



Design, Synthesis and Antibacterial Evaluation of some new 3,5-Diphenylcyclohex-2-en-1-one Derivatives

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ABSTRACT

The moiety of cyclohexene has been showed highly antibacterial activity. New compounds were synthesized from diphenylcyclohexenone via reaction with a variety of reagents to afford branched chain of 1,3-diphenylcyclohexene or fused heterocyclic systems including pyrazole, chromen and pyrrole derivatives. Cyclic ketoketene *s,s*-acetal can be prepared by reaction with CS₂/MeI under PTC conditions which in turn used as starting material for the synthesis of pyrazolyl and benzothiazolyl derivatives. Most of new synthesized compounds were characterized by using spectral data and were screened for their antibacterial activity.

Indexing terms/Keywords

Diphenylcyclohexene; Chromen; PTC; Benzothiazole; Antibacterial activity.

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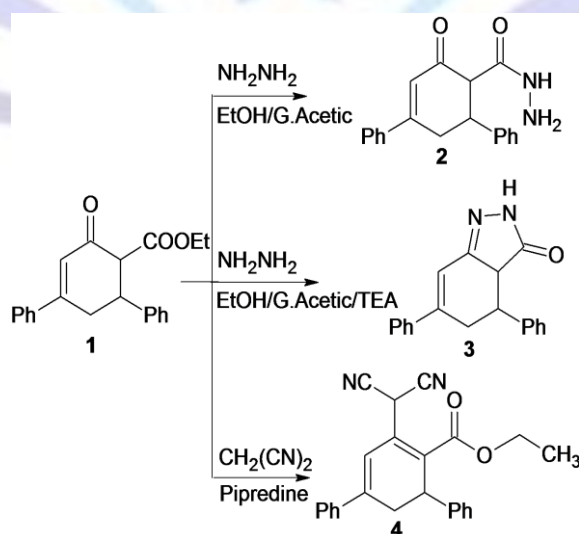
INTRODUCTION

Chalcones belong to a class of α,β -unsaturated aromatic ketones which occur abundantly in nature, and have drawn much attention because of their benefits to human application [1-3]. Michael addition of ethylacetoacetate to chalcone yields 4,6-diaryl-2-oxo-cyclohex-3-ene-1-carboxylate derivatives, which are efficient synthons for fused isoxazoles, pyrazoles and quinazolins [4,5]. Cyclohexenone derivatives are well known lead molecules for the treatment of inflammation and autoimmune diseases [6]. For example, Methyl substituted α,β -unsaturated cyclohexenones are an important class of compounds in organic synthesis [7-9], which found to be used as herbicides [10] and are employed in the construction of a wide variety of biologically and medicinally important products [11]. Yathirajan and co-workers have synthesized some new cyclohexenone derivatives, which already reported, the crystal and molecular structure studies of some of the related chalcones and cyclohexenone derivatives [12-17]. The compounds have conventionally been prepared by Knoevenagel condensation reaction of ethyl acetoacetate with suitable aldehyde in presence of a base, followed by the acid hydrolysis of the corresponding diesters to yield the substituted cyclohexenones [18]. Some of the compounds have also been prepared by tandem Michael-Dieckmann decarboxylative annulation reactions [19]. Moreover; a chiral primary–secondary diamines catalyst system could also efficiently catalyze the Michael–aldol–dehydration reaction between benzoylacetates and α,β -unsaturated ketones to provide functionalized chiral cyclohexenones in excellent enantioselectivities [20].

Several reports have pointed out the importance of cyclohexenones for antimicrobial and antitubercular activity [21]. Recently, Homogeneous Pd catalysts have been identified for the conversion of cyclohexenone and tetralone *O*-pivaloyl oximes to the corresponding primary anilines and 1-aminonaphthalenes *via* inspired method of Semmler–Wolff reaction [22]. Also, the dehydrogenation of cyclohexanones affords cyclohexenones or phenols *via* removal of 1 or 2 equiv of H_2 , respectively by using $Pd(DMSO)_2(TFA)_2$ which considered unique in its high chemoselectivity for the conversion of cyclohexanones to cyclohexenones, without promoting subsequent dehydrogenation of cyclohexenones to phenols [23]. Keeping in view of the useful findings of cyclic oxoketene *s,s*-acetal group in continuation of our work on 4,6-diaryl-2-oxo-cyclohex-3-ene-1-carboxylates [24].

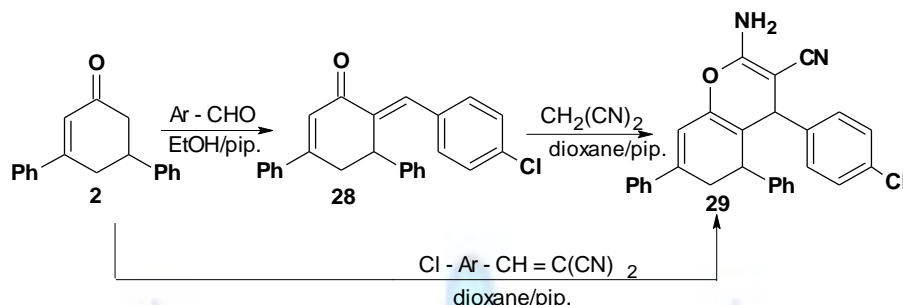
RESULTS AND DISCUSSION

Ethyl-3,5-diphenyl-2-en-1-one-6-carboxylate (**1**) was reacted with hydrazine directly to give 2-oxo-4,6-diphenyl-cyclohex-3-enecarboxylic acid hydrazide (**2**), while the same reaction was carried in presence of TEA to give 4,6-diphenyl-2,3a,4,5-tetrahydroindazol-3-one (**3**) (scheme 1). Their IR spectrum showed new absorption bands corresponding to C=O, NH, and NH_2 groups and disappeared absorption band for C=O_{ester}, where IR of compound **2** showed new absorption bands at 3421, 3350-3231 and 1708 cm^{-1} due to NH, NH_2 and C=O groups, while IR spectrum of compound **3** showed new absorption bands at 3440, 1661 cm^{-1} corresponding to NH and C=O groups. 1H -NMR spectra (δ , ppm) of compound **2** revealed new signals at δ 6.39, 3.16 due to NH_2 , NH groups, and the other signals were consistent to the proposed structure. Also the reaction was proved by mass spectra which given the perfect molecular weight $m/z = 306 (M^+)$. Moreover, 1H -NMR spectrum of compound **3** revealed new signals at δ 9.68, 4.20 due to NH (disappeared by D_2O) and $-CH-C=O$ groups. The ^{13}C -NMR spectrum showed new signal at δ 99.58 ppm due to $-CH-C=O$ group, the other signals were consistent to the proposed structure. On refluxing, compound **1** was allowed to react with malononitrile in presence of catalytic amount of piperidine to afford ethyl-2-dicyanomethylene-4,6-diphenylcyclohex-3-ene-1-carboxylate (**4**) (scheme 1). Its IR spectrum showed disappearance of absorption band corresponding C=O_{ketone} and appearance bands for CN groups at 2191 cm^{-1} . The 1H -NMR spectrum of compound **4** revealed new signal at δ 3.83 ppm due to CH-CN, also signals at δ 4.09(q), 1.65(t) due to CH_2 and CH_3 groups. ^{13}C -NMR spectrum showed new signal at δ 59.62, 158.70, 194.15 due to CH-CN, CN, C=O_{ester} groups, respectively (*cf.* experimental).



Scheme 1. Reaction of cyclohexenone ester **1** with NH_2NH_2 and malononitrile.

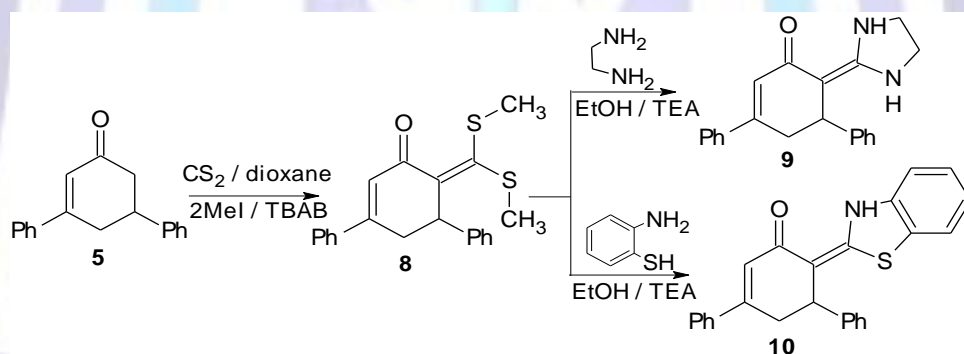
3,5-Diphenylcyclohex-2-enone (**5**) was synthesized *via* decarboxylation of compound **1** [4,25] and reacted with *p*-chlorobenzaldehyde to give chalcone derivatives **6**. The $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ signals of compound **6** consistent with the proposed structure (*cf.* experimental). (6*E*)-6-(4-chlorobenzylidene)-3,5-diphenylcyclohex-2-en-1-one (**6**) were subjected to react with malononitrile to afford 2-amino-4-(4-chlorobenzylidene-5,7-diphenyl-5,6-dihydro-4*H*-chromene-3-carbonitrile (**7**). By another way for the synthesis of compound **7** *via* the reaction of compound **5** with *p*-chlorobenzylidene malononitriles (scheme 2.). IR spectrum of compound **7** showed new bands corresponding to CN and NH_2 groups at 2202 and 3434-3321 cm^{-1} , respectively. The $^1\text{H-NMR}$ spectrum showed singlet signals (broad band) at δ 2.26 ppm due to NH_2 group and disappeared by D_2O , and the other signals consistent with the proposed structure.



Scheme 2. Synthesis of Chromen derivative.

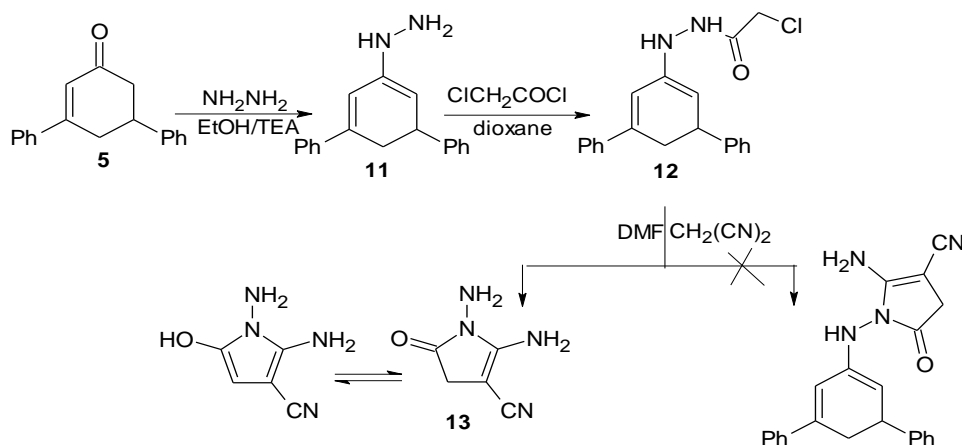
Ketoketene *S,S*-acetals derivative **8** was prepared *via* the reaction of compound **5** with a mixture of carbon disulfide and two moles of methyl iodide in one pot. reaction under PTC conditions. Its $^1\text{H-NMR}$ spectrum showed new two singlet signals corresponding to 2 S-CH_3 groups at δ 1.58, 1.33 ppm. The $^{13}\text{C-NMR}$ signals consistent with the proposed structure (*cf.* experimental). Moreover, the reaction was proved by mass spectrum which given the molecular ion peak $m/z = 350$ (M^+-2).

On the reaction of 6-(bis-methylsulfanyl)methylene)-3,5-diphenylcyclohex-2-enone (**8**) with ethylenediamine or *o*-aminothiophenol in ethanol gave the corresponding pyrazolyl and benzthiazolyl derivatives **9** and **10**, respectively (scheme 3.). Their $^1\text{H-NMR}$ spectra showed disappearance of signals corresponding to S-CH_3 groups and appeared signals corresponding two methylene group at δ 4.15, 4.25 ppm in compound **9** and new signal corresponding to NH group at δ 2.17 ppm which disappeared by D_2O (*cf.* experimental).



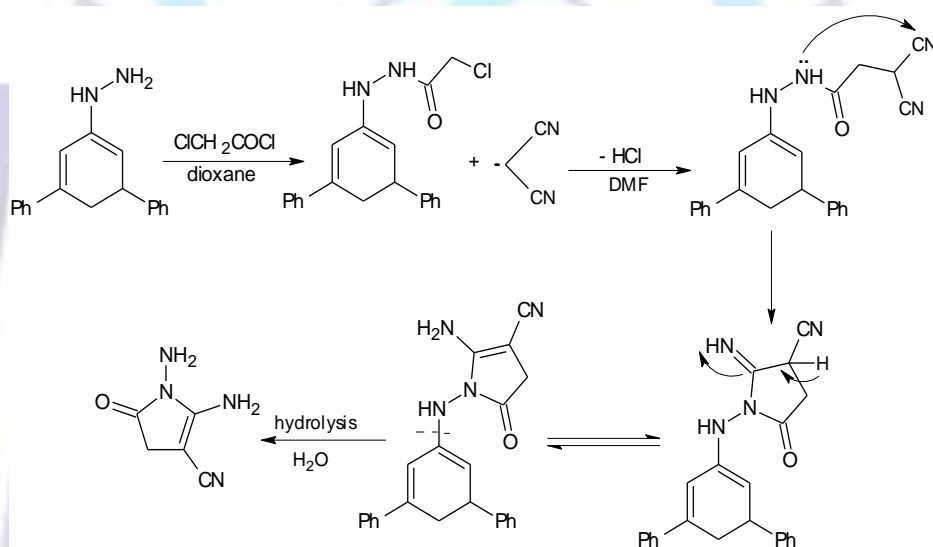
Scheme 3. Using *S, S*-acetal **8** in synthesis of pyrazolyl **9** and benzthiazolyl derivatives **10**.

3,5-Diphenylcyclohex-2-ene hydrazine (**11**) was synthesized through the reaction of compound **5** [26] with hydrazine, which reacted with chloroacetyl chloride to give [(2*E*)-2-(3,5-diphenylcyclohex-2-en-1-ylidene)hydrazino]chloride (**12**) in excellent yield. Its IR spectrum showed disappearance of absorption bands of NH_2 group and appearance of new absorption due to C=O and C-Cl at 1725, 914 cm^{-1} , respectively. $^1\text{H-NMR}$ spectrum showed new signal for $-\text{CH}_2\text{Cl}$ group at δ 3.12 ppm and the other signals consistent with the proposed structure (*cf.* experimental). 1,2-diamino-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (**13**) was formed through the reaction of compound **12** with malononitrile in DMF (scheme 4.). IR spectrum showed new absorption bands to C=O and NH_2 groups at 1660 and 3345-3220 cm^{-1} , also new absorption band corresponding to CN group at 2211 cm^{-1} . The $^1\text{H-NMR}$ spectrum was consistency with the proposed structure (*cf.* experimental).



Scheme 4. Reaction of alkylation product of compound **11** with malononitrile.

The mechanism for synthesis of compound **13** was assumed to proceed *via* acylation of compound **11** to afford compound **12** which in turn reacted with malononitrile in presence of DMF with elimination of HCl molecule followed by nucleophilic attack of NH group to cyano group to give the corresponding intermediate pyrrole derivative which was hydrolysed with one mole of H₂O to give diaminopyrrole **13** (scheme 5).



Scheme 5. Expected mechanism of synthesis of pyrrole derivative.

Antibacterial activity evaluation

The newly synthesized heterocyclic compounds **3**, **7**, **8**, **10**, **12** and **13** were tested for their inhibitory effect *in vitro* growth of broad spectrum of bacteria representing one Gram positive bacteria, namely; *Bacillus cereus* and two Gram negative bacteria, namely; *Pseudomonas aeruginosa* and *Escherichia coli*. These compounds exhibited highly antibacterial activity against the tested gram positive, but possess moderate to poor activity against gram negative comparable to chloramphenicol as a standard compound. The results of antibacterial activity are shown in Table 1.

The compounds were dissolved in DMSO. In order to ensure that the solvent had not effect on bacterial growth or enzymatic activity, negative control tests were performed using DMSO at the same concentrations. The inhibitory effect of compounds **3**, **7**, **8**, **10**, **12** and **13** *in vitro* growth of broad spectrum of bacteria was evaluated using agar diffusion method (cup and plate method) [27] by measuring the zone of inhibition on agar plates at three different concentrations 10,000 ppm, 30,000 ppm and 50,000 ppm. DMSO was used as solvent control. All plates were incubated at 37±0.5 °C for 24h. The zone of inhibition of compounds was measured using cm scale.

**Table 1.** Antibacterial screening results of the tested compounds

Type of Bacteria	<i>Bacillus Cereus</i>			<i>Pseudomonas Aeruginosa</i>			<i>Escherichia Coli</i>		
	Concentrations in ppm								
compound	10000	30000	50000	10000	30000	50000	10000	30000	50000
3	1.3	1.4	1.8	1.0	1.0	1.0	1.0	1.1	1.2
7	1.1	1.2	1.5	-	-	-	-	-	-
8	1.8	1.8	2.0	1.2	1.2	1.3	1.2	1.2	1.2
10	1.2	1.8	1.2	-	-	-	-	-	-
12	1.5	1.5	1.8	-	-	-	1.1	1.2	1.2
13	1.3	1.5	1.5	-	-	-	0.9	0.9	1.0

EXPERIMENTAL PROCEDURE

Melting points were determined using Kofeler melting point apparatus and were uncorrected. IR (cm^{-1}) spectra were recorded as KBr disc on a Shimadzu DR-8001 spectrophotometer. NMR spectra were carried out at both Micro analytical Unit, Cairo university and NMR lab., chemistry department, Sohag university on a Varian Gemini NMR spectrometer and a Varian Mercury- 300 BB respectively. NMR spectra 400 MHz for ^1H -NMR ($\text{DMSO}-d_6$) and 100 MHz for ^{13}C -NMR were recorded, the chemical shift is expressed in δ value (ppm) using TMS as an internal reference. Mass spectra were measured on a VG 7070E spectrometer (70eV, 200C, direct inlet). Elemental analyses were carried out on a Perkin-Elmer 240°C Microanalyzer.

Synthesis of 2-oxo-4,6-diphenyl-cyclohex-3-enecarboxylic acid hydrazide (2).

To a solution of compound 1 (3.21 g, 0.01 mol) in ethanol/glacial acetic acid (1:1, 20 ml), hydrazine hydrate (0.48 ml, 0.015 mol), was added. The reaction mixture was refluxed for 4 hrs. The excess of solvent was evaporated under reduced pressure; the solid obtained was collected and crystallized from ethanol as yellow crystal; yield: 59%; mp 303°C, IR (KBr max cm^{-1}): 3421 (NH), 3350-3231(NH_2), 3049(CH_{arom}), 2925(CH_{aliph}), 1708($\text{C}=\text{O}$), 1650($\text{C}=\text{O}$), 1601($\text{C}=\text{N}$); ^1H -NMR ($\text{DMSO}-d_6$, δ ppm): 7.51-7.24(m, 10H, CH_{arom}), 6.59(s, 1H, CH_{oliph}), 6.39(s, 2H, NH_2 , disappeared by D_2O), 3.16(s, 1H, NH, disappeared by D_2O), 2.96(d, 1H, $\text{CH}-\text{C}=\text{O}$), 2.72(d, 2H, CH_2) 2.38(m, 1H, $\text{CH}-\text{Ph}$); MS: (m/z, I%): 306.6(14.0), 257.8(100), 242(37.2), 199.7(25.6), 116.2(23.3), 94.8(88.4), 56.8(48.8). Anal. Calcd. For $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2$ (306.3): C, 74.49 %; H, 5.92 %; N, 9.14 %. Found: C, 74.55 %; H, 5.96 %; N, 9.24%.

Synthesis of 4,6-diphenyl-2,3a,4,5-tetrahydroindazol-3-one (3).

To a solution of compound 1 (3.21 g, 0.01 mol) in ethanol/glacial acetic acid (1:1, 20 ml), hydrazine hydrate (0.48 ml, 0.015 mol) and a catalytic amount of triethylamine were added. The reaction mixture was refluxed for 4 hrs. The excess of solvent was evaporated under reduced pressure; the solid obtained was collected and crystallized from ethanol as pale yellow crystal; yield: 93%; mp 202°C, IR (KBr max cm^{-1}): 3440(NH), 3060(CH_{arom}), 2931(CH_{aliph}), 1611($\text{C}=\text{O}$), 1516($\text{C}=\text{N}$); ^1H -NMR ($\text{DMSO}-d_6$, δ ppm): 9.68(s, 1H, NH, disappear by D_2O), 7.11-7.47(m, 10H, CH_{arom}), 6.76(s, 1H, CH_{oliph}), 4.20(d, 1H, $\text{CH}-\text{C}=\text{O}$), 3.18(m, 1H, $\text{CH}-\text{Ph}$), 2.93(d, 2H, CH_2); ^{13}C -NMR ($\text{DMSO}-d_6$, δ ppm): 145.75($\text{C}=\text{O}$), 140.61($\text{C}=\text{N}$), 136.72($\text{C}-\text{Ph}$), 129.06-125.52(C of Ph), 113.88(CH_{oliph}), 99.58($\text{CH}-\text{C}=\text{O}$), 36.64($\text{CH}-\text{Ph}$), 34.56(CH_2); MS: (m/z, %): 288(100), 271(16.3), 247(27.9), 198(14.0), 128(37.2), 103(34.9), 77(44.2), 59(7.0); Anal. Calcd. For $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}$ (288.4): C, 79.14 %; H, 5.59 %; N, 9.72 %. Found: C, 79.21%; H, 5.67 %; N, 9.57%.

Synthesis of ethyl-2-dicyanomethylene-4,6-diphenyl-cyclohex-3-ene-1-carboxylate (4).

A solution of compound 1 (3.21g, 0.01 mol) in (20 ml) ethanol reacted with malonitrile (0.66g, 0.01 mol), a few drops of piperidine was added. The mixture was heated under reflux for 2 hrs, then allowed to cool. The solid product was collected and recrystallized from ethanol as deep Brown crystal; yield: 82%; mp 194 °C, IR (KBr max cm^{-1}): 3396(OH), 3043(CH_{arom}), 2932(CH_{aliph}), 2863(CH_2), 2191(CN), 1731($\text{C}=\text{O}_{\text{ester}}$), 1656($\text{C}=\text{C}$); ^1H -NMR ($\text{DMSO}-d_6$, δ ppm): 7.66-7.29(m, 10H, CH of aromatic ring), 6.60(s, 1H, CH_{oliph}), 4.09(q, 2H, CH_2), 3.83(s, 1H, $\text{CH}-\text{CN}$), 3.11(d, 2H, CH_2), 3.04(s, 1H, $\text{CH}-\text{Ph}$), 1.65(t, 3H, CH_3); ^{13}C -NMR ($\text{DMSO}-d_6$, δ ppm): 13.97(CH_3), 36.17(CH_2), 44.18($\text{CH}-\text{Ph}$), 59.62($\text{CH}-\text{CN}$), 60.99($\text{CH}_2_{\text{ester}}$), 124.08(CH_{oliph}), 126.23-137.70(C of Ph), 141.00($\text{C}-\text{Ph}$), 147.12($\text{C}-\text{CH}-\text{CN}$), 158.70(CN), 169.32($\text{C}-\text{C}=\text{O}$), 194.15($\text{C}=\text{O}_{\text{ester}}$); Anal. Calcd. For $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_2$ (368.4): C, 78.24 %; H, 5.47 %; N, 7.60 %. Found: C, 78.25 %; H, 5.55 %; N, 7.51 %.

Synthesis of (6E)-6-(4-chlorobenzylidene)-3,5-diphenyl cyclohex-2-en-1-one (6).

To a mixture of compound 5 (2.48 g, 0.01 mol) and *p*-chloro benzaldehyde (1.18 ml, 0.01 mol) in ethanol (30 ml), a few drops of piperidine were added. The mixture was heated under reflux for 4 h, then allowed to cool. The solid product was collected and recrystallized from dioxane as white crystal; yield: 67%; mp 186 °C; IR (KBr max cm^{-1}): 3040 (CH_{arom}), 2986 (CH_{aliph}), 1660 ($\text{C}=\text{O}$), 1650 ($\text{C}=\text{N}$), 970($\text{C}-\text{Cl}$); ^1H -NMR ($\text{DMSO}-d_6$, δ ppm): 7.92-7.36 (m, 10H, CH_{arom}), 7.26(d, 1H, $=\text{CH}-\text{Ar}-\text{Cl}$) 6.45 (s, 1H, CH_{oliph}), 3.03 (d, 2H, CH_2), 2.83(t, 1H, $\text{CH}-\text{Ph}$); ^{13}C -NMR($\text{DMSO}-d_6$, δ ppm): 198.8 ($\text{C}=\text{O}$), 159.12($\text{C}-\text{Cl}$), 144.21($\text{C}-\text{Ph}-\text{NO}_2$), 138.51($\text{C}-\text{Ph}$), 130.60(C of ph- NO_2), 129.28-126.83(C of Ph), 124.65(CH_{oliph}),



44.04(=CH-Ar-Cl + CH-ph), 35.72(CH₂); Anal. Calcd. For C₂₅H₁₉ClO (370.87): C, 80.96 %; H, 5.16 %; Cl, 9.56 %. Found: C, 80.74 %; H, 5.28 %; Cl, 9.66 %.

Synthesis of 2-amino-4-(4-chlorobenzylidene-5,7-diphenyl-5,6-dihydro-4H-chromene-3-carbonitrile (7).

Method 1. A solution of compound **6** (3.70 g, 0.01 mol) in (20 ml) dioxane reacted with malonitrile (0.66 g, 0.01 mol), a few drops of piperidine was added. The mixture was heated under reflux for 2 hrs, then allowed to cool. The solid product was collected and recrystallized from dioxane.

Method 2. A solution of compound **5** (2.48 g, 0.01 mol) in (20 ml) dioxane reacted with *p*-chlorobenzylidene malonitrile (1.88 g, 0.01 mol), a few drops of piperidine was added. The mixture was heated under reflux for 2 hrs, then allowed to cool. The solid product was collected and recrystallized from dioxane as pale brown powder; yield: 54%; mp 284 °C; IR (ν_{max} cm⁻¹): 3434-3321(NH₂), 3044 (CH_{arom.}), 2929 (CH_{aliph.}), 2202 (CN), 1661 (C=N), 881(C-Cl); ¹H-NMR (DMSO-d₆, δ ppm): 8.65-7.23 (m, 14H, CH_{arom.}), 6.89 (s, 1H, CH_{oliph.}), 4.77 (s, 1H, CH-Ar-Cl), 3.75 (d, 2H, CH₂), 3.02(t, 1H, CH-Ph), 2.26(s, 2H, NH₂, disappeared by D₂O); Anal. Calcd. For C₂₂H₁₈N₂O (326.4): C, 80.96 %; H, 5.56 %; N, 8.58 %. Found: C, 80.75%; H, 5.66 %; N, 8.69 %.

Synthesis of 6-(bis-methylsulfanyl-methylene)-3,5-diphenyl-cyclohex-2-enone (8).

To a solution of compound **5** (2.48 g,10 mmol) in dioxane (15 ml) and catalytic amount of tetrabutyl ammonium bromide, dried potassium carbonate (3.5 g, 0.1 mol) was added and the mixture was stirred for 1hr at room temperature, carbon disulfide (0.72 ml, 12 mmol) was then added drop wise and the mixture stirred for additional 2 hrs, then iodomethane (1.24 ml,20 mmol) was added and the mixture stirred for 4 hrs at r.t. the reaction was quenched with water and the precipitate was filtered off, wash with water, recrystallized from ethanol as pale brown powder; yield: 89%; mp 79-81°C; IR (KBrymax cm⁻¹): 3057(CH_{aromatic}), 2952(CH_{aliph.}), 1656(C=O), 1126 (C-S); ¹H-NMR (DMSO-d₆, δ ppm): : 7.73-7.03(m, 10H, CH of aromatic), 6.45(s, 1H, CH_{oliph.}), 3.01(d, 2H, CH₂), 2.75(t, 1H, CH-Ph), 1.58(s, 3H, CH₃-S), 1.33(s, 3H, CH₃-S); ¹³C-NMR (DMSO-d₆, δ ppm): 198.87(C=O), 159.16(C-S), 144.11(C=C), 138.49(C-Ph), 130.58(C-Ph), 129.27-126.76(C of Ph), 121.23(CH_{oliph.}), 44.04(CH-Ph), 35.74(CH₂), 23.56(S-CH₃), 19.65(S-CH₃); MS: (m/z, %): 350, 320(0.7), 246(3.6), 203(3.2), 144.0(100), 102.2(11.0), 77.0(50.9); Anal. Calcd. For C₂₁H₂₀OS₂ (352.5): C, 71.55 %; H, 5.72 %; S, 18.19 %. Found: C, 71.51%; H, 5.56 %; S, 18.29%.

Synthesis of 6-imidazolidin-2-yl-3,5-diphenyl-cyclohex-2-enone (9).

A solution of compound **8** (3.52 g, 0.01 mol) in (20 ml) ethanol with ethylenediamine (0.66 ml, 0.01 mol), catalytic amount of triethyl amine was added. The mixture was heated under reflux for 4 hrs, then allowed to cool. The solid product was collected and recrystallized from ethanol as pale yellow powder; Yield: 44%; mp 170°C; IR (KBrymax cm⁻¹): 3420, 3291(2NH), 3049(CH_{arom.}), 2933(CH_{aliph.}), 1668(C=O), 1593(C=N), 1449(C=C)1126 (C-S); ¹H-NMR (DMSO-d₆, δ ppm): 7.55- 6.98(m, 10H, CH of aromatic), 6.26(s, 1H, CH_{oliph.}), 6.93(s, 1H, NH, disappeared by D₂O), 4.42(d, 2H, CH₂), 4.25(t, 2H, CH₂-NH), 4.15(t, 2H, CH₂-NH), 3.87(t, 1H, CH-Ph), 1.23(s, 1H, NH, disappeared by D₂O); MS: (m/z, I%): 316.7(7.9) (M⁺), 245(15.0), 204(11.0), 143.1(13.4), 104.8(100), 76.8(76.4), 54.8(10.2); Anal. Calcd. For C₂₁H₂₀N₂O (316.4): C, 79.72 %; H, 6.37 %; N, 8.85. Found: C, 79.51%; H, 6.47 S, 8.96%.

Synthesis of 6-(2,3-dihydro-benzothiazol-2-yl)-3,5-diphenyl-cyclohex-2-enone (10).

A solution of compound **8** (3.52 g, 0.01 mol) in (20 ml) ethanol with *o*-amino thiophenol (1.07 ml, 0.01 mol), catalytic amount of triethyl amine was added. The mixture was heated under reflux for 4 hrs, then allowed to cool. The solid product was collected and recrystallized from ethanol as deep brown powder; Yield: 69%; mp 138°C; IR (KBrymax cm⁻¹): 3445(NH), 3048(CH_{aromatic}), 2923(CH_{aliph.}), 1666(C=O), 1605(C=N), 1170 (C-S); ¹H-NMR (DMSO-d₆, δ ppm): : 7.73-6.61(m, 15H, CH of aromatic), 6.59(s, 1H, CH_{arylidene}), 4.25(d, 2H, CH₂ ring), 3.74(t, 1H, CH-Ph), 2.71(s, 1H, NH, disappeared by D₂O); Anal. Calcd. For C₂₅H₁₉NOS (381.4): C, 78.71 %; H, 5.02 %; N, 3.67 %; S, 8.41 %. Found: C, 78.60 %; H, 5.13 %; N, 3.55 %; S, 8.53%.

Synthesis of (3,5-diphenyl-cyclohexa-1,5-dienyl)-hydrazine (11).

To a solution of compound **5** (2.48 g, 0.01 mol) in ethanol (20 ml), hydrazine hydrate (0.48 ml, 0.015 mol) and a catalytic amount of triethylamine were added. The reaction mixture was refluxed for 6 h. The excess of solvent was evaporated under reduced pressure; the solid obtained was collected and crystallized from ethanol [literature 156 °C (27)] as yellow crystal; yield: 91%; mp 189-190°C; IR (ν_{max} cm⁻¹): 3447-3358(NH₂), 3205(NH), 3031(CH_{aromtic.}), 2929(CH_{aliph.}), 1645(C=N), 1562(C=C); ¹H-NMR (CDCl₃, δ ppm): 7.41-6.77(m, 10H, CH aromatic), 6.60(s, 1H, CH_{oliph.}), 5.18(s, 2H, NH₂, disappeared by D₂O), 3.10(d, 1H, CH=C-NH), 2.77(d, 2H, CH₂), 2.22-2.16(m, 1H, CH-Ph), 1.36 (s, 1H, NH, disappeared by D₂O); ¹³C-NMR (CDCl₃, δ ppm): 29.48(CH-Ph), 35.08(CH₂), 39.80(CH=C), 124.46(CH_{oliph.}), 124.77-128.81(C of Ph), 140.24(C of PH), 144.80 (C-NH), 150.25(C-Ph); MS: (m/z, %): 262(18.6), 244(100), 227(32.6), 126(30.2), 75(18.6), 50(27.9); Anal. Calcd. For C₁₈H₁₈N₂ (262): C, 82.41 %; H, 6.92 %; N, 10.68 %. Found: C, 82.50 %; H, 6.75 %; N, 10.76 %.

Synthesis of [(2E)-2-(3,5-diphenylcyclohex-2-en-1-ylidene)hydrazino]chloride (12).

To a solution of compound **11**(2.62 g, 0.01 mol) in dry dioxane (20 ml), chloroacetyl chloride (0.8ml, 0.01 mol) and catalytic amount of triethylamine were added. The reaction mixture was refluxed for 6 h. After cooling, the separated solids were collected, crystallized from ethanol as deep yellow crystal; yield: 45%; mp 172°C; IR (ν_{max} cm⁻¹): 3355(NH), 3155(NH), 3040(CH_{aromatic}), 2928(CH_{aliph.}), 1725(C=O), 1634(C=N), 914(C-Cl); ¹H-NMR (DMSO-d₆, δ ppm): 7.47-7.18 (m, 10H, CH_{aromatic}), 6.79 (s, 1H, CH_{oliph.}), 4.15 (s, 1H, NH), 3.63(s, 1H, NH), 3.39 (d, 1H, CH=C-NH), 3.12 (s, 2H, CH₂-Cl),



2.87(d, 2H, CH₂), 2.76(m, 1H, CH-ph); Anal. Calcd. For C₂₀H₁₉ClN₂O (338.8): C, 70.90 %; H, 5.65 %; Cl, 10.46 %; N, 8.27 %. Found: C, 70.65 %; H, 5.72 %; Cl, 10.57 %; N, 8.39 %.

Synthesis of 1,2-diamino-5-oxo-4,5-dihydro-1H-pyrrole-3-carbonitrile (13).

To a solution of compound **12** (3.38g, 0.01 mol) in (20 ml) dimethylformamide reacted with malonitrile (0.66g, 0.01 mol). The mixture was heated under reflux for 2 hrs, and then allowed to cool. The solid product was collected and recrystallized from DMF as deep brown crystal; yield: 62%; mp 272°C; IR (KBr)max cm⁻¹: 3345-3280(NH₂), 3156 (NH), 2929(CH_{aliph}), 2859(CH_{2 aliph}), 2211(CN), 1660(C=O), 1461(C=N); ¹H-NMR (DMSO-d₆, δ ppm): 9.54 (s, 1H, OH, disappeared by D₂O), 5.31(s, 2H, NH₂, disappeared by D₂O), 3.77(s, 1H, CH-C=OH); Anal. Calcd. For C₅H₆N₄O (138.1): C, 43.48 %; H, 4.38 %; N, 40.56 %. Found: C, 43.55 %; H, 4.49 %; N, 40.68 %.

CONCLUSION

The key intermediates ethyl-3,5-diphenylcyclohex-2-en-1-one-6-carboxylate (1) and 3,5 diphenylcyclohex-2-en-1-one (5) are used as effective synthons where it reacted with different reagents to afford pyrazole, chromen, ketoketene S,S-acetal, benzothiazole and Pyrrole derivatives. The new compounds were elucidated by chemical and spectroscopic data while some of them were tested for antibacterial effect and screened highly activity on Gram positive, and moderate to poor on Gram negative.

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