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# Synthesis of some new 1,3-oxazepine derivatives and evaluation of antibacterial activity

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## Abstract

This paper contained the synthesis of some new derivatives of 1,2,4-triazole ring from the reactions of 3-amino 1,2,4-triazole derivatives (I) with different substituted benzaldehyde (in absolute ethanol with present glacial acetic acid as catalyst) to prepare Schiff bases (IIa-c). The prepared new Schiff bases (IIa-c) reacted with maleic anhydride or 2-nitro phthalic anhydride in dry benzene to give oxazepines compounds (IIIa-e) (7-membered ring). The synthesized compounds were elucidated by some spectroscopy methods (IR ,UV and Elemental analysis (C.H.N)) besides the TLC was used to check the products. The biological activities of some prepared compounds (IIa, IIIa-e) were also studied against four different kinds of bacteria.

# تحضير بعض المشتقات الجديدة لـ ١،٣- اوكسازبين وتقييم فعاليتها المضادة للبكتريا

**ابتسام خليفة جاسم اسماعيل ياسين مجيد غزوان حسن عبد الوهاب الصميدعي**

## المستخلص

ان هذا البحث يتضمن تحضير بعض المشتقات الجديدة لحلقة ١,٢,٤-الاوكسازبين من تفاعل ٣-امينو-١,٢,٤-ترايازول (I) مع الديهايدات مختلفة التعويض في الايثانول المطلق وبوجود حامض الخليك الثلجي كعامل مساعد، وذلك لتحضير قواعد شيف (IIa-c). تم مفاعلة قواعد شيف الجديدة المحضرة (IIa-c) مع انهيدريد الماليك او انهيدريد ٢-نايتروفثاليك في البنزين الجاف ليعطي مركبات الاوكسازبين (IIIa-e)(سباعية الحلقة). المركبات المحضرة شخصت ببعض الطرق الطيفي (اطياف الأشعة تحت الحمراء و اطياف الأشعة فوق البنفسجية والمرئية و التحليل الدقيق للعناصر)، الى جانب ذلك تم تدقيق النواتج بكروموتوغرافيا الطبقة الرقيقة(TLC). كذلك درست الفعالية البايولوجية لبعض المركبات المحضرة (IIa, IIIa-e) ضد اربعة انواع من البكتريا.

## Introduction

The synthesis of heterocyclic compounds is due to potential biological and industrial applications[1-5], the new derivatives were derived from the Schiff bases, and linked to 1,2,4-triazole. The heterocyclic compounds showed a wide range of pharmacological properties as antibacterial[6], antiviral[7] and anti-inflammatory agent[8], also, heterocyclic compound ply an important role in biochemical process[9] because the side groups of the most typical and essential constituents of living cells are based on aromatic heterocycles. Between them, sulfur and nitrogen containing heterocyclic compounds have maintained the interest of researchers through the development of organic synthesis[10]. Triazole derivatives are antimycotic compounds widely used in both human and veterinary therapy and in culture, Because of their action, these compounds have been successfully used as systemic agricultural fungicides (against mildews and rusts of cereal grains[11], fruits[12], and vegetables[13]) and against both systemic and topical fungal diseases in humans and domestic animals [14]. Oxazepine belongs taking non-homologous structure which has 7-membered that contain 2-non-homologous atoms (oxygen and nitrogen)[15]. A sendin (as example) is an antidepressant with a mild sedative component to its action in animals (omoxazepine) reduced the uptake of noradrenalin and serotonin and blocked the response of dopamine receptors to dopamine [16]. These interesting biological activities attracted our attention to the chemistry of nitrogen heterocycles. Some of the prepared compounds were screened for their in vitro antimicrobial activity against different strains of bacteria.

## Experimental

All chemicals, used were of reagent grade (supplied by either Merck, Fluka or Aldrich) and used as supplied. The melting points were determined by Electrothermal Melting Point Apparatus 9300 in open capillary tubes and are uncorrected. Thin layer chromatography (TLC) was used for monitoring the reaction and to check purity. The FTIR spectra in the range (4000-200)$cm^{-1}$ were recorded as KBr disc on FTIR 8300 Shimadzu spectrophotometer. The UV-Visible spectra were measured in ethanol using Shimadzu UV-Vis, 160A-Ultra-violet spectrophotometer in the range (200-1000)nm. Elemental analysis (C.H.N) was preformed micro analytical uniton corlo Erba model (1106).

### Preparation of Schiff base compounds (II)[17]

**General procedure:**

A mixture of compound (I)(0.05 mole), appropriate aromatic aldehydes (0.05 mole)and glacial acetic acid (2 ml) in absolute ethanol (20 ml) was refluxed for 3 hrs. After cooling the mixture was filtered and the solid recrystallized from appropriate solvent. The some physical properties are listed in Table (1).

### Preparation of 4[3-imino-1,2,4-triazole]-sub. aryl 2,3-dihydro-1,3-oxazepine 4,7-dione (IIIa-e)[18].

A mixture of (0.03 mole) Schiff base with (0.03 mole) maleic anhydride or 2-nitro phthalic anhydride dissolved in (20 ml) dry benzene and the mixture was refluxed for 3 hrs in water bath, The precipitate was filtered and crystallized from dioxane or chloroform. The end of reaction checked by TLC. The some physical properties are listed in Table (2).

**Table (1): Physical properties of compounds (IIa-c)**

| Comp. No. | M.P. °C | Yield % | Molecular formula | Molecular weight | Recrys. solvent | cal/found | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| IIa | 250 | 98 | $C_{11}H_{12}N_4O_2$ | 232 | Ethanol | 56.89<br>56.00 | 5.17<br>5.00 | 24.13<br>24.01 |
| IIb | 150 | 90 | $C_{11}H_{11}N_5O_4$ | 277 | Ethanol | 47.65<br>47.05 | 3.97<br>3.00 | 25.27<br>24.99 |
| IIc | 200 | 80 | $C_{17}H_{12}N_4$ | 272 | Dioxane | 75.00<br>75.00 | 4.41<br>4.00 | 20.58<br>20.01 |

**Table (2): Physical properties of compounds (IIIa-e)**

| Comp. No. | M.P.°C | Yield % | Molecular formula | Molecular weight | Recrys. solvent | cal/found | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| IIIa | 180 | 75 | $C_{19}H_{16}N_4O_5$ | 380 | Dioxane | 60.00<br>59.80 | 4.21<br>4.00 | 14.73<br>14.00 |
| IIIb | > 250 | 10 | $C_{19}H_{14}N_5O_7$ | 424 | Dioxane | 53.77<br>53.00 | 3.30<br>3.00 | 16.50<br>15.80 |
| IIIc | 200 | 65 | $C_{15}H_{13}N_5O_7$ | 375 | Dioxane | 48.00<br>48.00 | 3.46<br>3.01 | 25.45<br>25.00 |
| IIId | 250 | 70 | $C_{25}H_{15}N_5O_5$ | 465 | Chloroform | 64.51<br>64.01 | 3.22<br>3.00 | 15.05<br>14.89 |
| IIIe | 200 | 80 | $C_{21}H_{14}N_4O_3$ | 370 | Chloroform | 68.10<br>67.90 | 3.78<br>3.00 | 15.13<br>15.00 |

**Table (3):Infra-red and Uv./Vis. spectral data for compounds (IIa-c).**

| Comp. No. | UV,λmax (nm),DMSO | ν N-H | vas. $CH_2$ vs. $CH_2$ | ν =C-H Ar. | ν C=C Ar. | ν C=N | C-N | N-N | Others |
|---|---|---|---|---|---|---|---|---|---|
| IIa | 260 | 3360 | 2940<br>2890 | 3106 | 1590,1481 | 1650 | 1394 | 1110 | --- |
| IIb | 269 | 3400 | 2900<br>2870 | 3097 | 1600,1477 | 1640 | 1390 | 1150 | $NO_2$<br>1550,1350 |
| IIc | 275,372 | 3450 | 2960<br>2840 | 3100 | 1600,1492 | 1610 | 1400 | 1170 | ν C-O-C<br>1245,1030 |

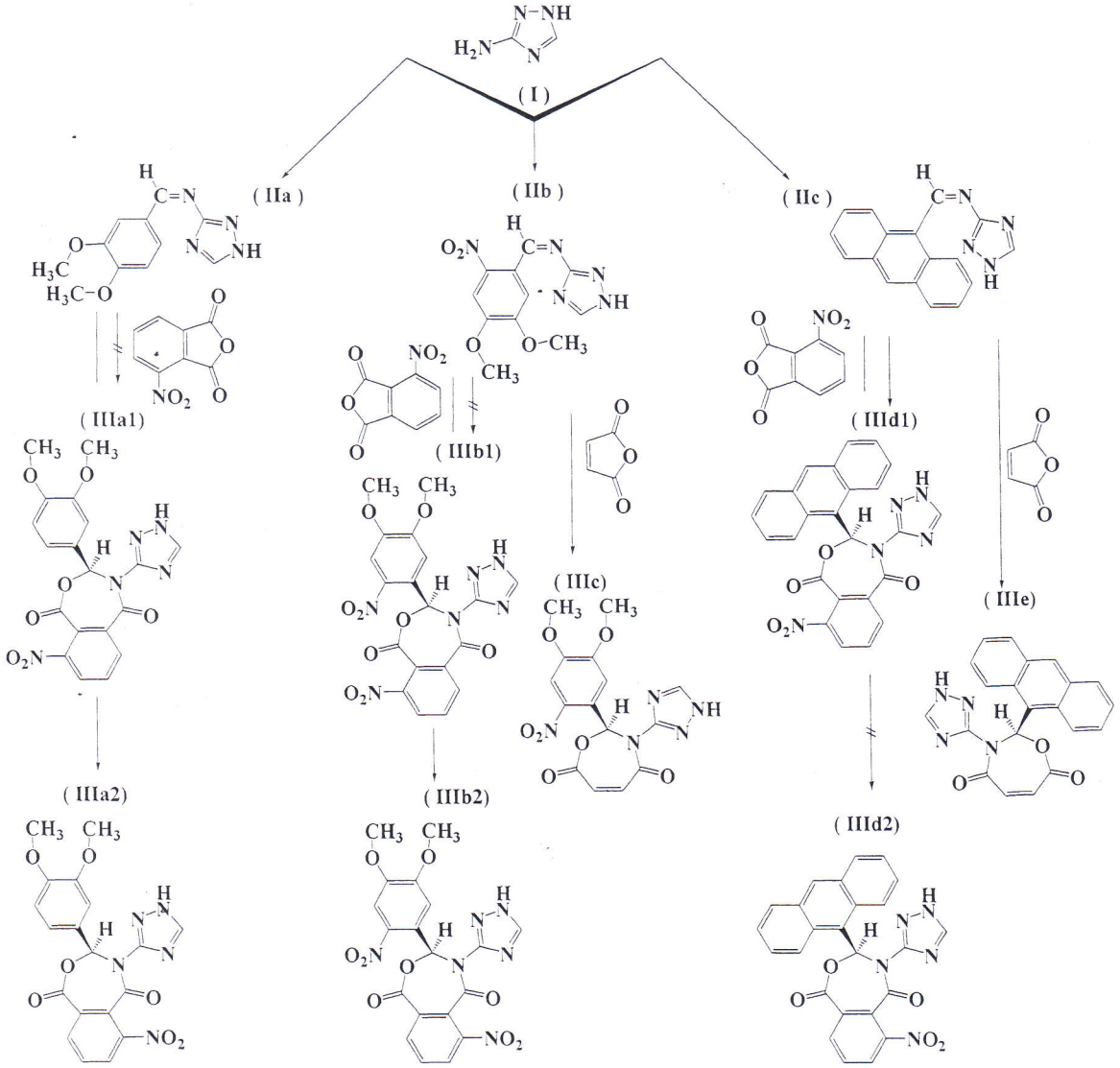
**Table (4):Infra-red and Uv./Vis. spectral data for compounds (IIIa-e).**

| Comp. No. | UV,λmax (nm),DMSO | ν =C-H Olef. | ν C=O | ν C=C Olef. | ν O=C-O and C-O | Heat of Formation (KJ) | |
|---|---|---|---|---|---|---|---|
| | | | | | | (1) | (2) |
| IIIa | 221 | 3014 | 1742 | 1605 | 1000 | 35.367 | 31.330 |
| IIIb | 250 | 3025 | 1750 | 1607 | 1105 | 84.758 | 62.398 |
| IIIc | 295 | 3040 | 1710 | 1606 | 1204 | ---- | ---- |
| IIId | 274,304 | 3051 | 1700 | 1610 | 1300 | 565.560 | 567.219 |
| IIIe | 245,336 | 3010 | 1745 | 1606 | 1250 | ---- | ---- |

**Table (5): Biological activity for compounds (IIIa-e).**

| Comp. No. | *Staph. aureus* | *E. coli* | *Sal. typhi* | *Ps. aeruginosa* |
|---|---|---|---|---|
| IIa | - | + | ± | - |
| IIIa | ± | - | ± | + |
| IIIb | ± | - | ± | - |
| IIIc | ++ | - | - | ± |
| IIId | - | ± | ± | ± |
| IIIe | + | - | + | ± |
| Ethanol | - | - | - | - |

**Key the symbols:** (-) = no inhibition, (±)= 6-9mm, (+)= 10-14mm, (++) = 15-22mm.




**Schem( I )**

## The biological activity

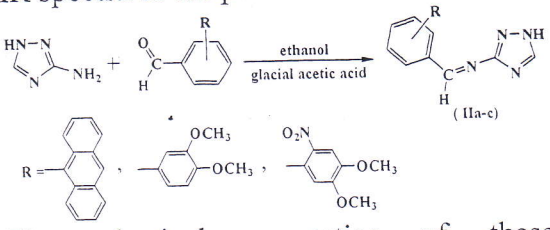
The bacteria species used are listed in Table (5). All strains were obtained from College of Medicine, Tikrit University. They were grown up to the stationary phase nutrient bath at 37 °C and a sample of 0.5 ml of each bacteria was spread over a surface of a nutrient agar plate[19].

## Antibacterial assay

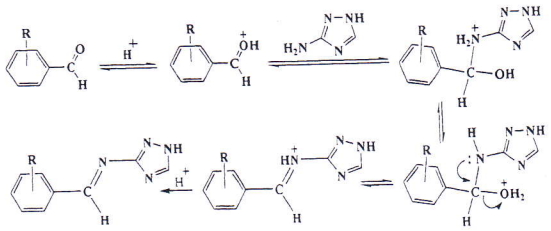
Disc of filter paper (6 mm diameter) were sterilized at 140 °C for 1 hr and impregnated with the germs, absolute ethanol was used as a solvent for compounds (IIIa-e). The same solvent was used for antibiotics, blank paper discs of absolute ethanol was used as control. The inoculated plates were incubated at 37 °C for 24 hrs, and the inhibition zones (mm) were measured [20]. In all experiments, the mean of each triplicate was measured.

## Results and Discussion

The Schiff bases compounds (IIa-c) were synthesized from 3-amino-1,2,4-triazole with different substituted benzaldehydes. The reaction was followed of disappearance of C=O absorption band of aldehyde and of $NH_2$ at 3500 $cm^{-1}$ and appearance of C=N absorption band in the IR spectra of the products.




The physical properties of these compounds are given in Table(1). The structures of these Schiff bases were identified from their mps, and IR spectra, see Table (3). The IR spectra showed the following absorption bands and the corresponding functional group [21]. Although the mechanism of this condensation is known and is acid catalyzed , it may be outlined as follows:



**Synthesis of 4-[3-imino-1,2,4-triazole]-sub. aryl-2,3,didihydro 1,3-oxazepine-4,7-dione**

The reaction of Schiff bases with maleic anhydride is a sort of cycloaddition reaction. Cycloaddition is a ring formation that results from the addition of π bonds to either δ-π bonds with formation of now δ bonds. This class of reaction and its reverse encompasses a large number of individual types. Huisgen[22] is has formulated a useful classification of diverse cycloadditions in terms of the new δ bonds, the ring size of the product , and the number of atoms in the components taking part in the cycloaddition . this cycloaddition is classified as 5+2→7, implying a 5-atom component plus 2-atom component leading to 7-membered heterocyclic ring, but the mechanism involves addition of one δ bond $CH_3COO$ to one π bond (C=N) to give 4- membered cyclic transition state which opens into maleic anhydride (5- membered cyclic ring)to give 7-membered cycling ring. The reaction actually involves interaction between the HOMO orbital of maleic anhydride with LUMO orbital of (C=N), since the oxygen has higher electro negativity than nitrogen, the energy gab between its LUMO orbital and the HOMO orbital of maleic anhydride is larger than it is between the LUMO orbital of azomethine and the HOMO orbital of maleic anhydride. Energetically, the interaction between the HOMO orbital of maleic anhydride and the LUMO orbital of azomethine is more favorable . This is dependent on the heat of formation of low conformational energy of some prepared compounds (the products of cyclization of 2-nitrophthalic anhydride

asymmetrical structure). The favorable probabilities of (IIIa2, IIIb2, IIId1) more than the probabilities of (IIIa1, IIIb1, IIId2) as indicated in Table (4), Fig. (1-6) Incidentally, even in the absence of (C=N) no interaction between the HOMO orbital of maleic anhydride and the LUMO orbital of (C=C) is observed for the same reason. It is obvious that the two absorption bands at (1740-1780) $cm^{-1}$ and at (1800-1850) $cm^{-1}$ in the IR spectrum of pure maleic anhydride [19] have disappeared when the anhydride became part of the 7-membered heterocyclic ring.The (C=O) group of the title compounds absorbs at (1700-1750) $cm^{-1}$ (oxazepine) and (C-O), (O=C-O) at (1000-1300)$cm^{-1}$. This confirms the assigned 7-membered heterocyclic ring structure. The U.V spectra gave absorption band at different wave lengths for the resulted Schiff bases and oxazepine (in % 95 EtOH), due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition and all these transition are listed in Table (3,4).

**Colors of steric conform ation**

| Atoms | C | O | N | H |
|---|---|---|---|---|
| Color | Black | Red | Blue | Gray |

**Fig. (1): IIIa1**

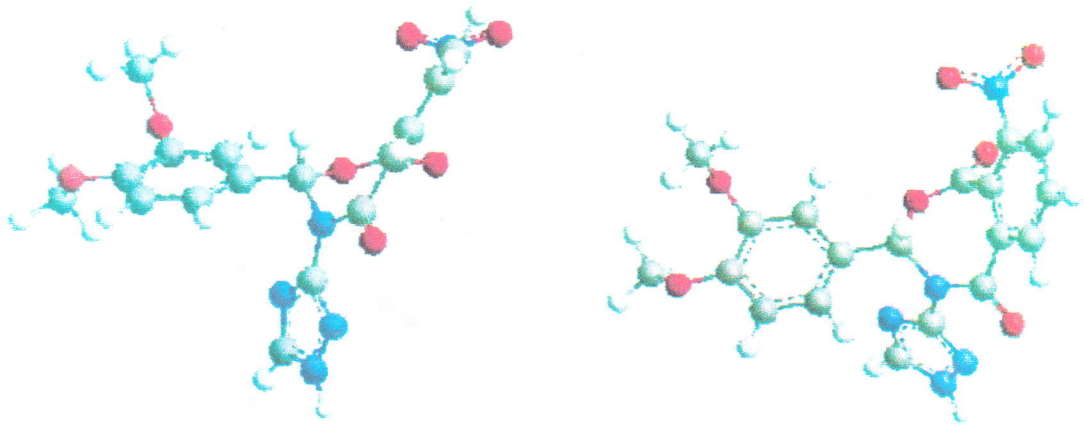


**Fig. (2): IIIa2**

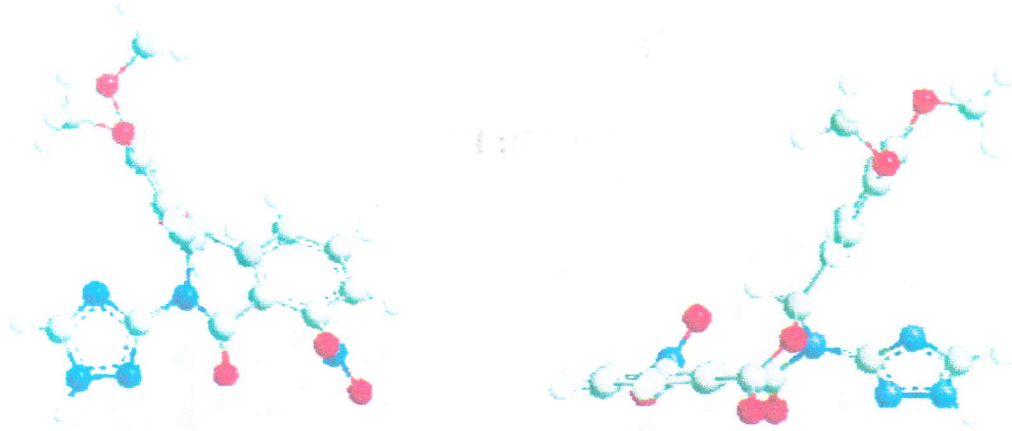


**Fig. (3): IIIb1**

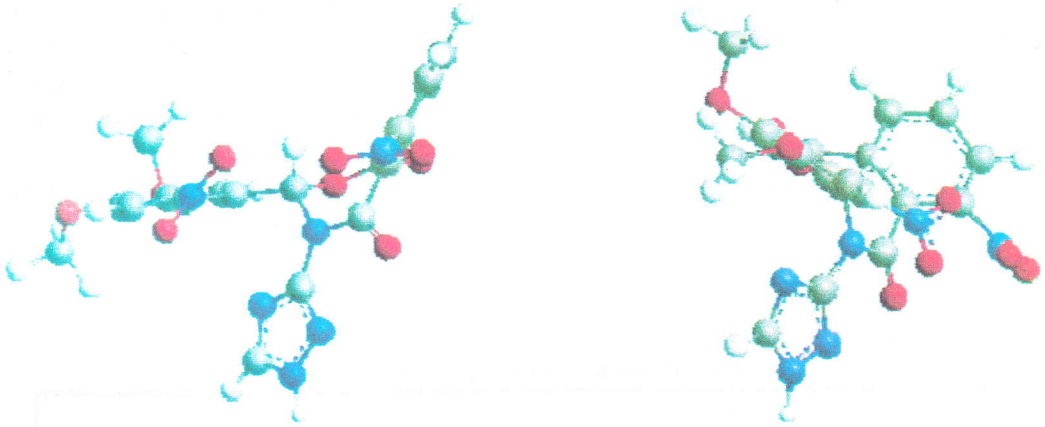


**Fig. (4): IIIb2**

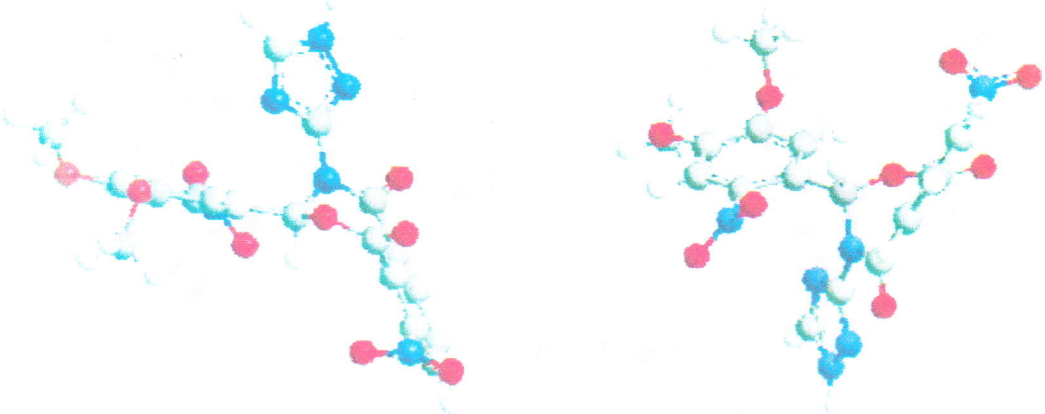


**Fig. (5): IIId1**

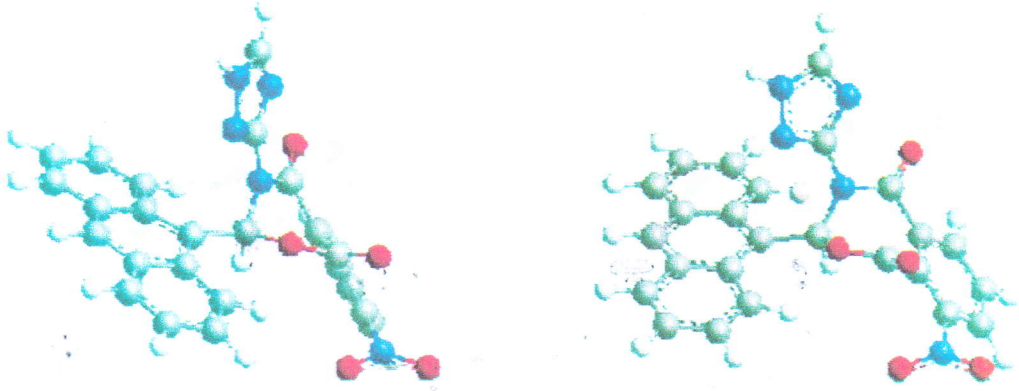
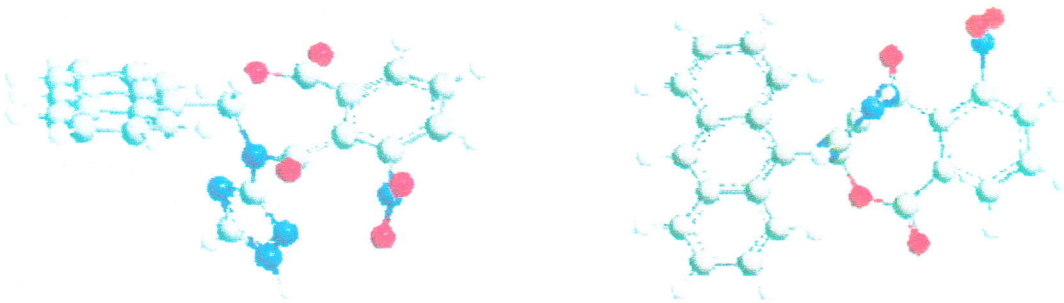


**Fig. (6): IIId2**



## Antimicrobial activity

The antimicrobial activity was tested using the cup-plate agar different method by measuring the zone of inhibition in mm [23]. All the compounds were screened in vitro for their antimicrobial activity against a variety of bacterial strains, such as *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi* and *Pseudomonas aeruginosa*. The diameter zone of inhibition was measured in mm and are represented by (+),(++) and (±) depending upon the diameter. The antimicrobial screening data are recorded in Table (5). Looking at the structure activity relation ship, compound (IIIc) exhibit significant activity against *Staphylococcus aureus* , compound (IIIe) showed good activity against *Staphylococcus aureus*, and *Salmonella typhi* .The preliminary screening results reveral that the compounds containing ($NO_2$) exhibit the highest antibacterial activity while the other compounds showed either low or no activity.

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