Synthesis and Modification of some Heterocyclic Compounds with Potential Biological Activity Coupled on Poly (Maleic Anhydride – Methyl Methacrylate)

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Abstract: This paper presents some results concerning the immobilization through chemical bonds of some biologically active compounds on the maleic anhydride- methyl methacrylate) copolymer. The high reactivity of the anhydride cycle of the polymer has allowed us to obtain conjugates in which the biologically active compounds of some heterocyclic compounds are immobilized on the polymeric support through amide bonds. The reaction products were characterized through elemental analysis, mass spectra, FTIR and ^{1}HNMR spectroscopy. The antimicrobial activity of the modified copolymer was tested against various microorganisms (Staphylococcus aureus, Escherichia coli, pseudomonas aeroginosa, Klebsiella and fungal, Aspergillus niger, Aspergillus Flavus and Fusarium oxyspoium). In general, the copolymers showed good antimicrobial activity against the previously mentioned microorganism. [Journal of American Science 2010; 6(8):512-524]. (ISSN: 1545-1003).

key words : Synthesis , Copolymer, Heterocyclic, Antibacterial activity.

1. Introduction:

Many polymers with reactive functional groups are now synthesized, tested and used not only for their macromolecular properties, but also for the properties of their functional groups. These functional groups provide an approach to a subsequent modification of the polymer for specific end applications (Vogl et al. 1985). Nowadays a strong demand prevails for functional polymers with very specific properties. Functional groups give the polymer structure of special characters substantially different from the inherent properties of the basic polymer chain (Vogl 1996). In recent years some comprehensive work has been published on functional monomer and their polymers (Godwin et al. 2004, Erol and Soykan 2003, Akelah and Moel 1990, Erol et al. 2001). The antimicrobial property of the polymers plays an important role for many of its applications. Contamination by microorganisms is of great concern in several areas such as medical devices, health care products, water purification systems,hospital and dental equipments, etc. One possible way to avoid the microbial contamination is to develop materials possessing antimicrobial activities. Consequently, biocidal polymers have received much attention in recent years (Worley and Sun 1996).

Thiosemicarbazones and the corresponding metal complexes are widely known as having a large range of biological applications, such as antiviral, antimalarial, antifungal, etc (West et al. 1991, El-Sawaf et al. 1997). The compound p-acetamidobenzaldehyde thiosemicarbazone, commercially available as thiacetazone, has long been employed in the treatment of tuberculosis (Beraldo et al. 1999). The activity of these compounds is strongly dependent upon the nature of the heteroaromatic ring and the position of attachment to the ring, as well as the form of the thiosemicarbazone moiety.

Some thiazole, thiosemicarbazole, imidazole, benzothiazole derivatives (Muthusubramanian et al. 2001, Chevica et al. 2003, Tolkova et al. 2001, Shaha et al. 2002, Paramashivappa et al. 2003) and isatin (Pandeya and Sriram 1998, Sarangapani and Reddy 1994, El-Sawi et al. 1998, Aanandhi et al. 2008) are mentioned in literature to show antimicrobial (Bartlett et al. 1992, Sunel et al. 2001, Basu et al. 2002, Koci et al., 2002) antifungal (Gbadamassi et al. 1988), antihelmitic (Hazelton et al., 1995) pesticide and herbicidal properties. The high reactivity of anhydride ring in the copolymers based on maleic anhydride toward the nucleophilic reagents (Angelescuu-Dogaru et al. 1999, Spiridn et al. 1997, Kysela et al. 1992, Staudner et al. 1992) would suggest the possibility of its opening by various nucleophilic compunds in order to obtain new products with potential biological activity. There are many systems mentioned in the literature (Jeong et al. 2002), obtained throught the opening of the anhydride ring of maleic anhydride copolymer with some vinyl monomers, especially with the methyl methacrylate,under the action of heterocyclic compounds. It must be mentioned that

these copolymers are biocompatible, and some of them present an important intrinsic biological activity (Stauner et al. 1997, Uglea et al. 1996).

In this work, some heterocyclic compounds have been prepared. These compounds were allowed to react with methylmethacrylate-maleic anhydride copolymer to obtain higher biological active products. Several studies have demonstrated the antimicrobial and antifungal action of these compounds using four bacterial and three fungi strains Staphlococcus aureus, Escherichia coli, pseudomonas aeroginosa, Klebsiella Aspergillus niger, Aspergillus Flavus and Fusarium oxysprium respectively.

2. Materials and Methods:

Methylmethacrylate(MMA) was supplied by Aldrich and was deinhibited by using sodium hydroxide. Maleic anhydride(MAN),purity 99.9% Merck,Germany) Thiosemicarbazide, 2-iminothiazolidine -4 –one, Thiophene aldehyde , 2 -acetyl thiophene,Isatin ,other compounds such as solvents, and other reagents were reagent grade and used without further purification.

Spectrophotometric measurements:

FTIR was carried out using Mattson 1000 FTIR spectrophotometer,Unicam,England in the range 400-4000 cm^{-1}.

NMR spectra were recorded on a Varian Mercury VX-3oo NMR spectrometer 1H spectra were run at 75.46 MHz in dimethylsulphoxide(DMSO-d6).

Mass spectra were measured on a GCMS-Gp 1000 EX spectrometer at 70 eV.

Elemental analyses carried out at the Microanalytical Center of Cairo University.

Synthesis of poly (methyl methacrylate- maleic anhydride) copolymer (p MMA/MAN):

The MMA-MAN used in this study was synthesized by a modified solution polymerization of the monomers methyl methacrylate,maleic anhydride, (MMA/MAN). The polymerization reaction was carried out in a reactor under intensive mixing and nitrogen atmosphere at 80 ^{0}C for 8 h. The copolymers were synthesized toluene benzoyl peroxide as initiator. Appropriate volume of the solvent was added to maintain the monomer concentration at 2 mol /L. The obtained copolymers were fractionated by precipitation in excess methanol to remove all the toluene and the non-reacted maleic anhydrid (MAN). The synthesis procedure used in this work is a modified version of similar methodologies used in the literature (Spridon wt al. 1997, Popa et al. 1997, Wilde and Smets 1950).

Synthesis of (1a)

To around bottom flask contaning 150 ml of boiling ethanol under stirring, 4.5 gm (50.2m mol) 0f thiosemicarbazide ,and 5.5 ml (50 .2 m mol) of 2-acetyl thiophene were added and the solution was allowed to cool at room temperature; then 2,4-drops of concentrated H_2SO_4 were added causing the precipitation of a pale yellow solid. After 24 hours of stirring the solid was separated by filtration and washed with cold ethanol and hexane (yield 65% (6.5 gm, 32.7 m mol) mp=132-133 ^{0}C).

Synthesis of (1b)

A mixture of compound 1a (0.01 mol) with $ClCH_2COOH$ (0.011mol) and KOH(0.02 mol) in ethyl alcohol was refluxed for 2-hours,cooled diluted with H_2O and stirred with KOH solution, filtered wased with H_2O dry, crystals from ethyl alcohol were obtained.

Synthesis of (1c):

In a reaction flash provided with a refluxing condenser 100 ml absolute ethyl alcohol were introduced and then 2.3 gm (0.01 mol) metallic sodium were added. To the obtained solution of natrium ethoxide 16.7 gm (0.01 mol) Ib were added in small portians under strring and gentle heating on a water bath for the solution homogenisation. 13.5 gm (0.11 mol) of benzoyl chloride were added as several doses to the hot alcoholic solution of the Ib sodium derivate the sodium chloride was then removed by filtration under vacuum and the obtained yellow solution is cooled to the room temperature and poured as thin thread, under strring, into cold water . Acream coloured precipitate is separated and filtered, dried and crystallized.

Preparation of compound (Id)

To a suspension of Ic (o.01mol) in absolute ethanol (20 Cm^3), hydrazine hydrate (0.015 mol; w=98%) was added and the reaction mixture was refluxed for 2h. The mixture was then cooled, treated with one drop HCl and the separated pale yellow product was filtered off,dried and crystallized.

Reaction of the compound (1d) with copolymer :

In a flash provided with a refluxing cooler 1 gm (0.005 mol) poly (MMA/MAN), 0.70 gm (0.005 mol) from Id and 50 ml anhydrous acetone were introduced. The mixture was refluxed on a water bath for 2-hours, where a homogeneous solution resulted. after removing the excess acetone by distillation under normal pressure until a volume of 4-5 mL, a mixture of anhydrous petroleum ether and ethyl ether (1:1) was added where an oily product separates. It

was submitted to repeated washings with ethyl acetate and then with anhydrous ethyl ether where it turned into a fine yellow powder, the final product was obtained in a yield (76%) after recrystallization from ethyl acetate and drying. (1e)

Synthesis of Compound (IIe):

In a reaction flash provided with a refluxing cooler l00 ml absolute ethyl alcohol were introduced and then 2.3 gm (0.01 mol) metallic sodium added to the obtained solution of natrium ethoxide 16.7 gm (0.01 mol) IIa were added as small portians under strring and gentle heating on a water bath for the solution homogenisation. 13.5 gm (0.11 mol) from ethyl chloro acetate were added as several doses to the hot alcoholic solution of the IIa sodium derivate the sodium chloride was them removed by filtration under vacuum and the obtained yellow solution was cooled to the room temperature and poured as thin thread, under strring, into cold water, a paleyellow coloured precipitate was separated and filtered off under vacuum and dried The crude product was purified by recrystallization from boiling ethyl alcohol .

Synthesie of compound (IIIe).

The schiff bases of isatin were synthesized by condensation of the keto group with thiosemcarbazide to give the compound(IIIa)and then reaction with monochloro acetic acid gives the structure(IIIb) and these when reacted with p-chlorobenzaldehyde give the structure(3c) which with addition to the copolymer gives the compound (IIIe) .

Synthesis of (IIIf).

Isatin (2gm, 13.6 m mol) and 3,4 diphenylether (1.36gm) (6.8 m mol) were dissolved in 35 ml warm ethanol containing 0.45 ml of acetic acid for 10 hours washed with ethanol ,recrystalized from ethanol (Schiff base) m.p > 260 ^{O}C.

Preparation of 2- iminothiazolidine – 4- one . (IV):

6 gram of thiourea with 7.2 gm of monochloro acetic acid in glacial acetic acid, are refluxed for half an hours, to give a solid, filter, and wash with methyl alcohol. Then dissolve in lest amount of water, then basified with sodium bicarbonate (3%) solution to give a white crystal. m.p=212 ^{0}C

This compound was reacted with thiosemicarbazide in ethanol (30 Cm^3) and refluxed for 3h. The formed yellow solid product was filtered off, drided and crystallized.

Preparation of(IVd).

A mixture of the acetic anhydride (0.01 mol) and compound (IVa) (0.012) in ethanol (30 Cm^3) was refluxed for 3 hours. The formed yellow solid product was filtered off, dried and crystallized.

Preparation of (IVg)

The reaction of 2-iminothiazolidine -4- one with formaldlehyde and primary aliphatic amine in molar ratio (1:2:1) under Mannich - type condition gave thiazolo (3,2-a) s-triazine . (IVf)

Mannich reaction

0.92 gm (8 m mole) of (IV) in 1.92 ml (0.0 24 mole) of formalin add dropwise with stirring 1gm (8m mol) of 25 % aqueous solution of aliphatic amine at 0-5 ˚C . After the addition is complete .The reaction mixture is stirred without cooling for another 15 min.after which it is treated with worm (30 -40 ˚C) benzene (four portions 20 ml each) .The benzene layer is drided with magnesium sulphate,the benzene is removed by distillation to one fifth of its original volume, to give ppt.(IVf)

The compound of (IVf) reacts with the copolymer gives the structure (IVg).

Procedure for the aldehyde with amine):

Amixture of the appropriate aldehydes (10 m mol) and (4-amino) (12 m mol) in glacial acetic acid ,the reaction mixture was left to stand at room temperature for overnight and the resulting crystalline material was collected by filtration washed with cold ethanol, and recrystallized from the proper solvent.

Evaluation of antimicrobial activity

The antibacterial and antifungal activities were carried out at the Regional Centre for Mycology, and Biotechnology at Microanalyticl Center, Cairo University, Egypt

Some of the newly synthesized compounds were screened for their antimicrobial activity using the diffusion agar techniques (EL-Merabani et al. 1972) were tested against four bacterial species namely. (Staphylococcus aureus, ,Escherichia coli,pseudomonas aeroginosa and Klebsiella, as well as against three fungal species namely Aspergillus niger , Aspergillus flavus and Fusarium oxysporium) for their antimicrobial activity using 5 mg /ml.of each compound in dimethylformamide. Inhibition Zone diameter (IZD) in cm was taken as the criterion for antimicrobial activity. The antimicrobial activity was assayed biologically using a spore suspension of the fungal pecies (1 ml of sterile water containing approximately 108 conidia) or spreading bacterial suspension over a solidified malt agar (Dawson 1957, Kucheria et al. 2005). The layer was allowed to set for 30 min. A solution of each of the tested

compounds (5 mg/ml) was placed onto sterile 5 mm filter paper discs and allowed to dry, and then the discs were placed onto the center of the malt agar plate and incubated at the optimum incubation temperature, 28 ºC. A clear zone around the disc was taken as an indication of the inhibition growth of the test organism. The size of the clear zone is proportional to the inhibitory action of the compound under investigation. The fungicide terbinafin and the bactericide Chloramphenicol were used as references to evaluate the potency of the tested compounds under the same conditions (Elamin et al. 2005, Abdel-Aziz et al. 2008). Measurements were considered after 72 h for fungi and 24h for bacteria. The results are contained in Table (1)

3. Results and Discussion:

The conversion of maleic anhydride moiety in heterocyclic compound to malemide was monitored by FTIR, ^{1}HNMR spectra and elemental analyses. This may be attributed to the improvement of rigidity of polymer chains because the imide ring was formed in the chemical modification.

The compound (1a) was prepared by reacting thiosemicarbazide with 2-acetylthiophene in ethanol following the addition of sulphuric acid. A yellow crystalline, air–stable compound in 65% yield was isolated. The compound solubility is in ethanol and other polar solvents.

Compound (I-Ie):

By heating the p (MMA/MAN) copolymer with compound (Id) in anhydrous acetone the amidlic compund (Ie) resulted according to the following reaction (in scheme 1) the reaction mechanism is supposed to be similar to that oxazolone decyclization by the nucleophilic reagents **(**Chevica et al. 2003, Sunel et al. 2001) the compound (Ie) derivative reacts by means of the NH_2 group due to the unshared p electrons on the nitrogen atom. the product purified by recrystallization from ethyl alcohol was obtained as yellow crystals. The FTIR, ^{1}HNMR spectral measurements along with the nitrogen analysis data confirm the structure of the reaction product as the found nitrogen content is 14:01 % in comparison with the calculated value, of 14:55%.m.p>300 ^{o}C. The FTIR spectrum of the synthesized compound (Ie) shows the characteristic absorbtion band : 1724.7 ,1626 cm^{-1} C=O, CO-NH, 2995 Cm^{-1} C-H aliphatic, 3407 cm^{-1} OH in COOH ,3245Cm^{-1} of NH group,1390Cm^{-1}CH_3 bend C=N at (1519) Cm^{-1} and 3046Cm^{-1}CH aromatic.

The ^{1}HNMR(δ,DMSO) also confirms the structure of the synthesized compound; δ(ppm) 3.0(s,3H,CH_3)),9.8(s,1H,NH) 7.2(s, 5H,aromatic), 5.5(m,1H,CH).

MS(Int.%):210(100),216(1.8),215(2,28)212(8.16)524 (0.87),523(1.17),521(2,14).Anal.Calcd.for: $C_{25}H_{26}O_6N_5S$(524):C,57.25,H,4.96,N,13.35,S,6.1.Fou nd:C,56.5,H,4.1,N,12.9,S,5.5. In scheme(1)

In order to obtain sulpha-drug (MMA /MAN) copolymer derivatives,the amino derivatives of such compounds were introduced to the anhydride ring of the copolymer(1:1 mol/mol) by heating them in DMF /acetone (1:1 v/v) at 70 0C for 12 h.The reaction of copolymer anhydride groups with such different functional compound is shown in (1g)In scheme(2).

The FTIR spectrum of the synthesized compound shows the following characteristic absorption bands : at 3410-3313 Cm^{-1} for NH_2 ,1585 Cm-1 of C=N, 1655 Cm-1 C=O, Ar-H st.at 3100 Cm-1 and SO_2 at 1370 Cm^{-1}.The ^{1}NMR(∂,DMSO),3.94 (s,3 CH_3),5.1(bs,2H,NH_2).Anal.Calcd for : $C_{22}H_{24}O_7N_4S_2$ (520):C,50.76,H,4.6,N,10.76,S,12.3.Found:C,51.2,H, 4.3,N,10.1,S,11.8.

Compound (IIe):

The studies in the present paper resulted also in the development of a new synthesis method of a compound (IIe) by using p(MMA / MAN). The reaction was carried out by adding the copolymer to (IIc) solution in an anhydrous solvent. The chemical equation is given in scheme (3). The structure was elucidated by means of,the FTIR ,MS and ^{1}HNMR spectral measurement, The FTIR spectum shows an 2996 ,2932 Cm^{-1} may be attributed to the asymmetric and symmetric C-H stretching of methylene group.1455 cm^{-1} CH group,1394 Cm $^{-1}$ may be bending ,1710 Cm^{-1} of C= O ,1148 Cm^{-1} C-O ,of group ,1630 Cm^{-1} methyl group, peak at N=C 1690 Cm^{-1},amides (1500-1600 Cm^{-1}) ,NH_2 at 3250 Cm^{-1} 2980 Cm^{-1} aliphatic ,SO_2 at 1430 Cm^{-1} and C=N at 1665 Cm^{-1}.The MS(Int.%):Base peak 361(100),433(4.23),408(5.47),302(20.83),317(5.3),30 0(15.52).

The structure of the synthesized compound was also confirmed by ^{1}HNMR spectrum PPm δ 2.4 (m,1H ,CH) ,δ 3.5(m,2H CH_2) , δ 2.1(s ,3H,CH_3) and δ 9.7 (s,1H,NH).

Anal.Calcd.for'$C_{19}H_{21}O_7N_5S$(463),C,49.24,H,4.54,N, 15.12,S,6.9.found:C,48.8,H,5.1,N,15.2,S,6.5.

Compound (IIIe):

The target compounds were prepared by using the reaction sequence in Scheme(4) The schiff bases of isatin were synthesized by condensation of the keto group with thiosemcarbazide to give the compound(IIIa)and then the reaction with monochloro acetic acid gives the structure(IIIb) and these when reacted with p-chlorobenzaldehyde give the structure(IIIc),and then react with hydrazine

hydrate, which adds to the copolymer and give the compound (IIIe) The chemical structures of these synthesized compounds were confirmed by means of FTIR, and ^{1}HNM spectra. In scheme (4).

The FTIR spectram showed peaks at 3300 Cm^{-1} (NH), 1680 Cm^{-1}(C=O), 1620 Cm^{-1}(C=N), and 798 Cm^{-1} for (C-Cl).and 669-603Cm^{-1} for (CH_2) aromatic.

The^{1}NMR(∂,DMSO):11.9(bs,1H,NH),4.2(s,3H,CH_3).

Anal.Calcd.for $C_{27}H_{23}O_7N_6Cl$(578.5) C,56,H,5.5,N,14.5,Cl,6.13. Found: C, 55.5, H, 6.1 N, 14.3, Cl, 5.83.

The compound (III) reacting with 3, 4, diaminodiphenyl ether gave the compound (IIIf) and when reacted with the copolymer gave the structure (IIIg).In scheme(5).

The structure of the synthesized compound was also confirmed by FTIR and ^{1}HNMR spectral measurements.

The FTIR spectrum shows an absorption peak at 1719 Cm^{-1} attributed to the carbonyl group, 3151 Cm^{-1} for N-H group and 1350 $Cm^{-1}$for C=S.

The ^{1}HNMR also confirms the structure of the synthesized compound: δ (ppm) 6.9-7.6(m,4H,Ar), and δ 11.3(s,1H, NH). Anal.Calcd.for $C_{29}H_{25}O_7N_3$ (527).C,66,H,4.74,N,7.96. Found C,65.4,H,4.1,N,7.2.

Compound (IVd):

The reaction of 2-iminothiazolidine 4-one (IV) with thiosemicarbazide gave the compound (IVa): FTIR specrum shows (IVa): 1370 for C=S, 1590-1605 for (C=N),1610 for (NH_2 def),3180 (NH) and ^{1}HNMR spectrum, δ 8.4(s 1H, CH=N), δ11.7 (br, 2H, NH_2) and when reacted with acetic anhydride gave the compound (IVb). The FTIR spectrum shows 1580 Cm^{-1} (C=N), 1663 (C=O), and 1350 Cm^{-1} (C=S): by treating the (IVb) through condensation. These compounds react with the copolymer according to scheme (6).

In the FTIR spectrm the frequency of the valence vibration of the structure shows the following characteristic absorption bands : C=O group is found at 1724 Cm^{-1}, that of N-H band at 3350-3400 Cm^{-1} and C=N at 1585 Cm^{-1}. And the ^{1}HNMR spectrum shows: δ (ppm) 11.3(s, 1H, NH), and 2.3 (3H, CH_3). Anal. Calcd. For $C_{17}H_{23}O_7N_7S$ (469) C, 43.49, H, 4.9, N, 20.9, S, 6.8. Found C, 44, H, 4.2, N, 21.2, S, 7.3.

The reaction of 2- iminothiazolidine -4-one (IV) with formaldehyde and primary aliphatic amines in molar ratio (1:2:1) under Mannich-type condensation gave thiazolo(3,2-a) s- triazine (IVg).The reaction was carried out by adding the copolymer to the compound (IVh) in an anhydrous solvent, the chemical equation is given in scheme (7).

The structure of the synthesized compound was also confirmed by FTIR and ^{1}HMNR spectral measurements.

The FTIR spectrum shows absorpation peaks at(1500-1600) Cm^{-1} for amides, 2921Cm^{-1} for (C-H) in (-CH3), 1712 Cm^{-1} for (-COOCH3), and 1657 Cm^{-1} for(C=N). The ^{1}NMR shows: δ(ppm):10.9(s,1H,NH), 2.4(3H,CH_3),and 9.6(H,OH).

Anal. Calcd. for $C_{14}H_{19}O_5N_5S$.(369) C,45.5, H,5.15,N,18.9,S,8.67.Found $C_{46}H_{4.8}N_{19.3}S_{7.8}$.

Notes:

N ratio If clar zone of inhibition is a) 15 mm = + b) 15-24 mm = + + c) 25-34 mm = +++ d) 35-44 mm = ++++ e) 45-54 = +++++

Antifungal agent is flucoral (150 mg / 10 ml H_2O).

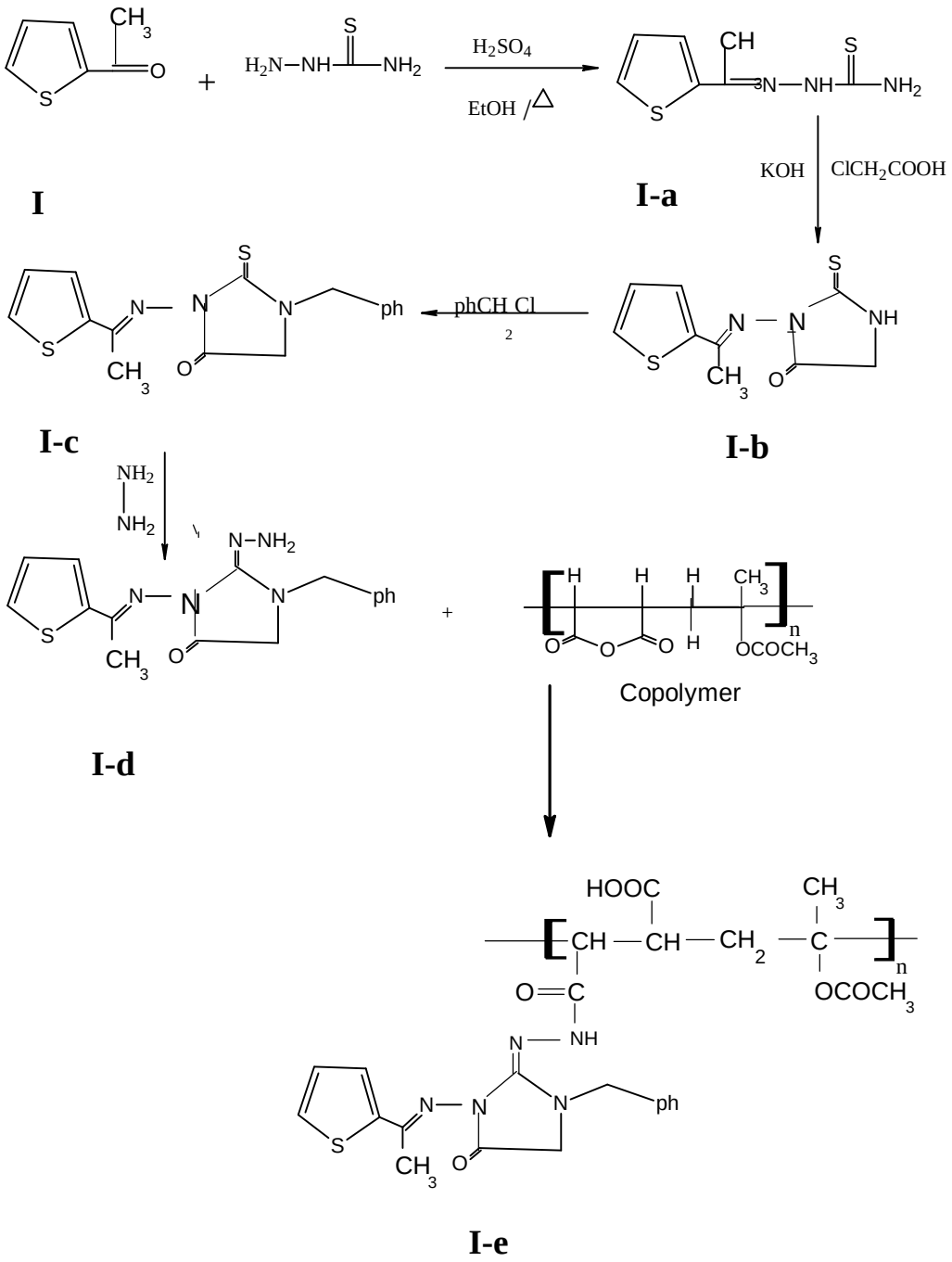
Antibacterial agent is Duricef (250 mg / 10 ml H_2O).

When we used the antibiotics tested with concentrations equal to that of the chemicals tested, No inhibition of growth for any microorganism was noted so we had to use a concentration fraction of antibiotics (standard) higher than that of the tested chemicals to ensure inhibition.

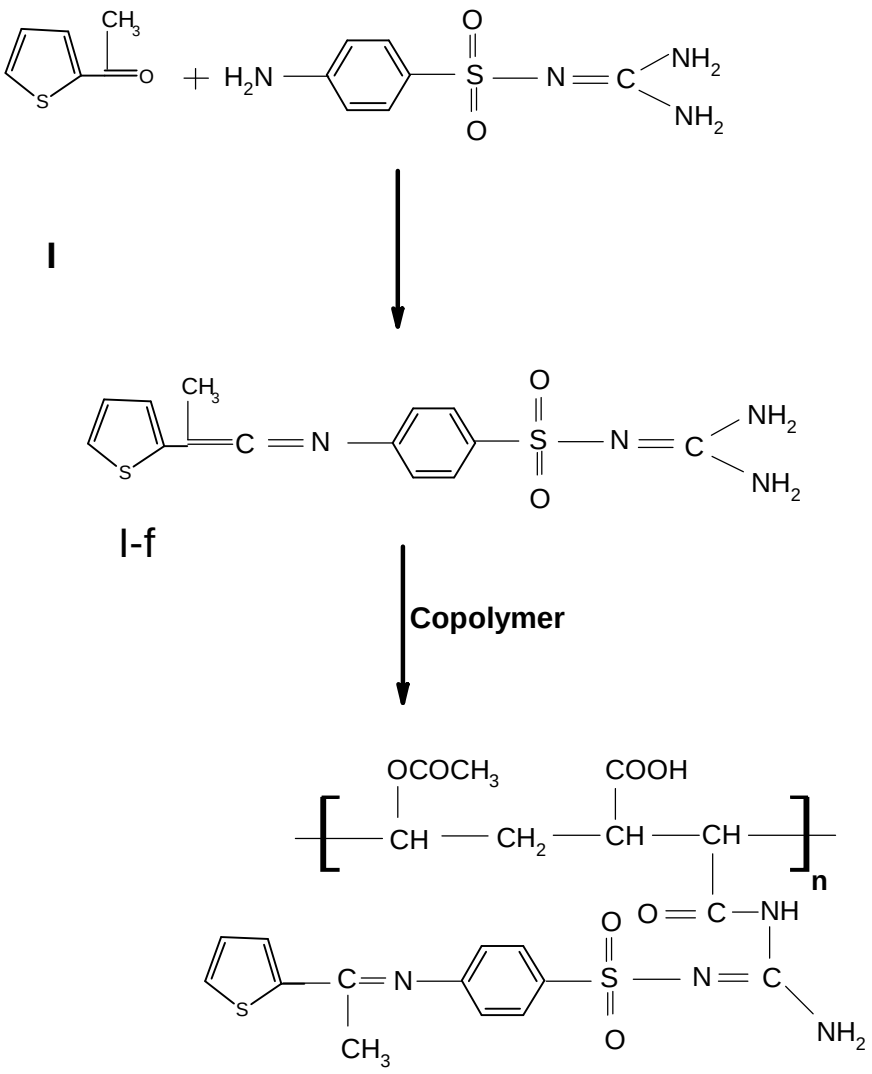
All the synthesized compounds were evaluated for their antimicrobial activities. The Zone of inhibition found for the compounds against gram positive, gram negative bacteria and fungi are presented in Table(1):

The results of antimicrobial activity showed that the heterocyclic compound (Id) was found to have exhibited effect against, (St),(Es),(Ps),(Kl) and (Fu).When reacted with copolymer to give the compound ((Ie) and found to have activity towards (Es),(Ps),(Kl) and (Fu); but the compound (Ig) with sulph-drug exhibited a highly effect against (St),(Es),(Ps),(Kl),(As-flavus) and(Fu).

Also the compound (IId) was found to have an effect against (Es) and (Kl) only but when the compound reacted with the copolymer gave the compound (IIe), which has an effect against (Es), (Ps),(Kl) and (Fu).The compound (IIId) exhibited a moderate effect against (Ps),(Kl),(As-niger) and (Fu).but the compound (IIIe) has an effect against (St),(Es),(Ps),(Kl) and (Fu); and the compound (IIIg) effect on (Ps),(kl) and (As-niger),and then the compound (VId), highly effect against (St),(Es),(Kl),(As-flavus) and (Fu), but the compound (IVc) exhibited a moderate effect against (Ps),(Kl) and (Fu). And while (IVg) has a highly effect toward (St),(Es),(Ps) and (Kl).



Scheme 1



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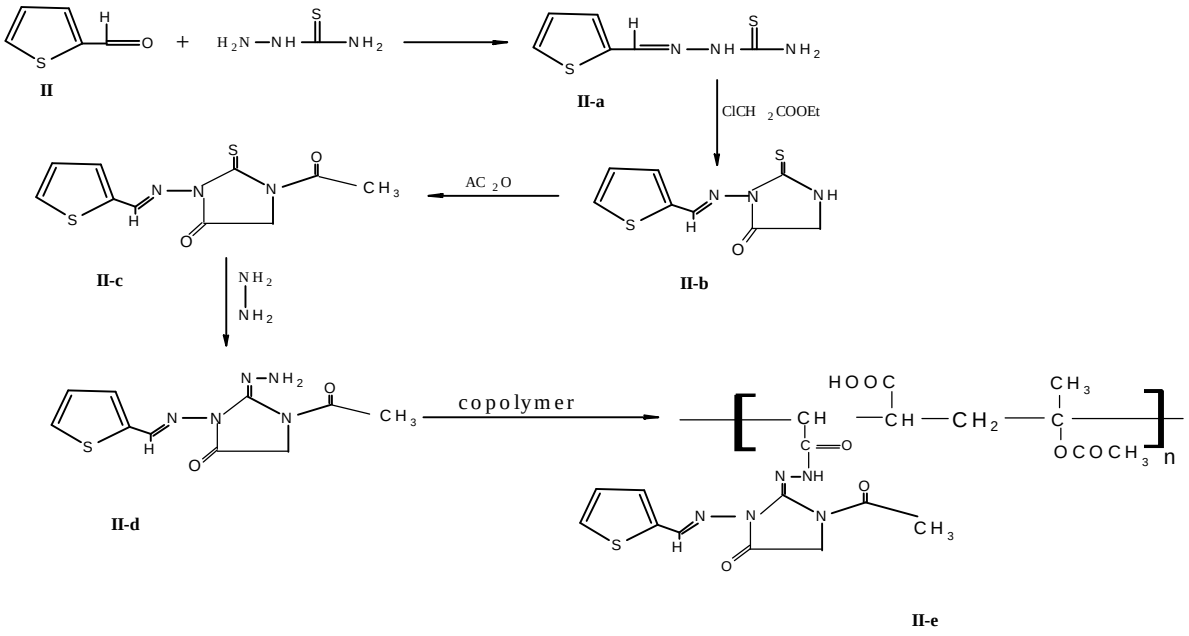

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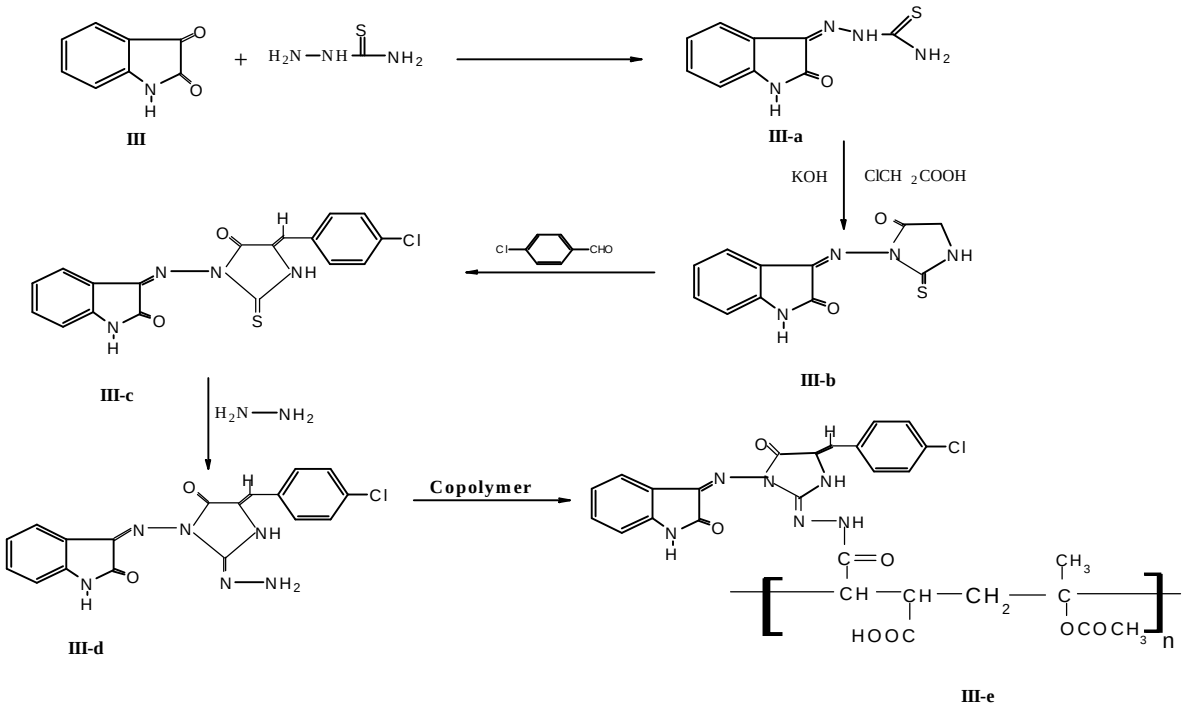
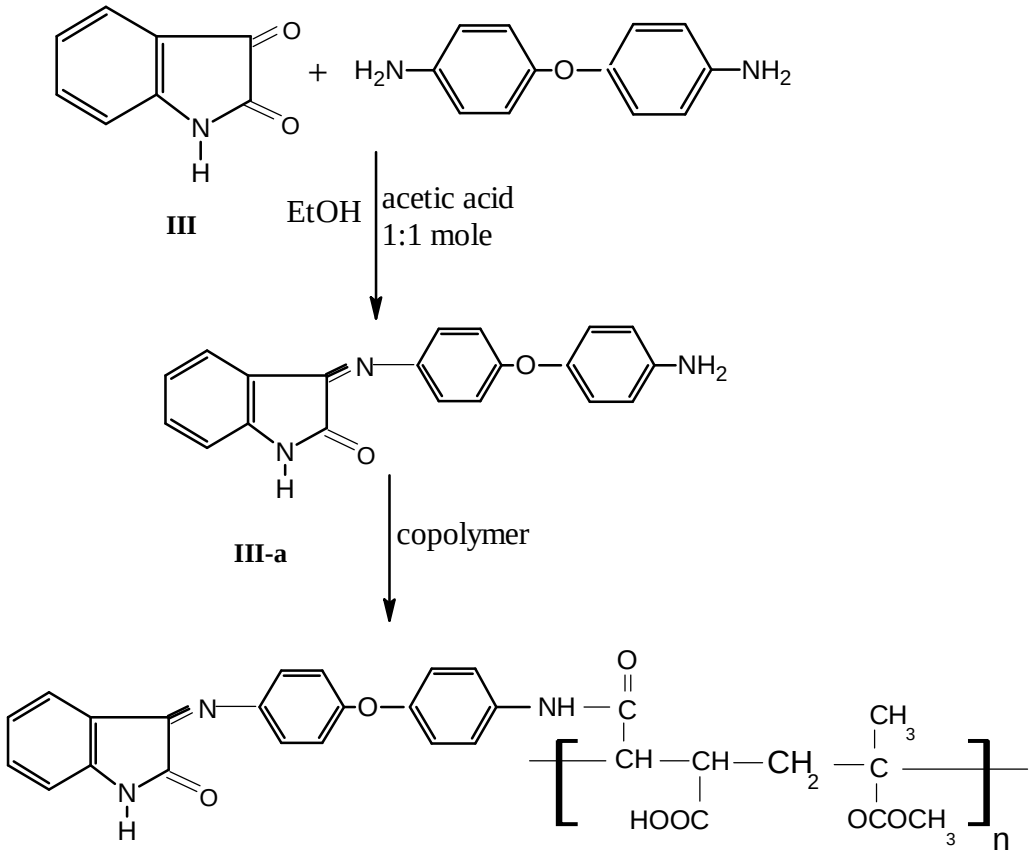
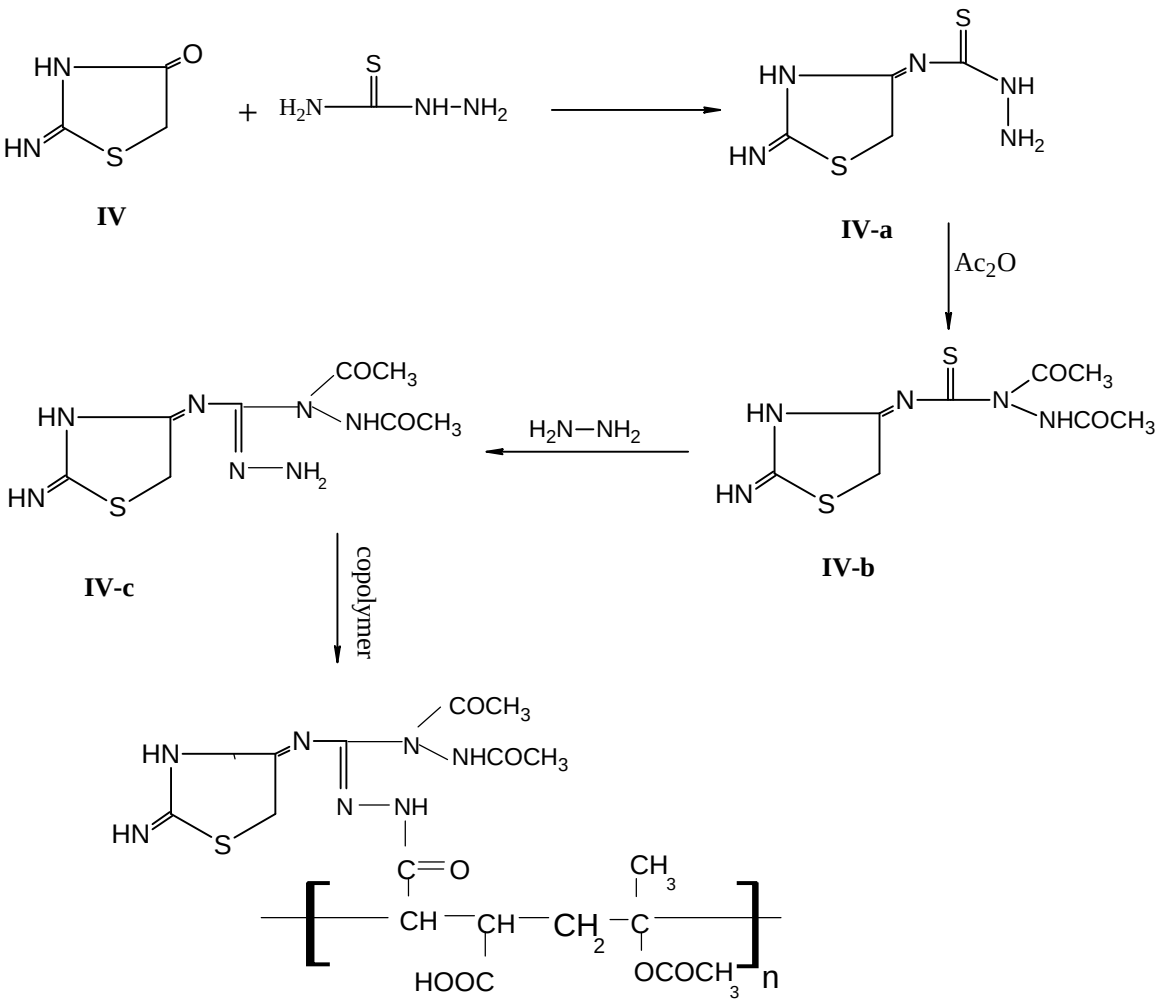


Scheme 4



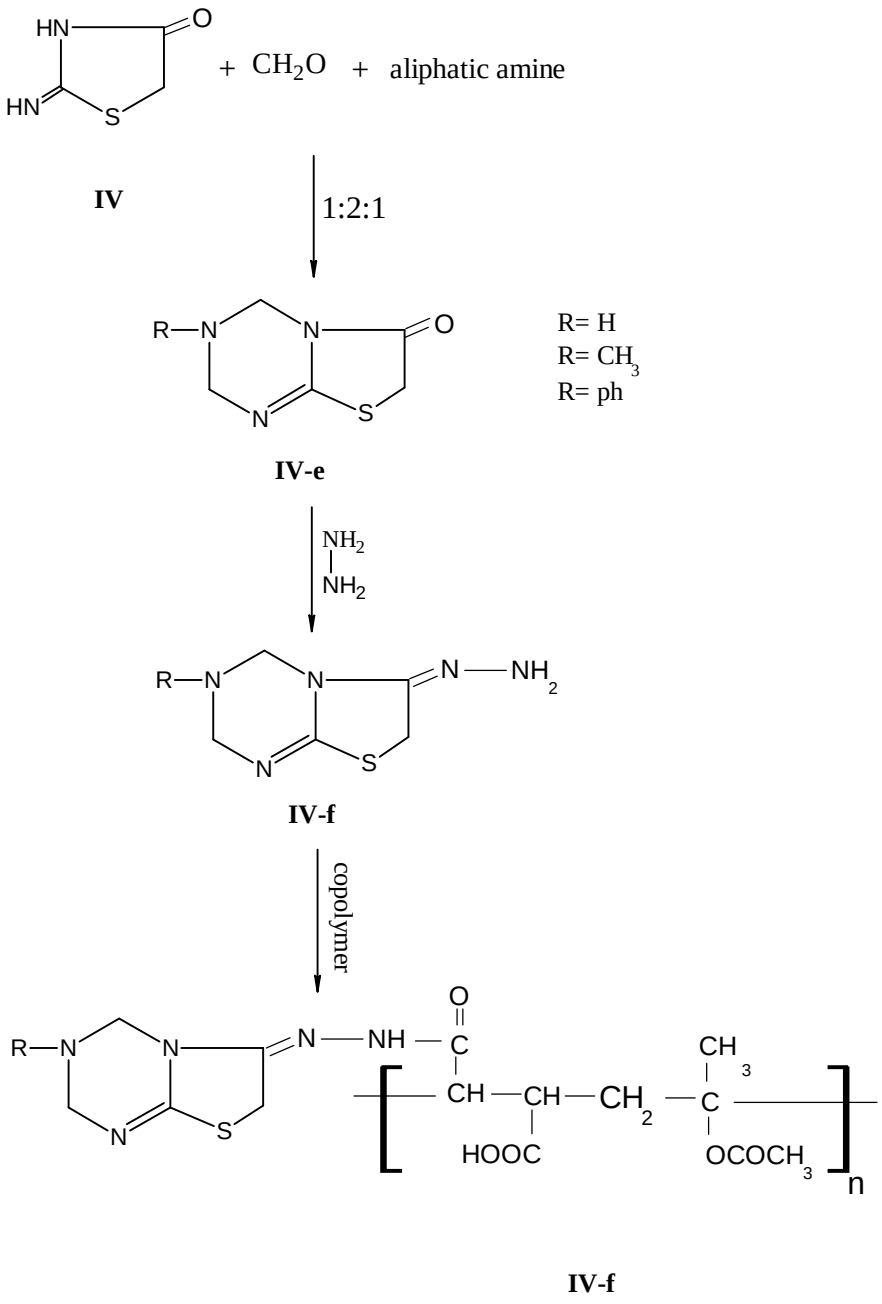
III **III-a** **III-b**

Scheme 5



IV **IV-a** **IV-b** **IV-c** **IV-d**

Scheme 6


HN
O
HN
S
+ CH2O + aliphatic amine
IV
1:2:1
R
N
N
O
N
S
R= H
R= CH3
R= ph
IV-e
NH2
NH2
N
NH2
IV-f
copolymer
NH
C
CH
CH
CH2
C
CH3
HOOC
OCOCH3
n

IV-f

Scheme 7

Table 1:Antimicrobial activity of chemical substances tested

Diameter of clear zone (mm)							Compound No.
Antifungal			Antibacterial				
Fusarium oxysporium	Aspergillus Flavus	Aspergillus niger	Klebsiella	Pseudomonas aeroginosa	Escherichia coli	Staphylococcus aureus	
20	-	-	14	19	18	19	1d
30	-	-	16	23	18	-	1e
-	-	-	30	28	17	29	1g
-	-	-	18	-	16	-	IId
25	18	-	35	26	40	24	IIe
30	-	21	15	15	-	-	IIId
30	-	-	13	19	16	15	IIIe
-	-	24	19	17	-	-	IIIf
20	-	-	15	12	14	12	IVc
50	20	-	32	-	21	13	IVd
40	-	-	19	21	17	-	IVh
-	-	-	50	33	No growth	No growth	Standard antibacterial agent
No growth	21	38	-	-	-	-	Standard antifungal agent

4. Conclusions:

The new synthesized compounds have been immobilised through amidic bonds, through the opening of the anhydride cycle of the poly (methyl methacrylate –maleic anhydride);the spectral analysis proved the obtaining poadation 3 of the polymer – biologically active principle conjugates.

The antimicrobial activity of the modified copolymers were tested against four bacterial and three fungi strains Staphylococcus aureus, Escherichia coli, pseudomonas aeroginosa ,Klebsiella, Aspergillus niger , Aspergillus Flavus and Fusarium oxysporium, respectively.

It was found that the diameter of inhibition zone varied according to the type of active group in the copolymer and also the examined microorganism.In general,the copolymer was further modified and showed antimicrobial activity against the tested microorganisms. However, the compound of the modified copolymer was found to be the most effective on bacteria and fungi species.

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