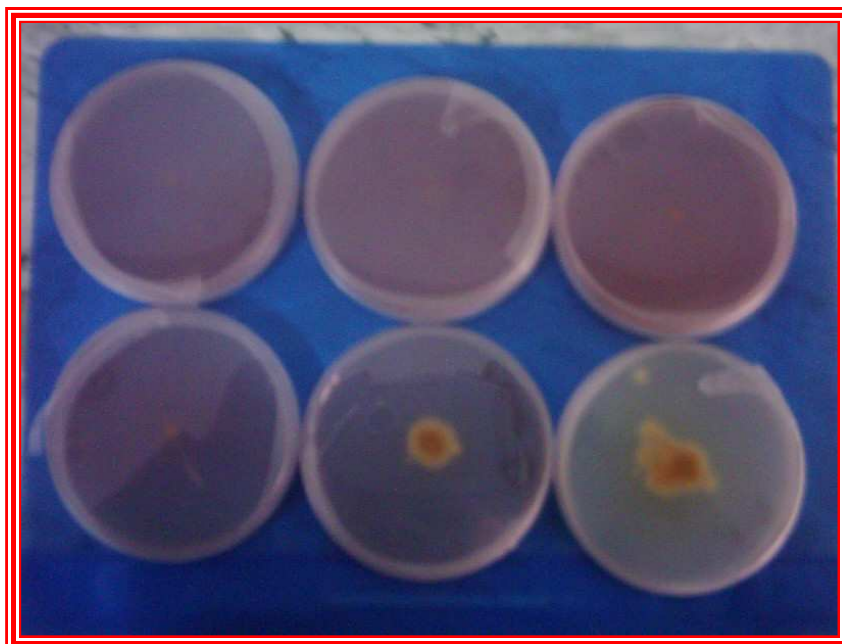


Figure (3-13): Effect of mixture compound (6_G) on the growth of Geotrichum Candidum after 48 hrs. of incubation

Table (3-5): Effects of mixture (6G) on the diameter of fungal colonies throughout 72 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	14	0	21	0
0.005 mg/ml	4	71.4	5	76.1
0.01 mg/ml	0	100	0	100
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

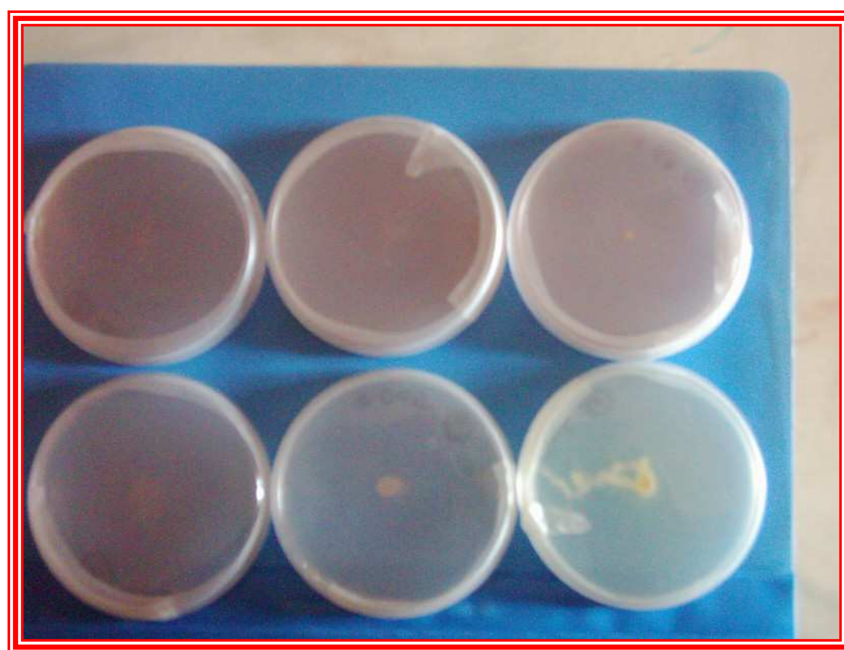


Figure (3-14): Effect of mixture compound (6_G) on the growth of Trichophyton rubrum after 72 hrs. of incubation

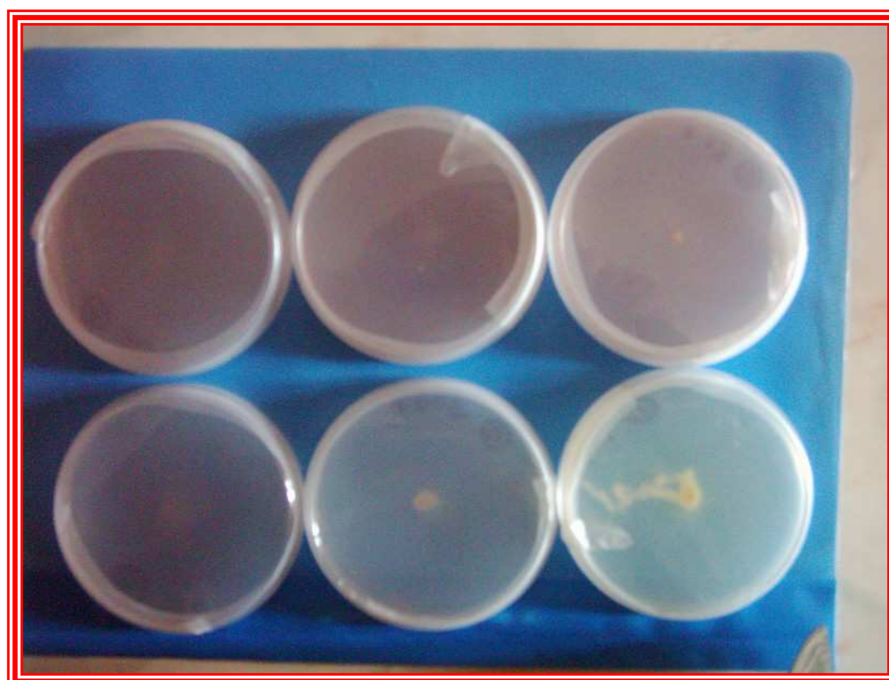


Figure (3-15): Effect of mixture compound (6_G) on the growth of Geotrichum Candidum after 72 hrs. of incubation

Table (3-6): Effects of mixture (6G) on the diameter of fungal colonies throughout 96 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	25	0	21	0
0.005 mg/ml	5	80	5	76.1
0.01 mg/ml	0	100	0	100
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

Figure (3-16): Effect of mixture compound (6_G) on the growth of Trichophyton rubrum after 96 hrs. of incubation

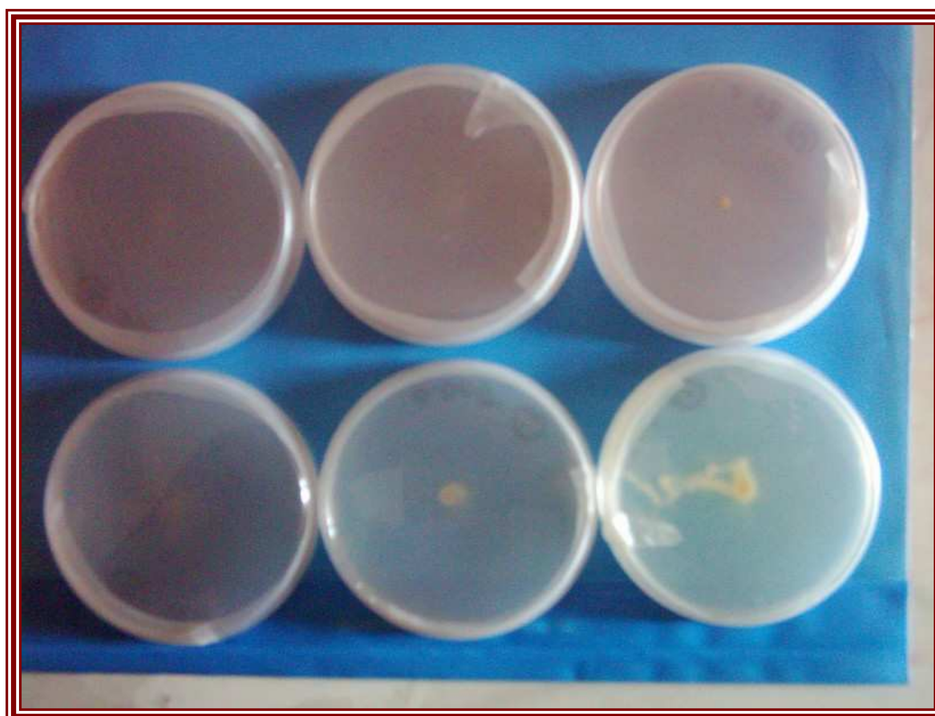


Figure (3-17): Effect of mixture compound (6_G) on the growth of Geotrichum Candidum after 96 hrs. of incubation

3.6.3 Effect of 2- thioacetic acid (4- amino phenyl) 1,3,4-oxadiazole (2_E) on growth of fungi

Throughout 48 hrs , of incubation , the growth of trichophyton rubrum and geotrichum candidum were inhibited by different concentration of compound 2E used. The perenctage of inhibition of both species 100% at concentrations 0.005 mg/ml ,0.01mg/ml ,0.015mg/ml , 0.02mg/ml ,and 0.03mg/ml respectively , as in table (3-7) and figures (3-18) and (3-19) .
Throughout 72 hrs . of incubation , the growth of trichophyton rubrum was inhibited by different concentration of compound 2E used . The percentage of inhibition was 100% as table (3-8) and figures (3-20) &(3-21) .
While the percentage of the inhibition of geotrichcum candidum by the same concentrations of compound (2E) reached to (75,100,100,100,100%)respectively to the concentrations (0.005mg/ml,0.01mg/ml,0.015mg/ml,0.02mg/ml,and 0.03mg/ml) .
Throughout 96 hrs .of incubation , the growth of Trichophyton rubrum and geotrichum candidum no effect by the time of incubation and indicated the same of percentage of inhibition in 72 hrs .of incubation .as shown in table (3-9) and figures (3-22) and (3-23) .

Table (3-7): Effects of compound (2E) on the diameter of fungal colonies throughout 48 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	15	0	15	0
0.005 mg/ml	0	100	0	100
0.01 mg/ml	0	100	0	100
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

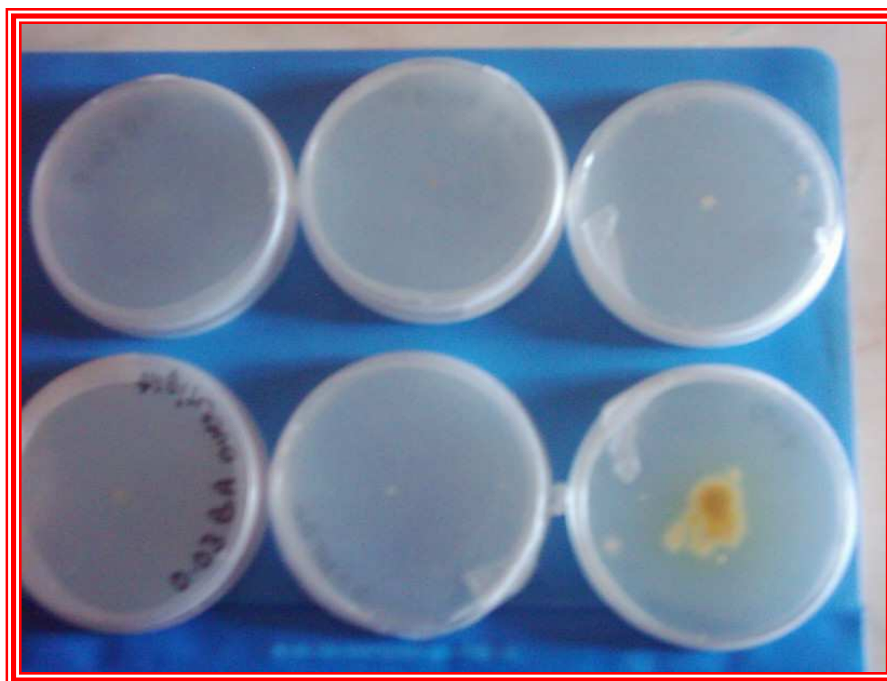


Figure (3-18): Effect of mixture compound (2E) on the growth of Trichophyton rubrum after 48 hrs. of incubation

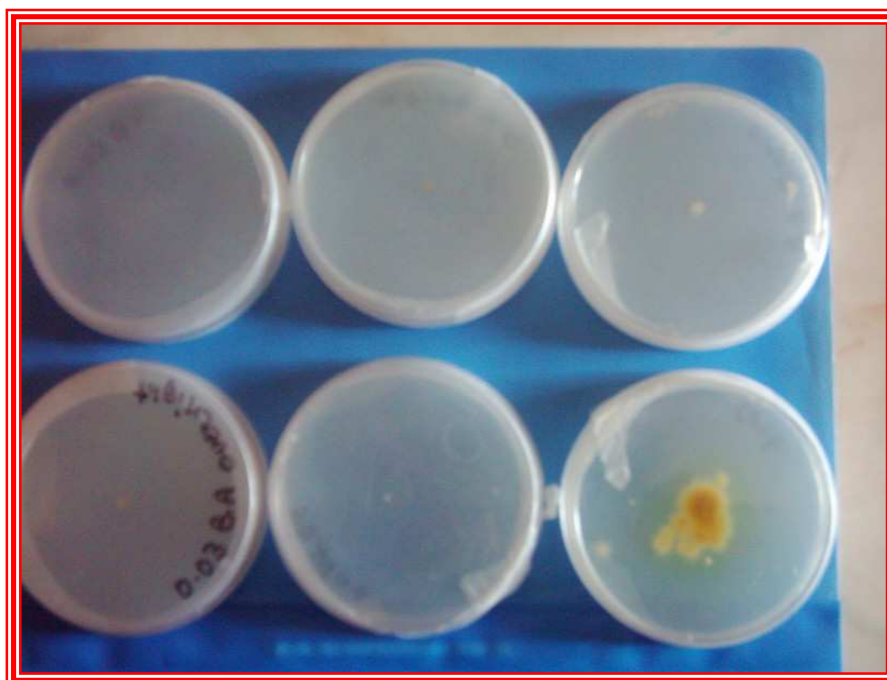


Figure (3-19): Effect of mixture compound (2E) on the growth of Geotrichum Candidum after 48 hrs. of incubation

Table (3-8): Effects of compound (2E) on the diameter of fungal colonies throughout 72 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	26	0	16	0
0.005 mg/ml	0	100	4	75
0.01 mg/ml	0	100	0	100
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

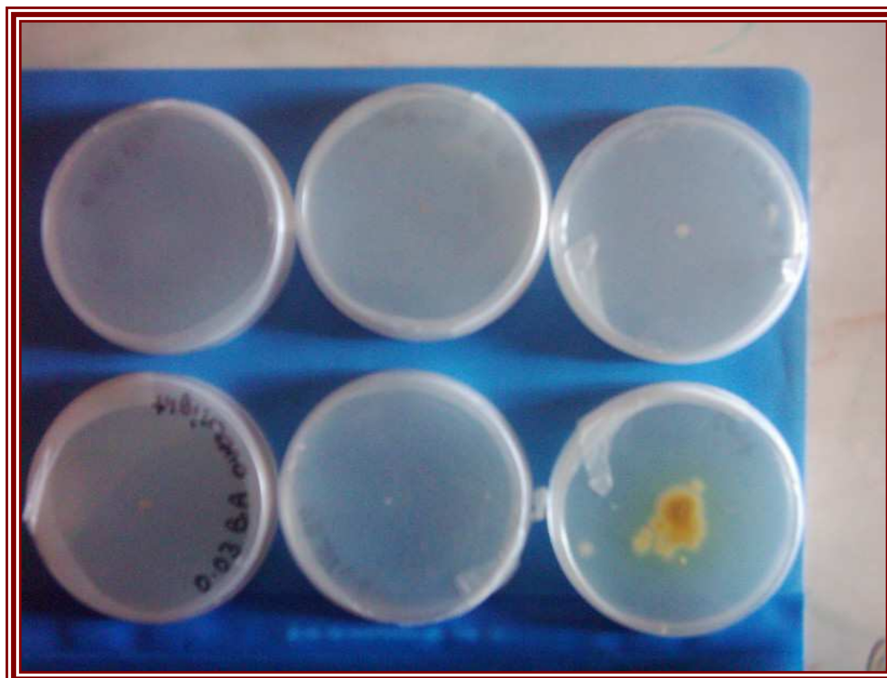


Figure (3-20)Effect of mixture compound (2E) on the growth of Trichophyton rubrum after 72 hrs. of incubation

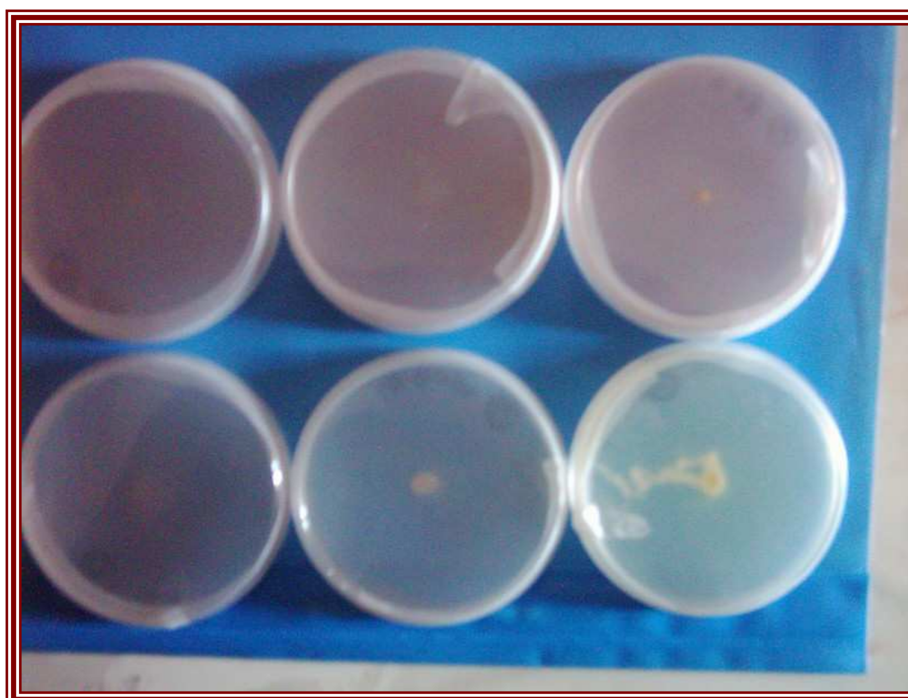


Figure (3-21)Effect of mixture compound (2E) on the growth of Geotrichum Candidum after 72 hrs. of incubation

Table (3-9): Effects of compound (2E) on the diameter of fungal colonies throughout 96 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	27	0	16	0
0.005 mg/ml	0	100	4	75
0.01 mg/ml	0	100	0	100
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

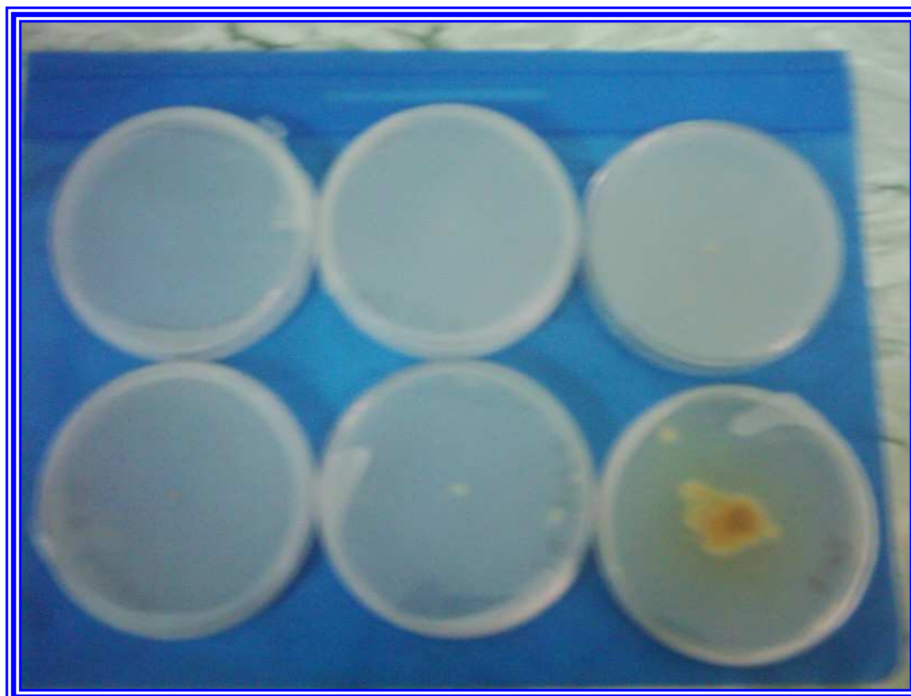


Figure (3-22)Effect of mixture compound (2E) on the growth of Trichophyton rubrum after 96 hrs. of incubation

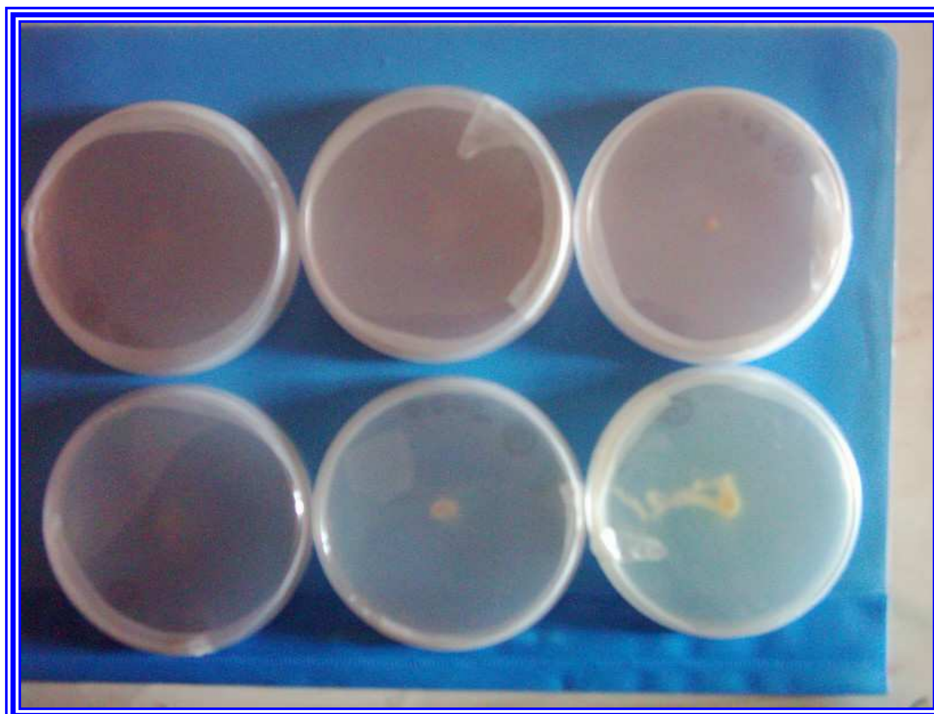


Figure (3-23)Effect of mixture compound (2E) on the growth of Geotrichum Candidum after 96 hrs. of incubation

3.6.4 Effect of 6- methyl -4- oxo-1,2,3,4- tetrahydro-2- thiopyrimidine (4G):

The compounds (4G) was no inhibitory effect against the fungi (Trichophyton rubrum and geotrichum candidum) in all concentrations , as in table (3-10) and figures (3-24) and (3-25) .

Table (3-10): Effects of compound (4G) on the diameter of fungal colonies throughout 48 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	85	0	87	0
0.005 mg/ml	80	5.88	80	8.04
0.01 mg/ml	70	17.64	73	16.09
0.015 mg/ml	75	11.76	70	19.54
0.03 mg/ml	70	17.64	65	25.28

Figure (3-24)Effect of mixture compound (4G) on the growth of Trichophyton rubrum after 48 hrs. of incubation

Figure (3-25)Effect of mixture compound (4G) on the growth of Geotrichum Candidum after 48 hrs. of incubation

3.6.5 effect of 2- hydrazino -6- methyl pyrimidine -4- (3H) one (5G) :

Throughout 48 hrs . of incubation , depending on our study , it was clear that trichophyton rubum was very sensitive to compound (5G) with a percentage of inhibition 100% for the concentrations used . while the percentage of the inhibition of geotrichum candidum by the same compound reached to (81.25,87.5,88.75,and 37.5) respectively to the concentrations (0.005 mg/ml,0.01mg/ml,0.015mg/ml,and 0.02mg/ml) , as shown in table (3-11) and figures (3-26) and (3-27)

Throughout 72 hrs . of incubation , the compound (5G) showed an inhibitory effect on the growth of both species . The percentage of inhibition of trichophyton rubrum at concentrations (0.005mg/m l,0.01mg/ml,0.015mg/ml ,and 0.02 mg/ml) were (100,76.47,68.23, and100%) respectively .

The percentage of inhibition of geotrichum candidum in these concentration were (84.61,74.35,74.35,100%) respectively , indicating that the best concentration of compound (5G) to inhibit the growth of geotrichum candidum was 0.02 mg/nl as shown in table (3-12) and figure (3-28) and (3-29) .

The inhibitory effect of compound (5G) no change after 96hrs of incubation that give the same of inhibition after 72 hrs . of incubation .as shown in table (3-12) and Figure (3-30) & (3-31)

Pyrimidine derivatives were used as antifungal , antiviruse , and antibacterial agent that depends on the active group that associated in the pyrimidine ring . Associated of amine group (NH2)in pyrimidine ring made the compound Very active against Microorganisms (increase the biological activity). [156]

The Mechanisms of action of antimicrobial diffetent according to the type compound . some of antimicrobial inhibition the protein synthesis (erythomycine) , some of other inhibitor the cell membrane (pencilline) and antifungal compounds (Ketoconazole) and amphotericine B. [157]

In genetal pharmaceutical studies of antifungal agents on drugs classified in to :

1- Drugs that disrupt the cell membrane .
2- Drugs that inhibit mitosis.
3- Drugs that inhibit (DNA) synthesis [158] .

Table (3-11): Effects of compound (5G) on the diameter of fungal colonies throughout 48 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	85	0	78	0
0.005 mg/ml	0	100	15	81.25
0.01 mg/ml	0	100	10	87.5
0.015 mg/ml	0	100	19	88.75
0.02 mg/ml	0	100	50	37.5

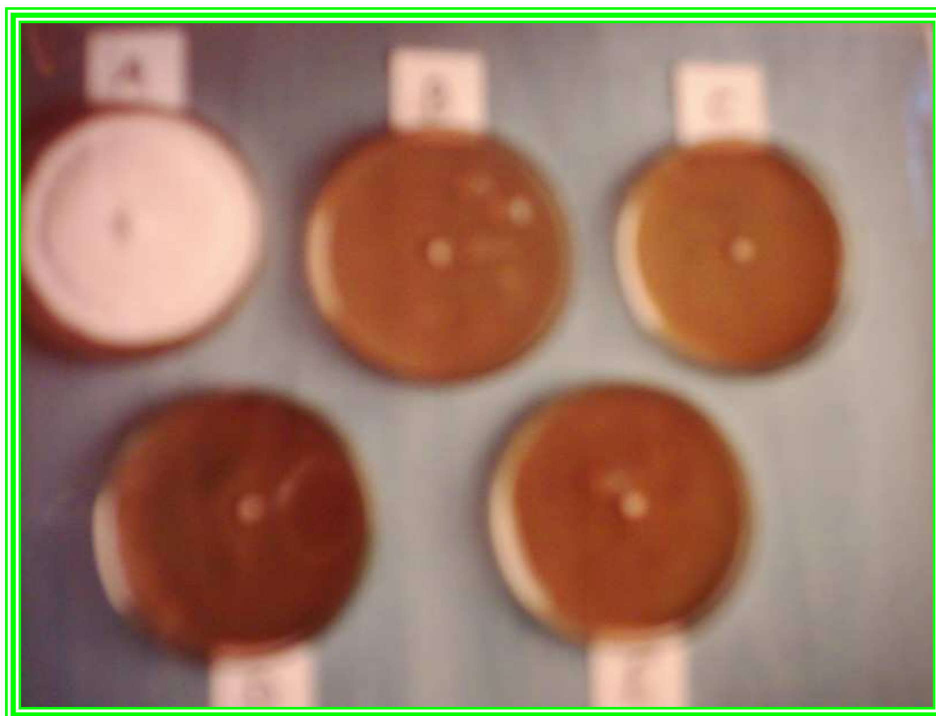


Figure (3-26)Effect of mixture compound (5G) on the growth of Trichophyton rubrum after 48 hrs. of incubation

Figure (3-27)Effect of mixture compound (5G) on the growth of Geotrichum Candidum after 48 hrs. of incubation

Table (3-12): Effects of compound (5G) on the diameter of fungal colonies throughout 72 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	85	0	80	0
0.005 mg/ml	0	100	12	84.61
0.01 mg/ml	20	76.47	20	74.35
0.015 mg/ml	27	68.23	20	74.35
0.02 mg/ml	0	100	0	100

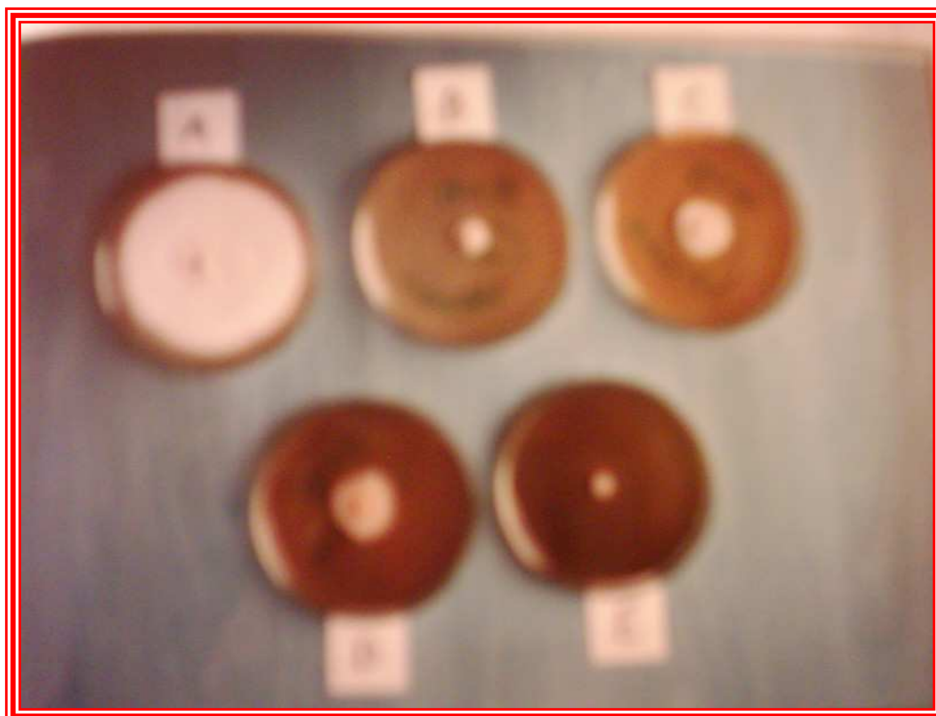


Figure (3-28)Effect of mixture compound (5G) on the growth of Trichophyton rubrum after 72 hrs. of incubation

Figure (3-29)Effect of mixture compound (5G) on the growth of Geotrichum Candidum after 72 hrs. of incubation

Table (3-13): Effects of compound (5G) on the diameter of fungal colonies throughout 96 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	85	0	78	0
0.005 mg/ml	0	100	12	84.61
0.01 mg/ml	20	76.47	20	74.35
0.015 mg/ml	27	68.23	20	74.35
0.02 mg/ml	0	100	10	100

Figure (3-30)Effect of mixture compound (5G) on the growth of Trichophyton rubrum after 96 hrs. of incubation

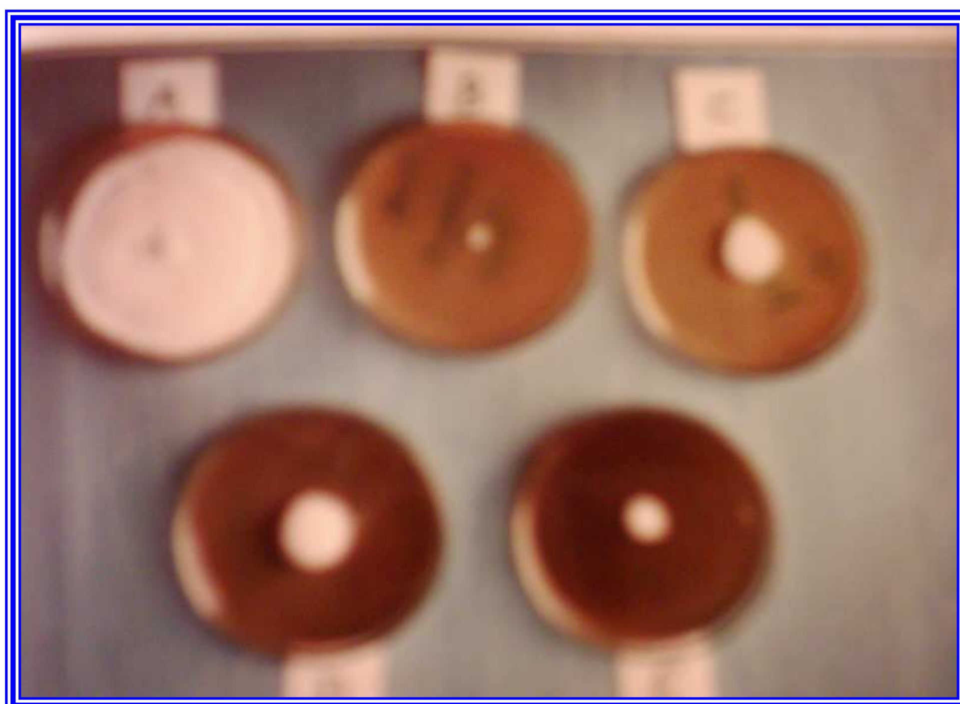


Figure (3-31)Effect of mixture compound (5G) on the growth of Geotrichum Candidum after 96 hrs. of incubation

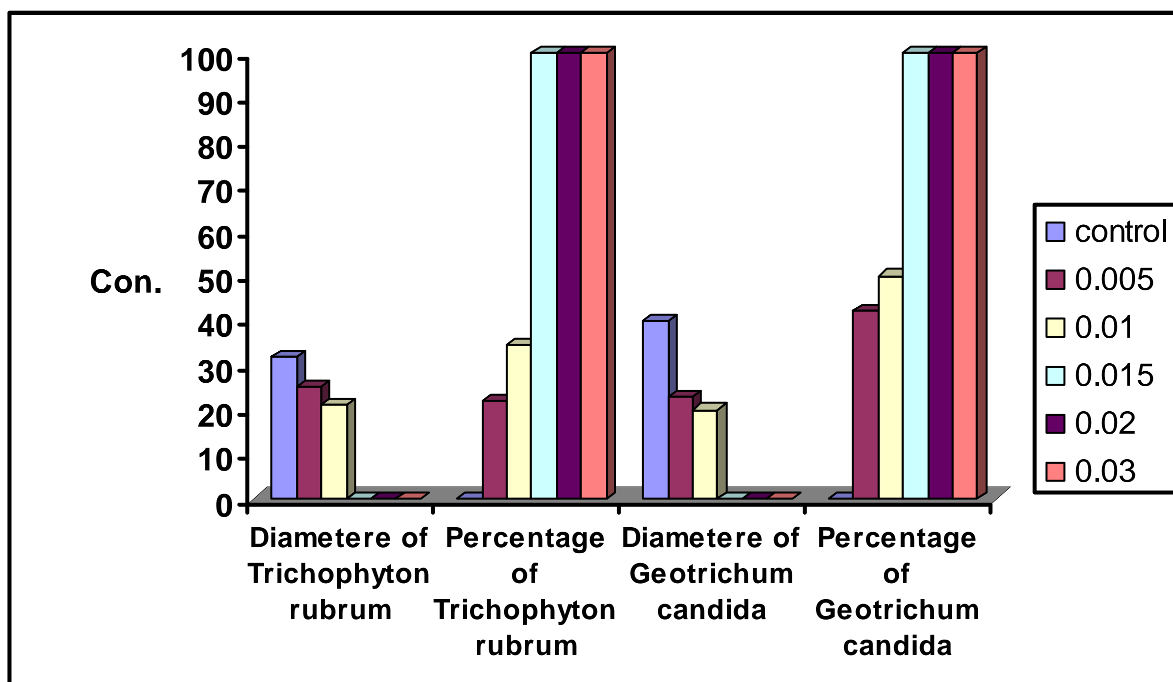


Figure (3-32): Effects of compound (1_G) on the diameter of fungal colonies throughout 48 hrs. of incubation.

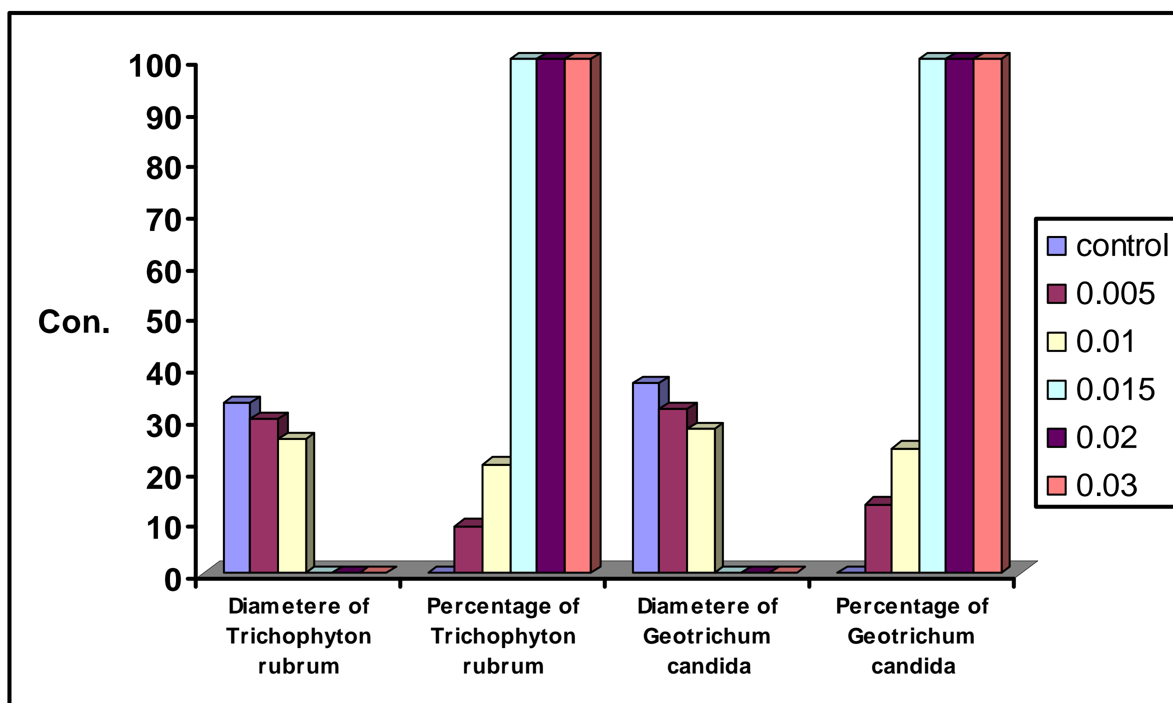


Figure (3-33): Effects of compound (1_G) on the diameter of fungal colonies throughout 72 hrs. of incubation.

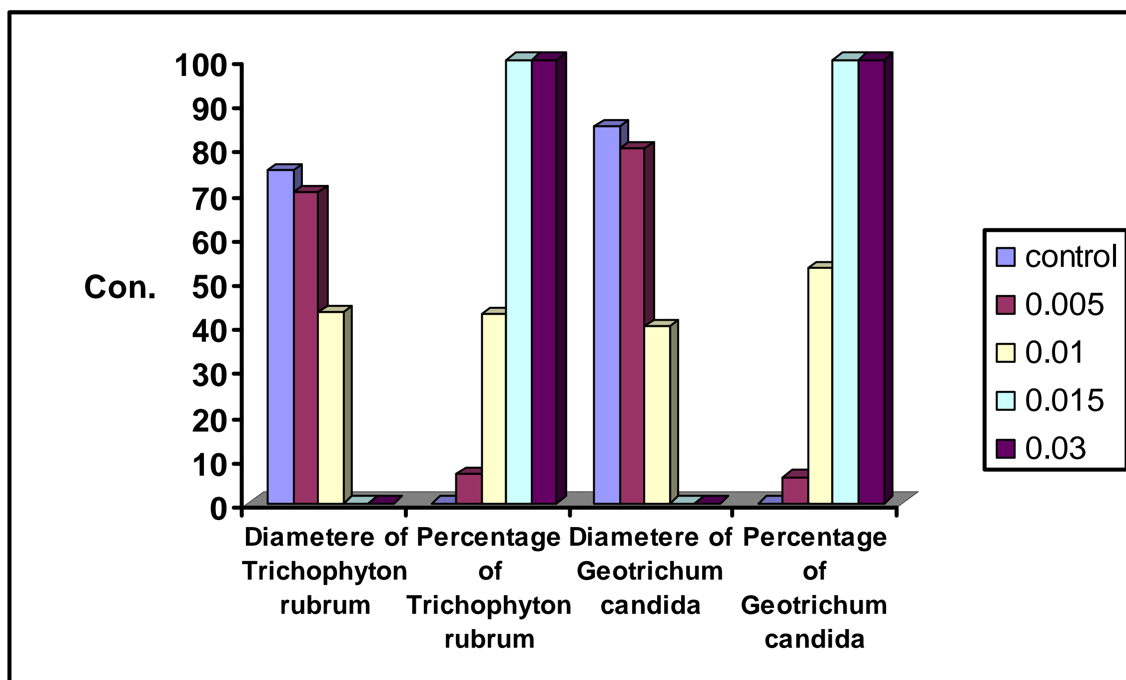


Figure (3-34): Effects of compound (1_G) on the diameter of fungal colonies throughout 96 hrs. of incubation.

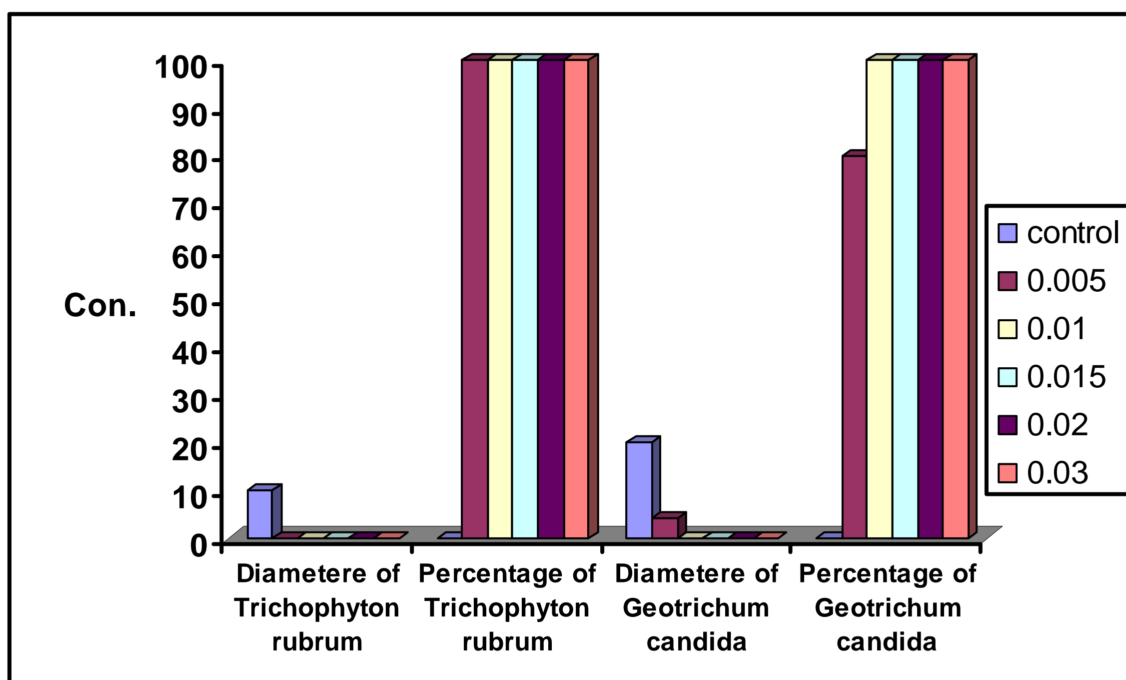


Figure (3-35): Effects of compound (6_G) on the diameter of fungal colonies throughout 48 hrs. of incubation.

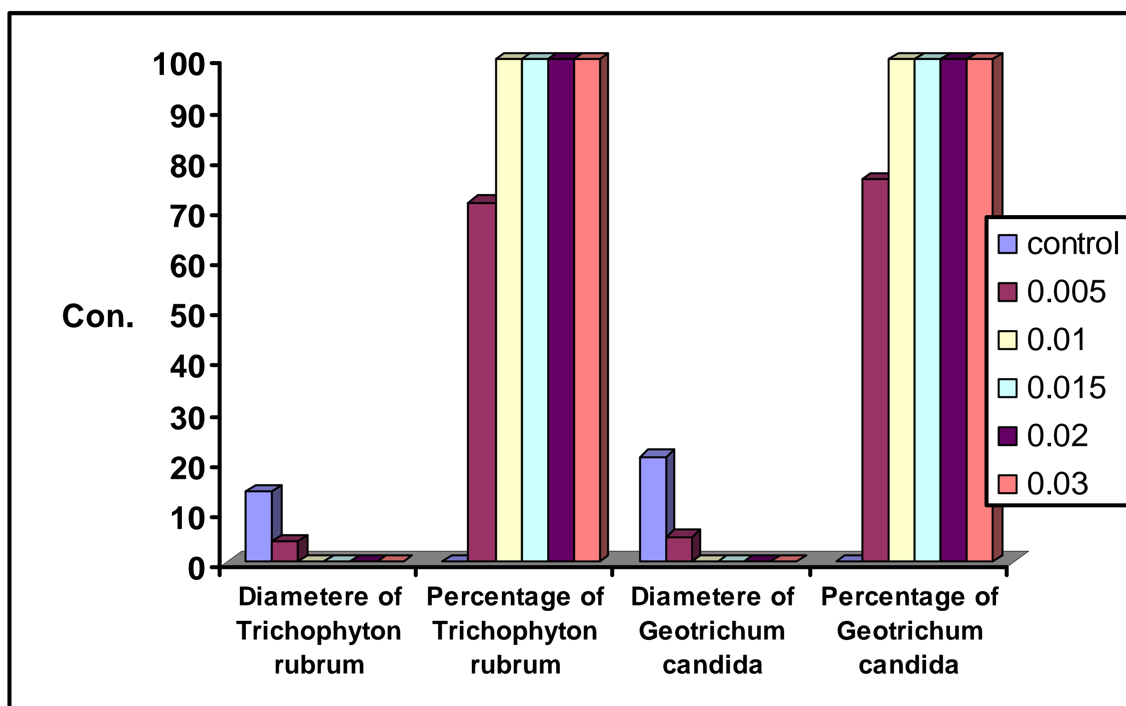


Figure (3-36): Effects of compound (6_G) on the diameter of fungal colonies throughout 72 hrs. of incubation.

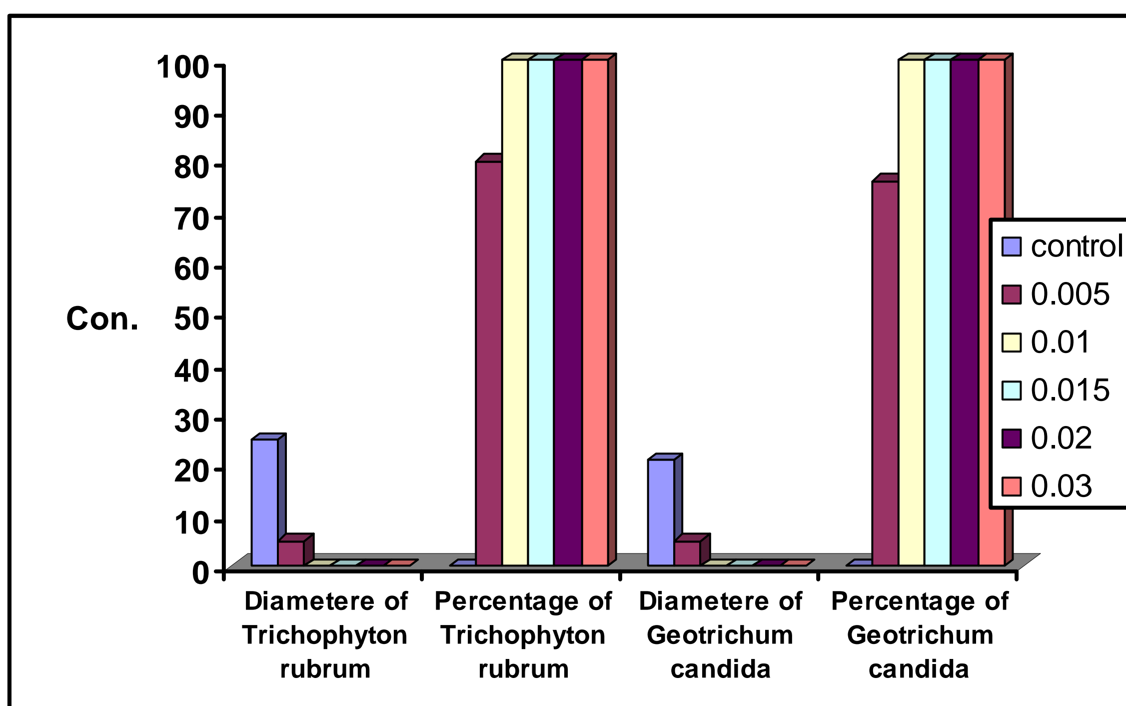


Figure (3-37): Effects of compound (6_G) on the diameter of fungal colonies throughout 96 hrs. of incubation.

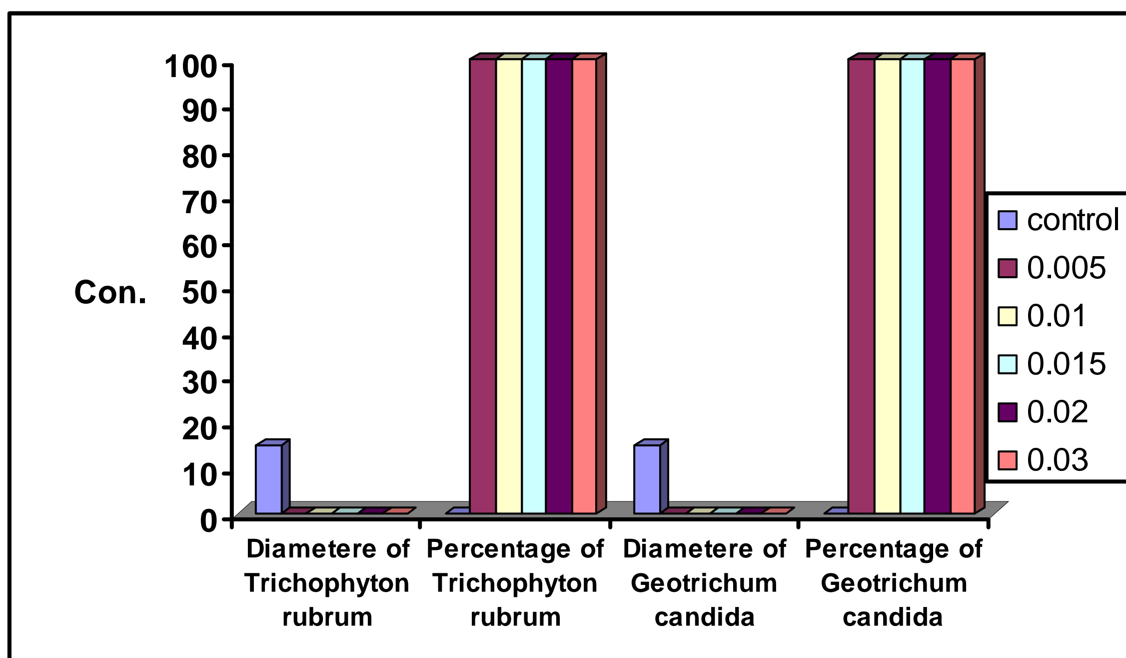


Figure (3-38): Effects of compound (2_E) on the diameter of fungal colonies throughout 48 hrs. of incubation.

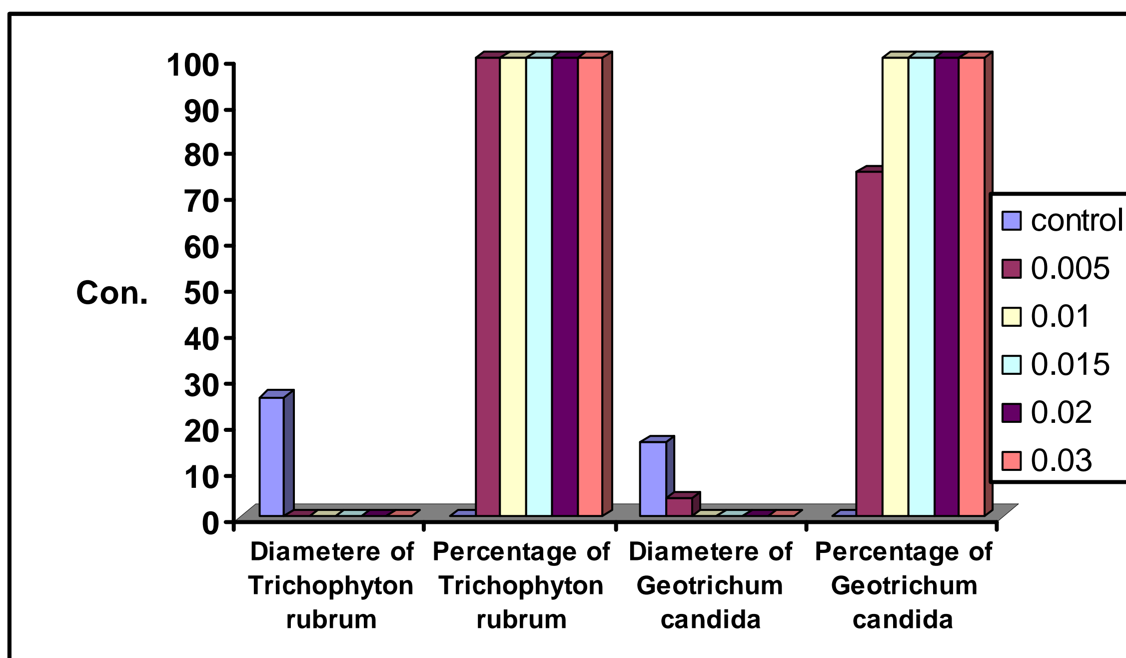


Figure (3-39): Effects of compound (2_E) on the diameter of fungal colonies throughout 72 hrs. of incubation.

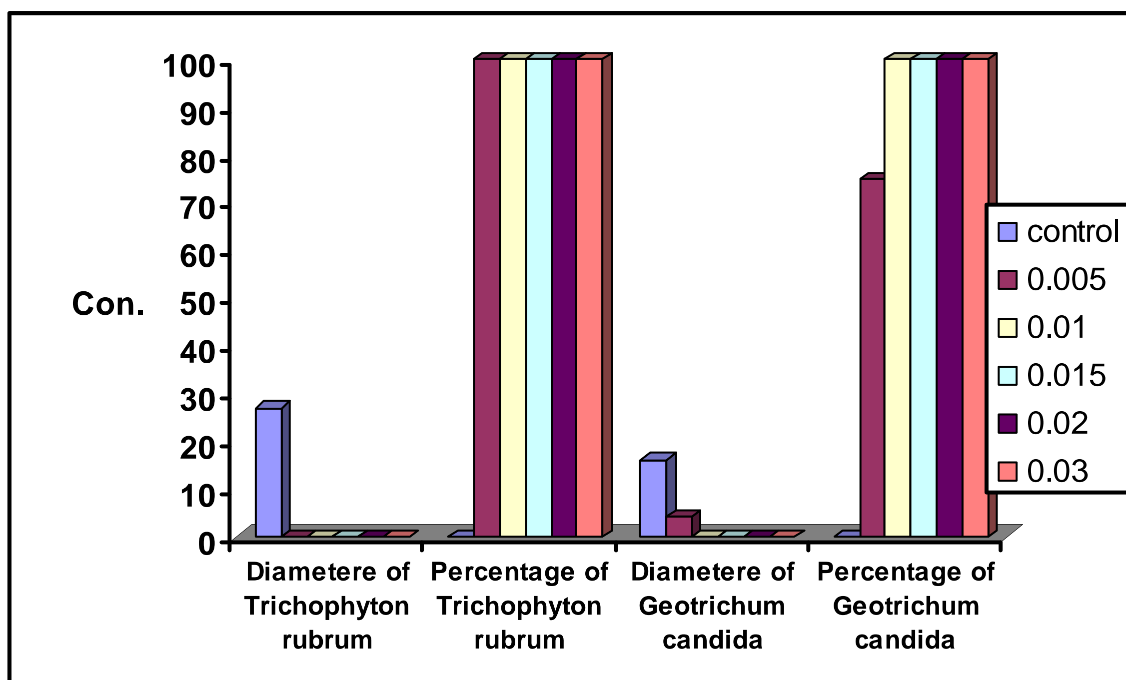


Figure (3-40): Effects of compound (2_E) on the diameter of fungal colonies throughout 96 hrs. of incubation.

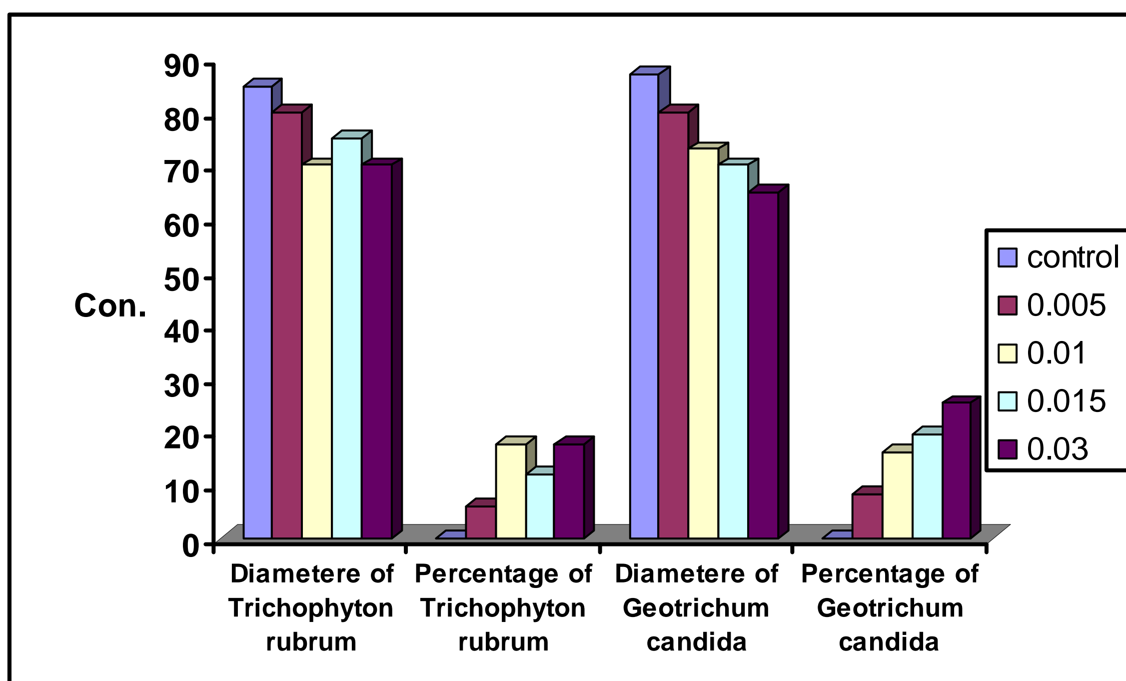


Figure (3-41): Effects of compound (4_G) on the diameter of fungal colonies throughout 48 hrs. of incubation.

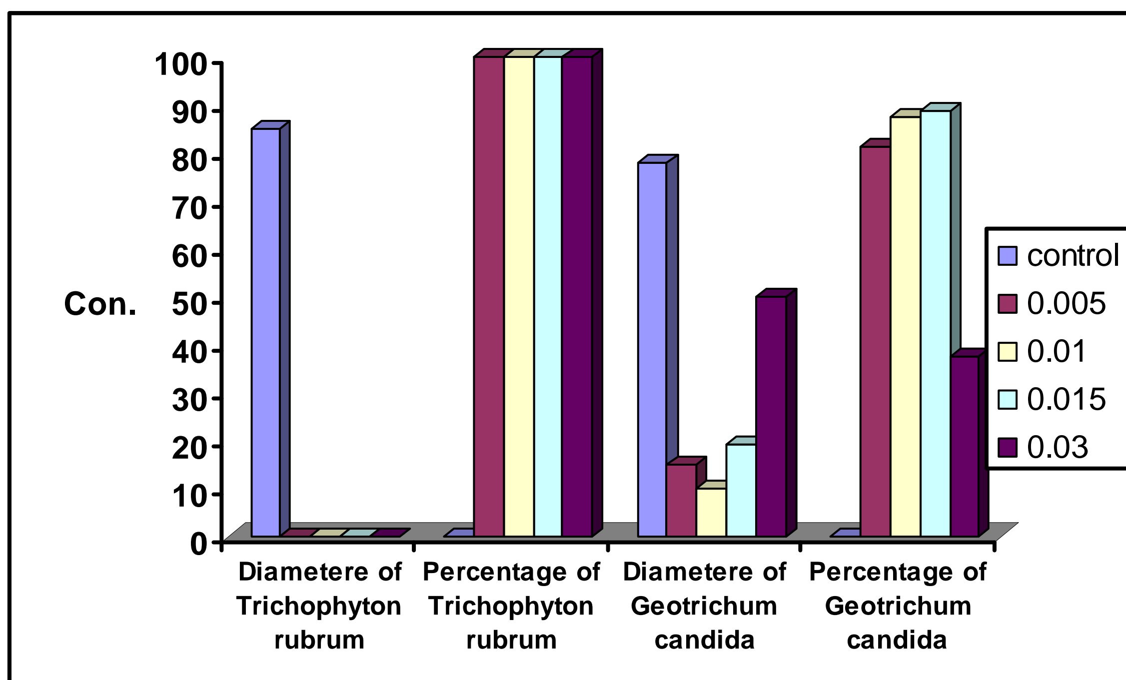


Figure (3-42): Effects of compound (5_G) on the diameter of fungal colonies throughout 48 hrs. of incubation.

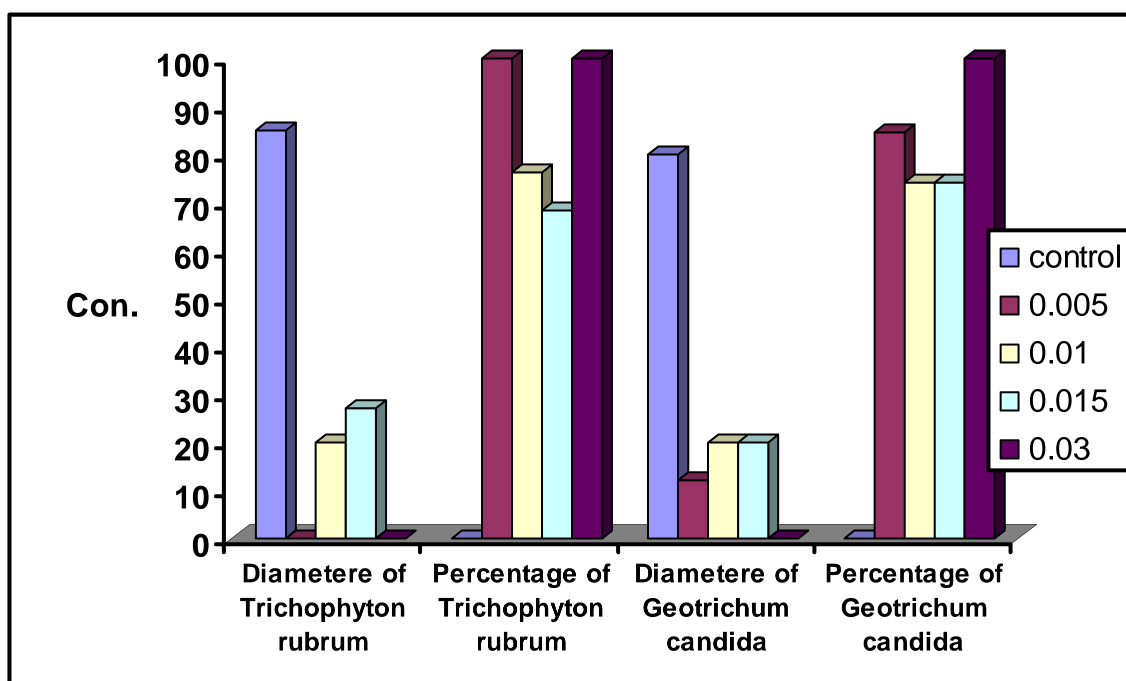


Figure (3-43): Effects of compound (5_G) on the diameter of fungal colonies throughout 72 hrs. of incubation.

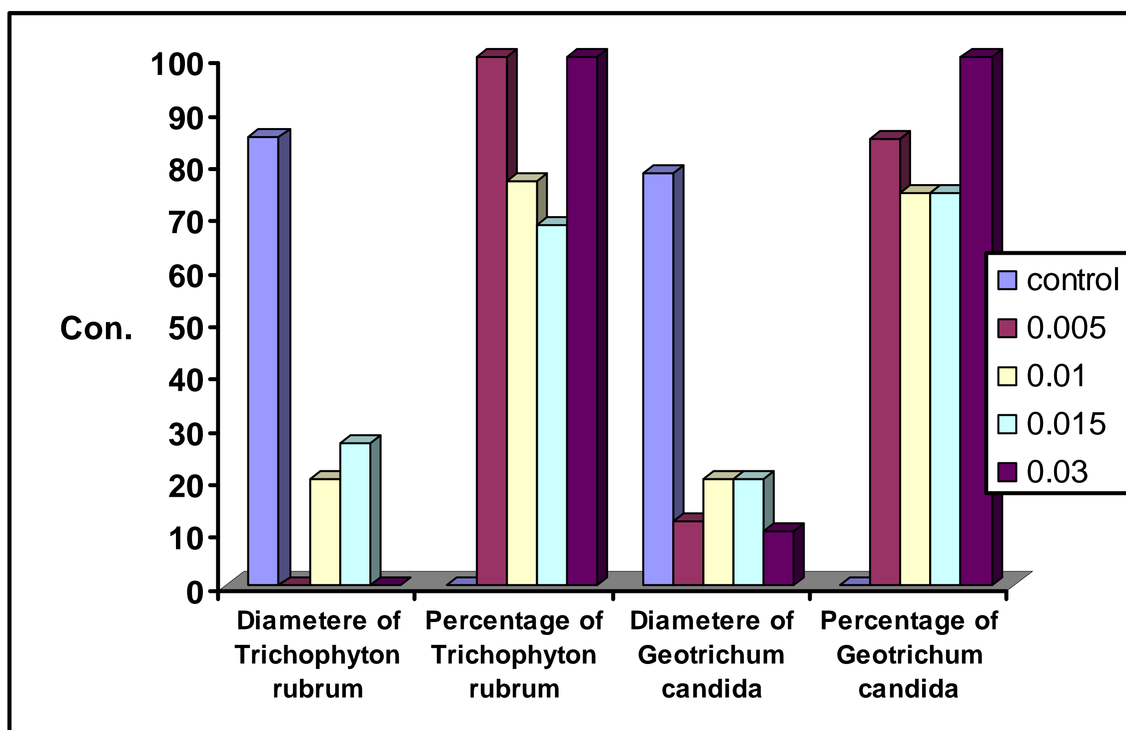


Figure (3-44): Effects of compound (5_G) on the diameter of fungal colonies throughout 96 hrs. of incubation.

Table (3-14): Show stander error of colonial diameter of Trichophyton rumbrum that effected by compound (1G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	A 32±0.176	A 33±0.696	B75±0.577
0.005 mg/ml	A 25±0.6	A 30±0.912	B 70±0.358
0.01 mg/ml	A 21±0.436	A 26±0.196	B 43±1.067

Different letter represent significant differences (P≤0.05) between means of the same column

Table (3-15): Show stander error of colonial diameter of Geotrichum candidum that effected by compound (1G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	A 40±0.760	A 37±0.328	B 85±0.216
0.005 mg/ml	A 23±0.834	B 32±0.353	C 80±0.335
0.01 mg/ml	A 20±1.341	A 28±0.566	B 40±0.632

Different letter represent significant differences (P≤0.05) between means of the same column

Table (3-16): Show stander error of colonial diameter of Trichophyton rumbrum that effected by compound (6G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	A 10±1.897	A 14±0.801	B 25±1.0
0.005 mg/ml	_	A 4±1.50	A 5±0.894

Different letter represent significant differences (P≤0.05) between means of the same column

Table (3-17): Show stander error of colonial diameter of Geotrichum candidum that effected by compound (6G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	A 20±1.118	A 21±2.182	A 21±2.182
0.005 mg/ml	A 4±1.0	A 5±0.447	A 5±0.447

Different letter represent significant differences (P≤0.05) between means of the same column

Table (3-18): Show stander error of colonial diameter of Trichophyton rumbrum that effected by compound (2E) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	A 15±0.516	A 26±0.89	B 27±0.962
0.005 mg/ml	_	_	_

Different letter represent significant differences (P≤0.05) between means of the same column

Table (3-19): Show stander error of colonial diameter of Geotrichum candidum that effected by compound (2E) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	A 15±0.516	A 16±0.5	A 16±0.5
0.005 mg/ml	_	B 4±1.0	B 4±1.0

Different letter represent significant differences (P≤0.05) between means of the same column

Table (3-20): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (4G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A 85±0.542	A 87±0.643
0.005 mg/ml	A 80±0.447	A 80±0.782
0.01 mg/ml	A 70±0.358	A 73±0.351
0.015 mg/ml	A 75±0.23	B 70±0.239
0.03 mg/ml	A 70±0.119	A 65±0.620

Different letter represent significant differences ($P \leq 0.05$) between means of the same column

Table (3-21): Show stander error of colonial diameter of Trichophyton rumbrum that effected by compound (5G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	A 85±0.65	A 85±0.65	A 85±0.65
0.005 mg/ml	_	_	_
0.01 mg/ml	_	B 20±0.447	B 20±0.447
0.015 mg/ml	_	B 27±0.384	B 27±0.384

Different letter represent significant differences ($P \leq 0.05$) between means of the same column

Table (3-22): Show stander error of colonial diameter of Geotrichum candidum that effected by compound (5G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	A 78±0.339	A 78±0.226	A 78±0.226
0.005 mg/ml	A 15±0.516	A 12±0.577	A 12±0.577
0.01 mg/ml	A 10±0.316	A 20±1.34	A 20±1.34
0.015 mg/ml	A 19±0.458	A 20±1.788	A 20±1.788
0.02 mg/ml	A 50±0.707	_	B 10±0.244

Different letter represent significant differences ($P \leq 0.05$) between means of the same column

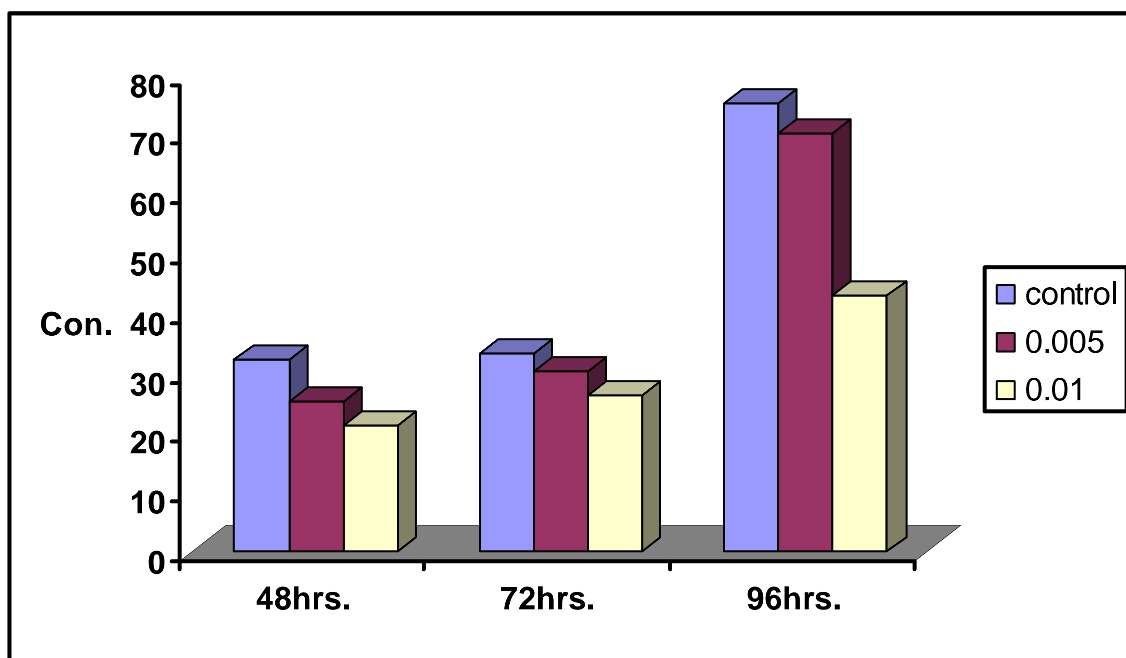


Figure (3-45): Show stander error of colonial diameter of Trichophyton rumbrum that effected by compound (1_G) throughout 48,72 and 96 hrs. of incubation.

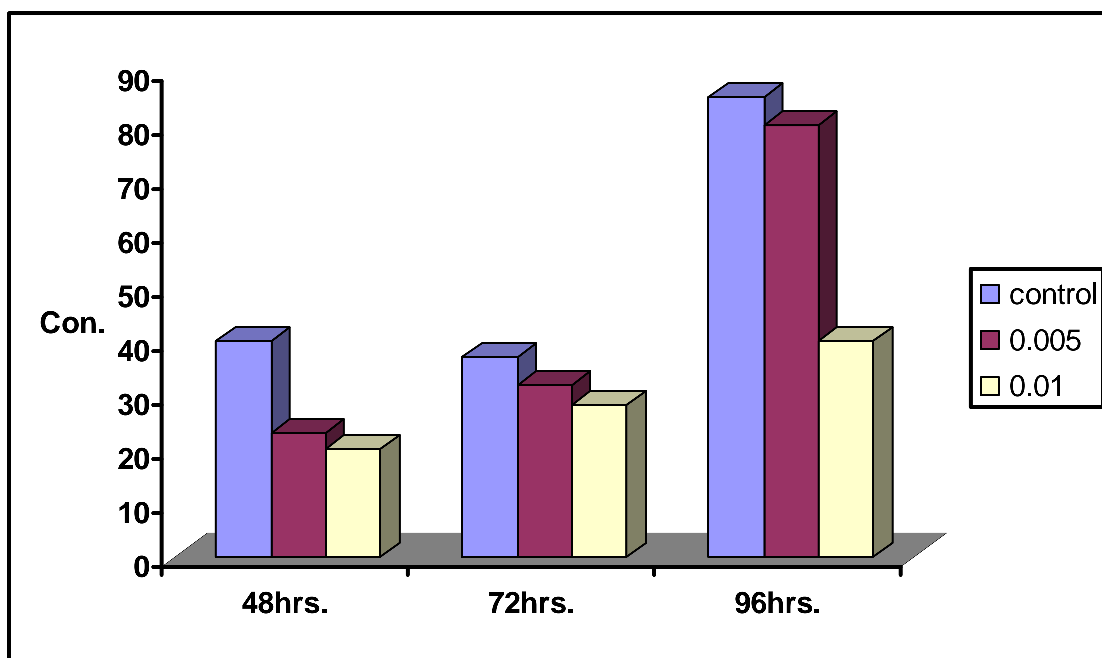


Figure (3-46): Show stander error of colonial diameter of Geotrichum candidum that effected by compound (1_G) throughout 48,72 and 96 hrs. of incubation.

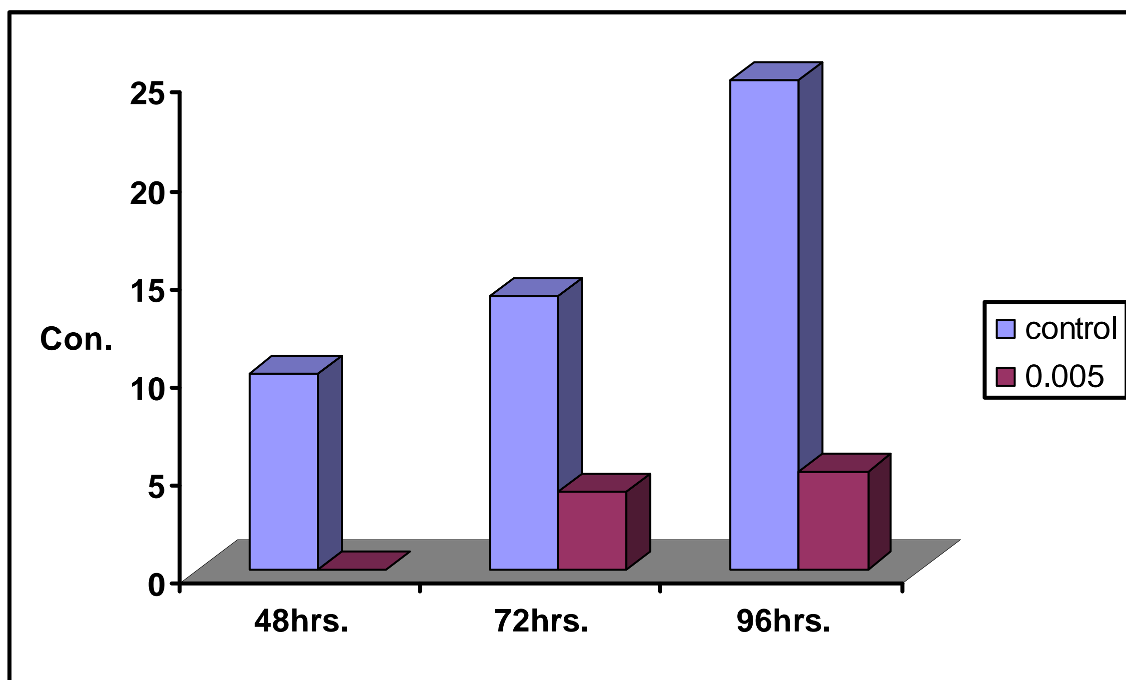


Figure (3-47): Show stander error of colonial diameter of Trichophyton rumbrum that effected by compound (6_G) throughout 48,72 and 96 hrs. of incubation.

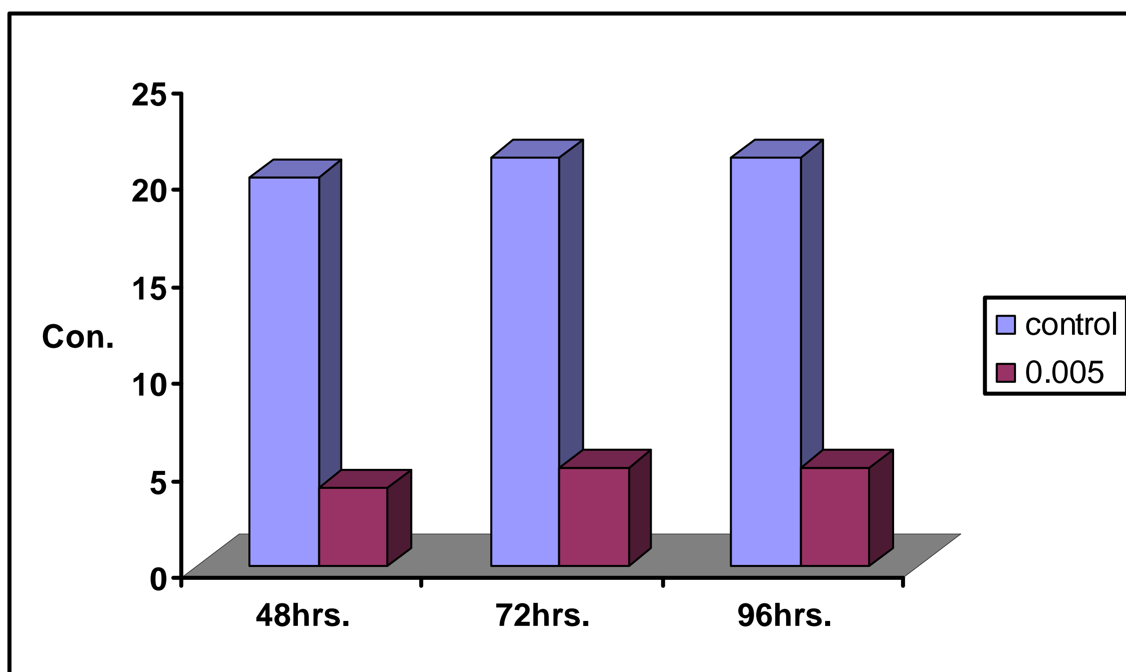


Figure (3-48): Show stander error of colonial diameter of Geotrichum candidum that effected by compound (6_G) throughout 48,72 and 96 hrs. of incubation.

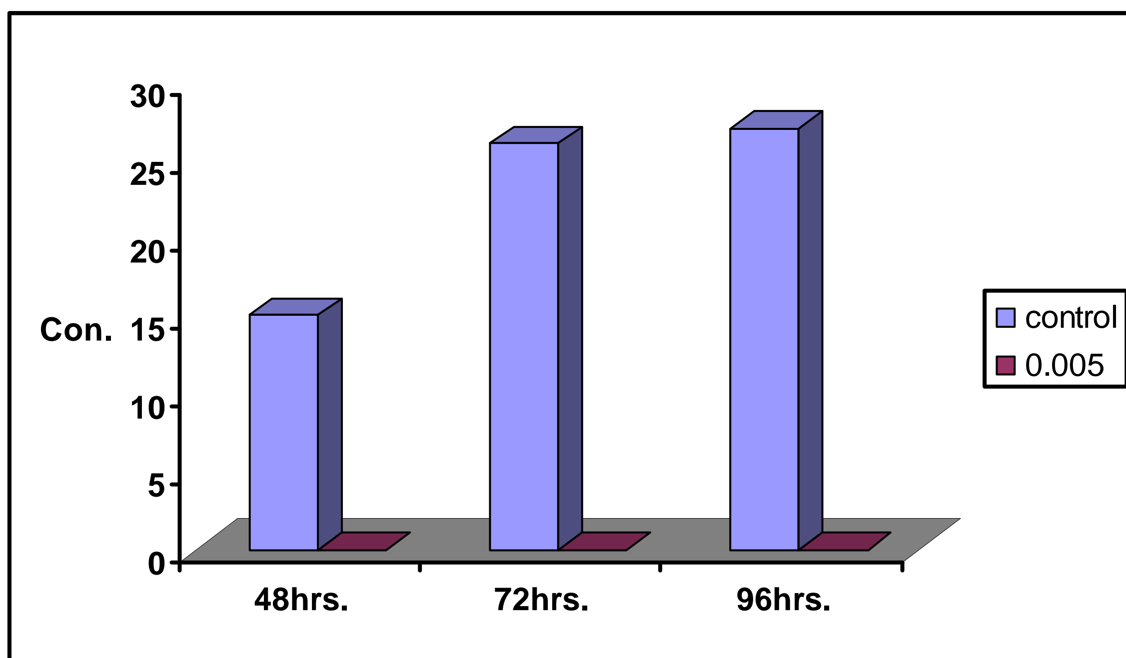


Figure (3-49): Show stander error of colonial diameter of Trichophyton rumbrum that effected by compound (2_E) throughout 48,72 and 96 hrs. of incubation.

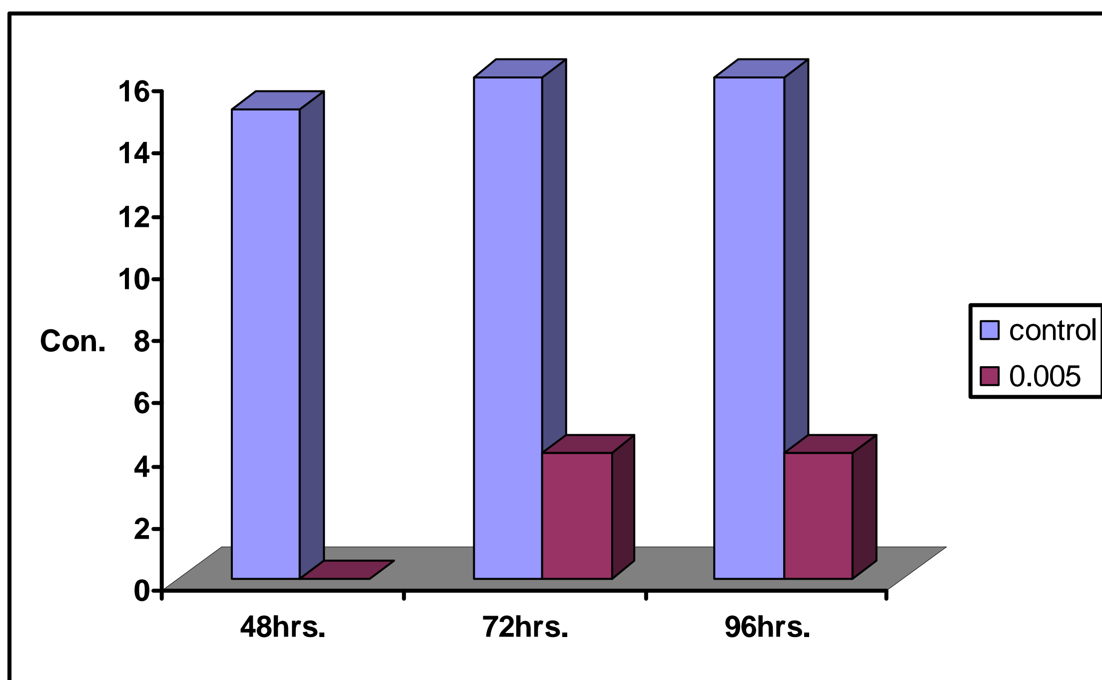


Figure (3-50): Show stander error of colonial diameter of Geotrichum candidum that effected by compound (2_E) throughout 48,72 and 96 hrs. of incubation.

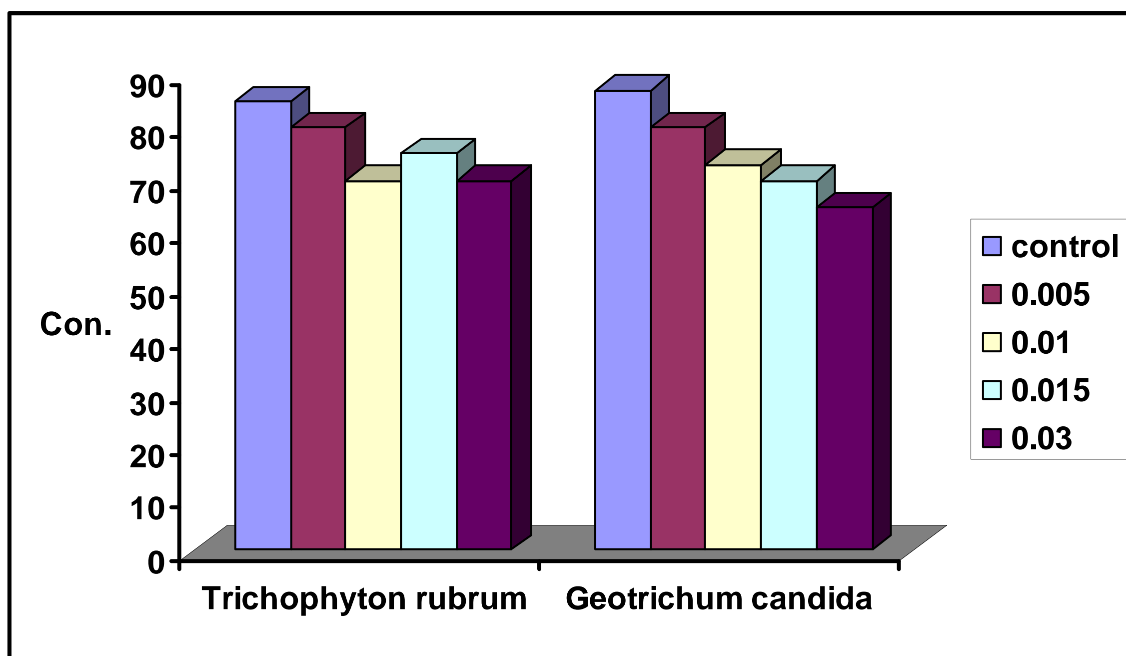


Figure (3-51): Show stander error of colonial diameter of Trichophyton rumbrum that effected by compound (4_G) throughout 48,72 and 96 hrs. of incubation.

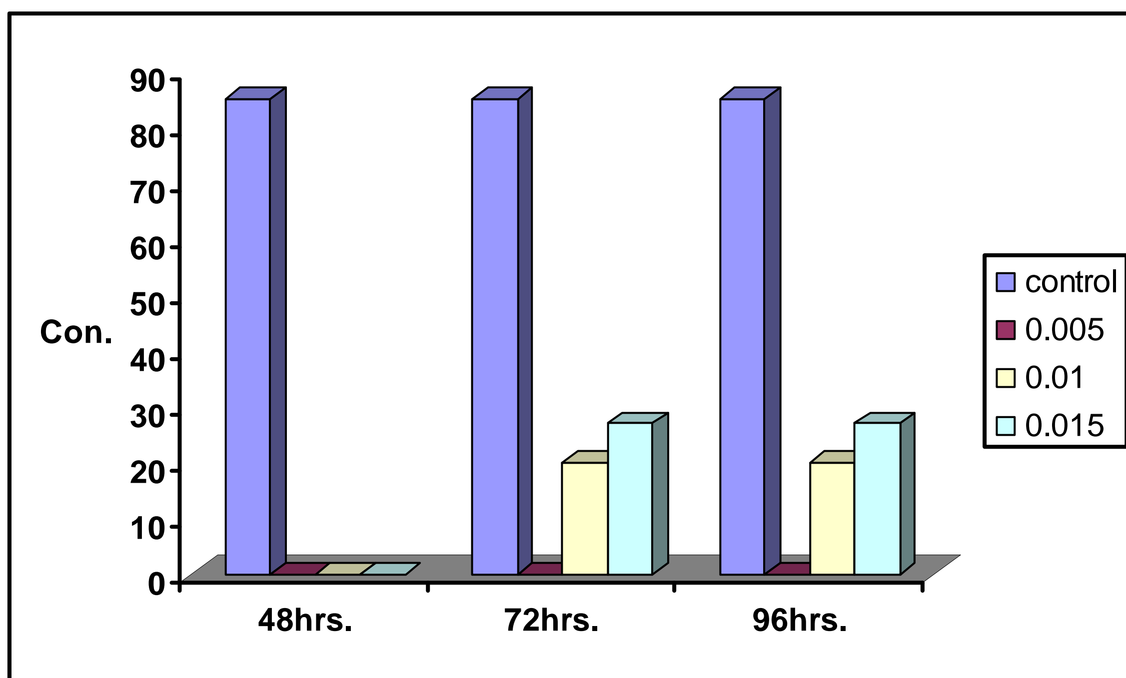


Figure (3-52): Show stander error of colonial diameter of Geotrichum candidum that effected by compound (5_G) throughout 48,72 and 96 hrs. of incubation.

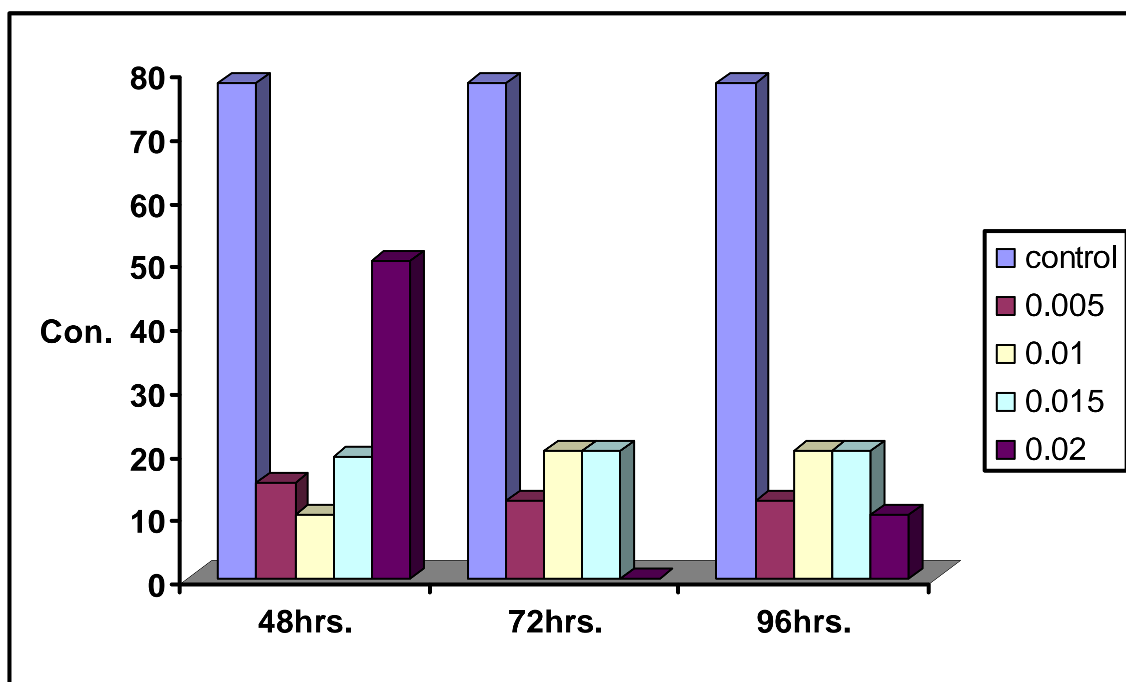


Figure (3-53): Show stander error of colonial diameter of Geotrichum candidum that effected by compound (5_G) throughout 48,72 and 96 hrs. of incubation.

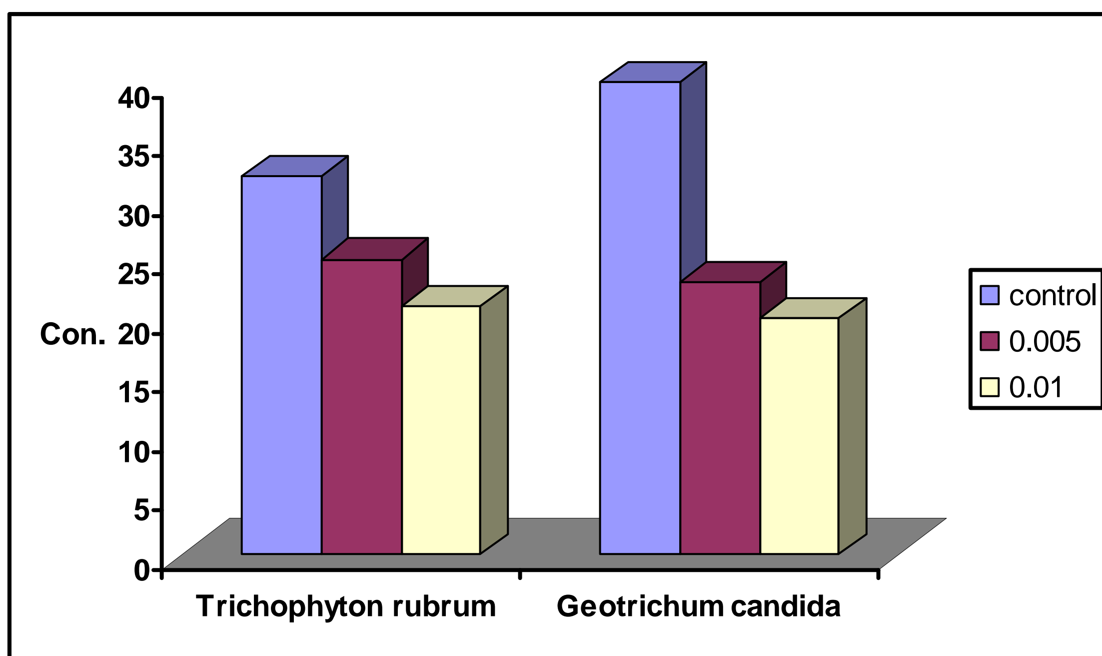


Figure (3-54): Show stander error of colonial diameter of Trichophyton rumbrum & Geotrichum candidum that effected by compound (1_G) throughout 48,72 and 96 hrs. of incubation.

Table (3-23): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (1G) throughout 48hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A32±0.176	A40±0.760
0.005 mg/ml	A25±0.6	A23±0.834
0.01 mg/ml	A21±0.436	A20±1.341

Different letter represent significant differences (P≤0.05) between means of the same column

Table (3-24): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (1G) throughout 72hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A33±0.696	A37±0.328
0.005 mg/ml	A30±0.912	A32±0.353
0.01 mg/ml	A26±0.196	A28±0.566

Different letter represent significant differences (P≤0.05) between means of the same column

Table (3-25): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (1G) throughout 96hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A75±0.577	A85±0.216
0.005 mg/ml	A70±0.358	B80±0.335
0.01 mg/ml	A43±1.067	A40±0.632

Different letter represent significant differences (P≤0.05) between means of the same column

Table (3-26): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (6G) throughout 48hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A10±1.897	A20±1.118
0.005 mg/ml	_	B4±1.0

Different letter represent significant differences (P≤0.05) between means of the same column

Table (3-27): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (6G) throughout 72hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A14±0.801	A21±2.182
0.005 mg/ml	A4±1.5	A5±0.447

Different letter represent significant differences ($P \leq 0.05$) between means of the same column

Table (3-28): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (6G) throughout 96hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A25±1.0	A21±2.182
0.005 mg/ml	A5±0.894	A5±0.447

Different letter represent significant differences ($P \leq 0.05$) between means of the same column

Table (3-29): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (2E) throughout 48hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A15±0.516	A15±0.516

Different letter represent significant differences ($P \leq 0.05$) between means of the same column

Table (3-30): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (2E) after A:72hrs. and B: 96hrs. of incubation.

A

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A26±0.89	B16±0.5
0.005 mg/ml	_	B4±1.0

B

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A27±0.962	B16±0.5
0.005 mg/ml	_	B4±1.0

Different letter represent significant differences ($P \leq 0.05$) between means of the same column

Table (3-31): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (4G) throughout 48hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A85±0.542	A87±0.643
0.005 mg/ml	A80±0.447	A80±0.782
0.01 mg/ml	A70±0.358	A73±0.351
0.015 mg/ml	A75±0.23	B70±0.239
0.03 mg/ml	A70±0.119	A65±0.620

Different letter represent significant differences ($P \leq 0.05$) between means of the same column

Table (3-32): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (5G) after A:48hrs. and B: 72hrs. of incubation.

A

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A85±0.65	A78±0.339
0.005 mg/ml	_	B15±0.516
0.01 mg/ml	_	B10±0.316
0.015 mg/ml	_	B19±0.458
0.02 mg/ml	_	B50±0.707

B

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A85±0.65	A78±0.226
0.005 mg/ml	-	B12±0.577
0.01 mg/ml	A20±0.447	A20±1.34
0.015 mg/ml	A27±0.384	A20±1.788
0.02 mg/ml	-	-

Different letter represent significant differences ($P \leq 0.05$) between means of the same column

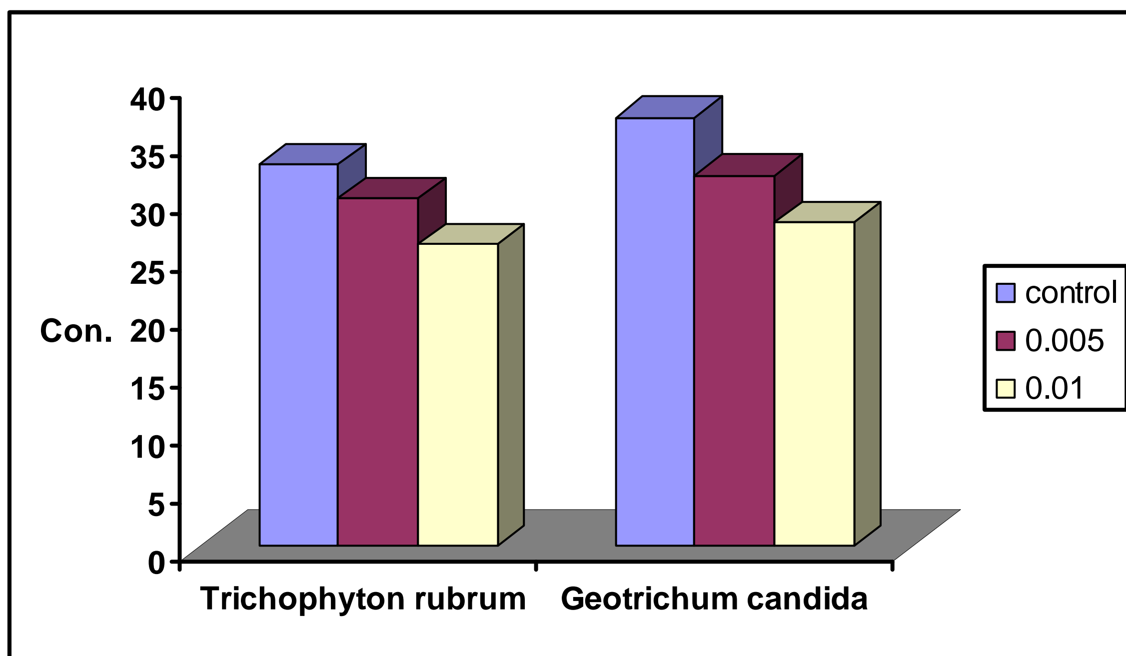


Figure (3-55): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (1_G) throughout 72hrs. of incubation.

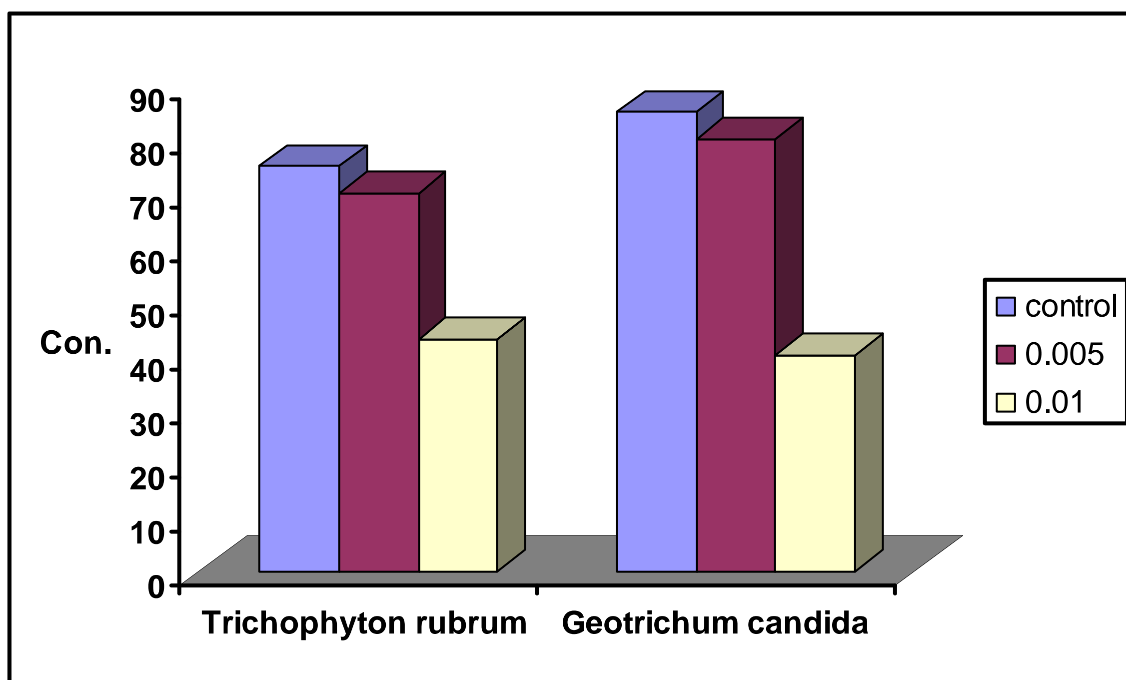


Figure (3-56): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (1_G) throughout 96hrs. of incubation.

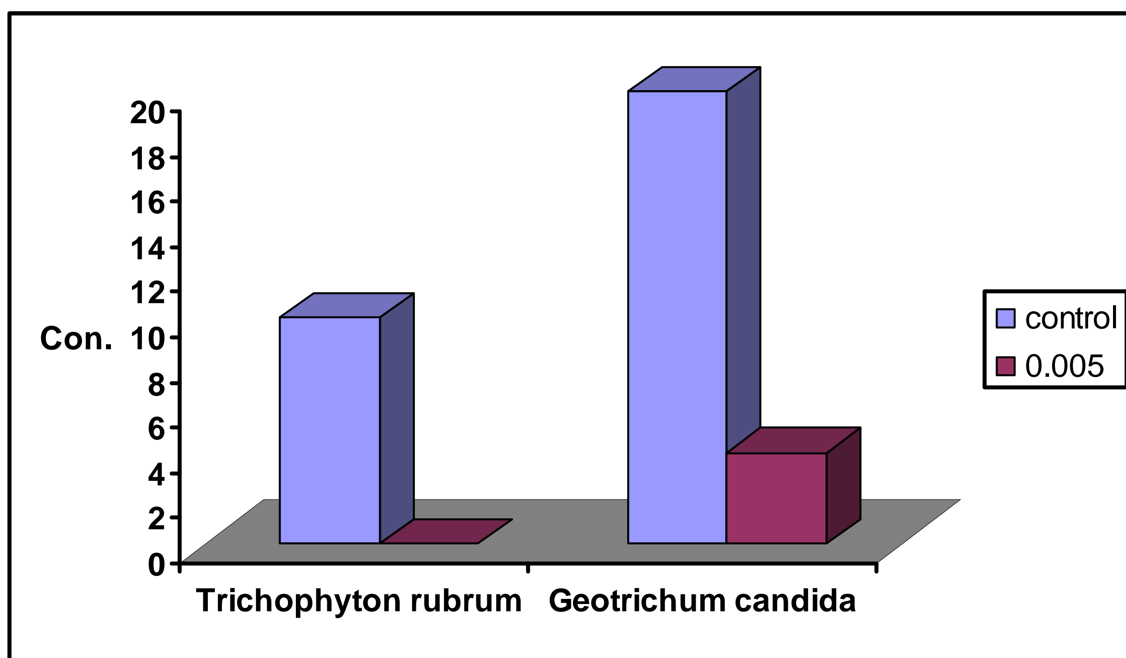


Figure (3-57): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (6_G) throughout 48hrs. of incubation.

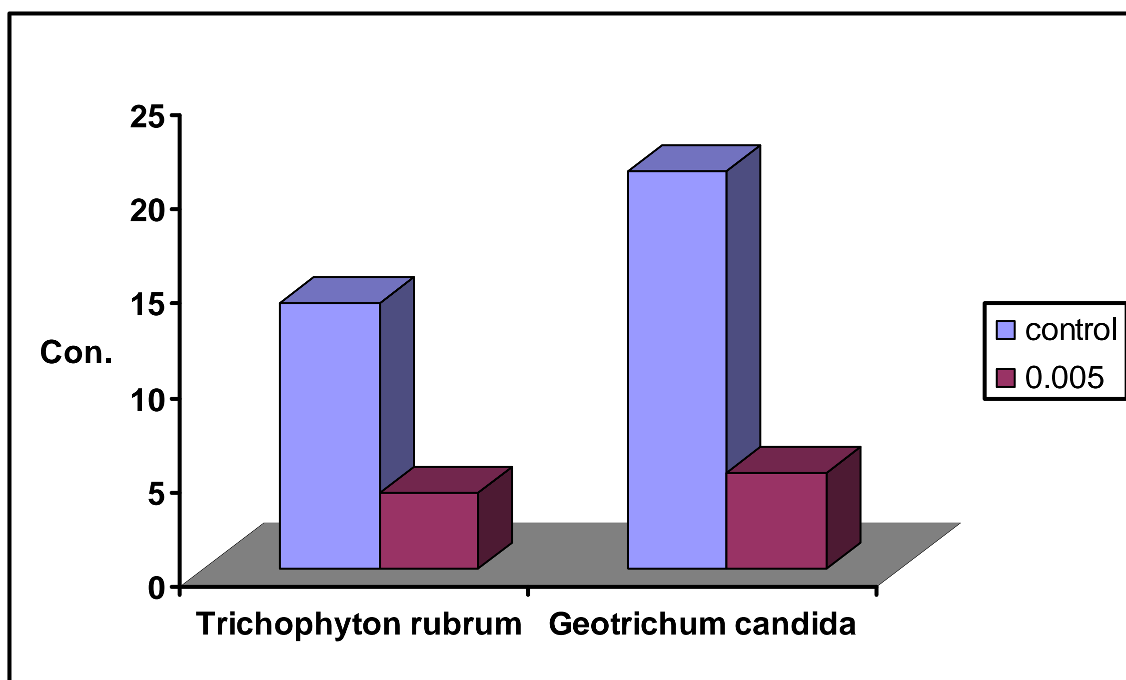


Figure (3-58): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (6_G) throughout 72hrs. of incubation.

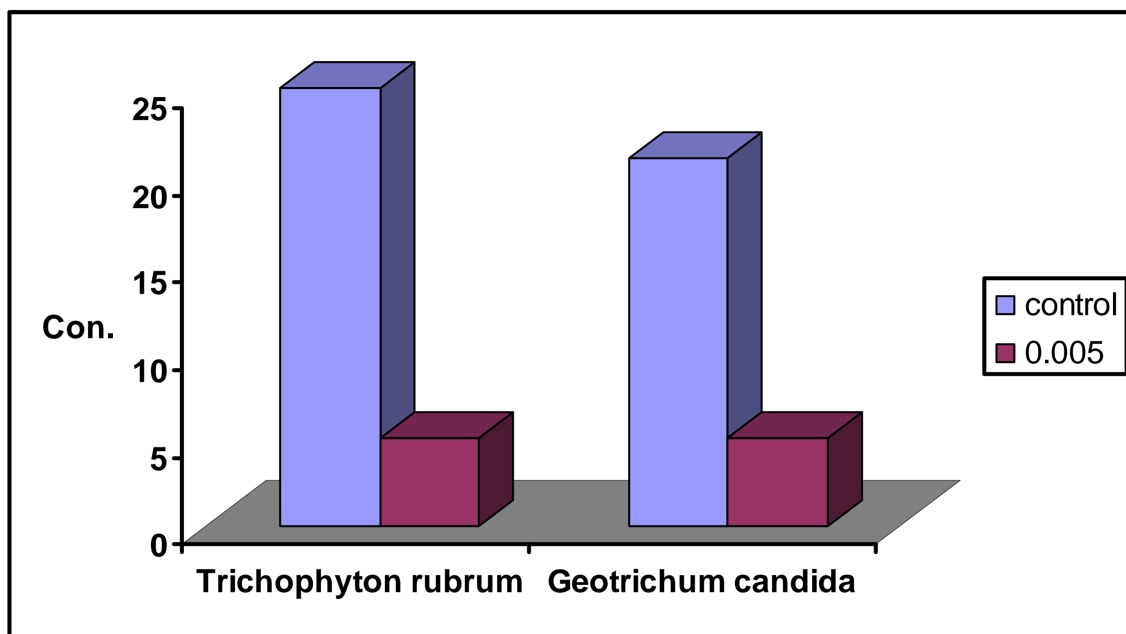


Figure (3-59): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (6_G) throughout 96hrs. of incubation.

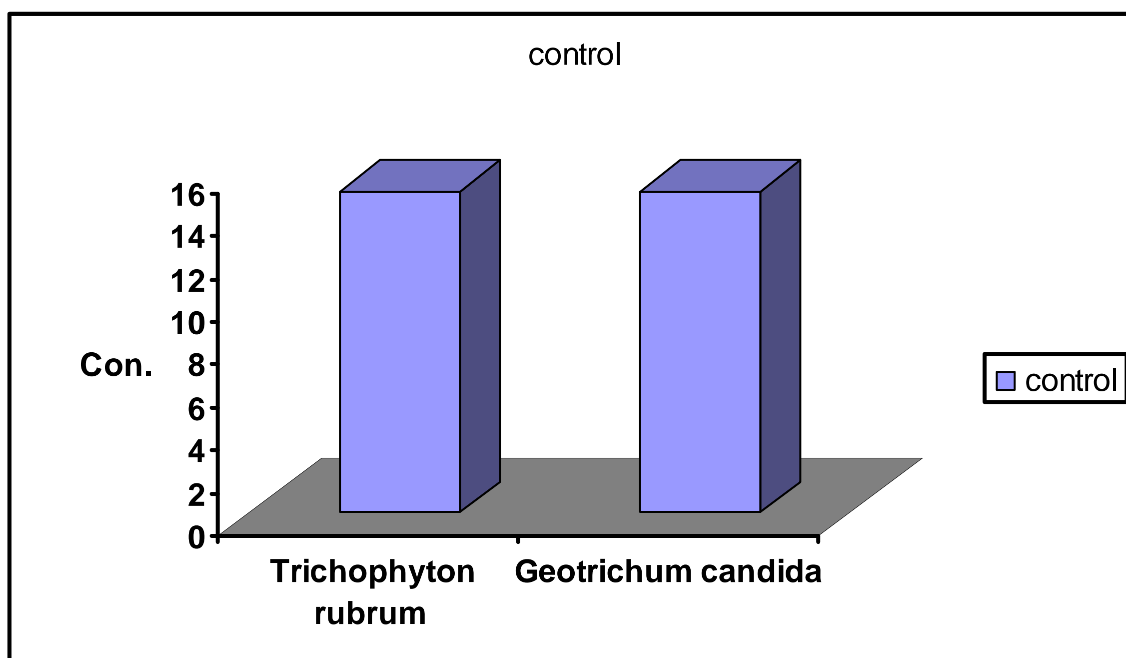
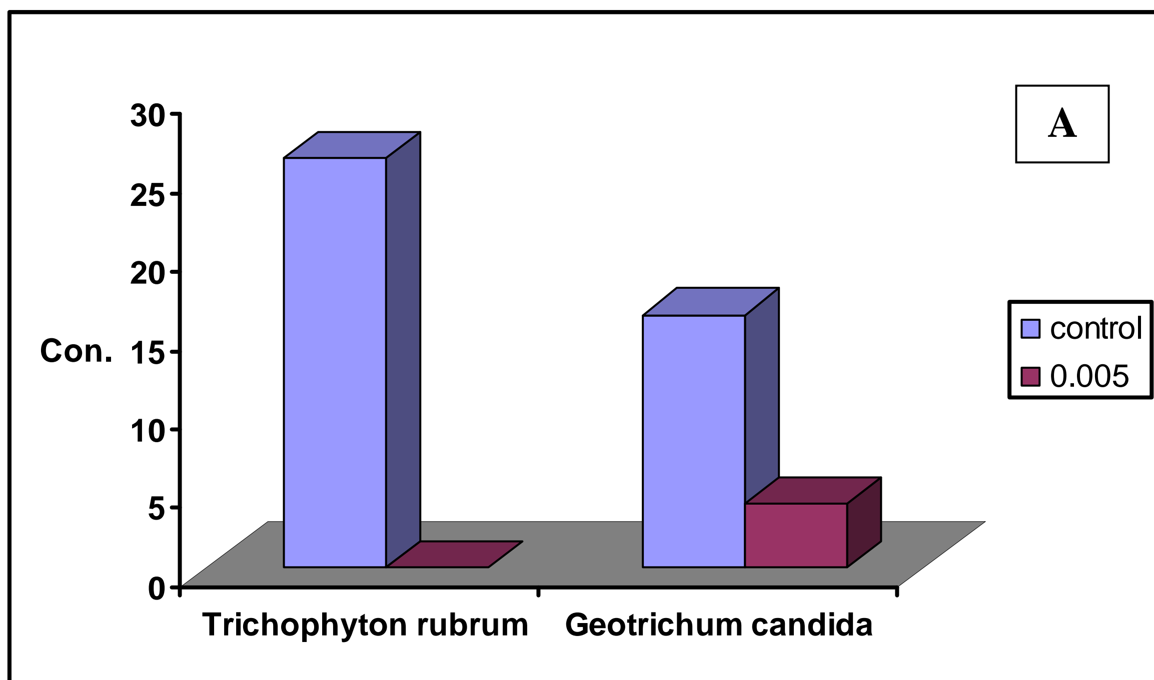


Figure (3-60): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (2_E) throughout 48hrs. of incubation.



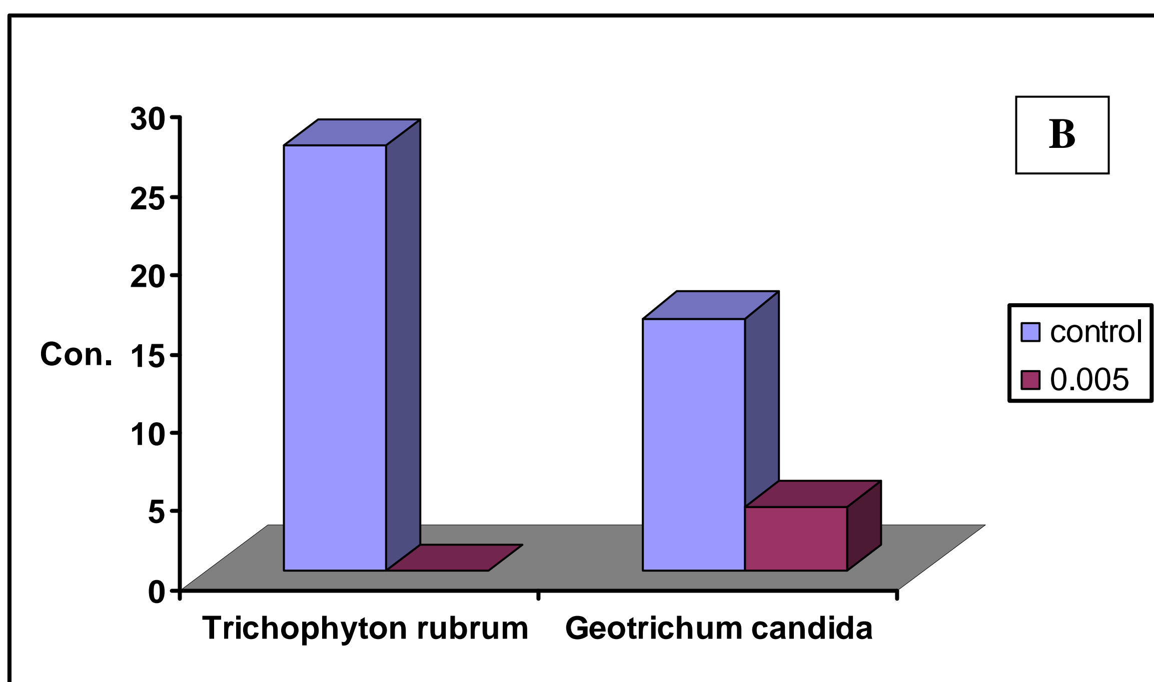


Figure (3-61): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (2E) after A:72hrs. and B: 96hrs. of incubation.

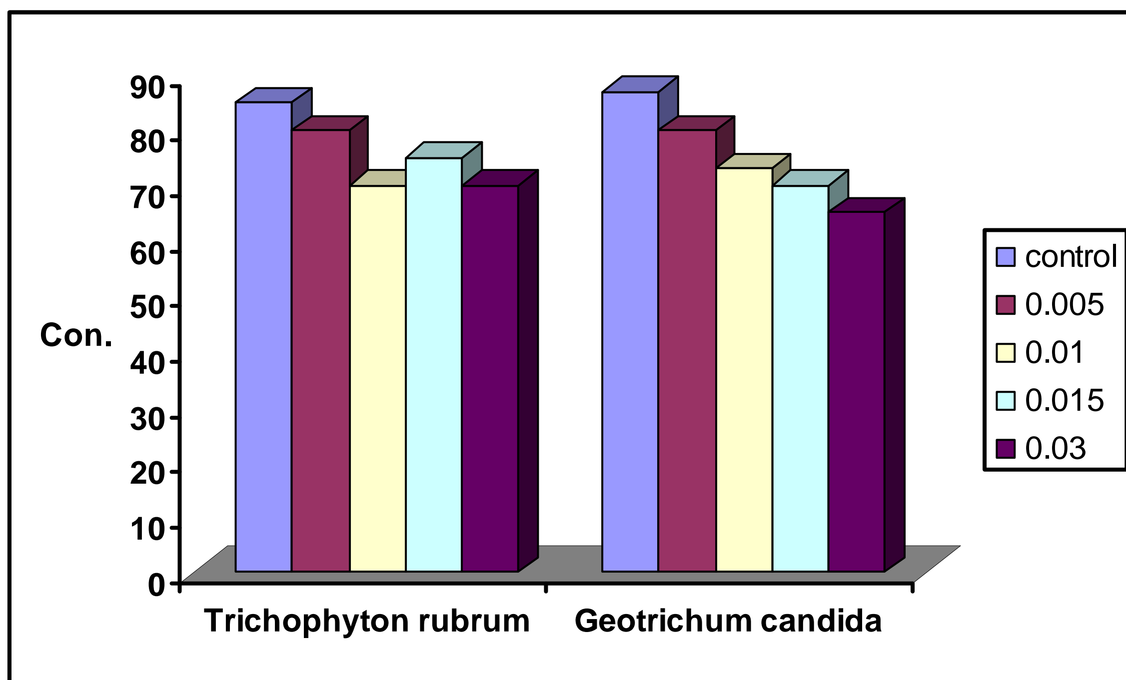
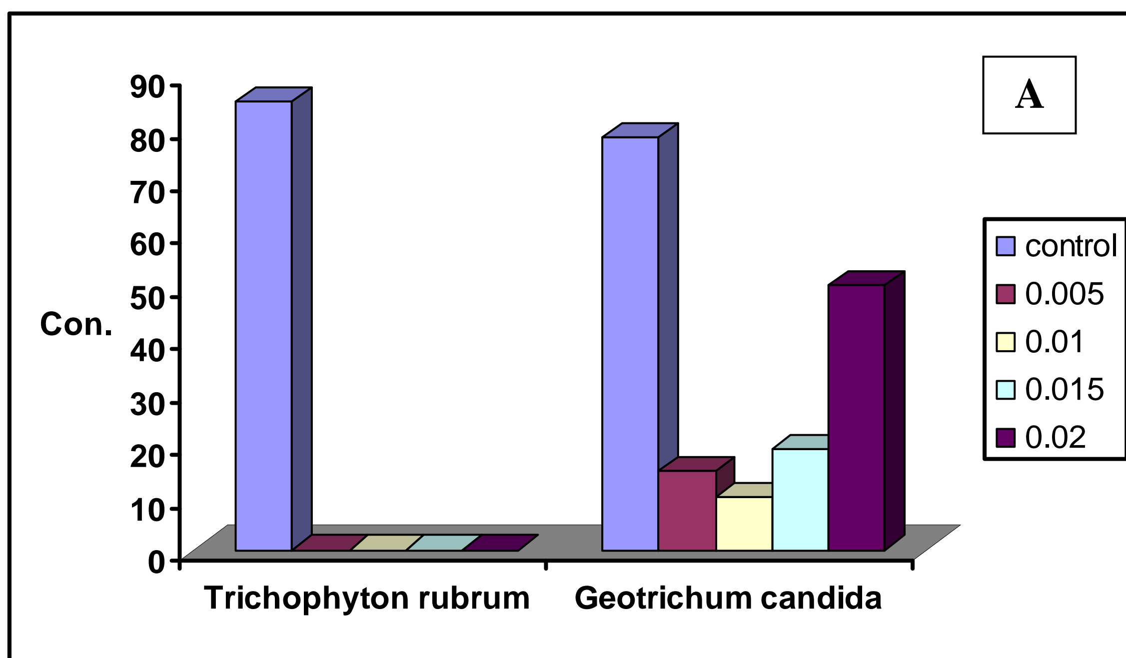


Figure (3-62): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (4_G) throughout 48hrs. of incubation.



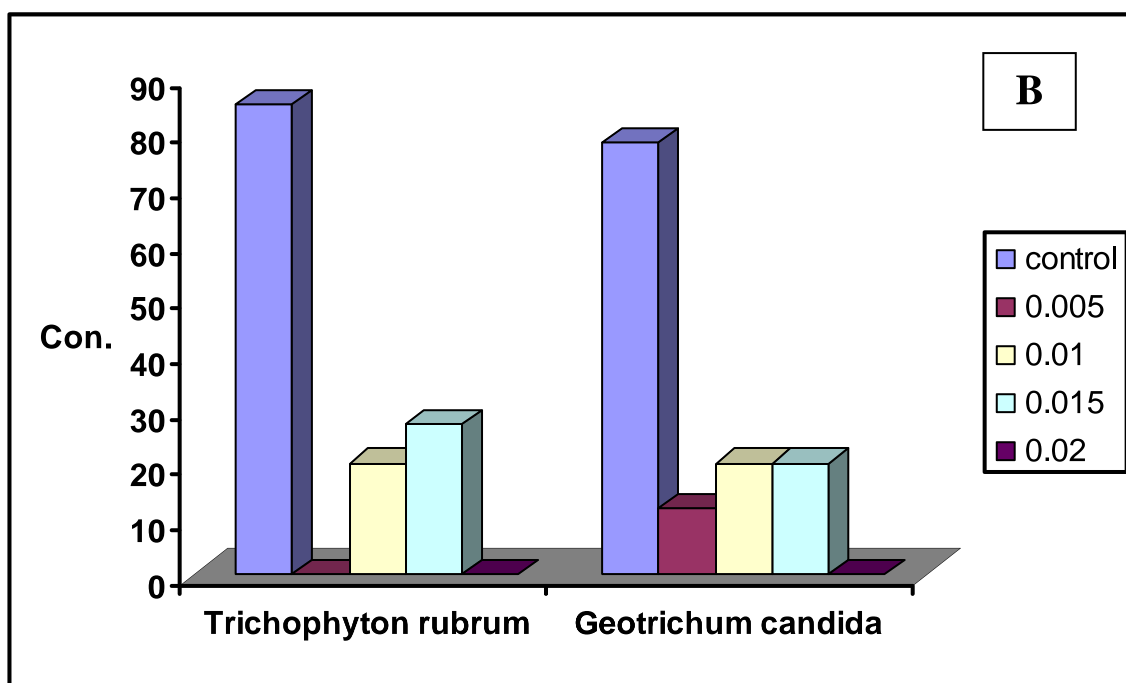


Figure (3-63): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (5_G) after A:48hrs. and B: 72hrs. of incubation.

Contents

List of Tables		VI
List of Figures		XI
Abstract		II
Chapter One : Introduction		
1.1	Chemotherapy	1
1.2	Principles of Antifungal Therapy	2
1.3	Azole Antifungals	3
1.31	Mechanism of Action	4
1.3.2	Ergostererol Biosythesis	5
1.3.3	Ketoconazole compound	10
1.3.3.1	Spectrum of Activity	11
1.3.3.2	pharmacokinetics	12
1.3.3.3	Hormonal effects	13
1.4	Biological activity of pyrimidine derivatives	13
1.5	Fungi	15
1.51	Pathogenic fungi	17
1.5.2	Trichophyton rubrum	18
1.5.3	Geotrichum candidum	19
1.6	Aim of the work	21
Chapter Two: Experimental		
2.1	Chemicals	22

2.2	**Instruments**	**23**
2.3	**Preparations**	**23**
2.4	**Mixture of ketoconazole (1_G) with caffeine**	**34**
2.5	***In vitro* study**	**34**
2.6	**Study of the Antimicrobial Activities**	**35**
2.7	**Biological study**	**35**
2.8	**Procedures**	**35**
2.8.1	**Sterilization methods**	**35**
2.8.2	**Preparation of culture media**	**35**
2.8.2.1	**Modified sabouraud dextrose agar**	**35**
2.8.2.2	**Potato dextrose agar**	**36**
Chapter Three: Results & Discussion		
3.1	**Synthesis and characterization of compound(1G)**	**37**
3.2	**Synthesis and characterization of ethyl -4- amino benzoate (2_G)**	**44**
3.3	**Synthesis and characterization of compound 2-thioacetic acid -5- (4- amino phenyl) 1,3,4-oxadiazole (2_E)**	**46**
3.4	**Synthesis and characterization of compound 6-methyl -4- oxo -1,2,3,4 –tetrahydro -2-thiopyrimidine (4_G)**	**49**
3.5	**Synthesis and characterization of compound 2-hydrazino- -6- methyl pyrimidine -4- (3H) one (5_G)**	**52**

3.6	***In vitro* study**	**54**
3.6.1	**Effects of ketoconazole compounds (1_G) on the growth of fungi**	**54**
3.6.2	**Mixture of ketoconazole with caffeine (6G)**	**64**
3.6.3	**Effects of 2- thioacetic acid (4- amino phenyl) 1,3,4-oxadiazole (2_E) on growth of fungi**	**72**
3.6.4	**Effects of 6- methyl -4- oxo-1,2,3,4- tetrahydro-2-thiopyrimidine (4G)**	**79**
3.6.5	**Effects of 2- hydrazino -6- methyl pyrimidine -4-(3H) one (5G)**	**81**
	Conclusion & Future work	
	Conclusion	**118**
	Future work	**120**
	References	**121**

List of Tables

No.	Name	Page
2.1	Chemicals and their manufactures	22
2.2	Instruments and their manufacturer company	23
3.1	Effects of compound (1G) on the diameter of fungal colonies throughout 48 hrs. of incubation	58
3.2	Effects of compound (1G) on the diameter of fungal colonies throughout 72 hrs. of incubation	60
3.3	Effects of compound (1G) on the diameter of fungal colonies throughout 96 hrs. of incubation	62
3.4	Effects of mixture (6G) on the diameter of fungal colonies throughout 48 hrs. of incubation	66
3.5	Effects of mixture (6G) on the diameter of fungal colonies throughout 72 hrs. of incubation	68
3.6	Effects of mixture (6G) on the diameter of fungal colonies throughout 96 hrs. of incubation	70
3.7	Effects of compound (2E) on the diameter of fungal colonies throughout 48 hrs. of incubation	73
3.8	Effects of compound (2E) on the diameter of fungal colonies throughout 72 hrs. of incubation	75
3.9	Effects of compound (2E) on the diameter of fungal colonies throughout 96 hrs. of incubation	77
3.10	Effects of compound (4G) on the diameter of fungal colonies throughout 48 hrs. of incubation	79

3.11	**Effects of compound (5G) on the diameter of fungal colonies throughout 48 hrs. of incubation**	**82**
3.12	**Effects of compound (5G) on the diameter of fungal colonies throughout 72 hrs. of incubation**	**84**
3.13	**Effects of compound (5G) on the diameter of fungal colonies throughout 96 hrs. of incubation**	**86**
3.14	**The standard error of colonial diameter of Trichophyton rumbrum that effected by compound (1G) throughout 48,72 and 96 hrs. of incubation**	**95**
3.15	**The standard error of colonial diameter of Geotrichum candidum that effected by compound (1G) throughout 48,72 and 96 hrs. of incubation**	**95**
3.16	**The standard error of colonial diameter of Trichophyton rumbrum that effected by compound (6G) throughout 48,72 and 96 hrs. of incubation**	**96**
3.17	**The standard error of colonial diameter of Geotrichum candidum that effected by compound (6G) throughout 48,72 and 96 hrs. of incubation**	**96**
3.18	**The standard error of colonial diameter of Trichophyton rumbrum that effected by compound (2E) throughout 48,72 and 96 hrs. of incubation**	**97**
3.19	**The standard error of colonial diameter of**	**97**

	Geotrichum candidum that effected by compound (2E) throughout 48,72 and 96 hrs. of incubation	
3.20	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (4G) throughout 48,72 and 96 hrs. of incubation**	**98**
3.21	**The standard error of colonial diameter of Trichophyton rumbrum that effected by compound (5G) throughout 48,72 and 96 hrs. of incubation**	**99**
3.22	**The standard error of colonial diameter of Geotrichum candidum that effected by compound (5G) throughout 48,72 and 96 hrs. of incubation**	**99**
3.23	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (1G) throughout 48hrs. of incubation**	**105**
3.24	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (1G) throughout 72hrs. of incubation**	**105**
3.25	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (1G) throughout 96hrs. of incubation**	**106**

3.26	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (6G) throughout 48hrs. of incubation**	**106**
3.27	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (6G) throughout 72hrs. of incubation**	**107**
3.28	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (6G) throughout 96hrs. of incubation**	**107**
3.29	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (2E) throughout 48hrs. of incubation**	**108**
3.30	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (2E) after A:72hrs. and B: 96hrs. of incubation**	**109**
3.31	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (4G) throughout 48hrs. of incubation**	**110**

3.32	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (5G) after A:48hrs. and B: 72hrs. of incubation**	**111**

List of Figures

No.	Name	Page
1.1	A zole compounds	4
1.2	An outline scheme for the biosynthesis of ergosterol from squalene , showing the points of inhibition of several types of antifungal agents	5
1.3	A zole antifungal agents	6
1.4	Antifungal agents that inhibit squalene expoxidation	7
1.5	Morpholine derivatives that are antifungal agents	9
1.6	Ketoconazole compound as antifungal agents	11
3.1	F.T.IR spectrum of compound (1_G)	43
3.2	F.T.IR spectrum of compound (2a)	45
3.3	F.T.IR spectrum of compound (2_E)	48
3.4	F.T.IR spectrum of compound (4_G)	51
3.5	F.T.IR spectrum of compound (5_G)	53
3.6	Effect of Ketoconazole compound (1_G) on the growth of Trichophyton rubrum after 48 hrs. of incubation	59
3.7	Effect of Ketoconazole compound (1_G) on the growth of Geotrichum Candidum after 48 hrs. of incubation	59
3.8	Effect of Ketoconazole compound (1_G) on the growth of Trichophyton rubrum after 72 hrs. of	61

	incubation	
3.9	Effect of Ketoconazole compound (1_G) on the growth of Geotrichum Candidum after 72 hrs. of incubation	61
3.10	Effect of Ketoconazole compound (1_G) on the growth of Trichophyton rubrum after 96 hrs. of incubation	63
3.11	Effect of Ketoconazole compound (1_G) on the growth of Geotrichum Candidum after 96 hrs. of incubation	63
3.12	Effect of mixture compound (6_G) on the growth of Trichophyton rubrum after 48 hrs. of incubation	67
3.13	Effect of mixture compound (6_G) on the growth of Geotrichum Candidum after 48 hrs. of incubation	67
3.14	Effect of mixture compound (6_G) on the growth of Trichophyton rubrum after 72 hrs. of incubation	69
3.15	Effect of mixture compound (6_G) on the growth of Geotrichum Candidum after 72 hrs. of incubation	69
3.16	Effect of mixture compound (6_G) on the growth of Trichophyton rubrum after 96 hrs. of incubation	71
3.17	Effect of mixture compound (6_G) on the growth of Geotrichum Candidum after 96 hrs. of incubation	71
3.18	Effect of mixture compound (2E) on the growth of Trichophyton rubrum after 48 hrs. of incubation	74

3.19	**Effect of mixture compound (2E) on the growth of Geotrichum Candidum after 48 hrs. of incubation**	**74**
3.20	**Effect of mixture compound (2E) on the growth of Trichophyton rubrum after 72 hrs. of incubation**	**76**
3.21	**Effect of mixture compound (2E) on the growth of Geotrichum Candidum after 72 hrs. of incubation**	**76**
3.22	**Effect of mixture compound (2E) on the growth of Trichophyton rubrum after 96 hrs. of incubation**	**78**
3.23	**Effect of mixture compound (2E) on the growth of Geotrichum Candidum after 96 hrs. of incubation**	**78**
3.24	**Effect of mixture compound (4G) on the growth of Trichophyton rubrum after 48 hrs. of incubation**	**80**
3.25	**Effect of mixture compound (4G) on the growth of Geotrichum Candidum after 48 hrs. of incubation**	**80**
3.26	**Effect of mixture compound (5G) on the growth of Trichophyton rubrum after 48 hrs. of incubation**	**83**
3.27	**Effect of mixture compound (5G) on the growth of Geotrichum Candidum after 48 hrs. of incubation**	**83**
3.28	**Effect of mixture compound (5G) on the growth of Trichophyton rubrum after 72 hrs. of incubation**	**85**
3.29	**Effect of mixture compound (5G) on the growth of Geotrichum Candidum after 72 hrs. of incubation**	**85**
3.30	**Effect of mixture compound (5G) on the growth of**	**87**

	Trichophyton rubrum after 96 hrs. of incubation	
3.31	**Effect of mixture compound (5G) on the growth of Geotrichum Candidum after 96 hrs. of incubation**	**87**
3.32	**Effects of compound (1_G) on the diameter of fungal colonies throughout 48 hrs. of incubation.**	**88**
3.33	**Effects of compound (1_G) on the diameter of fungal colonies throughout 72 hrs. of incubation.**	**88**
3.34	**Effects of compound (1_G) on the diameter of fungal colonies throughout 96 hrs. of incubation.**	**89**
3.35	**Effects of compound (6_G) on the diameter of fungal colonies throughout 48 hrs. of incubation.**	**89**
3.36	**Effects of compound (6_G) on the diameter of fungal colonies throughout 72 hrs. of incubation.**	**90**
3.37	**Effects of compound (6_G) on the diameter of fungal colonies throughout 96 hrs. of incubation.**	**90**
3.38	**Effects of compound (2_E) on the diameter of fungal colonies throughout 48 hrs. of incubation.**	**91**
3.39	**Effects of compound (2_E) on the diameter of fungal colonies throughout 72 hrs. of incubation.**	**91**
3.40	**Effects of compound (2_E) on the diameter of fungal colonies throughout 96 hrs. of incubation.**	**92**
3.41	**Effects of compound (4_G) on the diameter of fungal colonies throughout 48 hrs. of incubation.**	**92**

3.42	Effects of compound (5_G) on the diameter of fungal colonies throughout 48 hrs. of incubation.	93
3.43	Effects of compound (5_G) on the diameter of fungal colonies throughout 72 hrs. of incubation.	93
3.44	Effects of compound (5_G) on the diameter of fungal colonies throughout 96 hrs. of incubation.	94
3.45	The standard error of colonial diameter of Trichophyton rumbrum affected by compound (1_G) throughout 48,72 and 96 hrs. of incubation.	100
3.46	The standard error of colonial diameter of Geotrichum candidum affected by compound (1_G) throughout 48,72 and 96 hrs. of incubation.	100
3.47	The standard error of colonial diameter of Trichophyton rumbrum affected by compound (6_G) throughout 48,72 and 96 hrs. of incubation.	101
3.48	The standard error of colonial diameter of Geotrichum candidum affected by compound (6_G) throughout 48,72 and 96 hrs. of incubation.	101
3.49	The standard error of colonial diameter of Trichophyton rumbrum affected by compound (2_E) throughout 48,72 and 96 hrs. of incubation.	102
3.50	The standard error of colonial diameter of Geotrichum candidum affected by compound (2_E) throughout 48,72 and 96 hrs. of incubation.	102

3.51	**The standard error of colonial diameter of Trichophyton rumbrum affected by compound (4_G) throughout 48,72 and 96 hrs. of incubation.**	**103**
3.52	**The standard error of colonial diameter of Geotrichum candidum affected by compound (5_G) throughout 48,72 and 96 hrs. of incubation.**	**103**
3.53	**The standard error of colonial diameter of Geotrichum candidum affected by compound (5_G) throughout 48,72 and 96 hrs. of incubation.**	**104**
3.54	**The standard error of colonial diameter of Trichophyton rumbrum & Geotrichum candidum affected by compound (1_G) throughout 48,72 and 96 hrs. of incubation.**	**104**
3.55	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum affected by compound (1_G) throughout 72hrs. of incubation.**	**112**
3.56	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum affected by compound (1_G) throughout 96hrs. of incubation.**	**112**
3.57	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum affected by compound (6_G) throughout 48hrs. of incubation.**	**113**

3.58	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum affected by compound (6_G) throughout 72hrs. of incubation.**	**113**
3.59	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum affected by compound (6_G) throughout 96hrs. of incubation.**	**114**
3.60	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum affected by compound (2_E) throughout 48hrs. of incubation.**	**114**
3.61	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum affected by compound (2E) after A:72hrs. and B: 96hrs. of incubation.**	**115**
3.62	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum affected by compound (4_G) throughout 48hrs. of incubation.**	**116**
3.63	**The standard error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum affected by compound (5_G) after A:48hrs. and B: 72hrs. of incubation.**	**117**

وزارة التعليم العالي والبحث العلمي
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قسم الكيمياء

تقييم وتحضير مشتقات من الازول والبرميدين كمواد كيميائية مضادة لامراض الجلد

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مقدمة الى كلية العلوم جامعة النهرين
وهي جزء من متطلبات نيل درجة دكتوراه في الكيمياء الحياتية

من قبل

فراس عبد الله حسن

بكلوريوس علوم كيمياء جامعة النهرين ٢٠٠٠
ماجستير علوم كيمياء جامعة النهرين 2002

ربيع الاول ١٤٢٨هـ
اذار ٢٠٠٧م

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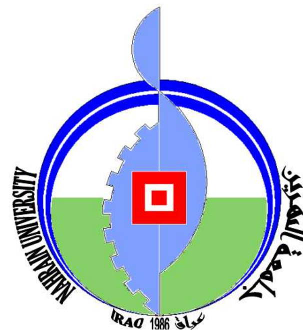

Evaluation & Synthesis Of Azole & Pyrimidine Derivatives As Chemotherapeutic Agents Against Dermatophyte Diseases

A thesis
Submitted to the College of Science / AL-Nahrain University
In partial fulfillment of the requirements for the degree of
doctor of philosophy in Biochemistry

By

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March 2007

Conclusion:

1- In this work new derivatives of Azole compound has been synthesized : 1- acety -4[4-[[2-(2,4- dichlorophenyl)-2- (1H-imidazole-1-methyl)-1,3 dioxolan -4-y1] methoxy]phenyl] piperazine , 2- thioacetic -5- (4-amino phenyl) 1,3,4- oxadiazole ,
and new derivaties of pyrimidine compound has been synthesized :6- methyl –4-oxo-1,2,3,4-tetrahydro-2- thiopyrimidine , 2- hydrazine -6- methyl pyrimidine by simple and efficiency methods .

2-The new derivatives were found to inhibition of growth of some type of fungi .

3-The new derivartives were found different in the inhibitory effect between both species of fungi (Trichophton rubrum and geotrichum candidum) in the same time of incubation .

4-*Invitro* study showed us that the highest inhibition of growth of fungal was found after 48 hrs .of incubation .

5-The best concentration of new derivatives to inhibit the growth of fungi were (0.001 mg/ml ,0.015,and 0.02 mg/ml.)

6-The inhibitory effect was found to increase as the concentrations of new derivaties increase .

7-The inhibitory effect was found to increase as the average of colonial diameter of fungi decrease and increase the percentage of inhibition .

8-The average of colonial diameters of fungi were found decrease as increase the concentrations of new derivatives .

9-The new derivatives of 6-methyl -4-oxo-1,2,3,4- tetrahydro -2- thirimidine (4G) was not effective against the both species of fungi at the different concentrations .

10-Caffeine compound was found to increase the activity against fungi when mixed with ketoconazole compound at the ratio 1.5:1.5 ml .

Future work :

1-Testing the effect of these compounds on bacteria .

2-Studying the invivo experimental work on the pharmacological action of these compounds .

3-Studying the invivo activity of new derivatives against sequamous cell carcinoma in the mice .

4-Studying the invitro activity of these compounds against plasmacytoma cell line .

5-Studying the *invitro* activity of Amphotericin B with ketococanzole as antifungal compound

TO My Father ,My Wife & My

Family

With My Love And Respect

Firas

References

1. Lewis , R.E., Kontoyiannis , D.P., J. Antimicrob. Chemother , **56**,887-892, (2005) .

2. Singh , N., paterson , D.L., clin. Microbiol . Rev., **18**,44-49, (2005) .

3. Martin , C.A., J. pharm. Pract ., **18** , 9- 17 , (2005).

4. Cuena –Estrella , M., J. Antimicrob. Chemother ., **54** , 854-869, (2004).

5. Barchiesi , F., spreghini, E., Maracci , M., fothergill, A.W. Baldassarri, I., Rinald , M.G., scalise , G., Antimicrob . Agents chemother., **48**,3317-3322,(2004) .

6. Johnson , M.D., Macdougall , C., ostrossky –zeichner , L., perfect , J.R., rex , J.H., Antimicrob. Agents chemother . **48**,693-715, (2004).

7. Diekema , D.J., Messer , S.A., Hollis , R.J., Jones, R.N, pfaller , M.A., J. clin . microbial , **41**,3623-3626, (2003) .

8. Bennett, J.E, N. Engl, J. Med., 301,126-131, (1979).

9. Benito , P., drug intell . clin . pharm . 21, 752,(1987).

10. Castanheira , G., curr. Ther . Res ., 43,369-373 (1988) .

11. Dismukes , W.E. J. Med ., 103, 861-872, (1985) .

12. Shadomy, S., J. Infect . Dis ., 152,1249-1256, (1985).

13. Lawrance A . Kaplan Amadeo J. pesce , ((clinical chemistry I theory , analysis and correlation)) 2nd ed ., Mosby company , USA , (1989) , PP . 45.

14. S.G. Avery ((drug Treatment : principles and practice of clinical pharmacology and theraputics)) Ed. Littletion . Am , publ. science group , Inc, (1976). PP. 865.

15. Lee. M.G., chiouwl ., drug metab. Dispos ., **26(5)** 401, (1998).

16. Wilson and gisvold , ((drug latentiation and prodrugs)) 3rd.ed., (1998) , P. 123-137.

17. L.S. Goodman and A . Gilman , ((The pharmacological bases of therapeutics)) , 4 th ed .,The macmilan company , London , (1970). P. 1665.

18. Gornali , A.G., Bardawill , C.J., David , M. M., J. Biol . chem. , **177**, 751-766, (1949).

19. Kwon , K.J. , and John E. Bennett , ((Medical Mycology)) . 5 th ed . Library of congress USA . (1992), P. 81-105.

20. Bulmer , G.S ((Introduction to medical Mycology)) , 2nd ed . , London , (1979), p. 80-100.

21. R.F. Doerge , ((Wilson and Givolds Text Book of organic Medicinal and pharmaceutical chemistry)) , 10th ed ., Lippincott company , London , Mexicocity , New York , (1998)., P.95.

22. W.A. Ralph and M.T. Bert , org . proced .Int ., **3 (6)** , 299, (1971).

23. Hardeastle , J. Ture love and H. Kostenbander ,J. pharm. Soc ., **96(2)** , 231 , (1980) .

24. Vanden Bossche , H., J. of Drug develop . Res., 8 , 287-298 , (1986).

25. Zurcher , R.M, Frey , B.M., and frey , F.J., J .clin. pharmacol ., 45,366-372, (1989).

26. MCE voy , GK, J. Amerc . soci . Healt ., 7, (1997).

27. Hansten , Horn J.K., ((Drug Interaction Analysis and management , 4th ed. ., London)) , (1998), P. 25-27.

28. Odds , F.C. , Arai , T. and Disalvo , A.F., J. Med . Mycol ., 30,1-10 , (1992).

29. Tatro, D ed ., ((Drug interaction)) , 3th ed ., USA , (1998) , P. 29-36.

30. Todd, A. orengo , C., and Thornto , J. Mol . Biol , **307**, 1113-1143, (2001).

31. Bongan , A. and Thorn , K. J. , J. Mol .Biol ., **280**,1-9, (1998) .

32. Bottger , V., Bottger , A. , Lane , E.B. and spruce, J., Mol .Biol . 247, 932-946, (1995).

33. Farisellil , P. , Pazos , F., Valencia . A. and casadio , R., Eur ., J Biochem ., 269,1356-1361, (2002).

34. Tello , D., Gold baum , F.A., Mariuzza , R.A., yseru, X., schawartz , F.P. and poljak , R., J. Biochem . Soc . Trans ., 21 ,943-946,(1993).

35. Hibbits , K.A., Gill , D.S. and Wilson , R.C., J Biochem. ,33,3584-3590, (1994).

36. Dondliker , W., Alonso , R., Desausseure , V., kireszenbann , F., Leviso , S. and schapiro , H., J . Biochem ., **6** , 1460-1467, (1967).

37. Yin , B.W., and liyod , K.O. , J. Biol . chem.., 276,2731-2735, (2001).

38. Hanisch, F.G. and dients , C., Eur . J. Biochem., 149,323-330, (1985).

39. Sundberg , E.J., J. Biochem , 39,15375-15387, (2000) .

40. Wibbenmeyer , J.A. , schuck , P. and smith –Gill , S., J. Biol . chem.., 274,16838-16842,(1999).

41. Venkatesh , N., Kishrawamy , S., Mearis,S., and murthy , G. S , Eur. J., Biochem. , 265,1061-1066, (1999).

42. Ross, p. D. and subramandan , S., J . Biochem., **20** , 3096-3112, (1981).

43. Chitarra, V., Alzari , P. M. and poljak , R.J., proc. Natl Acad. Sci., 90 , 7711-7715, (1993).

44. Soko-Anderson, M. ,J. Antimicrob. Agents Chemother., 32, 702-705, (1988).

45. Omray A., varmakc. Hindustan Antibiott. Bull., 23,33, (1981).

46. Olle , N., can. Ag J. , **1 (1)** , 1-8, (2003).

47. Kaaman , T. H and , J. dermato . Mycoses **31**,613-616, (1988).

48. Howell, S.A., Barnard , R.J. and Humphreys , F., J., Med. Micro ., 48, 33-40, (1999) .

49. Nichols , W.G, J . Med , 18, 295-312, (2003).

50. Dannaoui , E., Lortholary , O., Dromer , F., J., Antimicrob . Agents chemother. 48,970-978, (2004).

51. Liu, W., May, G.S., lionakis , M.S., Lewis , R.E., kontoyiannis , D.P., J.Antimicrob. Agents chemother., 48,2490-2496,(2004).

52. Muller , E. and loeffler , W., ((Mycology an out line for science and medical students)) ., 2nd ed., Georgthieme publishers Stuttgart , (1976) . P. 115-125.

53. Chothia , C. , J. Mol . Asp. Host . Inter. , 222, 501-508, (1997).

54. Chothia , C. and Janin , J. Nature , 256,705-708, (1975).

55. Sheienerman , F.B, Norel , and Honig , B. curr. Opin . struct . Biol ., 10, 153-159, (2000).

56. Faiman , G.A.and horovitz ,A,J., Biol . chem.., 272,31407-31411, (19970.

57. Jones , S., and Thornto , J., proc. Natl . Acad . Sci , 93 , 31-20, (1996).

58. Davis , S., davies , E., Tucknott, M., Jones, E. and vander merwe, J. . proc . Natl . Acad. Sci ., 95,5490-5494, (1998) .

59. Davis , R. and cohen . J. proc . Natl . Acad . Sci ., 93,7-12, (1996).

60. Maccallum., D.M., white , J.A., odds , F.C., J . Antimicrob . Agents chemother. ,49,3697-3701, (2005).

61. Lake – Bakaar, G., J. Intern., Med , 109, 471-473, (1998).

62. Lewis , J.H. J . Gastroentrtology , 86,503-513,(1984).

63. Van Epps . H.L. , Feldmesser , M., pamer , E.G., J. Antimicrob . Agents chemother . 47,1818-1823, (2003).

64. Philip, A., odabasi , Z.,Rodriguez, J., paetznick , V.L., che, ,E.,Rex, J.H., ostrosky – zenichner , L., J., Antimicrob. .Agents chemother ., 49, 1369-1376 (2005).

65. Shalit , I., shadkchan , Y., samra , Z., osherov, N., J. Antimicrob. Agents chemother. ,47,1416-1418, (2003).

66. Daneshmend , T. K., and warnok , E.W., J. clin . pharma., 14., 13-34, (1988).

67. Gulley , JM., Rebce GV ., pharmacol . Biochem., **63(1)** , 125,(1999).

68. Dowell , J.A., schranz , J., Baruch ,A., foster , G., J. clin . pharmacol.,45,1373-1382, (2005).

69. JC. Geesin , JS. Gordon and RA . Berg, J. skin pharmacol , 6(1), 65,(1993).

70. PJ. Clin . pharm . Ther. , 15(6), 419, (1990).

71. Andres G. and Elliot S.V., ((Medical pharamacology principles and concepts)), 11th ed ., C.V. Mosby company , (1984), P. 366.

72. Forrast .T. smith , O.Rondall clark , ((Drug Latentiation and Prodrugs)) , 4th ed ., (1998) , P. 125-133.

73. I.A.A. Rawi, R.W. Hebeeb and H.R. Rabbfat , J. Bulletin of Health research , 28,73 (1987).

74. Feetam C.L. , Leach R.H. and Meynell M.J., Toxicol . Appl pharmacol. , **31(3)** , 544, (1975).

75. Van vianen , W., de marie , S., ten kate , M.T., Mathot , R.A.A., Bakker- woudenberg , I.A. J.M., J. Antimicrob . chemother ., **57**,732-740, (2006).

76. Dennis , C.G., Greco , W.R., Brun , Y., Youn, R., slocum , H.K. , Bernacki, R.J., Lewis ,R., Wiederhold , N., Holland , S.M., petraintine , R., walsh , T., J., segal , B. H., J. Antimicrob. Agents chemother. ,50,422-427,(2006).

77. Heyn,K. , Tredu, A. S. Muller, Antimicrob. Agents chemother. , 49, 5157-5159, (2005).

78. Clemons , K.V., Espiritu , M., parmar , R., stevens , D.A., J. Antimicrob. Agents chemother. 49,4867-4875, (2005).

79. Schwartz, S., Ruhnke , M., Ribaud , P., corey, L. Driscoll, T., cornely , O.A., schuler , U., Lutsar, I., Troke , P., Thiel , E., J. clin . Microbiol . Rev., 106,2641-2645, (2005).

80. Mukherjee, P.K., Sheehan , D.J., Hitchcok , C.A., Ghannoum , M.A., J. clin . Microbiol . Rev., 18, 163-194, (2005).

81. Barchies , F., spreghini, E., Baldassarri, I., marigliano , A., Arzeni, D., Giannini, D., scalise , G., J. Antimicrob. Agents . chemother., 48,4056-4058, (2004).

82. Altwell , S. and wells , J.A., science , 278, 1125-1128, (1997).

83. Armstrong ,S.A.,Staunton , J.E., silverman , L. B., pieters , R., denboer , M.L. , Minden , M.D., sallan , S.E. , Lander ., E.S., Golub, T.R. and korsmeyer ,S.J., Nat.Genet ., 30,41-47, (2002).

84. Llyod, K.O., and Yin , B.W., Tumor Biol ., 22,77-82, (2001).

85. Iurisci, I., Tinaria , N., Natoli, C., Angelucci , D.,Cianchetti, E. and Iacobelli , S., clin . cancer Res., 6 , 1389-1393, (2000) .

86. Erickson , H.P., J. Mol . Biol ., 206, 465-474,(1989).

87. Antosiewicz, J., Mc cammon , J., and Gilson , M. , J., Mol . Biol ., 238,415-436,(1994).

88. Xiao, L. and Honig , B., J. Mol . Biol ., 289,1435-1444, (1999).

89. Cunningham , B. and wells , J., J., Mol . Biol ., 234,554-563,(1993).

90. Wilson , I. and stanfield , R., struct . Biol ., 3, 113-118, (1993).

91. Bassenge E., Fink B., Naunyn schmiedebergs , J.pharmacol , 353(3), 363, (1996).

92. JE. Halver and RW. Hardy , Biol . Med ., 72(9), 2354,(1994).

93. Y. Kumano , T. sakamoto , M., Egawa , M. Tanaka and I. Yammoto , Biol . pharmacol., 21(7) , 662, (1998).

94. Tannin, J., prog. Biophys . Mol . Biol., 64,145-165, (1996).

95. Nooren , and Thornton , J.M., J. Mol. Struct . Biol ., 9 ,293-300, (2003).

96. Gones , S., and Thornton , J.M., Biophys Mol. Biol ., 64,131-165, (1995).

97. Sylvia.S Mader, ((Biology)) , 6th ed ., McGraw-Hill companies , (1998), P. 540-548.

98. Richards , F., J., Mol . Biol , 82,1-14, (1974).

99. Davies, D.R. and padlan , E.A., curr. Biol ., 2, 254-256, (1992).

100. Ito , W., Iba, Y. and kurosawa, Y., J., Biol . chem. ., 268,16639-16647, (1993).

101. Perillo, NiL. , pace , K.E.seilhamer , J.J. and Baum , L.G. J. Mol .Med ., 76,402-412,(1995).

102. Goodsell , D.S. and olson , A.J., Biophys Biomol. Struct , 29,105-153, (2000).

103. Wilson . I.A. and stanfield , R.L., struct . Biol ., 4, 857-867, (1994).

104. Hajime , A., Hiroyki, N. and Tomoko, U., J. clin . oncol ., 30(4), 185-187, (2000) .

105. T. sudo , T. Miki , T. Matsumoto and T. satoch , J. Med . chem.., 35(9), 1618,(1992).

106. S.Tanuma , D.Shiokawa , Y. Tanimoto , M., lkekita , M. takeda and H. sakagmi, Biochem. Biophys .Res. , 194(1), 29,(1993).

107. Perillo, N.L. Marcus , M.E, and Baum , L.G., J. Mol Med ., 76,402-412, (1998).

108. Claudia , S., sovine , W., Johanses, L. and walter, , N., J. cell sci., 116(7), 1305-1318, (2002).

109. DC. Mahan , AJ.Lepine and Dabrowski., J. Anim . Soc., 72(9) , 2354,(1994).

110. Jensen , J.L., Liyods , S., Bondner , D., krantz , M. and Langenecker , B.M., Int . J., Biol . Mol ., 6 (1) 1-6, (1996).

111. Levy, M.H., N. Engl , J. Med ., **335 (15)**, 1124-1132,(1996).

112. Myszka, D.G., J. Mol . Biol ., 252,337-350, (1995).

113. Vaughan. C.K., Bukle ,A.M., and fersht , A.R., J. Mol. Biol , 286., 1487-1506, (1999).

114. Naseer F., Alam M. , J. Med .Antibiol ., 37(3) , 73, (1987).

115. Lennetta , E.H. Balows, A.Hansles and truant , ((Manual of clinical Microbiology)) , 3rd ed., American society for micro biology ,Washington , (1985).

116. AK. Naidu, M. Wiranowska , SH. Kori , LD. Prockop and AP. Kulkarni , Neurooncology , 16(1) , (1993).

117. Nago and J. Terao, Biochem . Biophys . Res. Commun. , 172(2), 385,(1990).

118. Saunders , C.M. and Baum , M., J ., Med ., **86**, 162-165, (1993).

119. Pfaller , M.A., Sheehan , D.J., Rex, J. H., J. clin . microbial . Rev., 17,268-280, (2004).

120. Chan , J. pharmacother ., 37, 595-597,(2003).

121. Straw GM., J. clin . psychopharmacol ., 9 (2), 130, (1989).

122. SP. Felton , Dukelow and HM. Felton, proc. Soc. Biol ., 215(3), 248, (1997).

123. T. kaneka , K. Kaji and M. Masuo , J. Biochem. Biophysc ., 304(1) , 167, (1993).

124. Butler , E.E.and Peterson , L. J., Endomycoses geotrichum, aperfect state of geotrichum candidum , J. Mycology , 64,365-374, (1972).

125. Ross, I.D., Reid , K.D. and speris , C.F., bronchopulmonary geotrichosis with sever asthma , J. Med ., 2, 1400-1402,(1966).

126. Bendove , R.A. and Ashe , B.I. , Geotrichum septicemia , J. Inter .Med , 89, 107-110,(1952).

127. Ghande ,A.R.,Landis , F.B. and snider , G.L. Bronchial Geotrichosis with fungemia complicating bronchgenic carcinoma , J. Mol .Biol ., 59,98-101, (19710.

128. Hoog , G.S., smith , M.T. and Gueho , E.A. Revision of th genus geothrichum and its telomrphs . stud. Mycol ., 29,1-13, (1986).

129. Pitt, J.I. and Hocking , A.D. ((fungi and food spoilage)), 2nd ed. , Blachie academia and professional , U.K., (1997), P. 144-145.

130. J. Heeres , J.H. Mostmans , and J. van cutsem , J.Med . chem. , 22, 8 ,(1979).

131. E.F.Godefroi, J. Heeres , J. van cutsem and J. Janssen , J. Med . chem. ., 12,781, (1969).

132. J. van custem and D. Thienpont , chemotherapy ,17,392,(19720.

133. R.T. Holt , Drugs , 9 ,401,(1975).

134. J.R. pate and M.N. Patel , J. Microbol .Sci. chem.. 26,817-823, (1989).

135. A.vogal , ((A Text Book of practical organic chemistry)) 3rd ed., Longman , London ., (1974), P. 1000.

136. Y. Watanbe , H. Yoshiwara and M. Kahao , J. Heterocyclic . chem. ., 30 195,(1993).

137. Cappuccino , J. and shermany , N., ((Microbiology a Laboratory Manual)) ,2 nd ed., Benjamin cummiimgs publishing , (1987), P. 53-63.

138. AL-Samarae , K.W, AL-Rekabi, S.and Ahmed , B.R., J. Med . Sci ., 30 40 ,(2001).

139. Finegold , S.M., Nartin, W.J. and scott , E.G., ((Antimicrobial susceptibility tests and assays in Baily and scotts Diagnostic microbiology)) 6th ed ., (1982) , P. 385-404.

140. Beneke ,E.S. and Rogers ,A.L., ((Medicinal Mycology Manual with human Mycosis Monograph)) , 4th ed., Minneapolis –Burgess publishing company , (1980), P. 20 -75.

141. M. Mahgoub and Moustafa J. chem.. soc., 67,216, (1990).

142. M. parra , J. Belmar , H. zunza ,C. zuniga, G. Fuentes and R. Martinez ,J. parc. Chem.., 337,239, (1995).

143. D.H. Willians and fleming , Trnslanted by J.U. sarkess ((spectroscopic methods In organic)) 1st ed. , Baghdad university , (1986), P. 87.

144. R.W.Silverstein , C.G. Bassler and T.C. Morvill , ((spectrometric Identification of organic compounds)) , 3rd ed., John wiley and sons , London ,(1974), P. 70-75.

145. R.S.Gordes and T.R.Matthews , J. Antimicob . Agents chemother., 967,378,(1986).

146. Como , Jackson A., J. Med ., 330(4), 263-272, (1994).

147. Thomas Novinson , Roland K. Robins , and Thomas R. Matthews , J. Med chem., 20 (2) , 299, (1978).

148. Clayton , J.P. Ger .and paoladini , J. Biol .chem. 11,441-453,(1974).

149. K.G. choneim et al., Egept pharm. Soc., 29,169-178, (1988).

150. Betiana , ((The chemistry and Biology of antibiotics)) , 3rd ed ., Elsevier scientific publishing company ,Amsterdam, (1983), P. 283-429.

151. F.E.Hahn , ((Antibiotics Mechanism of action of antibacterial agents)) , 5th ed., (1979), P. 176-213.

152. M.D. Dunston and E.Richler , J. Amer. chem. .soc., 78,5848, (1956).

153. Helecz, T. Breining and L. Redriguez, J. Med . chem.., 25,1140, (1962).

154. venturello , J. chem. .SOC ., 1,749,(1986).

155. T.L. ulbricht and C.C. price , J. org chem. ., 21,567,(1956).

156. R.A.Acheson , ((introduction to the chemistry of heterocyclic compounds)) , 3rd ed ., John wiley and sons .Inc ., New York , (1976). P-320-350.

157. D.S.copper and N. Engle , J. Med . chem. ., 31,1353,(1984).

158. Laurence , D.R., Bennett , P.N. and Brown , M.J. ((clinical pharmacology)) 8th ed., Churchill living stone , (1997), P.197 .

Summary

Chemotherapy is the science of selective toxicity. The goal of chemotherapeutic treatement is to selectively attenuate or destrory pathogenic microorganisms or cells with minimal side effects to the host . These target cells or organisms may be bacteria , viruses , fungi , or tumor cells .

In this work new derivatives of azole and pyrimidine compounds have been synthesized , which contain imidazole compound with a five membered ring containing two nitrogen which is pharmacologically active against dermatophyte diseases .

1-acetyl -4- [4-[[2,4-dicholorphenyl] -2-(1H –imidazole -1-yl –methyl)-1,3-dioxolan -4-yl]methoxy]phenyl] piperazine (1G) was synthesized by treating of [2-(2,4-dicholorphenyl] -2-(1H –imidazole -1-yl –methyl)-1,3-dioxolan -4-yl]methoxy methanesulfonate with piperazine dervatives.

Ethyl -4- aminobenzoate (2a) was synthesized by condensation reaction of -4- amino benzoic acid with HCl saturated ethanol .

2- thioacetic -5- (4-amino phenyl)1,3,4-oxadiazole (2E) was synthesized by treating compound 2-mercapto-5-(4-aminophenyl) 1,3,4-oxadiazole with chloroacetic acid .

1- methyl -4- oxo-1,2,3,4,-tetrahydro-2- thiopyrimidine (4G) was synthesized by reacting of (0.1mole) thiouria with (0.1mole) of ethylacetoacetate .

2- hydrazine -6- methyl pyrimidine -4- (3H) one (5G) was synthesized by reacting the hydrazine hydrate with compound (4G).

The purity of the compounds were characterized by using fourier transform infrared spectroscopy (FTIR) .

The effects of New compounds (1G,2E,6G,4G and 5G) one the activity of growth the fungal colonies were studied the effect of these compounds by using the tissue culture of fungi in the treatment of dermatophyte that found depend on the incubation time 48 hrs ., 72hrs ., and 96hrs .

The *invitro* study was used the Trichophyton rubrum and geotrichum candidum ,and used sabouraud agar and potato dextrose as culture .

Mixture of Ketoconazole compound with caffeine (6G) showed the highest inhibitory effect on the growth of fungi compared with ketoconazle (1G) alone , the least effective compound was (5G) after 72 hrs . of incubation and compound (4G) didnt inhibit the growth of fungal colonies at different concentration .

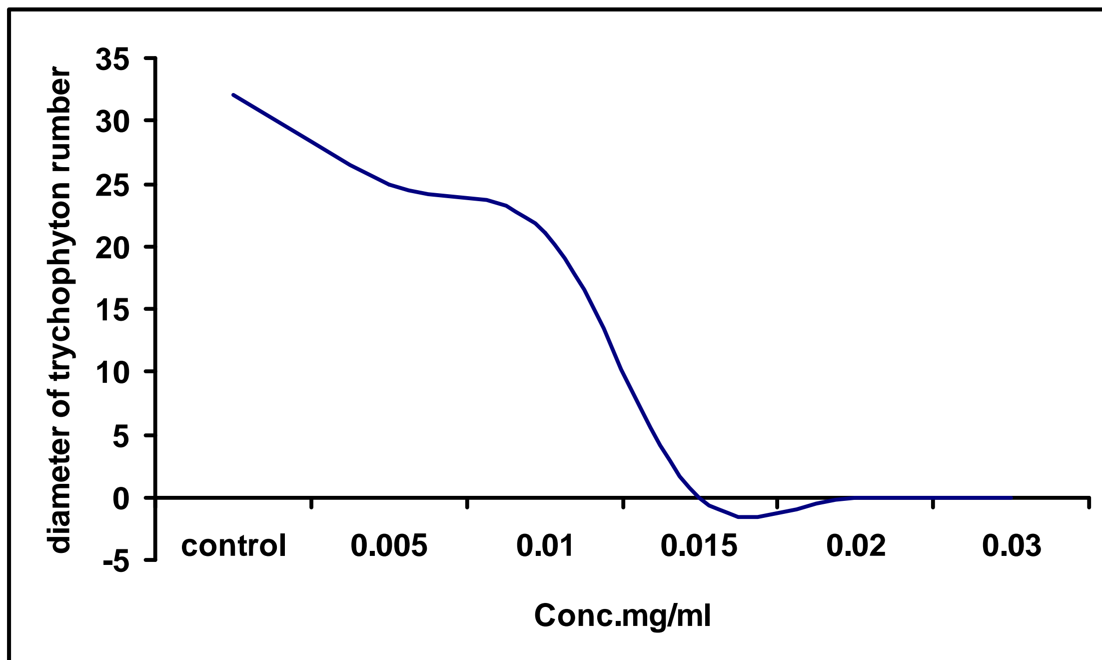
Compound (2E) was highly active against fungal colonies after 48hrs ., 72hrs.,and 96hrs .of incubations .

بسم الله الرحمن الرحيم

اقْرَأْ بِاسْمِ رَبِّكَ الَّذِي خَلَقَ۞خَلَقَ الْإِنسَانَ مِنْ عَلَقٍ۞اقْرَأْ وَرَبُّكَ الْأَكْرَمُ۞الَّذِي عَلَّمَ بِالْقَلَمِ۞عَلَّمَ الْإِنسَانَ مَا لَمْ يَعْلَمْ۞

صدق الله العظيم

سورة العلق {١-٥}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control
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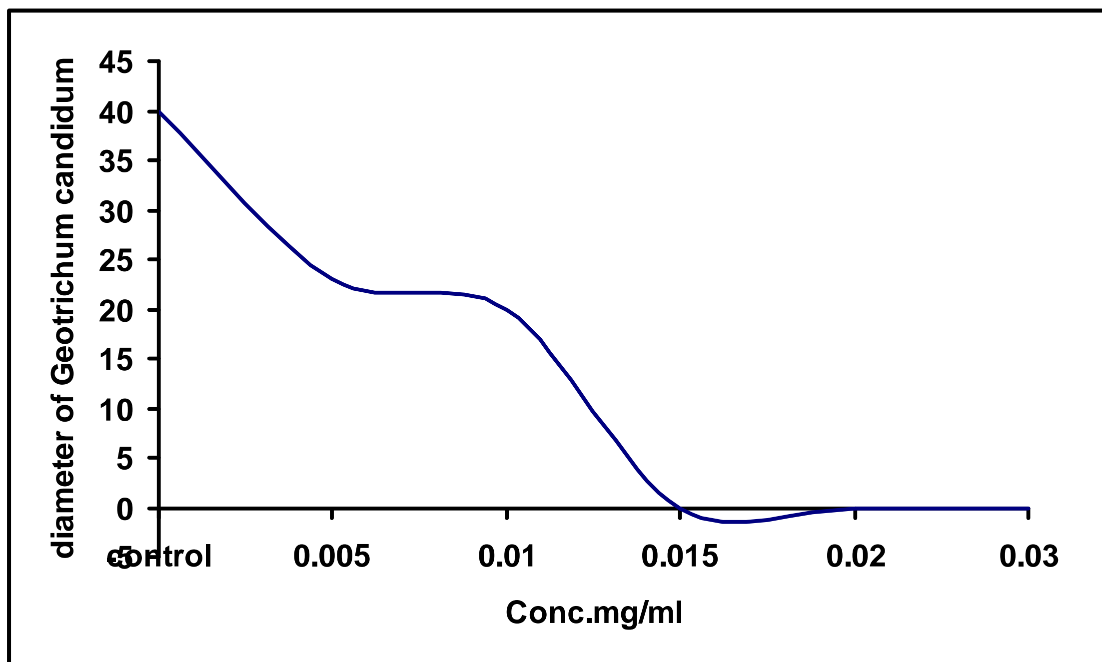
Conc.mg/ml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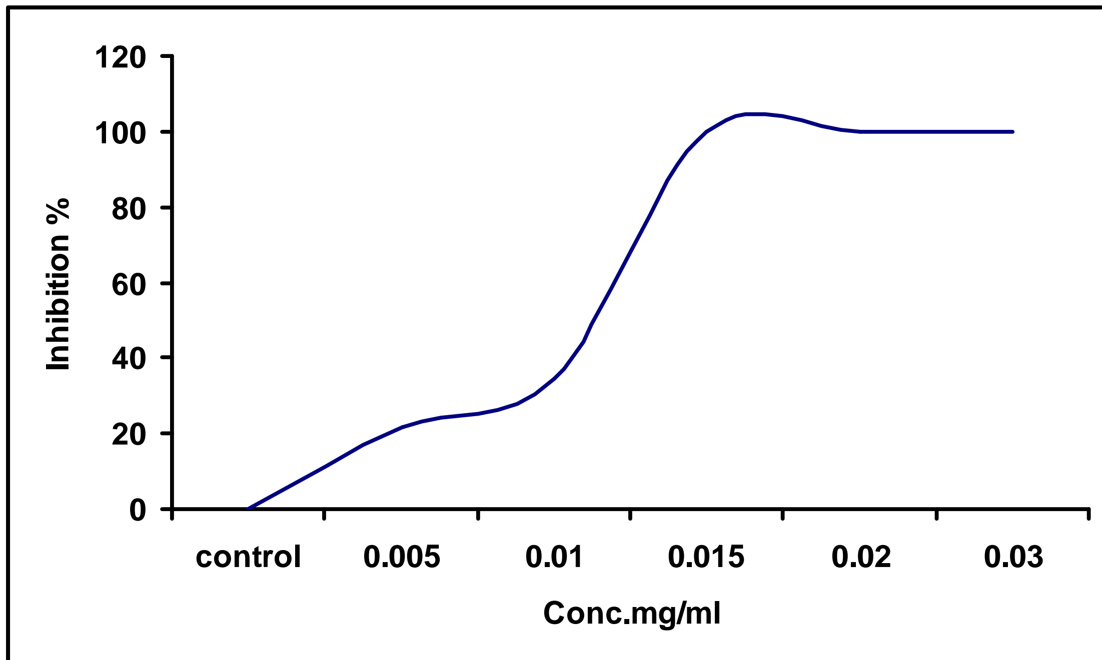
Conc.mg/ml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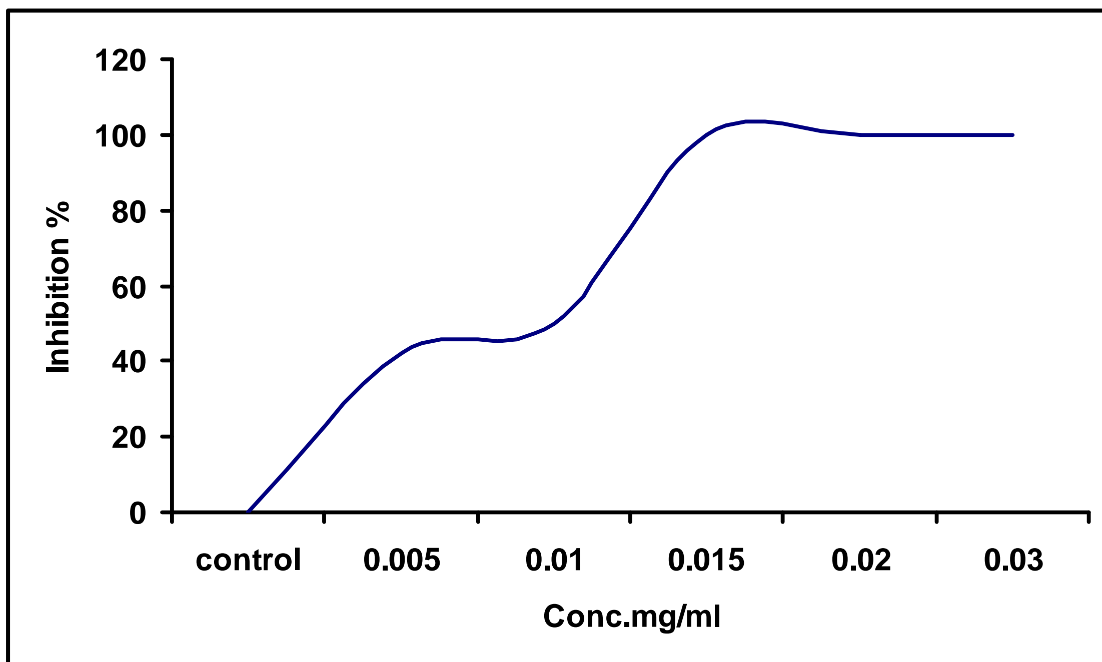
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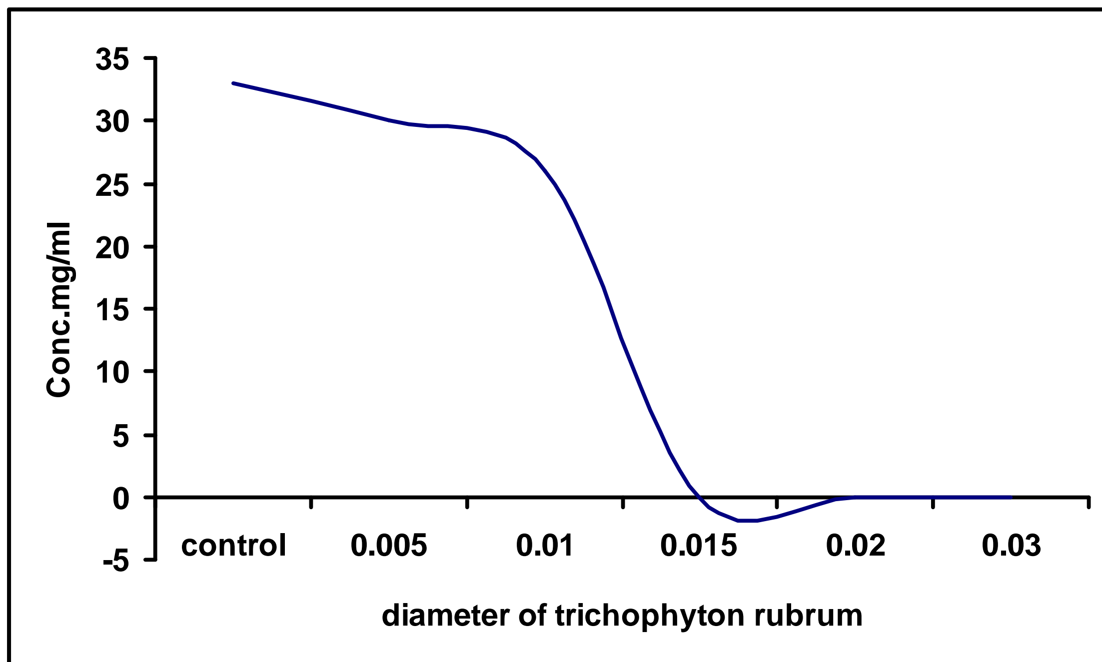
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Conc.mg/ml
control
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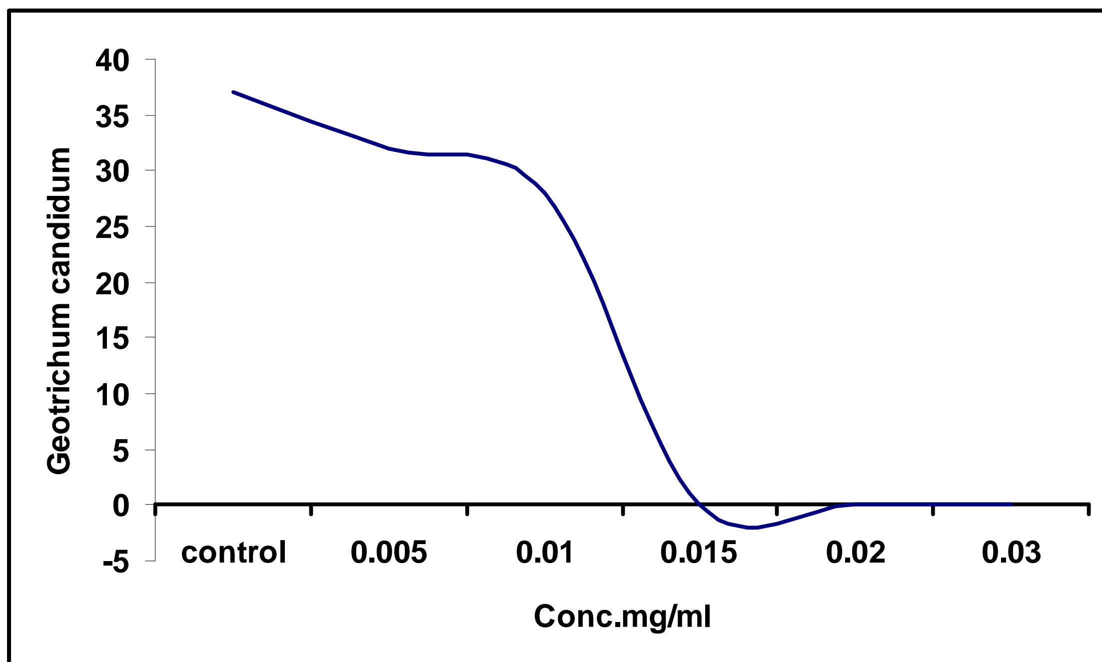
0.01
0.015
0.02
0.03
diameter of trichophyton rubrum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25
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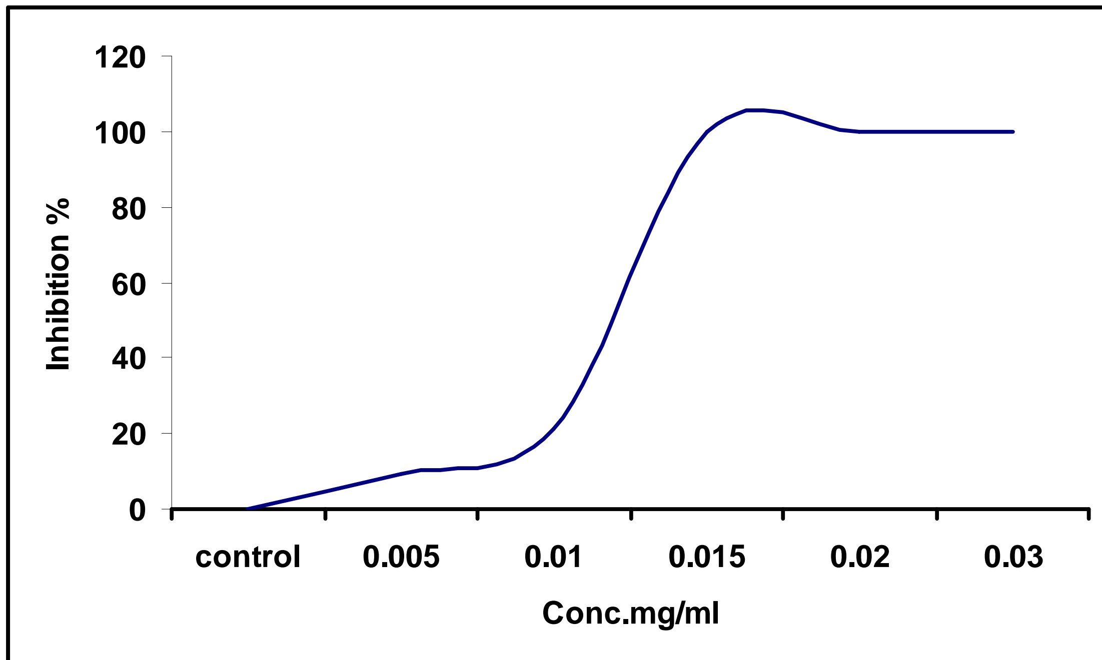
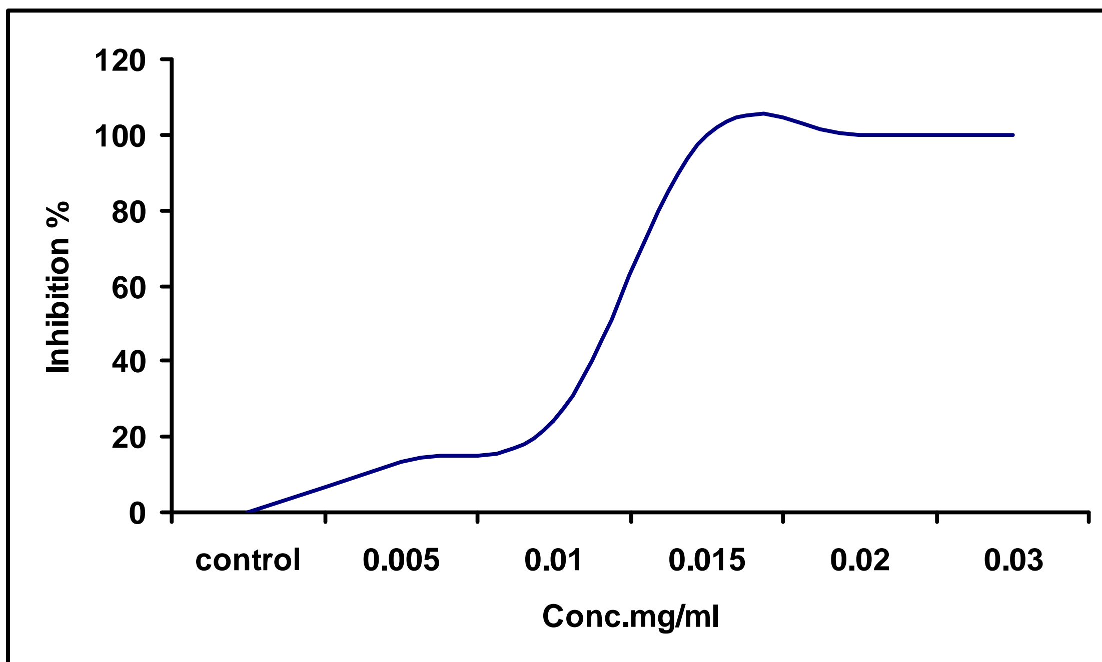
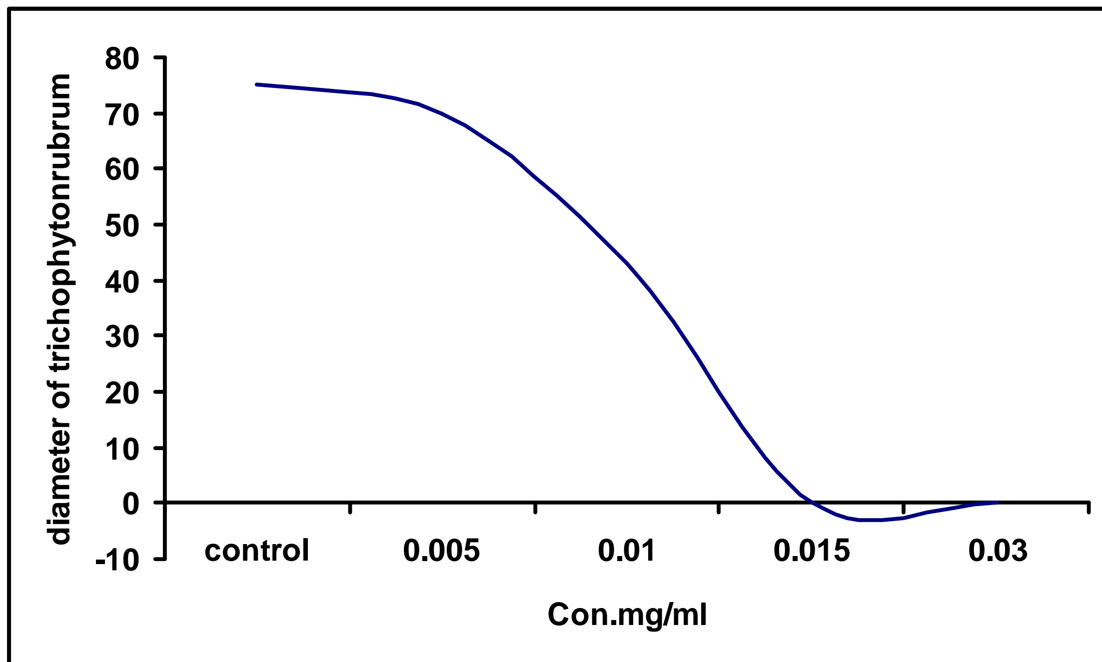
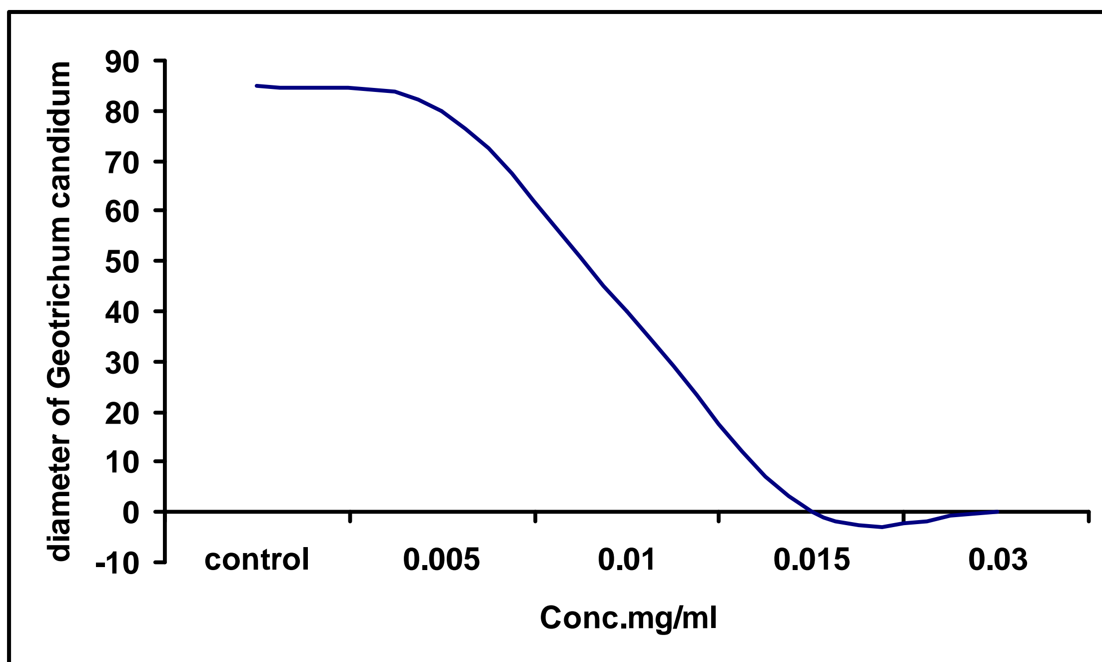
Geotrichum candidum
control
0.005
0.01
0.015
0.02
0.03
Conc.mg/ml


120
100
80
60
40
20
0
Inhibition %
control
0.005
0.01
0.015
0.02
0.03
Conc.mg/ml

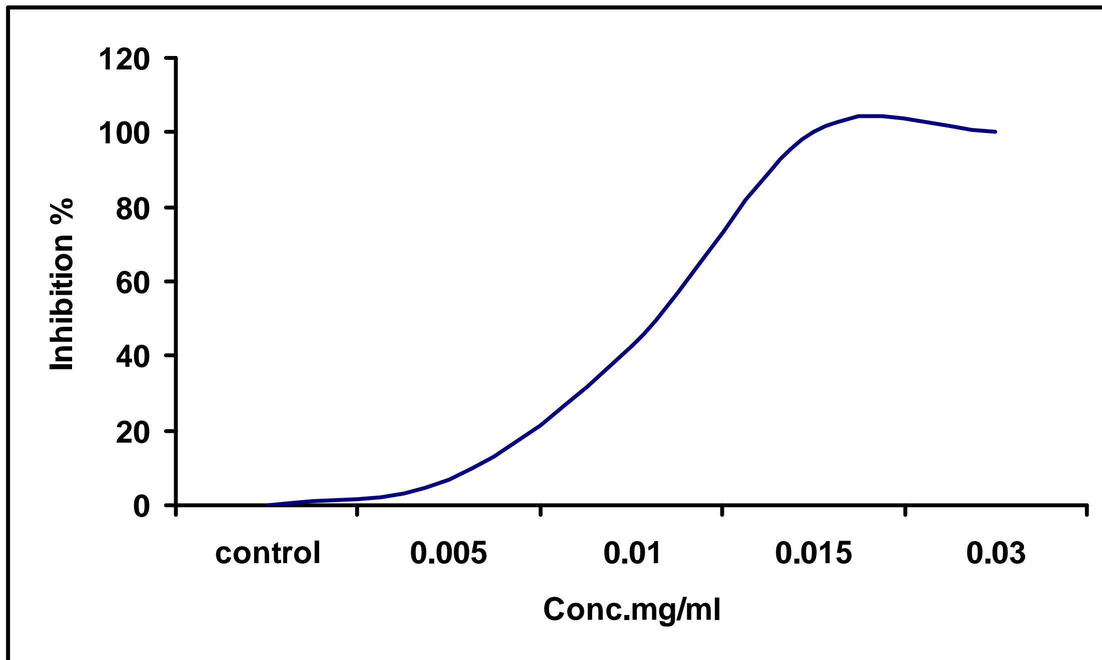

120
100
80
60
40
20
0
Inhibition %
control
0.005
0.01
0.015
0.02
0.03
Conc.mg/ml

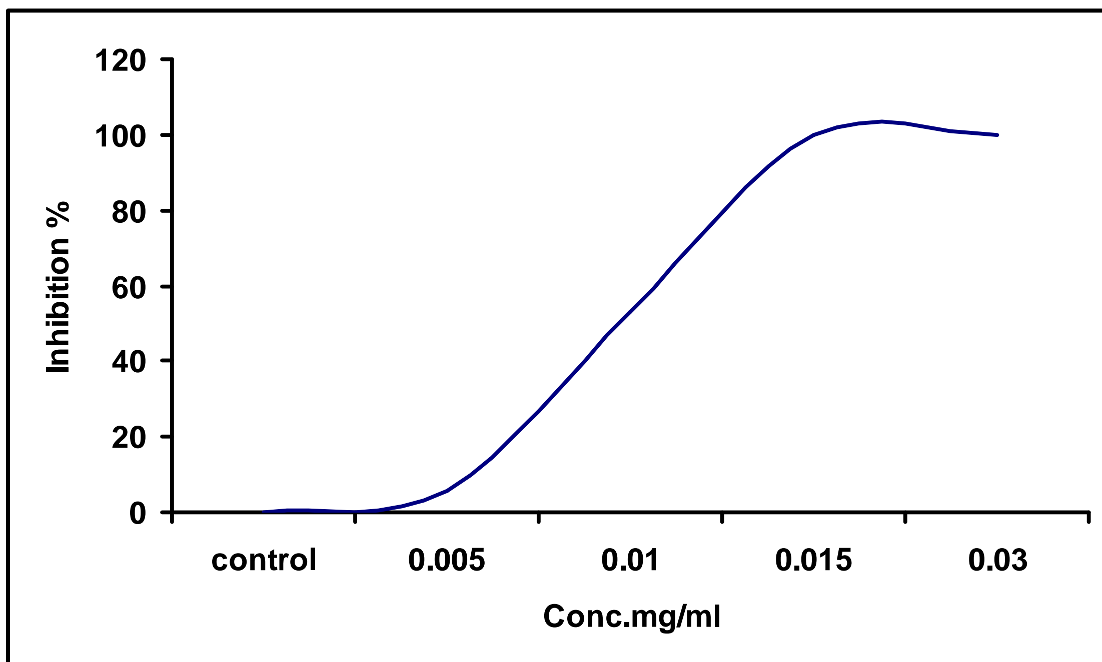


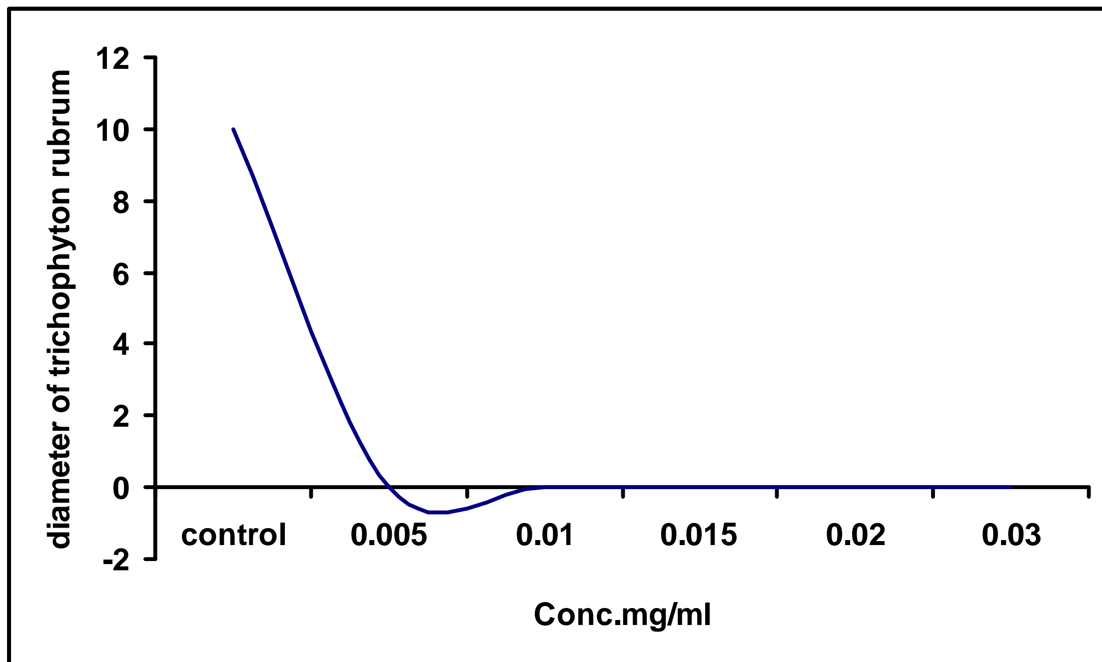
80
70
60
50
40
30
20
10
0
-10
diameter of trichophytonrubrum
control
0.005
0.01
0.015
0.03
Con.mg/ml

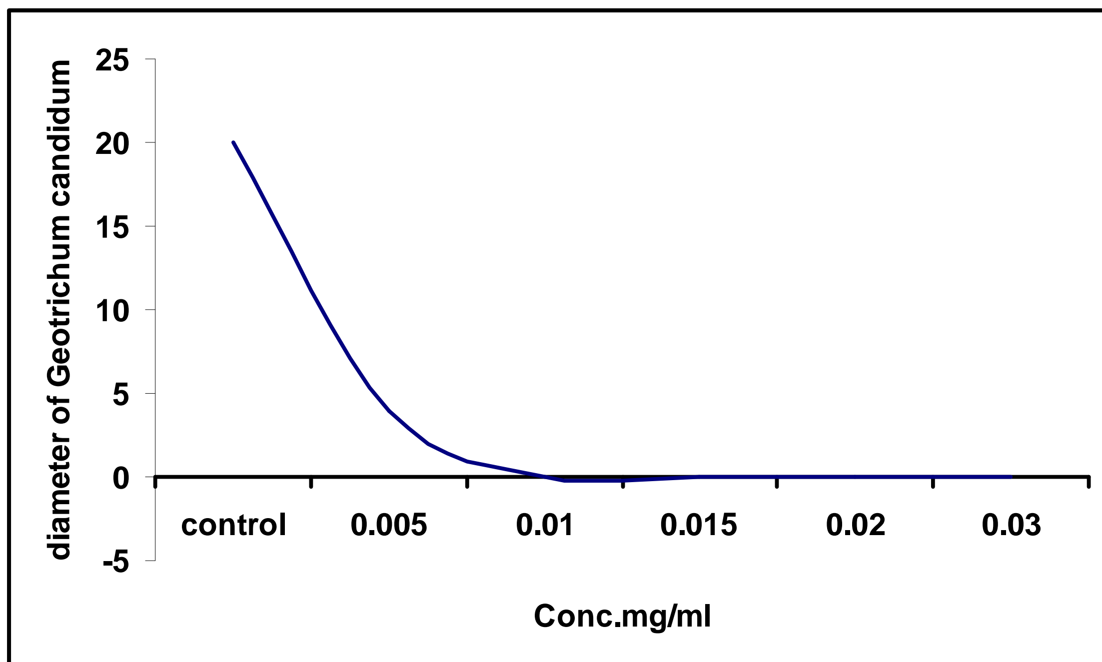


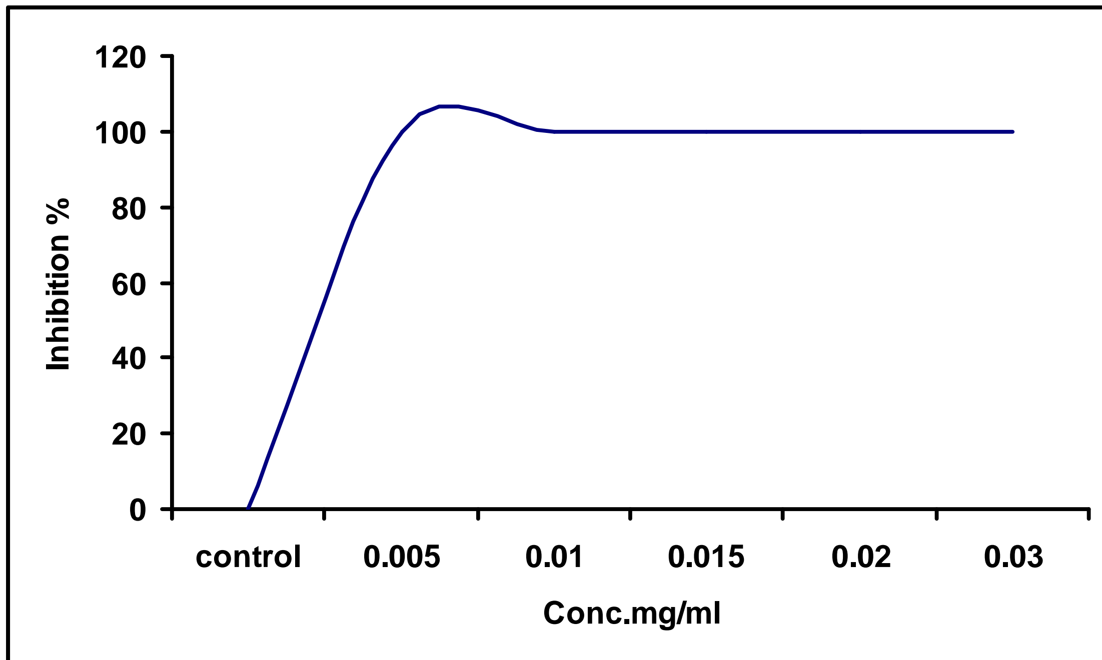
90
80
70
60
50
40
30
20
10
0
-10
diameter of Geotrichum candidum
control
0.005
0.01
0.015
0.03
Conc.mg/ml

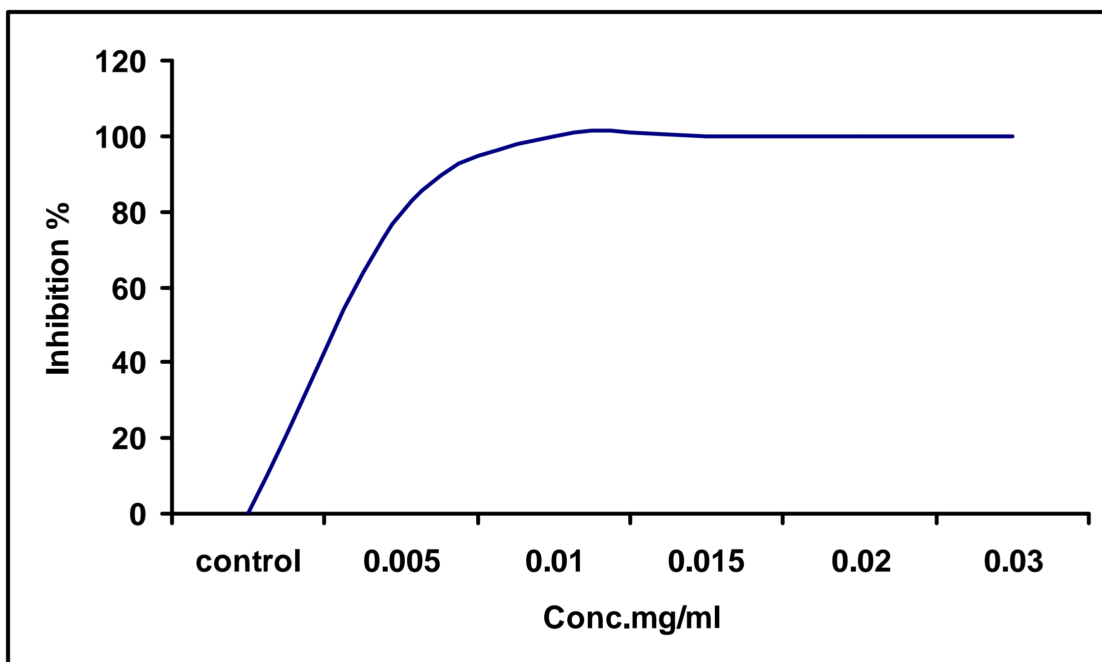

120
100
80
60
40
20
0
Inhibition %
control
0.005
0.01
0.015
0.03
Conc.mg/ml

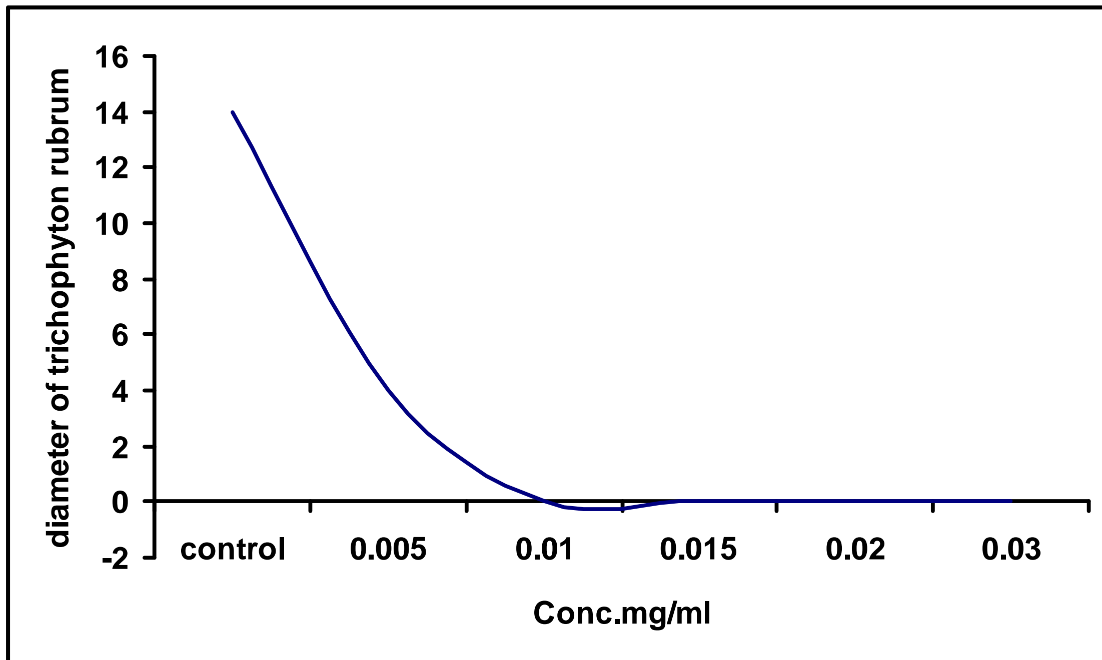

120
100
80
60
40
20
0
Inhibition %
control
0.005
0.01
0.015
0.03
Conc.mg/ml


diameter of trichophyton rubrum
12
10
8
6
4
2
0
-2
control
0.005
0.01
0.015
0.02
0.03
Conc.mg/ml

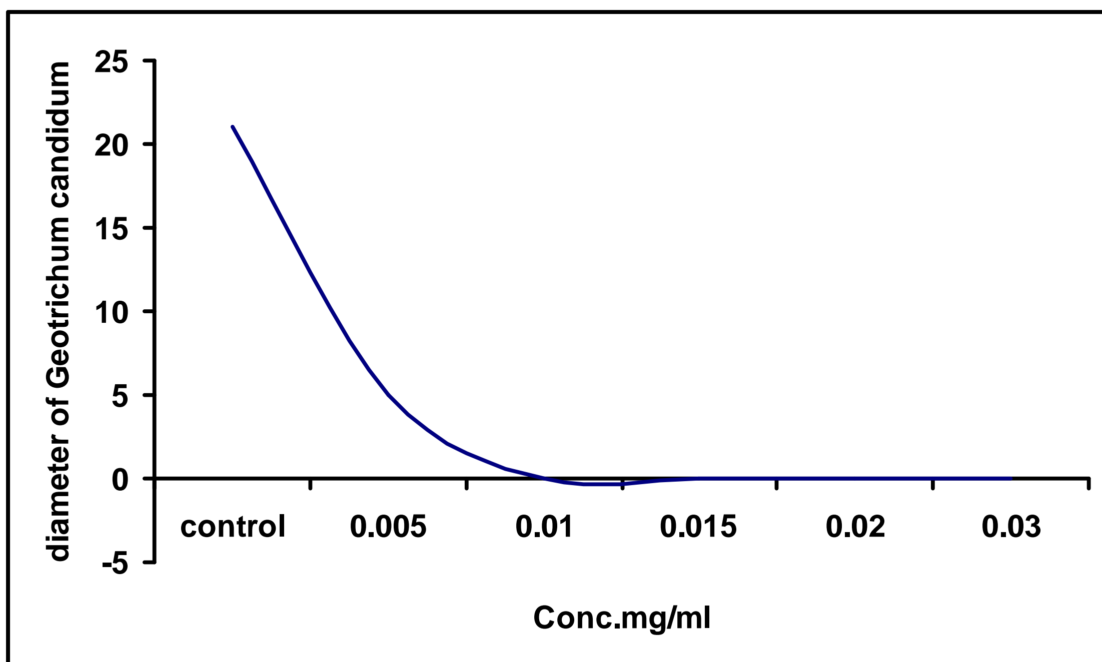

diameter of Geotrichum candidum
25
20
15
10
5
0
-5
control
0.005
0.01
0.015
0.02
0.03
Conc.mg/ml


120
100
80
60
40
20
0
Inhibition %
control
0.005
0.01
0.015
0.02
0.03
Conc.mg/ml

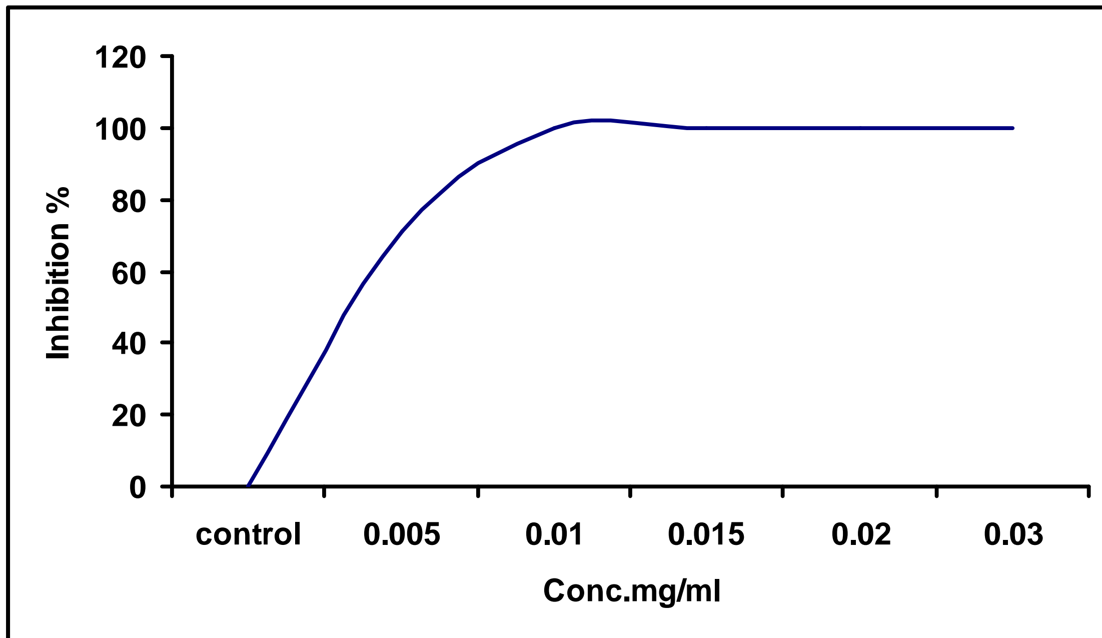

120
100
80
60
40
20
0
Inhibition %
control
0.005
0.01
0.015
0.02
0.03
Conc.mg/ml

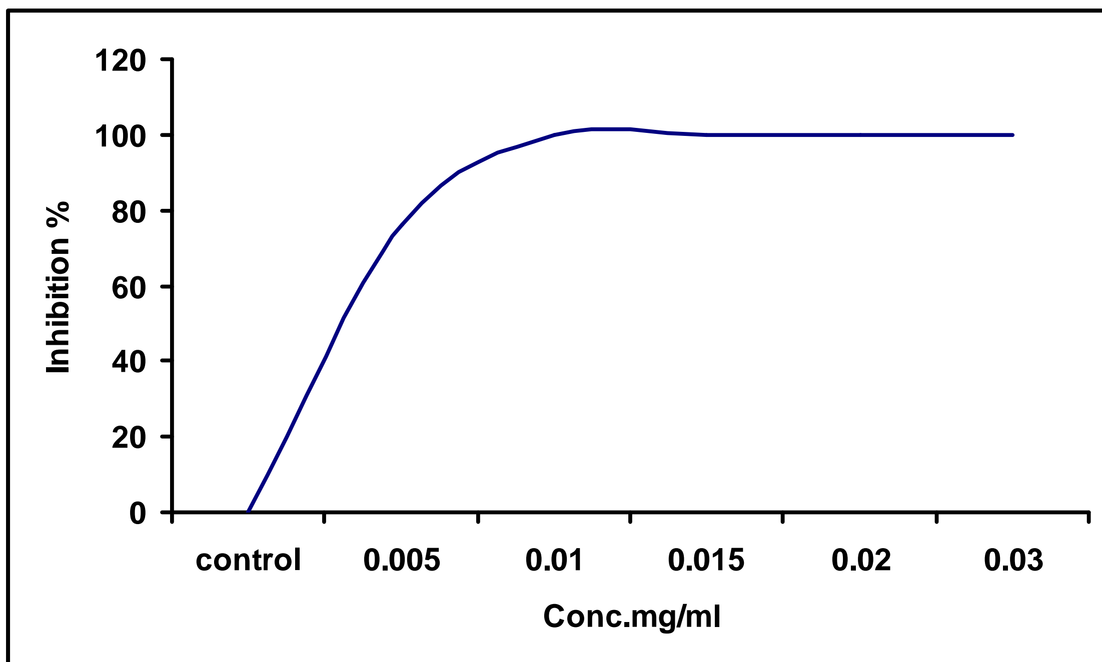


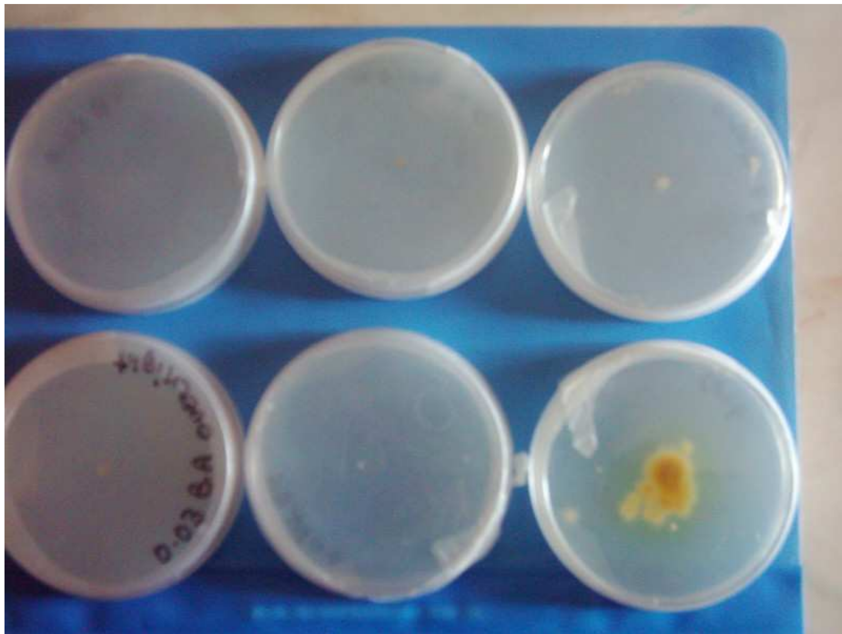
diameter of trichophyton rubrum
16
14
12
10
8
6
4
2
0
-2
control
0.005
0.01
0.015
0.02
0.03
Conc.mg/ml

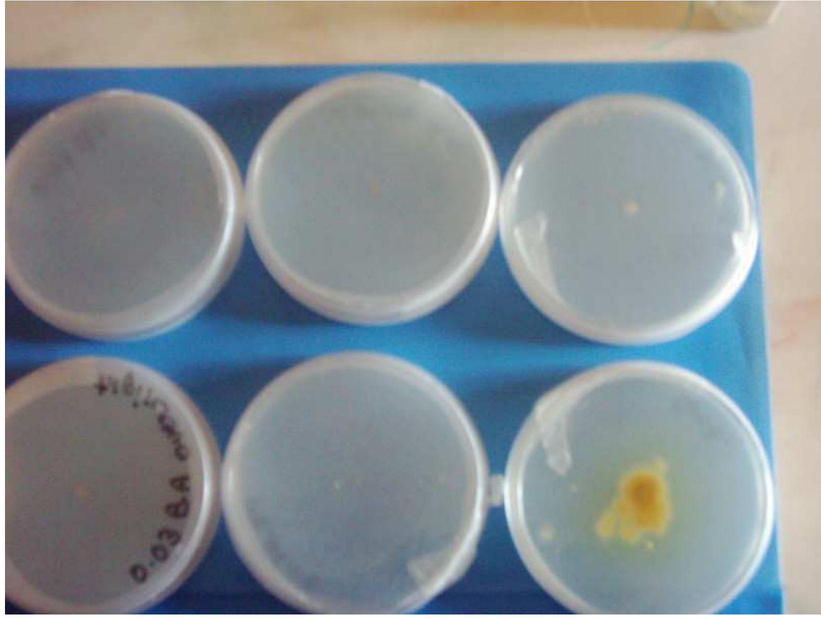


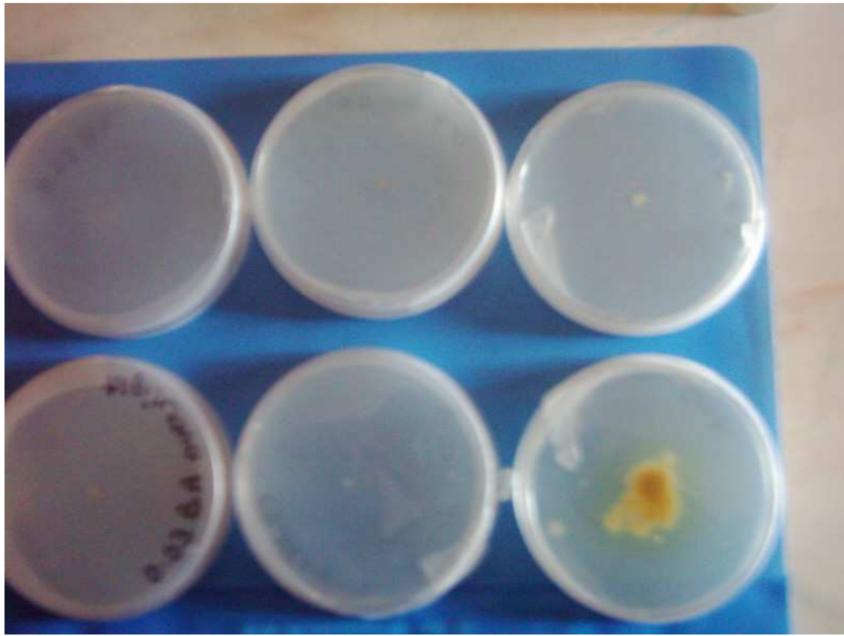
diameter of Geotrichum candidum
25
20
15
10
5
0
-5
control
0.005
0.01
0.015
0.02
0.03
Conc.mg/ml

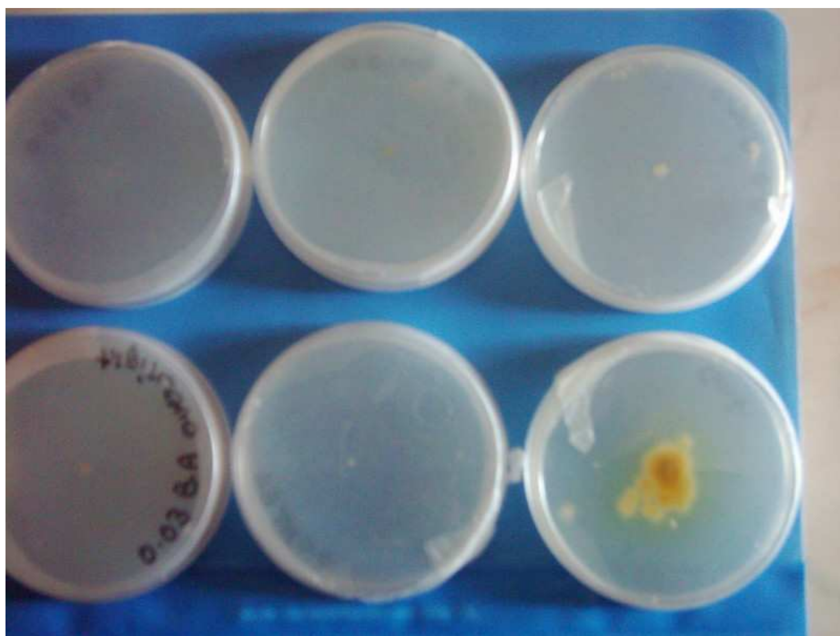

120
100
80
60
40
20
0
Inhibition %
control
0.005
0.01
0.015
0.02
0.03
Conc.mg/ml

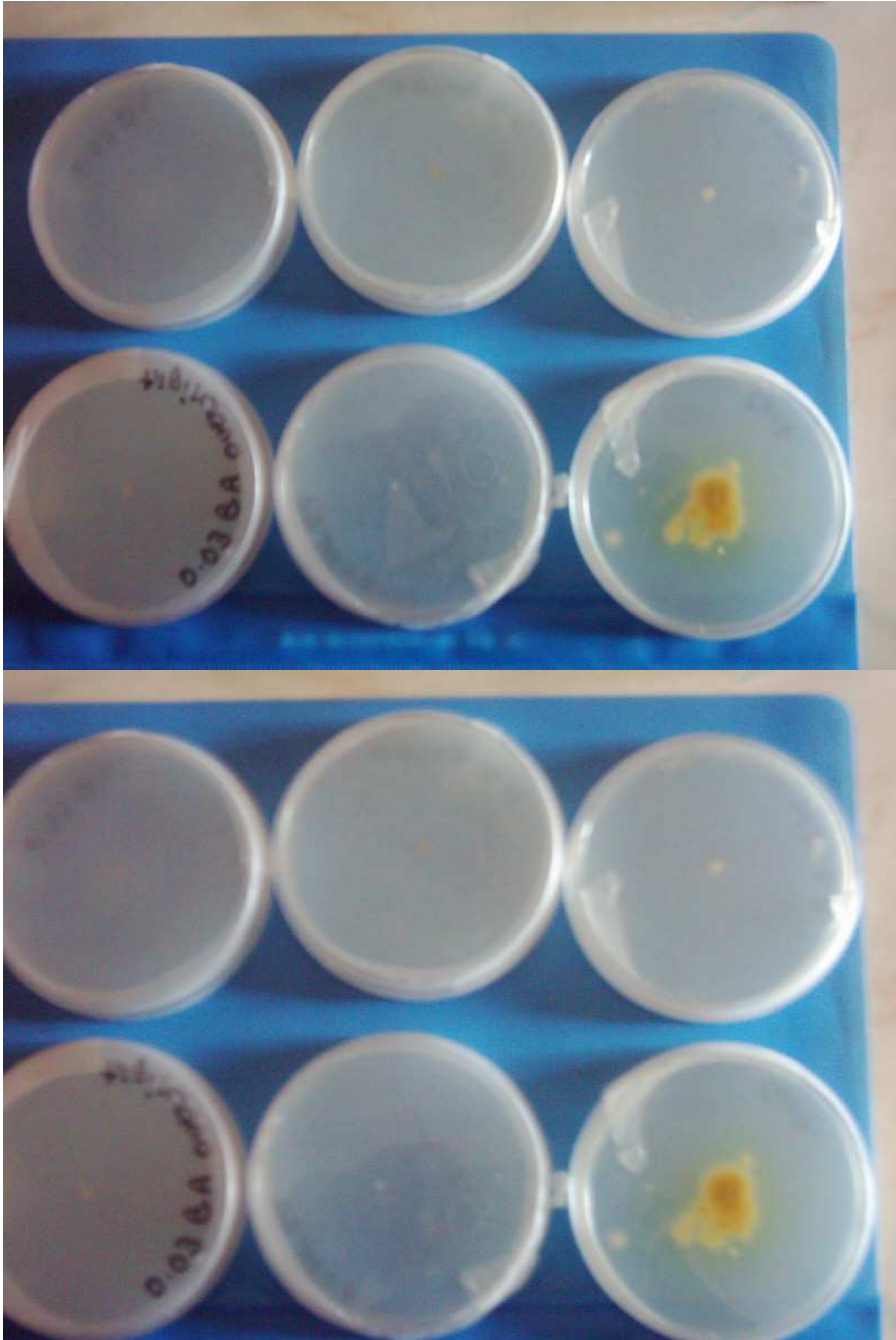

120
100
80
60
40
20
0
Inhibition %
control
0.005
0.01
0.015
0.02
0.03
Conc.mg/ml

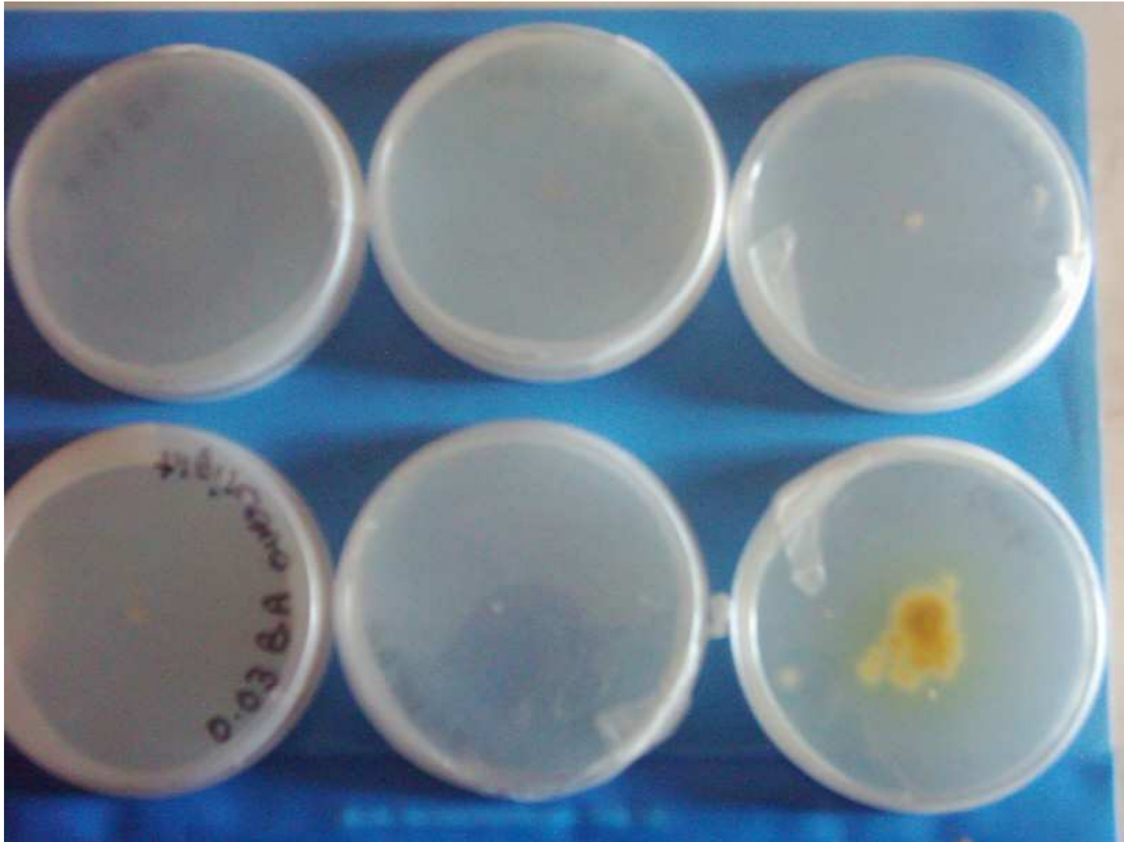


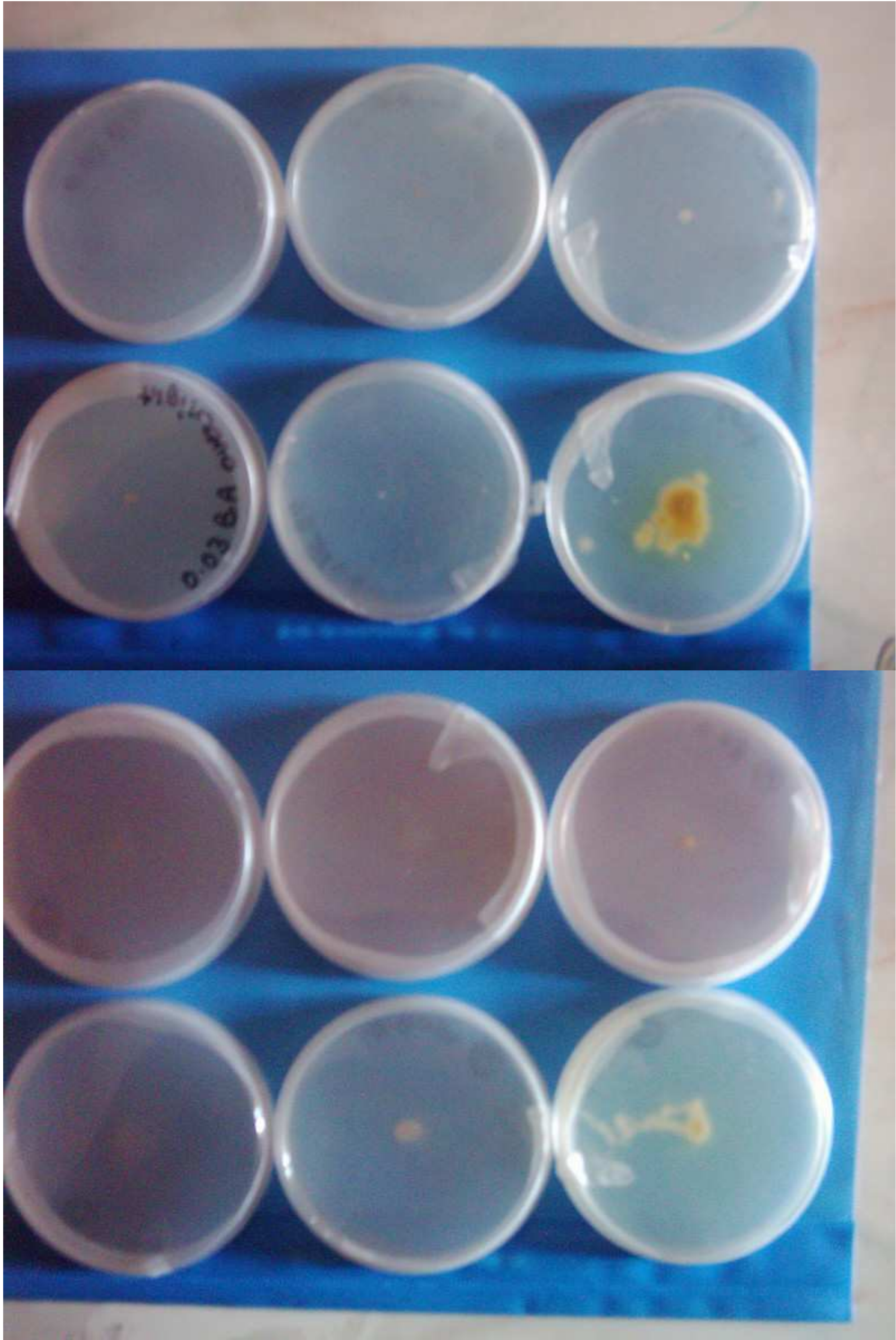

0.03 B.A

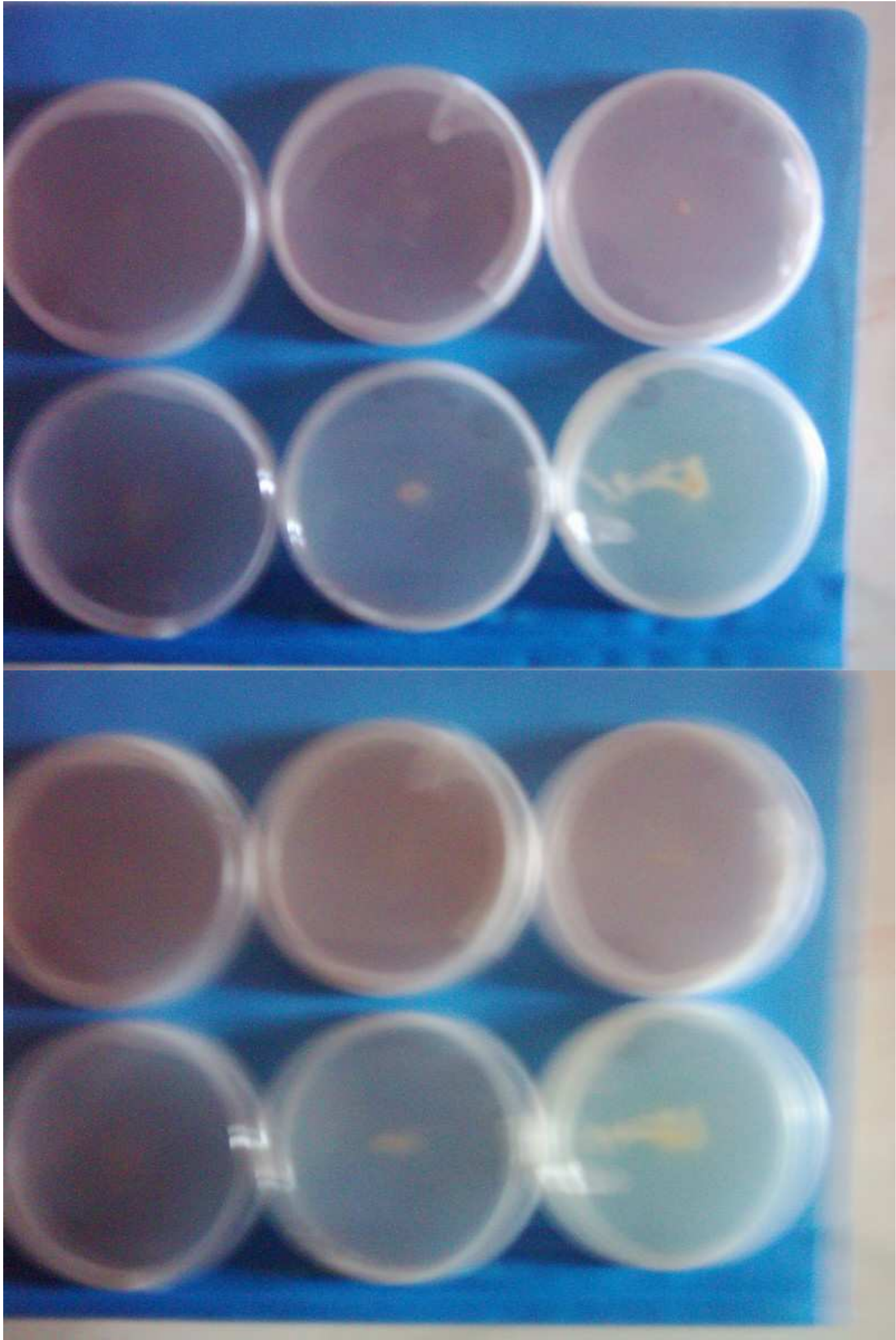

0.03 B.A

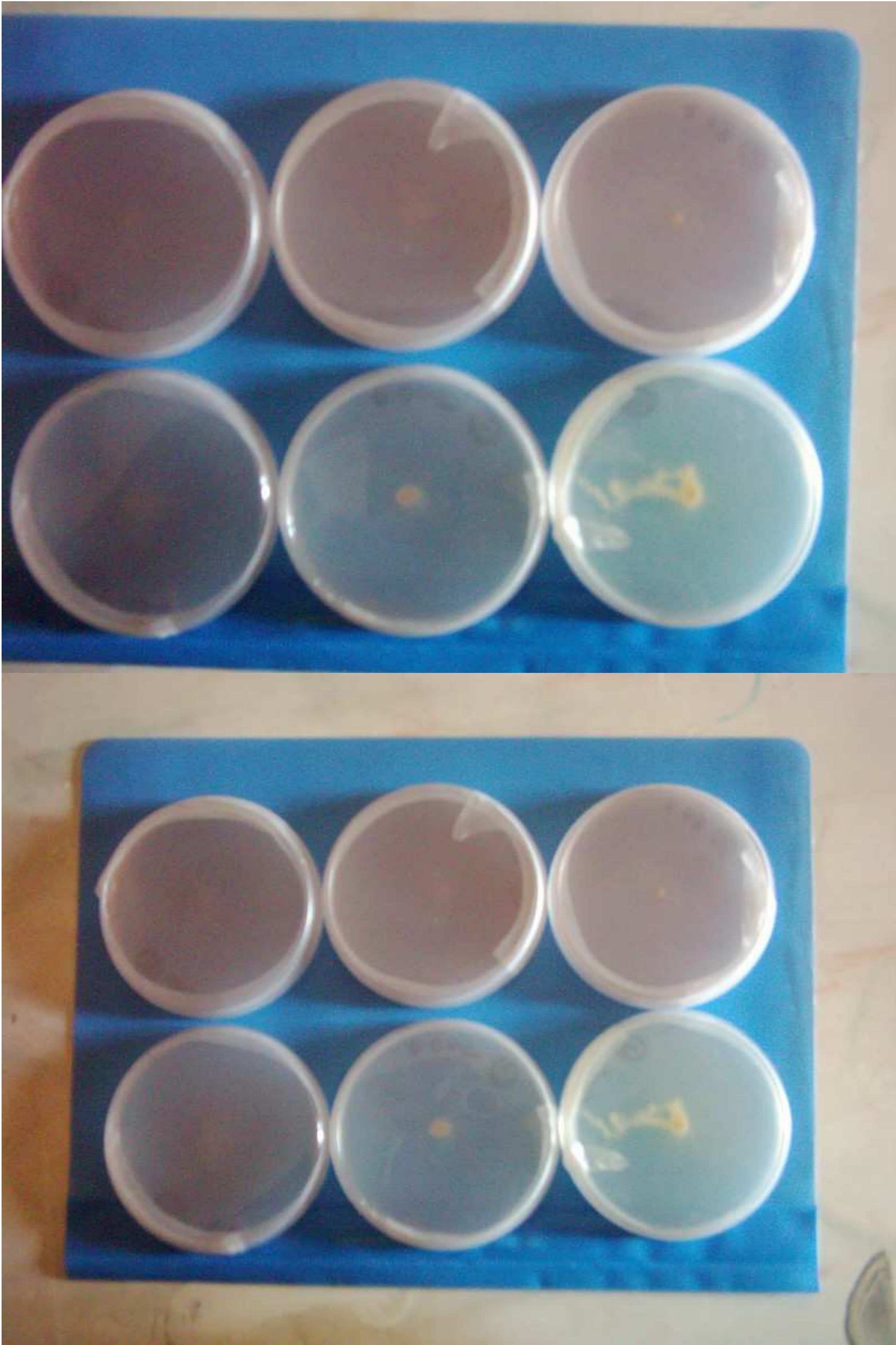


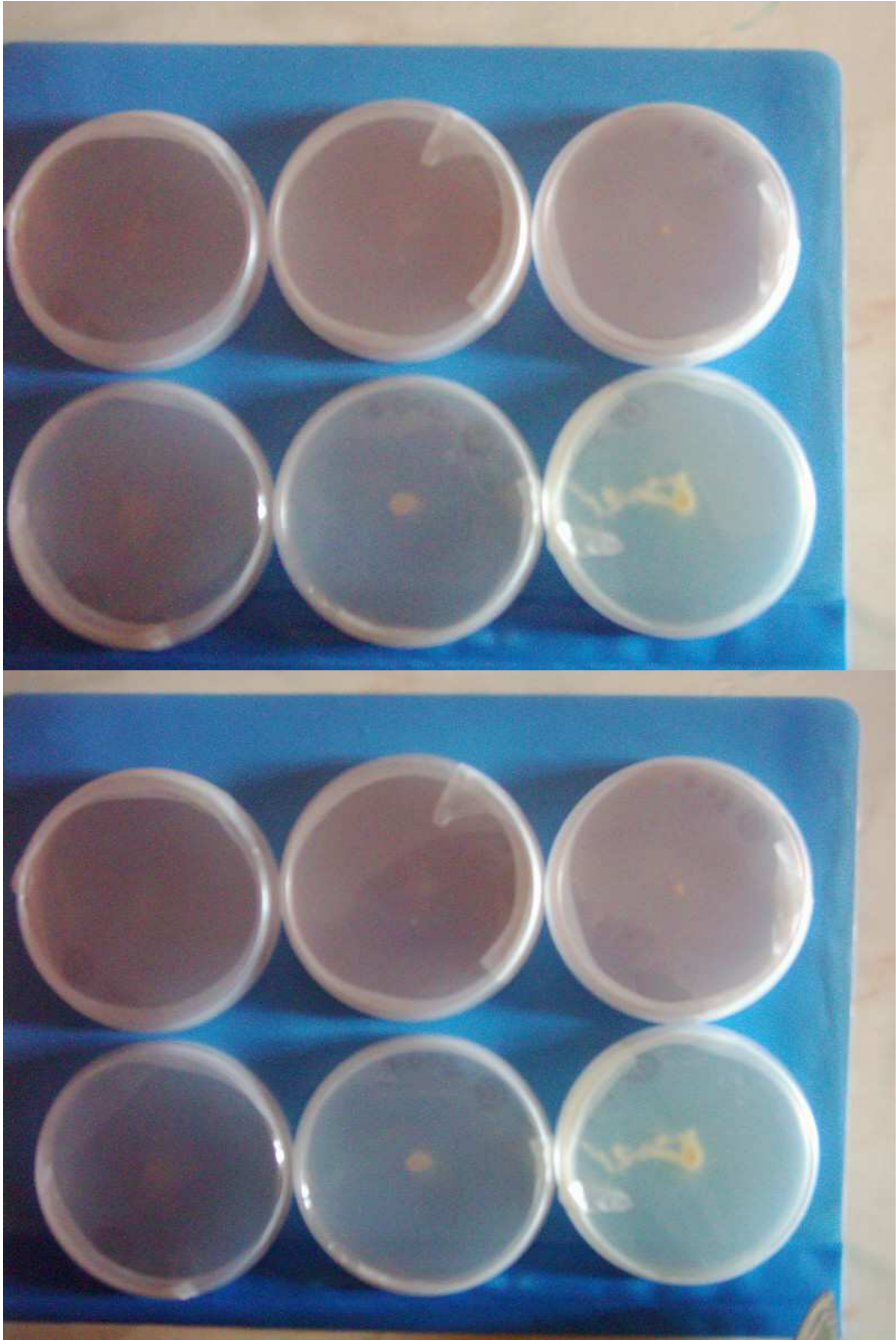


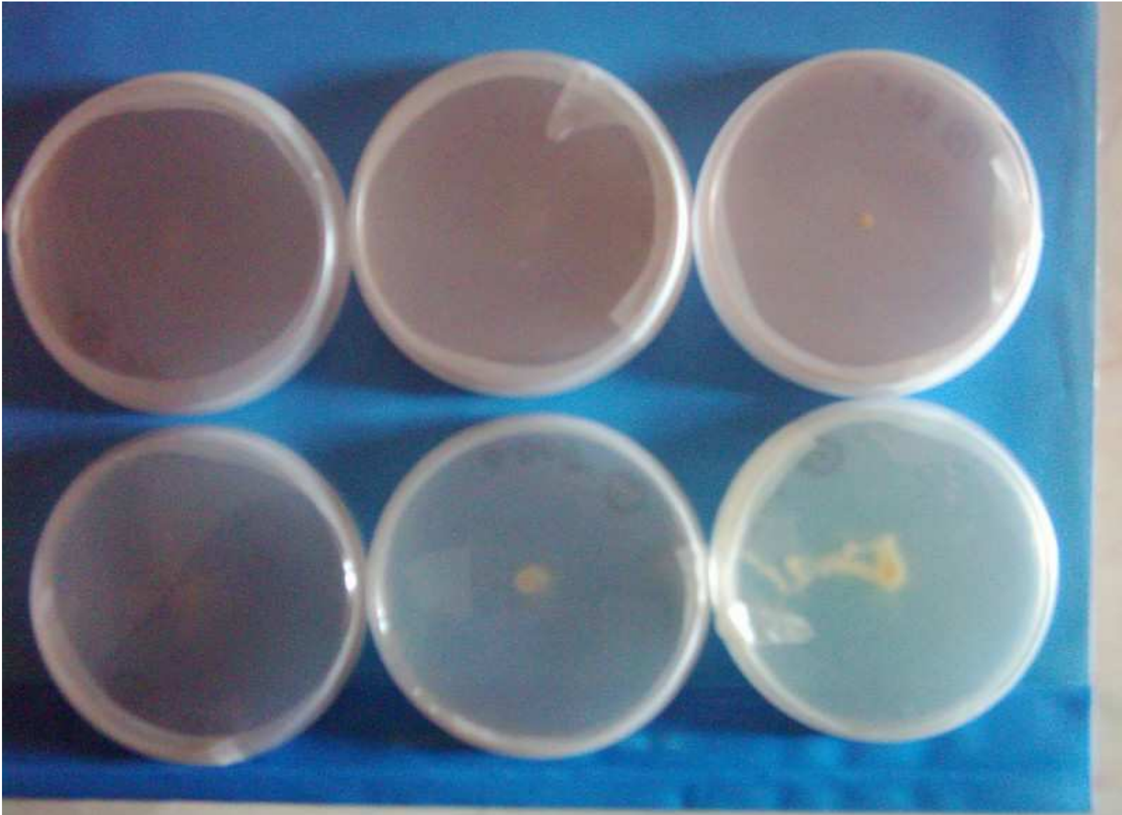

0.03 B.A

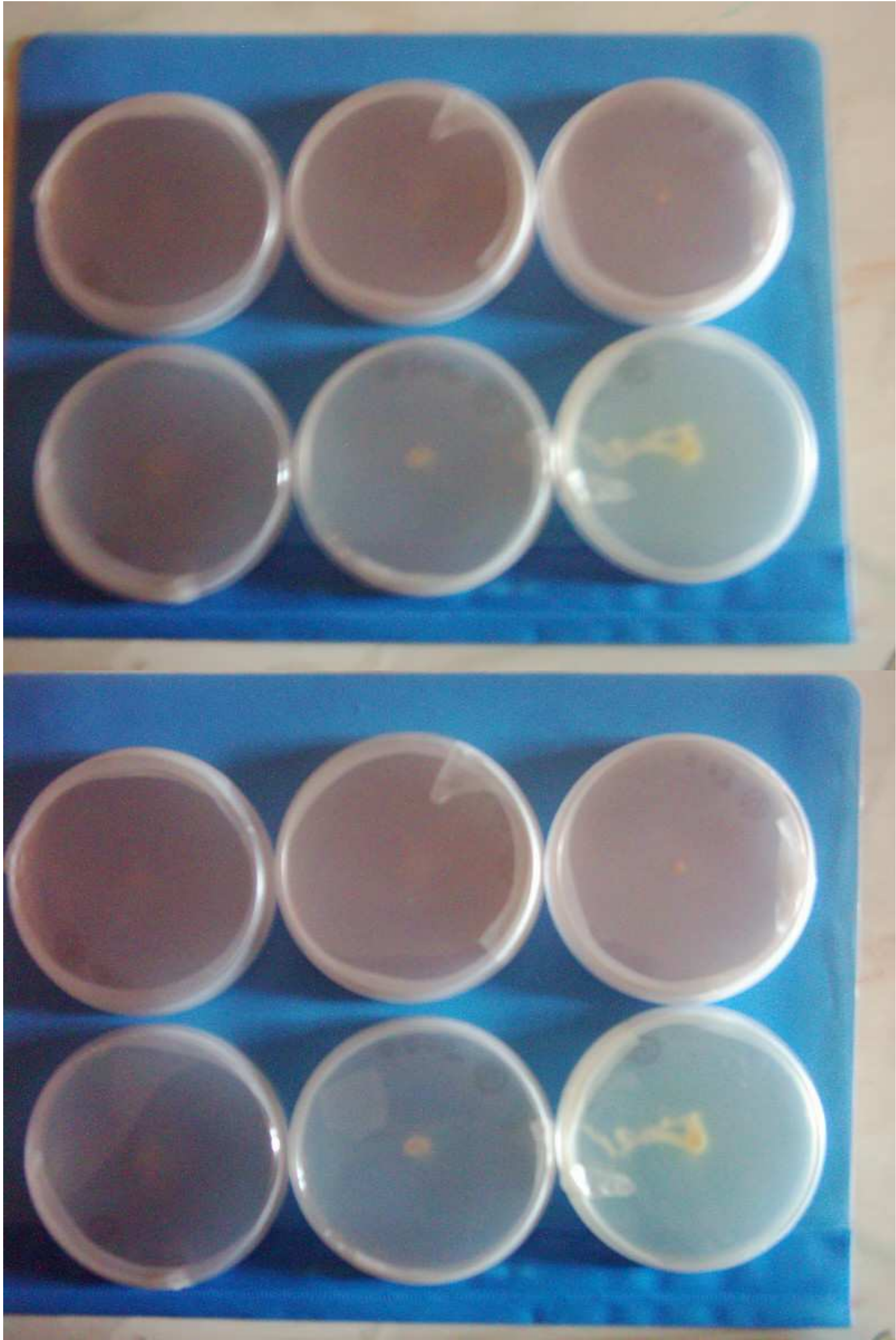


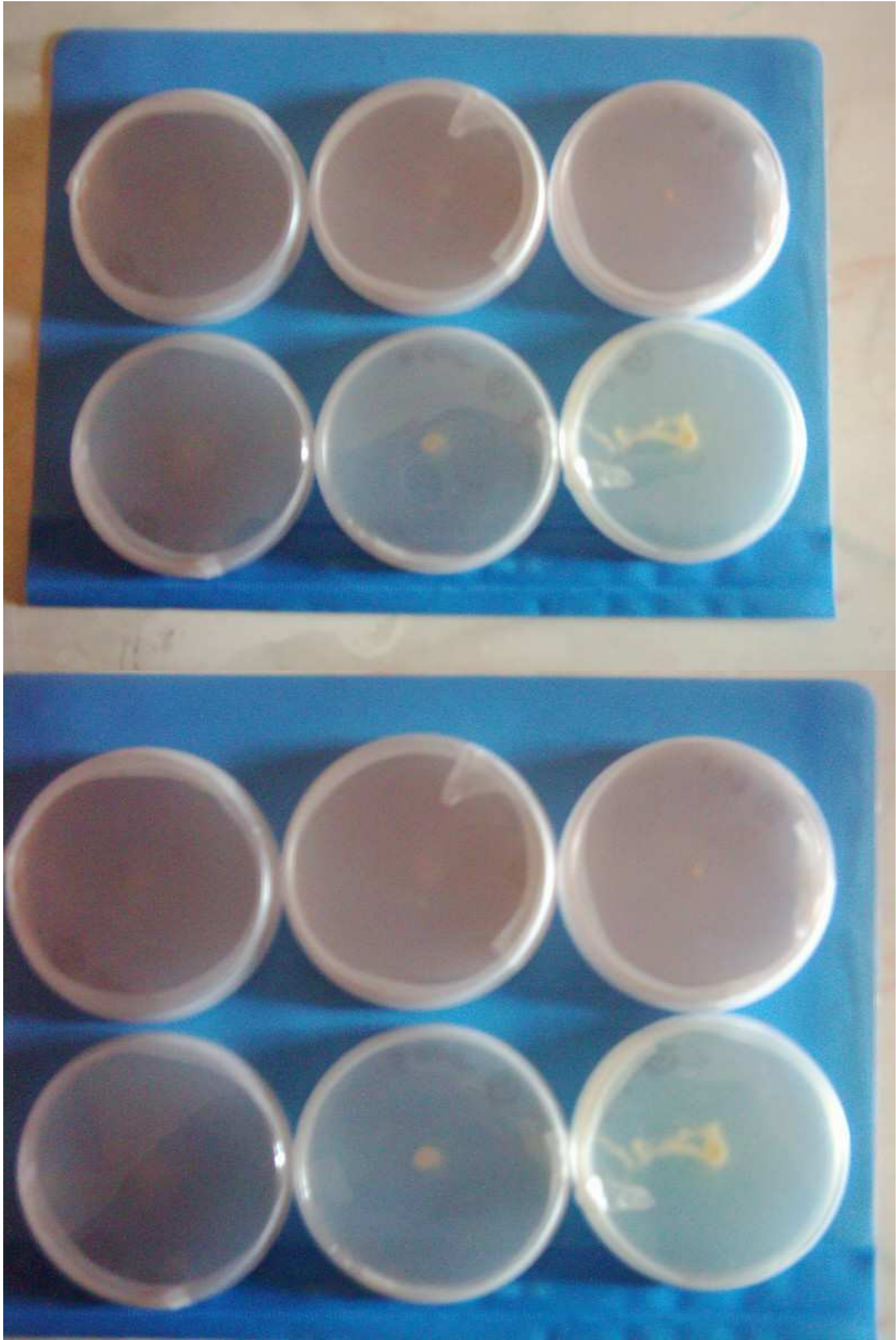


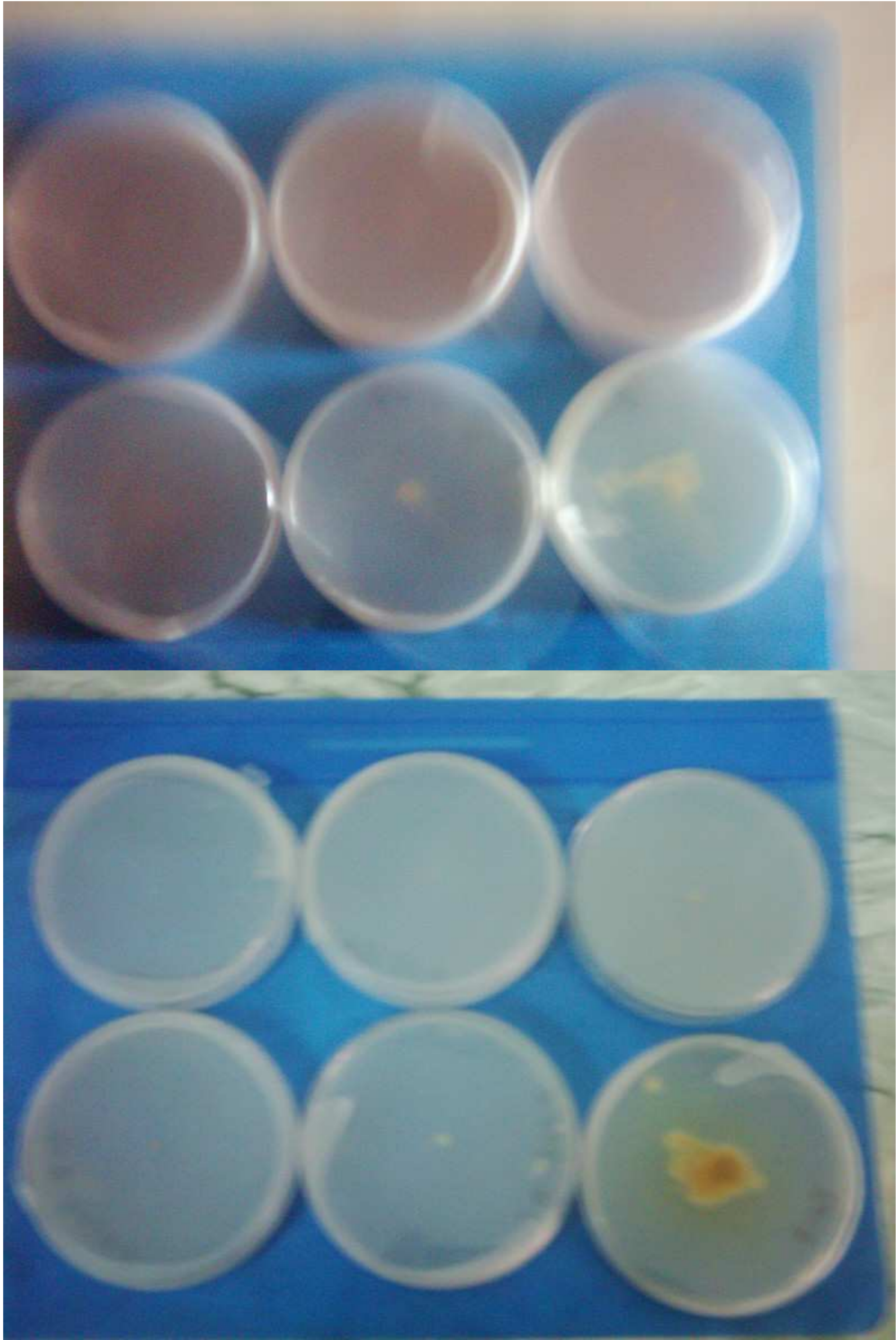


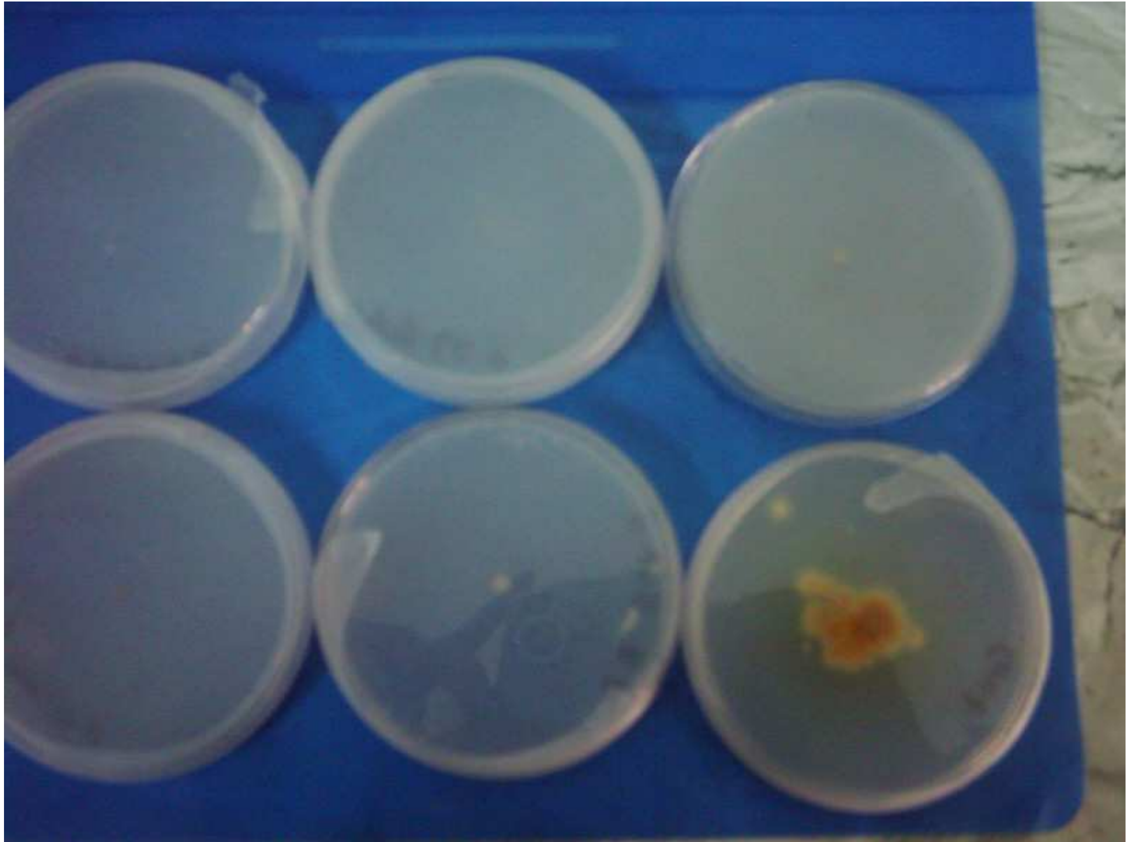


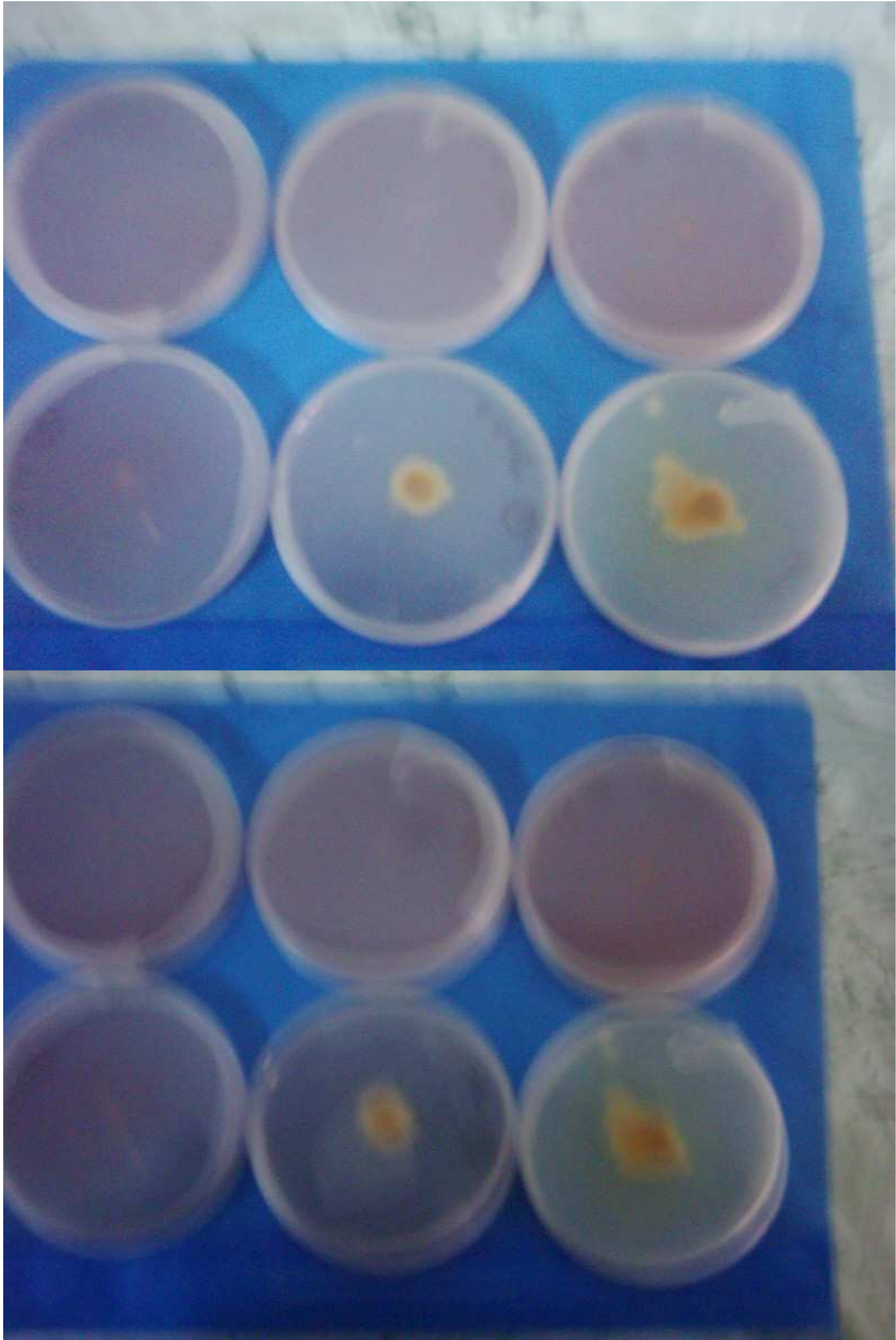


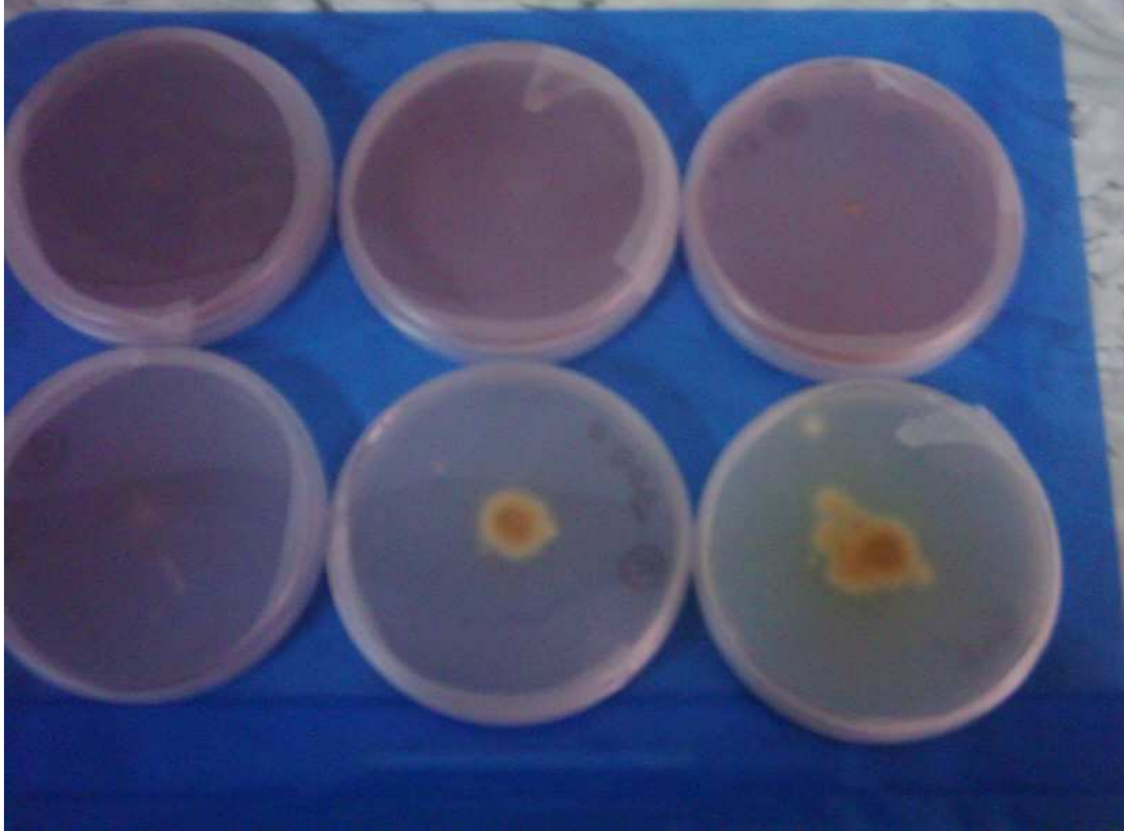


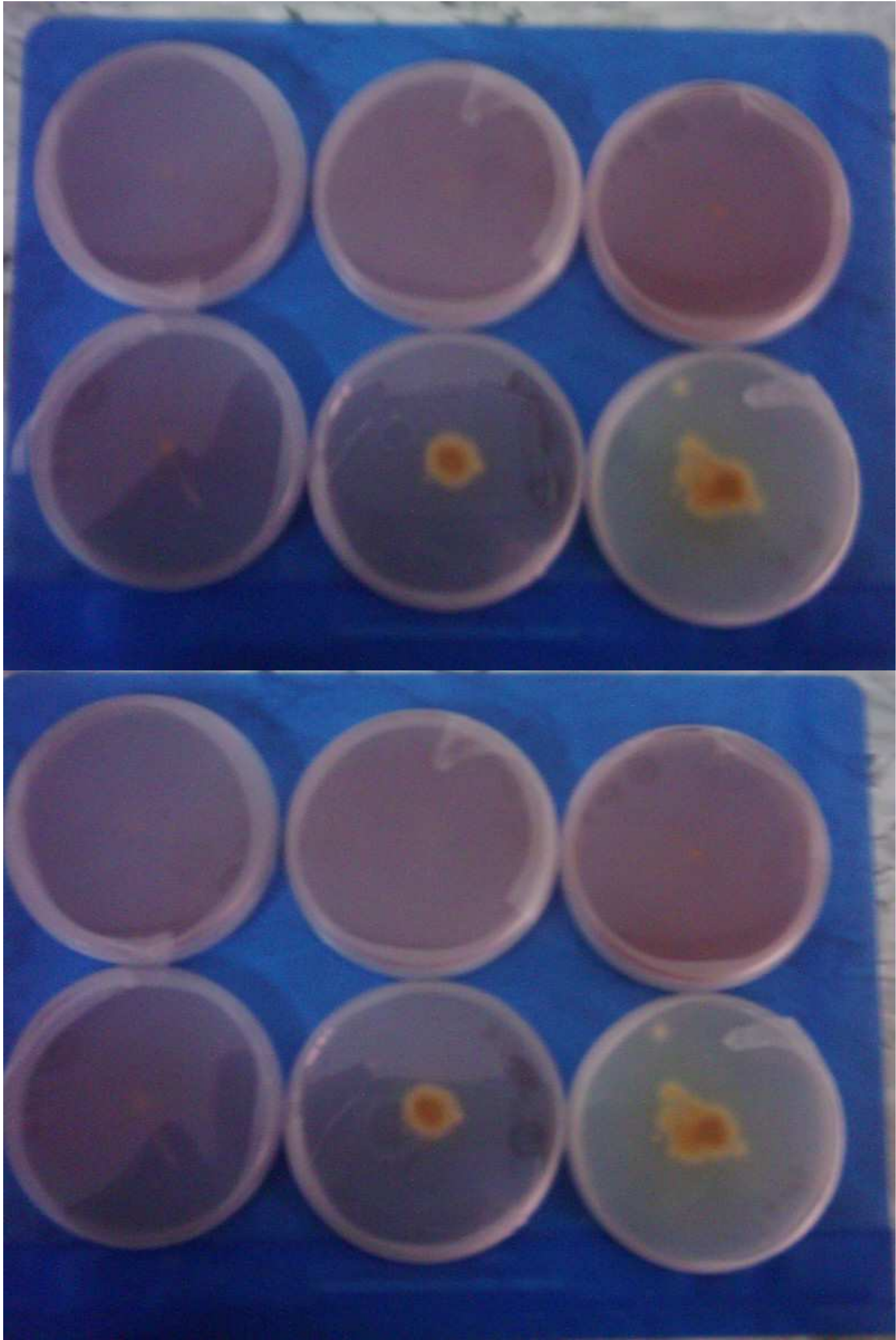


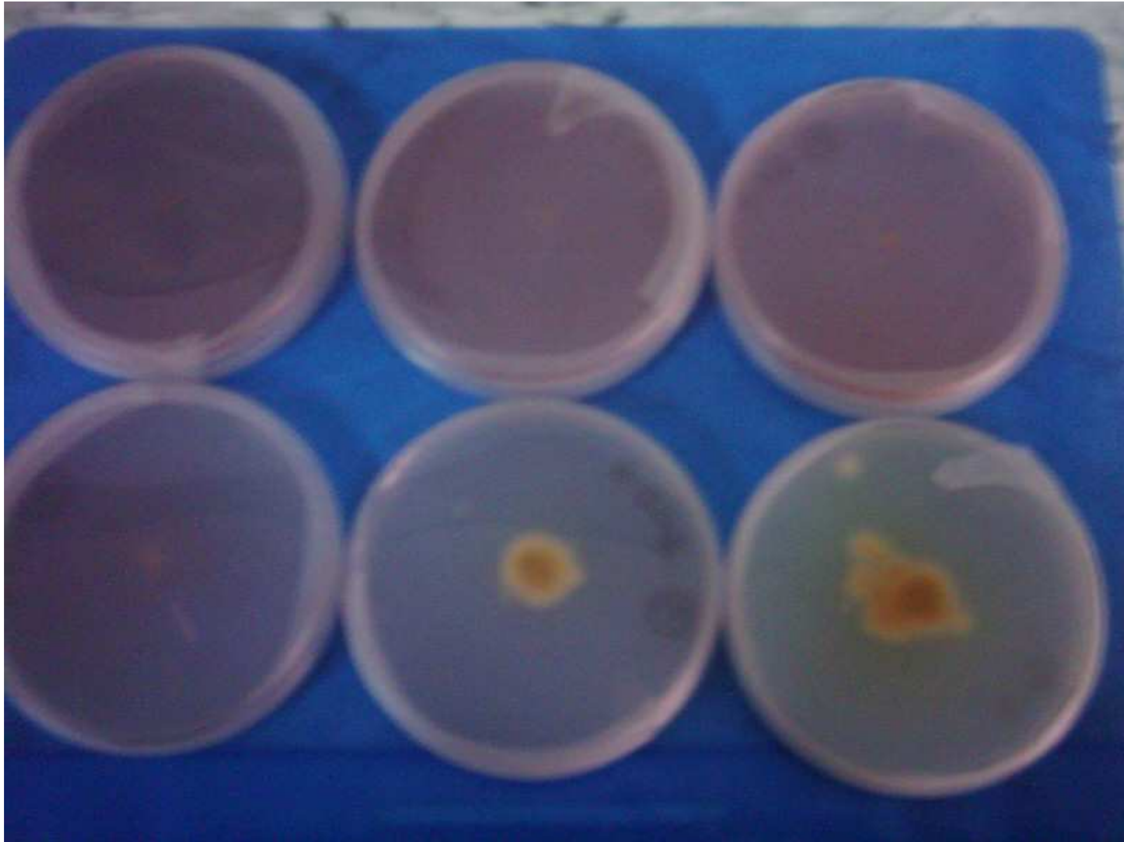


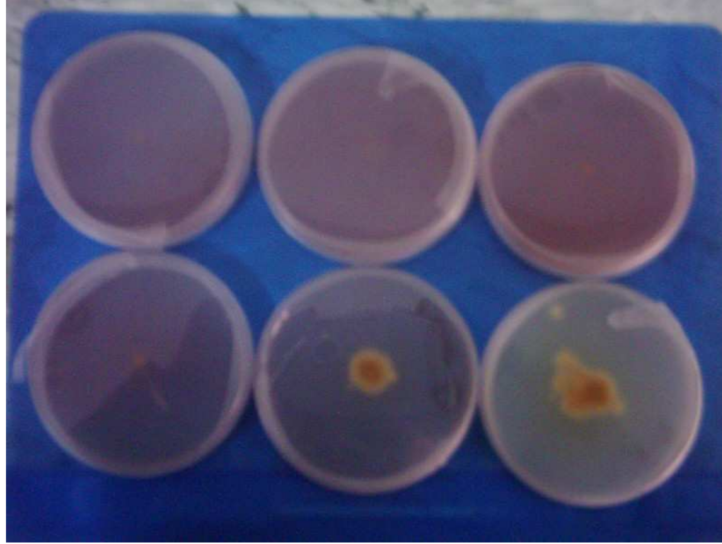


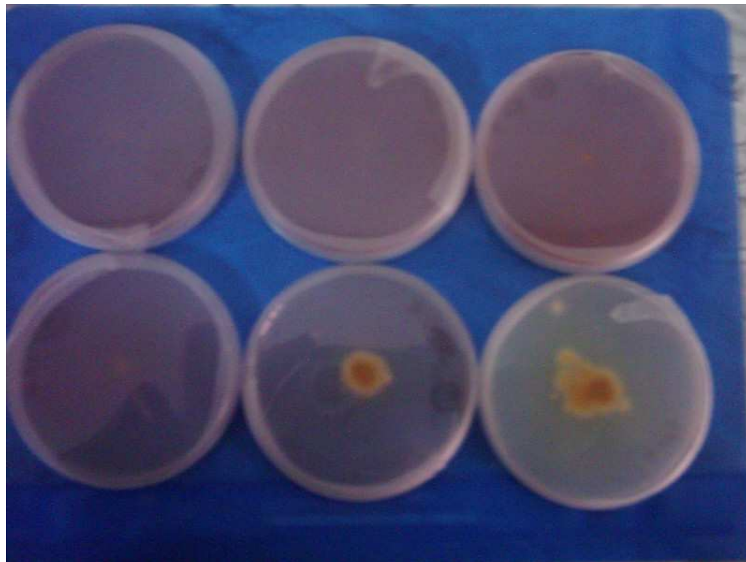




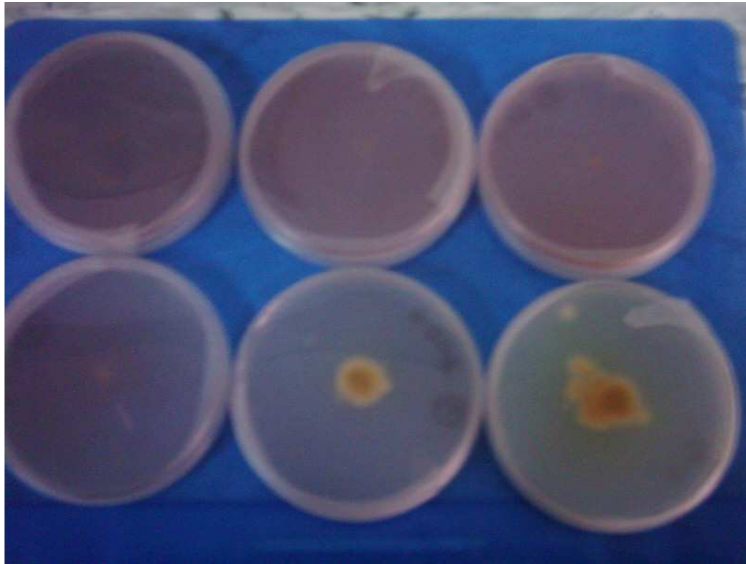


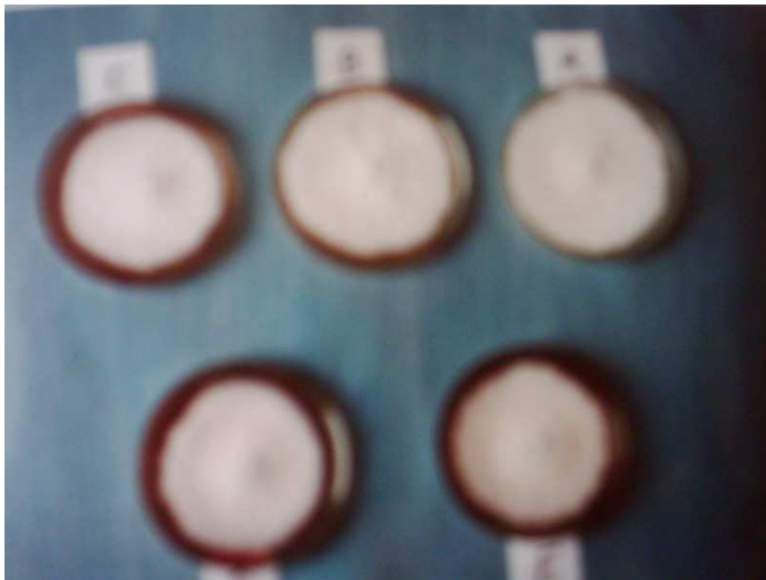






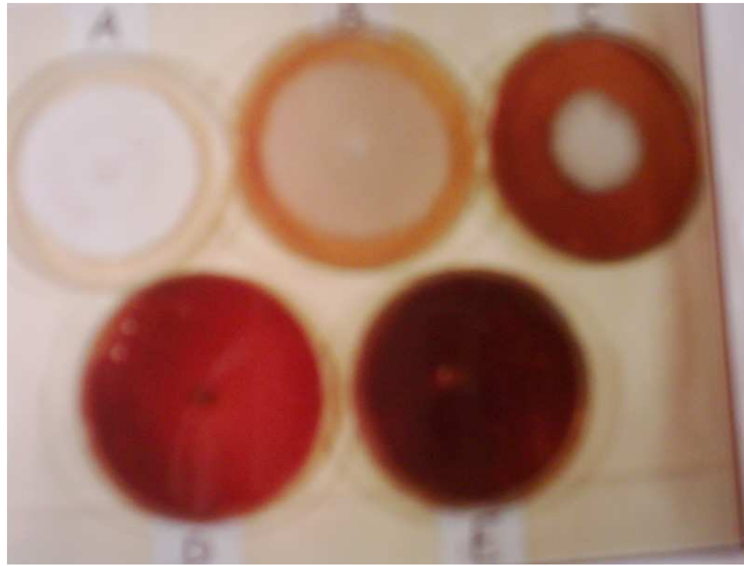
2

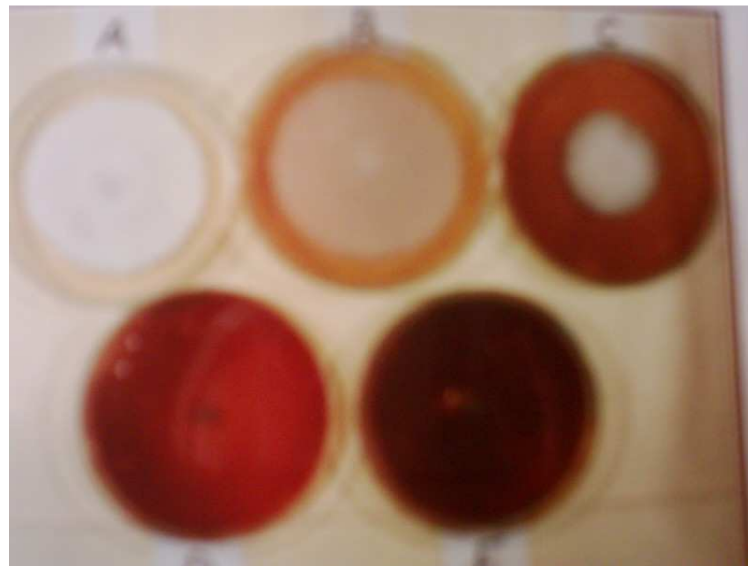




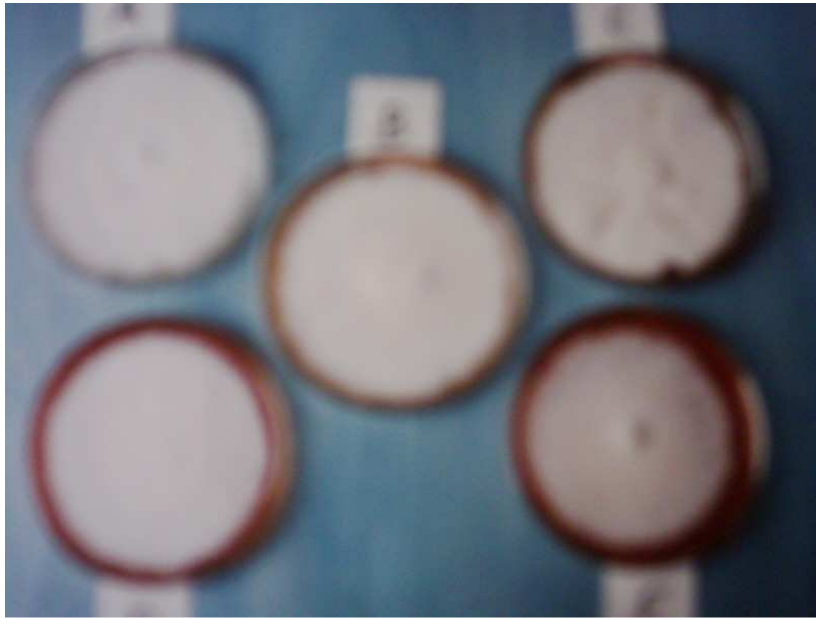
A
C
B
D
E

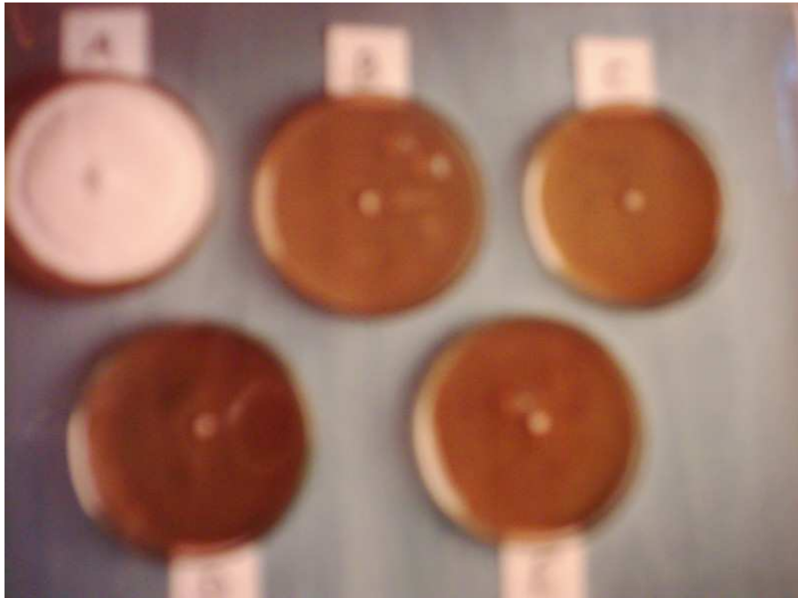
4

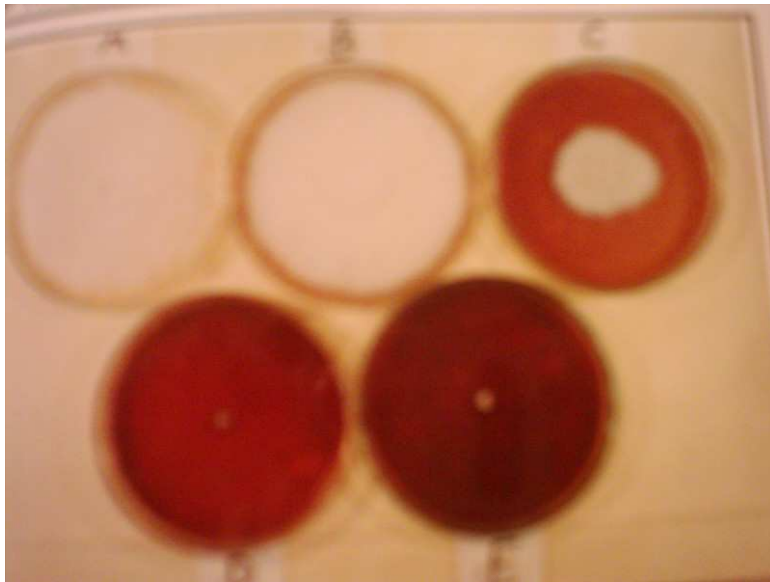




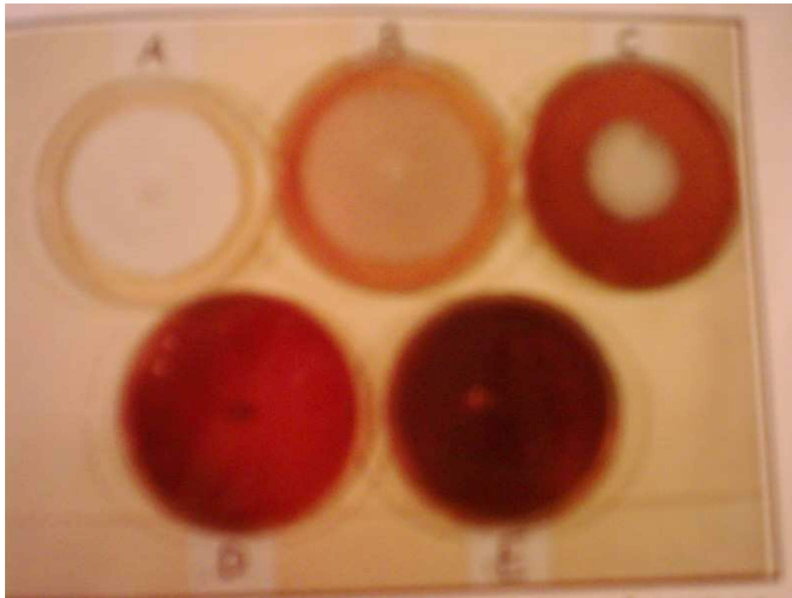
5

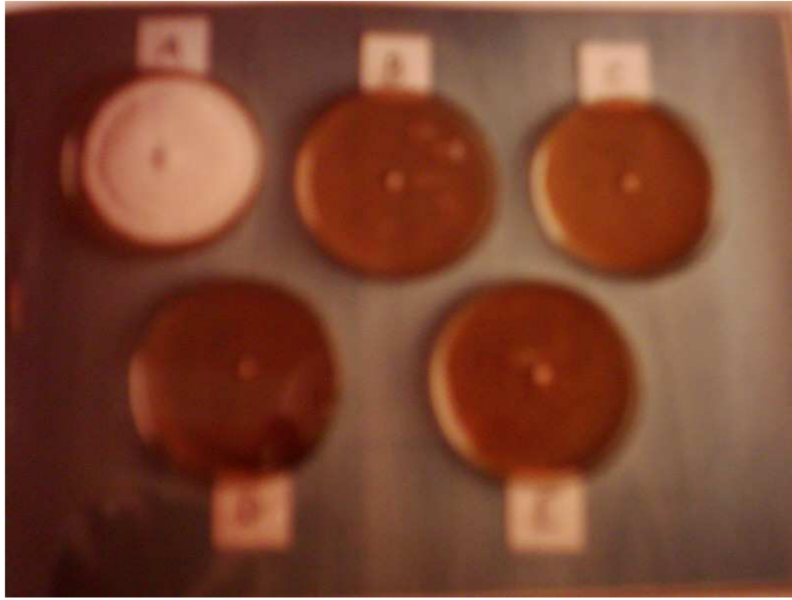


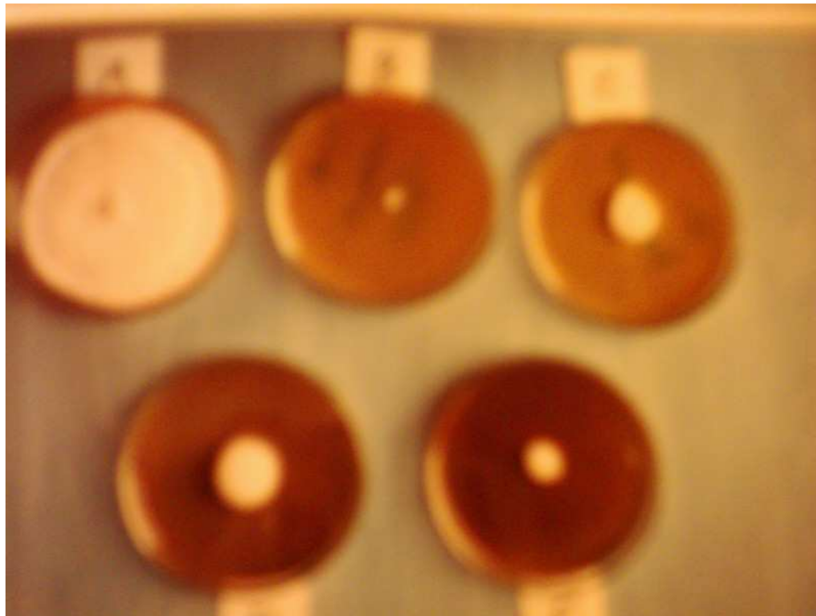


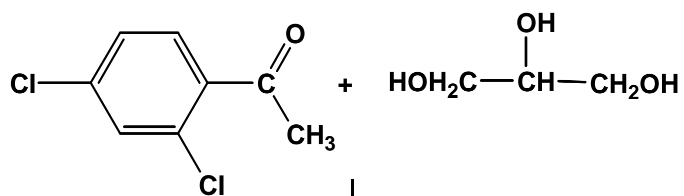

A
B
C

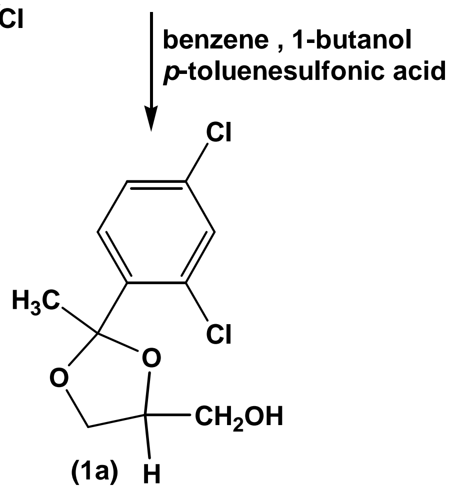
8

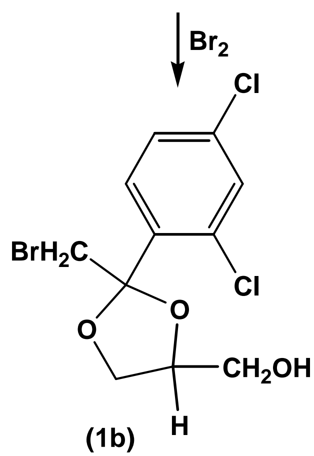


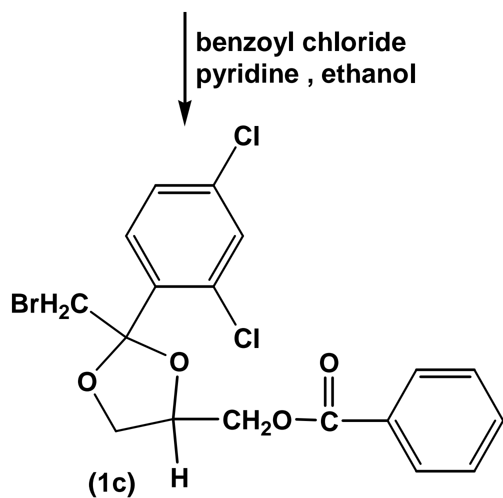


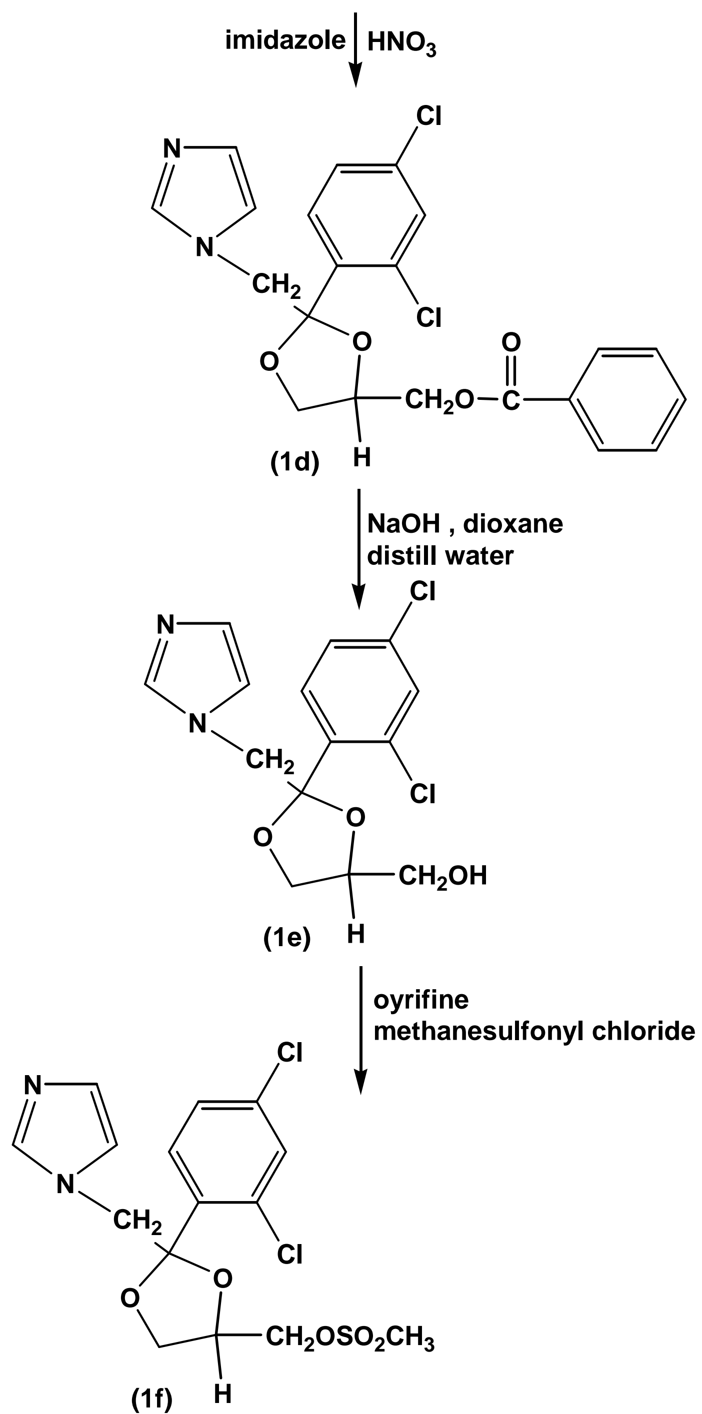


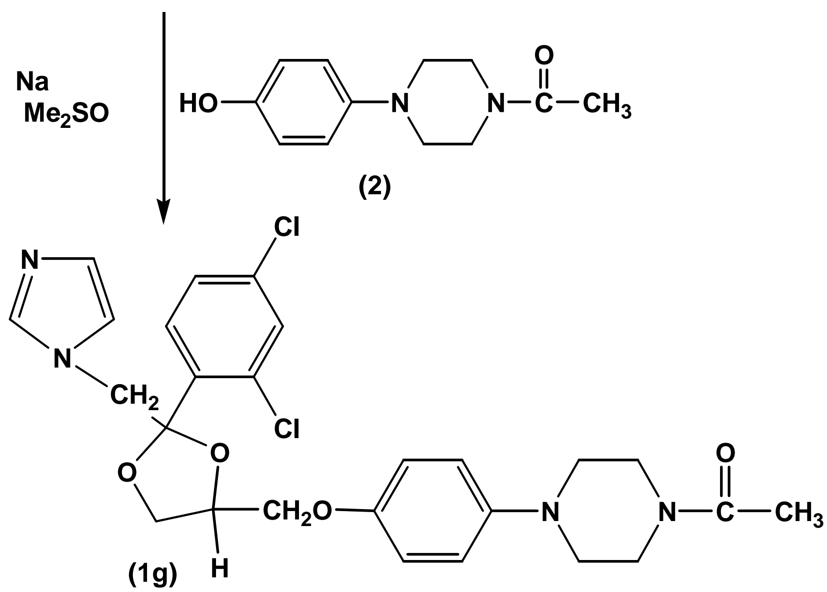

Cl
C
O
CH3
Cl
+
OH
HOH2C—CH—CH2OH

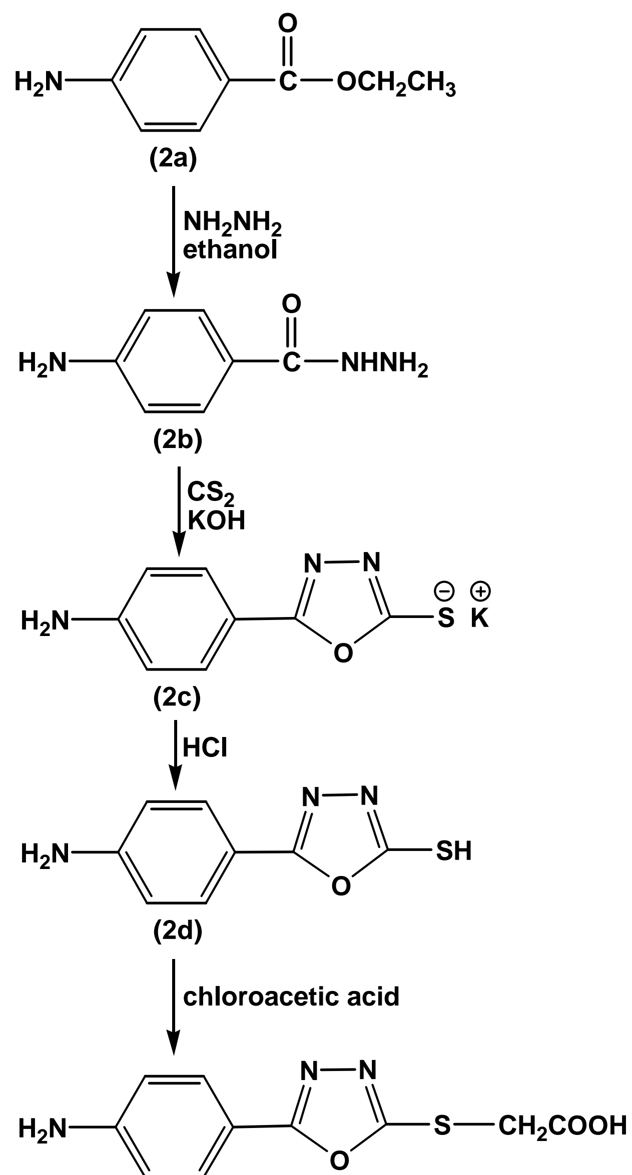

benzene , 1-butanol
p-toluenesulfonic acid
Cl
H3C
Cl
O
O
CH2OH
(1a)
H

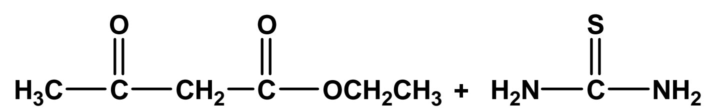

Br2
Cl
BrH2C
Cl
O
O
CH2OH
H
(1b)

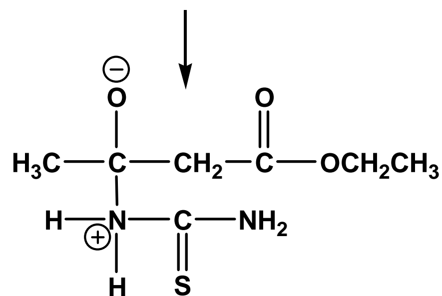

benzoyl chloride
pyridine , ethanol
Cl
BrH2C
Cl
O
O
O
CH2O—C
(1c)
H

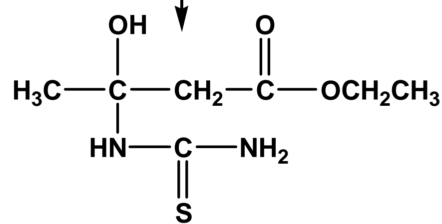

imidazole
HNO3
Cl
N
N
CH2
Cl
O
O
O
CH2O
C
(1d)
H
NaOH , dioxane
distill water
Cl
N
N
CH2
Cl
O
O
CH2OH
(1e)
H
oyrifine
methanesulfonyl chloride
Cl
N
N
CH2
Cl
O
O
CH2OSO2CH3
(1f)
H

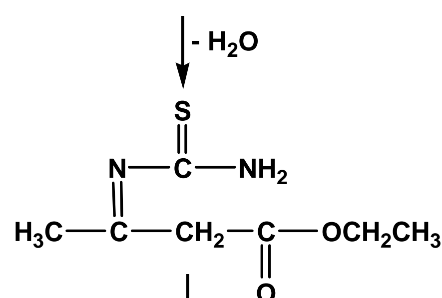

Na
Me2SO
HO
N
N
C
O
CH3
(2)
Cl
N
N
CH2
Cl
O
O
CH2O
N
N
C
O
CH3
(1g)
H

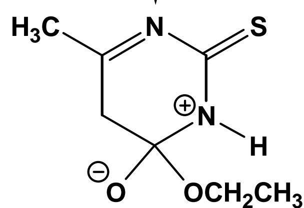

H2N
C—OCH2CH3
O
(2a)
NH2NH2
ethanol
C—NHNH2
O
(2b)
CS2
KOH
N—N
O
S K
(2c)
HCl
SH
(2d)
chloroacetic acid
S—CH2COOH

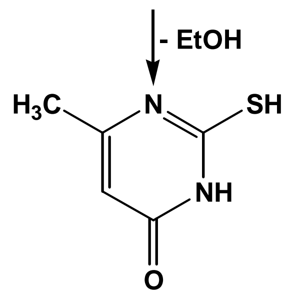




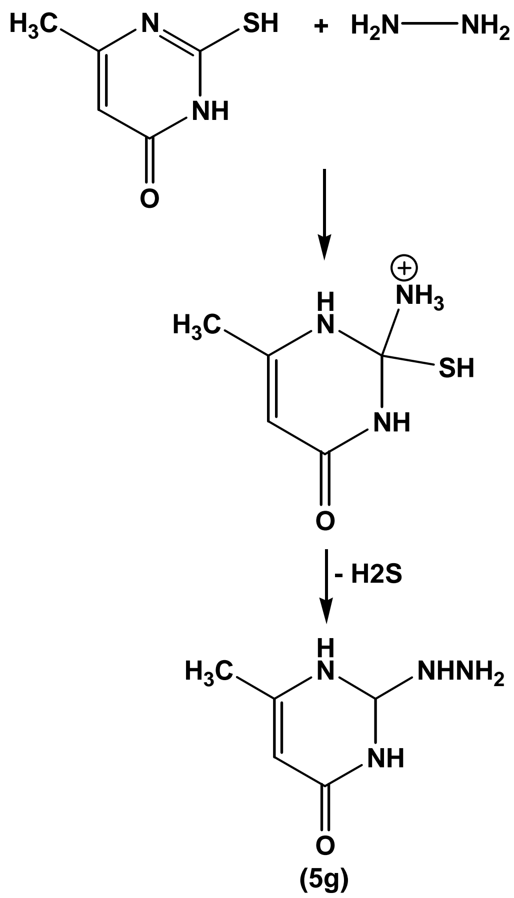


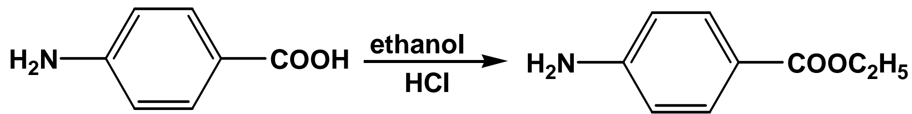


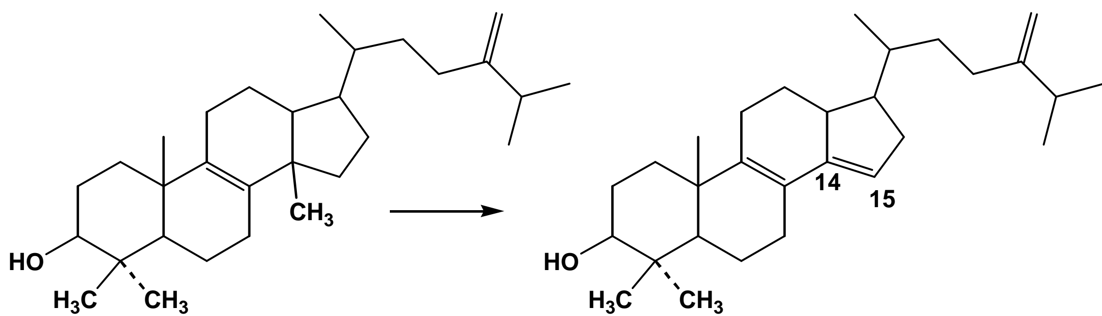


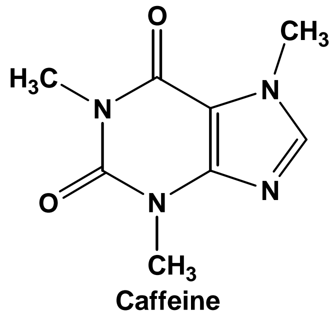


(4g)

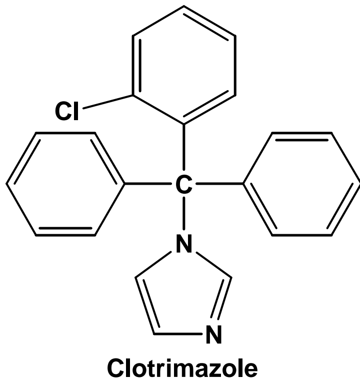

H3C
N
SH
+ H2N—NH2
NH
O
H
N
NH3
SH
NH
O
- H2S
H
N
NHNH2
NH
O
(5g)


H2N
COOH
ethanol
HCl
H2N
COOC2H5

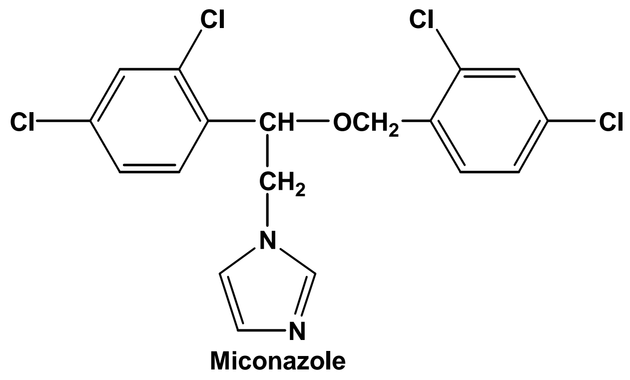

HO
H3C
CH3
CH3
HO
H3C
CH3
14
15



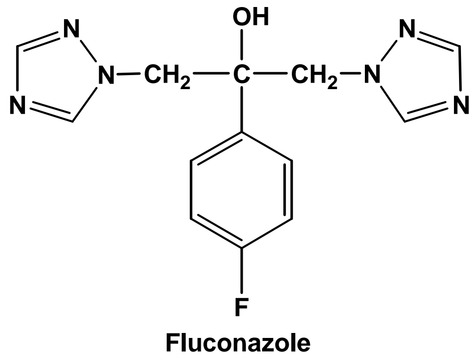
Caffeine



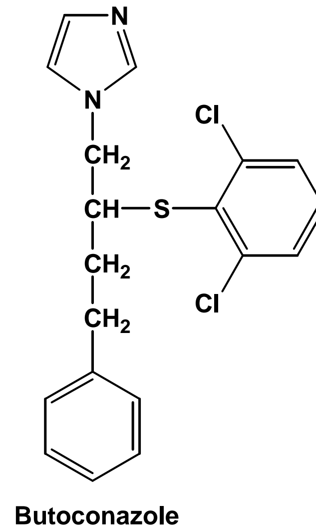
Clotrimazole



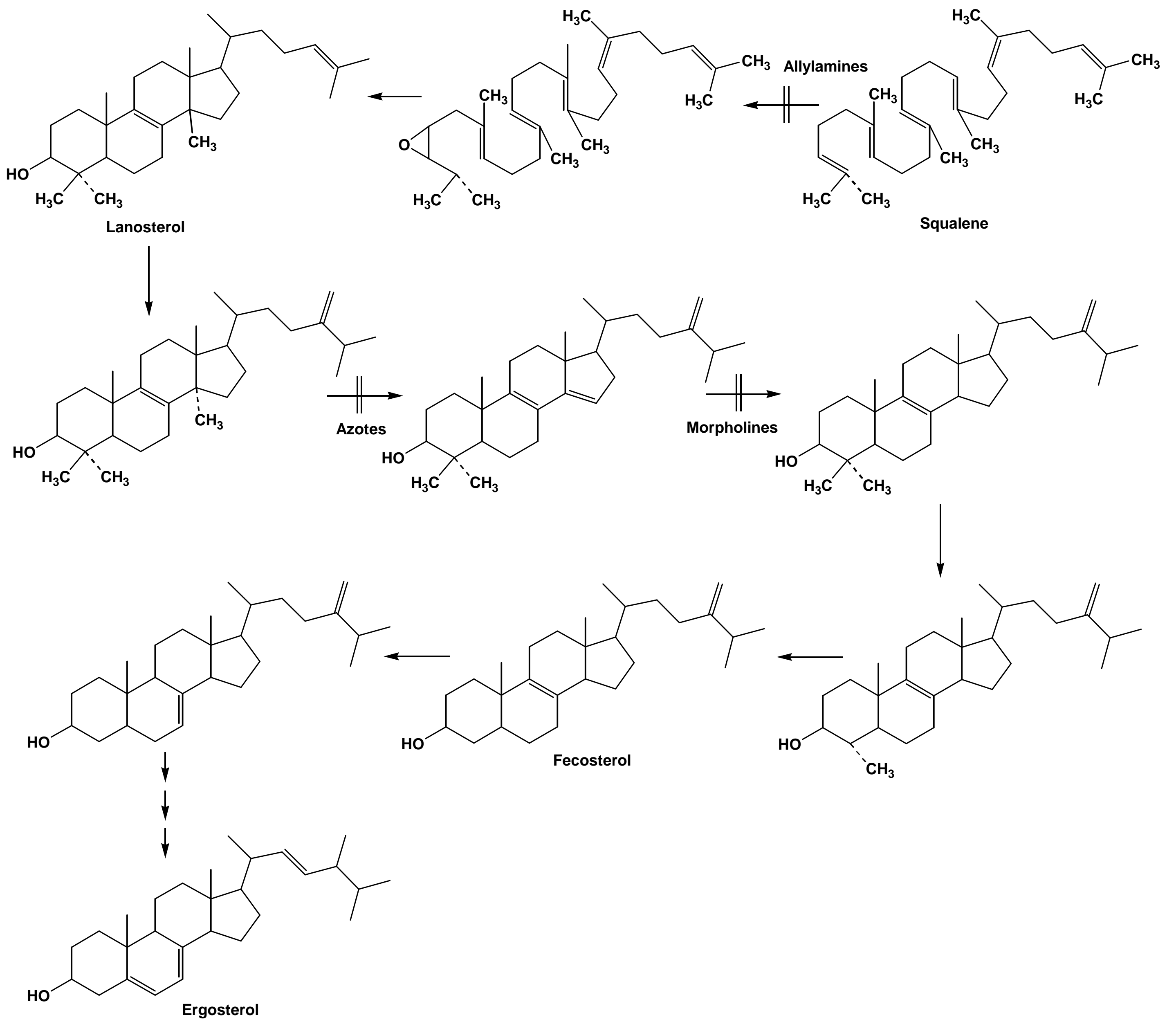
Miconazole



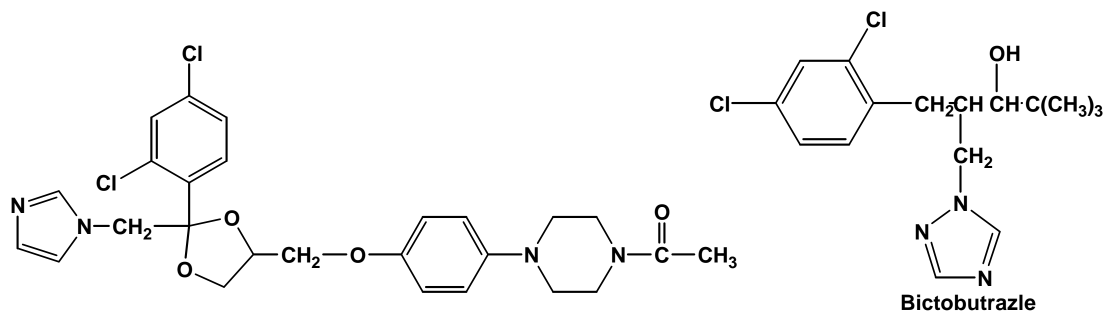
Fluconazole



Butoconazole

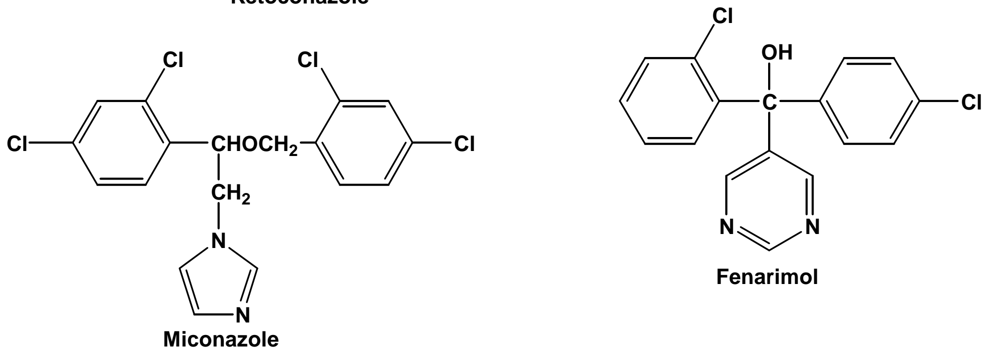


Lanosterol
Squalene
Allylamines
Azotes
Morpholines
Fecosterol
Ergosterol



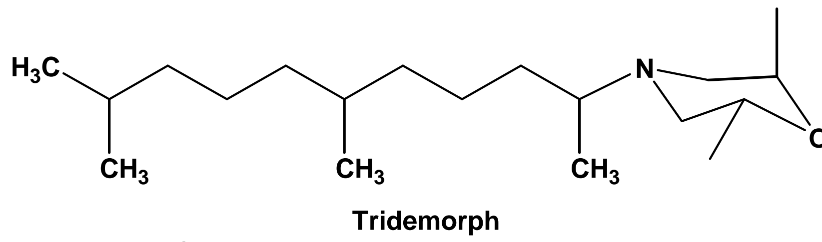
Bictobutrazle

Ketoconazole

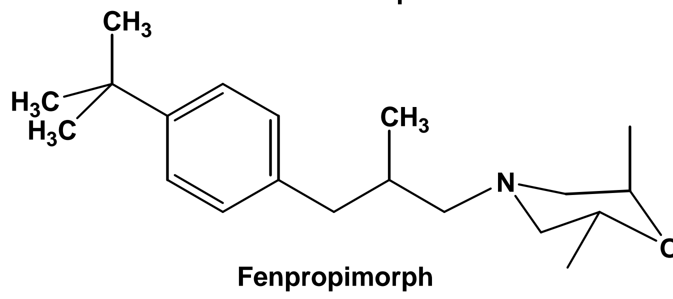


Fenarimol

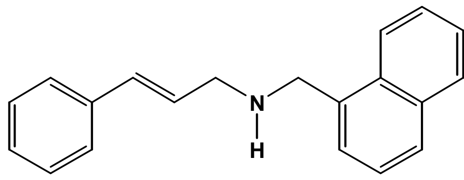
Miconazole

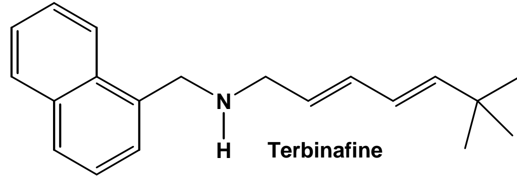


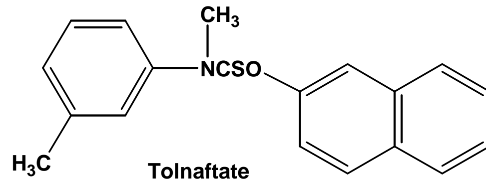
Tridemorph

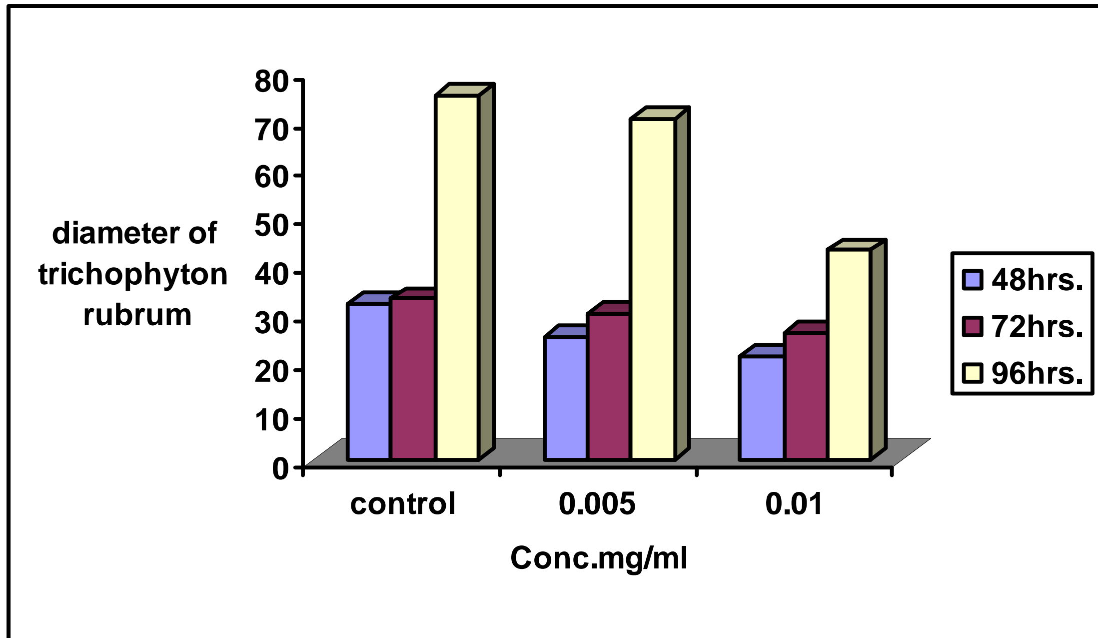


Fenpropimorph

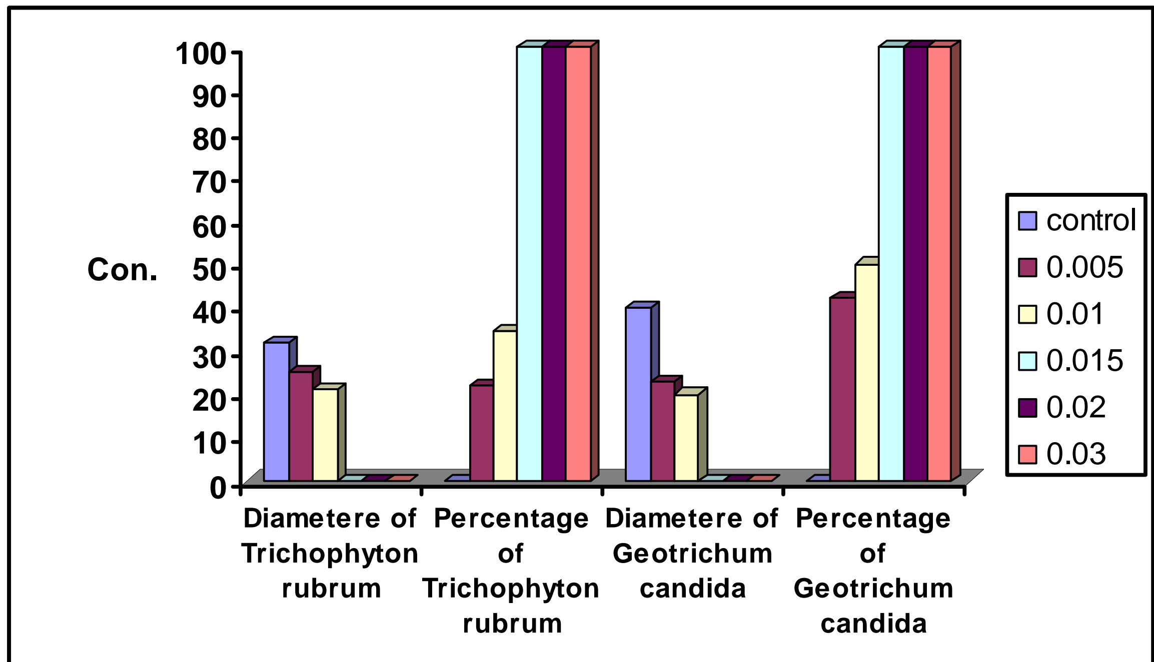

N
H
Naftifine

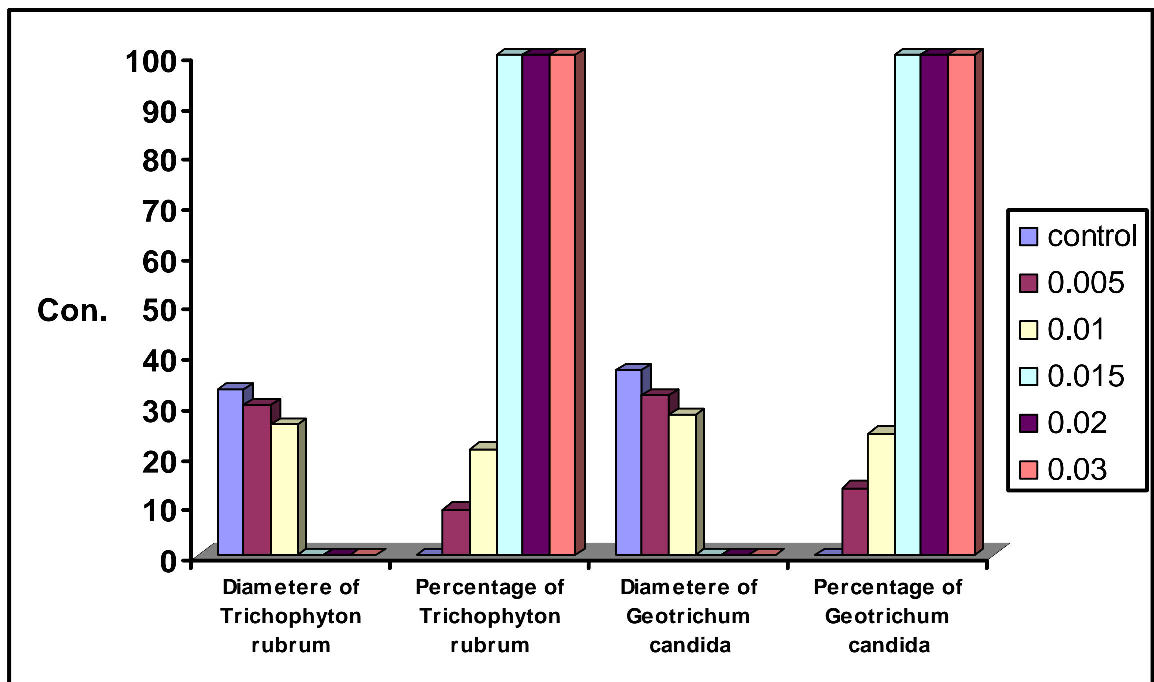

N
H
Terbinafine

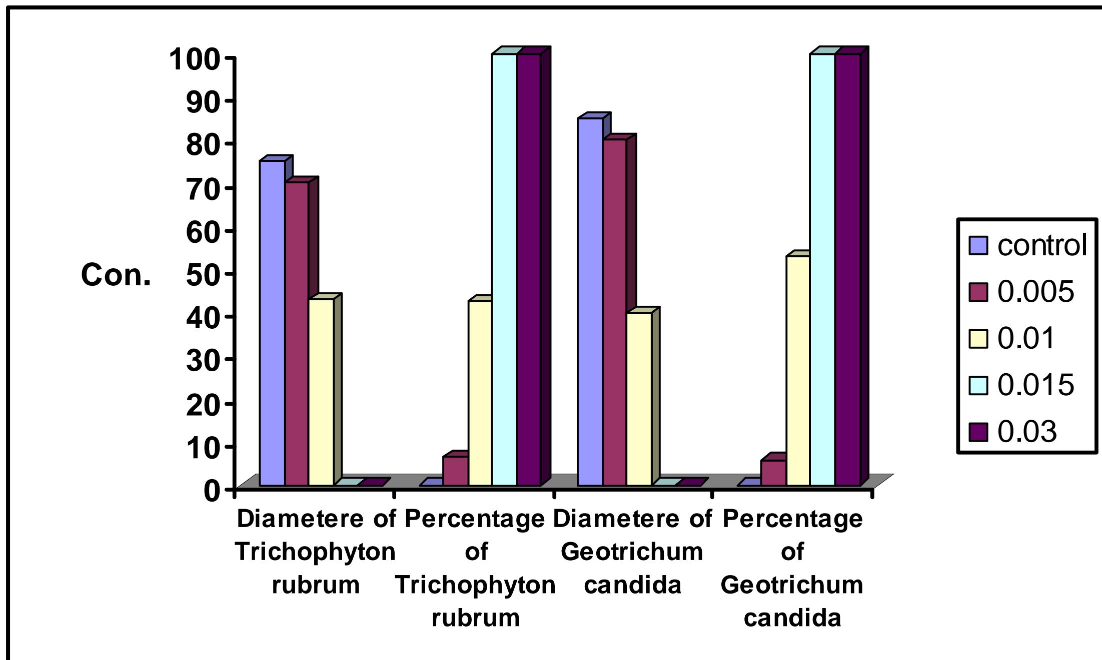

CH3
NCSO
H3C
Tolnaftate

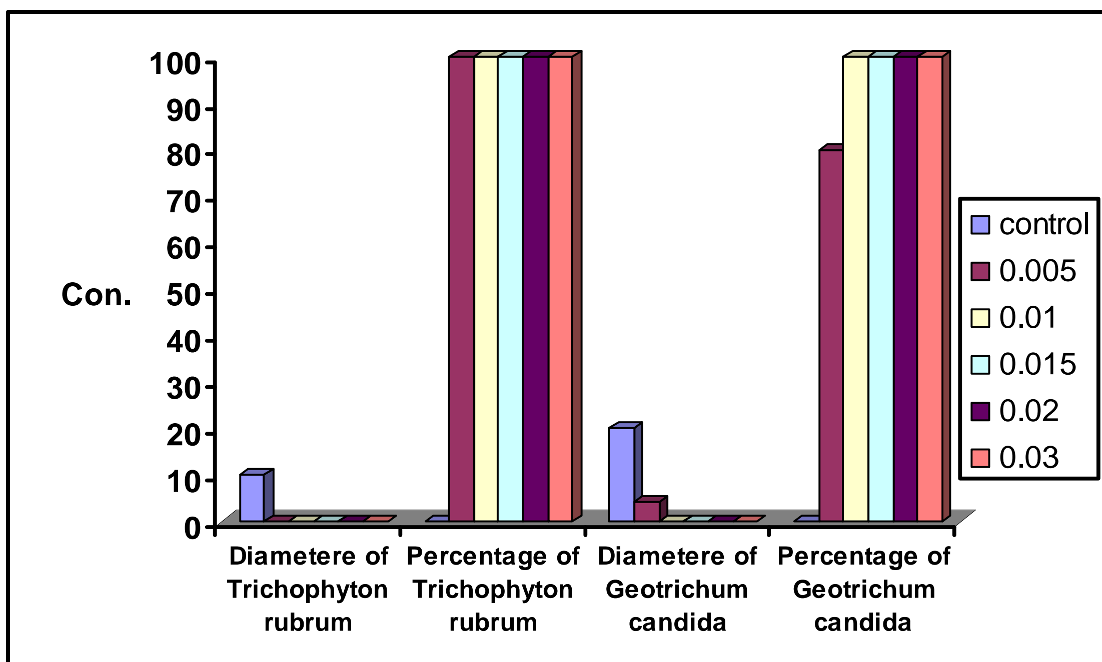


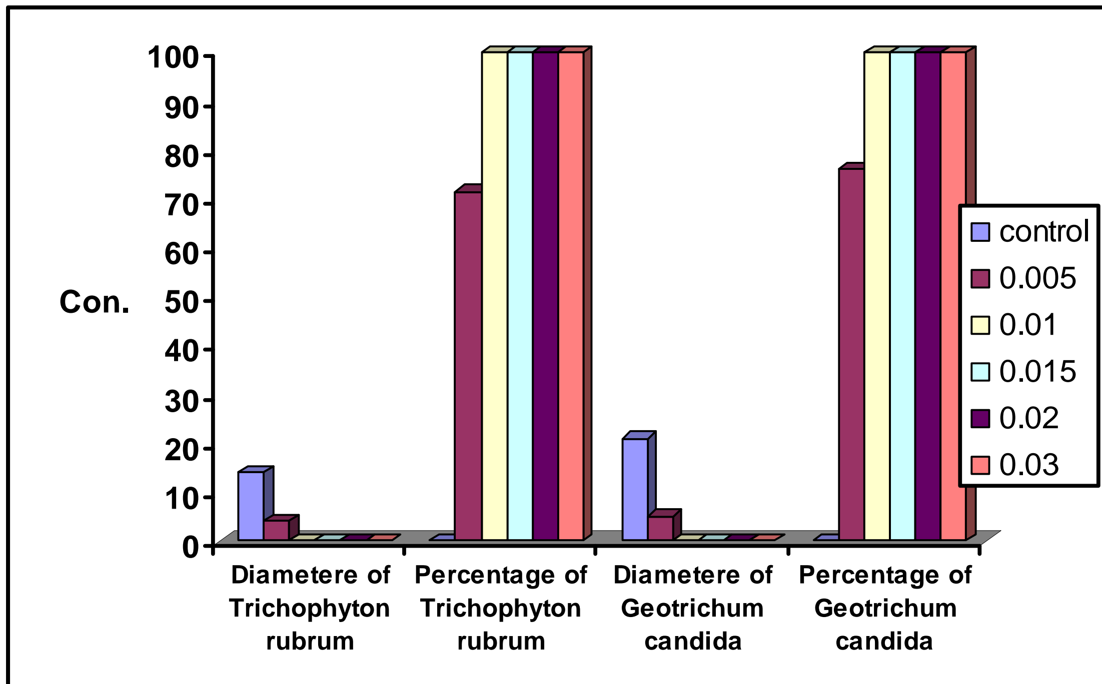
80
70
60
50
40
30
20
10
0
diameter of trichophyton rubrum
control
0.005
0.01
Conc.mg/ml
48hrs.
72hrs.
96hrs.

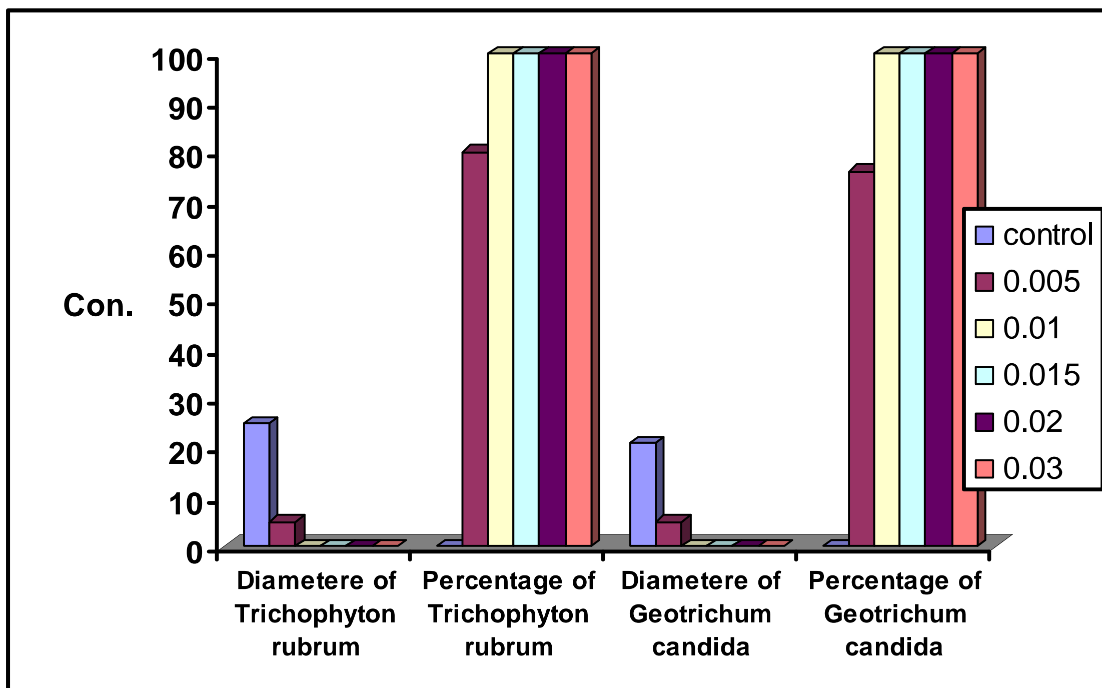

100
90
80
70
60
Con.
50
40
30
20
10
0
Diametere of Trichophyton rubrum
Percentage of Trichophyton rubrum
Diametere of Geotrichum candida
Percentage of Geotrichum candida
control
0.005
0.01
0.015
0.02
0.03

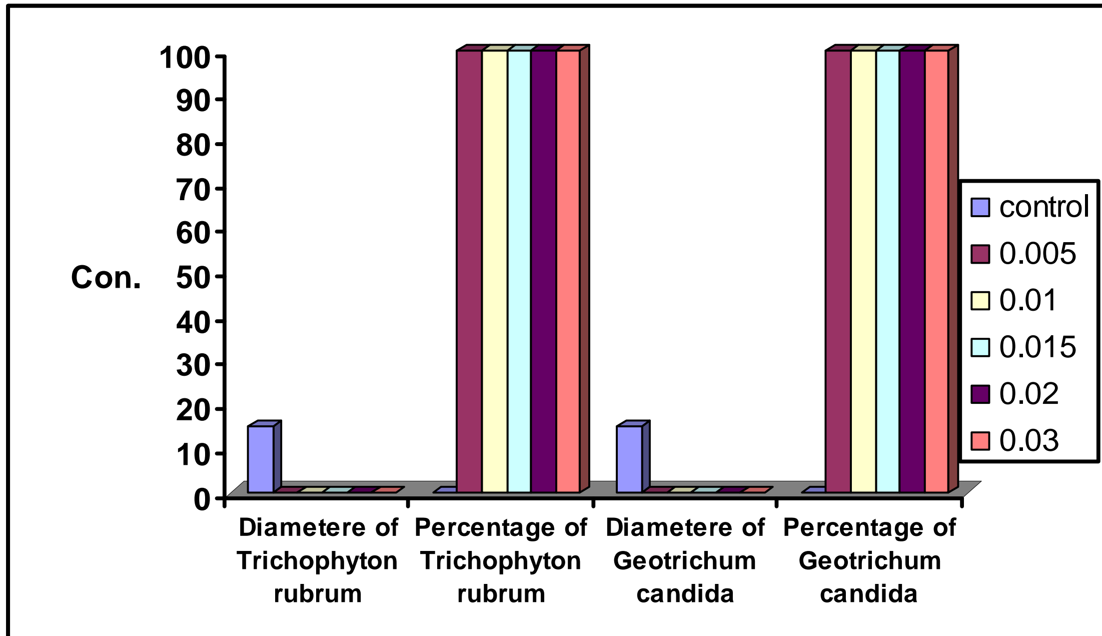

100
90
80
70
60
Con.
50
40
30
20
10
0
Diametere of Trichophyton rubrum
Percentage of Trichophyton rubrum
Diametere of Geotrichum candida
Percentage of Geotrichum candida
control
0.005
0.01
0.015
0.02
0.03

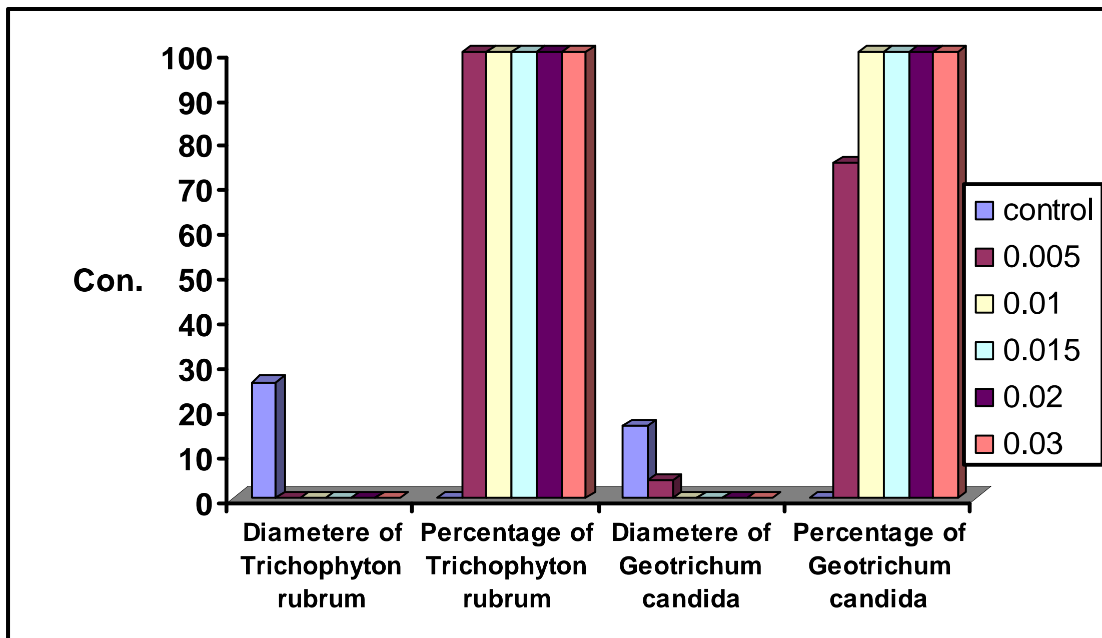

100
90
80
70
60
Con.
50
40
30
20
10
0
Diametere of Trichophyton rubrum
Percentage of Trichophyton rubrum
Diametere of Geotrichum candida
Percentage of Geotrichum candida
control
0.005
0.01
0.015
0.03

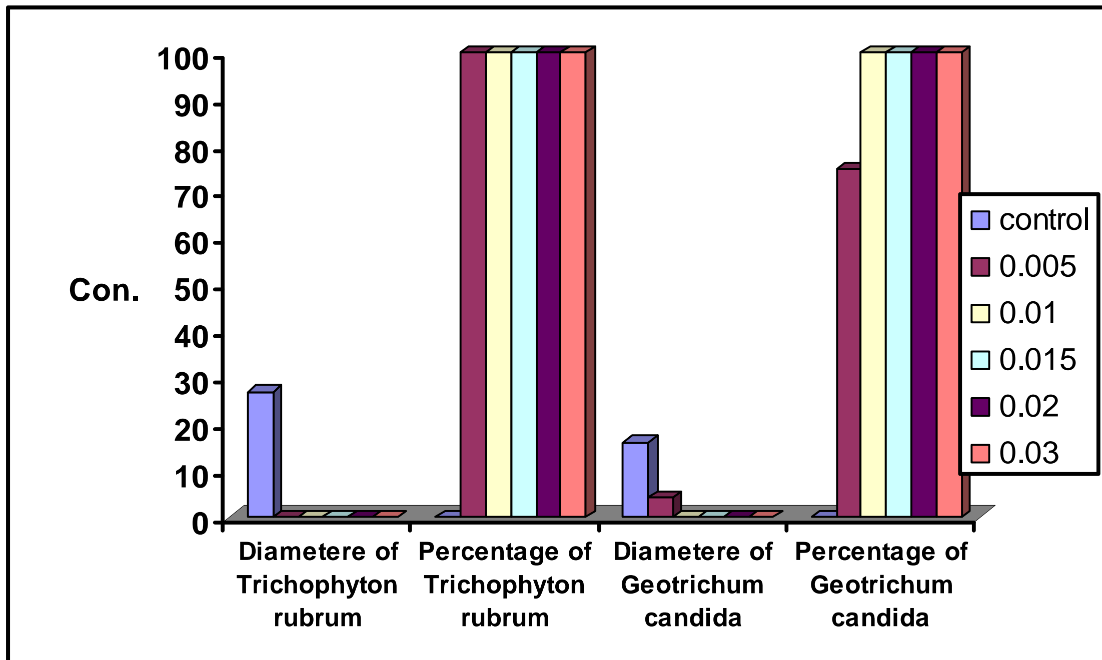

100
90
80
70
60
Con.
50
40
30
20
10
0
Diametere of Trichophyton rubrum
Percentage of Trichophyton rubrum
Diametere of Geotrichum candida
Percentage of Geotrichum candida
control
0.005
0.01
0.015
0.02
0.03

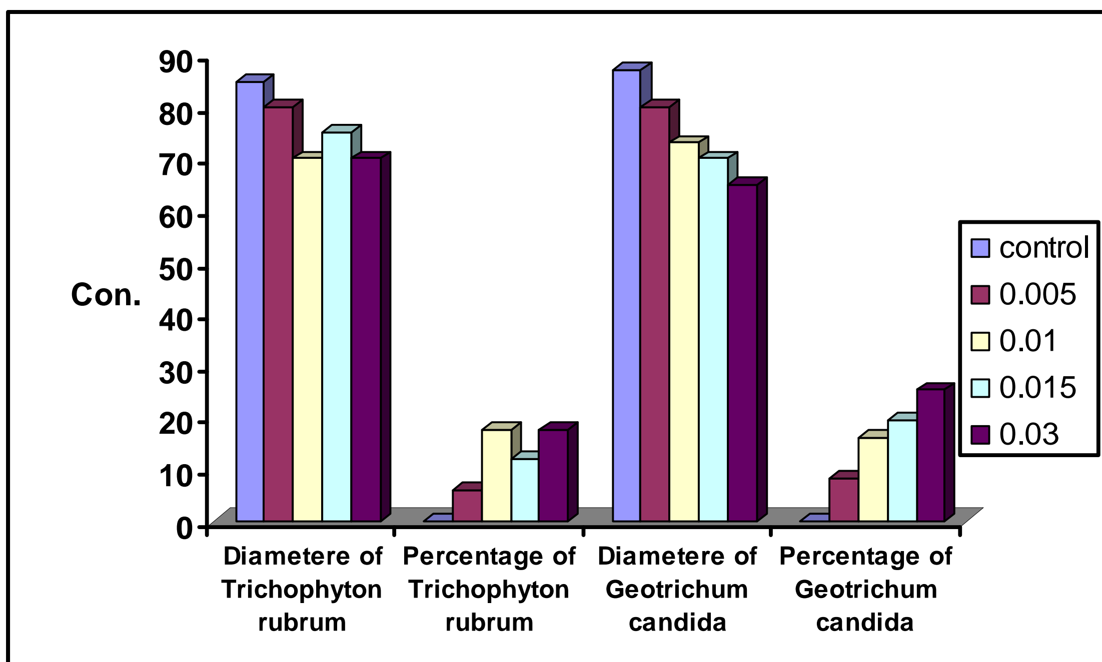

100
90
80
70
60
Con.
50
40
30
20
10
0
Diametere of Trichophyton rubrum
Percentage of Trichophyton rubrum
Diametere of Geotrichum candida
Percentage of Geotrichum candida
control
0.005
0.01
0.015
0.02
0.03

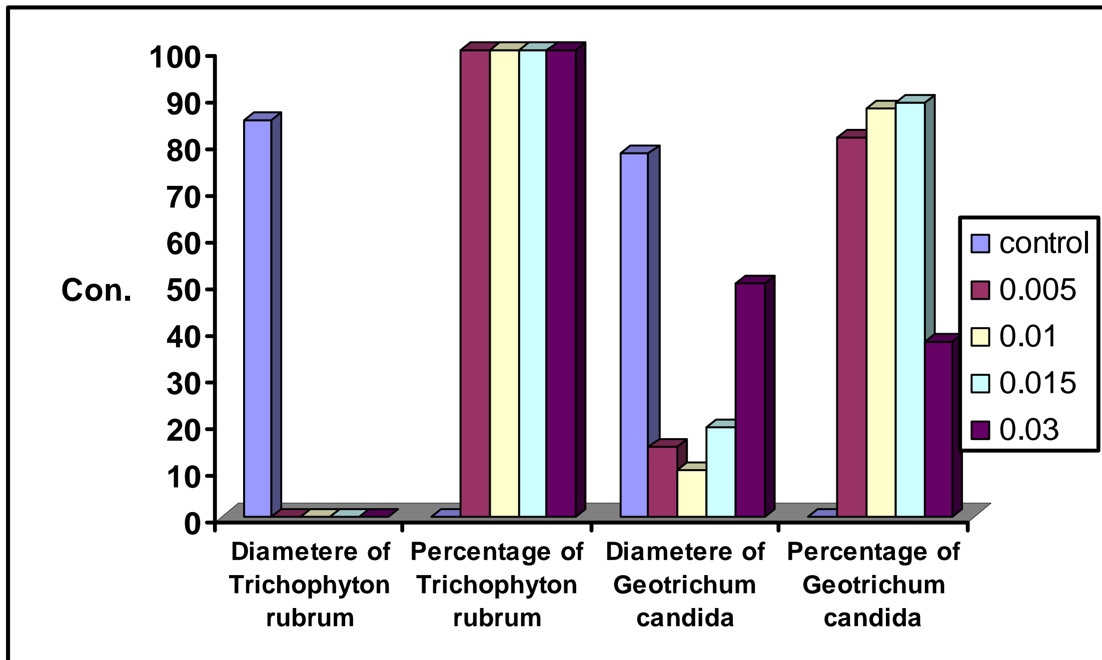

100
90
80
70
60
Con.
50
40
30
20
10
0
Diametere of Trichophyton rubrum
Percentage of Trichophyton rubrum
Diametere of Geotrichum candida
Percentage of Geotrichum candida
control
0.005
0.01
0.015
0.02
0.03

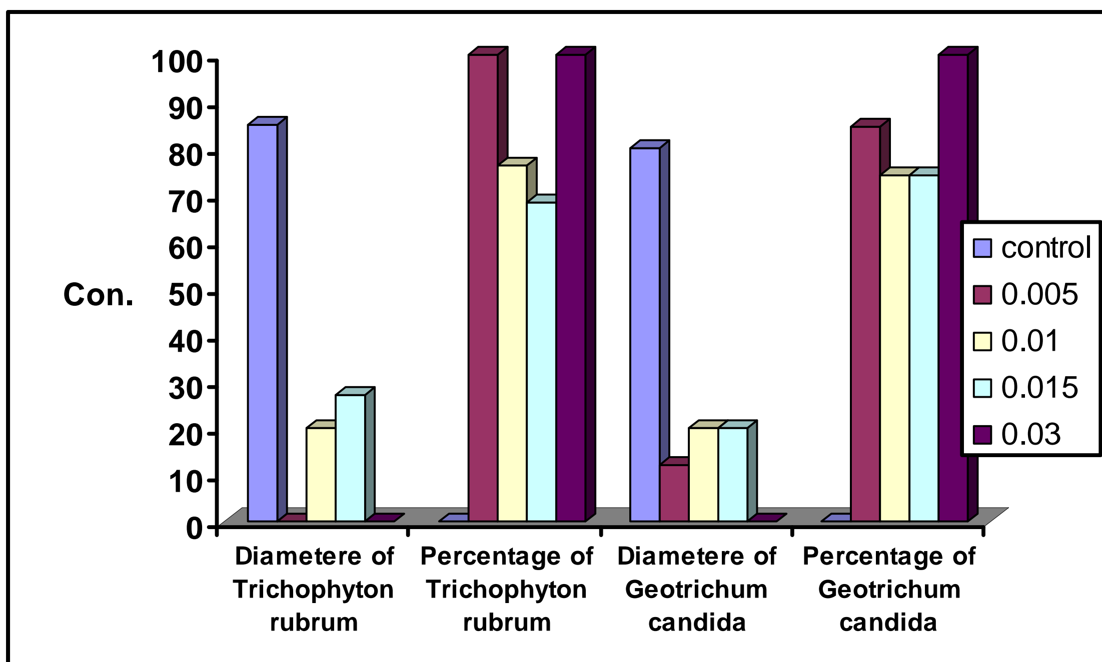

100
90
80
70
60
Con.
50
40
30
20
10
0
Diametere of Trichophyton rubrum
Percentage of Trichophyton rubrum
Diametere of Geotrichum candida
Percentage of Geotrichum candida
control
0.005
0.01
0.015
0.02
0.03

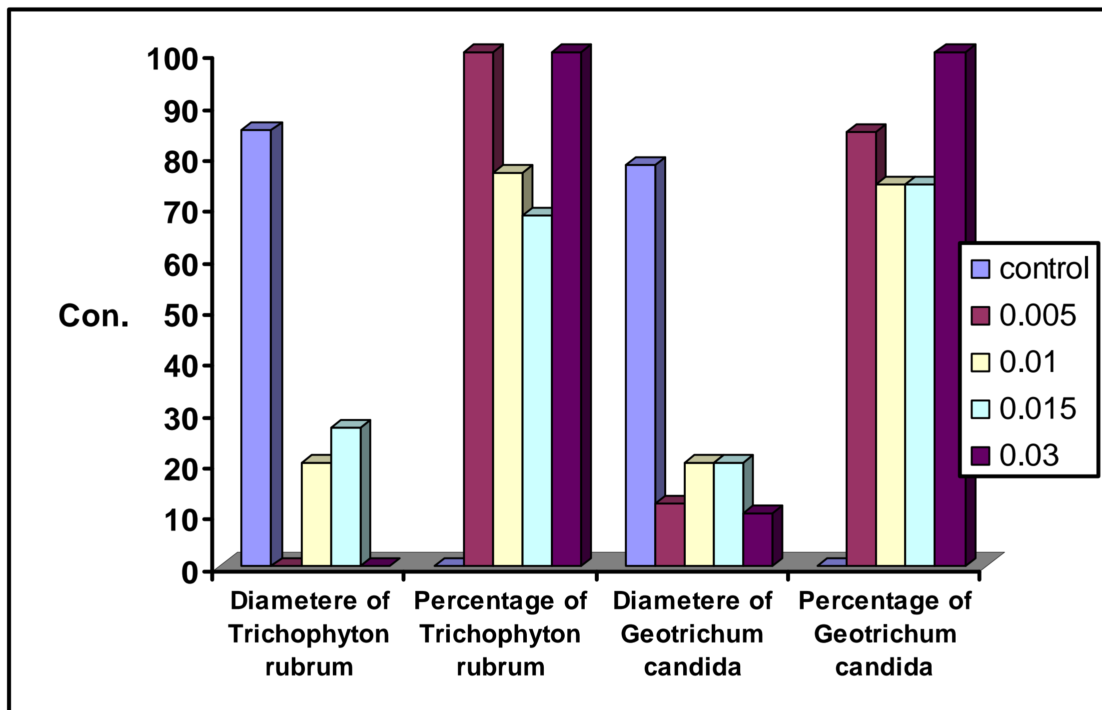

100
90
80
70
60
Con.
50
40
30
20
10
0
Diametere of Trichophyton rubrum
Percentage of Trichophyton rubrum
Diametere of Geotrichum candida
Percentage of Geotrichum candida
control
0.005
0.01
0.015
0.02
0.03

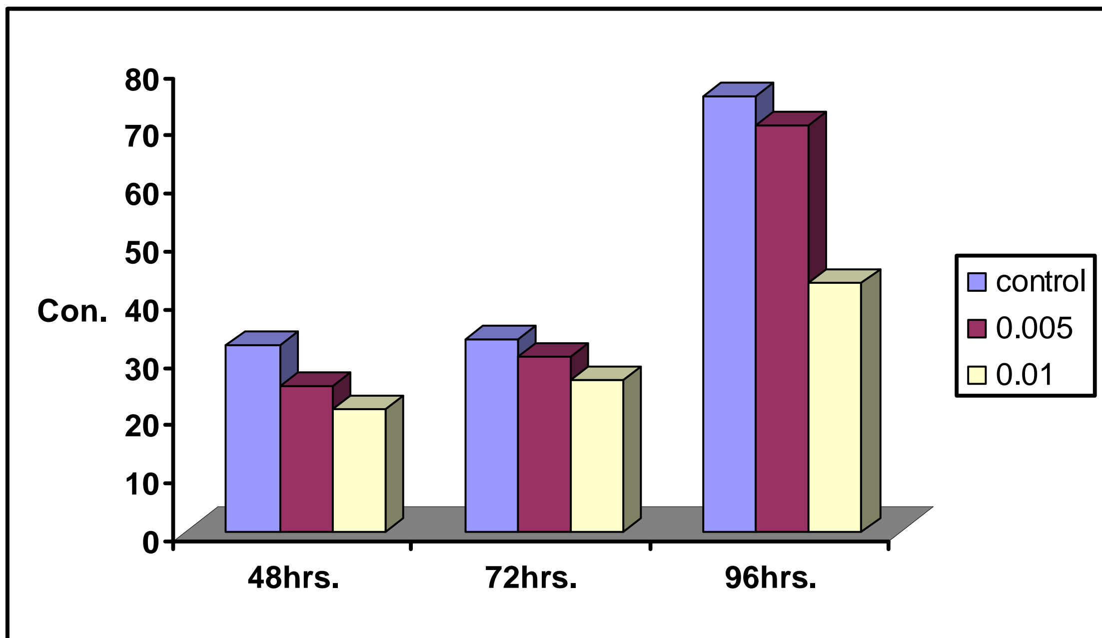

100
90
80
70
60
Con.
50
40
30
20
10
0
Diametere of Trichophyton rubrum
Percentage of Trichophyton rubrum
Diametere of Geotrichum candida
Percentage of Geotrichum candida
control
0.005
0.01
0.015
0.02
0.03


90
80
70
60
50
Con.
40
30
20
10
0
Diametere of Trichophyton rubrum
Percentage of Trichophyton rubrum
Diametere of Geotrichum candida
Percentage of Geotrichum candida
control
0.005
0.01
0.015
0.03

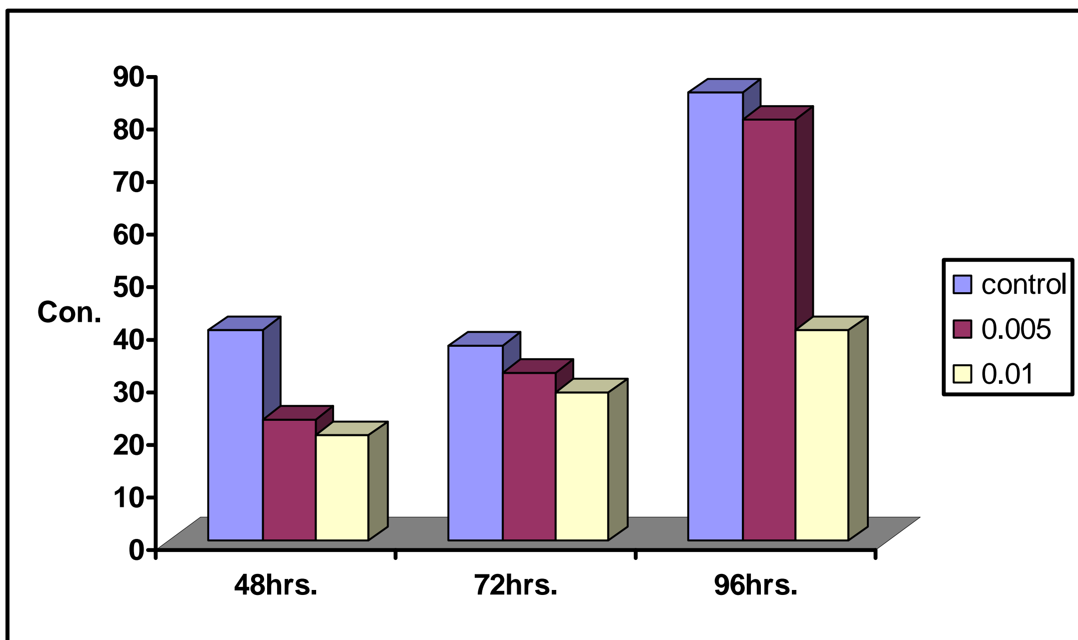

100
90
80
70
60
Con.
50
40
30
20
10
0
Diametere of Trichophyton rubrum
Percentage of Trichophyton rubrum
Diametere of Geotrichum candida
Percentage of Geotrichum candida
control
0.005
0.01
0.015
0.03


100
90
80
70
60
Con.
50
40
30
20
10
0
Diametere of Trichophyton rubrum
Percentage of Trichophyton rubrum
Diametere of Geotrichum candida
Percentage of Geotrichum candida
control
0.005
0.01
0.015
0.03

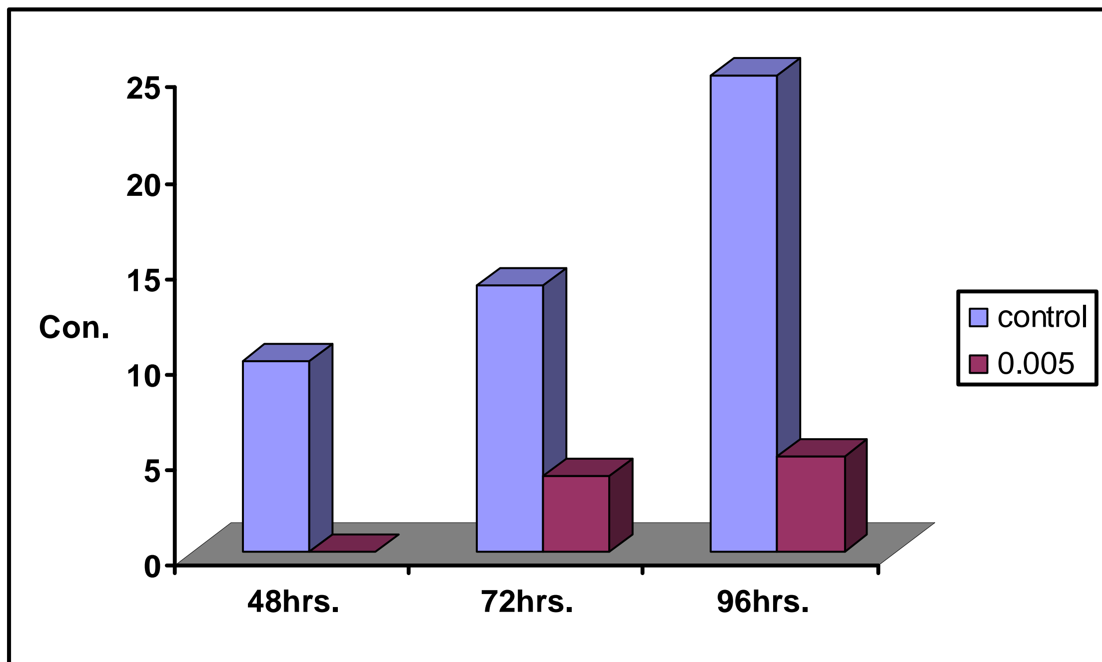

100
90
80
70
60
50
40
30
20
10
0
Con.
control
0.005
0.01
0.015
0.03
Diametere of Trichophyton rubrum
Percentage of Trichophyton rubrum
Diametere of Geotrichum candida
Percentage of Geotrichum candida

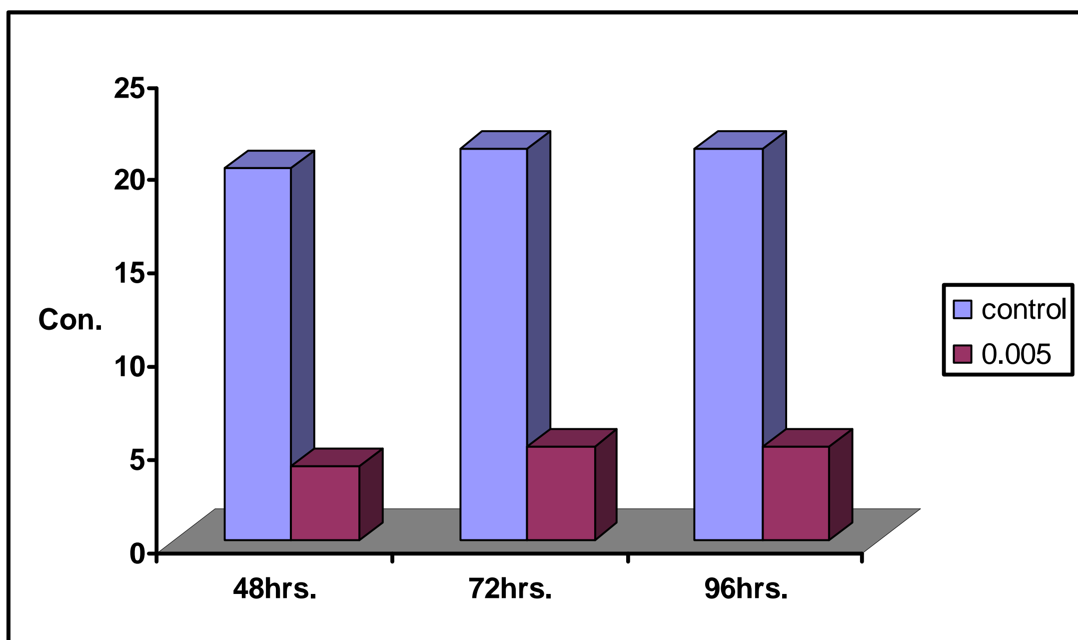


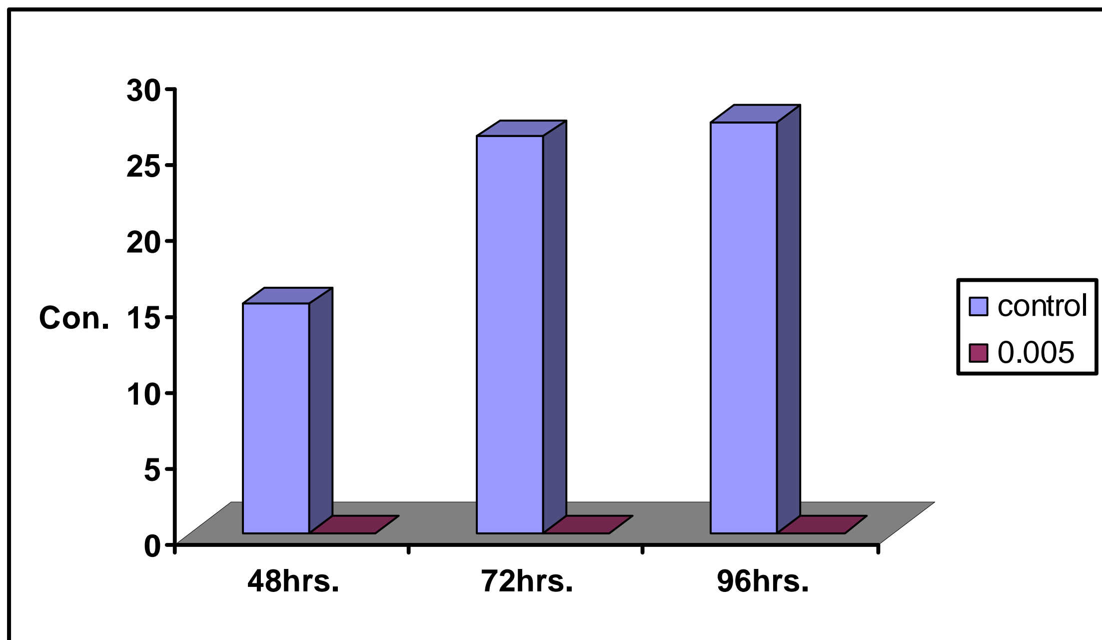
80
70
60
50
Con. 40
30
20
10
0
48hrs.
72hrs.
96hrs.
control
0.005
0.01

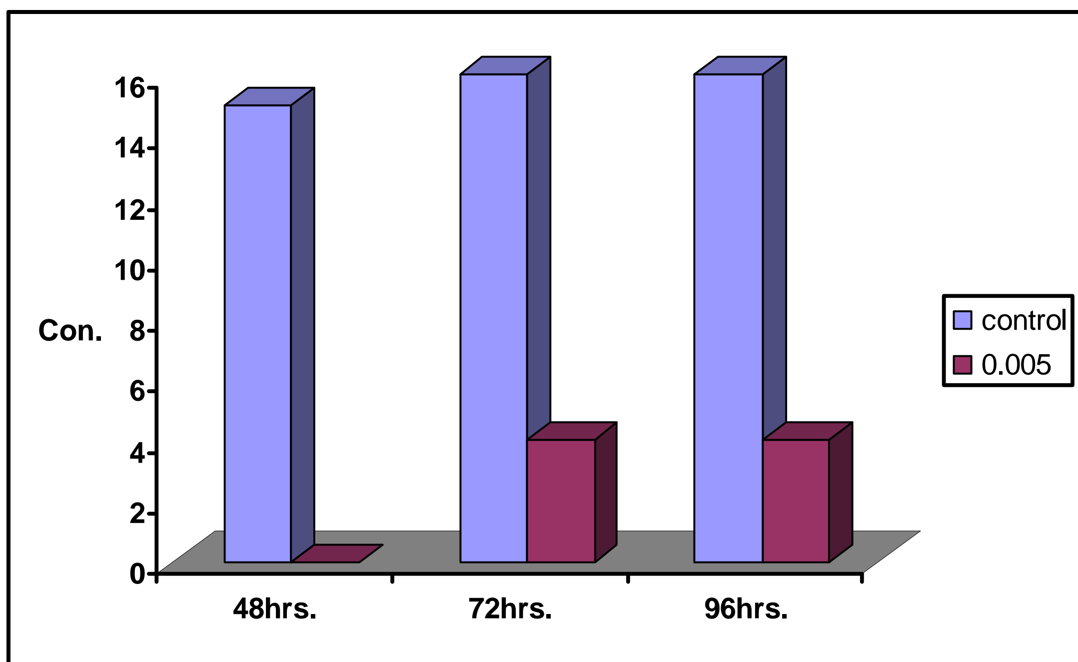


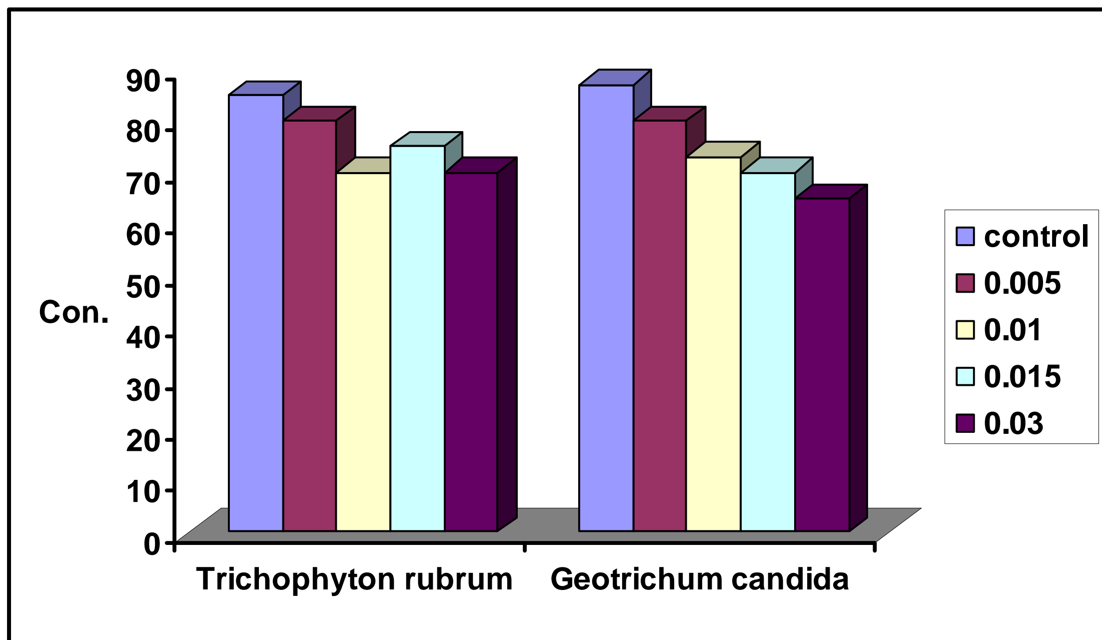
90
80
70
60
50
Con.
40
30
20
10
0
48hrs.
72hrs.
96hrs.
control
0.005
0.01

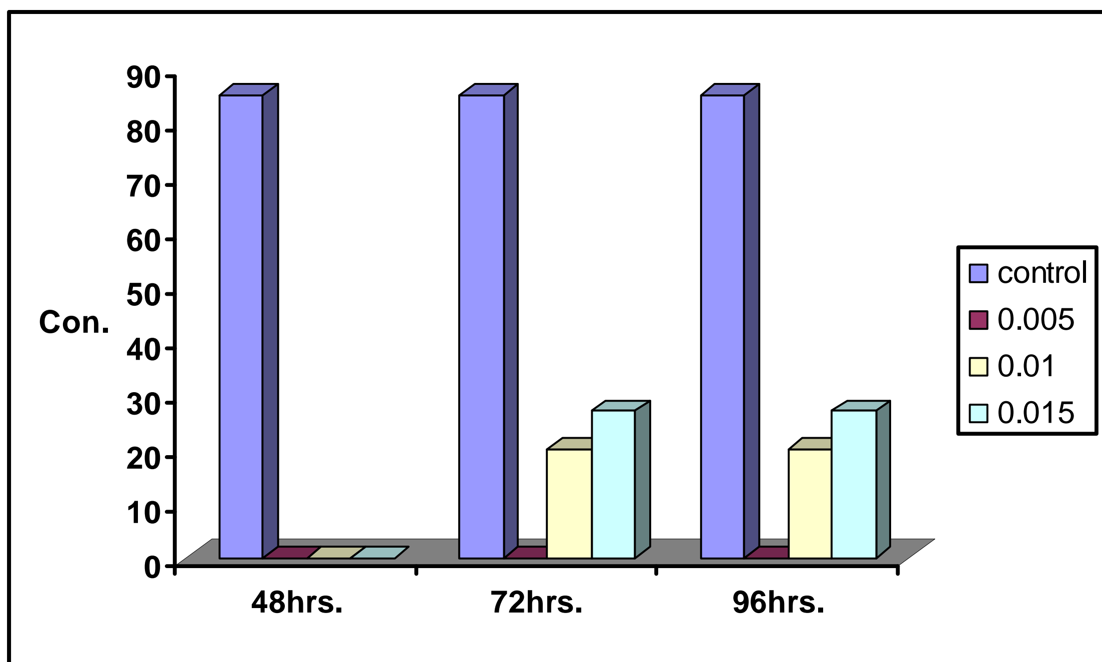

25
20
15
Con.
10
5
0
48hrs.
72hrs.
96hrs.
control
0.005

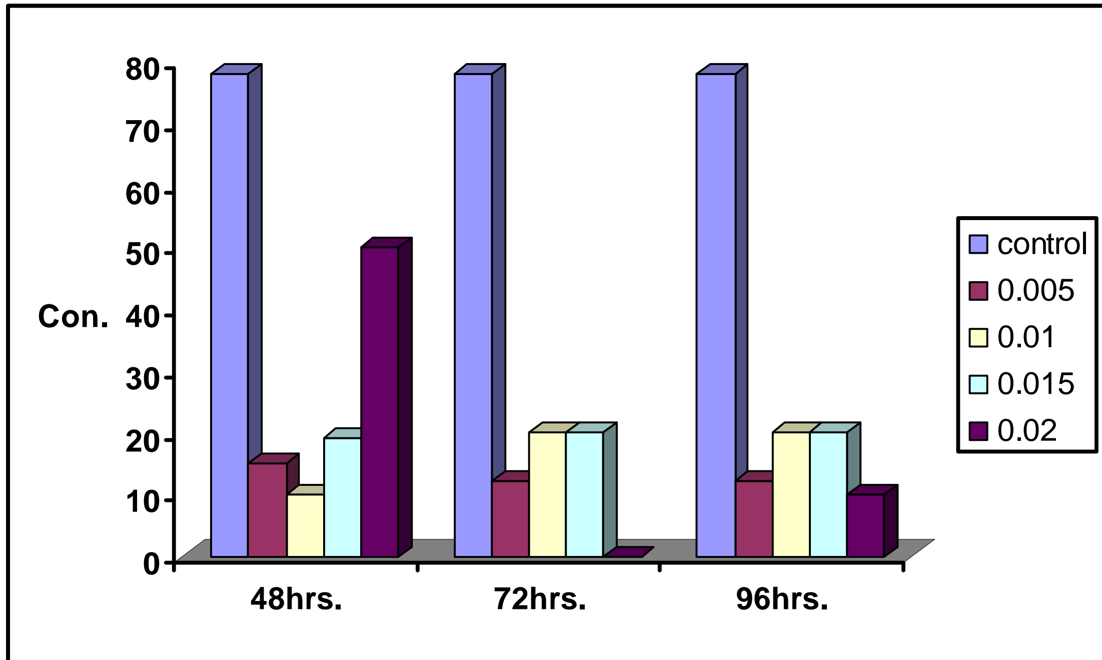

25
20
15
Con.
10
5
0
48hrs.
72hrs.
96hrs.
control
0.005


30
25
20
Con. 15
10
5
0
48hrs.
72hrs.
96hrs.
control
0.005

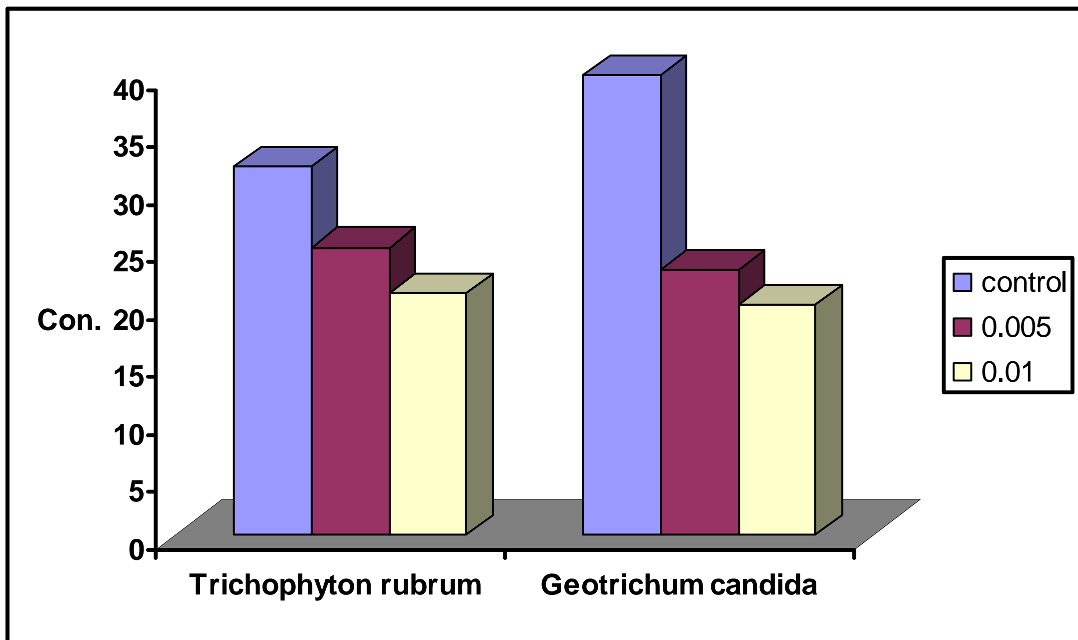

16
14
12
10
Con. 8
6
4
2
0
48hrs.
72hrs.
96hrs.
control
0.005


90
80
70
60
50
40
30
20
10
0
Con.
Trichophyton rubrum
Geotrichum candida
control
0.005
0.01
0.015
0.03

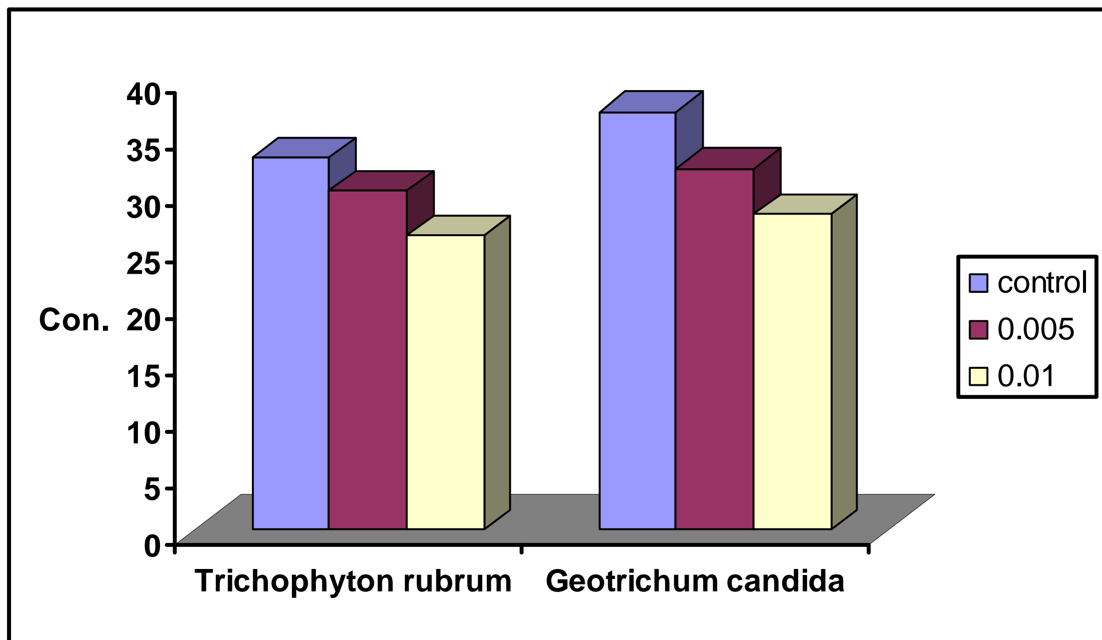

90
80
70
60
50
40
30
20
10
0
Con.
48hrs.
72hrs.
96hrs.
control
0.005
0.01
0.015

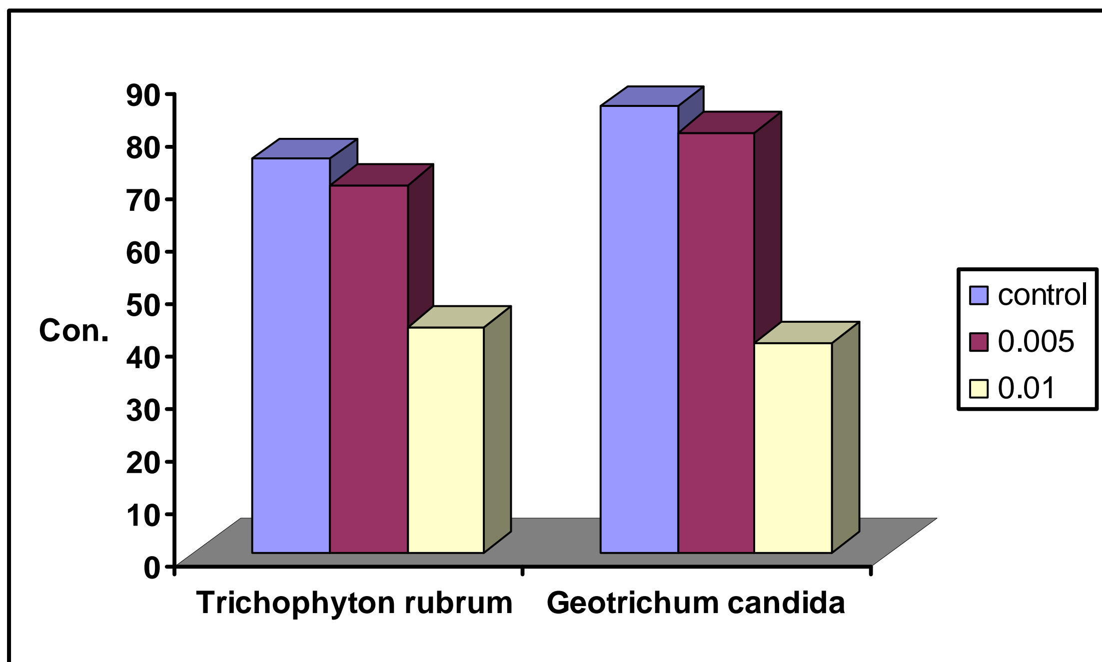


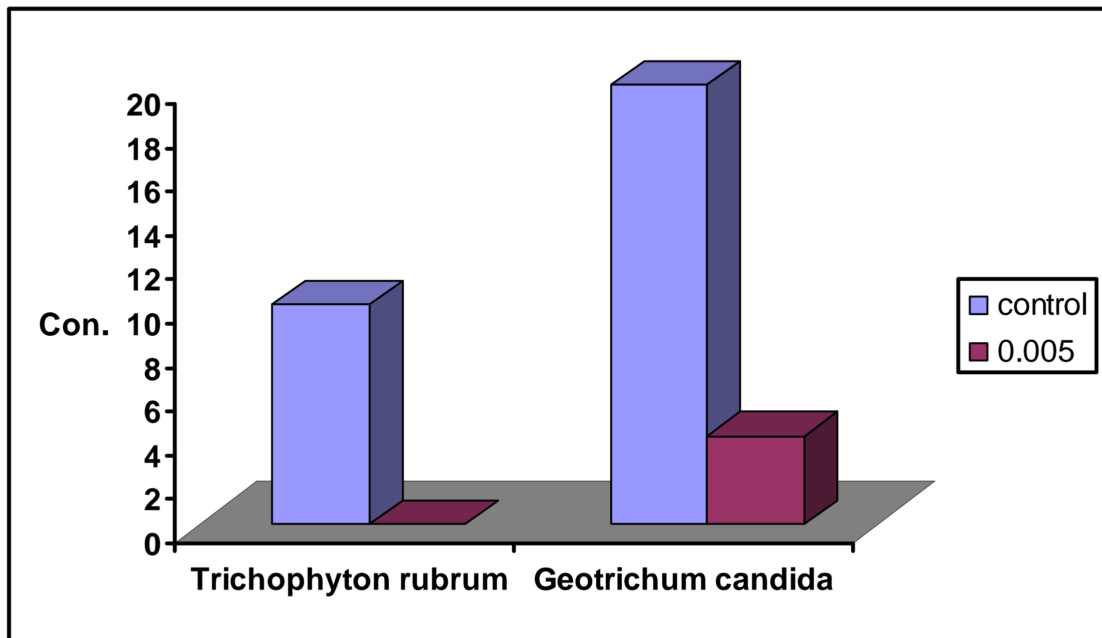
80
70
60
50
Con. 40
30
20
10
0
48hrs.
72hrs.
96hrs.
control
0.005
0.01
0.015
0.02

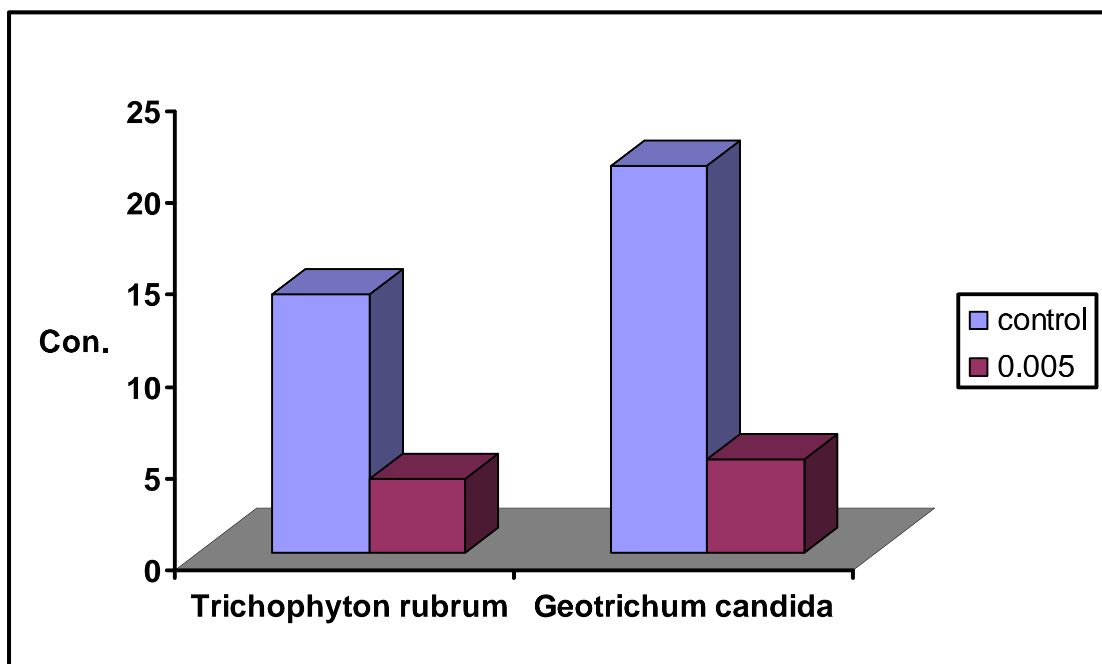


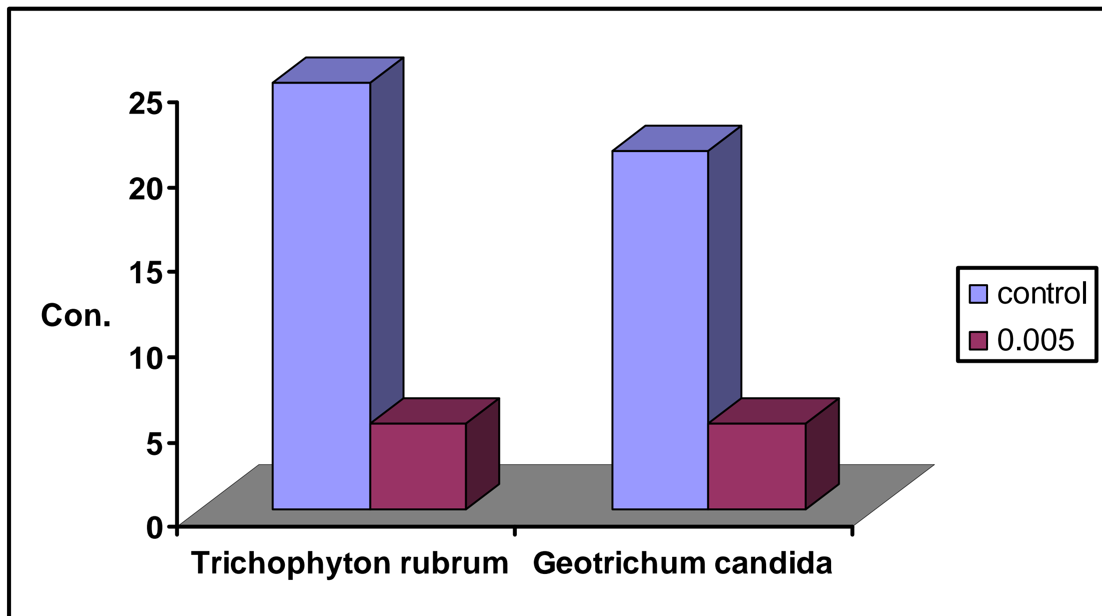
40
35
30
25
Con. 20
15
10
5
0
Trichophyton rubrum
Geotrichum candida
control
0.005
0.01

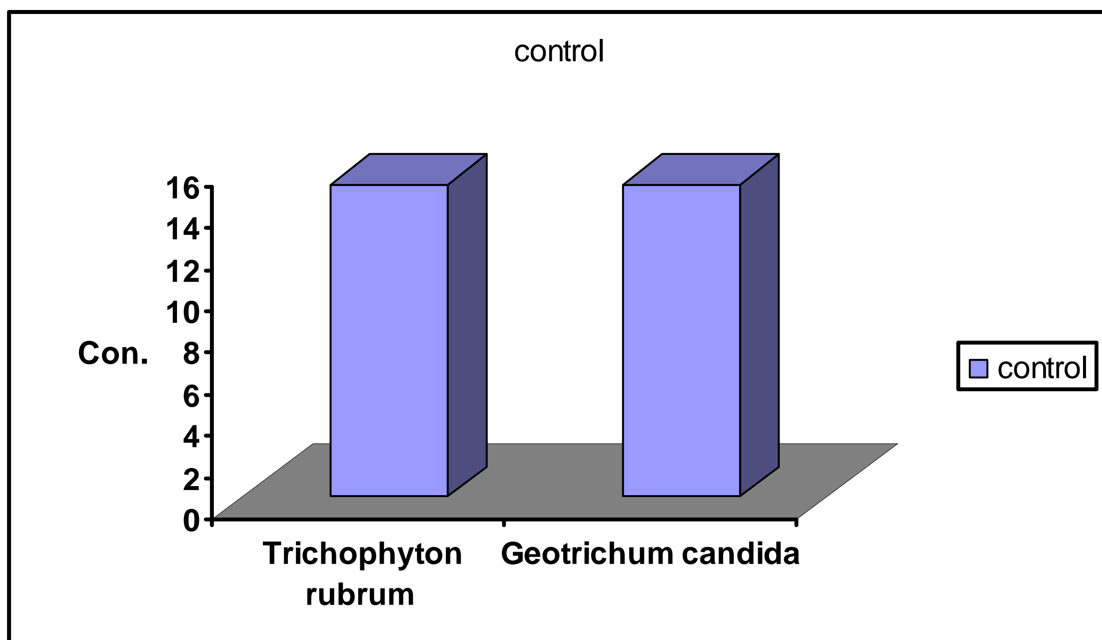

40
35
30
25
Con.
20
15
10
5
0
Trichophyton rubrum
Geotrichum candida
control
0.005
0.01

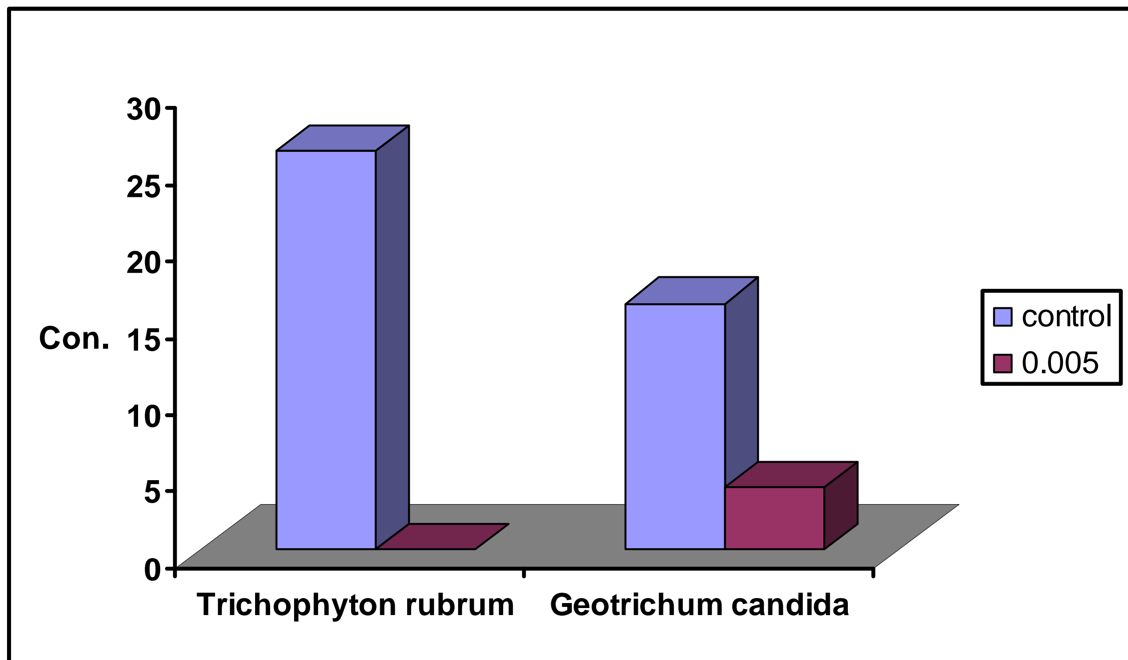

90
80
70
60
50
Con.
40
30
20
10
0
Trichophyton rubrum
Geotrichum candida
control
0.005
0.01

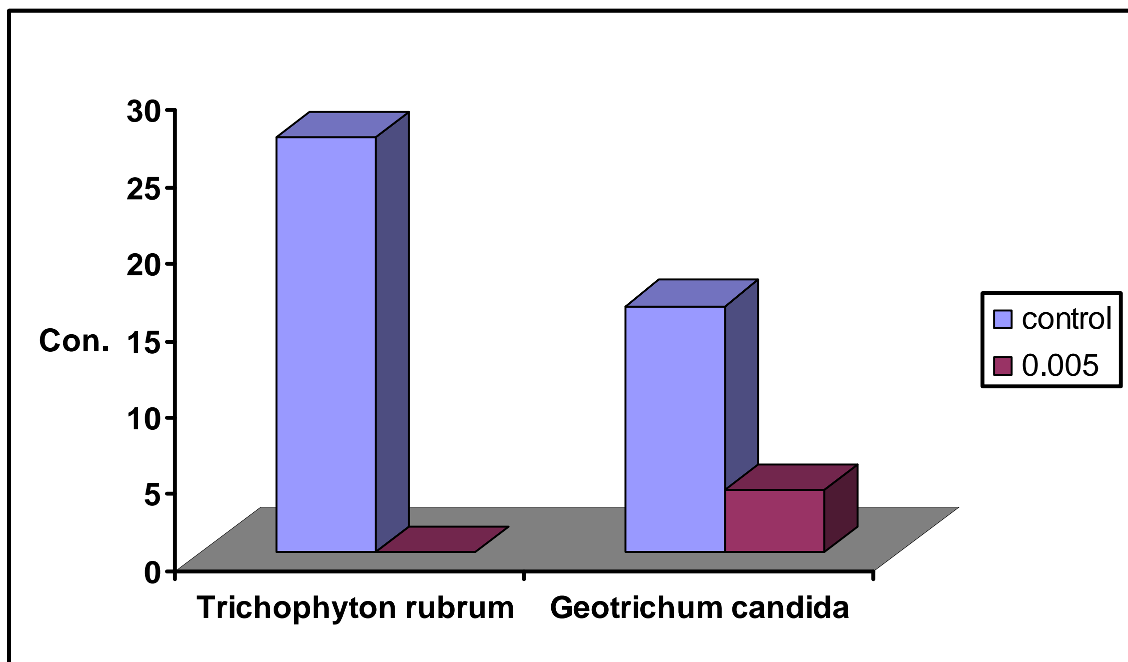

Con.
0
2
4
6
8
10
12
14
16
18
20
Trichophyton rubrum
Geotrichum candida
control
0.005

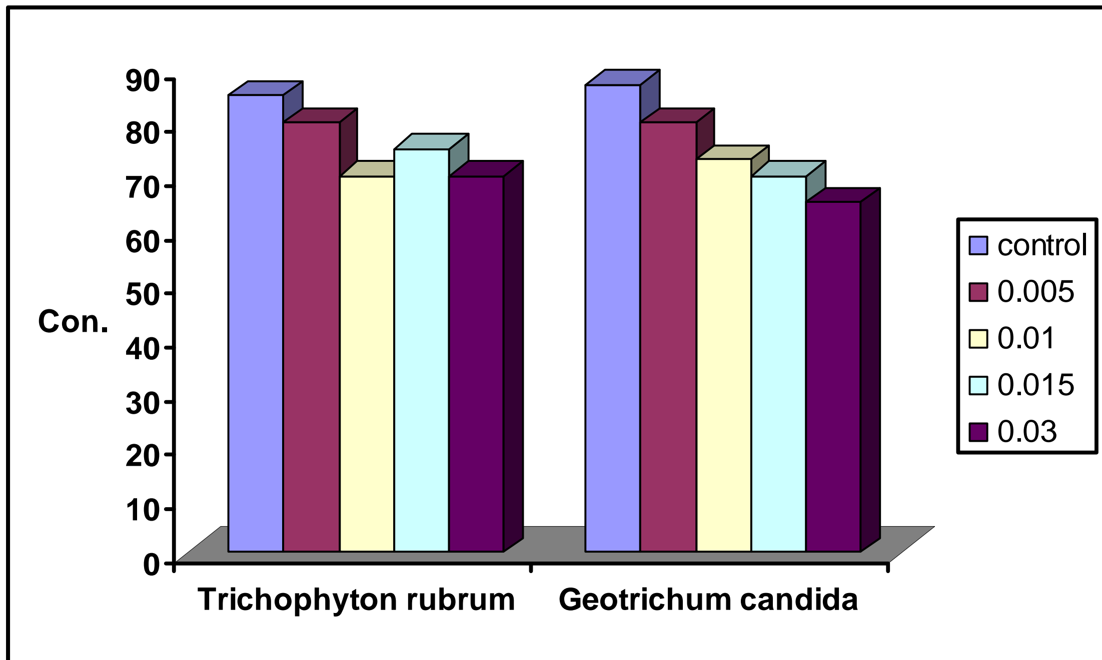

Con.
0
5
10
15
20
25
Trichophyton rubrum
Geotrichum candida
control
0.005

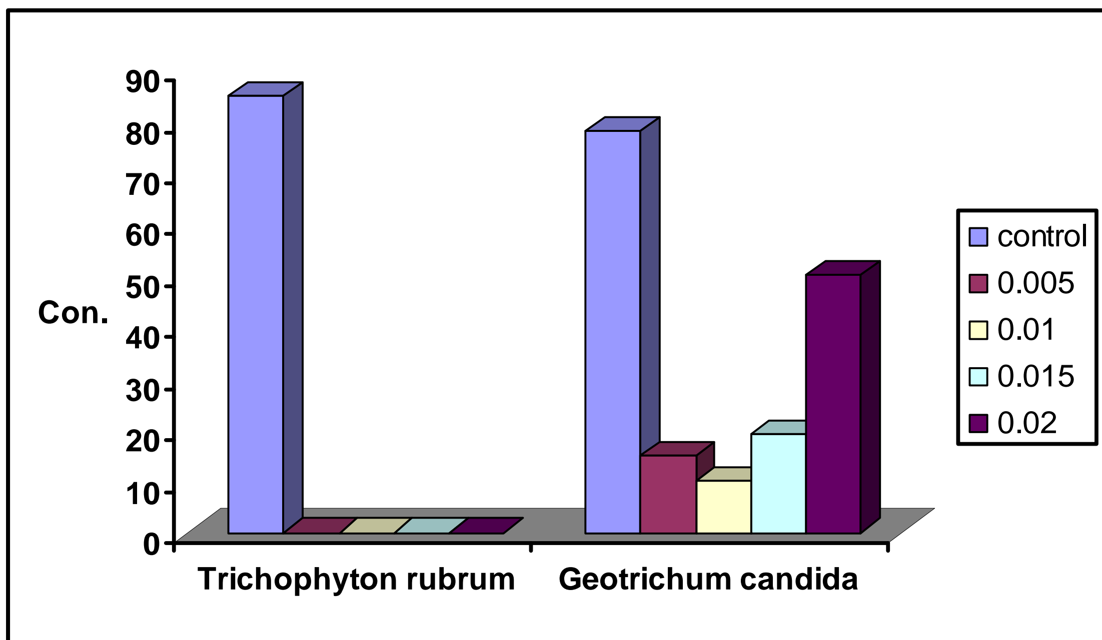

25
20
15
10
5
0
Con.
Trichophyton rubrum
Geotrichum candida
control
0.005


control
16
14
12
10
8
6
4
2
0
Con.
Trichophyton rubrum
Geotrichum candida
control


30
25
20
Con. 15
10
5
0
Trichophyton rubrum
Geotrichum candida
control
0.005


30
25
20
Con. 15
10
5
0
Trichophyton rubrum
Geotrichum candida
control
0.005


Con.
0
10
20
30
40
50
60
70
80
90
Trichophyton rubrum
Geotrichum candida
control
0.005
0.01
0.015
0.03


Con.
0
10
20
30
40
50
60
70
80
90
Trichophyton rubrum
Geotrichum candida
control
0.005
0.01
0.015
0.02

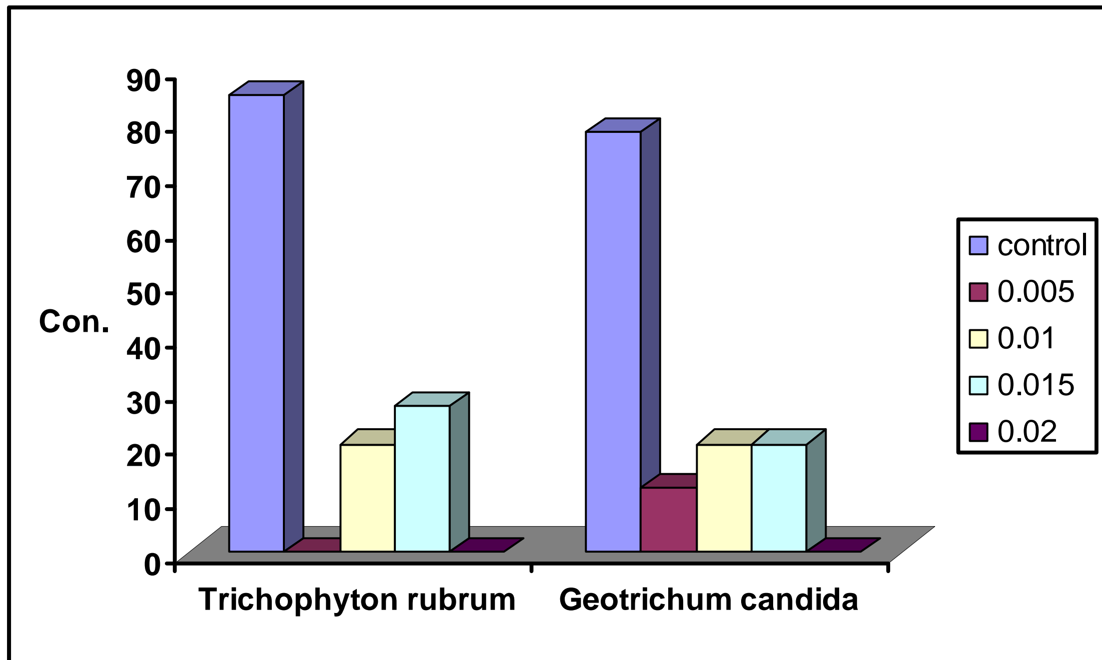

90
80
70
60
50
40
30
20
10
0
Con.
Trichophyton rubrum
Geotrichum candida
control
0.005
0.01
0.015
0.02

Table (3-1): Effects of compound (1G) on the diameter of fungal colonies throughout 48 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	32	0	40	0
0.005 mg/ml	25	21.8	23	42.5
0.01 mg/ml	21	34.37	20	50
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

Table (3-2): Effects of compound (1G) on the diameter of fungal colonies throughout 72 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	33	0	37	0
0.005 mg/ml	30	9.09	32	13.51
0.01 mg/ml	26	21.2	28	24.32
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

Table (3-3): Effects of compound (1G) on the diameter of fungal colonies throughout 96 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	75	0	85	0
0.005 mg/ml	70	6.66	80	5.88
0.01 mg/ml	43	42.66	40	52.9
0.015 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

Table (3-4): Effects of mixture (6G) on the diameter of fungal colonies throughout 48 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	10	0	20	0
0.005 mg/ml	0	100	4	80
0.01 mg/ml	0	100	0	100
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

Table (3-5): Effects of mixture (6G) on the diameter of fungal colonies throughout 72 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	14	0	21	0
0.005 mg/ml	4	71.4	5	76.1
0.01 mg/ml	0	100	0	100
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

Table (3-6): Effects of mixture (6G) on the diameter of fungal colonies throughout 96 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	25	0	21	0
0.005 mg/ml	5	80	5	76.1
0.01 mg/ml	0	100	0	100
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

Table (3-7): Effects of compound (2E) on the diameter of fungal colonies throughout 48 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	15	0	15	0
0.005 mg/ml	0	100	0	100
0.01 mg/ml	0	100	0	100
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

Table (3-8): Effects of compound (2E) on the diameter of fungal colonies throughout 72 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	26	0	16	0
0.005 mg/ml	0	100	4	75
0.01 mg/ml	0	100	0	100
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

Table (3-9): Effects of compound (2E) on the diameter of fungal colonies throughout 96 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	27	0	16	0
0.005 mg/ml	0	100	4	75
0.01 mg/ml	0	100	0	100
0.015 mg/ml	0	100	0	100
0.02 mg/ml	0	100	0	100
0.03 mg/ml	0	100	0	100

Table (3-10): Effects of compound (4G) on the diameter of fungal colonies throughout 48 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	85	0	87	0
0.005 mg/ml	80	5.88	80	8.04
0.01 mg/ml	70	17.64	73	16.09
0.015 mg/ml	75	11.76	70	19.54
0.03 mg/ml	70	17.64	65	25.28

Table (3-11): Effects of compound (5G) on the diameter of fungal colonies throughout 48 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	85	0	78	0
0.005 mg/ml	0	100	15	81.25
0.01 mg/ml	0	100	10	87.5
0.015 mg/ml	0	100	19	88.75
0.02 mg/ml	0	100	50	37.5

Table (3-12): Effects of compound (5G) on the diameter of fungal colonies throughout 72 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	85	0	80	0
0.005 mg/ml	0	100	12	84.61
0.01 mg/ml	20	76.47	20	74.35
0.015 mg/ml	27	68.23	20	74.35
0.02 mg/ml	0	100	0	100

Table (3-13): Effects of compound (5G) on the diameter of fungal colonies throughout 96 hrs. of incubation.

concentration	Trichophyton rumbrum		Geotrichum candidum	
	Average of colonial diameter	Percentage of incubation	Average of colonial diameter	Percentage of incubation
Control	85	0	78	0
0.005 mg/ml	0	100	12	84.61
0.01 mg/ml	20	76.47	20	74.35
0.015 mg/ml	27	68.23	20	74.35
0.02 mg/ml	0	100	10	100

Table (3-14): Show stander error of colonial diameter of Trichophyton rumbrum that effected by compound (1G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	32±0.176	33±0.696	75±0.577
0.005 mg/ml	25±0.6	30±0.912	70±0.358
0.01 mg/ml	21±0.436	26±0.196	43±1.067

Table (3-15): Show stander error of colonial diameter of Geotrichum candidum that effected by compound (1G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	40±0.760	37±0.328	85±0.216
0.005 mg/ml	23±0.834	32±0.353	80±0.335
0.01 mg/ml	20±1.341	28±0.566	40±0.632

Table (3-16): Show stander error of colonial diameter of Trichophyton rumbrum that effected by compound (6G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	10±1.897	14±0.801	25±1.0
0.005 mg/ml	_	4±1.50	5±0.894

Table (3-17): Show stander error of colonial diameter of Geotrichum candidum that effected by compound (6G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	20±1.118	21±2.182	21±2.182
0.005 mg/ml	4±1.0	5±0.447	5±0.447

Table (3-18): Show stander error of colonial diameter of Trichophyton rumbrum that effected by compound (2E) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	15±0.516	26±0.89	27±0.962
0.005 mg/ml	_	_	_

Table (3-19): Show stander error of colonial diameter of Geotrichum candidum that effected by compound (2E) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	15±0.516	16±0.5	16±0.5
0.005 mg/ml	_	4±1.0	4±1.0

Table (3-20): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (4G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	85±0.542	87±0.643
0.005 mg/ml	80±0.447	80±0.782
0.01 mg/ml	70±0.358	73±0.351
0.015 mg/ml	75±0.23	70±0.239
0.03 mg/ml	70±0.119	65±0.620

Table (3-21): Show stander error of colonial diameter of Trichophyton rumbrum that effected by compound (5G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	85±0.65	85±0.65	85±0.65
0.005 mg/ml	_	_	_
0.01 mg/ml	_	20±0.447	20±0.447
0.015 mg/ml	_	27±0.384	27±0.384

Table (3-22): Show stander error of colonial diameter of Geotrichum candidum that effected by compound (5G) throughout 48,72 and 96 hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error		
	48 hrs.	72 hrs.	96 hrs.
control	78±0.339	78±0.226	78±0.226
0.005 mg/ml	15±0.516	12±0.577	12±0.577
0.01 mg/ml	10±0.316	20±1.34	20±1.34
0.015 mg/ml	19±0.458	20±1.788	20±1.788
0.02 mg/ml	50±0.707	_	10±0.244

Table (3-23): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (1G) throughout 48hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A32±0.176	A40±0.760
0.005 mg/ml	A25±0.6	A23±0.834
0.01 mg/ml	A21±0.436	A20±1.341

Table (3-24): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (1G) throughout 72hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A33±0.696	A37±0.328
0.005 mg/ml	A30±0.912	A32±0.353
0.01 mg/ml	A26±0.196	A28±0.566

Table (3-25): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (1G) throughout 96hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A75±0.577	A85±0.216
0.005 mg/ml	A70±0.358	B80±0.335
0.01 mg/ml	A43±1.067	A40±0.632

Table (3-26): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (6G) throughout 48hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A10±1.897	A20±1.118
0.005 mg/ml	_	B4±1.0

Table (3-27): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (6G) throughout 72hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A14±0.801	A21±2.182
0.005 mg/ml	A4±1.5	A5±0.447

Table (3-28): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (6G) throughout 96hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A25±1.0	A21±2.182
0.005 mg/ml	A5±0.894	A5±0.447

Table (3-29): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (2E) throughout 48hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A15±0.516	A15±0.516

Table (3-30): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (2E) after A:72hrs. and B: 96hrs. of incubation.

A

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A26±0.89	B16±0.5
0.005 mg/ml	_	B4±1.0

B

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A27±0.962	B16±0.5
0.005 mg/ml	_	B4±1.0

Table (3-31): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (4G) throughout 48hrs. of incubation.

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A85±0.542	A87±0.643
0.005 mg/ml	A80±0.447	A80±0.782
0.01 mg/ml	A70±0.358	A73±0.351
0.015 mg/ml	A75±0.23	B70±0.239
0.03 mg/ml	A70±0.119	A65±0.620

Table (3-32): Show stander error of colonial diameter of Trichophyton rumbrum and Geotrichum candidum that effected by compound (5G) after A:48hrs. and B: 72hrs. of incubation.

A

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A85±0.65	A78±0.339
0.005 mg/ml	_	B15±0.516
0.01 mg/ml	_	B10±0.316
0.015 mg/ml	_	B19±0.458
0.02 mg/ml	_	B50±0.707

B

Concentration	Average of colonial diameter in different time of incubation with stander error	
	Trichophyton rumbrum	Geotrichum candidum
control	A85±0.65	A78±0.226
0.005 mg/ml	-	B12±0.577
0.01 mg/ml	A20±0.447	A20±1.34
0.015 mg/ml	A27±0.384	A20±1.788
0.02 mg/ml	-	-