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Synthesis and biological evaluation of some *N*-ethoxyphthalimido-4-phenyl-6-subsitutedphenyl-2,3*a*,4,5-tetrahydro-3*H*-indazol-3-one via Robinson annulations reaction

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Abstract: Compounds 4-[4-substitutedphenyl]-6-phenyl-2,3*a*,4,5-tetrahydro-3*H*-indazol-3-one (**3a-d**) were synthesized via robinson annulation. Robinson annulation is michael addition reaction followed by aldol condentation. α β unsaturated carbonyl compounds (**1a-d**) were cyclized with ethylacetoacetate produced ethyl 6-[4-substitutedphenyl]-2-oxo-4-phenyl cyclohex-3-ene-1-carboxylate (**2a-d**). Compounds (**2a-d**) were refluxed with hydrazine hydrate in the presence of acetic acid yielded 4-[4-substitutedphenyl]-6-phenyl-2,3*a*,4,5-tetrahydro-3*H*-indazol-3-one (**3a-d**). In the final step compounds (**3a-d**) were treated with bromoethoxyphthalimide gave final products N-ethoxyphthalimido-4-[4-substituted phenyl]-6-phenyl-2,3*a*,4,5-tetrahydro-3*H*-indazol-3-one (**5a-d**). In another route pyrazolo benzodiazepine compounds containing alkoxyphthalimide moiety have been synthesized through a multiple steps pathway starting from substituted chalcones (**la-c**)**.** Cyclisation of these with hydrazine hydrate in acetic acid afforded 1-[5-(4-substitutedphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl]ethanone (**6a-c**). Base catalyzed condensation of (**6a-c**) with benzaldehyde yielded 1-[{5-(4-substitutedphenyl-3-phenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol -1-yl]ethanone (**7a-c**)**.** These compounds treated with o-phenylenediamine gave compounds (**8a-c**). These (**8a-c**) refluxed with bromoethoxyphthalimide afforded final compounds N-ethoxyphthalimido-2-(phenyl)-4-[5-(4-substitutedphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-1*H*-benzo(*b*)[1,5] diazepine (**9a-c**). In the another route compounds (**2a-d**) cyclised with hydroxylamine and furnish (**10a-d**). The structures of all the synthesized compounds were supported by spectral and analytical studies.

Keywords: Robinson annulations, Aldol condensation, Michael addition, Substituted aldehydes, Bromoethoxy- phthalimide, Spectral data.

Introduction

Azoles have played a crucial part in the history of heterocyclic chemistry and also been used extensively as important synthons in organic synthesis. Owing to the versatile chemotherapeutical activities of azoles, a significant amount of research activity has been directed towards this class. Indazole plays framework an essential role in biologically active compounds and therefore represents an interesting template for combinatorial as well as medicinal chemistry [1-5]. The indazol nucleus is a ubiquitous feature of pharmacological interest and has been proven to be a fertile source of medicinal agents such as antibacterial [6] antifungal [7] antiviral [8] antitubercular [9] antiamoebic [10] antiandrogenic [11] etc. Some of these compounds have also exhibited anti-inflammatory [12] antidiabetic [13] anaesthetic [14], analgesic [15] and antiparasitic [16] properties. Substituted chalcones, cyclohexenone and indazole rings possess a wide antimicrobial and antitubercular activity [17-20]. Derivatives of Cyclohexenone and indazole exhibit a variety of pharmacological properties like anticancer [21] antitumor [22] antiasthametic [23] antipyretic [24] antiviral [25] and tyrosine kinases inhibitor [26] activity. Benzodiazepines have recently received a lot of attention because of their wide range of therapeutic and pharmacological properties. Many members of the diazepine family are now a day's widely used as anti-anxiety, antidepressant, sedative, hypnotic, anticonvulsant, analgesic and anti-inflammatory agents [27-29]. Benzodiazepine derivatives also find commercial use as dyes for acrylic fibers [30] In addition, 1,5-benzodiazepines are important

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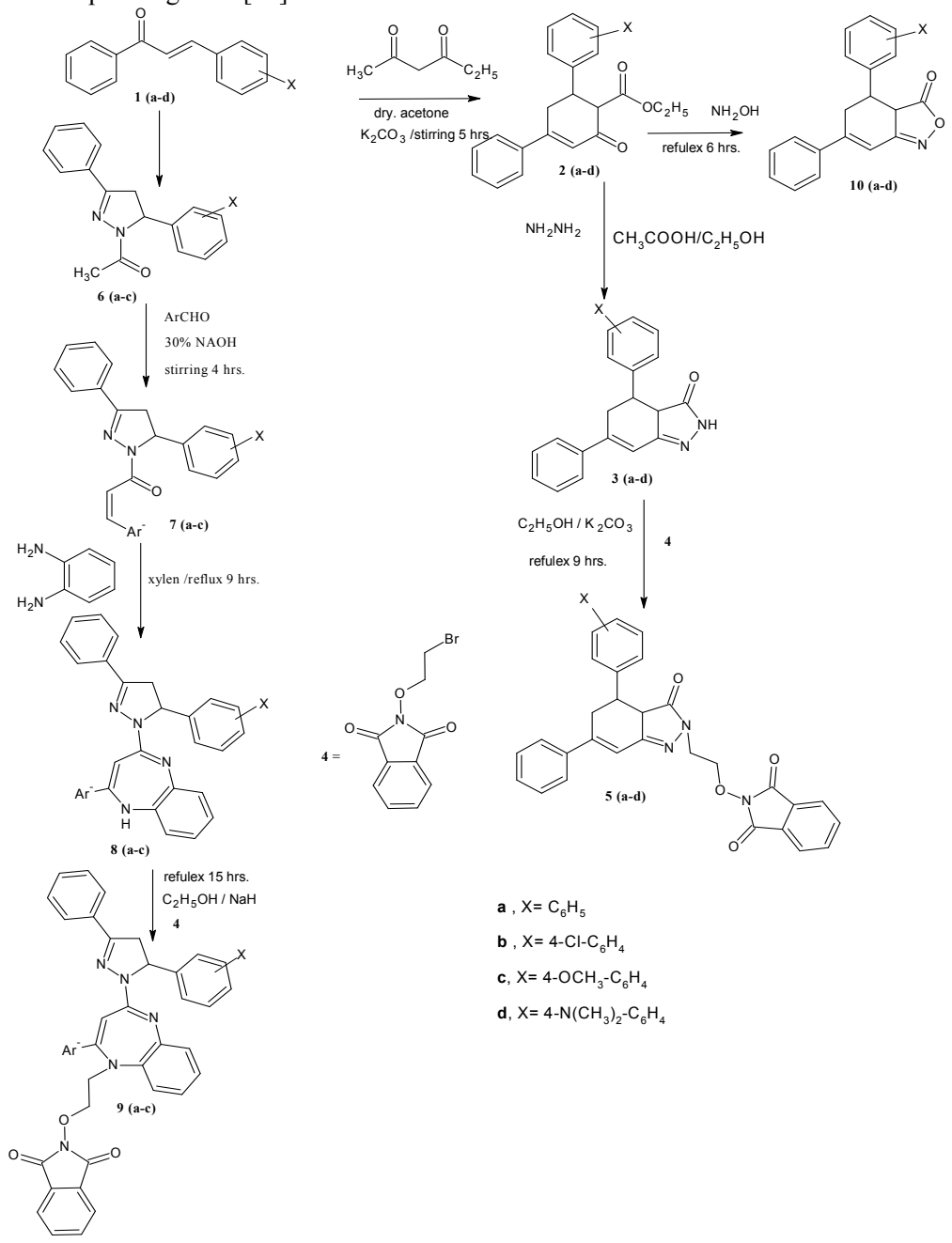
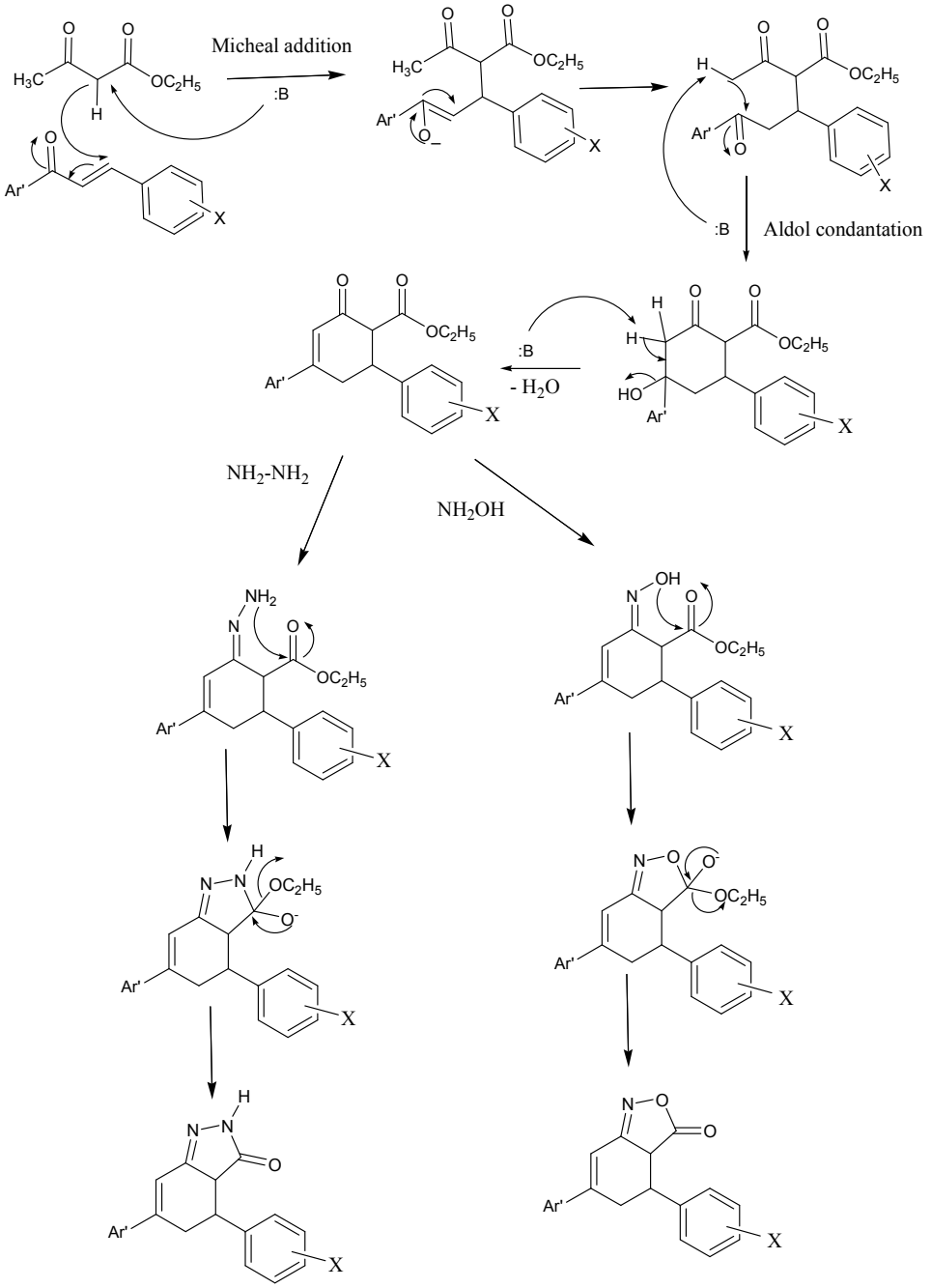
intermediates for the synthesis of various fused ring heterocyclic compounds such as oxazino-oxadiazolo-, furano- and triazolo-benzodiazepines [31]. Due to their wide range of biological, industrial and synthetic applications, the development of mild, efficient and environmentally friendly protocols continues to be a challenging endeavor in synthetic organic chemistry. 1,5-Benzodiazepines are one of the most important classes of the therapeuticagents [32]. It has anti-inflammatory [33] analgesic [34] antagonists [35] and antipyretic [36] properties. Pyrazole containing compounds have practical applications in the medicinal and agrochemical field and the biological activity of pyrazoles [37-40] and its derivatives are well documented. These heterocyclic rings attached to alkoxyphthalimide group have been synthesized [41] and tested for antimicrobial [42] and antimalarial [43] activities.



Scheme 1:

Results and discussion

In the present work, an attempt has been made to undertake the synthesis of N-ethoxyphthalimido-4-phenyl-6-subsitutedphenyl-2,3*a*,4,5-tetrahydro-3*H*-indazol-3-one **5a-d** through a multi step process.



Scheme 2: Mechanism of synthesized compounds via Robinson annulation reaction

For this purpose, the required Ethyl-6-[4-substitutedphenyl]-2-oxo-4-phenylcyclohex-3-ene-1-carboxylate **2a-d** were prepared by cyclisation of substituted chalcones **1a-d** with ethylacetoacetate using anhydrous K_2CO_3 as catalyst, formation of the product was confirmed by a quartet of CH_2 at δ 3.9 and triplet of CH_3 at δ 1.12. in ^{1}HNMR spectra. Compounds **2a-d** were converted to 4-[4-substitutwdphenyl]-6-phenyl-2,3*a*,4,5-tetrahydro-3*H*-indazol-3-one **3a-d** by cyclisation of **2a-d** with hydrazine hydrate in the presence of acetic acid. Insertion of nitrogen in the ring was characterized by appearance of band at 3351 cm^{-1}

stretching of (N-H) group. Hydrogen of N-H in indazole ring was replaced by ethoxyphthalimide group by treating **3a-d** with phthalimidoxyethylbromide using K_2CO_3 as a base to furnish N-ethoxyphthalimido-4-phenyl-6-(4-substitutedphenyl)-2,3*a*,4,5-tetrahydro-3*H*-indazol-3-one **4a-d**. In another route 1-[5-(4-substitutedphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]ethanone **6a-c** were obtained on reacting substituted chalcones with hydrazine hydrate in acetic acid. Formation of **6a-c** was confirmed by the presence of C=O stretching at 1718 cm^{-1} in IR spectrum. Compounds **6a-c** undergo condensation with benzaldehyde to form 3-phenyl-1-[5-(4-substitutedphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]prop-2-en-1-one **7a-c**.

Table 1: Physical data of synthesized compounds

Comp.	X	Mol. Weight	Reflux time	M.P ºC	Yield %
2a	H	320	-	92	79
2b	Cl	354	-	121	72
2c	OCH_3	350	-	116	76
2d	$N(CH_3)_2$	363	-	110	65
3a	H	288	6	206	74
3b	Cl	322	7	187	77
3c	OCH_3	318	6	212	71
3d	$N(CH_3)_2$	331	8	198	79
5a	H	477	9	156	67
5b	Cl	511	11	159	73
5c	OCH_3	507	7	167	69
5d	$N(CH_3)_2$	520	10	148	76
6a	H	264	10	120	78
6b	Cl	298	12	145	81
6c	OCH_3	294	12	132	79
7a	H	352	-	85	70
7b	Cl	356	-	101	73
7c	OCH_3	382	-	94	77
8a	H	440	9	165	69
8b	Cl	474	12	170	70
8c	OCH_3	470	11	125	73
9a	H	629	15	218	77
9b	Cl	663	11	190	67
9c	OCH_3	659	14	230	70
10a	H	289	6	192	81
10b	Cl	323	8	198	77
10c	OCH_3	319	6	210	79
10d	$N(CH_3)_2$	332	7	208	85

Structure of compound **7a-c** was elucidated on the basis of two doublet at δ 6.7 (CH) and 7.4 (CH) in ^{1}HNMR spectra. Compounds **7a-c** were treated with o-phenyldiamine in presence of xylene furnished corresponding pyrazolo diazepine derivatives **8a-c** which is confirmed by presence of a band at δ 3216 cm^{-1} of NH group. Subsequently, the NH proton was replaced by bromoethoxyphthalimide moiety to yielded final N-ethoxyphthalimido-2-phenyl-4-[5-(4-chlorophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-1*H*-benzo(*b*)[1,5]diazepine **9a-c**. In another path way **2a-d** treated with hydroxylamine furnished 4-(4-substitutedphenyl)-6-phenyl-4,5-dihydro-2,1-benzisoxazol-3(3a*H*)-one(**10a-d**).

All the synthesized compounds are tested for anti bacterial and anti fungal activity. In these compounds **5b** and **5c** shows good activity against bacterial and **5a**, **5b** and **5c** gave good activity against fungal and rest of compounds show moderate activity.

Conclusion

In the synthesized compounds **5b** and **5c** give good activity and others show moderate activity against all four bacterial and **5a**, **5b** and **5c** give good activity against two fungal.

Experimental section

Apparatus

Melting points were taken in open capillary tubes and therefore uncorrected. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using n-hexane and ethyl acetate as solvent system. The visualization of spots were carried out in an iodine chamber. The IR spectra of the compounds were recorded in the 4000-450 cm^{-1} ranges using KBr discs on FTIR Perkin Elmer spectrometers and ^{1}H NMR were recorded on a Bruker DRX-300 MHz spectrometer ($CDCl_3$) using TMS as an internal standard. The mass spectra were recorded on a Jeol SX-102 (FAB) mass spectrometer. Structure of all the synthesized compounds was assigned on basis of their analytical and spectral data.

Antimicrobial Activity

Eleven synthesized compounds were *in vitro* screened for their antibacterial and antifungal activity using 500 ppm concentrations in DMF by cup and well method. The micro-organisms *Proteus mirabilis, Bacillus subtilis, Klebsiella pneumoniae, Escherichia coli* were used as antibacterial, *Candida albicans* and *Aspergillus fumigatus* were used as fungal strains. The activity is presented as zone of inhibition in mm and compared with activity of controls C_1 and C2 (for antibacterial activity CI= ciprofloxacin for antifungal activity C2= flucanazole) to give activity index value **(**Table **2).** All the compounds showed poor activity against *K pneumoniae* and *E. colt* where as moderate to strong

activity was shown against *P. mirabilis* and *B. subtilis.* Activity index value against *P. mirabilis* and *B. subtilis* was more than one for majority of compounds. It was interesting to note that all the compounds showed stronger activity than the standard used against *Candida albicans* and *Aspergillus fumigatus.* It was concluded from the activity study that compound **5b** was found to be the strongest amongst all synthesized compounds. Compounds under study showed more comprehensive fungus-inhibiting properties than that of the bacterial. Even two folds antifungal activity was observed for these compared to standard.

Table 2. Antimicrobial activity of the synthesized compounds **5a-d** and **10a-d**

	Antibacterial activity				Antifungal activity	
S.No	Protius Mirabilis	Bacillus Subtilis	Klebsilla Pneumonia	Escherichia Coli	Candida Albicans	Aspergillus Fumigatus
5a	16 (.88)	15 (.88)	17 (.94)	19 (1.05)	22 (1.10)	21(1.05)
5b	24 (1.33)	22 (1.29)	20 (1.11)	22 (1.22)	25 (1.25)	23 (1.15)
5c	21 (1.16)	23 (1.35)	21 (1.16)	24 (1.33)	23 (1.15)	24 (1.20)
5d	14 (.77)	16 (.94)	18 (1.00)	23 (1.27)	21 (1.05)	22 (1.10)
9a	18 (1.0)	14(.70)	16 (.88)	19 (1.05)	20 (1.00)	21 (1.05)
9b	16 (.88)	17 (1.00)	16 (.88)	20 (1.11)	18 (.90)	20 (1.0)
9c	19 (1.05)	20 (1.17)	18 (1.0)	18 (1.0)	20 (1.0)	19 (.95)
10a	21(1.16)	17(1.0)	16(.88)	17(.94)	21(1.05)	20(1.0)
10b	20(1.11)	20(1.17)	19(1.05)	18(1.0)	22(1.1)	21(1.05)
10c	17(.94)	17(1.0)	19(1.05)	17(.94)	20(1.0)	19(.95)
10d	19(1.05)	19(1.11)	17(.94)	19(1.05)	19(.95)	19(.95)
C1	18	17	18	18	-	-
C2					20	20

(Activity index) = Inhibition zone of compound/Inhibition zone of the standard drug
For antibacterial activity: C_1 = Ciprofloxacin
For antifungal activity: C_2 = flucanazole

Synthesis of ethyl 2-oxo-4,6-diphenylcyclohex-3-enecarboxylate (2a):

A solution of (**Ia**) (0.01 mole) and ethylacetoacetate (0.01 mole) in dry acetone (20 ml) add catalytic amount of anhydrous K_2CO_3 (0.04 mole) was stirred at RT for 5 hrs. The reaction mixture was filtered and excess of solvent was removed under vacuum to get the solid product, which was purified by recrystallization from ethanol. Similarly **2b-d** compounds are also synthesized by minor change in reflux time. Yield 79%, m.p. 92°C; IR (KBr) cm^{-1} : 3065 (Ar-H), 2931 (C-H), 1721 (C=O ester), 1685 (C=O cyclic), ^{1}H NMR ($CDCl_3$) δ :1.12 (3H, t, $-CH_2-CH_3$), 2.13 (2H, m, CH_2), 3.9 (2H, q, $-CH_2-CH_3$), 3.1 (1H, d,), 4.0 (1H, m, CH), 5.5 (1H, s, C=CH), 6.89-7.55 (m, Ar-H), Anal. calcd for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29%. Found: C, 78.78; H, 6.43%.

Ethyl 6-(4-chlorophenyl)-2-oxo-4-phenylcyclohex-3-ene-1-carboxylate (2b):

Yield 72%, m.p. 121°C; IR (KBr) cm^{-1}: 3071 (Ar-H), 2939 (C-CH), 1736 (C=O ester), 1692 (C=O cyclic), 743 (C-Cl); ^{1}H NMR ($CDCl_3$) δ : 1.14 (3H, t, $-CH_2-CH_3$), 2.21 (2H, m, CH_2), 3.2 (1H, d, CH), 4.00 (2H, q, $-CH_2-CH_3$), 4.3(1H, m, CH), 5.7 (1H, s, C=CH), 6.92-7.61 (m, Ar-H, Anal. calcd for $C_{21}H_{19}ClO_3$: C, 71.08; H, 5.40%. Found: C, 71.13; H, 5.38%.

Ethyl 6-(4-methoxyphenyl)-2-oxo-4-phenylcyclohex-3-ene-1-carboxylate (2c):

Yield 76%, m.p. 116°C; IR (KBr) cm^{-1} : 3066 (Ar-H), 2938 (C-CH), 1728 (C=O ester), 1689 (C=O cyclic); ^{1}H NMR ($CDCl_3$) δ : 1.12 (3H, t, $-CH_2-CH_3$), 2.18 (2H, m, CH_2), 3.2 (1H, d, CH), 4.0 (2H, q, $-CH_2-CH_3$), 4.1(1H, m, CH), 5.7 (1H, s, C=CH), 6.88-7.60 (m, Ar-H) 3.77 (s, OCH_3), Anal. Calcd. for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33%. Found: C, 75.39; H, 6.37%.

Ethyl-6-(4-N,N,dimethylphenyl)-2-oxo-4-phenylcyclohex-3-ene-1-carboxylate (2d):

Yield 65%, m.p. 110° C; IR (KBr) cm^{-1}: 3068 (Ar-H), 2941 (C-CH), 1731 (C=O ester), 1685 (C=O cyclic); ^{1}H NMR ($CDCl_3$) δ : 1.10 (3H, t, $-CH_2-CH_3$), 2.20 (2H, m, CH_2), 3.1 (1H, d, CH), 3.9 (2H, q, $-CH_2-CH_3$), 3.8 (1H, m, CH), 5.6 (1H, s, C=CH), 6.87-7.56 (m,Ar-H), 2.86(s,6H, $N(CH_3)_2$, Anal. calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93%. Found: C, 76.07; H,6.96%.

Synthesis of 4,6-diphenyl-2,3a,4,5-tetrahydro-3H-indazol-3-one (3a):

A mixture of **2a** (0.01 mole) and hydrazine hydrate (0.02 mole) in ethanol (25 ml) containing glacial acetic acid (1 ml) as a catalyst was refluxed over a water bath for 6 hrs.

The solid separated cooled, separated, dried and purified by recrystallization from ethanol. Similarly **3b-d** compounds are also synthesized by minor change in reflux time. Yield 74%, m.p. 206° C; IR (KBr) cm^{-1}: 3351 (N-H), 3073 (Ar-H), 1685 (C=O), 1648 (C=N); ^{1}H NMR ($CDCl_3$) : δ 8.1 (1H, -NH) 2.35 (2H, m), 5.1 (1H, d), 3.9 (1H, m, CH), 5.9 (1H, s), 6.91-7.61 (7H, m, Ar-H), ^{13}CNMR : δ 29.4, 38.5, 54.3, 109.2, 126.4, 126.5, 126.8, 128.0, 128.5, 130.1, 135.8, 143.0, 148.5, 151.0, 169.6. Anal. calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59%. Found: C, 79.13; H, 5.64%.

4-(4-chlorophenyl)-6-phenyl-2,3a,4,5-tetrahydro-3H-indazol-3-one (3b):

Yield 77%, m.p. 187°C; IR (KBr) cm^{-1}: 3357 (N-H), 3079 (Ar-H), 1689 (C=O), 1652 (C=N), 747 (C-Cl); ^{1}H NMR ($CDCl_3$) : δ 8.3 (1H, -NH), 2.41 (2H, m, CH_2), 5.3 (1H, d, CH), 4.4 (1H, m, CH), 6.0 (1H, s,C=CH), 6.98-7.75 (7H, m, Ar-H), ^{13}CNMR : δ 29.5, 39.1, 54.8, 109.4, 125.0, 127.3, 128.,6 128.9, 129.3, 133.7, 137.9, 143.2, 147.4, 151.0, 170.5. Anal. calcd for $C_{19}H_{15}ClN_2O$: C, 75.45; H, 5.70%. Found: C, 75.48; H, 5.75%.

4-(4-methoxyphenyl)-6-phenyl-2,3a,4,5-tetrahydro-3H-indazol-3-one (3c):

Yield 71%, m.p. 212°C; IR (KBr) cm^{-1} : 3355 (N-H), 3076 (Ar-H), 1688 (C=O), 1648 (C=N); ^{1}H NMR ($CDCl_3$) : δ 8.1 (1H, -NH), 2.39 (2H, m, CH_2), 5.3 (1H, d, CH), 4.3 (1H, m, CH), 5.9 (1H, s, C=CH), 6.94-7.69 (7H, m, Ar-H), 3.69 (s, OCH_3), ^{13}CNMR : δ 29.0, 38.2, 56.3, 110.3, 112.4, 126.9, 128.4, 128.9, 129.5, 140.2, 141.5, 146.8, 155.7, 159.2, 169.2. Anal. calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70, N, 8.80%. Found: C, 71.13; H, 5.38; N, 8.78%.

4-(4-N,N,dimethylphenyl)-6-phenyl-2,3a,4,5-tetrahydro-3H-indazol-3-one (3d):

Yield 79%, m.p. 198°C; IR (KBr) cm^{-1}: 3351 (N-H), 3079 (Ar-H), 1686 (C=O), 1650 (C=N); ^{1}H NMR ($CDCl_3$) : δ 8.15 (1H, -NH), 2.37 (2H, m, CH_2), 5.3 (1H, d, CH), 4.0 (1H, m, CH), 5.8 (1H, s, C=CH), 6.89-7.74 (7H, m, Ar-H), 2.91 (s, $N(CH_3)_2$), ^{13}CNMR : δ29.4, 39.5, 42.8, 54.0, 109.3, 116.7, 122.3, 125.7, 127.9, 128.4, 143.6, 145.8, 147.9, 148.5, 149.5, 155.7, 168.0; Anal.calcd for $C_{21}H_{21}N_3O$: C, 76.11; H, 6.39; N, 12.68%. Found: C, 76.07; H, 6.41; N, 12.73%.

Synthesis of N-ethoxyphthalimido-4,6-diphenyl-2,3a,4,5-tetrahydro-3H-indazol-3-one (5a):

A mixture of **3a** (0.01 mole), phthalimidoxyethylbromide **4** (0.01 mole) and add K_2CO_3 (0.01 mole) in ethanol (25 ml) were refluxed for 9 hrs. The solid filtered, cooled, separated, dried and purified by recrystallization from ethanol. Similarly 5b-d compounds are also synthesized by minor change in reflux time. Yield 67%, m.p. 156°C; IR (KBr) cm^{-1}: 3085 (Ar-H), 1718 (C=O), 1652 (C=N); ^{1}H NMR ($CDCl_3$) : δ 4.23-4.27 (t, O-CH_2), 3.40-3.45 (t, N-CH_2), 2.83-2.93 (2H, m, CH_2), 5.24 (1H, d, CH), 4.34-4.46 (1H, m, CH), 6.75 (1H, s, C=CH), 6.94-7.74 (m, Ar-H), ^{13}CNMR : δ 31.8, 40.5, 47.4, 59.6, 65.1, 112.9, 124.5, 125.5, 126.3, 127.0, 127.8, 128.3, 129.2, 130.6, 133.2, 133.5,9 139.4, 145.7, 148.2, 157.9, 173.0; Anal. calcd for $C_{29}H_{23}N_3O_4$: C, 72.94; H, 4.85%. Found: C, 72.86; H,5.38%.

N-ethoxyphthalimido-4-phenyl-6-(4-chlorophenyl)-2,3a,4,5-tetrahydro-3H-indazol-3-one (5b):

Yield 73%, m.p. 159°C; IR (KBr) cm^{-1} : 3093 (Ar-H), 1726 (C=O), 1658 (C=N), 751 (C-Cl); ^{1}H NMR ($CDCl_3$) : δ 4.31-4.28 (t, O-CH_2), 3.43-3.48 (t, N-CH_2), 2.84-2.95 (2H, m, CH_2), 5.30 (1H, d, CH), 4.38-4.49 (1H, m, CH), 6.81 (1H, s, C=CH), 6.90-7.81 (m, Ar-H), ^{13}CNMR : δ 31.9, 41.5, 47.8, 58.3, 65.3, 113.9, 124.8, 125.0, 126.3, 126.7, 126.8, 128.0, 128.5, 131.3, 132.3, 139.5, 142.6, 148.7, 157.2, 171.6; Anal. calcd for $C_{29}H_{22}ClN_3O_4$: C, 68.04; H, 4.33; N,8.31 %. Found: C, 68.09; H,4.38; N, 8.26%.

N-ethoxyphthalimido-4-phenyl-6-(4-methoxyphenyl)-2,3a,4,5-tetrahydro-3H-indazol-3-one (5c):

Yield 69%, m.p. 167°C; IR (KBr) cm^{-1} : 3090 (Ar-H), 1721 (C=O), 1653 (C=N); ^{1}H NMR ($CDCl_3$) : δ 4.28-4.33 (t, O-CH_2), 3.43-3.46 (t, N-CH_2), 2.82-2.94 (2H, m, CH_2), 5.28 (1H, d, CH), 4.37-4.49 (1H, m, CH), 6.77 (1H, s, C=CH), 6.89-7.76 (m, Ar-H), 3.63 (s, OCH_3). ^{13}CNMR : δ 31.4, 40.4, 49.9, 55.6, 65.7, 109.3, 116.9, 116.0, 124.9, 126.3, 127.8, 128.4, 132.7, 133.9, 140.6, 147.9, 150.5, 157.2, 163.7, 175.8; Anal. calcd for $C_{30}H_{25}N_3O_5$: C, 70.99; H, 4.96; N, 8.28%. Found: C, 70.96; H,4.95; N, 8.34%.

N-ethoxyphthalimido-4-phenyl-6-(4-N,N,dimethylphenyl)-2,3a,4,5-tetrahydro-3H-indazol-3-one (5d):

Yield 76%, m.p. 148°C; IR (KBr) cm^{-1} : 3089 (Ar-H), 1719 (C=O), 1650 (C=N); ^{1}H NMR ($CDCl_3$) : δ 4.29-4.31 (t, O-CH_2), 3.42-3.47 (t, N-CH_2), 2.80-2.91 (2H, m, CH_2), 5.30 (1H, d, CH), 4.36-4.47 (1H, m, CH), 6.74 (1H, s, C=CH), 6.80-7.70 (m, Ar-H), 2.79 (s, 6H,(N-CH_3)$_2$. ^{13}CNMR : δ 32.4, 41.7, 44.2, 49.7, 55.8, 68.9, 109.3, 114.6, 126.7, 126.1, 127.6, 128.0, 129.7, 132.6, 133.9, 138.8, 139.3, 145.0, 148.5, 155.2, 163.9, 175.8, Anal. calcd for $C_{37}H_{28}N_4O_4$: C, 71.52; H, 5.42; N; 10.76%. Found: C, 71.58; H, 5.46; N, 10.72%.

Synthesis of 1-[5-(phenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl]ethanone (6a):

A mixture of chalcone **1a** (0.01 mole), hydrazine hydrate (0.01 mole) and acetic acid (60 ml) was heated at reflux for 10 hrs, then poured in to crushed ice. The precipitate was separated by filtration, washed with water, and crystallized from methanol. Compounds **6b-c**

were also prepared in a similar way with minor modification in refluxed time. Yield 78%, m.p. 120°C; IR (KBr, cm^{-1}): 3063 (C-H str., Ar-H), 1718 (C=O), 1618 (C=N str.); ^{1}H NMR ($CDCl_3$): δ (ppm): 2..08 (s, 3H, CH_3), 7.08-7.76 (m, 10H, Ar-H), 2.5 (d, 2H, CH_2), 4.6 (t, 1H, CH); Anal. calcd for $C_{17}H_{16}N_2O$: C,77.25; H, 6.10; N; 10.60%. Found: C, 77.12; H, 5.97; N, 10.71%.

Synthesis of 1-[{5-(4-chlorophenyl-3-phenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl] ethanone (6b):

Yield 81%, m.p. 145°C; IR (KBr, cm^{-1}): 3078 (C-H str., Ar-H), 1731 (C=O), 1624 (C=N str.), 738 (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.13 (s, 3H, CH_3), 7.18-7.93 (m, 9H, Ar-H), 2.8 (d, 2H, CH_2), 4.9 (t, 1H, CH); Anal. calcd for $C_{17}H_{15}ClN_2O$: C,68.34; H, 5.06; N; 9.38%. Found: C, 68.21; H, 5.14; N, 9.47%.

Synthesis of 1-[5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl]ethanone (6c):

Yield 79%, m.p. 132°C; IR (KBr, cm^{-1}): 3072 (C-H str., Ar-H), 1728 (C=O), 1622 (C=N str.), 1208 (C-O-C str.); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.1 (s, 3H, CH_3), 7.93-7.82 (m, 9H, Ar-H), 2.7 (m, 2H, CH_2), 4.7 (t, 1H, CH), 3.6 (s, OCH_3). Anal. calcd for $C_{18}H_{18}N_2O_2$: C,73.45; H, 6.16; N; 9.52%. Found: C, 73.56; H, 6.25; N, 9.39%.

Synthesis of 3-(phenyl)-1-[5-(phenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl]prop-2-en-1-one (7a):

A mixture of compound **2** (.001 mole), benzaldehyde (.01 mole) in ethanol (30 ml) and then add drop wise aqueous solution of NaOH 30% (15 ml) was added to it, mixture was stirred 4 hrs. The mixture was kept overnight at room temperature and then it was poured into crushed ice and acidified with dilute hydrochloric acid. The chalcone derivative precipitates out as solid. Then it was filtered and crystallized from ethanol. Yield 70%, m.p. 85°C; IR (KBr, cm^{-1}): 3089 (C-H str., Ar-H), 1726 (C=O), 1625 (C=N str.), ^{1}H NMR ($CDCl_3$): δ (ppm) , 7.08-7.786 (m, Ar-H), 2.8 (d, 2H, CH_2), 4.7 (t, 1H, CH), 6.7 (d, CH), 7.4 (d, CH); ^{13}CNMR : δ 52.5, 83.6, 118.9, 126.6, 126.5, 127.3, 128.0, 128.3, 128.6, 128.8, 129.0, 130.3, 132.4, 134.6, 140.5, 144.7, 149.4, 162.8. Anal. calcd for $C_{24}H_{20}N_2O$: C,81.79; H, 5.72; N; 7.95%. Found: C, 81.89; H, 5.64; N, 7.81%. Compounds 7b-c were also prepared by similar method with minor change in reaction conditions, mole ratio of reagents, reflux time.

3-(phenyl)-1-[5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl]prop-2-en-1-one (7b):

Yield 73%, m.p. 101°C; IR (KBr, cm^{-1}): 3095 (C-H str., Ar-H), 1735 (C=O), 1627 (C=N str.), 742 (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ 7.06-7.86 (m, Ar-H), 3.1 (m, 2H, CH_2), 5.1 (t, 1H, CH),), 6.9 (d, CH), 7.6 (d, CH). ^{13}CNMR : δ 53.6, 84.3, 118.9, 126.5, 127.3, 127.9, 128.3, 128.7, 129.4, 130.5, 131.5, 132.6, 135.8, 141.5, 144.7, 148.3, 161.8. Anal. calcd for $C_{24}H_{19}ClN_2O$: C,74.51; H, 4.95; N; 7.24%. Found: C, 77.12; H, 5.97; N, 10.71%.

3-(phenyl)-1-[5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl]prop-2-en-1-one (7c):

Yield 77%, m.p. 94° C; IR (KBr, cm^{-1}): 3092 (C-H str., Ar-H), 1731 (C=O), 1626 (C=N str.), 1214 (C-O-C str.); ^{1}H NMR ($CDCl_3$): δ (ppm), 6.89-7.6 (m, Ar-H), 3.0 (d, 2H, CH_2), 4.9 (t, 1H, CH), 6.84 (d, CH), 7.6 (d, CH), 3.5 (s, OCH_3). ^{13}CNMR : δ 53.2, 62.3, 84.7, 114.5, 117.3, 126.8, 127.5, 128.1, 128.3, 129.0, 129.5, 131.3, 133.6, 135.8, 136.3, 143.8, 152.7, 156.2, 163.6; ^{13}CNMR : δ 52.4, 55.9, 81.9, 101.4, 116.5, 118.5, 121.5, 123.7, 126.8, 127.4, 127.9, 128.0, 128.3, 128.8, 129.1, 129.7, 131.5, 132.6, 134.6, 135.8, 136.3, 139.3, 149.3, 157.0, 160.3. Anal. calcd for $C_{18}H_{18}N_2O_2$: C,73.45; H, 6.16; N; 9.52%. Found: C, 73.56; H, 6.25; N, 9.39%

Synthesis of 2-(phenyl)-4,[5-(phenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-1H-benzo(b) [1,5]diazepine (8a):

Compound **3** (0.01 mole) and o-phenylenediamine (0.01 mole) were dissolved in xylene and refluxed for 9 hrs. The reaction mixture was filtered and remove solvent by reduce pressure. The solid obtained was recrystallized from ethanol. Yield 69%, m.p. 165°C; IR (KBr, cm^{-1}): 3216 (NH), 3082 (C-H str., Ar-H), 1637 (C=N str.); ^{1}H NMR ($CDCl_3$): δ (ppm), 3.5 (s, NH), 6.83-7.68 (m, Ar-H), 2.5 (m, 2H, CH_2), 3.3 (t, 1H, CH), 4.0 (s, CH); ^{13}CNMR : δ 54.6, 79.4, 102.5, 115.6, 120.3, 124.5, 126.5, 126.9, 127.0, 127.1,127.4, 127.9, 128.0,128.7, 129.0,130.3, 131.9, 133.8, 134.9, 138.9, 143.9, 149.8, 151.9, 164.3. Anal. calcd for $C_{30}H_{24}N_4$: C,81.79; H, 5.49; N; 12.72%. Found: C, 81.89; H, 5.31; N, 12.82%

Compounds 8b-c were also prepared by similar method with minor change in reaction conditions.

Synthesis of 2-(phenyl)-4-[5-(4-chlorophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-1H-benzo(b)[1,5] diazepine (8b):

Yield 70%, m.p.170°C; IR (KBr, cm^{-1}): 3218 (NH), 3089 (C-H str., Ar-H), 1639 (C=N str.),732 (C-Cl); ^{1}H NMR ($CDCl_3$): δ (ppm),3.8 (s, NH), 6.89-7.71 (m, Ar-H), 2.8 (d, 2H, CH_2), 3.6 (t, 1H, CH), 4.2 (s, CH); ^{13}CNMR : δ 52.5, 80.3, 103.4, 117.4, 120.5, 123.1, 126.3, 126.9, 127.0, 127.9, 128.3, 128.8, 128.9, 129.1, 129.8, 131.2, 132.3, 134.0,135.3, 138.2, 142.5, 129.3, 153.9, 162.7. Anal. calcd for $C_{30}H_{23}ClN_4$: C,75.86; H, 4.88; N; 11.80%. Found: C, 75.98; H, 4.70; N, 11.69%

Synthesis of 2-(phenyl)-4-[5-(4-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-1H-benzo(b)[1,5] diazepine (8c):

Yield 73%, m.p. 125°C; IR (KBr, cm^{-1}): 3213 (NH), 3085 (C-H str., Ar-H), 1638 (C=N str.); ^{1}H NMR ($CDCl_3$): δ (ppm), 3.8 (s, NH), 7.01-7.79 (m, Ar-H), 2.8 (d, 2H, CH_2), 3.5 (t, 1H, CH), 4.2 (s, CH), 3.21 (s,

OCH_3); ^{13}CNMR : δ 52.4, 55.9, 81.9, 101.4, 116.5, 118.5, 121.5, 123.7, 126.8, 127.4, 127.9, 128.0, 128.3, 128.8, 129.1, 129.7, 131.5, 132.6, 134.6, 135.8, 136.3, 139.3, 149.3, 157.0, 160.3. Anal. calcd for $C_{37}H_{26}N_4O$: C,79.12; H, 5.57; N; 11.91%. Found: C, 79.01; H, 5.71; N, 12.04%

Synthesis of N-ethoxyphthalimido-2-(phenyl)-4-[5-(phenyl)-3-phenyl-4,5-dihydro pyrazol-1-yl]-1H-benzo(b)[1,5]diazepine (9a):

A mixture of **8a** (0.01mole) and phthalimidoxyethylbromide (0.01mole) were dissolved in DMF. Pyridine (0.02 mole) was added to this reaction mixture as a base. The reaction mixture was refluxed for 15 hrs. The filtrate was poured into crushed ice and the solid obtained was filtered, dried and recrystallized from ethanol. Yield 77%, m.p. 218° C; IR (KBr, cm^{-1}): 3084 (C-H str., Ar-H), 1734 (C=O),1655 (C=N str.); ^{1}H NMR ($CDCl_3$): δ (ppm), 6.92-7.59 (m, Ar-H), 3.16 (d, 2H, CH_2), 3.71-3.75 (t, 1H, CH), 4.8 (s, CH), 3.43-3.47 (t, N-CH_2), 4.13-4.19 (t, OCH_2); ^{13}CNMR : δ 51.7, 55.7, 66.7, 76.9, 103.5, 116.9, 120.3, 123.8, 125.2, 126.0, 127.6, 127.3, 128.0, 128.2, 128.6, 129.0, 129.5, 129.6, 129.9, 131.9, 132.5, 133.3, 134.6, 135.8, 136.9, 139.3, 142.6, 149.5, 152.6, 161.8, 164.7. Anal. calcd for $C_{40}H_{31}N_5O_3$: C,76.29; H, 4.96; N; 11.12%. Found: C, 76.38; H, 4.79; N, 11.00%, Compounds 9b-c were also prepared by similar method with minor change in reaction conditions, mole ratio of reagents, reflux time.

Synthesis of N-ethoxyphthalimido-2-(phenyl)-4-[5-(4-chlorophenyl)-3-phenyl-4,5-dihydro pyrazol-1-yl]-1H-benzo(b)[1,5]diazepine (9b):

Yield 67%, m.p. 190° C; IR (KBr, cm^{-1}): 3087 (C-H str., Ar-H),1740 (C=O), 1649 (C=N str.), 737 (C-Cl); ^{1}H NMR ($CDCl_3$): δ (ppm), 6.92-7.59 (m, Ar-H), 3.0-3.16 (d, 2H, CH_2), 3.7 (t, 1H, CH), 4.8 (s, CH), 3.43-3.47 (t, N-CH_2), 4.13-4.19 (t, OCH_2); ^{13}CNMR : δ 51.9, 55.5, 68.9, 72.4, 103.4, 118.6, 121.4, 123.6, 126.7, 127.5, 127.8, 128.1, 128.2, 128.5, 128.7, 128.9, 129.3, 129.7, 130.5, 132.4, 133.5, 134.7, 134.9, 135.6, 138.8, 140.5, 152.4, 160.4, 164.8. Anal. calcd for $C_{40}H_{30}N_5O_3$: C,72.34; H, 4.55; N; 10.54%. Found: C, 72.34; H, 4.71; N, 10.41%

Synthesis of N-ethoxyphthalimido-2-(phenyl)-4-[5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro pyrazol-1-yl]-1H-benzo(b)[1,5]diazepine (9c):

Yield 70%, m.p. 230° C; IR (KBr, cm^{-1}): 3081 (C-H str., Ar-H), 1737 (C=O), 1652 (C=N str.); ^{1}H NMR ($CDCl_3$): δ (ppm), 6.92-7.59 (m, Ar-H), 3.0-3.16 (d, 2H, CH_2), 3.7 (t, 1H, CH), 4.8 (s, CH), 3.43-3.47 (t, N-CH_2), 4.13-4.19 (t, OCH_2), 3.21 (s, OCH_3); ^{13}CNMR : δ 51.9, 55.6, 59.0, 68.9, 74.6, 107.4, 114.5, 116.7, 118.9, 124.5, 126.5, 127.5, 127.9, 128.2, 128.4, 128.5, 129.0, 129.7, 131.5, 132.6, 133.5, 133.7, 134.6, 134.9, 135.8, 138.5, 152.6, 156.4, 161.7, 165.7. Anal. calcd for $C_{41}H_{33}N_5O_4$: C,74.64; H, 5.04; N; 10.62%. Found: C, 74.79; H, 4.86; N, 10.78%

Synthesis of 4-(phenyl)-6-phenyl-4,5-dihydro-2,1-benzisoxazol-3(3aH)-one (10a):

A mixture of **2a** (0.01mole) and hydroxylamine (0.01mole) were dissolved in ethanol acetic acid (1mL) was added to this reaction mixture as a catalyst. The reaction mixture was refluxed for 6 hrs. The solid obtained was filtered, dried and recrystallized from ethanol. Yield 81%, m.p. 192°C; IR (KBr, cm^{-1}): 3063 (C-H str., Ar-H), 1735 (C=O), 1612 (C=N str.); ^{1}H NMR ($CDCl_3$): δ (ppm), 6.72-7.39 (m, Ar-H), 2.5 (d, 1H, CH-C=O), 4.8 (m, 1H, CH), 2.8 (dd, CH), 3.1 (dd, CH), 5.5 (s, CH); ^{13}CNMR : δ 51.9, 55.6, 59.0, 68.9, 74.6, 107.4, 114.5, 116.7, 118.9, 124.5, 126.5, 127.5, 127.9, 128.2, 128.4, 128.5, 129.0, 129.7, 131.5, 132.6, 133.5, 133.7, 134.6, 134.9, 135.8, 138.5, 152.6, 156.4, 161.7, 165.7. Anal. calcd for $C_{19}H_{15}NO_2$: C,78.87; H, 4.84; N; 5.23%. Found: C, 78.86; H, 4.89; N, 5.28% Compounds 10b-d were also prepared by similar method with minor change in reaction conditions, mole ratio of reagents, reflux time.

Synthesis of 4-(4-chlorophenyl)-6-phenyl-4,5-dihydro-2,1-benzisoxazol-3(3aH)-one(10b):

Yield 77%, m.p. 198°C; IR (KBr, cm^{-1}): 3068 (C-H str., Ar-H), 1745 (C=O), 1624 (C=N str.),785 (C-Cl), ^{1}H NMR ($CDCl_3$): δ (ppm), 6.90-7.42 (m, Ar-H), 2.9 (d, 1H, CH-C=O), 5.1 (m, 1H, CH), 3.0 (dd, CH), 3.5 (dd, CH), 5.8 (s, CH); ^{13}CNMR : δ 25.7, 33.4, 58.3, 106.5, 126.5, 126.8, 128.2, 128.9, 131.5, 139.4, 146.5, 151.8, 162.5, 169.8. Anal. calcd for $C_{19}H_{14}ClNO_2$: C,70.48; H, 4.36; N; 4.33%. Found: C, 70.52; H, 4.41; N, 4.31%

Synthesis of 4-(4-methoxyphenyl)-6-phenyl-4,5-dihydro-2,1-benzisoxazol-3(3aH)-one (10c):

Yield 79%, m.p. 210°C; IR (KBr, cm^{-1}): 3060 (C-H str., Ar-H), 1739 (C=O), 1620 (C=N str.), 1228 (C-O-C); ^{1}H NMR ($CDCl_3$): δ (ppm), 6.72-7.39 (m, Ar-H), 2.5 (d, 1H, CH-C=O), 4.8 (m, 1H, CH), 2.8 (dd, CH), 3.1 (dd, CH), 5.5 (s, CH); ^{13}CNMR : δ 35.2, 48.3, 59.4, 62.1, 105.76, 114.7, 126.5, 127.6, 127.5, 128.5, 128.9, 135.5, 142.7, 152.6, 159.3, 162.6, 169.0. Anal. calcd for $C_{20}H_{17}NO_3$: C,75.22; H, 5.37; N; 4.39%. Found: C, 75.26; H, 5.31; N, 4.30%

Synthesis of 4-(4-N,N-dimetylaminephenyl)-6-phenyl-4,5-dihydro-2,1-benzisoxazol-3(3aH)-one (10d):

Yield 85%, m.p. 208°C; IR (KBr, cm^{-1}): 3068 (C-H str., Ar-H), 1740 (C=O), 1618 (C=N str.); ^{1}H NMR ($CDCl_3$): δ (ppm), 6.72-7.39 (m, Ar-H), 2.5 (d, 1H, CH-C=O), 4.8 (m, 1H, CH), 2.8 (dd, CH), 3.1 (dd, CH), 5.5 (s, CH); ^{13}CNMR : δ 36.1, 45.7, 48.5, 52.1, 62.6, 108.5, 114.5,

125.5, 126.8, 127.2, 128.9, 140.2, 145.6, 151.6, 163.6, 168.9. Anal. calcd for $C_{21}H_{20}N_2O_2$: C,75.88; H, 6.06; N; 8.43%. Found: C, 75.91; H, 6.12; N, 8.39%

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