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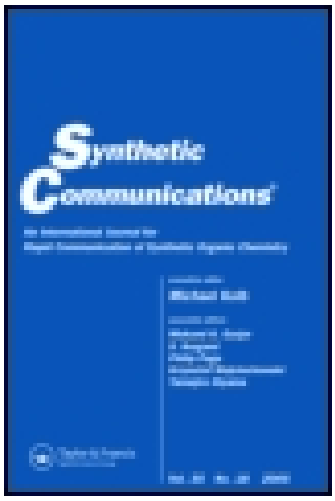

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# Synthesis, Structural Stability Calculation and Antibacterial Evaluation of Novel 3,5-Diphenylcyclohex-2-en-1-one Derivatives

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# SYNTHESIS, STRUCTURAL STABILITY CALCULATION AND ANTIBACTERIAL EVALUATION OF NOVEL 3,5- DIPHENYLCYCLOHEX-2-EN-1-ONE DERIVATIVES

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## Abstract

Starting with 3,5-diphenylcyclohex-2-en-1-one, 3,5-diphenylcyclohex-2-en-1-semicarbazone; 1-chloro-3,5-diphenylcyclohex-2-en-2-carbaldehyde and 3,5-diphenylcyclohex-2-en-1-hydrazone were synthesized via the reactions with semicarbazide hydrochloride; $POCl_3$ / DMF and hydrazine hydrate, respectively. These products were used as key intermediates for the preparation of novel series of tetrahydrobenzothiadiazol-1-oxide, indazole, benzo- thiazepines, pentahydroxyhexylidene and N-thiazines. Some of these derivatives exhibit highly antibacterial activity against gram positive bacteria.

**KEYWORDS:** diphenylcyclohexenone, tetrahydrobenzothiazepine, thiazolidinone, indazole, pentahydroxyhexylidene, antibacterial.

## INTRODUCTION

Cyclohexenones are efficient synthons in building spiranic compounds[1] or intermediates in the synthesis of fused heterocyclic derivatives. Ethyl-3,5-diarylcyclohexenone-6-carboxylate has been used as an effective synthon in some projected synthesis of spiro cyclo- hexanones[7]and carbazol derivatives[8]. Allylic oxidation of olefins to α, β-

unsaturated ketones, particularly cyclohexene to cyclohexenone, is an important and useful transformation in both chemical and pharmaceutical industries[2-6], since α,β-unsaturated ketones were used as herbicides and employed in the construction of a wide variety of biologically and medicinally important products. From this point of view and extending our previous work on the preparation of azolo compounds[9- 14] we tackled this work to fuse cyclohexenone moiety with well-known pharmacophoric moieties of potential anti-microbal activities such as thiadiazole[15], pyrazole, isoxazole[16], thiazepine or carbazole rings[17]and evaluate the anti-bacterial activity of some of these derivatives.

## RESULTS AND DISCUSSION

The parent compound 3,5-diphenylcyclohex-2-en-1-one **(1)** can be prepared according to the literature in fairly good yield by decarboxylation of 6-carbethoxy-3,5-diphenyl-cyclohex-2-en-1-one under either acidic or basic conditions[18,19] and has been used as an effective synthon by Padmavathi *et al*. for the synthesis of a range of heterocyclic derivatives[16.]

In this study, compound **1** was reacted with semicarbazide hydrochloride/sodium acetate in refluxing ethanol to give 3,5-diphenylcyclohex-2-en-1-semicarbazone **(2)** (Scheme 1). Its IR spectrum showed new signals at 3555, 3458 and 3200 $cm^{-1}$ attributing to $NH_2$ and NH groups. Its Mass spectrum analysis showed the molecular ion peak at m/z = 305($M^+$) of the molecular formula $C_{19}H_{19}ON_3$.

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Regarding to the reactivity of the methylene and the semicarbazone groups of compound **2**, its treatment with thionylchloride in $CH_2Cl_2$ or phosphursoxy chloride in DMF [20] (Vilsmeier- reagent) afforded 5,7-diphenyl-2,6,7,7a-tetrahydrobenzo [*d*][1,2,3] thiadiazol-1-oxide **(3)** and 3-carbaldehyde-4,6-diphenyl-2,3,3a,4,5,7a-hexahydro-2*H*-indazole **(4)**, respectively (Scheme 1). IR spectra of compounds **3** and **4** pointed to the absence of the bands corresponding to the amino ($NH_2$) group, while showed the presence of new bands at 3462 and 1019 $cm^{-1}$ assigned to NH and S=O groups in compound **3** and at 3454, 3403, 1682 $cm^{-1}$ assigned to 2NH and C=O groups in compound **4**. Mass spectral analysis revealed the molecular ion peaks of compounds **3** and **4** at m/z = 308.3($M^+$) and m/z = 304($M^+$), corresponding to the molecular weight of the molecular formula $C_{18}H_{16}N_2OS$ and $C_{20}H_{20}N_2O$ respectively. Spectral analyses of these compounds were consistent with the proposed structures.

The relative stability of tautomeric structures of compound **4** and its relation with compound **1** have been conducted through using **3D modeling** procedure. The structures were fully optimized using Gaussian03 package with density functional theory (DFT) method, at B3LYP level of approximation. Calculations were carried out with 6-311G (d, p) basis set[21, 22].

The investigation of the electronic structure at highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) positions shows the location of the active site. The difference between the energy of HOMO and LUMO positions was calculated to give the energy gap of compound **1** compared with the energy gap of each

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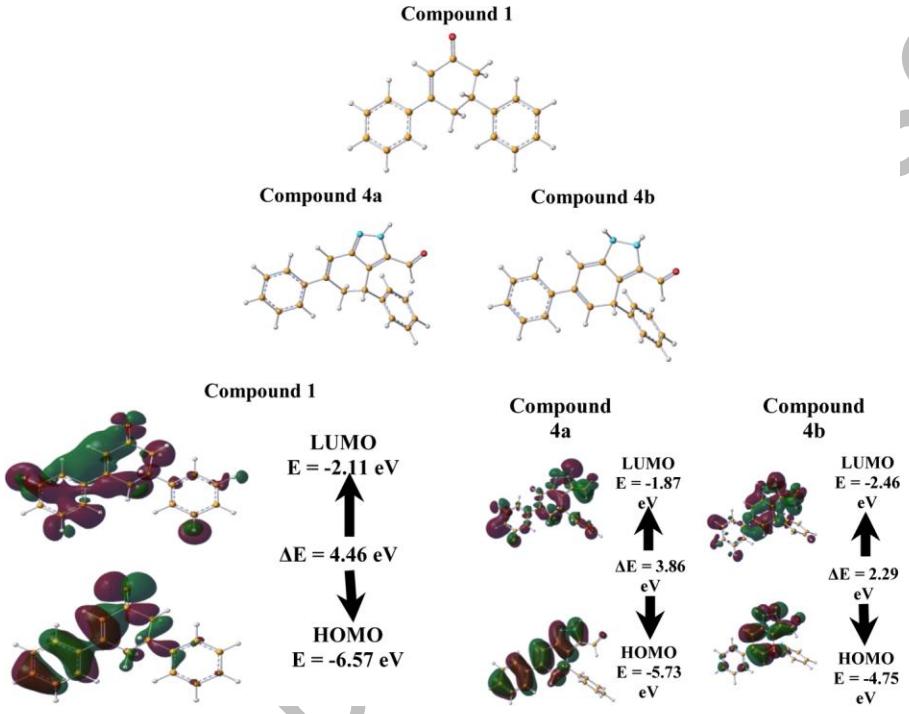
tautomeric structures of compound **4**. This confirmed that the compound **4** is more stable than compound **1** and tautomer **4a** is more stable than $\mathbf{4_b}$ by -38.65 kcal / mol ( Table 1) ensuring the existing of the reaction with the stable product of low energy. Another evidence of its stability appears from larger chemical hardness **η** in addition to its high energy gap ***ΔE*** (Table 2). So, the spectral analyses are constituent with the theoretical analyses[23].




The presence of the active methylene group (O=C-$CH_2$) in compound **1** leads to its condensation reaction with thiourea / $I_2$ in refluxing isopropanol to form 5,7-Diphenyl-6,7-dihydro-2(3*H*)-imino-1,3-benzo[*d*]thiazole **(5)** in a good yield (Scheme 2). IR spectrum revealed disappearance of the C=O group and the appearance of two bands at 3383 and 3297$cm^{-1}$ for 2NH groups. Its mass spectrum showed a molecular ion peak at m/z = 303($M^+$-1) corresponding to the molecular weight minus one of the molecular formula $C_{19}H_{16}N_2S$.

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2-Chloro-4,6-diphenylcyclohex-2,4-diene-1-carbaldehyde **(6)** was prepared in a good yield (60 %) under Vilsmeier condition through the reaction of compound **1** with $POCl_3$ in boiling DMF (Scheme 2). The structure of compound **6** was confirmed on the bases of their spectral data. The IR spectrum of compound **6** showed the presence of new bands at 1743 and 757$cm^{-1}$,indicating the presence of C=O and C-Cl groups respectively.

Compound **6** was used as an intermediate for the preparation of a new series of polyfused heterocyclic derivatives. In this work the reactivity of the Cl and CHO groups in compound **6** toward the condensation reactions with the bidentates was investigated. Thus when 2-chloro-cyclohexadiene-1-carbaldehyde derivative **6** was treated with hydrazine hydrate, ethylene diamine and /or cystamine hydrochloride, it formed the corresponding fused heterocyclic compounds, namely 4,6- diphenyl- 4,5-dihydro-1*H*-indazole (**7**), 6,8-diphenyl-2,3,4,6-tetra- hydro-1*H*-benzo[1,4-e] diazepine (**8**) and 6,8-diphenyl-2,3,4,6-tetrahydro-1*H*-benzo[1,4- f] thiazepine (**9**) (sheme 2). These reactions took place via the initial nucleophilic displacement of the chloride ion with the amino group in hydrazine hydrate and ethylene diamine molecules or with SH group in cystamine hydrochloride molecule. The formed intermediates in situ were cyclized by the condensation reaction of the reset amino group with the aldehyde group. IR spectral data of compounds **7- 9** showed that there were no bands at 1743 and 757 $cm^{-1}$ for C=O and C-Cl groups.

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Finally, compound **6** was allowed to react with ethyl mercaptoacetate upon boiling in ethanolic sod.ethoxide solution to afford 4,6-diphenyl-5,6-dihydrobenzo[*b*]thiophene derivative (**10**) through the nucleophilic displacement of the chloride ion with the SH group as in the previous mechanism. The formed intermediate underwent intramolecular cyclization reaction via the condensation reaction of the active methylene group with aldehyde group (Scheme 2). Spectral analyses of these compounds as in the experimental section confirmed the suggested structures.

3,5-Diphenylcyclohex-2-en-1-hydrazone **(11)** was formed according the literature[24] through the condensation reaction of compound **1** with hydrazine hydrate. The formed hydrazone derivative was used as a key intermediate for the preparation of 2*E*-(3,5-diphenylcyclohex-2-en-1-ylidene)hydrazene-*N*'[(2*R*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl- idene **(12)** and (3,5-diphenylcyclohex-2-en-1-ylidene)hydrazene-*N'*-(4-nitrobenzylidene) **(13)** *via* its condensation reaction with both of the *D(+)* glucose in boiling DMF or 4-nitro- benzaldehyde in refluxing glacial acetic acid with the elimination of water molecules (Scheme 4). The structures of compounds **12** and **13** were verified by spectroscopic data. For example, the IR spectra of these products revealed the lack of the amino group ($NH_2$) and the appearance of characteristic bands at 3433, 1637 $cm^{-1}$ pointed to OH, N-H, C=N groups of compound **12**, and at 1518, 1339 $cm^{-1}$ attributed to $NO_2$ group of compound **13**. These results revealed that the hydrazone derivative **11** reacted with –CHO group of both of *D(+)*glucose and 4-nitrobenzaldehyde molecules.

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Compound **13** was reacted with thioglycolic acid in boiling dry benzene to afford 3-(3, 5-diphenylcyclohexa-1,5-dienylamino)-2-(4-nitrophenyl)-1,3-thiazolidin-4-one **(14)** through the nucleophilic addition reaction of thioglycolic acid at the (Ar-CH=N-) group of compound **13**. The formed intermediate spontaneously was cyclized *via* the elimination of water molecule where the structure of the product was supported by spectroscopic data (Scheme 3).

On the other hand, the nucleophilic addition reaction of 3,5-diphenylcyclohex-2-en-1-hydrazone **(11)** at phenylisothiocyanate took place in a new experimental method in refluxing dioxane furnished the functionalized thiosemicarbazied derivative[24] **15** which in turn used for the preparation of *N*- thiazole and N-thiazine derivatives **16, 17** *via* the cyclization reaction with chloroacetyl chloride or malonyldichloride in refluxing DMF and triethylamine (Scheme 4). IR spectrum of compound **16** showed two new bands at 3359 and 3155 $cm^{-1}$ resulting from the presence of the hydroxyl (OH) and imino (NH) groups. Also, $^{1}$H-NMR data displayed singlet signals at δ 4.23 and 8.95 ppm for CH- and OH groups of N-thiazole ring point to the formation of the totumer forms $-COCH_2 \leftrightarrow HOC=CH$, whereas IR spectrum of compound **17** showed the new bands at 3407 and 1733 $cm^{-1}$ ascertaining the presence of OH and C=O groups.

Alkylation reaction of compound **11** with ethyl bromoacetate in boiling dioxane and triethyl amine afforded ethyl 2-[2-(3,5-diphenylcyclohex-2-en-1-ylidene)hydrazinoacetate **(18)** in a moderate yield. The suggested mechanism path way as shown in Scheme 5 took place via the hydrolysis of some hydrazone molecules with HBr

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resulted from the reaction of the formed $(Et)_3N^{+}\cdot HBr^{-}$ with water forming hydrazine molecules.Then, hydrazine molecules reduced C=N group in the synthesized hydrazoacetoacetate derivative to afford compound **18**. The later could be easily converted to 2-[2-(3,5-diphenylcyclohex-2-en-1-ylidene)hydrazino] acetohydrazide(**19**) upon boiling in ethanolic solution of hydrazine hydrate (Scheme 4). The chemical structures of compounds **18** and **19** were established on the basis of their spectral data. The reaction of hydrazied derivative **19** with acetylacetone in refluxing ethanolic solution furnished the functionalized pyrazole derivative **20** (Scheme 5). The spectral analyses of the latter product pointed to the formation of the suggested structure.

## EXPERIMENTAL

All melting points are uncorrected and were determined by Kofeler melting point apparatus. IR ($cm^{-1}$) spectra were recorded (KBr disc) on a Shimadzu DR-8001 spectrophotometer. $^{1}$H-NMR (DMSO-$d_6$ or $CDCl_3$) spectra were recorded at 400 MHz on a Varian Gemini NMR spectrometer and also 400 MHz on a Varian Mercury- 300 BB at Sohag University, the chemical shift is expressed in δ value (ppm) using TMS as an internal reference. Mass spectra were performed on Micro mass 7070 E`1spectrometer using Direct Inlet and Shimadzu Qp-2010 Plus mass spectrometer using Electronic Ionization mode operating at 70 ev.

### Synthesis Of 3,5-Diphenylcyclohex-2-En-1-Semicarbazone (2)

To a solution of semicarbazide hydrochloride (6.0 g, 0.05 mol) and sodium acetate (9.0 g, 0.1 mol) in 30 ml of water, a solution of 3,5-diphenylcyclohex-2-en-1-one (1) (12.4 g,



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0.05 mol), in ethanol (200 ml) was added. The reaction mixture was refluxed for 4 hrs, after cooling the semicarbazone product was separated, filtered off and crystallized from ethanol as white fine powder ; yield: 96%; mp 187-189ºC; IR (λ max,$cm^{-1}$): 3555-3458($NH_2$), 3200(NH), 3044($CH_{arom}$) , 2924($CH_{aliphatic}$), 1674 (C=O) , 1562 (C=N),1438 (C=C); $^1$H-NMR (DMSO-$d_6$), δ ppm: 9.36(s,1H,NH, disappeared by $D_2O$) ,7.55-7.25 (m,10H,$CH_{arom.}$), 6.67(s, 1H, $CH_{oliph.}$), 6.34 (s, 2H, $NH_2$, disappeared by $D_2O$),5.85 (s, 1H,NH, disappeared by $D_2O$), 3.16-3.14 (d,1H, CH=C), 3.02-2.98(d,2H,$CH_2$), 2.81-2.77(m,1H,CH-Ph); MS (m/z,I%): 305($M^+$), 304.6 (20.9) ($M^+$-1),261.8(17.8),246(25.6),215(24.0),203(11.6),143(28.7),117(20.2),105(30.2),91(100.0), 77 (31.8), calc. for $C_{19}H_{19}ON_3$(M. wt = 305).

**Synthesis Of 5,7-Diphenyl-2,6,7,7a-Tetrahydrobenzo[*D*][1,2,3]Thiadiazol-1-Oxide (3)**

Freshly distilled thionyl chloride (8 ml ) was taken to a round bottom flask (50 ml) placed in a salt-ice bath at about -10 $^o$C, 3,5-diphenylcyclohex-2-en-1-semicarbazone (2) (3.05g, 0.01 mol) was added in three portions maintaining temperature between 0 $^o$C and -10 $^o$C. After complete addition, the reaction mixture was allowed to stand at room temperature, 25 ml of dichloromethane was added and the mixture was stirred for another 2 hrs. Excess thionyl chloride was decomposed by slowly adding sodium carbonate solution (15-20 ml) to the reaction mixture , the organic layer was separated, washed thoroughly with water, sodium bicarbonate (5%) solution and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure , the separated solid was filtered off and crystallized from water as pale green fine powder.

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**Synthesis Of 4,6-Diphenyl-2,4-Dihydro-1*H*-Indazole-3-Carbaldehyde (4)**

A mixture of DMF (2.3 ml, 0.3 mole) and $POCl_3$ (2.8 ml, 0.3 mole) was stirred at 0 $^oC$ for 10 min, a solution of the 3,5-diphenylcyclohex-2-en-1-semicarbazone (2) (3.05 g,0.1 mol) in DMF (10 ml) was added drop wise. The reaction mixture was stirred at room temperature for 1 hrs and then heated at 70 $^oC$ for 4 hrs. After cooling at room temperature, the mixture was neutralized with cold potassium carbonate solution. The separated solid was filtered off, washed with water, dried and crystallized from ethanol as yellow crystal.

**Synthesis Of 5,7-Diphenyl-6,7-Dihydro-2(3*H*)-Imino-1,3-Benzo[*D*]Thiazol (5)**

To a solution of 3,5-diphenylcyclohex-2-en-1-one (1) (0.39 g, 0.0015 mol) and thiourea (0.11 g, 0.0015 mol) in isopropanol (40 ml), iodine (0.25 g, 0.002 mol) was added. The reaction mixture was refluxed for 6-8 hrs. The excess of the solvent was removed under reduced pressure, aqueous $NaHCO_3$ solution was added and the obtained semisolid was extracted with ether. The ether layer was washed thoroughly with water, dried over anhydrous $Na_2SO_4$, evaporate and the separated solid was collected as yellow crystal.

**Synthesis Of 2-Chloro-4,6-Diphenylcyclohexa-2,4-Diene-1-Carbaldehye (6)**

To a solution of 3,5-diphenylcyclohex-2-en-1-one **(1)** (2.48 g, 0.01 mol) in dry DMF (20 ml), a solution of phosphorusoxychloride $POCl_3$ (4.10 g, 0.03 mole) in dimethylformamide (30 ml) was added drop wise with stirring for 1hrs. at 0 $^OC$. The reaction mixture was then stirred for an additional 4 hrs at 70 $^OC$. After cooling, the

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mixture neutralized with cold potassium carbonate solution, the precipitate was filtered off, washed with water and crystallized from dioxane as yellow crystal; yield: 47%; mp 169-170ºC; the molecular formula $C_{19}H_{15}OCl$ (mol. Wt.= 294.5); IR (λ max, $cm^{-1}$): 3043(CH $_{arom.}$), 2940(CH $_{\boldsymbol{aliphatic}}$), 1743(CHO), 1602 (C=C),757(C-Cl); $^{1}$H-NMR(DMSO-$d_6$), δ ppm: 7.71(s,1H,CHO), 7.70-7.24(m, 10H, $CH_{arom.}$) , 6.46 (s,1H, CH $_{\boldsymbol{oliph.}}$),3.02-3.01(d,1H,CH-CHO), 2.84-2.76(m, 1H, CH-Ph),2.56-2.55(d, 1H, CH=);$^{13}$C-NMR (DMSO-$d_6$),δ ppm: 34.74(CH=), 35.73(CH-ph), 44.06 (CH-CHO), 124.66 ($CH_{\boldsymbol{oliph.}}$),126.83-138.5(C of Ph),144.21(C-Ph), 159.12 (C-Cl), 198.8 (CHO); MS (m/z, I%): 293.8(20.0)($M^{+}$-1),107.6(20.0),81.2(30.0),59.8(100.0),51.4(20.0),calc.for $C_{19}H_{15}ClO$(M. wt.= 294.7) .

**Synthesis Of 4,6-Diphenyl-4,5-Dihydro-1*H*-Indazole (7)**

To a solution of compound 6 (2.95g, 0.01 mol) in ethanol (20 ml), hydrazine hydrate (0.31 ml, 0.015mol) and a catalytic amount of triethyl amine were added. The reaction mixture was refluxed for 6 hrs. The excess of solvent was evaporated under reduced pressure , the obtained solid was collected, dried and crystallized from ethanol as yellow crystal.

**Synthesis Of 6,8-Diphenyl-2,3,4,6-Tetrahydro-1*H*-Benzo[1,4-*E*] Diazepine (8) And 6,8-Diphenyl -2,3,4,6-Tetrahydro-1*H*-Benzo[1,4-*F*] Thiazepine (9)**

To a solution of compound **7** (2.95 g, 0.01 mol) in ethanol (20 ml), the proper amine (ethylenediamine or cystamine hydrochloride) (0.01 mol) and triethyl amine (1.4 ml, 0.01

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mol) were added. The reaction mixture was refluxed for 6 hrs. The separated product was filtered off and crystallized from suitable solvent.

**Synthesis Of Ethyl 4,6-Diphenyl-4,5-Dihydro-1-Benzo[*B*]Thiophen-2-Yl-2-Carboxylate (10)**

A mixture of compound **7** (2.95 g, 0.01 mol), ethyl mercaptoacetate (1.096 ml, 0.01 mol) and sodium ethoxide solution (0.23 g of Na dissolved in 20 ml of ethanol) was refluxed for 6 hrs. The mixture was concentrated , the formed precipitate was filtered off and crystallized from ethanol as yellow crystal.

**Synthesis Of 2*E*-(3,5-Diphenylcyclohex-2-En-1-Ylidene)Hydrazene-*N'*[(*2R,3R,4R,5R*)-2,3, 4,5,6–Pentahydroxyhexylidene (12)**

To a solution of compound **11** (2.62g, 0.01mol) in dimethylformamide (20 ml), *D(+)* glucose (1.80 g, 0.01 mol) and (0.1 ml) acetic acid were added. The mixture was heated under reflux on a water-bath for 2 hrs. The separated solid on cooling was filtered off and crystallized from ethanol as pale brown crystal.

**Synthesis Of (3,5-Diphenylcyclohex-2-En-1-Ylidene)Hydrazene-*N'*-(4-Nitrobenzylidene) (13)**

A mixture of compound **5** (2.62 g, 0.01 mol) and p-nitrobenzaldhyde (1.51 g, 0.01 mol) in glacial acetic acid (20 ml) was refluxed with stirring for 5 hrs. After cooling, the formed solid was filtered off and recrystallized from ethanol as pale yellow crystal.

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**Synthesis Of 3-(3,5-Diphenylcyclohexa-1,5-Dienylamino)-2-(4-Nitrophenyl)-1,3-Thia- Zolidin-4-One (14)**

Thioglycolic acid (0.69 ml, 0.01mol) was added drop by drop to a solution of compound **13** (3.95g, 0.01mol) in dry benzene (30 ml). The reaction mixture was refluxed for 10 hrs and the solvent evaporated under reduced pressure. The solid was triturated with petroleum ether (60-80 $^{O}$C), filtered off, dried and crystallized from $CHCl_3$/ pet.ether (40-60 $^{O}$C) as deep yellow crystal.

**Synthesis Of 2-(3,5-Diphenylcyclohex-2-Enylidene)-N-Phenyl Hydrazine Carbothioamide (15)**

A solution of compound **11** (2.62 g, 0.01 mol) and phenylisothiocyanate (0.135 g, 0.01 mol) in dry dioxane (30 ml) was refluxed for 5hrs. The reaction mixture was concentrated under reduced pressure, the obtained solid was filtered off and recrystallized from ethanol.

**Synthesis Of 3-(3,5-Diphenylcyclohexa-1,5-Dienylamino)-2-Phenyliminothiazolidin-4-One (16) And 3-(3,5-Diphenyl-Cyclohexa-1,5-Dienylamino)-6-Hydroxy-2-Phenylimino-2,3-Di- Hydro[1,3] Thiazine-4-One (17)**

A mixture of compound **11** (3.97 g, 0.01 mol) and a proper dihalocompounds (chloroacetyl-chloride or malonyldichloride) (0.01 mol) was refluxed in dry DMF (20 ml) for 4 hrs. After cooling, the formed solid was filtered off, and recrystallized from the proper solvent.

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**Synthesis Of Ethyl [(2*E*)-2-(3,5-Diphenylcyclohex-2-En-1-Ylidene)Hydrazine]Acetate (18)**

To a solution of compound **11** (2.62 g, 0.01 mol) in dioxane (20 ml), ethyl bromoacetate (1.10 ml, 0.01mol) and triethyl amine (1.4 ml, 0.01mol) were added. The reaction mixture was refluxed for 6 hrs. After cooling, the separated solid was collected and crystallized from ethanol as yellow crystal.

**Synthesis Of 2-[(2*E*)-2-(3,5-Diphenylcyclohex-2-En-1-Ylidene)Hydrazine]Acetohydrazide (19)**

A mixture of compound **18** (3.48 g, 0.01 mol), hydrazine hydrate (0.31 ml, 0.01 mol) in ethanol (20 ml), was refluxed for 5 hrs. and allowed to cool. The solid product was collected and crystallized from ethanol as yellow crystal.

**Synthesis Of 1-(3,5-Dimethyl-1*H*-2,3-Dihydropyrazole-1-Yl)-2-[(2*E*)-(3,5-Diphenyl-Cyclohexa – 1-En ) Hydrazinyl )Ethanone (20)**

A mixture of compound **19** (3.33 g, 0.01 mol), acetyl acetone (0.31 ml, 0.01 mol) and a catalytic amount of triethyl amine in ethanol (20 ml), was refluxed for 7 hrs. After cooling the solid product was collected and crystallized from ethanol as deep green powder.

## ANTIMICROBIAL EVALUATION

The newly synthesized heterocyclic compounds **5, 6, 7, 8, 13, 15-18** and **20** were tested for their inhibitory effect in vitro growth of broad spectrum of bacteria representing one

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Gram positive bacteria, namely; *Bacillus cereus* and two Gram negative bacteria, namely; *Pseudomonasaeruginosa* and *Escherichia coli*. These compounds exhibited highly antibacterial activity against the tested gram positive, but possess potent activity against gram negative comparable to chloramphenicol as a standard compound. The results of antibacterial activity are shown in (able 3). The compounds were dissolved in DMSO in order to ensure that the solvent had no effect on bacterial growth or enzymatic activity, negative control tests were performed using DMSO. The inhibitory effect of compounds **5, 6 ,7, 8** , **13, 15-18** and **20** *in vitro* growth of broad spectrum of bacteria representing one Gram positive bacteria, (*Bacillus cereus)* and the two Gram negative bacteria, (*Pseudomonasaeruginosa* and *Escherichia coli)* were evaluated using agar diffusion method (cup and plate method)[25] by measuring the zone of inhibition on agar plates at three different concentrations 10000 ppm, 30000 ppm and 50000 ppm. All plates were incubated at 37±0.5$^{o}$C for 24 hrs. The zone of inhibition of the compounds was measured using cm scale. The results in ( Table 3 ) revealed that the most compounds with good inhibitory effect at low concentrations ( 10000 and 30000 ppm) and with high effect at high concentration (50000 ppm) against Gram positive bacteria (Bacillus cereus), except compounds **7** and **16** revealed the higher effect at (30000 ppm) and the lowest effect at (10000 and 50000 ppm).

The ionizable forms (A) and (B) are the active forms resulting from the ionization reactions of compounds **7** and **16** , respectively (Scheme 6) , These ionizable forms were stabilized by the presence of the conjugation between $N^-$ with the double bonds and the free electrons of different hetero atoms of the compounds **7** and **16**. Their interaction

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with different types of bacteria having the maximum effect at 30000 ppm compared with that of at 50000 ppm. This may be explained on the basis that the concentration of $H^+$ increase results in the reversible reaction and decreases the concentration of the ionizable form (Scheme 6), which in turn, decreases the effect of compounds **7** and **16** against Gram positive bacteria. The weak effect of these compounds against Gram positive bacteria at 10000 ppm is an expected result because of the lower concentration of the ionizable form.

At the three different concentrations 10000 ppm, 30000 ppm and 50000 ppm only compound **5** showed a good effect against Gram negative bacteria namely (*Escherichia coli and Pseudomonasaeruginosa*), whereas compounds **8, 17** exhibited a good inhabitation zone against Gram negative bacteria only (*Escherichia coli*). The reset of the tested compounds **( 6 ,7, 13, 15,16,18** and **20 )** have no effect against Gram negative bacteria.

## CONCLUSIONS

2-Chloro-4,6-diphenylcyclohex-1,3-diene-1-carbaldehyde **(6)** and 3,5-diphenylcyclohex-2-en -1- hydrazone (**11)** were used as the starting materials for the synthesis of pyrazol, thiophene, thiazepine, diazepine and thiazelidene derivatives containing 3,5-diphenyl-cyclohex-2-en moiety. The antibacterial activities for some of these derivatives were screened.

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Table 1 Energy of formation Formation

| Compound | Total E (Kcal/mol) | Δ E |
|---|---|---|
| 1 | -483778.83 | |
| 4a | -600326.27 | -116547.43 |
| 4b | -600288.62 | -116509.78 |

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Table 2 Calculated Electronic Parameters

| Compound | HOMO | LUMO | $\Delta E$ | $\eta$ | $\mu$ | $\omega$ |
|---|---|---|---|---|---|---|
| 1 | -6.57 | -2.11 | 4.46 | 2.23 | -4.34 | 4.23 |
| 4a | -5.73 | -1.87 | 3.86 | 1.93 | -3.80 | 3.74 |
| 4b | -4.75 | -2.46 | 2.29 | 1.15 | -3.60 | 5.67 |

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Table 3 Antibacterial screening of compounds 5-8, 13, 15-18 and 20

| Type of Bacteria | *Bacillus Cereus* | | | *Pseudomonas Aeruginosa* | | | *Escherichia Coli* | | |
|---|---|---|---|---|---|---|---|---|---|
| | Concentrations in ppm | | | | | | | | |
| | *10000* | *30000* | *50000* | *10000* | *30000* | *50000* | *10000* | *30000* | *50000* |
| **5** | 1.3 | 1.4 | 1.8 | 1.0 | 1.0 | 1.0 | 1.0 | 1.1 | 1.2 |
| **6** | 1 | 1.2 | 1.5 | - | - | - | - | - | - |
| **7** | 1.2 | 1.8 | 1 | - | - | - | - | - | - |
| **8** | 1.3 | 1.5 | 1.5 | - | - | - | 0.9 | 0.9 | 1.0 |
| **13** | 1.3 | 1.3 | 1.5 | - | - | - | - | - | - |
| **15** | 1.1 | 1.4 | 1.7 | - | - | - | - | - | - |
| **16** | 1.2 | 1.8 | 1.2 | - | - | - | - | - | - |
| **17** | 1.5 | 1.5 | 1.8 | - | - | - | 1.1 | 1.2 | 1.2 |
| **18** | 1.1 | 1.5 | 1.7 | - | - | - | - | - | - |
| **20** | 1.1 | 1.5 | 1.7 | - | - | - | - | - | - |

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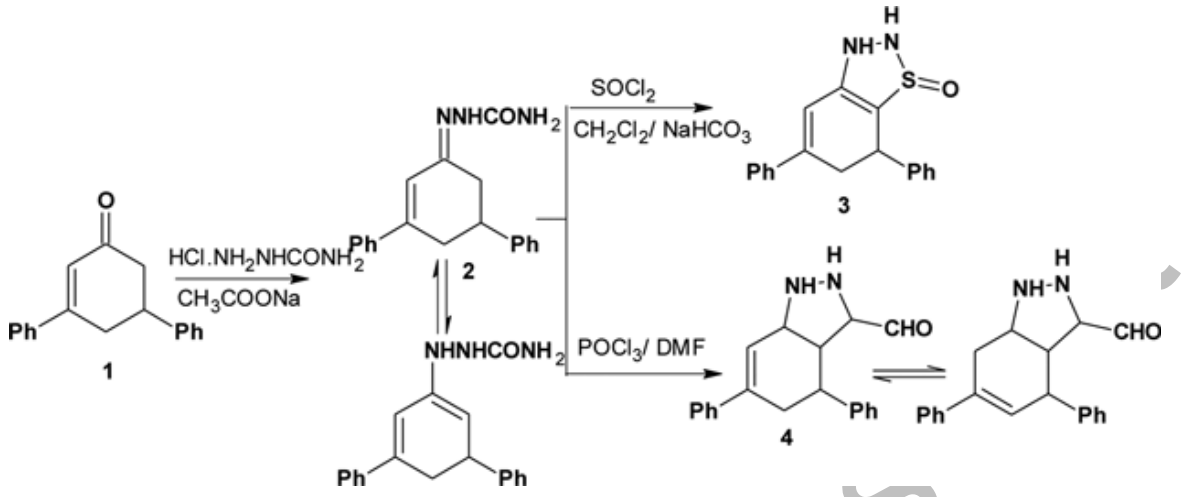
Scheme 1

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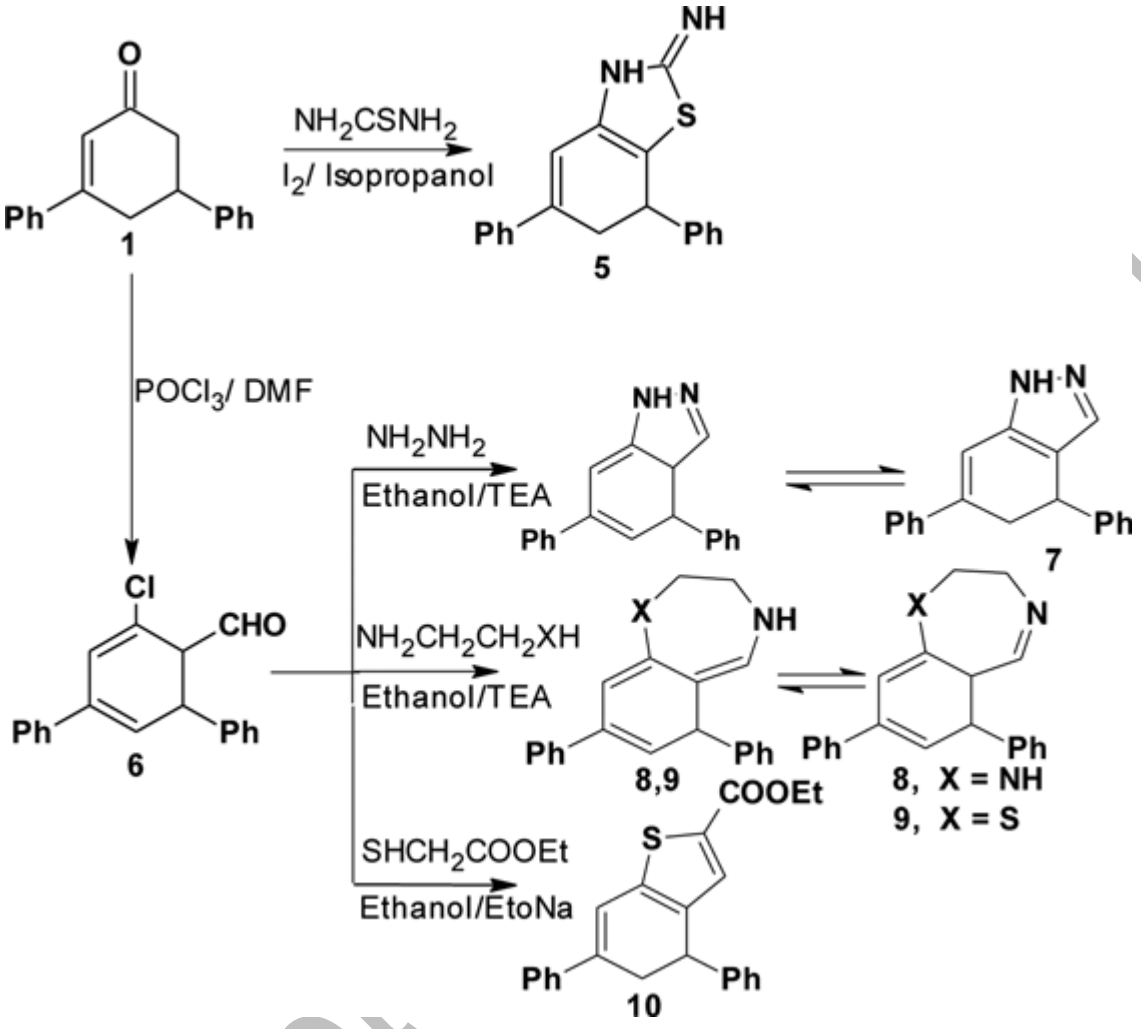
Scheme 2

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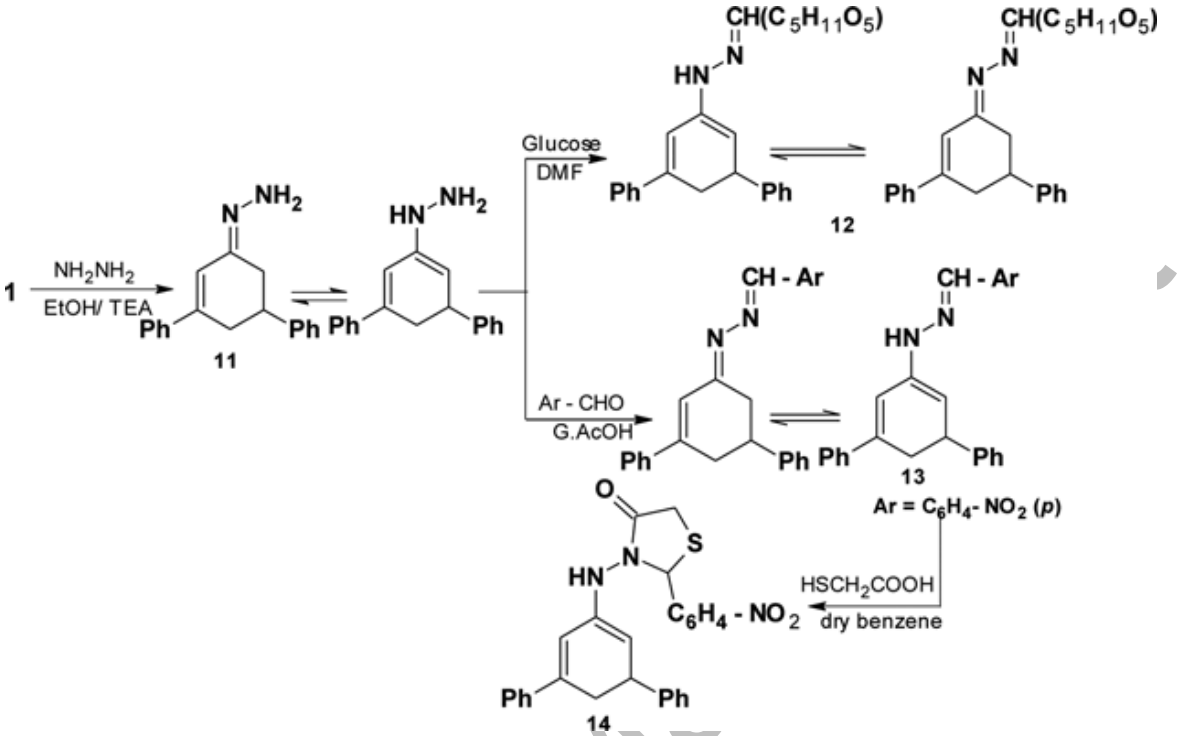
Scheme 3

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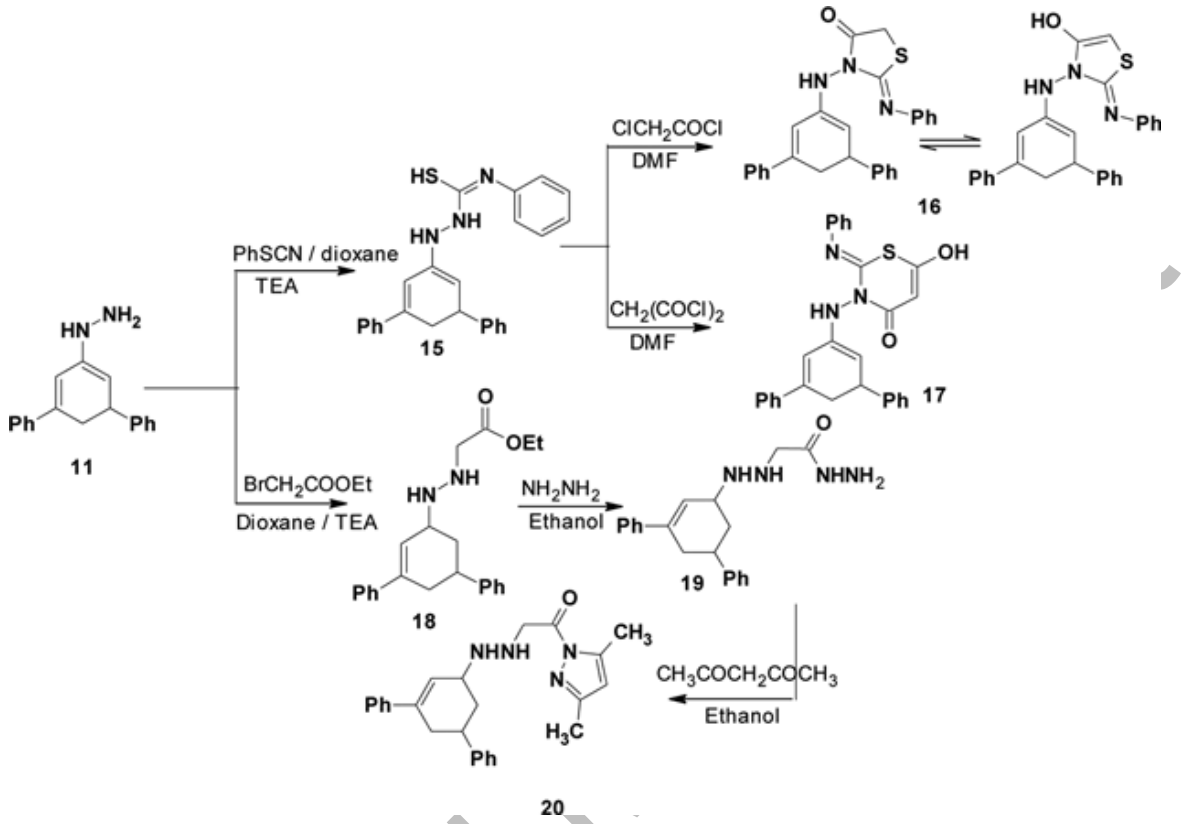
Scheme 4

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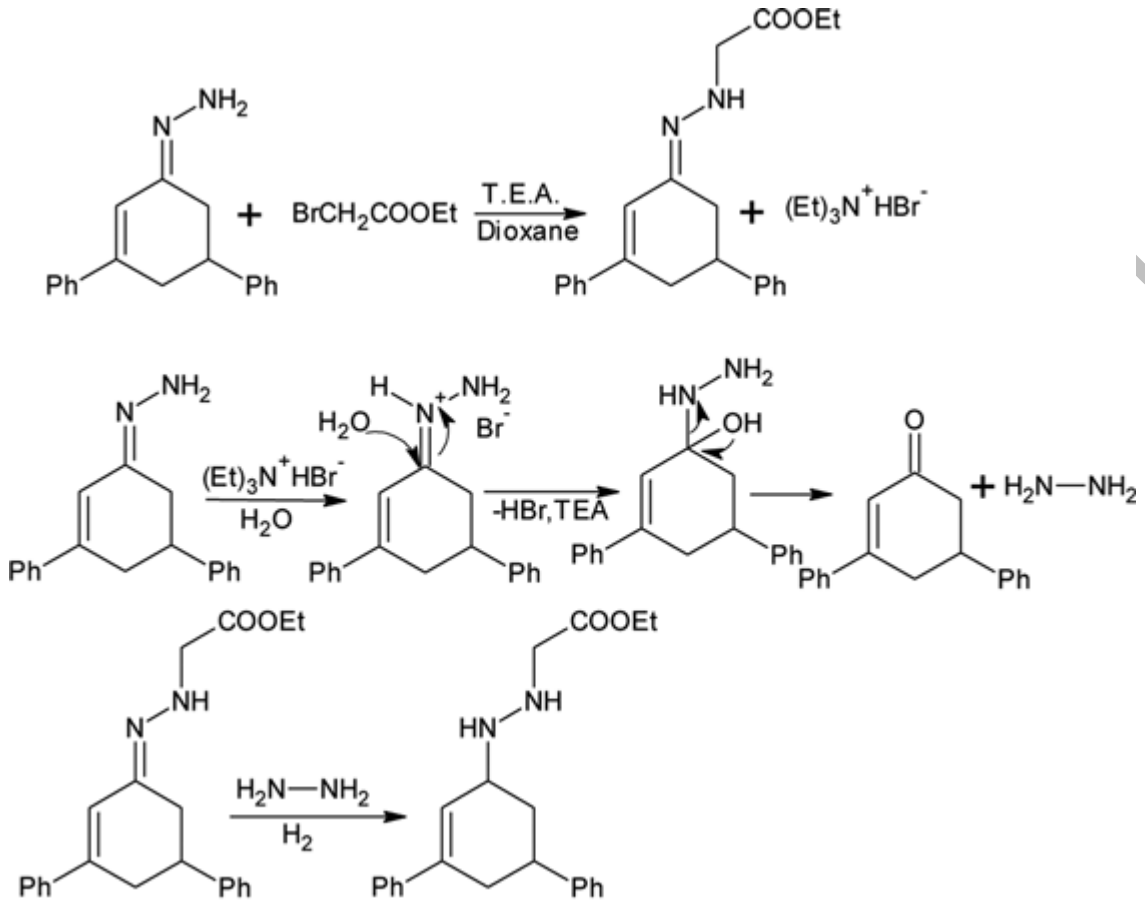
Scheme 5

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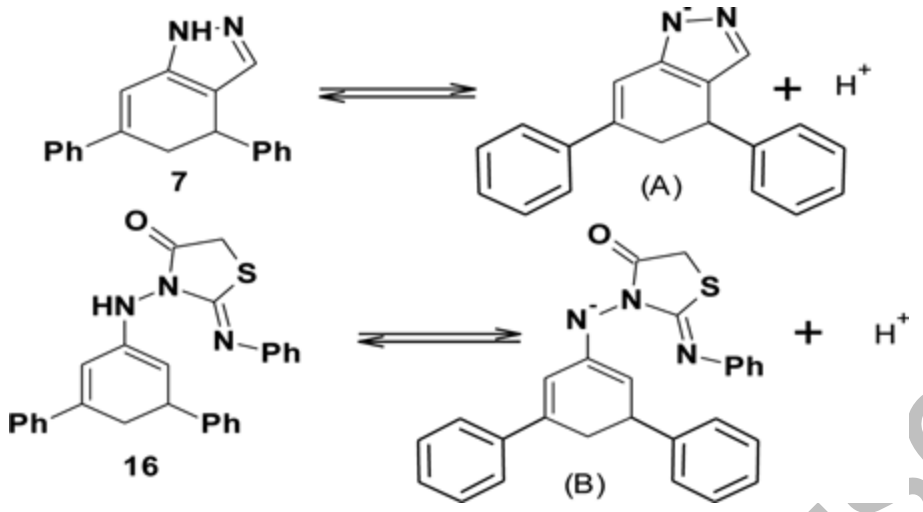
Scheme 6

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