Synthesis of Some New Dibenzodiazepine Derivatives from Cyclic β Diketones as Antipsychotic Agents

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ABSTRACT

Two new series of nonclassical dibenzodiazepine derivatives; namely; 8-chloro-2, 3, 4, 5,10,11-hexahydro-11-substituted-1H-dibenzo[b,e] [1,4] diazepine-1-ones and their 3,3-dimethyl analogs (4-21) were prepared via internal *Mannich* reaction of 3-[(2- amino-4-chlorophenyl) amino]-2-cyclohexen-1-one and its 5,5-dimethyl analog, respectively, with different aromatic aldehydes at room temperature in ethanol containing catalytic amounts of glacial acetic acid. Pharmacological evaluation of dibenzodiazepine derivatives (4-21) revealed that compounds 4 and 13 which bearing 4-bromophenyl moiety at 11-position of dibenzodiazepine skeleton possess higher antipsychotic activity than the reference drug clozapine upon using ptosis test on male Albino mice at a dose of 1.5mg/kg meanwhile they showed nonsignificant agranulocytosis which is fatal side effect often induced during the course of clozapine treatment.

Key words: Synthesis, dibenzodiazepine derivatives, clozapine, antipsychotic activity, agranulocytosis

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INTRODUCTION

Schizophrenia is a serious mental disease that affects 0.5–1.0% of the population and often has a chronic course. Antipsychotic drugs effectively control psychotic symptoms, but may cause important side effects, significantly increasing morbidity and mortality [1,2]. In more than 20% of schizophrenic patients, traditional typical antipsychotic drugs e.g. chloropromazine and haloperidol (figure 1) do not produce sufficient responses [3,4].
Despite the extensive research aimed at developing new antipsychotic drugs, clozapine remains the drug of choice for patients who do not respond to antipsychotic drugs [5-7]. Clozapine is chemically a dibenzodiazepine derivative which is superior to many other antipsychotics in the management of patients with treatment resistant schizophrenia [8]. Moreover, clozapine is also associated with significant reductions in hospitalization [9], hostility [10] and suicidality [11].

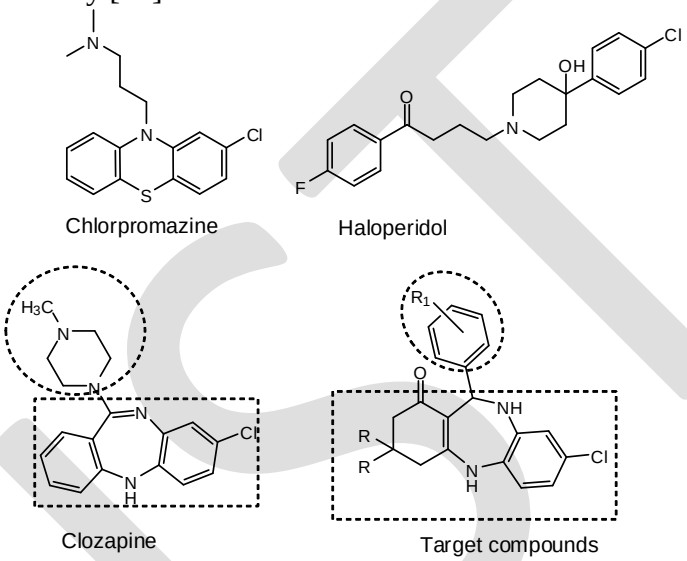


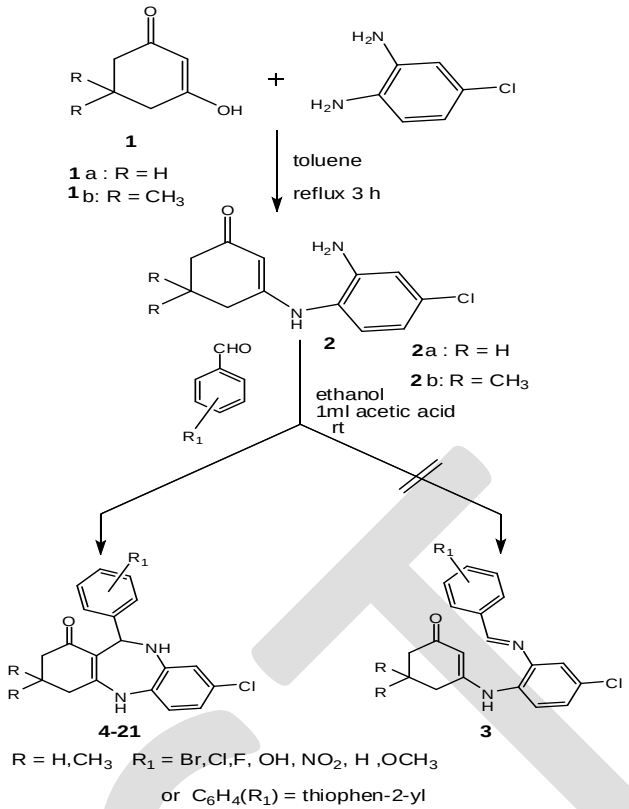
Figure 1. Design concept of novel dibenzodiazepine derivatives

Although the use of atypical clozapine in treatment of schizophrenia avoided the main disadvantage of typical ones e.g. extrapyrimidal side effects, still its use is limited due to the ability to induce a potentially fatal agranulocytosis [12,13] and other side effects [14,15].
Based on the above facts, new compounds structurally related to the aforementioned dibenzodiazepine derivatives (figure 1) will be synthesized with the aim to be clozapine-like antipsychotics but with no or lesser fatal agranulocytosis side effect which often induced during the course of clozapine treatment.

RESULTS AND DISCUSSION

CHEMISTRY

In the present work, new nonclassical dibenzodiazepine derivatives (**4-21**) were synthesized as shown in scheme 1.



Scheme 1. The synthetic pathway for preparation of the target dibenzodiazepine derivatives (**4-21**)

In continuation to our previous work, two enaminones (**2a** and **2b**) were synthesized in good yields by condensation of equimolar amounts of 4-chloro-l,2-diaminobenzene and 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cycl-ohexandionevia heating under reflux in toluene for 3 hours as the reported method [16].

The 4-chloro-1,2-diaminobenzene reacts satisfactorily in this way provided that a 1: 1 molar ratio of the reactants was used where there was no amount of products from two molecules of 1,3-cyclic diketones and one molecule of the respective amine[17]. The structures of the novel enaminones were confirmed using elemental analyses and different spectroscopic methods. ^{1}HNMR spectra showed a singlet at δ = 4.41-4.65 ppm for the vinylic proton as well as a singlet at δ = 4.95-5.11 ppm integrating two protons of the amino group. In addition,the appearance of singlet at δ = 7.9-8.19 ppm integrating one proton of the imino group.

The novel nonclassical dibenzodiazepine derivatives (**4-21**) were prepared via internal *Mannich* reaction by allowing the 3-(2-amino-4- chloro-phenyl)amino-2-cyclohexen-l-one (**2a**) or the 5,5-dimethyl analog (**2b**) to react at room temperature with different aldehydes in ethanol containing drops of glacial acetic acid as catalyst as shown in scheme 1. The high reactivity of the enaminones (**2a** and **2b**) towards the aldehydes can be attributable to the enaminone structure in which α-position is particularly reactive to electrophilic reagents. The reaction was characterized by being almost quantitative and without by-product (compound **3**). The dibenzodiazepine derivatives (**4-21**) were characterized using elemental analyses, IR, ^{1}HNMR and mass spectroscopic methods. ^{1}HNMR showed no singlet at δ = 4.41 ppm for the vinylic proton as well as no singlet at δ = 4.95 ppm for the amino group of the starting enaminones. In addition, the appearance of very characteristic doublet at δ = 5.45-5.69 ppm

integrating one proton of the benzylic H at 11-position which become singlet after D_2O as well as a doublet at δ = 6.25- 6.67 integrating one proton of NH at 10-position of the di-benzodiazepine skeleton.

PHARMACOLOGICAL STUDIES

Compounds **4–21** were subjected to preliminary screening *in vivo* to explore their antipsychotic activity using ptosis test [16,18] in comparison with the reference drug clozapine [18]. Compounds **4,11,13** and **20** were selected owing to their high activity while other compounds were excluded. The selected compounds (**4, 11 , 13** and **20**) were tested for antipsychotic and sedative activities via ptosis and sleeping time[19] tests respectively using clozapine as a reference drug. In addition, the animals were subjected to leucocytic count [20] to investigate the presence or absence of agranulocytosis which often induced during the course of clozapine treatment as a side effect.

1- Ptosis test

It was carried out according to the method described by Chen and Bohner [18]. The ptosis was rated as the fraction of the eyelid closure from normal. The effect of clozapine and the new chosen compounds (**4,11 , 13** and **20**) at a dose of 1.5 mg/kg on male mice using ptosis test were recorded in table (1).

2- Sleeping time test

The effects of the selected compounds(**4,11 , 13**, **20**) and clozapine at a dose of 1.5 mg/kg on male mice on sleeping time were conducted according to the method described by Alpermann [19]. The time from losing to regaining of the lighting reflex was determined and recorded in table (2).

3- Leucocytic count method

The selected compounds (**4,11 , 13**, **20**) and clozapine were injected at a dose of 1.5 mg/kg / day for three successive days on mice and then blood samples were collected after one, two and seven days of the last dose in all groups. Total leucocytes were counted according to the method of Schalm [20] and then recorded in table (3).

Table 1. The effect of clozapine and the new chosen compounds (1.5 mg / kg i.p) on male mice using ptosis test (n= 6)

Compounds	Ptotic scoring	% effect
Control	0 (no ptosis)	0.00
Clozapine	3 (3/4 ptosis)	100.0
4	4 (complete ptosis)	133.3
11	2 (1/2 ptosis)	66.60
13	4 (complete ptosis)	133.3
20	2 (1/2 ptosis)	66.60

Table 2. The effect of clozapine and the new chosen compounds (1.5 mg / kg i.p) on the sleeping time of mature mice

Compounds	Onset time (min)	#% effect	Sleeping time (min)	#% effect
Control	0	0.00	0	0.00
Clozapine	8.16±0.38	100.0	32.7±0.41	100.0
4	6.31±0.24***	77.2	93.8±0.68***	286.8
11	8.0±0.16	98.0	27.16±0.37***	83.2
13	7.6±0.07	93.1	56.6±0.78***	173.1
20	15.6±0.15***	191.2	25.3±0.22***	77.4

#% effect (% of sleeping time of tested compounds/ sleeping time of clozapine). Values were expressed as mean ± standard deviation of 6 animals. *** P>0.0001 compared with Clozapine group (Independent-sample T test).

Table 3. The effect of clozapine and the new chosen compounds (1.5 mg / kg / day for three days) on the leucocytic count ($10^3/mm^3$) n = 6

Compounds	Post-treatment					
	One day	% effect	Two days	% effect	One week	% effect
Control	10.53+0.91	(100)	10.46+0.85	(100)	10.43+0.78	(100)
Clozapine	7.381+ 0.225*	(70.0)	5.63+0.436***	(53.8)	4.02+0.38**	(38.5)
4	9.981+ 0.138	(94.7)	8.65+0.237	(82.6)	9.81+0.3	(93.9)
11	7.951+0.76	(75.4)	5.11+0.4***	(48.7)	4.11+0.42***	(39.3)
13	9.051+0.464	(85.9)	8.25+0.23	(78.8)	8.81+0.148	(84.4)
20	7.92+0.136*	(75.2)	7.81+0.192*	(74.5)	7.21+0.171*	(69.0)

Values were expressed as mean ± standard deviation of 6 animals; *** P>0.0001, ** P>0.001 and * P>0.05 compared with control group (Independent-sample T test).

PHARMACOLOGICAL RESULTS

Compound 4 (nonmethylated analog of compound 13)

It showed 33.3% higher antipsychotic activity than clozapine (Table 1). The onset of sedation of compound 4 was 6.3 min. which was shorter than that of clozapine by 22.8%. Surprizingly , its duration of action was longer by 186.8% than that of clozapine (Table 2). Luckily, compound 4 showed nonsignificant decrease (6.1 % from control) in white blood cells (WBCs) count while clozapine exhibted significant decrease (61.5 % from control) leading to

agranulocytosis after one week post- treatment (Table 3). On the other side, dibenzodiazepine **13** showed 33.3% higher antipsychotic activity than that of clozapine (Table 1).
Through analysis of table 2, the compounds can be arranged as follows:

a) According to their onset of sedation into:
Compound **4** (77.2%) < compound **13** (93.1%) < clozapine (100%)
b) According to the duration of sedative effect into:
Compound **4** (286.8%) > compound **13** (173.1%) > clozapine (100%).

It is apparent that dibenzodiazepines **4** and **13** have higher antipsychotic and sedative activities than clozapine due to the presence of 4-bromophenyl moiety in each. Indeed, the halogen substituent in different antipsychotic diarylazepine analogs has been considered as an important structural element in the drug-receptor interaction [21]. Its favorable influence might be related not only to electron-withdrawing effect but also the increased lipophilicity [22]. In addition, the methylated derivative (compound **13**) showed a lower sedative effect than the nonmethylated one (compound **4**) due to the presence of geminal methyl groups which may affect the planarity of the molecule. Compound **13** showed nonsignificant decrease in leucocytic count by 15.6% from control which is considered very low if compared with that of clozapine (61.5%) after one week post -treatment (Table 3).

Compound 11 (nonmethylated analog of compound 20)

It showed moderate antipsychotic activity which represents 33.3% lower than that of clozapine (Table 1). Moreover, its onset time of sedation was nearly the same as clozapine while its duration of action is shorter than that of clozapine by 16.8% (Table 2). Compound 11 causes significant decrease in leucocytic count by 60.7% which is nearly similar to clozapine after one week post - treatment (Table 3).

On the other side, dibenzodiazepine **20** exhibited 33.3% lower antipsychotic activity than that of clozapine Table (3) .In addition, compound **20** (methylated derivative) showed a lower sedative effect than both clozapine and compound **11** (Table 2). The geminal methyl groups of compound **20** may be responsible for the difference in sedative activity because of their expected effect on the planarity of tricyclic skeleton. Dibenzodiazepine **20** also causes neutropenia which was lesser than that of clozapine (31% for compound **20** and 61.5% for clozapine) after one week post- treatment (Table 3).

CONCLUSIONS

It could be concluded that new dibenzodiazepine derivatives (**4-21**) were synthesized with high yields at room temperature starting from cyclic β-diketones by application of *Mannich* conditions. Pharmacological study revealed that both dibenzodiazepines **4** and **13** which bearing 4-bromophenyl moiety at 11-position of dibenzodiazepine skeleton possess greater antipsychotic activity than that of the reference drug clozapine upon using ptosis test on male Albino mice at a dose of 1.5mg/kg meanwhile they showed nonsignificant agranulocytosis which is fatal side effect associated with clozapine treatment. Despite of their greater antipsychotic activity , these compound (**4** and **13**) may be preferred to be promising as hypnotic compounds. So, further future pharmacological studies should be carried out to cover this point.

EXPERIMENTAL

CHEMISTRY

Melting points were determined with a Gallenkamp (London,U.K.) melting point apparatus and are uncorrected. IR spectra (KBr,cm-1) were recorded on Bruker Vector, 22FT- IR (Fourier Transform Infrared (FTIR)) (Germany) spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini-200 (200-MHz, Foster City, Calif.**,** USA) and Varian Mercury-300 (300-MHz, City: Palo Alto, State: Calif., USA) spectrometers using dimethylsulphoxide (DMSO)-*d6* as a solvent and tetramethylsilane (*TMS*) as an internal standard (Chemical shift in d, ppm). Mass spectra were determined using Mass spectrometers GC/MS Shimadzu QP 1000 EX(Shimadzu Corporation, Tokyo, Japan) with ionization energy 70 eV. Elemental analyses were determined using Automatic Elemental Analyzer CHN Model 2400 Perkin Elmer (USA) at Microanalytical Center, Faculty of Science, Cairo University, Egypt. All the results of elemental analyses corresponded to the calculated values within experimental error. Progress of the reaction was monitored by thin-layer chromatography (TLC) using precoated TLC sheets with Ultraviolet (UV) fluorescent silica gel (Merck 60F254) and spots were visualized by iodine vapors or irradiation with UV light (254 nm). All the chemicals were purchased from *Sigma-Aldrich*.

General procedure for preparation of compounds 2a and 2b

A mixture of equimolar amounts of 1,3-cyclohexanedione or 5,5-dimethyl -1,3-cyclohexanedione and 4-chloro-1,2-diaminobenzene (0.02 mol) was heated at reflux in toluene(40ml) for 3hours.The reaction mixture was concentrated and then allowed to cool to room temperature. The separated crystalline product was filtered, dried and crystallized from toluene.

3-[(2-Amino-4-chlorophenyl)amino]-2-cyclohexen-1-one (2a)

Yield: 86%; mp.: 147-149^{0}C; IR: υ = 3480, 3400, 3310 (NH_2,NH), 3040 (CH aromatic), 2960 (CH aliphatic), 1630 (CO)cm^{-1}; ^{1}HNMR(300 MHz): δ= 1.60 -2.45 (m ,6H. 3x CH_2), 4.41 (s, 1H,CH =C),4.95 (s, 2H, NH_2 , exch.), 6.21-7.01 (m, 3H, ArH), 7.91 (s,1H, NH, exch.) ppm. Anal. calcd for $C_{12}H_{13}C1N_2O$ (236.70): C, 60.89 ; H, 5.54; N,11.84.Found: C, 60.71 H, 5.63; N,11.62 %.

3-[(2-Amino-4-chlorophenyl)amino]-5,5-dimethyl-2-cyclohexen-1-one (2b)

Yield: 90%; mp.: 190-192^{0}C; IR: υ = 3420,3300,3210 (NH_2,NH), 3010 (CH aromatic), 2930 (CH aliphatic),1610 (C=O) cm^{-1}; ^{1}HNMR (300 MHz): δ = 1.01 (s, 6H, 2CH_3), 2.02 (s, 2H, CH_2), 2.35 (s, 2H, CH_2), 4.65 (s, 1H, vinylic H), 5.11(s, 2H, NH_2, exch.),6.53-7.12 (m, 3H, ArH), 8.19(s, 1H, NH, exch.) ppm. Anal. calcd for $C_{14}H_{17}C1N_2O$ (264.75): C, 63.51 ; H, 6.47; N, 10.58.Found: C, 63.72; H, 6.43; N, 10.42%.

General procedure for preparation of compounds 4-21.

To a stirred solution of the respective enaminone **2a** or **2b** (0.0042 mol) in 15 ml ethanol, were added the appropriate aldehyde (0.0042 mol) and 1 ml of glacial acetic acid and the resulting mixture was stirred at room temperature for 12 hours. The separated crystalline product was filtered, dried and crystallized from the appropriate solvent.

11-(4-Bromophenyl)-8-chloro-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one(4)

Yield: 85%; mp.: 242-244^{0}C; crystallized from dioxane /H_2O (3/1); IR: υ = 3370, 3290 (NH), 3070 (CH, aromatic), 2940 (CH, aliphatic), 1610 (C=O), 1570 (C=C) cm^{-1}; ^{1}HNMR (200 MHz): δ = 1.85 - 2.10 (m, 2H, CH_2), 2.22-2.35 (m, 2H, CH_2), 2.55 -2.74 (m, 2H, CH_2), 5.53(d, 1H, CH at 11-position, after D_2O becomes s), 6.41 (d, 1H, NH, at 10-position,exch.), 6.51-7.31 (m, 7H, ArH), 8.75 (s, 1H, NH, at 5-position,exch.) ppm. Anal. calcd for $C_{19}H_{16}BrClN_2O$ (403.70): C,56.53;H, 3.99; N,6.94. Found: C,56.33; H,4.12; N,6.73%.

8-Chloro-11-(3-chlorophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (5)

Yield: 83%; mp.: 206-208 ^{0}C; crystallized from ethanol/ H_2O (3:1) ; IR: υ = 3340, 3210 (NH), 3040 (CH, aromatic) 2920 (CH, aliphatic), 1600 (C=O), 1560 (C=C) cm^{-1}; ^{1}HNMR (200 MHz): δ = 1.80 - 2.11 (m, 2H, CH_2), 2.12-2.31 (m, 2H, CH_2), 2.52 -2.65 (m, 2H, CH_2), 5.58(d, 1H, CH at 11-position, after D_2O becomes s), 6.28 (d, 1H, NH, at 10-position,exch.), 6.42-7.24 (m, 7H, ArH), 8.62 (s, 1H, NH, at 5-position, exch.) ppm. Anal. calcd for $C_{]9}H_{16}Cl_2N_2O$ (359.22):C,63.52; H,4.49; N,7.80;Found:C, 63.42; H, 4.34; N, 7.65 %.

8-Chloro-11-(4-chlorophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (6)

Yield: 85%; mp.: 237-238 ^{0}C; crystallized from dioxane /H_2O (3/1); IR: υ = 3360, 3230 (NH), 3070 (CH, aromatic), 2950 (CH, aliphatic),1610 (C=O), 1580 (C=C) cm^{-1}; ^{1}HNMR (200 MHz): δ = 1.84 - 2.13 (m, 2H, CH_2), 2.23-2.37 (m, 2H, CH_2), 2.52 -2.72 (m, 2H, CH_2), 5.51(d, 1H, CH at 11-position, after D_2O becomes s), 6.40 (d, 1H, NH, at 10-position,exch.), 6.46-7.35 (m, 7H, ArH), 8.74 (s, 1H, NH, at 5-position,exch.) ppm. Anal. calcd for $C_{]9}H_{16}Cl_2N_2O$ (359.22):C, 63.52; H, 4.49; N, 7.80; Found: C, 63.63; H, 4.43; N, 7.91 %.

8-Chloro-11-(4-fluorophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (7).

Yield: 80%; mp.: 217-218 ^{0}C; crystallized from ethanol; IR: υ = 3340, 3210 (NH), 3030 (CH, aromatic), 2920 (CH, aliphatic), 1600 (C=O), 1570 (C=C) cm^{-1}; ^{1}HNM R (90 MHz): δ = 1.75-2.01 (m, 2H, CH_2), 2.12 -2.31 (m, 2H, CH_2), 2.61-2.82 (m, 2H, CH_2), 5.52 (d, 1H, CH at 11-position, after D_2O becomes s), 6.41 (d, 1H, NH, at 10-position,exch.), 6.81 -7.13 (m, 7H,ArH), 8.75 (s, 1H, NH, exch.) ppm.Anal. calcd for $C_{19}H_{16}Cl$ FN_2O (342.79):C, 66.57; H, 4.70; N, 8.17; Found: C,66.41; H,4.52;N, 8.34%.

8-Chloro-11-(4-hydroxyphenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (8)

Yield: 78%; mp.:266-267 ^{0}C; crystallized from ethanol; IR: υ = 3550 (br, OH) , 3360,3290 (NH), 3070 (CH, aromatic), 2960 (CH, aliphatic), 1620 (C=O), 1580 (C=C) cm^{-1}; ^{1}HNMR (200 MHz): δ = 1.77-2.03 (m, 2H, CH_2), 2.15 -2.32 (m, 2H, CH_2), 2.63-2.84 (m, 2H, CH_2), 5.58(d, 1H, CH at 11-position, after D_2O becomes s), 6.50(d, 1H, NH at 10-position, exch.) 6.80-7.20(m, 7H,ArH), 8.71(s, 1H, NH, exch.), 9.14(s, 1H, OH, exch.) ppm; Anal. calcd for $C_{19}H_{17}Cl$ N_2O_2 (340.80): C, 66.96; H, 5.03; N, 8.22 ; Found: C, 67.11 ; H, 5.22 ;N, 8.41%.

8-Chloro-11-(4-nitrophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (9)

Yield: 83%; mp.: 250-252 ^{0}C; crystallized from dioxane /H_2O (3/1); IR: υ = 3380, 3280 (NH), 3090 (CH, aromatic), 2950 (CH, aliphatic), 1610 (C=O), 1580 (C=C), 1540 (NO_2), 1350 (NO_2) cm^{-1}; ^{1}HNMR(200 MHz): δ = 1.78-2.13 (m, 2H, CH_2), 2.25 -2.35 (m, 2H, CH_2), 2.65-2.85 (m, 2H, CH_2), 5.65-5.68(d, *J*= 6.0Hz, 1H, CH at 11-position, after D_2O becomes s), 6.57-6.60(d, *J*= 6.0 Hz,1H, NH at 10-position, exch.) 6.86-7.55(m, 7H,ArH), 8.97(s, 1H, NH, exch.) ppm. Anal. calcd for $C_{19}H_{16}CIN_3O_3$ (369.80): C, 61.71; H, 4.36; N, 11.36; Found: C,61.92; H,4.62; N,11.51%.

8-Chloro-11-phenyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (10)

Yield: 80%; mp.:248-250^{0}C; crystallized from ethanol; IR: υ = 3330, 3210 (NH), 3030 (CH, aromatic), 2920 (CH, aliphatic), 1600 (C=O), 1560 (C=C) cm^{-1}; ^{1}HNM R(300 MHz): δ = 1.68-2.13 (m, 2H, CH_2), 2.12-2.18 (m, 2H, CH_2), 2.55-2.65 (m, 2H, CH_2), 5.60-5.62(d, *J*= 6.0 Hz, 1H, CH at 11-position, after D_2O becomes s), 6.50-6.52(d, *J*= 6.0 Hz, 1H, NH at 10-position, exch.) 6.64-7.10(m, 8H,ArH), 8.85(s, 1H, NH, exch.) ppm. Anal. calcd for $C_{19}H_{17}ClN_2O$ (324.80):C, 70.26; H, 5.28; N, 8.62; Found: C,70.13; H, 5.25 ; N,8.52%.

8-Chloro-11-(thiophen-2-yl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (11)

Yield: 79%; mp.: 259-261 ^{0}C; crystallized from ethanol/ H_2O (3:1) ; IR: υ = 3340, 3220 (NH), 3080 (CH, aromatic), 2960 (CH, aliphatic), 1610 (C=O), 1570 (C=C) cm^{-1}; ^{1}HNMR(200 MHz): δ = 1.78-2.03 (m, 2H, CH_2), 2.12-2.18 (m, 2H, CH_2), 2.48-2.63 (m, 2H, CH_2), 5.66-5.69(d, *J* = 6 Hz, 1H, CH at 11-position, after D_2O becomes s), 6.61-6.64(d, *J*= 6.0 Hz, 1H, NH at 10-position, exch.) 6.75-7.36(m, 6H,ArH), 8.89(s, 1H, NH, exch.) ppm; Anal. calcd for $C_{17}H_{15}ClN_2OS$ (330.83):C, 61.72; H, 4.57; N, 8.47; Found: C, 61.54 ; H, 4.83 ; N,8.75%.

8-Chloro-11-(4-methoxyphenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (12)

Yield: 78%; mp.: 240-241 ^{0}C; crystallized from ethanol ; IR: υ = 3350, 3230 (NH), 3070 (CH, aromatic), 2950 (CH, aliphatic), 1600 (C=O), 1580 (C=C) cm^{-1}; ^{1}HNMR (90): δ = 1.85-2.01 (m, 2H, CH_2), 2.12 -2.31 (m, 2H, CH_2), 2.61-2.82 (m, 2H, CH_2), 3.55 (s,3H, OCH_3), 5.51(d, lH, CH at 11-position, after D_2O become s), 6.20(d, 1H, NH, at 10-position,exch.), 6.70-7.25 (m, 7H, ArH), 8.62 (s, 1H, NH, exch.) ppm. Anal. calcd for : $C_{20}H_{19}Cl\ N_2O_2$ (354.83) : C, 67.70; H, 5.40; N, 7.89 ; Found: C, 67.51; H, 5.63; N, 7.75 %.

11-(4-Bromophenyl)-8-chloro-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (13)

Yield: 90%; mp.: 287-189^{0}C; crystallized from dioxane /H_2O (3/1); IR: υ = 3360, 3250 (NH), 3080 (CH, aromatic), 2960 (CH, aliphatic), 1610 (C=O), 1590 (C=C) cm^{-1}; ^{1}HNMR(200 MHz): δ = 1.01, 1.06(two s, 6H, $2CH_3$), 2.06-2.27 (m, 2H, CH_2) ,2.8 (s, 2H, CH_2),5.64-5.67(d, *J*= 6 Hz , 1H, CH at 11-position after D_2O becomes s), 6.61-6.64(d, *J*= 6 Hz, 1H, NH, exch.),6.76- 7.414 (m, 7H,ArH), 8.985(s, 1H, NH, exch.) ppm. Anal. calcd for $C_{21}H_{20}BrClN_2O$ (431.75) : C, 58.42; H, 4.67; N, 6.49 ; Found : C, 58.62 ; H, 4.91 ; N,6.73%.

8-Chloro-11-(3-chlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e] [1,4]diazepin-1-one (14)

Yield: 84 %; mp.: 228-230^{0}C; ethanol/ H_2O (3:1); IR: υ = 3320, 3210 (NH), 3050 (CH, aromatic) 2920 (CH, aliphatic), 1600 (C=O), 1560 (C=C) cm^{-1}; ^{1}HNMR(200 MHz): δ = 1.03, 1.08(two s, 6H, 2CH_3), 2.14-2.27 (m, 2H, CH_2) ,2.81 (s, 2H, CH_2),5.62-5.65(d, *J*= 6 Hz , 1H, CH at 11-position after D_2O becomes s), 6.59-6.62(d, *J*= 6 Hz, 1H, NH, exch.),6.70-7.25 (m, 7H,ArH),8.96(s, 1H, NH, exch.) ppm. Anal. calcd for $C_{21}H_{20}Cl_2N_2O$ (387.30): C, 65.12; H, 5.20; N, 7.23 ; Found: C, 65.21; H, 5.11 ; N, 7.00 %.

8-Chloro-11-(4-chlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e] [1,4]diazepin-1-one (15)

Yield: 92 %; mp.: 278-280^{0}C; ethanol/ H_2O (3:1); IR: υ = 3350, 3230 (NH), 3080 (CH, aromatic), 2940 (CH, aliphatic), 1610 (C=O), 1580 (C=C) cm^{-1}; ^{1}HNMR(200 MHz): δ =1.01, 1.07(two s, 6H, 2CH_3), 2.05-2.26 (m, 2H, CH_2), 2.72 (s, 2H, CH_2) ,5.65 (d, 1H,CH at 11-position, after D_2O becomes s), 6.61(s, 1H, NH at 10-position, exch.) 6.75-7.27(m, 7H,ArH), 8.97(s, 1H, NH, exch.) ppm; Anal. calcd for $C_{21}H_{20}Cl_2N_2O$ (387.30): C, 65.12; H, 5.20; N, 7.23 ; Found: C, 65.00; H, 5.00 ; N, 7.10 %.

8-Chloro-11-(4-fluorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e] [1,4]diazepin-1-one (16)

Yield: 88 %; mp.: 227-229^{0}C; crystallized from dioxane; IR: υ = 3310, 3200 (NH), 3040 (CH, aromatic), 2910 (CH, aliphatic), 1590 (C=O), 1540 (C=C) cm^{-1}; ^{1}HNM R(200 MHz): δ = 1.02,1.06 (two s, 6H, 2CH_3), 2.11-2.23 (m, 2H, CH_2) ,2.84 (s, 2H, CH_2), 5.57-5.60(d, *J*= 6 Hz, 1H, CH at 11-position, after D_2O becomes s), 6.45-6.48(d, *J*= 6 Hz, 1H, NH at 10-position, exch.) 6.50-7.20(m, 7H,ArH), 8.84(s, 1H, NH, exch.) ppm; Anal. calcd for $C_{21}H_{20}ClFN_2O$ (370.85): C, 68.01; H, 5.44; N, 7.55; Found: C, 68.22 ; H, 5.2 3; N,7.41 %.

8-Chloro-11-(4-hydroxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e] [1,4]diazepin-1-one (17)

Yield: 87 %; mp.: 248-250 ^{0}C; crystallized from ethanol/ H_2O (3:1); IR: υ = 3560 (br, OH) , 3370,3280 (NH), 3060 (CH, aromatic), 2950 (CH, aliphatic), 1630 (C=O), 1590 (C=C) cm^{-1}; ^{1}HNMR(200 MHz): δ = 1.01,1.06 (two s, 6H, 2CH_3), 2.13-2.25 (m, 2H, CH_2) ,2.87 (s, 2H, CH_2), 5.570-5.596(d, *J*= 5.2 Hz, 1H, CH at 11-position, after D_2O becomes s), 6.453-6.483(d, *J*= 6.0 Hz, 1H, NH at 10-position, exch.) 6.71-7.31(m, 7H,ArH), 8.85(s, 1H, NH, exch.), 9.16(s, 1H, OH, exch.) ppm; Anal. calcd for $C_{21}H_{21}ClN_2O_2$ (368.86):C, 68.38; H, 5.74 ; N, 7.59 ; Found: C, 68.21 ; H, 5.81; N,7.42 %.

8-Chloro-3,3-dimethyl-11-(4-nitrophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4] diazepin-1-one (18)

Yield: 91 %; mp.: 270-271^{0}C; crystallized from ethanol/ H_2O (3:1); IR: υ = 3360, 3270 (NH), 3080 (CH, aromatic), 2960 (CH, aliphatic), 1610 (C=O), 1580 (C=C), 1530, 1340 (NO_2) cm^{-1}; ^{1}HNMR(200 MHz): δ = 1.02,1.07 (two s, 6H, 2CH_3), 2.16-2.27 (m, 2H, CH_2), 2.85 (s, 2H, CH_2),5.65-5.68(d, *J*= 6.0Hz, 1H, CH at 11-position, after D_2O becomes s), 6.57-6.60(d, *J*= 6.0 Hz,1H, NH at 10-position, exch.) 6.84-7.54(m, 7H,ArH), 8.96(s, 1H, NH,

exch.) ppm. Anal. calcd for $C_{21}H_{20}ClN_3O_3$(397.85): C, 63.40; H, 5.07; N, 10.56; Found: C,63.23; H,4.94; N, 10.72 %.

8-Chloro-3,3-dimethyl-11-phenyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (19)

Yield: 90 %; mp.: 257-258^{0}C; crystallized from ethanol/ H_2O (3:1); IR: υ = 3310, 3210 (NH), 3040 (CH, aromatic), 2910 (CH, aliphatic), 1590 (C=O), 1560 (C=C) cm^{-1}; ^{1}HNMR(300 MHz): δ = 1.02,1.07 (two s, 6H, $2CH_3$), 2.12-2.29 (m, 2H, CH_2), 2.81 (s, 2H, CH_2), 5.63-5.65(d, *J*= 6.0 Hz, 1H, CH at 11-position, after D_2O becomes s), 6.51-6.53(d, *J*= 6.0 Hz, 1H, NH at 10-position, exch.) 6.74-7.22(m, 8H,ArH), 8.87(s, 1H, NH, exch.) ppm. Anal. calcd for $C_{21}H_{21}ClN_2O$ (352.86):C, 71.48; H, 6.00; N,7.94; Found: C, 71.32 ; H, 6.22 ; N, 8.13%.

8-Chloro-3,3-dimethyl-11-(thiophen-2-yl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4] diazepin-1-one (20)

Yield:91%; mp.:238-239^{0}C; crystallized from ethanol; IR: υ = 3320, 3210 (NH), 3040 (CH, aromatic), 2920 (CH, aliphatic), 1600 (C=O), 1580 (C=C) cm^{-1}; ^{1}HNM R(200 MHz): δ =1.03, 1.06 (two s, 6H, $2CH_3$), 2.06-2.29 (m, 2H, CH_2),2.83 (s, 2H, CH_2), 5.65-5.68(d, *J*= 6.0 Hz, 1H, CH at 11-position, after D_2O becomes s), 6.64-6.67(d, *J*= 6.0 Hz, 1H, NH at 10-position, exch.) 6.71-7.26(m, 6H,ArH), 8.97(s, 1H, NH, exch.) ppm; Anal. calcd for $C_{19}H_{19}Cl\ N_2OS$ (358.88): C, 63.59; H, 5.34; N, 7.81; Found: C, 63.43; H, 5.51 ; N, 7.92%.

8-Chloro-11-(4-methoxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e] [1,4]diazepin-1-one (21)

Yield: 88%; mp.:218-219^{0}C; crystallized from ethanol/ H_2O (3:1); IR: υ = 3340, 3230 (NH), 3060 (CH, aromatic) 2940 (CH, aliphatic), 1600 (C=O), 1560 (C=C) cm^{-1}; ^{1}HNMR (200 MHz): δ = 1.05, 1.10 (two s, 6H, $2CH_3$), 2.11-2.23 (m, 2H, CH_2), 2.85 (s, 2H, CH_2),3.55 (s,3H, OCH_3), 5.51(d, lH, CH at 11-position, after D_2O become s), 6.20(d, 1H, NH, at 10-position,exch.), 6.40-6.95 (m, 7H, ArH), 8.61 (s, 1H, NH, exch.) ppm. Anal. calcd for $C_{22}H_{23}ClN_2O_2$ (382.88): C, 69.01; H, 6.05;N, 7.32; Found: C, 69.21; H, 6.13; N, 7.23%.

PHARMACOLOGICAL STUDIES

Adult male Albino mice weighing 20-25 g were obtained from the Laboratory Animal Services Center, Faculty of Veterinary Medicine, Zagazig University, Zagazig, Egypt. The animals were maintained on a 12 h-light/dark cycle under regulated temperature (25 ± 2^{o}C) and humidity (50 ± 10%) as well as fed with standard diet and water *ad libitum*. They were allowed to acclimate seven days before use. This protocol was approved by the Animal Care and Use Committee of the Pharmacology department, Faculty of Veterinary Medicine, Zagazig University.

1-Ptosis test

It was carried out according to the method described by Chen and Bohner [18]. Thirty six male Albino mice weighing 25-35 g were used. They were divided into 6 equal groups (n = 6). The first group was labeled as control and injected intraperitoneally (i.p.) with the solvent dimelhylsulfoxide (DMSO) while the second group was injected (i.p.) with clozapine at a dose of 1.5 mg/kg . The tested compounds (**4, 11 , 13** and **20**) were injected (i.p.) to the other

groups at a dose of 1.5 mg/kg. Every mouse was observed for the presence or absence of complete ptosis. The ptosis was rated as the fraction of the eyelid closure from normal.The ptosis ratio was made 4 for complete ptosis, 3 for 3/4 , 2 for 1/2 and one for 1/4 ptosis . Two readings of each mouse were taken, averaged and then recorded in (table 1).

2- Sleeping time test

The effects of the tested drugs on sleeping time were conducted according to the method described by Alpermann [19]. Thirty six adult male Albino mice weighing 25-35 g were used. They were divided into 6 equal groups (n = 6) . The first group was left as control and injected (i.p.) with the solvent (DMSO) while the second group administered (i.p.) clozapine at a dose of 1.5 mg/kg . The tested compounds (**4, 11 , 13** and **20**) were injected (i.p.) to the remaining groups at a dose of 1.5 mg/kg . The time from losing to regaining of the lighting reflex was determined and then recorded in table 2.

3-Leucocytic count method

Thirty six adult male mice weighing 25-35 g were used for white blood cells (WBCs) count. Mice were divided into 6 groups (n = 6). The first group was left as control and injected (i.p) with the solvent (DMSO). The second group was injected (i.p) with clozapine at a dose of 1.5 mg/kg / day for three successive days. The tested compounds (**4, 11 , 13** and **20**) were injected (i.p.) to the other groups at a dose of 1.5 mg / kg / day for three days . Blood samples were collected in tubes containing sodium citrate 3.8% as anticoagulant for haematological studies . Blood samples were collected after one, two and seven days of the last dose for all groups. Total leucocytes were counted according to the method of Schalm [20] and then recorded in table 3.

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