Iftikhar Ahmed Hussein et al /J. Pharm. Sci. & Res. Vol. 10(10), 2018, 2461-2469

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Synthesis and Biological Activities of Some New Derivatives Based on Bis (4, 4'- diamino phenoxy) Ethane Containing Oxazpines, Terazole Rings

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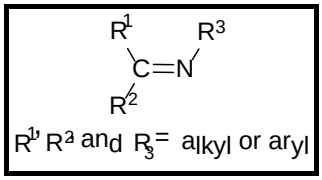
Abstract

In this work, Bis (4, 4'- diamino phenoxy) ethane [C_1] were synthesized from the reacting (p-hydroxy aniline) with dibromo ethane. Schiff bases [C_2-C_7] were synthesized by reacting the compound (C_1) with various aromatic aldehyde. Then reacting [C_2, C_4, C_6] with different anhydrides (3-Nitrophathalic anhydride, succinic anhydride) and sodium azide gave oxazepine [C_8-C_{13}] and tetrazole [C_{14}-C_{16}] respectively .The prepared derivatives were identified by infrared spectra, ^{1}HNMR, and physical properties. The antibacterial strains and Fungi have been investigated: an activity was shown against Gram (+ve) bacterial (stapylococus, Gram (-ve) bacteria (Esherichiacoli) and (+ve) (Candida albicans).

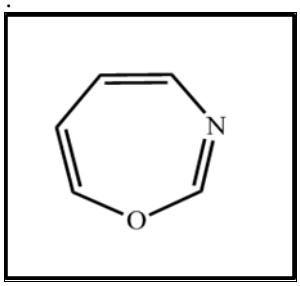
Key words: Schiff bases, heterocyclic rings, biological activity.

INTRODUCTION

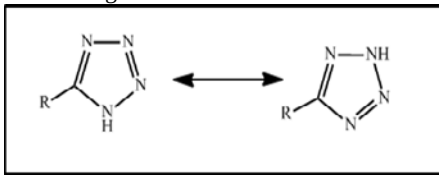
The development of synthetic routes to broadly used organic compound by using readily obtainable reagents is one of the major aims of organic synthesis. Schiff bases are an important class of organic compounds because of their broad spectrum of biological activities such as antimalarial[1], antitumar[2], antifungal[3], antibacterial[4] , antitubercular[5], antiviral[6], anticancer[7], and proliferative[8].On the principle, it is prepared in the reaction of an aldehyde (respectively a ketone) with a primary amine[9]. Sometime the addition glacial acetic acid acts as assistant factor. These compounds have known structural feature is the azomethine group.



Oxazepine, is every seven membered ring that contains oxygen in place one and nitrogen in place three in adding to the five carbonatoms[11,12] .



By time, the synthesis of oxazepine has been documented, investigated. It is made through the reaction of Schiff base or hydrazone with different anhydrides [13-17]. Oxazepine derivatives were found to display massive change of biological activities like antifungal,hypnotic muscle relaxant, inflammatory,antibacterial agents [11,17]. Tetrazoles are a type of heterocyclic compounds contains of four nitrogen and one carbonatom[18].



Tetrazoles are privileged, heterocyclic scaffolds that possess numerous applications, especially in the field of pharmaceutical chemistry. They also have applications in organic chemistry, coordination chemistry, agriculture, and photography [19], as well as in various materials science applications including polymers, photosensitive agents, energy materials, and explosives. [2]

MATERIALS AND METHODS

All chemicals were supplied from diverse corporations such as Thomas baker, Merck, BDH, GCC and Scharlau and used without further purification. Melting points were resolute on an electro thermal melting point apparatus (Stuart Germany),they were uncorrected. End of purity,and reaction of very compounds were tested on aluminum coated TLCplates 60 F245 (E. Merck) by using absolute ethanol as the mobile phase and imagined under iodine vapor. Resolves of infrared spectra were done and recorded as a KBr disks in the range of (400 -4000 cm^{-1}) using FTIR Shimadzu (Japan).The proton 1H-NMR spectra were tested for the synthesized compounds using Bruker DMX-500 spectrophotometer (500 MHZ, solvent DMSO-d_6).

Synthesis Bis (4,4'- diamino phenoxy) ethane (C_1) [21]

Alcoholic sodium hydroxide (8gm, 0.2mol) was added to 20m absolute ethanol with (0.02mol, 2.91gm) (p-hydroxy aniline). The admixture was mixed until all the solid parts dissolved, then it was solved with (0.01mol, 0.64ml) (dibromo ethane). Then it is refluxed for 4 hrs. After the end of reaction ,it was checked byTLC .Then the reaction was poured into ice cold water to give solidity and the solute was added to poured crushed ice distilled water , the solute then filtered and purified in ethanol absolute. The physical properties of compounds [C_1] are shown in table (1).

Synthesis of (Schiff bases) compounds [C_2-C_7] [22]

A mixture of compound [C_1] (2gm,0.008mol) and different aldehydes {benzaldehyde, 4-hydroxybenzaldehyde, 4-chlorobenzaldehyde, 4-Nitrobenzaldehyde, 4-bromobenbenzaldehyde, N- Dimethyl amino benzaldehyde } (0.016 mol) were dissolved in (20 mL) of absolute ethanol with few drops of glacial acetic acid that was refluxed for (8-10) hrs. Solid that resulted was filtered,and purified from absolute ethanol. Physical properties of compounds [C_2-C_7] are shown in table (1).

Synthesis of (oxazepines)compounds [C_8-C_{13}] [23]

A mixture of [C_2,C_4,C_6] (0.001 mol) was dissolved in (10mL) ethanol with different anhydrides (succinic anhydride and phathalic anhydride) (0.002mol) and were refluxed for (5 hrs.) (checked by T.L.C).The reaction mixture then was cooled , filtered , purified from ethanol. Physical properties of compounds [C_8-C_{13}] are shown in table (1).

Synthesis of (tetrazole)compounds [C_{14}-C_{16}] *(24)*

Schiff base [C_2, C_4, C_6] (0.001mol) was dissolved in (10 ml) of THF followed by adding (0.002mol, 0.13gm) sodium azide. The mixture was heated in water bath at (60-70)ºC for (10hrs). then, the mixture of reaction was filtered, the resulted was purified by absolute ethanol. Table (1) shows physical properties of compounds [C_{14}-C_{16}].

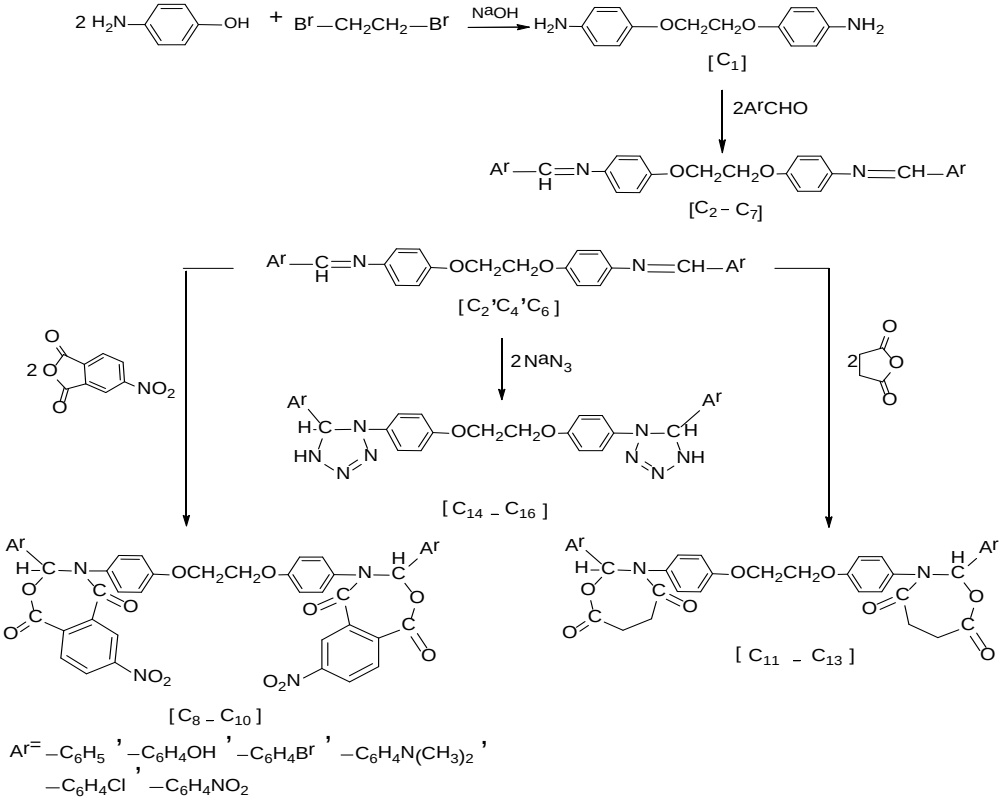
RESULTS AND DISCUSSION

The general reaction is briefed in Scheme (1)

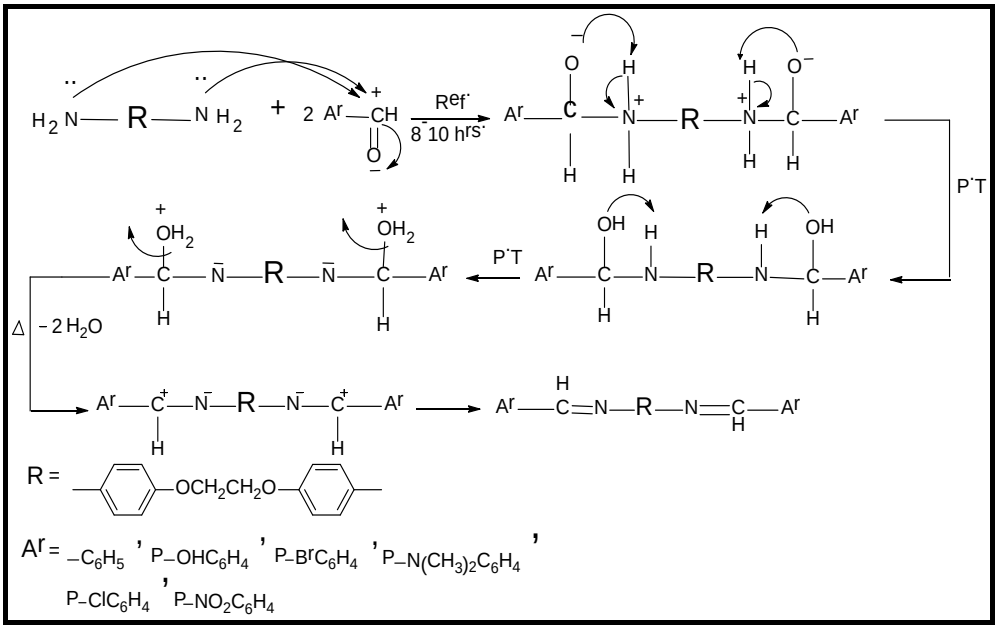
Compound [C_1] was prepared by reacting p-hydroxy aniline with dibromo ethane in the presence of NaOH ethanol. The structure of compound [C_1] was diagnosed by FT-IR spectrum showed disappearance of stretching vibration of (OH) group and stretching vibration of υ (C-O-C) which appeared at (1234) cm^{-1} .Absorption band at (3417, 3375) cm^{-1} belonged to υ (NH_2) asymmetric and symmetric, and a number of other bands are described in table (2). Heating at refluxing of compound [C_1] with equimolar amounts of different carbonyl compounds in absolute ethanol with few drops of glacial acetic acid leads to the production of new series of Schiff bases . The mechanism included nucleophilc attack of amine group on the carbon carbonyl group of aldehyde to form unstable compounds followed by losing H_2O molecule to give an imine compounds [25]. The mechanism or the reaction can be outlined in scheme (2). Schiff bases from [C_2-C_7] were characterized by (FT-IR).These spectra showed disappearance of bands due to NH_2 symmetric and asymmetric at (3417,3375) cm^{-1} and the appearance of bands was due to υ (CH=N)group . FTIR spectrum of compound [C_2] showed absorption band at (1622) cm^{-1} which belonged to υ (CH=N). Other absorptions Schiff base compounds are found in the table (2). Characterization of compound [C_5] was performed also by ^{1}H-NMR spectra which gave [C_5] the following signals δ: (6.6-7.6)ppm due to (m, 16H, Ar-H), (3.34-3.37)ppm for (t, 4H, $CH_{2methylene}$), (2.99-3.04) ppm due to (s, 12H, N-CH_3),(9.62) ppm due to (s, 2H, CH=N), (2.45)ppm due to DMSO.

We reacted the Schiff base with different anhydrides to give oxazepine derivatives. The suggested mechanism[26] for the formation of the oxazepine derivatives is shown in scheme (3). The oxazepine derivatives from [C_8 –C_{13}] were characterized by (FT-IR). The FTIR spectrum of [C_8], indicated the appearance of vibration of oxazepine respectively, ring at (1739) cm^{-1}, at (1651) cm^{-1} of ν(C=O) of Lactone and lactame. The FTIR spectrum of [C_9], indicated the appearance of vibration of oxazepine respectively, ring at (1739) cm^{-1},at (1701) cm^{-1} of ν (C=O) of Lactone and lactame, and a number of other bands are described in table (2). The characterization of compound [C_{12}] was performed also by ^{1}H-NMR spectra which gave [C_{12}] the following signals δ: (8.9) ppm due to (s, 2H, CH-N), (6.5-7.7)ppm due to (m, 16H, Ar-H), (3.69-4.42)ppm for (t, 4H, $CH_{2methylene}$), (2.97-3.06) ppm due to(t, 4H, CH_2) in oxazepine rings (2.45)ppm due to DMSO.

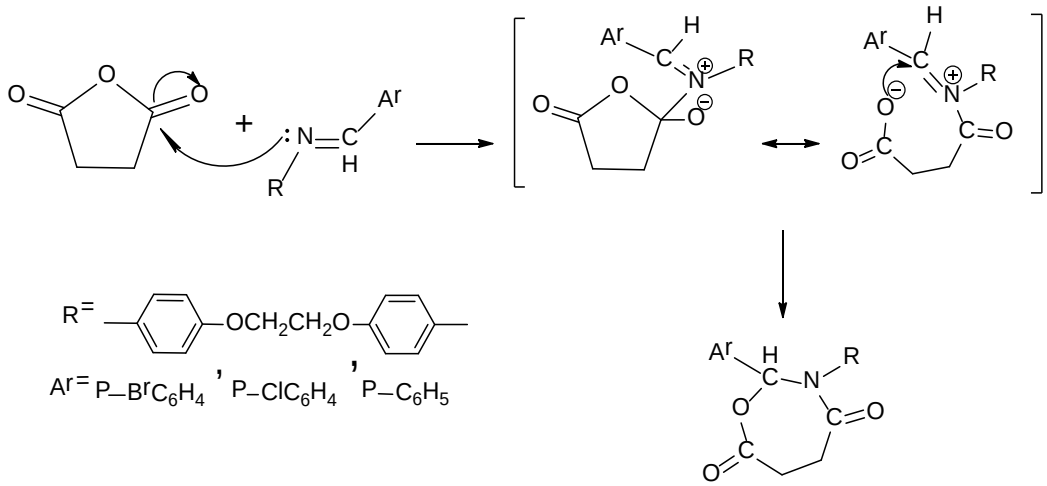
Tetrazole compound[C_{14}-C_{16}] is a result of interaction between Schiff base compound with azide group and it includes an attack by azide group on the azomethin in (1,3) a dipolar cycloaddition, after that there is a lone pair on the (N)atom in the (azomethine group) which in the end leads to the formation of (N-N)bond . The suggested mechanism [27]for the formation of the Tetrazole derivatives is shown in scheme (4). FTIR spectra of tetrazole compounds absorption band at (2137-2048) cm^{-1} which belonged to (N-N=N) group. FTIR spectrum of [C_{14}] showed absorption band at (3232) cm^{-1} that belonged to υ (NH), at(2117,2052) cm^{-1} due to υ (N-N=N). FTIR spectrum of [C_{15}] showed absorption band at(3302) cm^{-1} which is due to υ (NH) , at(821) cm^{-1} absorption band which is due to υ (C-Cl) and υ (N-N=N) 2125,2052, and a number of other bands are described in table



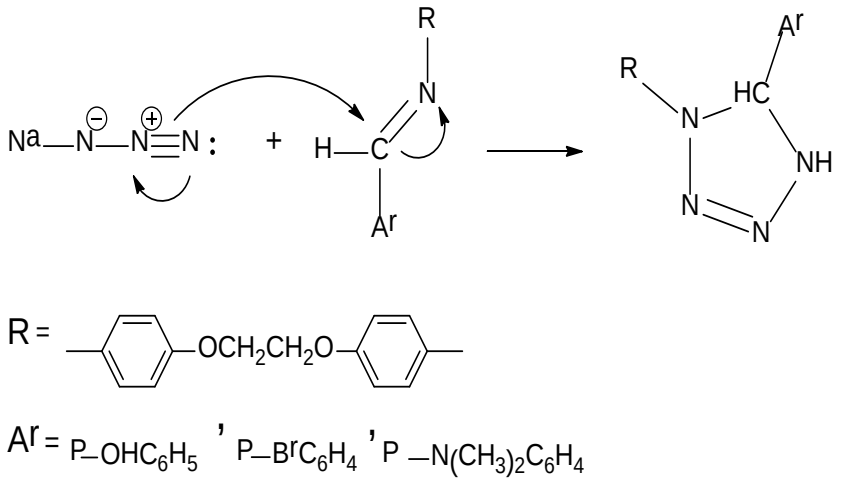
Scheme 1: Path way for Synthesis [C_1-C_{16}] compounds.



Scheme 2: The mechanism steps for the synthesis of Schiff base.

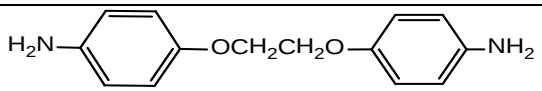
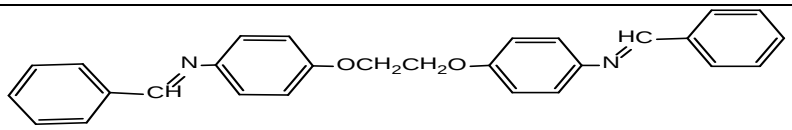
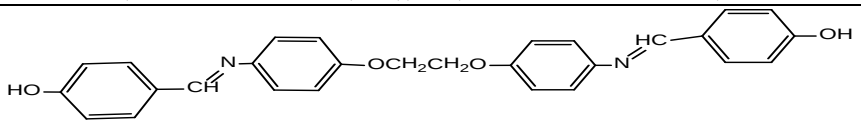
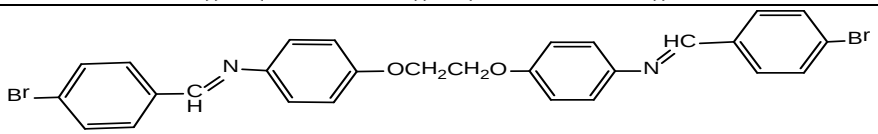
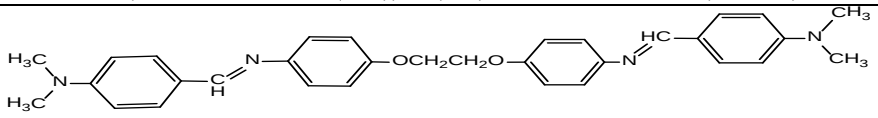
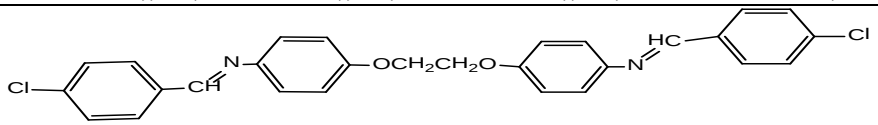
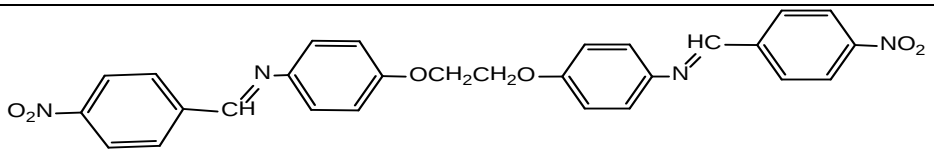
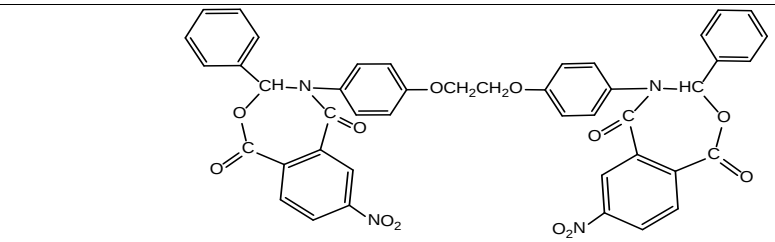
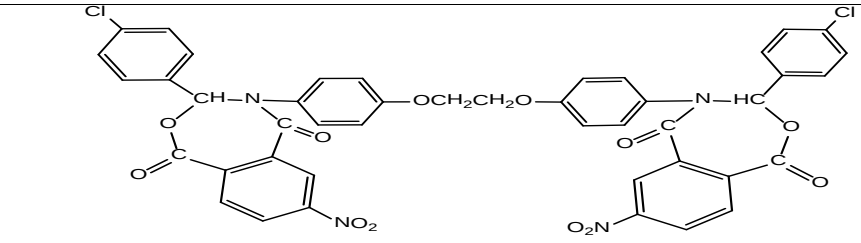


Scheme 3: Mechanism steps of oxazepine derivatives synthesis.



Scheme 4: Mechanism steps of tetrazole derivatives formation.

Table 1: Physical Properties of Synthesized Compounds [C_1-C_{16}]

Comp. No	Structure of compound	Yield %	Color	M.p °C
C_1	 4,4'-(ethane-1,2-diylbis(oxy))dianiline	65	violet	200-202
C_2	 4,4'-(ethane-1,2-diylbis(oxy))bis(*N*-benzylideneaniline)	60	Dark red	184-186
C_3	 4,4'-((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene))diphenol	70	Magenta	150-152
C_4	 4,4'-(ethane-1,2-diylbis(oxy))bis(*N*-(4-bromobenzylidene)aniline)	68	violet	118-120
C_5	 4,4'-((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene))bis(*N*,*N*-dimethylaniline)	50	Dark orange	156-158
C_6	 4,4'-(ethane-1,2-diylbis(oxy))bis(*N*-(4-chlorobenzylidene)aniline)	59	violet	166-168
C_7	 4,4'-(ethane-1,2-diylbis(oxy))bis(*N*-(4-nitrobenzylidene)aniline)	52	Dark yellow	160-162
C_8	 4,4'-((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(7-nitro-3-phenyl-3,4-dihydrobenzo[*e*][1,3]oxazepine-1,5-dione)	80	Red	190-192
C_9	 4,4'-((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(3-(4-chlorophenyl)-7-nitro-3,4-dihydrobenzo[*e*][1,3]oxazepine-1,5-dione)	73	Pale	73

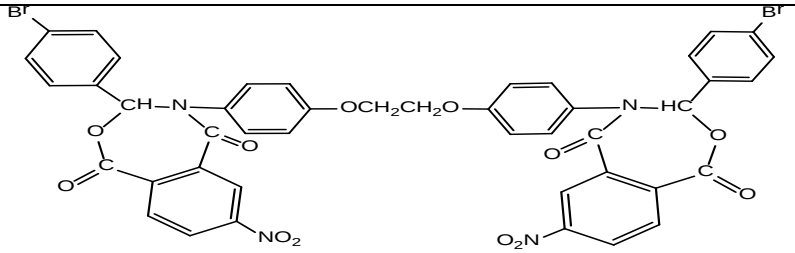
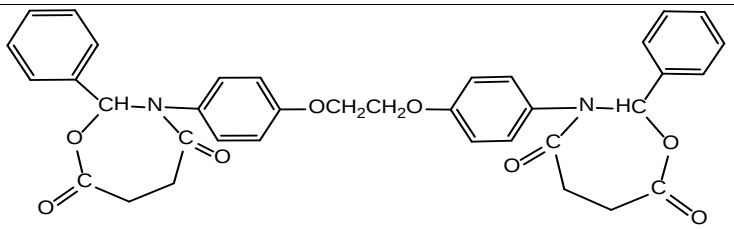
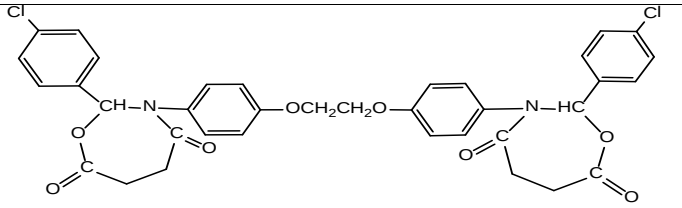
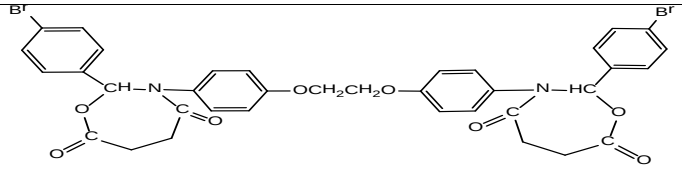
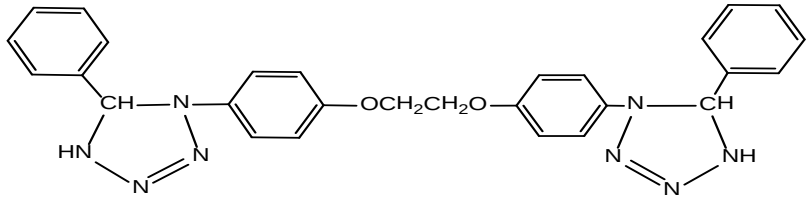
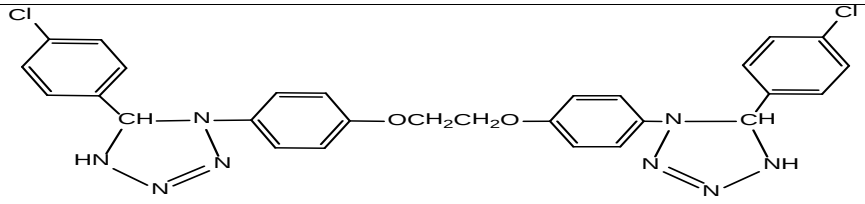
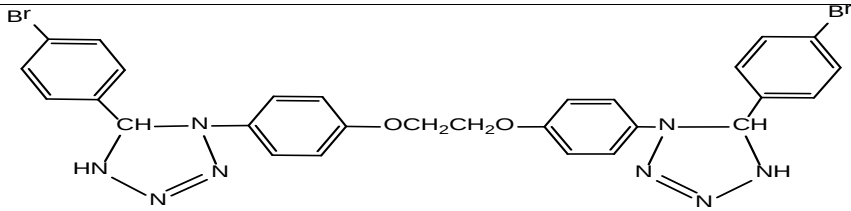
Comp. No	Structure of compound	Yield %	Color	M.p °C
C_{10}	 4,4'-((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(3-(4-bromophenyl)-7-nitro-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione)	81	Pale	81
C_{11}	 3,3'-((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(2-phenyl-1,3-oxazepane-4,7-dione)	62	Dark pink	175-177
C_{12}	 3,3'-((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(2-(4-chlorophenyl)-1,3-oxazepane-4,7-dione)	60	Pale	60
C_{13}	 3,3'-((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(2-(4-bromophenyl)-1,3-oxazepane-4,7-dione)	66	Dark pink	130-132
C_{14}	 1,2-bis(4-(5-phenyl-4,5-dihydro-1*H*-tetrazol-1-yl)phenoxy)ethane	62	Brown	190-192
C_{15}	 1,2-bis(4-(5-(4-chlorophenyl)-4,5-dihydro-1*H*-tetrazol-1-yl)phenoxy)ethane	50	Brown	200-202
C_{16}	 1,2-bis(4-(5-(4-bromophenyl)-4,5-dihydro-1*H*-tetrazol-1-yl)phenoxy)ethane	59	Brown	150-152

Table 2: Spectral Data ofCompounds [C_1-C_{16}]

Comp. NO	*v(NH)*	*v(C-H) aromatic*	*v(C-H) aliphatic*	*v(C=O) lactone*	*v(C=O) lactame,*	*v(C=N)*	*v(C-N)*	*v(C-O-C)*	*Others*
C_1	-	3076	2970, 2885	-	-	-	1350	1234	*v(NH_2):* 3417, 3375 *v(C=C): aromatic* 1512
C_2	-	3084	2976, 2821	-	-	1622	1350	1230	-
C_3	-	3031	2966, 2835	-	-	1666	1315	1288	*v(OH):* 3425
C_4	-	3074	2978, 2885	-	-	1645	1395	1230	*v(C-Br):* 717
C_5	-	3035	2908, 2819	-	-	1662	1369	1234	-
C_6	-	3089	2908, 2819	-	-	1651	1369	1230	*v(C-Cl):* 825
C_7	-	3028	2964, 2891	-	-	1658	1367	1238	v(C-NO_2): 1558
C_8	-	3039	2978, 2831	1708	1624	-	1365	1222	v(C-NO_2): 1558
C_9	-	3029	2978, 2881	1739	1701	-	1396	1226	v(C-NO_2): 1597 *v(C-Cl):* 825
C_{10}	-	3074	2938, 2820	1712	1625	-	1365	1215	v(C-NO_2): 1562 *v(C-Br):* 771
C_{11}	-	3035	2927, 2831	1716	1620	-	1373	1226	-
C_{12}	-	3074	2966, 2819	1716	1624	-	1396	1226	*v(C-Cl):* 829
C_{13}	-	3071	2970, 2820	1724	1635	-	1369	1234	*v(C-Br):* 752
C_{14}	3252	3075	2924, 2854	-	-	-	1373	1283	*v(N=N-N):*2117, 2052
C_{15}	3302	3084	2947, 2843	-	-	-	1392	1230	*v(N=N-N):*2125, 2052 *v(C-Cl):* 821
C_{16}	3291	3071	2947, 2889	-	-	-	1369	1234	*v(N=N-N):*2112, 2048

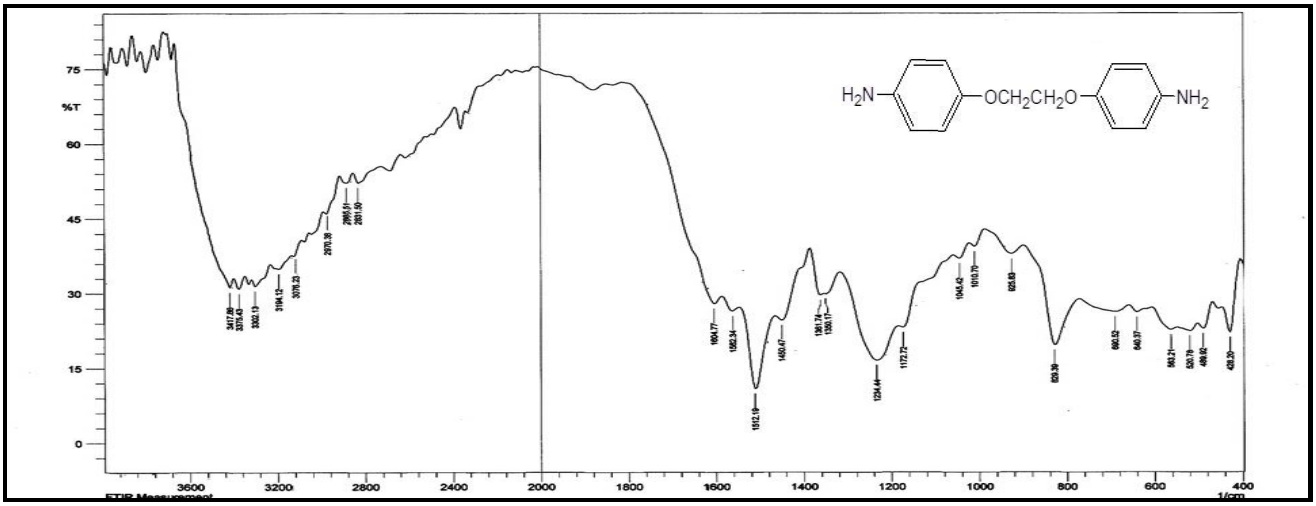


Figure 1:FT-IR Spectrum forCompound[C_1]

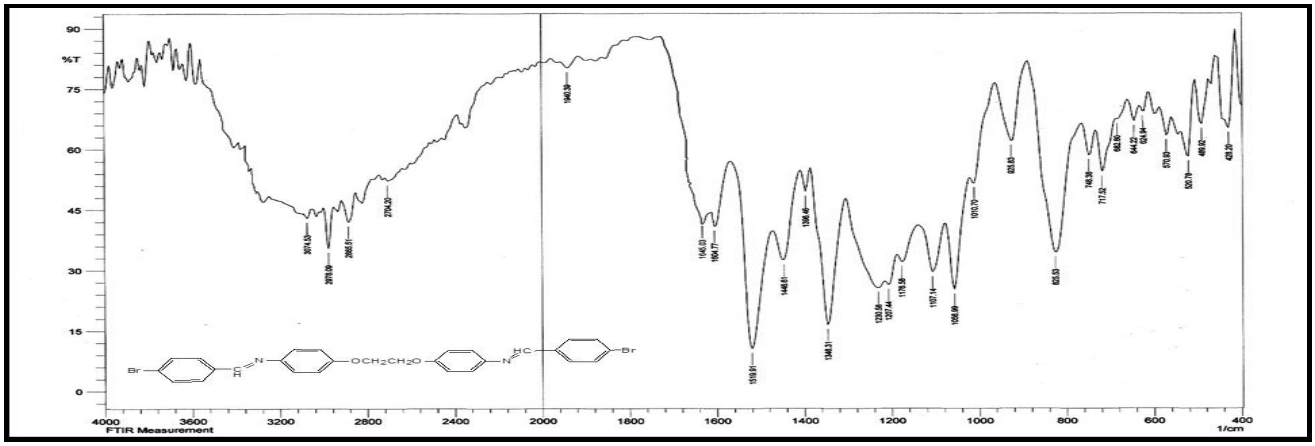


Figure 2:FT-IR Spectrum forCompound[C_4]

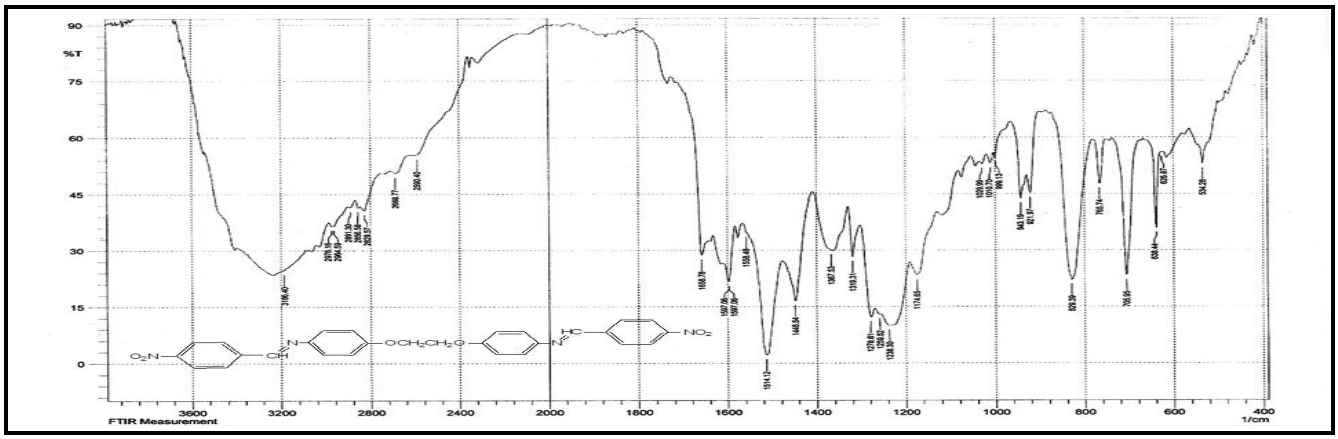


Figure 3:FT-IR Spectrum forCompound[C_7]

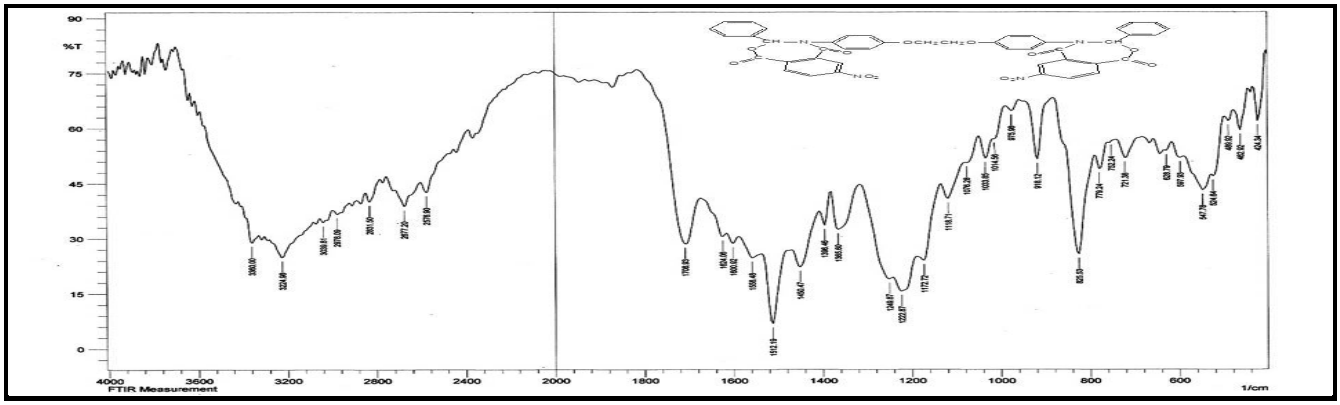


Figure 4:FT-IR Spectrum forCompound[C_8]

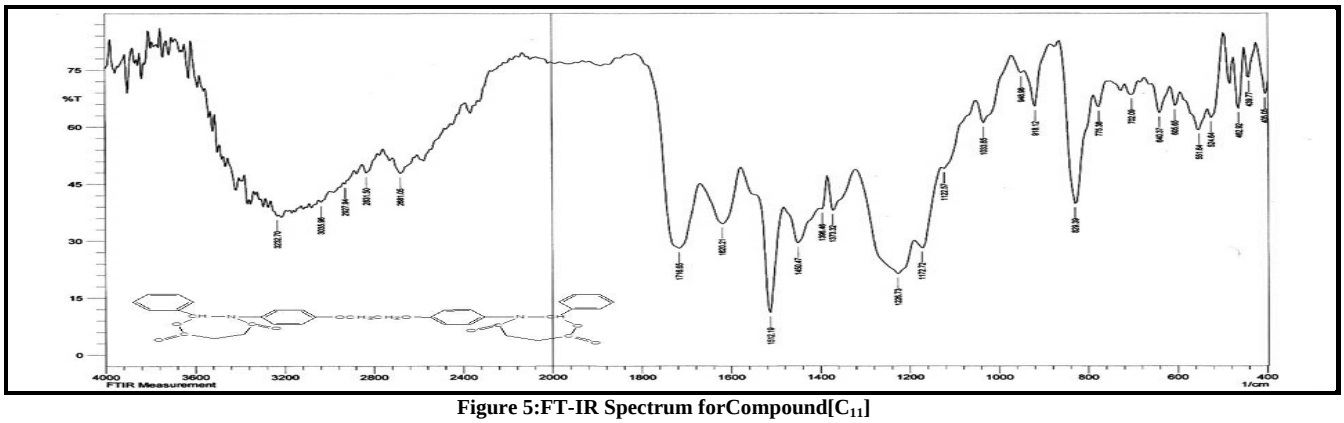


Figure 5:FT-IR Spectrum forCompound[C_{11}]

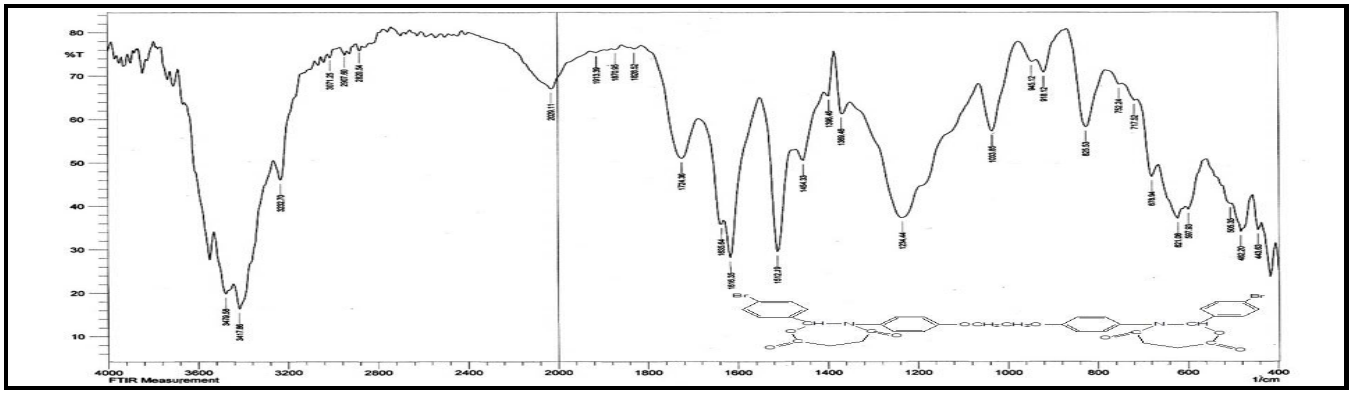


Figure 6:FT-IR Spectrum forCompound[C_{13}]

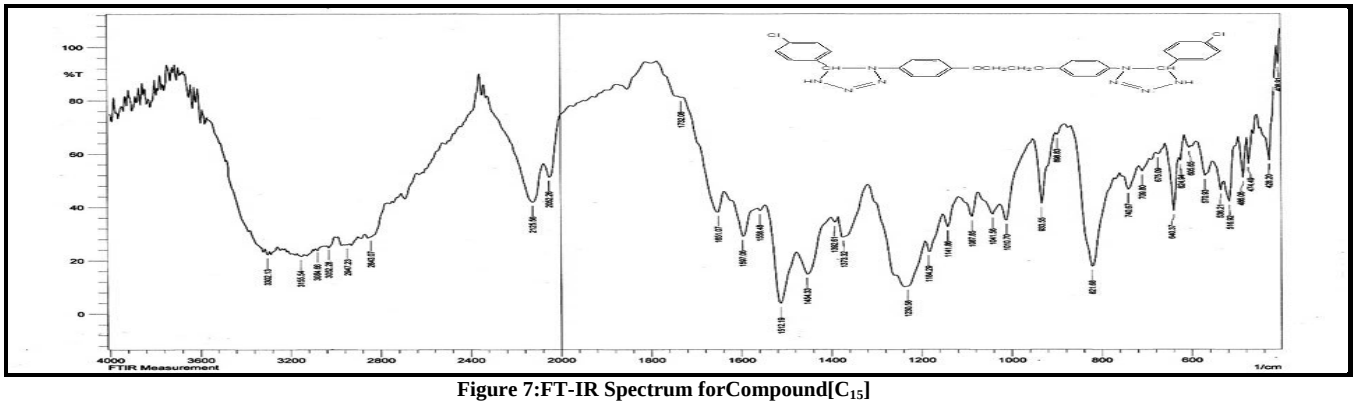


Figure 7:FT-IR Spectrum forCompound[C_{15}]

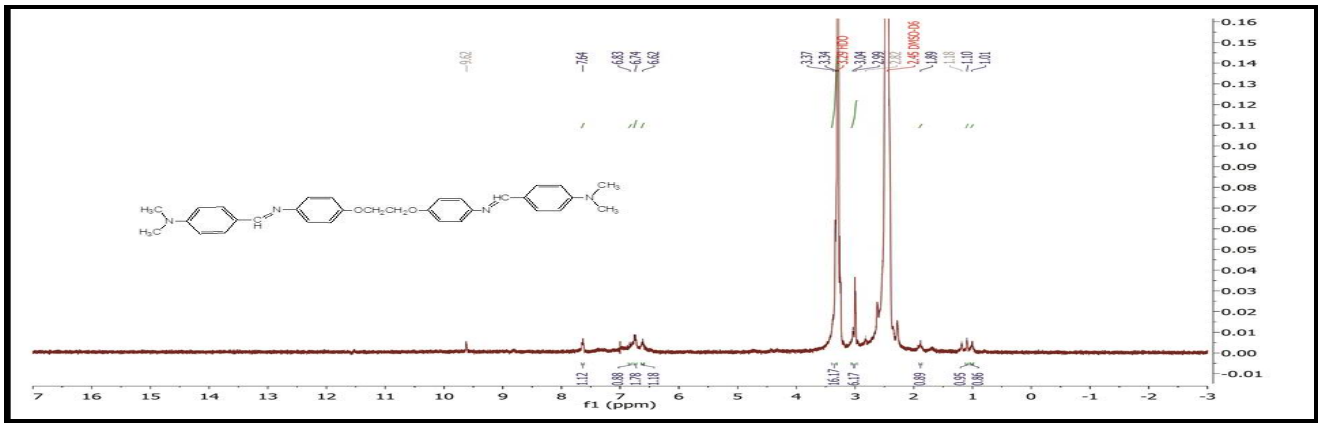


Figure 8:The^{1}H-NMR of Compound [C_5]

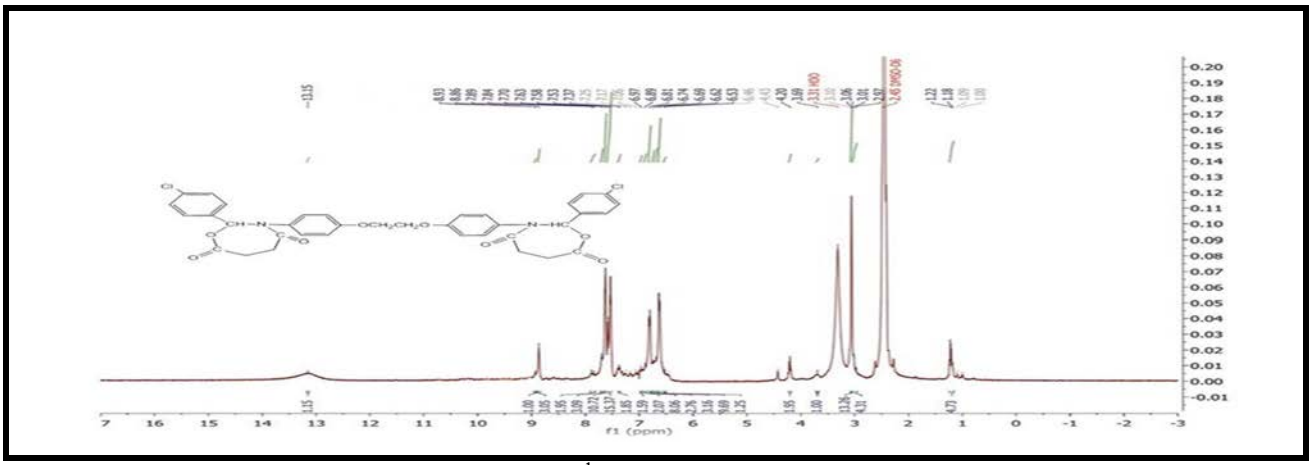


Figure 9:The^{1}H-NMR of Compound [C_{12}]

Biological Part

This study has used two kinds of bacteria which are [Esherichiacoli and Staphylococcus] and one kind of fungi which is Candida albicaus. The selection of these types of bacteria and fungi is because of their importance in the medical field as cause for various different diseases. The method used in the inhibitory effect of chemical compound account on these kinds has been (Ager Diffusion Method).

Table 3: Biological Bacteria

Compound No 1000 ppm	Inhibition zone (MM.)		
	Gram positive	Gram Negative	Fungi
	Staphylococcus aureus	E-coil	Caudidaalbicas
C_6	12	Nil	12
C_{10}	17	18	24
C_{16}	15	10	20

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