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Synthesis, Anxiolytic and Tranquilizing Activity of Some New 1, 4-Diazepine Derivatives.

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ABSTRACT

Synthesis of certain new fused 1,4-diazepine derivatives, namely, cyclopentathienodiazepinones and their benzothieno analogues **IV** to produce new compounds of possible CNS depressant activity. Eleven compounds **IV 1, 5, 6, 7, 12, 13, 15, 19, 20, 21 & 26** were selected and submitted to pharmacological evaluation for anxiolytic and tranquilizing activity in the open field test.

Keywords: 1,4-Diazepine derivatives, Open-Field test, Anxiolytic and Tranquilizing Activity

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INTRODUCTION

1,4-Diazepine derivatives exhibited versatile biological activities such as CNS activity (antipsychotic, antidepressant, anxiolytic, sedative, anticonvulsant and tranquilizer).[1-26] Certain 1,4-benzodiazepine derivatives such **1 (R=CH_3, C_2H_5)** possess sedative properties,[2] and are used as spasmolytic and hypnotic drugs. [3-5]. Also **(1, R=H)** was found to have an anticonvulsant, muscle relaxant and tranquilizing activities. [6] Similarly the hydroxy compound **2 (Oxazepam)** and its isomer *N*-oxide **3** have sedative, muscle relaxant, and anticonvulsive effects.[8] On the other hand it was found that tetrahydrobenzothienodiazepinone **4** is useful as anticonvulsant and antianxiety. [13-15] Furthermore, the thieno derivative **5** possesses neuroleptic activity. [16] The above findings directed the attention to the synthesis of certain new fused 1,4-diazepine derivatives **IV** hoping to produce new compounds of possible CNS depressant activity. Figure.1.

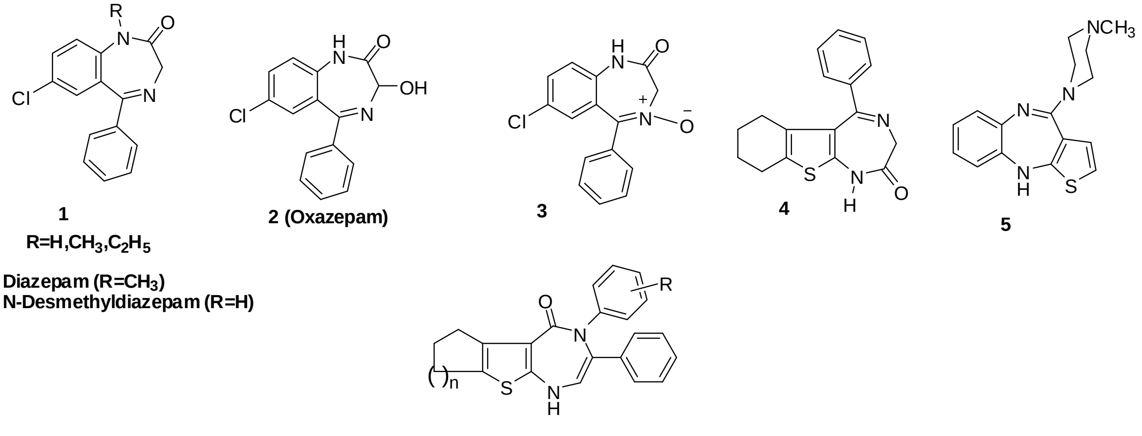


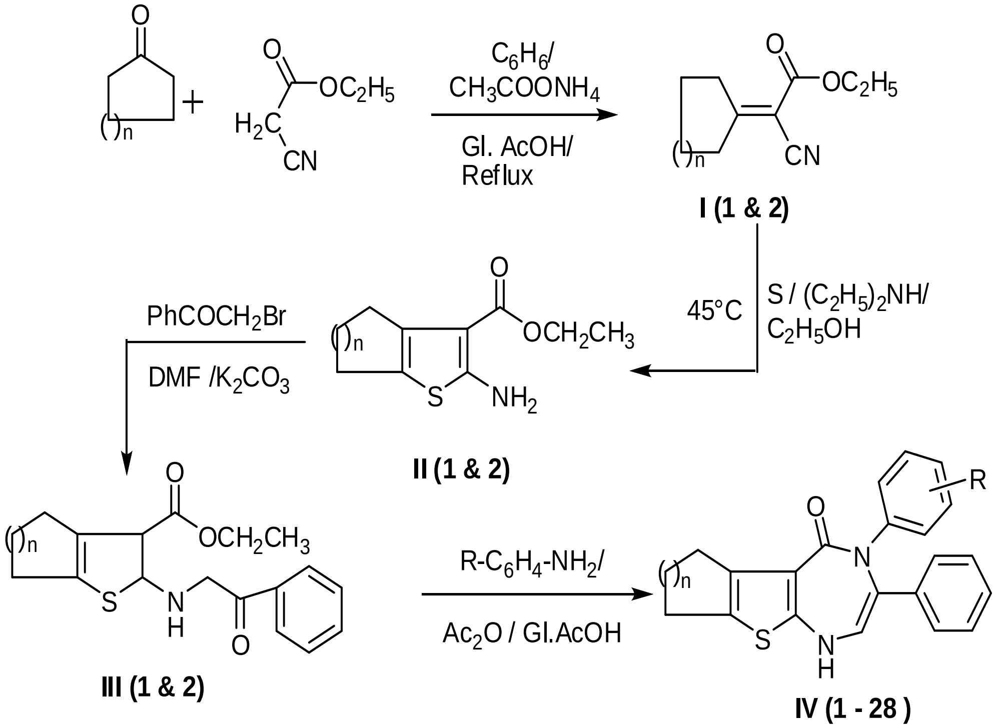
Figure 1: **Reported 1,4-diazepine derivatives 1-5 with antipsychotic, anxiolytic and tranquilizing activities, together with our target compounds IV**

RESULTS AND DISCUSSION

Chemistry

Starting with the reaction of cyclohexanone and cyclopentanone with ethyl cyanoacetate followed by cyclization with sulfur applying Gewald's reaction conditions [27-30] to afford ethyl 2-amino-4,5,6,7-tetrahydro[1]benzothiophene-3-carboxylate **(II 1)** and ethyl 2-amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carboxylate **(II 2)**. Reaction of **II** with phenacyl bromide yielded **III 1&2**. The presence of signals of aromatic protons in the ^{1}H NMR spectrum in addition to out of plane bending absorption bands at 768, 699 cm^{-1} pointed to the presence of phenyl groups and the formation of compounds **III**. Target Compounds **IV 1-28** were obtained via reaction of **III 1&2** with different anilines in acetic anhydride/ glacial acetic acid mixture (10:1).[31]

The reaction can be expected to follow through two steps. **The first step** may be through condensation between the amine and the ketone carbonyl group. **The second step** is the cyclization of the produced Schiff's base [32, 33] in acetic anhydride in presence of acetic acid as catalyst. **(Scheme 1)**

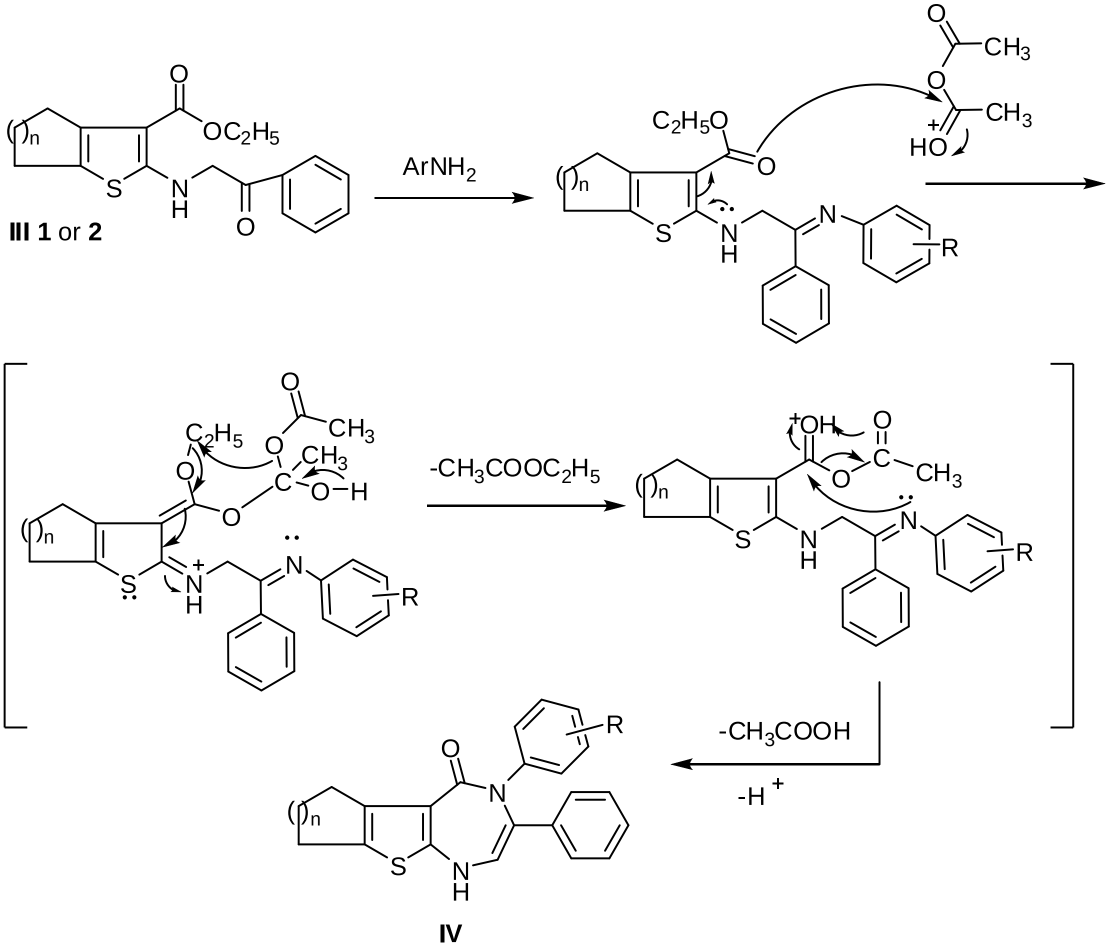


I V 1- 28

IV		R	IV		R
n=2	n=1		n=2	n=1	
1	15	H	8	22	4-NH_2
2	16	2-C_2H_5	9	23	4-NO_2
3	17	4-F	10	24	2-OH
4	18	4-Cl	11	25	4-OH
5	19	4-Br	12	26	4-OCH_3
6	20	4-CN	13	27	4-OC_2H_5
7	21	4-CF_3	14	28	3-OH, 4-COOH

Scheme 1: Synthesis of 4-aryl-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5(4*H*)-ones and 4-aryl-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-5(4*H*)ones (IV 1-28)

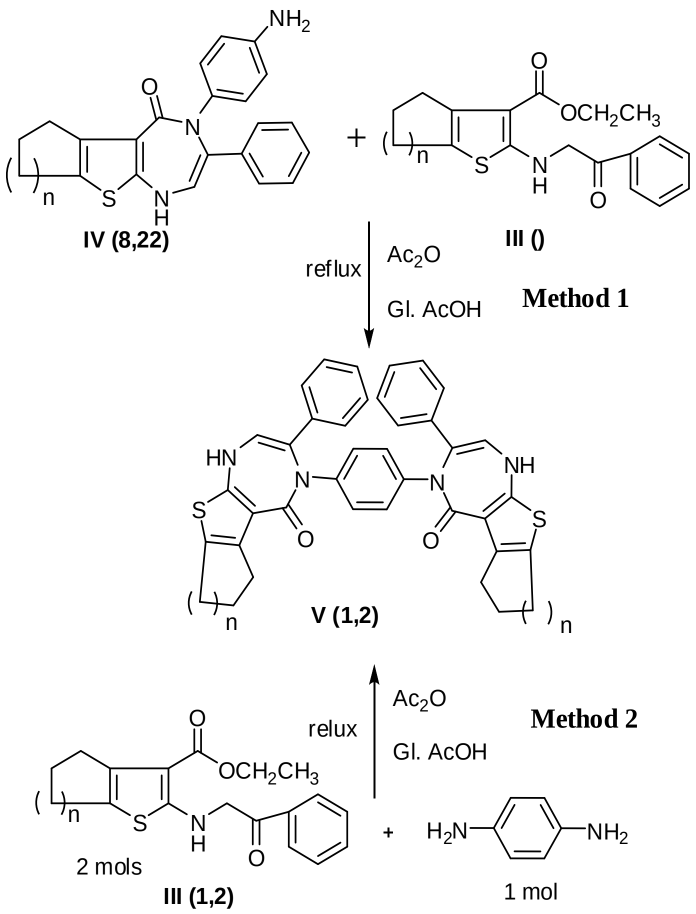
A suggested plausible mechanism can be illustrated as follows.



Acetic anhydride can react with the weak reactive ester to obtain the stronger electrophile (mixed anhydride). The latter can easily cyclized with the =N-Ar group with elimination of acetic acid. Structures of the produced compounds were established and confirmed by analytical and spectral data. For compound **IV 2 & 16** there are triplet signals at δ1.2 & 1.1 ppm which indicate the presence of -CH_3 group in addition to quartet signals for -CH_2 group. For compounds **IV 4 & 18** the appearance of $M+H+2]^{\bullet+}$ at 409 and 395 in addition to the molecular ion peak at m/z 406 and 392 respectively indicate the presence of -Cl atom. The presence of absorption bands in IR spectrum at 2221 and 2218 cm^{-1} indicate the presence of CN group for compounds **IV 6 & 20** respectively. Furthermore the IR spectral data indicate the presence of -NH_2 in addition to -NH absorption at 3301, 3175 cm^{-1} for compound **IV 8** and 3302, 3178 cm^{-1} for **IV 22**, which appeared as D_2O exchangeable signals in ^1H NMR at δ 9.85 & 9.76 ppm. For compounds **IV 10, 11, 24 & 25**, the **IR** in addition to ^1H NMR approves the structures due to the presence of broad absorption bands at 3449, 3423, 3454 & 3424 cm^{-1}. The ^1H NMR showed singlet signals at 9.80, 10.53, 9.20, 10.00, 9.37, 9.93 which exchanged by D_2O for -NH & -OH absorption for the previous structures.

The structure of **IV 12 & 26** were confirmed by ^{1}H NMR due to the appearance of singlet signals at δ 3.70 & 3.69 ppm respectively in addition to the other functional groups. Moreover the structure of **IV 13 & 27** also confirmed by ^{1}H NMR due to the appearance of triplet signals at 1.28 & 1.29 ppm for–OCH_2CH_3 and quartet signals at 3.96 & 3.95 ppm for –OCH_2CH_3. Finally compounds **IV 14&28** were confirmed by IR spectra due to the appearance of broad absorption bands for 2 –OH and –NH groups at 3438 & 3450-3352 cm^{-1} which also appeared as an exchangeable D_2O signals. **(Scheme 1)**

Compounds **V1 & 2** were furnished via two different methods the first was through the reaction of 4-(4-aminophenyl)-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5(4*H*)-one **(IV8)** or 4-(4-aminophenyl)-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno-[2,3-*e*][1,4]diazepin-5(4*H*)one **(IV 22)** with ethyl 2-(2-oxo-2-phenylethyl-amino)-4,5,6,7-tetrahydro[1]benzothiophene-3-carboxylate **(III 1)** or ethyl 2-(2-oxo-2-phenylethylamino)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carboxylate **(III 2)** in acetic anhydride / glacial acetic acid mixture (10:1) under reflux for 48 hours.[32] The increase of the reaction time may be attributed to steric factor. The second method was through the reaction of the compounds **III 1 or 2** (0.02 mol) with 1,4-phenylenediamine (0.01 mol) in acetic anhydride / glacial acetic acid mixture (10:1) under reflux for 48 hours. It was found that the second method was more favorable than the first one as it needs less time and gave higher overall yield. The structure of products was confirmed by element analysis in addition to IR and mass spectral data. Absence of absorption band of -NH_2 group in IR spectra and the appearance of molecular ion peak at m/z 666 and 638 in the mass spectra in addition to element analysis confirm the structure **V 1&2** respectively. (Scheme 2)



V 1 or 2

V	n
1	2
2	1

Scheme 2: Synthesis of 4,4̀-benzene-1,4-diyl-*bis*[3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,-4]-diazepin-5(4*H*)-one] and 4,4̀-benzene-1,4-diyl-*bis*[3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3*e*][1,4]diazepin-5(4*H*)-one] (V 1&2)

Pharmacological screening

For preliminary examination of the impact of electronic effect on the behavioral study of such compounds which based on the fact that the more electron withdrawing the substituent the higher its efficacy as CNS acting drug. Eleven compounds of the new synthesized 1,4-diazepine derivatives **IV 1, 5, 6, 7, 12, 13, 15, 19, 20, 21 & 26** were screened for their anxiolytic and tranquilizing activity. Results showed that compounds **IV 6, 12, 13, 15, 19, 21 & 26** significantly reduced the exploratory activity and the emotionality of the rats in the open-field test compared to chlorpromazine (as a standard anxiolytic and tranquillizer drug). Consequently, these compounds were suggested to have CNS depressant activity. These results (inhibition of exploration and emotionality) are in agreement with the effect of tranquillizers, sedatives and anxiolytics in the same conditions.[34, 35] However, compounds **IV 1, 5, 7 & 20** did not show any significant anxiolytic, tranquillizing or sedative activity. It is noteworthy that electronic characters dose not play any role in the activity of such compounds, compounds **IV** containing cyclohexane ring give activity when the substitution was ($-OCH_3$, -CN, and $-OC_2H_5$) while compounds containing cyclopentane ring were active when there is no substitution or when it was ($-OCH_3$, -Br & $-CF_3$). This indicates that the presence of the tetrahydrobenzo or cyclopenta groups is essential for the reactivity of the compounds. The compounds that showed promising activity needs further investigations to emphasize their specific effects and their toxicity.

The open-field test represents a novel mild stressful situation.[34] However, it was observed that the majority of the test compounds produced a significant anxiolytic action displayed as a considerably decreased explorating and emotionality behavioral parameter similar to the reference anxiolytic agent chlorpromazine.

Behavioral parameters for exploratory activity:

Latency time: time from putting the animal at the middle of the apparatus until decided to move.[36]

Ambulation frequency: number of squares crossed by the animal.[34, 37]

Rearing frequency: number of times the animal stood stretched on its hindlimbs with or without forelimbs support. [34, 38-40]

Behavioral parameters for emotionality:

Grooming frequency: number of occurrence of grooming activity indicated by face washing and scratching with the hind leg, licking of the paws and genitals, as well as combing.[34, 38, 40]

Defecation: defecation was indicated by the number of fecal pellets.[34, 36]

EXPERIMENTAL:

Chemistry:

All melting point were taken on Electrothermal LA9000 series, Digital Melting point Apparatus were uncorrected. IR Spectra were determined using KBr disc technique on Nikolet IR 200 FT IR Spectrophotometer at Pharmaceutical Analytical Unit, Faculty of Pharmacy, Al-Azhar University, and values are represented in (cm^{-1}). The ^1H NMR Spectra was recorded on Varian Gemini EM-300MHz, NMR Spectrometer at Research Service Unit, Faculty of Science, Cairo University. DMSO-d_6 and $CDCl_3$ were used as solvents; Chemical shifts were measured in δ ppm, relative to TMS as internal standard. Mass Spectrum were recorded at 70 ev on DI-50 unit of Schimadzu GC/ MS- QP5050A Spectrometer at Regional Center for Mycology and Biotechnology

(RCMB), At–Al-Azhar University represented as m/z (relative abundance %)(formula). Element Analysis (C,H,N) were carried out at Regional Center for Mycology and Biotechnology, Al-Azhar University, the values were found to be within ± 0.4 % of the theoretical ones unless otherwise indicated. Progress of the reaction was monitored by TLC using TLC sheets precoated with UV fluorescent silica gel Merck 60 F254 plates and was visualized using UV lamp.

Ethyl 2-cyano-2-cyclohexylideneacetate (I 1) and ethyl 2-cyano-2-cyclopentylideneacetate (I 2)

Prepared using reported procedure. [30]

Ethyl 2-amino-4,5,6,7-tetrahydro[1]benzothiophene-3-carboxylate (II 1) and ethyl 2-amino-5, 6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carboxylate (II 2).

Prepared using reported procedure. [29, 30]

Ethyl 2-(2-oxo-2-phenylethylamino)-4,5,67-tetrahydro[1]benzothiophene-3-carboxylate (III 1) and ethyl 2-(2-oxo-2-phenylethylamino)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carboxylate (III 2)

A mixture of compound **II 1 or 2** (0.01 mol), phenacyl bromide (1.99 g, 0.01 mol) and anhydrous K_2CO_3 (0.5 g) in *N*, *N*-dimethylformamide (10 mL) was heated under reflux for 8 hrs. The reaction mixture was cooled, poured onto ice-cold water, filtered, washed with water, then dried and crystallized from ethanol to give compound **III**;

For III 1: Yield**:** 82%; m.p.: 150-152ºC; IR (υ/cm^{-1}): 3301 (NH); 3079 (Ar-H); 2934, 2850 (aliphatic C-H); 1720, 1659 (2C=O); 768, 699 (phenyl);^{1}H NMR (δ/ppm): 1.34 (t, 3H, CH_3); 1.55-1.82 (m, 4H, $2CH_2$ at positions 5, 6); 2.50-2.70 (2t, 4H, $2CH_2$ at positions 4, 7); 2.9 (d, 2H, NH$\underline{CH_2}$CO); 4.30 (q, 2H, $\underline{CH_2}CH_{3)}$; 7.22-7.69 (m, 5H, Ar-H); 8.44 (t, 1H, NH exchangeable by D_2O); MS (m/z %): 343 (2.04) ($M^{\bullet+}$), 179 (100) ($C_9H_9NOS^{\urcorner\,\bullet+}$); Anal. Calcd for $C_{19}H_{21}NO_3S$; C, 66.45; H, 6.16, N, 4.08; Found: C, 66.52, H, 6.21, N 4.22.

For III 2 Yield**:** 76%; m.p.: 170-171ºC; IR (υ/cm^{-1}): 3417 (br. NH); 3070 (Ar-H); 2943, 2860 (aliphatic C-H); 1710, 1658 (2C=O): 760, 697(phenyl); ^{1}H NMR (δ/ppm): 1.23 (t, 3H, CH_3); 1.36-1.46 (m, 2H, CH_2 at position 5); 1.67-1.73 (m, 4H, $2CH_2$); 3.47-4.10 (m, 2H, NH$\underline{CH_2}$CO); 4.17-4.35 (q, 2H, $\underline{CH_2}CH_3$); 6.59-8.25 (m, 5H, Ar-H); 8.45 (s, 1H, NH exchangeable by D_2O); Anal. Calcd for $C_{18}H_{19}NO_3S$; C, 65.63; H, 5.81, N, 4.25; Found: C, 65.68, H, 5.84, N 4.37.

4-Aryl-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5(4*H*) ones (IV1-14) and 4-aryl-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno-[2,3-*e*][1,4]diazepin-5(4*H*)ones (IV15-28)

General procedure:

A mixture of the appropriate ketoester III (1 or 2) (0.01mol) and the respective amine (0.01mol) in acetic anhydride (10 mL) and glacial acetic acid (1mL) was heated under reflux for 10 hrs. After cooling, the reaction mixture was concentrated under reduced pressure and the product was triturated with diethyl ether. The separated solid was filtered and crystallized from the suitable solvent.

3,4-Diphenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5(4*H*)-one (IV 1)

Yield: 75 %; m.p.: >300 ^{o}C (crystallized from ethanol); IR (υ/cm^{-1}): 3302 (NH); 3086 (Ar-H); 2938, 2850 (aliphatic C-H); 1661(C=O); 751, 700 (phenyl); ^{1}H NMR(δ/ppm): 1.71-1.80 (m, 4H, 2CH$_2$); 1.90 (s, 2H, CH$_2$); 2.20-2.24 (m, 2H, CH$_2$); 7.00-7.54 (m, 11H, 10 Ar-H and 1H at position 2-); 10.90 (s, 1H, NH exchangeable by D$_2$O); MS m/z: 371 (1.98) (M-1$]^{+}$), 171 (100) (C$_{11}$H$_9$NO$]^{\bullet+}$); Anal. Calcd for C$_{23}$H$_{20}$N$_2$OS; C, 74.16; H, 5.41; N, 7.52; Found: C, 74.24; H, 5.48; N, 7.79.

4-(2-Ethylphenyl)-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5(4*H*)-one (IV 2)

Yield: 85%; m.p.: 210-213 ^{o}C (crystallized from ethanol); IR (υ/cm^{-1}): 3366 (NH); 3068 (Ar-H); 2959, 2870 (aliphatic C-H); 1689 (C=O); 758, 700 (*o*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.25 (t, 3H, CH$_3$); 1.66-1.72 (m, 4H, 2CH$_2$); 2.27-2.39 (m, 6H, 3CH$_2$); 6.91-7.97 (m, 10H, 9Ar-H and 1H at position 2-); 8.34 (s, 1H, NH exchangeable by D$_2$O); Anal. Calcd for C$_{25}$H$_{24}$N$_2$OS; C, 74.97; H, 6.04; N, 6.99; Found: C, 74.94; H, 6.03; N, 7.14.

4-(4-Fluorophenyl)-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5(4*H*)-one (IV 3)

Yield: 90%; m.p.: 133-134 ^{o}C (crystallized from glacial acetic acid); IR (υ/cm^{-1}): 3287 (NH); 3070 (Ar-H); 2932, 2850 (aliphatic C-H); 1665 (C=O); 834, 766, 699 (*p*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.70 (s, 2H, CH$_2$); 1.90 (s, 2H, CH$_2$); 2.02 (s, 2H, CH$_2$); 2.20 (s, 2H, CH$_2$); 7.08-7.60 (m, 10H, 9Ar-H and 1H at position 2-); 9.94 (s, 1H, NH exchangeable by D$_2$O); MS (m/z %): 390 (83.74) (M$^{\bullet+}$), 264 (100) (C$_{16}$H$_{12}$N$_2$S$]^{+}$); Anal. Calcd for C$_{23}$H$_{19}$FN$_2$OS; C, 70.75; H, 4.90; N, 7.17; Found: C, 70.81; H, 4.93; N, 7.28.

4-(4-Chlorophenyl)-3-phenyl-6, 7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5-(4-*H*)-one (IV 4)

Yield: 95%; m.p.: 170-172 ^{o}C (crystallized from ethanol); IR (υ/cm^{-1}): 3301 (NH); 3069 (Ar-H); 2936, 2850 (aliphatic C-H); 1670 (C=O); 827, 750, 702 (*p* -substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 2.03 (s, 4H, 2CH$_2$); 2.17 (s, 2H, CH$_2$); 2.20 (s, 2H, CH$_2$); 7.31-7.61 (m, 10H, 9Ar-

H and 1H at position 2-); 10.03 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 409 (100) (M+H+2$\urcorner^{+}$), 406 (88.95) ($M^{\bullet+}$); Anal. Calcd for $C_{23}H_{19}ClN_2OS$; C, 67.89; H, 4.71; N, 6.88; Found: C, 67.97; H, 4.78; N, 6.97.

4-(4-Bromophenyl)-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5(4-*H*)-one (IV 5)

Yield: 99%; m.p.: >300 °C (crystallized from ethanol); IR (υ/cm^{-1}): 3293 (NH); 3062 (Ar-H); 2945, 2860 (aliphatic C-H); 1666 (C=O); 825, 750, 698 (*p*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.90 (s, 2H, CH_2); 2.06 (s, 4H, $2CH_2$); 2.22 (s, 2H, CH_2); 7.00-7.80 (m, 10H, 9Ar-H and 1H at position 2-); 9.68 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 451(21.04) (M+1$\urcorner^{\bullet+}$), 51 (100) ($C_4H_3\urcorner^{+}$); Anal. Calcd for $C_{23}H_{19}BrN_2OS$; C, 61.20; H, 4.24; N, 6.21; Found: C, 61.22; H, 4.28; N, 6.24.

4-(5-oxo-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-4(5*H*) yl)benzonitrile (IV 6)

Yield: 85%; m.p.: 183-185 °C (crystallized from ethanol); IR (υ/cm^{-1}): 3290 (NH); 3058 (Ar-H); 2934, 2860 (aliphatic C-H); 2221 (CN); 1672 (C=O); 836, 753, 703 (*p*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 2.08 (s, 8H, $4CH_2$); 7.75 (s, 10H, 9Ar-H and 1H at position 2-); 10.34 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 397 (0.25) ($M^{\bullet+}$), 63 (100) ($C_5H_3\urcorner^{+}$); Anal. Calcd for $C_{24}H_{19}N_3OS$; C, 72.52; H, 4.82; N, 10.57; Found: C, 72.63; H, 4.95; N, 10.78.

3-Phenyl-4-(4-trifluoromethylphenyl)-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3*e*] [1,4]diazepin-5(4*H*)-one (IV 7)

Yield: 80%; m.p.: 240-242 °C (crystallized from glacial acetic acid); IR (υ/cm^{-1}): 3340 (NH); 3062 (Ar-H); 2935, 2850 (aliphatic C-H); 1688 (C=O); 842, 756, 698 (*p*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.90 (s, 2H, CH_2); 1.95 (s, 2H, CH_2); 2.08 (s, 2H, CH_2); 2.19 (s, 2H, CH_2); 7.50-7.79 (m, 10H, 9Ar-H and 1H at position 2-); 10.27 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 440 (0.54) ($M^{\bullet+}$), 161 (100) ($C_7H_6F_3N\urcorner^{\bullet+}$); Anal. Calcd for $C_{24}H_{19}F_3N_2OS$; C, 65.44; H, 4.35; N, 6.36; Found: C, 65.48; H, 4.41; N, 6.65.

4-(4-Aminophenyl)-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5(4-*H*)-one (IV 8)

Yield: 95%; m.p.: 270-272 °C (crystallized from ethanol); IR (υ/cm^{-1}): 3301, 3175 (NH_2 & NH); 3083 (Ar-H); 2932, 2860 (aliphatic C-H); 1661 (C=O); 831, 749, 690 (*p*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 2.00 (s, 8H, $4CH_2$); 7.46 (s, 10H, 9Ar-H and 1H at position 2-); 9.85 (br s, 3H, NH_2 & NH exchangeable by D_2O); MS (m/z %): 388 (0.14) (M+1$\urcorner^{\bullet+}$), 387 (0.15) ($M^{\bullet+}$), 108 (100) ($C_6H_8N_2\rceil^{\bullet+}$ &/or $C_6H_4S\rceil^{\bullet+}$); Anal. Calcd for $C_{23}H_{21}N_3OS$; C, 71.29; H, 5.46; N, 10.84; Found: C, 71.38; H, 5.59; N, 11.16.

4-(4-Nitrophenyl)-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5(4-*H*)-one (IV 9)

Yield: 93%; m.p. 172-175 °C (crystallized from ethanol); IR (υ/cm^{-1}): 3286 (NH); 3094 (Ar-H); 2940, 2850 (aliphatic C-H); 1683 (C=O); 850,750, 703 (*p*-substituted phenyl and phenyl); 1515, 1320 (NO_2); ^{1}H NMR (δ/ppm): 1.90 (s, 2H, CH_2); 1.95 (s, 2H, CH_2); 2.11 (s, 2H, CH_2); 2.20 (s, 2H, CH_2); 7.62-8.33 (m, 10H, 9Ar-H and 1H at position 2-); 10.52 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 417 (37.56) ($M^{\bullet+}$), 108 (100) ($C_6H_6NO\rceil^{+}$ &/or $C_6H_4S\rceil^{\bullet+}$). Anal. Calcd for $C_{23}H_{19}N_3O_3S$; C, 66.17; H, 4.59; N, 10.07; Found: C, 66.21; H, 4.62; N, 10.15.

4-(2-Hydroxyphenyl)-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]-diazepin-5(4*H*)-one (IV 10)

Yield: 87%; m.p.: 250-251 °C (crystallized from ethanol); IR (υ/cm^{-1}): 3449 (br. OH & NH); 3060 (Ar-H); 2938, 2860 (aliphatic C-H); 1670 (C=O); 752, 699 (*o*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.92 (s, 2H, CH_2); 2.00 (s, 2H, CH_2); 2.06 (s, 2H, CH_2); 2.11 (s, 2H, CH_2); 6.46-8.21 (m, 10H, 9Ar-H and 1H at position 2-); 9.80, 10.53 (2s, 2H, NH & OH exchangeable by D_2O); Anal. Calcd for $C_{23}H_{20}N_2O_2S$; C, 71.11; H, 5.19; N, 7.21; Found: C, 71.15; H, 5.22; N, 7.29.

4-(4-Hydroxyphenyl)-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]-diazepin-5(4*H*)-one (IV 11)

Yield: 86%; m.p.: 180-181 °C (crystallized from ethanol); IR (υ/cm^{-1}): 3423 (br. OH & NH); 3039 (Ar-H); 2940 (aliphatic C-H); 1654 (C=O); 843, 749, 695 (*p*-substituted phenyl and phenyl); ^{1}HNMR (δ/ppm): 1.70-1.80 (m, 2H, CH_2); 1.90 (s, 2H, CH_2); 2.02 (s, 2H, CH_2); 2.23 (s, 2H, CH_2); 6.80-7.58 (m, 10H, 9Ar-H and 1H at position 2-); 9.20, 10.00 (2s, 2H, NH & OH exchangeable by D_2O); MS (m/z %): 388 (0.55) ($M^{\bullet+}$), 77 (100) ($C_6H_5\rceil^{+}$); Anal. Calcd for $C_{23}H_{20}N_2O_2S$; C, 71.11; H, 5.19; N, 7.21; Found: C, 71.09; H, 5.23; N, 7.42.

4-(4-Methoxyphenyl)-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]-diazepin-5(4*H*)-one (IV 12)

Yield: 84%; m.p.: 203-205 °C (crystallized from ethanol); IR (υ/cm^{-1}): 3296 (NH); 3081 (Ar-H); 2938, 2880 (aliphatic C-H); 1667 (C=O); 817, 765, 697(*p*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.65-1.70 (m, 2H, CH_2); 1.95 (s, 2H, CH_2); 2.20 (s, 2H, CH_2); 2.24 (s, 2H, CH_2); 3.70 (s, 3H, OCH_3); 6.83-7.47 (m, 10H, 9Ar-H and 1H at position 2-); 9.80 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 402 (1.12) ($M^{\bullet+}$), 105 (100) ($C_8H_9\rceil^{+}$); Anal. Calcd for $C_{24}H_{22}N_2O_2S$; C, 71.62; H, 5.51; N, 6.96; Found: C, 71.71; H, 5.49; N, 7.13.

4-(4-Ethoxyphenyl)-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5(4*H*)-one (IV 13)

Yield: 95%; m.p.: 132-135°C (crystallized from ethanol); IR (υ/cm^{-1}): 3280 (NH); 3071 (Ar-H); 2979, 2934, 2870 (aliphatic C-H); 1659(C=O); 829, 746, 710 (*p*-substituted phenyl & phenyl); ^{1}H NMR (δ/ppm): 1.28 (t, 3H, OCH_2CH_3); 1.98 (s, 4H, $2CH_2$); 2.49 (s, 4H, $2CH_2$); 3.96 (q, 2H, OCH_2CH_3); 6.81-7.46 (m, 10H, 9Ar-H and 1H at position 2-); 9.76 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 416 (1.43) ($M^{\bullet +}$), 108 (100) ($C_6H_6NO^{\urcorner +}$, $C_7H_8O^{\urcorner \bullet +}$ &/or $C_6H_4S^{\urcorner \bullet +}$); Anal. Calcd for $C_{25}H_{24}N_2O_2S$; C, 72.09; H, 5.81; N, 6.73; Found: C, 72.13; H, 5.85; N, 6.78.

2-Hydroxy-4-(5-oxo-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-4(5*H*)-yl)benzoic acid (IV 14)

Yield: 88%; m.p.: 160-162 °C (crystallized from benzene); IR (υ/cm^{-1}): 3438 (br. 2OH & NH); 3068 (Ar-H); 2936, 2850 (aliphatic C-H); 1671 (2C=O, acidic & amidic); 826, 758, 701 (phenyl and substituted phenyl); ^{1}H NMR (δ/ppm): 1.71 (s, 2H, CH_2); 1.95 (s, 2H, CH_2); 2.00 (s, 2H, CH_2); 2.20 (s, 2H, CH_2); 4.30 (s, 1H, OH phenolic); 6.85-8.23 (m, 9H, 8Ar-H and 1H at position 2-); 9.83 (s, 1H, NH exchangeable by D_2O); 10.30 (s, 1H, acidic OH exchangeable by D_2O); Anal. Calcd for $C_{24}H_{20}N_2O_4S$; C, 66.65; H, 4.66; N, 6.48; Found: C, 66.63; H, 4.62; N, 6.61.

3,4-Diphenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-5(4*H*)-one IV 15

Yield: 87 %; m.p.: >300 °C (crystallized from ethanol); IR (υ/cm^{-1}): 3367 (NH); 3050 (Ar-H); 2942, 2850 (aliphatic C-H); 1647 (C=O); 756, 691 (phenyl); ^{1}H NMR (δ/ppm): 1.90 (s, 2H, CH_2); 2.08 (s, 2H, CH_2); 2.19 (s, 2H, CH_2); 7.24-8.02 (m, 11H, 10Ar-H and 1H at position 2-); 10.26 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 357 (33.19) ($M-1^{\urcorner +}$), 355 (100) ($M-3^{\urcorner +}$); Anal. Calcd for $C_{22}H_{18}N_2OS$; C, 73.71; H, 5.06; N, 7.82; Found: C, 73.78; H, 5.13; N, 7.98.

4-(2-Ethylphenyl)-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-5(4*H*)one (IV 16)

Yield: 83%; m.p.: >300 °C (crystallized from benzene/ethanol); IR (υ/cm^{-1}): 3411 (NH); 3066 (Ar-H); 2961, 2863 (aliphatic C-H); 1688 (C=O); 761, 699 (*o*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.10 (t, 3H, CH_2CH_3); 1.95 (s, 2H, CH_2); 2.04 (s, 2H, CH_2); 2.16 (s, 2H, CH_2); 2.39 (q, 2H, CH_2CH_3); 7.12-7.39 (m, 10H, 9Ar-H and 1H at position 2-); 9.25 (s, 1H, NH exchangeable by D_2O). MS (m/z %): 386 (1.00) ($M^{\bullet +}$), 77 (100) ($C_6H_5^{\urcorner +}$); Anal. Calcd for $C_{24}H_{22}N_2OS$; C, 74.58; H, 5.74; N, 7.25; Found: C, 74.45; H, 5.48; N, 7.59.

4-(4-Fluorophenyl)-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-5(4*H*)one (IV 17)

Yield: 80%; m.p.: >300 ^{o}C (crystallized from ethanol); IR(υ/cm^{-1}): 3288 (NH); 3077 (Ar-H); 2946, 2850 (aliphatic C-H); 1667 (C=O); 849, 740, 702 (*p*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.90 (s, 2H, CH_2); 2.02 (s, 2H, CH_2); 2.12 (s, 2H, CH_2); 7.08-7.60 (m, 10H, 9Ar-H and 1H at position 2-); 9.96 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 376 (100) ($M^{\bullet+}$); Anal. Calcd for $C_{22}H_{17}FN_2OS$; C, 70.19; H, 4.55; N, 7.44; Found: C, 70.23; H, 4.62; N, 7.58.

4-(4-Chlorophenyl)-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-5(4*H*)one (IV 18)

Yield: 96%; m.p.: 159-160 ^{o}C (crystallized from glacial acetic acid); IR (υ/cm^{-1}): 3297 (NH); 3079 (Ar-H); 2963, 2860 (aliphatic C-H); 1669 (C=O); 829, 753, 701 (*p*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.91 (s, 2H, CH_2); 1.95 (s, 2H, $2H_2$); 2.04 (s, 2H, CH_2); 7.31-7.61 (m, 10H, 9Ar-H and 1H at position 2-); 10.02 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 395 (3.99) (M+H+2┐$^{+}$), 392 (4.94) ($M^{\bullet+}$), 126 (100) (C_6H_5ClN┐$^{+}$); Anal. Calcd for $C_{22}H_{17}ClN_2OS$; C, 67.25; H, 4.36; N, 7.13; Found: C, 67.57; H, 4.33; N, 6.17.

4-(4-Bromophenyl)-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-5(4*H*)one (IV 19)

Yield: 80%; m.p.: >300 ^{o}C (crystallized from ethanol); IR (υ/cm^{-1}): 3278 (NH); 3071 (Ar-H); 2977, 2932, 2850 (aliphatic C-H); 1656 (C=O); 829, 747, 700 (*p*- substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.90 (s, 2H, CH_2); 2.06 (s, 2H, CH_2); 2.22 (s, 2H, CH_2); 7.06-7.78 (m, 10H, 9Ar-H and 1H at position 2-); 9.69 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 439 (100) (M+H+2┐$^{+}$), 437 (67.26) (M+H┐$^{+}$); Anal. Calcd for $C_{22}H_{17}BrN_2OS$; C, 60.42; H, 3.92; N, 6.41; Found: C, 60.39; H, 4.05; N, 6.72.

4-(5-Oxo-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-4(5*H*)-yl)benzonitrile (IV 20)

Yield: 86%; m.p.: >300 ^{o}C (crystallized from glacial acetic acid); IR (υ/cm^{-1}): 3267 (NH); 3040 (Ar-H); 2977, 2890 (aliphatic C-H); 2218 (CN); 1675 (C=O); 838, 760, 700 (*p*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.91 (s, 2H, CH_2); 2.09 (s, 4H, $2CH_2$); 7.75 (s, 10H, 9Ar-H and 1H at position 2-); 10.34 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 383 (100) ($M^{\bullet+}$); Anal. Calcd for $C_{23}H_{17}N_3OS$; C, 72.04; H, 4.47; N, 10.96; Found: C, 72.12; H, 4.43; N, 10.11.

3-Phenyl-4-(4-triflouromethylphenyl)-1,6,7,8-tetrahydrocyclopenta[4,5]thieno [2,3-*e*][1,4]diazepin-5(4*H*)one (IV 21)

Yield: 85%; m.p.: >300 ^{o}C (crystallized from ethanol); IR (υ/cm^{-1}): 3422 (NH); 3068 (Ar-H); 2954, 2850 (aliphatic C-H); 1686 (C=O); 847, 761, 696 (*p*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.90 (s, 2H, CH_2); 2.08 (s, 4H, $2CH_2$); 6.96-7.74 (m, 10H, 9Ar-H and 1H at position 2-); 10.35 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 426 (59.43) ($M^{•+}$), 287 (100) ($C_{19}H_{15}N_2O^{\rceil +}$); Anal. Calcd for $C_{23}H_{17}F_3N_2OS$; C, 64.78; H, 4.02; N, 6.57; Found: C, 64.85; H, 4.11; N, 6.69.

4-(4-Aminophenyl)-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-5(4*H*)one IV 22

Yield: 89%; m.p.: 273-274 °C (crystallized from ethanol); IR (υ/cm^{-1}): 3302, 3178 (NH_2 & NH); 3080 (Ar-H); 2997, 2840 (aliphatic C-H); 1667 (C=O); 834, 748, 699 (*p*-substituted phenyl and phenyl); ^1H NMR (δ/ppm): 1.91 (s, 2H, CH_2); 2.01 (s, 2H, CH_2); 2.17 (s, 2H, CH_2); 7.15-7.65 (m, 10H, 9Ar-H and 1H at position 2-); 9.76 (br. s, 3H, NH & NH_2 exchangeable by D_2O); Anal. Calcd for $C_{22}H_{19}N_3OS$; C, 70.75; H, 5.13; N, 11.25; Found: C, 70.82; H, 5.18; N, 11.42.

4-(4-Nitrophenyl)-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-5(4*H*)one (IV 23)

Yield: 97%; m.p.: 137-140 °C (crystallized from glacial acetic acid); IR (υ/cm^{-1}): 3276 (NH); 3074 (Ar-H); 2930, 2870 (aliphatic C-H); 1658 (C=O); 1517, 1320 (NO_2); 834, 746, 695 (*p*-substituted phenyl and phenyl); ^1H NMR (δ/ppm): 1.90 (s, 2H, CH2); 1.99 (s, 2H, CH_2); 2.16 (s, 2H, CH_2); 6.81-7.46 (m, 10H, 9Ar-H and 1H at position 2-); 9.69 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 403 (0.03) (M•+), 63 (100) ($C_5H_3^{\rceil +}$); Anal. Calcd for $C_{22}H_{17}N_3O_3S$; C, 65.49; H, 4.25; N, 10.42; Found: C, 65.46; H, 4.28; N, 10.53.

4-(2-Hydroxyphenyl)-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-5(4*H*)one (IV 24)

Yield: 89%; m.p.: 150-152 °C (crystallized from ethanol); IR (υ/cm^{-1}): 3454 (br. OH & NH); 3050 (Ar-H); 2956, 2850 (aliphatic C-H); 1655 (C=O); 750, 696 (*o*-substituted phenyl and phenyl); ^1H NMR (δ/ppm): 2.08, 2.29 (2s, 6H, $3CH_2$); 7.10-7.86 (m, 10H, 9Ar-H and 1H at position 2-); 9.37 (s, 2H, NH & OH exchangeable by D_2O); MS (m/z %): 373 (0.23) ($M-1^{\rceil +}$), 109 (100) ($C_6H_7NO^{\rceil •+}$); Anal. Calcd for $C_{22}H_{18}N_2O_2S$; C, 70.57; H, 4.85; N, 7.48; Found: C, 70.68; H, 4.90; N, 7.67.

4-(4-Hydroxyphenyl)-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-5(4*H*)one IV 25

Yield: 89%; m.p.: 190-191 °C (crystallized from ethanol); IR (υ/cm^{-1}): 3424 (br. OH & NH); 3077 (Ar-H); 2960, 2850 (aliphatic C-H); 1673 (C=O); 838, 765, 698 (*p*-substituted phenyl and phenyl).; ^1H NMR (δ/ppm): 1.95 (s, 2H, CH_2); 2.03 (s, 2H, CH_2); 2.23 (s, 2H, CH_2); 7.01-7.58 (m, 10H, 9Ar-H and 1H at position 2-); 9.93 (br. s, 2H, NH & OH exchangeable by D_2O); Anal. Calcd for $C_{22}H_{18}N_2O_2S$; C, 70.57; H, 4.85; N, 7.48; Found: C, 70.63; H, 4.91; N, 7.66.

4-(4-Methoxyphenyl)-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-5(4*H*)one (IV 26)

Yield: 79%; m.p.: >300 ^{o}C (crystallized from benzene); IR (υ/cm^{-1}): 3413 (NH); 3063 (Ar-H); 2939, 2850 (aliphatic C-H); 1700 (C=O); 830, 761, 697 (*p*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.74 (s, 2H, CH_2); 1.90 (s, 2H, CH_2); 2.15 (s, 2H, CH_2); 3.69 (s, 3H, OCH_3); 6.83-7.47 (m, 10H, 9Ar-H and 1H at position 2-); 9.76 (s, 1H, NH exchangeable by D_2O); MS (m/z %): 388 (1.17) ($M^{\bullet +}$), 63 (100) ($C_5H_3\urcorner^{+}$); Anal. Calcd for $C_{23}H_{20}N_2O_2S$; C, 71.11; H, 5.19; N, 7.21; Found: C, 71.19; H, 5.23; N, 7.22.

4-(4-Ethoxyphenyl)-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-5(4*H*)one (IV 27)

Yield: 99%; m.p.: 140-141 ^{o}C (crystallized from ethanol); IR (υ/cm^{-1}): 3274 (NH); 3072 (Ar-H); 2980, 2930, 2870 (aliphatic C-H); 1655(C=O); 831, 745, 700 (*p*-substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.29 (t, 3H, OCH_2CH_3); 1.99 (s, 6H, $3CH_2$); 3.95 (q, 2H, OCH_2CH_3); 6.82-7.47 (m, 10H, 9Ar-H and 1H at position 2-); 9.73 (s, 1H, NH exchangeable by D_2O); Anal. Calcd for $C_{24}H_{22}N_2O_2S$; C, 71.62; H, 5.51; N, 6.96; Found: C, 71.71; H, 5.49; N, 7.11.

2-Hydroxy-4-(5-oxo-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-4(5H)-yl)benzoic acid (IV 28)

Yield: 90 %; m.p.: 155-157 ^{o}C (crystallized from glacial acetic acid); IR (υ/cm^{-1}): 3450-3352 (br. OH & NH); 3095 (Ar-H); 2961 (aliphatic C-H); 1721, 1658 (2 C=O); 851, 773, 697 (substituted phenyl and phenyl); ^{1}H NMR (δ/ppm): 1.91 (s, 2H, CH_2); 2.05 (s, 2H, CH_2); 2.19 (s, 2H, CH_2); 7.09-8.15 (m, 9H, 8Ar-H and 1H at position 2-); 9.95 (s, 1H, NH exchangeable by D_2O); 10.12 (s, 1H, OH exchangeable by D_2O); 13.00 (br. s, 1H, COOH); MS (m/z %): 418 (0.02) ($M^{\bullet +}$), 52 (100) ($C_4H_4\urcorner^{\bullet +}$); Anal. Calcd for $C_{23}H_{18}N_2O_4S$; C, 66.01; H, 4.34; N, 6.69; Found: C, 65.98; H, 4.44; N, 6.67.

4,4̀-Benzene-1,4-diyl-*bis[*3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5(4*H*)-one] (V1) and 4,4̀-benzene-1,4-diyl-*bis*[3-phenyl-1,6,7,8-tetrahydro-cyclopenta[4,5]thieno[2,3-*e*][1,4]diazepin-5(4*H*)-one] (V 2)

Method 1:

A mixture of **IV 8** or **22** (0.01 mol) and **III 1** or **2** (0.01 mol) in acetic anhydride (10 mL) and glacial acetic acid (1 mL) was heated under reflux for 48 hrs. After cooling, the solvent was concentrated under reduced pressure; the product was triturated with diethyl ether and the separated solid was filtered and crystallized from ethanol.

Method 2:

A mixture of **III 1** or **2** (0.02 mol) in acetic anhydride (10 mL) and glacial acetic acid (1 mL) was heated then the 1,4-phenylenediamine (0.01 mol) was added. The mixture was heated under reflux for 48 hrs. After cooling, the solvent was concentrated under reduced pressure; the product was triturated with diethyl ether and the separated solid was filtered and crystallized from ethanol.

For V1: Yield: 65 %; for method 1 and 75% for method 2; m.p: >300˚C; IR (υ/cm^{-1}): 3336 (NH); 3062 (Ar-H); 2936, 2850 (aliphatic C-H); 1688 (C=O); 748, 690 (phenyl); MS (m/z %): 666 (0.27) ($M^{\bullet+}$), 107 (100) ($C_6H_7N_2{}^{\urcorner +}$); Anal. Calcd for $C_{40}H_{34}N_4O_2S_2$; C, 72.04; H, 5.14, N, 8.40; Found: C, 72.02; H, 5.18, N, 8.42.

For V2: Yield: 53 %; for method 1 and 67% for method 2; m.p: 180-181˚C; IR (υ/cm^{-1}): 3397 (NH); 3061 (Ar-H); 2930, 2860 (aliphatic C-H); 1680 (C=O); 745, 683 (phenyl); MS (m/z %): 638 (3.66) ($M^{\bullet+}$), 77 (100) ($C_6H_5{}^{\urcorner +}$); Anal. Calcd for $C_{40}H_{34}N_4O_2S_2$; C, 71.45; H, 4.73, N, 8.77; Found: C, 71.48; H, 4.70, N, 8.67.

Anxiolytic activity:

For the evaluation of the anxiolytic activity of compounds **IV 1, 5, 6, 7, 12 , 13, 15, 19, 21 and 26**, the open-field test was used. It represents a novel mild stressful situation.[34]

Materials and Methods:

Seventy eight Sprague Dawley male rats (100-150 g) were obtained from the animal house lab Veterinary of VACSERA, Cairo, Egypt. These animals were divided into equal 13 groups (6 rats each) as follows:

Group 1: received saline orally (1mL/ kg body weight) and served as negative control.

Groups 2-12: received 50 mg/ Kg of test compounds orally. [41]

Group 13*:* received 2 mg/ Kg intraperitoneal (I.P.) of the standard drug, chlorpromazine (CPZ) as positive control.

Experimental:

Each animal was placed in the center of a square arena 80 cm x 80 cm x 40 cm in high,[38] with red sides and white floor.[42] The floor of the field was divided by black lines into squares 4 x 4 cm^2. The test was performed under white light in a quiet room.[43]

One hour before the experiment, all animals were taken to test situation removing food and water from the home cage. Experimental animals were taken from their cages alternately; placed individually in to the central squares of the open-field and observed during 3 minutes period. The floor and walls were scrubbed after the testing of each rat. During the experiment a time schedule was used indicating the moment at which each experimental rat was injected or taken to the open-field. All animals were returned to their home cages after the injection or the open-field test. The behavior of the experimental rat in the open-field was continuously recorded during the 3 minutes period. Observation period using coded symbols for the previous parameters.

Statistical analysis:

Data was expressed as the mean ± S.E.M. and multiple comparisons were performed using one-way ANOVA followed by Tukey as a post hoc test as appropriate to calculate significance of the difference between treatments. The 0.05 level of probability was used as the criterion for significance. All statistical analyses were performed using GRAPHPAD INSTAT version 3 software package. [44]

Table 1: Open–Field test: comparative behavioral changes induced by oral dose of 50 mg / Kg (41) of 4-aryl-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5(4*H*)-ones (IV 1, 5, 6, 7, 12 & 13) and 4-aryl-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]-thieno[2,3-*e*][1,4]diazepin-5(4*H*)-ones (IV 15, 19, 20, 21& 26).

Parameters Drugs	**Latency (seconds)**	**Ambulation Frequency**	**Rearing Frequency**	**Grooming Frequency**	**Defecation (no. of pellets)**
Control (Saline)	1.166±0.201	36.167±1.352	15.000±0.683	4.166±0.307	3.833±0.307
IV 1	1.333±0.210	36.333±1.687	11.833±1.195	4.333±0.494	3.166±0.307
IV 5	1.167±0.166	38.166±1.195	12.500±1.088	4.666±0.422	3.333±0.422
IV 6	1.866*±0.117	19.000*±1.633	8.833*±0.833	2.166*±0.307	1.166*±0.167
IV 7	1.750*±0.235	38.166±1.537	12.833±0.910	5.000±0.258	3.000±0.258
IV 12	1.333±0.210	19.333*±1.606	9.333*±0.558	2.833*±0.307	1.000*±0.258
IV 13	1.683±0.164	20.500*±1.765	8.500*±0.885	2.500*±0.224	1.333*±0.333
IV 15	1.333±0.210	20.500*±1.765	8.666*±0.715	2.333*±0.333	1.166*±0.167
IV 19	1.916*±0.114	21.833*±2.197	10.833±1.014	2.166*±0.307	1.500*±0.223
IV 20	1.167±0.166	35.333±2.499	12.833±1.138	4.833±0.477	3.166±0.307
IV 21	1.916*±0.114	22.667*±1.801	7.666*±0.760	2.833*±0.307	1.333*±0.211
IV 26	1.750*±0.235	21.333*±2. 076	6.500*±0.845	2.000*±0.365	1.500*±0.223
Chlorpromazine	1.333±0.167	19.500*±0.764	9.000*±0.683	2.166*±0.307	1.333*±0.333

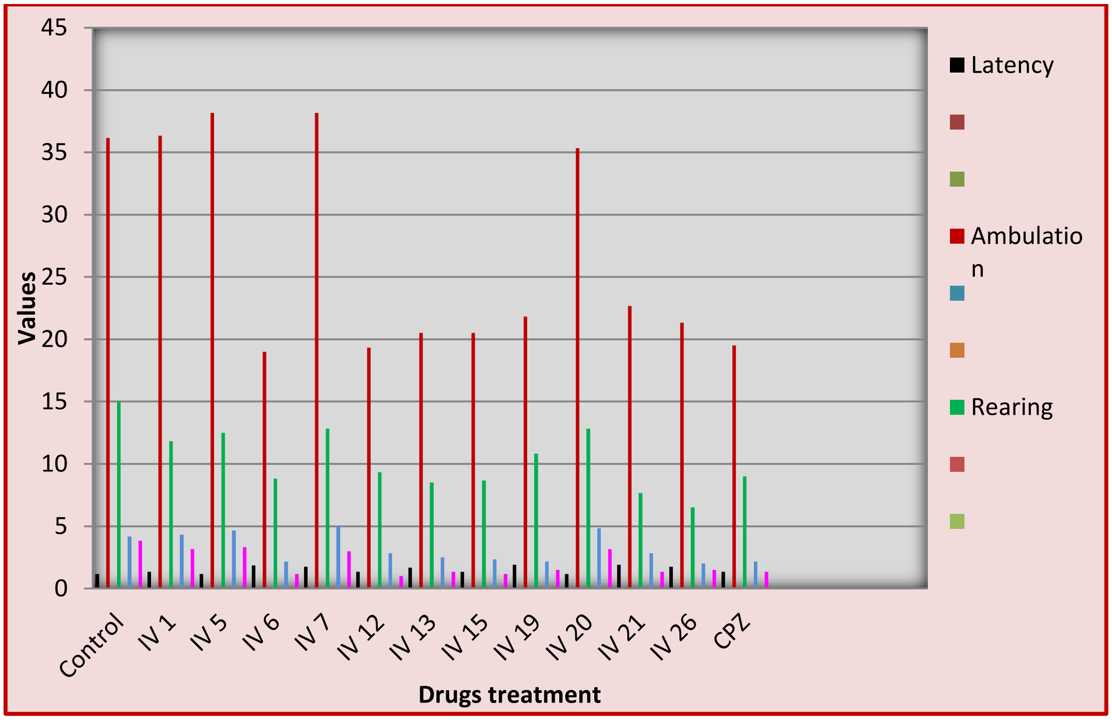


Figure 2: : Open–Field test: comparative behavioral changes induced by oral dose of 50 mg / Kg[41] of 4-aryl-3-phenyl-6,7,8,9-tetrahydro-1*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-5(4H)-ones (IV 1, 5, 6, 7, 12 & 13) and 4-aryl-3-phenyl-1,6,7,8-tetrahydrocyclopenta[4,5]thieno[2,3-e][1,4]diazepin-5(4H)-ones (IV 15, 19, 20, 21& 26).

CONCLUSIONS:

In this study a new synthetic procedure for synthesis of fused 1,4-diazepine system is shown, the results of this study demonstrated that the selected compounds have an anxiolytic and tranquilizing activity effect at the test dose (50 mg/kg) in the animal models of anxiety. It was well observed that compounds IV containing cyclohexan moiety in their structure gave activity when the substitution was (–OCH_3, -CN, and –OC_2H_5). On the other hand compounds IV containing cyclopentan moiety showed significant activity if there is no substitution or it was electron donating group such as (-OCH_3).

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