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Synthesis and Tranquillizing Effect of New 1,4-Benzoxazepines

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A SERIES of new 1,4-benzoxazepin-5(4*H*)-ones was prepared by alkylation of salicylamides with phenacyl bromides followed by cyclodehydration of the resulting amides. Treatment of the 1,4-benzoxazepine-5(4*H*)-ones with phosphorus pentasulphide afforded the corresponding 1,4-benzoxazepine-5(4*H*)-thiones. *N*-alkylation of the 1,4- benzoxazepin-5(4*H*)-ones and *S*-alkylation of the 1,4-benzoxazepine-5(4*H*)-thiones were described. Some of the new compounds were subjected to preliminary screening for their tranquilizing effect.

Keywords: 1,4-Benzoxazepin-5(4*H*)-ones, 1,4-Benzoxazepine-5(4*H*)-thiones, *N*-alkylation, *S*- alkylation, Tranquilizers and Diazepam.

Although 1,4-benzoxazepines display numerous bioactivities[1-5], yet a few of them have been studied as tranquilizers[6]. Therefore, it appears desirable to synthesize new 1,4-benzoxazepin-5(4*H*)-ones and 1,4-benzoxazepine-5(4*H*)-thiones with a wider range of substituents including their *N*-alkyl and *S*-alkyl derivatives to investigate their tranquilizing effect.

Results and Discussion

The synthesis of 3-aryl-1,4-benzoxazepin-5(4*H*)-ones (4) and the corresponding thiones 6 was carried out as depicted in Scheme 1. The intermediate *O*-alkylsalicylamides (3) were prepared by alkylation of salicylamides (1) with phenacyl bromides (2). Cyclodehydration of the intermediate (3) in toluene using *p*-toluenesulphonic acid as catalyst according to Schenker's procedure [7] yielded the desired 1,4-benzoxazepin-5(4*H*)-ones (4). Structure of the 1,4-benzoxazepin-5(4*H*)-ones (4) was confirmed by spectroscopy and elemental analyses. IR spectra of compounds 4 showed disappearance of the bands due to the amide NH_2 group and the ketonic CO group. The ^{1}H NMR spectra of compounds 4 showed two characteristic singlet peaks, one for the single olefinic proton at position 2 at δ 6.9 ppm, while the NH amidic proton appeared at δ 9.8-10.0 ppm.

Alkylation of the 1,4-benzoxazepin-5(4*H*)-ones (4c and d) with methyl iodide in the presence of sodium hydride in tetrahydrofuran yielded the corresponding *N*-methyl derivatives (5a and b) regioselectively. The IR spectra of compounds 5 showed the disappearance of the NH band while the ^{1}H NMR spectra confirmed the absence of NH signal and showed the presence of the methyl protons at δ 2.9 ppm.

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The 1,4-benzoxazepin-5(4*H*)-ones (4) (X = H, Br; R = H, Br, Cl) were reacted with phosphorus pentasulphide in dry pyridine to give the corresponding 1,4-benzoxazepine-5(4*H*)- thiones (6a-f). The IR spectra of compounds 6 revealed the disappearance of CO amide band. On the other hand, the ^{1}HNMR spectra showed a significant downfield shift of the NH proton adjacent to the thiocarbonyl group at δ 12.0 ppm. This is attributed to the increased magnetic anisotropy of the thiocarbonyl moiety resulting from the high polarisability of the C=S bond [8,9]. The benzoxazepinethiones (6) (X = H, Br; R = H, Br, Cl) underwent *S*-alkylation when treated with each of methyl iodide, ethyl bromoacetate and *β*-diethylaminoethyl chloride hydrochloride in tetrahydrofuran in the presence of sodium hydride to give the corresponding sulfanyl derivatives7. The IR spectra of compounds 7 showed the absence of the NH band, while the ^{1}H NMR spectra showed the aliphatic proton signals corresponding to the alkyl groups in addition to the aromatic protons and the C-2 hydrogen.

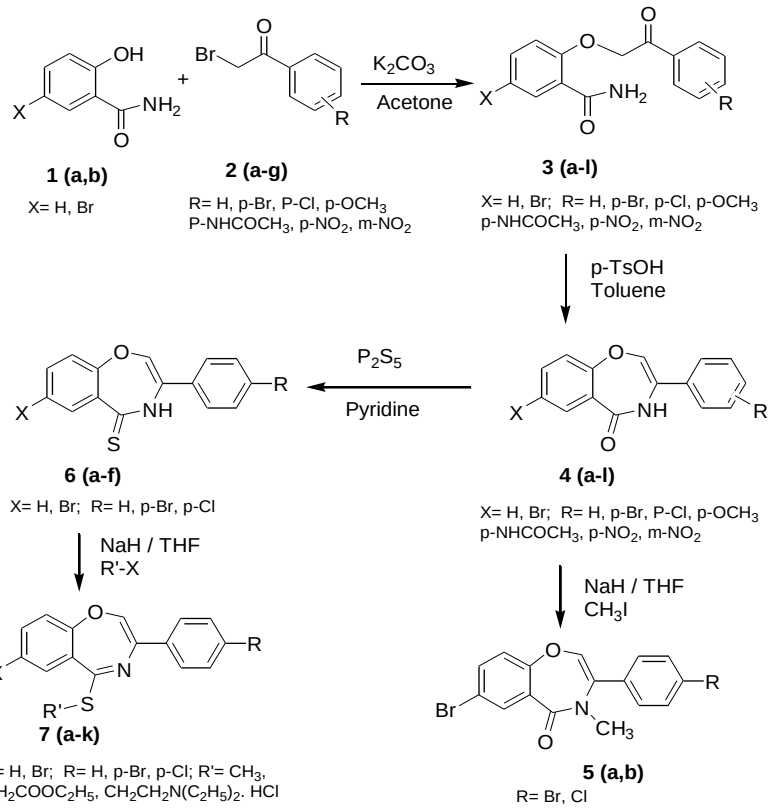
The tranquilizing effect of the synthesized 1,4-benzoxazepines was examined using the open field test [10-13], diazepam was used as a standard. The effect of the tested compounds on latency time, ambulation, grooming and rearing frequencies as well as those of diazepam was recorded in Table 1. The results revealed that diazepam, 5a, 5b and 7k significantly increased the latency time. The ambulation frequency is significantly reduced with diazepam, 4c, 5a, 5b, 6c and 7k. Further, diazepam, 4c, 5a, 5b, 6c, 7g and 7k significantly reduced the grooming frequency. The rearing frequency was significantly reduced with only diazepam and 5a.

Conclusion

It is observed from Table 1 that 1,4-benzoxazepinones 4c and thiones 6c & 6d did not alter the tested behavioral parameters. *N*-methylation of the lactam nitrogen decreased the behavioral activity as shown in compounds 5a & 5b. On the other hand, *S*-alkylation of thiolactam compounds did not show any change in their behavioral activity as shown by compounds 7c and 7g. However, compound **7**k decreased the behavioral activity in mice.

Experimental

Melting points were determined with a Griffin or Stuart apparatus in open capillaries. IR spectra (KBr) were recorded using Shimadzu IR 435 spectrophotometer. ^{1}H NMR were determined on Jeol FXQ-90 MHz and Gemini 200MHz spectrometers using DMSO-d_6 as a solvent and TMS as an internal standard (chemical shifts are recorded in δ, ppm). Mass spectra were run on Hewlett Packard 5988 spectrometer. Elemental analyses were performed at the Microanalytical Center, Faculty of Science, Cairo University, Giza, Egypt and their results corresponded to the calculated values within experimental error. TLC was performed on silica gel (Merck 60 F254) and spots were visualized using UV lamp. The starting materials were purchased from Sigma-Aldrich. The intermediate phenacyl bromides[14-17], 5-bromosalicylamide [18] and 3-(4-chlorophenyl)-1,4-benzoxazepin-5(4*H*)-one [19] were prepared according to the reported procedures.



Scheme 1.

TABLE 1. The latency time, ambulation, grooming and rearing frequencies of the tested 1,4-benzoxazepines using the open field test in mice.

Groups	The open field test Mean ± S.E.			
	Latency time (seconds)	Ambulation Frequency Square/3min	Grooming Frequency no/3min	Rearing Frequency no/3min
normal	0.3±0.2	69.3±3.0	7.8±0.9	10.8±0.8
Diazepam	180.0±0.0*	0.0±0.0*	0.0±0.0*	0.0±0.0*
4c	0.6±0.0	41.8±0.9*	1.6±0.5*	7.8±2.4
5a	12.1±5.1*	33.5±4.0*	0.8±0.4*	3.8±0.4*
5b	16.5±6.1*	38.0±9.2*	0.6±0.3*	12.0±3.7
6c	0.6±0.2	32.1±8.2*	1.0±0.3*	10.5±3.6
6d	0.0±0.0	57.3±3.8	4.5±0.2	10.6±1.3
7c	1.0±0.8	54.0±7.3	6.5±1.1	10.0±1.7
7g	0.5±0.2	64.0±5.7	3.3±0.8*	16.0±4.7
7k	6.1±1.1*	37.0±3.7*	1.8±0.5*	9.6±1.6

* Significantly different from control at $p \leq 0.05$

2-(2-Aryl-2-oxoethoxy)-5-substitutedbenzamides (3a-l)

General procedure

A mixture of the appropriate salicylamide 1 (0.07 mol), substituted phenacyl bromide 2 (0.08 mol), potassium carbonate (20 g), potassium iodide (0.2 g) and dry acetone (175 ml) was heated under reflux with stirring for 7hr. The reaction mixture was evaporated to dryness under reduced pressure, the resultant solid was extracted with $CHCl_3$ (4X20 ml), washed with 1N sodium hydroxide solution, water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was crystallized from the suitable solvent.

5-Bromo-2-(2-oxo-2- phenylethoxy)benzamide (3a)

Crystallized from methanol; yield 75 %; m.p. 190-2^oC; IR (KBr), cm^{-1}: 3400, 3200 (NH_2), 1700 (C=O), 1675 (C=O); MS (70eV), *m/z* (%): 333,335 [5.3:5.3] $(M)^{+\cdot}$; 105 [100]; Anal. Calcd for $C_{15}H_{12}BrNO_3$: C, 53.91; H, 3.61; N, 4.10. Found: C, 54.28; H, 3.77; N, 4.42.

2-(2-(4-Bromophenyl)-2-oxoethoxy)benzamide (3b)

Crystallized from methanol; yield 85 %; m.p. 202-4^oC; ^1H NMR (90MHz, DMSO) , *δ,* ppm: 5.7 (s, 2H, OCH_2CO), 7.0-8.0 (m, 8H aromatic 8H's), 8.4 (2H, NH_2, D_2O exchangeable); IR (KBr), cm^{-1} : 3400, 3200 (NH_2), 1700 (C=O), 1660 (C=O); MS (70eV), *m/z* (%): 333,335 [1.1:1.3] $(M)^+$; 121 [100]; Anal.Calcd for $C_{15}H_{12}BrNO_3$: C, 53.91; H, 3.61; N, 4.10.Found: C, 54.21; H, 3.91; N, 4.18.

2-(2-(4-Bromophenyl)-2-oxoethoxy)-5-bromobenzamide (3c)

Crystallized from ethyl acetate; yield 81 %; m.p. 217-8^oC; ^1H NMR (200MHz, DMSO-d_6), *δ,* ppm: 5.8 (s, 2H, OCH_2CO), 7.3-8.0 (m, 7H, aromatic H's), 8.4 (2H, NH_2, D_2O exchangeable). IR (KBr), cm^{-1}: 3400, 3200 (NH_2), 1700 (C=O), 1660 (C=O); MS (70eV), *m/z* (%) :411,413,415 [2.7:5.1:2.5] $(M)^{+\cdot}$; 183,185 [95.1:100]; Anal. Calcd for $C_{15}H_{11}Br_2NO_3$: C, 43.61; H, 2.68;
N, 3.39. Found: C, 43.64; H, 2.70; N, 3.55.

5-Bromo-2-(2-(4-chlorophenyl)-2-oxoethoxy)benzamide (3d)

Crystallized from acetone; yield 79 %; m.p. 220-221^oC; ^1H NMR (200MHz, DMSO-d_6) , *δ,* ppm: 5.8 (s, 2H, OCH_2CO), 7.3-8.0 (m, 7H aromatic H's), 8.4 (2H, NH_2, D_2O exchangeable); IR (KBr),cm^{-1}: 3400, 3200 (NH_2), 1700 (C=O), 1660 (C=O); MS(70eV),*m/z* (%): 367 ,369, 371[4.4:5.7:1.4] $(M)^+$; 139,141 [100:27.7]; Anal. Calcd for $C_{15}H_{11}BrClNO_3$: C, 48.87; H, 3.00; N, 3.79. Found: C, 49.12; H, 3.23; N, 3.92.

2-(2-(4-Nitrophenyl)-2-oxoethoxy)benzamide (3e)

Crystallized from ethanol; yield 85 %; m.p. 216-218^oC; IR (KBr), cm^{-1}: 3400, 3320 (NH_2), 1710 (C=O), 1660 (C=O), 1520, 1320 (NO_2); MS (70eV), *m/z* (%) : 300 [2.1] $(M)^{+\cdot}$; 121 [100]; Anal. Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.02; N, 9.33. Found: C, 60.06; H, 4.20; N, 9.25.

5-Bromo-2-(2-(4-nitrophenyl)-2-oxoethoxy)benzamide (3f)

Crystallized from methanol; yield 75 %; m.p. 230-2°C; IR (KBr) cm^{-1}: 3400, 3320 (NH_2), 1710 (C=O), 1660 (C=O), 1520, 1320 (NO_2); MS (70eV), *m/z* (%): 378,380 [10.4:14.4] $(M)^{+\cdot}$; 199, 201 [100:79]; Anal. Calcd for $C_{15}H_{11}BrN_2O_5$: C, 47.51; H, 2.92; N, 7.38. Found:C, 47.60 ; H, 2.90; N, 7.32.

2-(2-(3-Nitrophenyl)-2-oxoethoxy)benzamide (3g)

Crystallized from methanol; yield 82 %; m.p. 182-4°C; IR (KBr), cm^{-1}: 3400, 3200 (NH_2), 1700 (C=O), 1660 (C=O), 1520, 1320 (NO_2); MS (70eV), *m/z* (%): 300 [3.5] $(M)^{+\cdot}$; 121 [100]; Anal. Calcd for $C_{15}H_{12}N_2O_5$**:** C, 60.00; H, 4.02; N, 9.33. Found: C, 59.80; H, 4.24; N, 9.43.

5-Bromo-2-(2-(3-nitrophenyl)-2-oxoethoxy)benzamide (3h)

Crystallized from methanol; yield 78 %; m.p. 215-6°C; IR (KBr), cm^{-1}: 3400, 3200 (NH_2), 1700 (C=O), 1660 (C=O), 1520, 1320 (NO_2); Anal. Calcd for $C_{15}H_{11}BrN_2O_5$: C, 47.51; H, 2.92; N, 7.38. Found: C, 47.82; H, 3.06; N, 7.39.

2-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzamide (3i)

Crystallized from acetone; yield 84 %; m.p. 178-180°C; IR (KBr), cm^{-1}: 3400, 3170 (NH_2), 1680 (C=O), 1640 (C=O); MS (70eV), *m/z* (%): 285 [7.5] $(M)^{+\cdot}$; 135 [100]; Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.29; N, 4.91. Found: C, 67.50; H, 5.26; N, 4.86.

5-Bromo-2-(2-(4-methoxyphenyl)-2-oxoethoxy)benzamide (3j)

Crystallized from ethyl acetate; yield 73 %; m.p. 194-6°C; ^{1}H NMR (90MHz, DMSO-d_6) , *δ,* ppm: 3.9 (s,3H, OCH_3), 5.7 (s, 2H, OCH_2CO), 7.0-8.0 (m, 7H, aromatic H's), 8.4 (2H, NH_2, D_2O exchangeable); IR (KBr) cm^{-1}: 3400, 3170 (NH_2), 1680 (C=O), 1640 (C=O); MS (70eV), *m/z* (%) : 363,365 [1.8:1.6] $(M)^{+\cdot}$; 135 [100]; Anal. Calcd for $C_{16}H_{14}BrNO_4$: C, 52.76; H, 3.87; N, 3.84. Found: C, 52.54; H, 3.77; N, 3.82.

2-(2-(4-Acetamidophenyl)-2-oxoethoxy)benzamide (3k)

Crystallized from ethanol; yield 89 %; m.p. 212-4 °C; ^{1}H NMR (200MHz, DMSO-d_6), *δ,* ppm: 2.1(s, 3H, CH_3CO), 5.7 (s, 2H, OCH_2CO), 7.0-8.0 (m, 8H aromatic H's), 8.45 (2H, NH_2, D_2O exchangeable), 10.3 (1H, NH, D_2O exchangeable); IR (KBr),cm^{-1}: 3400, 3300 (NH_2), 1700 (C=O), 1680 (C=O), 1660 (C=O); MS (70eV), *m/z* (%): 312[11.6] $(M)^+$; 192 [26.6]; 162 [100]; Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.96. Found: C, 65.26; H, 5.20; N, 9.06.

2-(2-(4-Acetamidophenyl)-2-oxoethoxy)-5-bromobenzamide (3l)

Crystallized from acetone; yield 83 %; m.p. 228-230°C; ^{1}H NMR (200MHz, DMSO-d_6), *δ,* ppm: 2.1 (s,3H,CH_3CO), 5.8(s,2H,OCH_2CO), 7.3-8.1(m,7H,aromatic H's), 8.5 (2H, NH_2, D_2O exchang eable), 10.4 (1H, NH, D_2O exchangeable); IR (KBr) , cm^{-1} : 3400, 3300 (NH_2), 1700 (C=O), 1680 (C=O), 1660 (C=O); MS (70eV), *m/z* (%) : 390,392 [3.6:3.8] $(M)^+$; 162 [100]; Anal.

Calcd for $C_{17}H_{15}BrN_2O_4$: C, 52.19; H, 3.86; N, 7.16. Found: C, 52.22; H, 3.71; N, 7.13.

3-Aryl-7-substituted-1,4-benzoxazepin-5(4H)-ones (4a-l)

General procedure

The appropriate benzamide 3 (0.04 mol) was dissolved in 45 ml dry toluene at 70 ^oC**,** and then 4-toluenesulphonic acid (0.25 g) was added. The reaction mixture was heated under reflux using water separator for 5-10hr (till all equivalent moles of water was separated). The reaction mixture was cooled. The precipitate was collected by filtration and crystallized from the suitable solvent.

7-Bromo-3-phenyl-1,4-benzoxazepin-5(4H)-one (4a)

Crystallized from dioxan; yield 97 %; m.p. 205-7^oC; ^1H NMR (200MHz, DMSO-d_6) , *δ,* ppm: 6.9 (s, 1H, alkene H at C-2), 7.2-7.9 (m, 8H aromatic 8H's), 10.0 (1H, NH, D_2O exchangeable); IR (KBr), cm^{-1}: 3200 (NH), 1660 (C=O); MS (70eV),*m/z* (%): 315,317 [46.4:54.0] $(M)^+$; 104 [100]; Anal. Calcd for $C_{15}H_{10}BrNO_2$: C, 56.98; H, 3.18; N, 4.43. Found: C, 57.00; H, 3.30; N, 4.53.

3-(4-Bromophenyl)-1,4-benzoxazepin-5(4H)-one (4b)

Crystallized from toluene; yield 95 %; m.p. 216-7^oC; ^1H NMR (200MHz, DMSO-d_6) , *δ,* ppm: 6.9 (s,1H, alkene H at C-2), 7.1-7.8 (m, 8H aromatic 8H's), 9.8 (1H, NH, D_2O exchangeable); IR (KBr), cm^{-1}: 3220 (NH), 1650 (C=O); MS (70eV), *m/z* (%): 315,317 [12.8:12.8] $(M)^+$; 134 [100].; Anal. Calcd for $C_{15}H_{10}BrNO_2$: C, 56.98; H, 3.18; N, 4.43. Found: C, 57.03; H, 3.40;N, 4.30.

7-Bromo-3-(4-bromophenyl)-1,4-benzoxazepin-5(4H)-one (4c)

Crystallized from toluene; yield 93%; m.p. 256-8^oC; ^1H NMR (200MHz, DMSO-d_6), *δ,* ppm: 6.98 (s, 1H, alkene H at C-2), 7.16-7.9 (m, 7H arom H's), 10.0 (1H, NH, D_2O exchangeable); IR (KBr), cm^{-1}: 3200 (NH), 1650 (CO); MS(70eV), *m/z* (%): 393,395,397 [25.6:39.9: 23.6] $(M)^+$; 182,184 [94.6:100]; Anal. Calcd for $C_{15}H_9Br_2NO_2$: C, 45.60; H, 2.29; N, 3.54. Found: C, 45.82; H, 2.39; N, 3.24.

7-Bromo-3-(4-chlorophenyl)-1,4-benzoxazepin-5(4H)-one (4d)

Crystallized from toluene; yield 92 %; m.p. 250-1^oC; ^1H NMR (200MHz, DMSO) , *δ,* ppm: 6.9 (s, 1H, alkene H at C-2), 7.1-7.8 (m, 7H aromatic 7H's), 10.0 (1H, NH, D_2O exchangeable); IR(KBr), cm^{-1}: 3200 (NH), 1660 (C=O); MS (70eV), *m/z* (%) : 349,351 [12.4:15.0] $(M)^+$; 138,140 [100:31.9]; Anal. Calcd for $C_{15}H_9BrClNO_2$: C, 51.38; H, 2.58; N, 3.99. Found: C, 51.45; H, 2.56; N, 4.13.

3-(4-Nitrophenyl)-1,4-benzoxazepin-5(4H)-one (4e)

Crystallized from ethanol; yield 85 %; m.p. 231-2^oC; IR (KBr), cm^{-1}: 3220 (NH), 1660 (C=O). Anal. Calcd for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.92. Found: C, 63.84; H, 3.82; N, 10.01.

7-Bromo-3-(4-nitrophenyl)-1,4-benzoxazepin-5(4H)-one (4f)

Crystallized from ethanol; yield 83 %; m.p. 290-1°C; IR (KBr), cm^{-1}: 3220 (NH), 1660 (C=O) MS (70eV), *m/z* (%): 360, 362 [23.9:23.7] $(M)^{+\cdot}$; 212:214 [100:95.7]; Anal.Calcd.for $C_{15}H_9BrN_2O_4$: C, 49.88; H, 2.51; N, 7.75. Found: C, 50.12; H, 2.69; N, 7.81.

3-(3-Nitrophenyl)-1,4-benzoxazepin-5(4H)-one (4g)

Crystallized from ethanol; yield 88 %; m.p. 201-3°C; IR (KBr), cm^{-1} : 3200 (NH), 1660 (C=O) Anal. Calcd.for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.92. Found: C, 63.55; H, 3.65; N, 10.21.

7-Bromo-3-(3-nitrophenyl)-1,4-benzoxazepin-5(4H)-one (4h)

Crystallized from ethanol; yield 82 %; m.p. 230-2°C; IR (KBr), cm^{-1} : 3200 (NH), 1660 (C=O) Anal. Calcd. for $C_{15}H_9BrN_2O_4$: C, 49.88; H, 2.51; N, 7.75. Found: C, 50.02; H, 2.61; N, 7.70.

3-(4-Methoxyphenyl)-1,4-benzoxazepin-5(4H)-one (4i)

Crystallized from acetone; yield 75 %; m.p. 190-1°C; IR (KBr), cm^{-1}: 3200 (NH), 1650 (C=O) MS (70eV), *m/z* (%): 267 [9.0] $(M)^{+\cdot}$; 134 [100]; Anal. Calcd.for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.95; H, 4.80; N, 5.15.

7-Bromo-3-(4-methoxyphenyl)-1,4-benzoxazepin-5(4H)-one (4j)

Crystallized from acetone; yield 72 %; m.p. 204-6°C; IR (KBr), cm^{-1}: 3200 (NH), 1650 (C=O); Anal. Calcd.for $C_{16}H_{12}BrNO_3$: C, 55.51; H, 3.49; N, 4.04. Found: C, 55.64; H, 3.66; N, 3.95.

3-(4-Acetamidophenyl)-1,4-benzoxazepin-5(4H)-one (4k)

Crystallized from methanol; yield 91 %; m.p. 244-6°C; ^{1}H NMR (200MHz, DMSO-d_6) , *δ,* ppm: 2.1 (s, 3H, CH_3CO), 6.9 (s, 1H, alkene H at C-2), 7.1-7.8 (m, 7H aromatic H's), 9.8 (1H, NH, D_2O exchangeable), 10.1 (1H, NH, D_2O exchangeable); IR (KBr),cm^{-1} : 3200 (NH), 1680 (C=O), 1650 (C=O); MS (70eV), *m/z* (%): 294 [28.3] $(M)^{+\cdot}$; 161 [100]; Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.51. Found: C, 69.32; H, 4.65; N, 9.80.

3-(4-Acetamidophenyl)-7-Bromo-1,4-benzoxazepin-5(4H)-one (4l)

Crystallized from methanol; yield 90 %; m.p. 234-5°C; IR (KBr), cm^{-1}: 3200 (NH), 1680 (C=O), 1650 (C=O); Anal. Calcd.for $C_{17}H_{13}BrN_2O_3$: C, 54.71; H, 3.51; N, 7.50. Found: C, 54.33; H, 3.54; N, 7.55.

3-Aryl-7-bromo-4-methyl-1,4-benzoxazepin-5(4H)-ones (5a&5b)

General procedure

A stirred suspension of benzoxazepinone 4 (2 mmol) in dry THF (17 ml), under nitrogen gas, was treated with NaH, 60 % dispersed in liquid paraffin, (0.096 g, 2.4 mmol). After 30 min the homogenous solution was treated

dropwise with methyl iodide (0.295 ml, 3mmol). The mixture was stirred at room temperature for 3hr. The reaction mixture was poured into ice-cold water. The aqueous mixture was extracted with chloroform, the organic extract was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was crystallized from the suitable solvent.

7-Bromo-3-(4-bromophenyl)-4-methyl-1,4-benzoxazepin-5(4H)-one (5a)

Crystallized from ethanol; yield 60 %; m.p. 162-4^{o}C; ^{1}H NMR (200MHz, DMSO-d_6) , *δ,* ppm: 2.9 (s,3H, NCH_3), 6.9 (s, 1H, alkene H at C-2), 7.1-7.8 (m, 7H, aromatic H's); IR (KBr),cm^{-1} : 2950-2900 (CH aliphatic), 1645 (C=O); MS (70eV), *m/z* (%) : 407,409 [5.4:3.9] $(M)^{+\cdot}$; 75 [100]; Anal. Calcd for $C_{16}H_{11}Br_2NO_2$: C, 46.97; H, 2.71; N, 3.42. Found: C, 47.15; H, 2.51; N, 3.40.

7-Bromo-3-(4-chlorophenyl)-4-methyl-1,4-benzoxazepin-5(4H)-one (5b)

Crystallized from methanol; yield 65 %; m.p. 158-9^{o}C; ^{1}H NMR (200MHz, DMSO-d_6), *δ,* ppm: 2.9 (s, 3H, NCH_3), 6.9 (s, 1H, alkene H at C-2), 7.1-7.8 (m, 7H aromatic H's); IR (KBr), cm^{-1}: 2950 -2900 (CH aliphatic), 1640 (C=O); Anal. Calcd.for $C_{16}H_{11}BrClNO_2$: C, 52.70; H, 3.04; N, 3.84. Found: C, 52.73; H, 3.16; N, 3.71.

3-Aryl-7-substituted-1,4-benzoxazepine-5(4H)-thiones (6a-f)

General procedure

A solution of the appropriate benzoxazepinone 4 (2 mmol) and phosphorus pentasulphide (1.78 g, 4 mmol) in dry pyridine (8 ml) was heated under reflux with stirring for 3hr and then allowed to cool. The cooled mixture was poured into ice cold water and acidified with 10% HCl. The precipitate was collected by filtration, washed with water and crystallized.

7-Bromo-3-phenyl-1,4-benzoxazepine-5(4H)-thione (6a)

Crystallized from ethanol; yield 75 %; m.p. 174-5^{o}C; IR (KBr), cm^{-1}**:** 3120 (NH), 1600, 1520 (C=C), 1200 (C=S); MS (70eV), *m/z* (%): 331,333 [10.0:11.4] $(M)^{+\cdot}$; 121 [100]; Anal. Calcd for $C_{15}H_{10}BrNOS$: C, 54.23; H, 3.03; N, 4.21. Found: C, 54.45; H, 3.36; N, 4.26.

3-(4-Bromophenyl)-1,4-benzoxazepine-5(4H)-thione (6b)

Crystallized from toluene; yield 78 %; m.p. 170 -2^{o}C; ^{1}H NMR (200MHz, DMSO-d_6) , *δ,* ppm: 7.3 (s, 1H, alkene H at C-2), 7.14-8.1 (m, 8H aromatic H's), 12.0 (1H, NH, D_2O exchangeable); IR(KBr),cm^{-1}: 3120 (NH), 1580, 1520 (C=C), 1200 (C=S); Anal. Calcd.for $C_{15}H_{10}BrNOS$: C, 54.23; H, 3.03; N, 4.21. Found: C, 54.17; H, 3.14; N, 4.21.

7-Bromo-3-(4-bromophenyl)-1,4-benzoxazepine-5(4H)-thione (6c)

Crystallized from toluene; yield 88 %; m.p. 210-2^{o}C; ^{1}H NMR (200MHz, DMSO-d_6), *δ,* ppm: 7.2 (s, 1H, alkene H at C-2), 7.0-8.1 (m, 7H aromatic H's), 12.0 (1H, NH, D_2O exchangeable); IR(KBr),cm^{-1} : 3120 (NH), 1600, 1520

(C=C), 1180 (C=S); Anal. Calcd for $C_{15}H_9Br_2NOS$: C, 43.82; H, 2.20; N, 3.40. Found: C, 44.06; H, 2.36; N, 3.40.

3-(4-Chlorophenyl)-1,4-benzoxazepine-5(4H)-thione (6d)

Crystallized from ethanol; yield 76 %; m.p. 166-8°C; ^{1}H NMR (200MHz, DMSO-d_6), *δ*,ppm: 7.28 (s, 1H, alkene H at C-2), 7.14-8.1 (m, 8H aromatic H's), 12.0 (1H, NH, D_2O exchangeable); IR (KBr), cm^{-1}: 3120 (NH), 1600, 1520 (C=C), 1210 (C=S); Anal. Calcd for $C_{15}H_{10}ClNOS$: C, 62.61; H, 3.50; N, 4.87. Found: C, 62.90; H, 3.86; N, 4.80.

7-Bromo-3-(4-chlorophenyl)-1,4-benzoxazepine-5(4H)-thione (6e)

Crystallized from acetone; yield 85 %; m.p. 200-2°C; ^{1}H NMR (200MHz, DMSO-d_6), *δ,* ppm: 7.2 (s1H, alkene H at C-2), 7.0-8.1 (m, 7H aromatic H's), 12.0 (1H, NH, D_2O exchangeable); IR (KBr), cm^{-1}: 3120 (NH), 1590, 1520 (C=C), 1190 (C=S); MS (70eV), *m/z* (%): 365,367,369 [25.2:38.7:10.4] $(M)^{+\cdot}$; 138,140 [100:33.4]; Anal. Calcd.for $C_{15}H_9BrClNOS$: C, 49.13; H, 2.47; N, 3.82. Found: C, 49.28; H, 2.50; N, 3.90.

3-Aryl-5-methylsulfanyl-7-substituted-1,4-benzoxazepines (7a-e)

General procedure

A solution of the appropriate benzoxazepinethione 6 (1 mmol) in dry THF (4 ml) was added dropwise to a stirred suspension of NaH, 60 % dispersed in liquid paraffin, (0.048 g, 1.2 mmol) in dry THF (2 ml) and stirred at room temperature for 20 min under nitrogen gas. Iodomethane (0.195 cm^3, 2 mmol) was added dropwise and stirring was continued for 2hr. The solvent was evaporated under reduced pressure, the residue was taken up in chloroform and the resulting solution was washed with water and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was crystallized from the suitable solvent.

7-Bromo-5-methylsulfanyl-3-phenyl-1,4-benzoxazepine (7a)

Crystallized from methanol; yield 85 %; m.p. 60-1°C; IR (KBr), cm^{-1}: 2990-2900 (CH aliphatic), 1610 (C=N), 1545-1460 (C=C aromatic); Anal. Calcd.for $C_{16}H_{12}BrNOS$: C, 55.50; H, 3.49; N, 4.04. Found: C, 55.75; H, 3.63; N, 4.20.

3-(4-Bromophenyl)-5-methylsulfanyl-1,4-benzoxazepine (7b)

Crystallized from methanol; yield 80 %; m.p. 55-6°C; IR (KBr), cm^{-1}: 2990-2910 (CH aliphatic), 1600 (C=N), 1545-1480 (C=C aromatic); Anal. Calcd for $C_{16}H_{12}BrNOS$: C, 55.50; H, 3.49; N, 4.04. Found: C, 55.51; H, 3.77; N, 4.19.

7-Bromo-3-(4-bromophenyl)-5-methylsulfanyl-1,4-benzoxazepine (7c)

Crystallized from toluene; yield 85 %; m.p. 118-120°C; ^{1}H NMR (200MHz, DMSO-d_6), *δ*,ppm: 2.6 (s, 3H, SCH_3), 6.9 (s, alkene H at C-2), 7.1-7.8 (m, 7H, aromatic H's); IR (KBr),cm^{-1}: 2950, 2900 (CH aliphatic), 1580 (C=N), 1520-1460 (C=C aromatic); MS (70eV), *m/z* (%): 423,425,427 [12.7:25.1:13.1] $(M)^{+\cdot}$; 227,229 [95.8:100]; Anal. Calcd.for $C_{16}H_{11}Br_2NOS$: C, 45.20; H, 2.60; N, 3.29. Found: C, 45.46; H, 2.40; N, 3.19.

3-(4-Chlorophenyl)-5-methylsulfanyl-1,4-benzoxazepine (7d)

Crystallized from methanol; yield 83 %; m.p. 49-50^{o}C; IR (KBr), cm^{-1}: 2950-2900 (CH aliphatic), 1600 (C=N), 1570-1490 (C=C aromatic); Anal. Calcd.for $C_{16}H_{12}ClNOS$: C, 63.67;H, 4.00; N, 4.64. Found: C, 63.51; H, 4.02; N, 5.01.

7-Bromo-3-(4-chlorophenyl)-5-methylsulfanyl-1,4-benzoxazepine (7e)

Crystallized from ethanol; yield 85 %; m.p. 112-114^{o}C; ^{1}H NMR (200MHz, DMSO), *δ,ppm:*2.6 (s, 3H, SCH_3), 6.9 (s, alkene H at C-2), 7.1-7.8 (m, 7H, aromatic H's); IR (KBr),cm^{-1}: 2900 (CH aliphatic), 16010 (C=N), 1595-1475 (C=C aromatic); MS (70eV), *m/z* (%): 379,381,383 [12.0:6.1:1.4] $(M)^{+\cdot}$; 137,139 [100:30.3]; Anal. Calcd.for $C_{16}H_{11}BrClNOS$: C, 50.48; H, 2.91; N, 3.68. Found: C, 50.02; H, 2.81; N, 3.63.

Ethyl-2-(3-Aryl-7-substituted-1,4-benzoxazepin-5-yl sulfanyl) ethanoates (7f-h)

General procedure

A solution of the appropriate benzoxazepinethione 6 (1 mmol) in dry THF (4 ml) was added dropwise to a stirred suspension of NaH, 60 % dispersed in liquid paraffin, (0.048 g, 1.2 mmol) in dry THF (2 ml) and stirred at room temperature for 20 min under nitrogen gas. Ethyl bromoacetate (0.112 ml, 1 mmol) was added dropwise and stirring was continued for 2hr. The solvent was evaporated under reduced pressure, the residue is taken up in chloroform and the resulting solution was washed with water and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was crystallized from the suitable solvent.

Ethyl-2-(7-bromo-3-(4-bromophenyl)-1,4-benzoxazepin-5-yl sulfanyl) ethanoate (7f)

Crystallized from ethanol; yield 91 %; m.p. 122^{o}C; ^{1}H NMR (200MHz, DMSO-d_6), *δ*,ppm: 1.2 (t,3H,$\underline{CH_3}CH_2$) 4.1 (s, 2H, SCH_2CO), 4.2 (q, 2H, $CH_3\underline{CH_2}O$), 6.98 (s, 1H, alkene H at C-2), 7.19-7.9 (m, 7H aromatic 7H's); IR (KBr),cm^{-1}: 2990 (CH aliphatic), 1740 (C=O), 1590 (C=N), 1490 (C=Carom); MS (70eV), *m/z* (%): 495,497,499 [2.9:5.7:3.4] $(M)^{+\cdot}$; 227:229 [100:97.7]; Anal. Calcd.for $C_{19}H_{15}Br_2NO_3S$: C, 45.90; H, 3.04; N, 2.81. Found: C, 46.08; H, 2.88; N, 2.75.

Ethyl-2-(3-(4-chlorophenyl)-1,4-benzoxazepin-5-yl sulfanyl) ethanoate (7g)

Crystallized from methanol; yield 85 %; m.p. 70-1^{o}C; ^{1}H NMR (200MHz, DMSO-d_6), *δ*,ppm: 1.2 (t, 3H, $\underline{CH_3}CH_2$), 4.1 (s, 2H, SCH_2CO), 4.2 (q, 2H, $CH_3\underline{CH_2}O$), 6.97 (s, 1H, alkene H at C-2),7.2-7.7 (m, 8H, aromatic H's); IR (KBr), cm^{-1}: 2990-2900 (CH aliphatic), 1730 (C=O), 1590 (C=N),1480 (C=C aromatic); MS (70eV), *m/z* (%) : 373,375 [10.6:3.8] $(M)^{+\cdot}$; 149 [100]. Anal. Calcd for $C_{19}H_{16}ClNO_3S$: C, 61.04; H, 4.31; N, 3.74. Found: C, 61.27; H, 4.21; N, 3.79.

Ethyl-2-(7-bromo-3-(4-chlorophenyl)-1,4-benzoxazepin-5-yl sulfanyl) ethanoate (7h)

Crystallized from methanol; yield 87%; m.p. 95-6°C; ^{1}H NMR (200MHz, DMSO-d_6), δ, ppm: 1.1(t, 3H, $\underline{CH_3}CH_2$), 4.0 (s, 2H, SCH_2CO), 4.1 (q, 2H, $CH_3\underline{CH_2}O$), 6.9 (s, 1H, alkene H at C-2), 7.1-7.8 (m, 7H, aromatic H's); IR (KBr),cm^{-1}: 2990-2950 (CH aliphatic), 1735 (C=O), 1600 (C=N), 1480 (C=C aromatic). Anal. Calcd for $C_{19}H_{15}BrClNO_3S$: C, 50.40; H, 3.33; N, 3.09. Found: C, 50.00; H, 3.55; N, 3.41.

3-Aryl-5-(2-diethylaminoethylsulfanyl)-1,4-benzoxazepine hydrochlorides (7i-k)

General procedure

A solution of the appropriate benzoxazepinethione 6 (1 mmol) in dry THF (4 ml) was added dropwise to a stirred suspension of NaH, 60% dispersed in liquid paraffin, (0.096 g, 2.4 mmol) in dry THF (2 ml) and stirred at room temperature for 20 min under nitrogen gas. *β*-Diethylaminoethyl chloride hydrochloride (0.17 g, 1 mmol) was added in one batch and the mixture was heated under reflux for 10hr. The solvent was evaporated under reduced pressure, the semi solid residue was taken up in diethyl ether and the resulting solution was washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, the oily base was treated with ethanolic HCl solution and the separated hydrochloride salt was crystallized.

5-(2-Diethylaminoethylsulfanyl)-1,4-benzoxazepine hydrochloride (7i)

Crystallized from ethanol; yield 70 %; m.p. 170-1°C; IR (KBr), cm^{-1}: 2990-2850 (CH aliphatic), 1600 (C=N), 1580, 1520 (C=C); MS (70eV), *m/z* (%): 352 [1.3%] $(M)^{+\cdot}$; 99 [100%]. Anal. Calcd.for $C_{21}H_{25}ClN_2OS$: C, 64.84; H, 6.47; N, 7.20. Found: C, 64.60; H, 6.40; N, 7.32.

3-(4-Chlorophenyl)-5-(2-diethylaminoethylsulfanyl)-1,4benzoxazepinehydrochloride (7j)

Crystallized from ethanol; yield 72 %; m.p. 188-9°C; IR (KBr) cm^{-1}: 2920-2850 (CH aliphatic), 1600 (C=N), 1560, 1520 (C=C). Anal. Calcd.for $C_{21}H_{24}Cl_2N_2OS$: C, 59.57; H, 5.71; N, 6.61. Found: C, 59.50; H, 5.62; N, 6.60.

7-Bromo -3- (4-bromophenyl)-5- (2- diethylaminoethylsulfanyl)- 1, 4 benzoxazepine hydrochloride (7k)

Crystallized from ethanol; yield 75 %; m.p. 230-1°C; ^{1}H NMR (200MHz, DMSO-d_6), δ,ppm: 1.2 (t, 6H, CH_3CH_2), 3.1 (q, 4H, $CH_3CH_2N^+$), 3.3 (t, 2H, $SCH_2CH_2N^+$), 4.0 (t, 2H, $SCH_2CH_2N^+$), 6.9(s, 1H, alkene H at C-2), 7.1-8.1(m, 7H, aromatic H's), 10.9 (s, N^+H, D_2O exchangeable); IR (KBr),cm^{-1}: 2940-2850 (CH aliphatic), 1590 (C=N), 1520, 1480 (C=C). Anal. Calcd for $C_{21}H_{23}Br_2ClN_2OS$: C, 46.13; H, 4.24; N, 5.12. Found: C, 46.40; H, 4.10; N, 5.32.

Pharmacology

Eight compounds: 4c, 5a, 5b, 6c, 6d, 7c, 7g, 7k were suspended in saline using Tween 80. Several groups, each consisting of 6 mice (17-25 gm) were injected i.p. with tested compounds at a dose level 25 mg/Kg. Another group

received diazepam 25 mg/Kg as a standard, and the last group received saline containing few drops of Tween 80 and served as normal group. Thirty minutes following the administration, each mouse was observed for 3 min. Effect of the compounds on latency time, ambulation, grooming and rearing frequencies as well as that of diazepam were recorded and presented in Table 1.

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تشـــييد ودراســـة التـــأثير المطمـــئن لمركبـــات جديـــدة مـــن ١، ٤- بنزوكسازيبينات

سمير بطرس صليب، باسم حشمت نجيب و عبد الجابر نصر عثمان
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تم تحضير سلسلة من مركبات ٤،١-بنزوكسازيبين-٥ (٤يد) –ونات عن طريق ألكلة مركبات الساليسلاميدات بمستبدل بروميد الفيناسيل متبوعا بحلقنة الاميدات الناتجة. وبتفاعل مركبات ٤،١-بنزوكسازيبين-٥ (٤يد) –ونات مع خماسي كبريتيد الفوسفور انتج مركبات ٤،١-بنزوكسازيبين-٥ (٤يد) –ثيونات المقابلة. بالاضافة الى شرح طرق ألكلة مركبات ٤،١-بنزوكسازيبين-٥ (٤يد) –ونات على ذرة النيتروجين ومركبات ٤،١-بنزوكسازيبين-٥ (٤يد) –ثيونات على ذرة الكبريت. وبالإضافة إلى ما تقدم، فقد تضمن البحث أيضاً عمل مسح مبدئى لبعض المركبات المنتخبة لتبيان ما قد يكون لها من نشاط حيوى كمطمئنات.