A Synthesis and Evaluation the Hypnotic and Anticonvulsion Activities of Some Aminopyrido[2,3-b][1,5]benzodiazepine derivatives

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Abstract: The present work compress the synthesis of 5-amino2,4-dimethyl-11H-pyrido[2,3b][1,5]benzodiazepine derivatives3 by condensation of 2-chloronicotinic acid 1 with o-phenylenediamine 2 which react with malononitrile to form 4 and with phenylisocyanate to give phenyl urea 5 and react with some aromatic and heterocyclic aldehyde to produce Schiff bases which react with formaldehyde to producehydroxymethyl derivatives that converted into chloromethylderivated,then reacted with prop0anolamine and with diethanolamine.Some of the prepared compounds were preliminary screened for CNS depressant andanticonvulsant activities.
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1. Introduction

Benzodiazepines constitute an important class of bioactive compounds due to their central nervous system depressing effect. They are widely prescribed as psychotropic drugs[1,2]. GABA is well known inhibitory neurotransmitter in the mammalian CNS[3,4]. Benzodiazepine derivatives bind to the gamma subunit of the GABA-A receptor. Their binding causes an allosteric modification of the receptor activity, which leads to an increase in chloride conductance and inhibition of the action potential[5-7]. Benzodiazepines are used in treatment of anexiety[8], insomnia[9]and seizures[10,11]. However 1,4-benzodiazepines have some undesirable side effects which limit their use such as memory impairment[12], cognition motor disturbances and the ability to induce both physical and psychological dependence[13]. Some studies have shown that a number of these adverse effects are less severe when using 1,5-benzodiazepines[14]. Some pyridobenzodiazepines could be used for treatment of psychosis[15] and anexiety disorders[16]. Clozapine (a dibenzodiazepine)[16] was found to be very active against psychotic symptoms and it contains a substituted amino group at the position 5. The current work aims to synthezise some pyrido[1,5]benzodiazepines containing a substituted amino group at the position 5 and evaluate their activities as hypnotics and anticonvulsants.

2. Experimental

Infrared spectra were recorded on Shimadzu 435 spectro-photometer, ^{1}HNMR on Varian-Gemini 200 MHz spectrophotometer and mass spectra on Hewlett Pacard 5988 spectrometer. All these spectral analysis were carried out at the microanalytical center at Cairo University. Melting points were uncorrected and measured in open capillary tubes using Griffin apparatus.

2.1. Synthesis of the compounds

2.1.1. 2, 4-Dimethyl, 5-amino, 11H-pyrido [2,3-b][1,5] benzodiazepine 3 $C_{14}H_{14}N_4$

To a mixture of (0.01 mole) 2-chloro-4,6-dimethyl-nicotinonitrile and (0.01 mole) o-phenylenediamine in 5ml absolute ethanol a catalytic amount of piperidine was added. The reaction mixture was heated under reflux for 6 hours, then left to cool. The precipitate formed was filtered and crystallized from ethanol to give **3**. m.p. 198-191°C; yield 70%; ^{1}HNMR (DMSO) δ = 2.37 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 5.8 (s, 2H, NH_2) 6.65 (s, 1H, pyridyl), 6.80 - 7.10 (m, 4H, ArH), 8.02 (s, ^{1}H, NH); Ms: m/z = 239.1 (M^++1); IR (cm^{-1}): 3450-3350 (NH_2) ,3240 (NH).

2.1.2 2,4-Dimethyl, 5-(2-amino, 1-cyanothenyl) amino 11H-pyrido[2,3-b)[1,5]_benzodiazepine. 4 $C_{17}H_{16}N_6$

A 0.01 mole of **3** was mixed with 0.01 mole of malononitrile and dissolved in 5ml of abs.ethanol in presence of few drops of piperdine and heated under reflux, the precipitate so formed was crystallized with ethanol .m.p. 300- 301°C; yield 95%; ^{1}HNMR (DMSO) δ = 2.49 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.38 (s, 1H, CH), 6.1(s, 2H, NH_2), 6.70 (s, 1H, pyridyl), 7.2 - 7.7 (m, 4H, ArH), 12.3 (s, 1H, NH); MS: m/z = 304

(M^+); IR (cm^{-1}): 3408- 3330 (NH_2), 3240 (NH),3150(NH), 2220 (CN).

2.1.3 2,4-Dimethyl, 5-phenylcarbamyl amino, 11H-pyrido [2,3-b][1,5] benzodiazepine 5 $C_{21}H_{19}N_5O$

A mixture of 0.01 mole of **3** and 0.01 mole phenyl isocyanate was heated on water bath for 10 hours. The reaction mixture was washed with ethanol and crystallized with ethanol. m.p. 110-112°C yield 90%; ^{1}HNMR (DMSO): δ = 2.39 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 6.60 (s, 1H, pyridyl) 7.05 - 7.55 (m, 9H, ArH) 10.04 (s, 1H, NH), 12.60 (s, 1H, NH-CO); MS: m/z = 357 (M^+); IR (cm^{-1}), 3240, 3260, 3300 (NH_2, NH), 1670 (CO).

2.1.4. Synthesis of Schiff bases 6

General procedure 0.01 mole of **3** was mixed with 0.01 mole of an aldehyde in 20 ml of ethanol and refluxed for 6 hours in presence of few amount of piperidene, after cooling the precipitate was crystallized with ethanol.

2.1.4.1. 2,4-Dimethyl, 5-o-hydroxybenzaldimino, 11H-pyrido [2,3-b][1,5] benzodiazepine 6a $C_{21}H_{18}N_4O$

m.p. 180-183°C; yield 90%; ^{1}HNMR (DMSO): δ = 2.49 (s, 3H, CH_3) 2.51 (s, 3H, CH_3), 4.74 (s, 1H, OH), 6.9 (s, 1H, pyridyl) 7.02-7.68 (m, 8H, ArH), 8.06 (s, 1H, benzaldimine) 8.1 (s, 1H, NH); MS: m/z = 342 (M^+); IR (cm^{-1}), 3480 (OH), 3250 (NH), 1622 (C = N).

2.1.4.2 2,4-Dimethyl- 5- furfuraldimino, 11H-pyrido [2,3-b][1,5] benzodiazepine 6b $C_{19}H_{16}N_4O$

m.p 140-14°C ; yield 75%; ^{1}HNMR (DMSO): δ = 2.29, (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 5.59 - 630 (m, 3H, furfuryl), 6.51, (s, 1H, pyridyl), 7.0 - 7.56 (m, 4H, ArH), 7.90 (s, 1H - furfur aldimine), 8.1, (s, H, NH); MS: m/z = 316 (M^+); IR (cm^{-1}): 3225 (NH), 1680 (C=N).

2.1.4.3 2,4-Dimethyl, 5-p-methoxy benzaldimino, 11H pyrido [2,3-b][1,5] benzodiazepine 6c $C_{22}H_{20}N_4O$

m.p. 219- 221°C, yield 70%; 'HNMR (DMSO): δ = 2.39 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 6.02 (s, 1H, pyridyl), 6.9 - 7.4 (m, 8H, ArH), 7.92 (s, 1H, benzaldimine), 8.6 (s, 1H, NH); MS: m/z = 357 (M+1); IR (cm^{-1}): 3227 (NH), 1630 (C=N).

2.1.4.4. 2,4-Dimethyl, 5-(4-hydroxy, 2-nitrobenzaldimino, 11H-pyrido [2,3-b][1,5] benzodiazepine 6d $C_{21}H_{17}N_5O_3$

m.p. 210 - 213°C; yield 82%; ^{1}HNMR (DMSO): δ = 2.37 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.02 (s, 1H, OH), 5.58 (s, 1H, NH), 6.60 (s, 1H, pyridyl), 7.21 - 7.88 (m, 7H, ArH), 8.05 (s, 1H, benzaldimine) 8.70 (s, 1H, NH); MS: m/z = 387 (M^+); IR (cm^{-1}): 3480 (OH), 3231 (NH), 1625 (C=N).

2.1.5 N-hydroxymethylation of Schiff bases 7 General procedures:

0.01 mole of **6** (a or b) was mixed with 2 ml formaldehyde, 20ml of acetic acid, 1ml ethanol and 3 ml water. The reaction mixture was stirred at room temperature for 24 hours. The obtained precipitate was filtered. The solid so formed was crystallized from ethanol/water.

2.1.5.1. 2,4-Dimethyl, 5-o-hydroxy benzaldimino, 11-hydroxymethyl pyrido [2,3-b][1,5] benzodiazepine 7a $C_{22}H_{20}N_4O_2$

m.p. 249-252°C; yield 89%; ^{1}HNMR (DMSO): δ = 2.40 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 4.70 (s, 1H, OH), 4.92 (s, 1H, OH), 5.01 - 5.10 (m.2H N-CH_2-O) 6.73 (s, 1H, pyridyl), 7.05 - 7.70 (m, 8H, ArH), 7.91 (s, 1H benzaldimine); MS: m/z = 372 (M^+); IR (cm^{-1}),3430 - 3400 (OH), 1620 (C=N).

2.1.5.2 2,4-Dimethyl, 5-furfuraldimino, 11-hydroxy methyl pyrido [2,3-b][1,5] benzyodiazepine 7b $C_{20}H_{18}N_4O_2$

m.p. 280 - 282°C; yield 85%; ^{1}HNMR (DMSO): δ 2.35 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.91 (s, 1H, OH), 5.05 - 5.10 (m, 2H, N-CH_2 -O), 6.38 - 6.48 (m, 3H, furfuryl), 6.73 (s, 1H, pyridyl), 7.22 - 7.75 (m, 4H, ArH), 7.92 (s, 1H - furfuraldimine) MS: m/z = 346 (M^+); IR (cm^{-1}): 3427 (OH), 1617 (C=N).

2.1.6. Action of thionyl chloride on 7, 8

10 m mole of **7a** or **7b** were dissolved in 20 ml DMF. Thionyl chloride (20 m mole) were added dropwise at 5°c. The reaction mixture was stirred for one hour, then poured onto ice water. The produced precipitate was filtered, crystallized from ethanol.

2.1.6.1 2,4-Dimethyl, 5-o-hydroxybenzaldimino, 11-chloromethyl pyrido [2,3-b] [1,5] benzodiazepine 8a $C_{22}H_{19}ClN_4O$

m.p. 120 -123°C; yield 80%; ^{1}HNMR(DMSO): δ = 2.37 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.10 (s, 1H, OH) 4.95 (s, 2H, N-CH_2Cl), 6.20, (s, 1H, pyridyl), 7.06 - 7.42 (m, 8H, ArH), 7.97 (s, 1H, benzaldimine); MS: m/z = 392 (M^+); IR (cm^{-1}): 3420 (OH), 1620 (C=N).

2.1.6.2 2,4-Dimethyl, 5-furfuraldimino, 11-chloro methyl pyrido [2,3-b][1,5] benzodiazepine 8b $C_{20}H_{17}Cl\ N_4O$

m.p. 124 - 127°C; yield 84%; ^{1}HNMR (DMSO):

δ = 2.34 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 4.98 (s, 2H, N-CH_2Cl), 6.12 - 6.25 (m, 3H, furfuryl), 6.72 (s, 1H, pyridyl), 7.06 - 7.50 (m, 4H, ArH), 7.98 (s, 1H, furfuraldimine); MS: m/z = 366 (M^++2); IR (cm^{-1}) 1620 (C=N).

2.1.7. Reaction of 8 with amines 9 , 10

General procedure: 0.01 mole of **8a** or b was mixed with 2ml of n-propanolamine or with diethanolamine and heated at 100°C for 6 hours. The reaction mixture was poured onto ice water, filtered and crystallized from ethanol.

2.1.7.1 2,4-Dimethyl, 5-o-hydroxy benzaldimino 11-propylaminomethyl pyrido [2,3-b][1,5] benzodiazepine 9a $C_{24}H_{25}N_5O_2$

m.p.90 °C; yield 85%; ^{1}HNMR (DMSO): δ = 1.60 - 1.77 (m, 2H, C- CH_2-C), 2.23 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.50 - 2.55 (m, 2H, C-CH_2- N), 3.38 - 3.45 (m, 2H, C-CH_2-O), 3.61 - 3.83 (m, 2H_2, N - CH_2 - N), 4.5 (s, 1H, OH), 6.61 (s, 1H, pyridyl), 7.23 - 7.62 (m, 8H, ArH), 7.98 (s, 1H - benzaldimine) 8.23 (s, 1H, NH); MS : m/z = 429 (M^+); IR (cm^{-1}) 3450 (OH), 3215 (NH), 1620 (C=N).

2.1.7.2. 2,4-Dimethyl, 5-furfuradimino, 11-propamino methyl pyrido [2,3-b][1,5] benzodiazepine 9b $C_{23}H_{25}N_5O_2$

m.p.100°C; yield 70%; ^{1}HNMR (DMSO); δ = 1.56 - 1.63 (m, 2H, C-CH_2-C), 2.35 (m, 3H, CH_3) 2.46 (m, 3H, CH_3), 2.55 - 2.60 (m, 2H, C-CH_2 - N), 3.52 - 3.55 (m, 2H, C-CH_2 - O), 4.30 - 4.35 (m, 2H, N-CH_2-N), 4.50 (s, 1H, OH), 6.22 - 6.37 (m, 3H, furfuryl), 6.56 (s, 1H, pyridyl) 7.00 - 7.55 (m, 4H, ArH), 8.01 (s, 1H, furfuraldimino) 8.20 (s, 1H, NH); MS: m/z = 403 (M^+), IR (cm^{-1}): 3420 (OH), 3230 (NH), 1620 (C=N).

3.1.7.3 2,4-Dimethyl, 5-o-hydroxybenzaldimino, 11-diethanolamino methyl pyrido [2,3-b][1,5] benzodiazepine 10a, $C_{26}H_{29}N_5O_3$

m.p.40°C;yield 90% ;^{1}HNMR (DMSO) :δ = 2.31-3.35(m,4H,2N-CH_2-C), 2.41 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.0- 3.23 (m, 4H, 2 -CH_2-O), 3.95 (s, 2H, N-CH_2 - N), 4.9, 5.01 (s, 2H, 2 OH), 6.50 (s, 1H, pyridyl), 7.10 - 7.65 (m, 8H, ArH), 7.96 (s, 1H, benzaldimine); MS: m/z = 458 (M^+ - 1); IR (cm^{-1}), 3400 - 3450 (OH), 1620 (C=N).

2.1.7.4 2,4-Dimethyl, 5-furfuraldimino, 11-diethanolamino methyl pyrido [2,3-b][1,5] benzodiazepine 10b $C_{24}H_{27}N_5O_3$

m.p.60°C; yield 76%; ^{1}HNMR (DMSO): δ = 2.37 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.50 - 2.55 (m, 4H, 2CH_2- N), 3.59 - 3.63 (m, 4H, 2CH_2-O), 4.02 (s, 2H, N-CH_2-N), 6.32 - 6.47 (m, 3H, furfuryl), 6.70 (s, 1H, pyridyl), 6.98 - 7.44 (m, 4H, ArH), 8.05 (s, 1H-furfuraldimine); MS: m/z= 434 (M^+ +!); IR (cm^{-1}): 3420 (OH), 1620 (C=N).

3. Results and Discussion

3.1. Synthesis

Cyclization reaction between pyridine-1,2-diamine and various carboxylic acids in presence of PPA was used to prepare pyridobenzodizepines[17].

H-Pyrido[2,3-b][1,5]benzodiazepine-5-ones were synthesized through condensation of 2-chloronicotinic acid with o-phenylene-diamine, and they showed CNS-depressant and anticonvulsant activities[18]. The reaction was carried out in t-butoxyethanol at 150°c. In our synthesis route 2-chloro, 3-cyano, 4,6-dimethyl pyridine[(19)]. 1 was reacted with o-phenylenediamine 2 to give 5-amino-2,4-dimethyl-11H-pyrido [2,3-b][1,5] benzodiazepine 3.

Structure of 3 was confirmed by IR, ^{1}HNMR and mass spectra. The IR spectrum showed the absence of CN-group and appearance of bands at 3430-3250cm^{-1} for primary and secondary amino groups. The ^{1}HNMR spectrum showed two singlets at δ 2.37 and 2.44 ppm for CH_3 , singlet at δ 5.2 ppm for NH_2 and at δ 8.03 ppm for NH. The mass spectrum showed M^+ +1 at 393m/z.

Beside the aim to prepare pyridobenzodiazepine containing substituted amino group at position 5, the chemical activities of the free amino group of 3 were tested. Malononitrile was reacted with 3 through addition of the free amino group to one cyano group to produce the adduct 4. The infrared spectrum indicated the appearance of cyano group, while the ^{1}HNMR spectrum showed methylene group attached to cyano group at δ 4.3 ppm. Mass spectrum indicated the m/z at 304 for molecular ion peak. Reaction of the free amino group with phenyl isocyanate lead to formation of phenyl urea derivative 5 with molecular ion peak at 357 m/z. The presence of carbonyl group of urea was indicated at 1670 cm^{-1} in IR spectrum, Schiff base formation was done through reaction of 3 with some aromatic and heterocyclic aldehydes. In all the produced Schiff bases 6 δ 7.8-8.1 ppm were seen in ^{1}HNMR spectra Schiff bases were produced in good yields.

To study the biological effect of substitution of the secondary amino group of the diazepine ring, formaldehyde was reacted with the Schiff bases 6a and 6b. The products 7a and 7b containing hydroxyl methyl groups were produced. They showed δ5.1 ppm in the ^{1}HNMR spectra indicating a methylene group located between N and O atoms. Reaction of 7 with thionyl chloride converted them into chloromethyl derivatives 8a and 8b which decreased the ^{1}HNMR Schift of methylene group into δ 4.95 ppm due to substitution to chlomine instead of hydroxyl group. The chloro compounds 8a and 8b reacted with propanolamine and with diethanolamine to produce

the compounds 9a,b and 10a,b. The later compounds are similar to the acyclic nucleosides but containing nitrogen atom at the acyclic side chain. The ^{1}HNMR and mass spectra indicated the proposed structures of these compounds

3.2 Biological evaluation

3.2.1 Evaluation of CNS-depressant effect:

The screening for CNS-depressant effect depends upon measuring the sleeping time in animals using the righting reflex method in thiopentone anaesthetized mice .

Groups of 6 mices (20-35 g of both sex) were intraperitoneally (IP) injected with single dose of 5,10,15 mg/kg body weight of the tested compounds **(3, 4,5,6a,6b,6d ,7a ,8a ,9a,10a)** and a group was IP injected with diazepam with the same doses , Then all groups was IP injected with thiopentone sodium (TPS) in a dose of 65 mg/ kg body weight [20]. The control group were IP injected with thiopentone sodium alone. The sleeping time for each mice was calculated and the data were analyzed. Statistical analysis was done according to student[21] , t test, significan t≤ 0.05.

The results indicated that all tested compounds **(3, 4,5,6a,6b,6d,7a,8a,9a,10a**) and diazepam at the three graded doses of 5 ,10, 15 mg/kg body weigh, produced significant increase in the sleeping time of thiopentone sodium anaesthetized mice as compared with the control group indicating that they potentiated the depressant effect of thiopentone sodium **(Table 1 , Fig.,1a-c) .**

It was observed from these results in comparison with diazepam that there is an enhancing of the effect in case of monosubstitution of amino group at position 5 (comp. 4,5) .One hydrogen atom should be attached to nitrogen to increase the activity . Schiff bases showed lower activity than diazepam. Substitution at the secondary amino group of the diazepine ring does not elevate the activity.

Table 1: Effect of tested compounds on sleeping time of thiopentone anaesthetized mice

P. value	Sleeping time(minutes) Mean±SE	Dose mg/kg	Compound number
	16 ± 0.456	65	TPS const
<0.05	38 ± 0.512	5	TPS+ Diazepam
<0.05	50± 0.431	10	
<0.05	60±0.690	15	
<0.05	30 ± 0.227	5	TPS+ 3
<0.05	35 ±0.279	10	
<0.05	48 ± 0.572	15	
<0.05	45± 0.438	5	TPS+ 4
<0.05	58± 0.738	10	
<0.05	68± 0.802	15	
<0.05	40 ± 0.377	5	TPS+5
<0.05	55 ± 0.367	10	
<0.05	65 ± 0.298	15	
<0.05	29 ± 0.408	5	TPS+6a
<0.05	3 ± 50.310	10	
<0.05	46± 0.295	15	
<0.05	27 ± 0.675	5	TPS+ 6b
<0.05	32 ± 0.532	10	
<0.05	44 ± 0.266	15	
<0.05	23 ± 0.250	5	TPS+6d
<0.05	27 ± 0.350	10	
<0.05	40 ± 0.332	15	
<0.05	29 ± 0.518	5	TPS+7a
<0.05	36 ± 0.809	10	
<0.05	40 ± 0.345	15	
<0.05	28 ± 0.323	5	TPS+8a
<0.05	35 ± 0.192	10	
<0.05	39 ± 0.249	15	
<0.05	25 ± 0.892	5	TPS+9a
<0.05	30 ± 0.412	10	
<0.05	36 ± 0.318	15	
<0.05	22 ± 0.608	5	TPS+10a
<0.05	28 ± 0.267	10	
<0.05	33± 0.260	15	

S.E. : Stander error of deviation

P. value : Probability of the difference between thiopentone alone and thiopentone + test compound

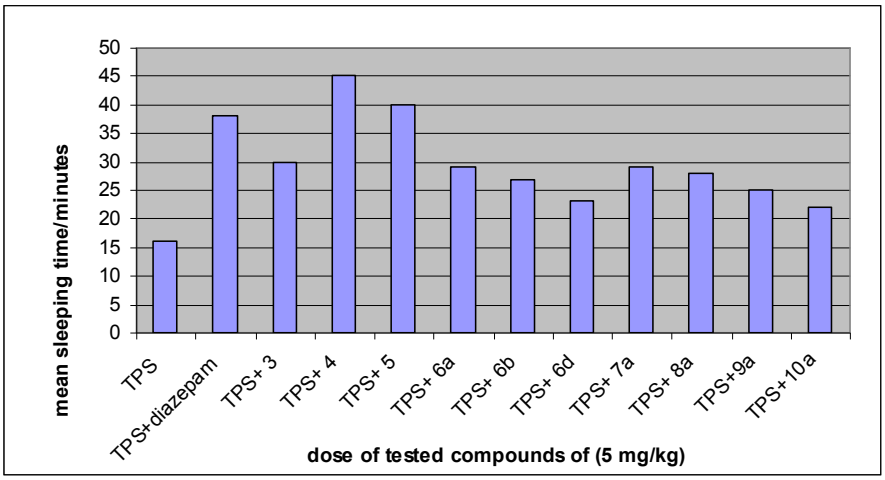

Fig.(1a)

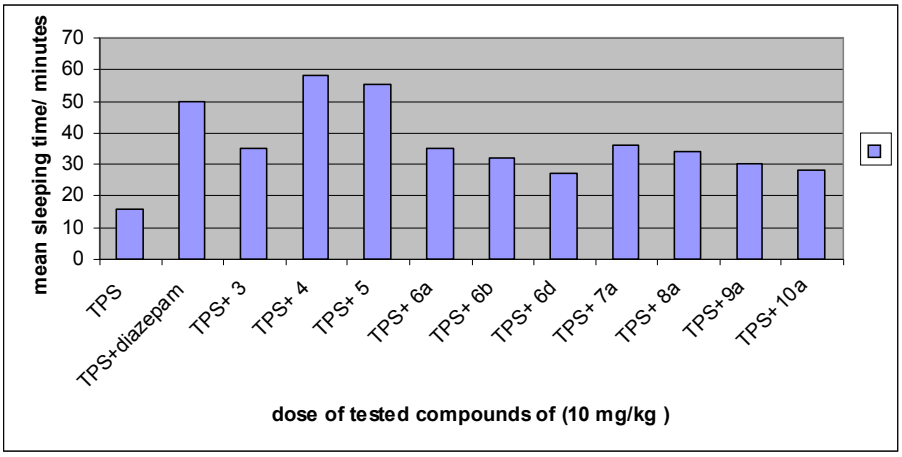

Fig.(1b)

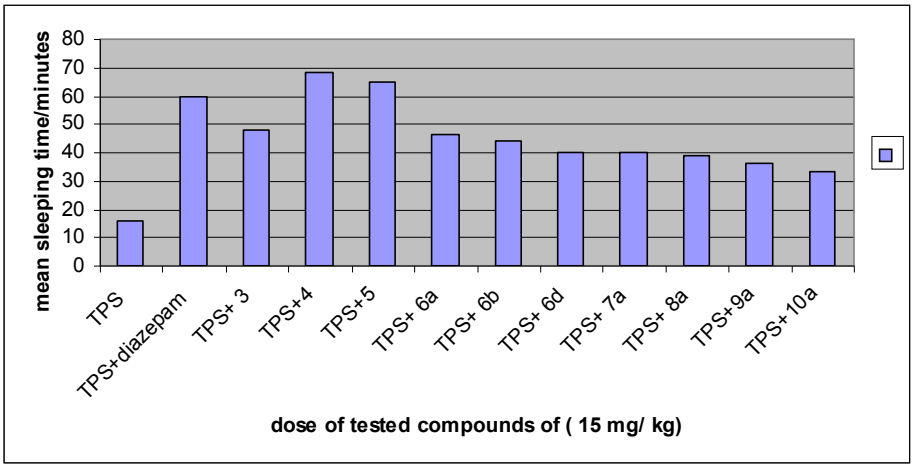

Fig.(1c)

Fig 1: Showed the mean value of sleeping time/minutes of different doses

3.2.2 Evaluation of Anticonvulsant effect

The compounds **(3,4,5,6a,6b,6d,7a,8a,9a,10a)** were tested for anticonvulsant effect in comparison to diazepam . Groups of 6 mice (20-35 g of both sex) were given three graded doses of the tested compounds or diazepam (5,10, 15 mg/kg body weight) intraperitoneally in a single dose. After one hour all animals were injected with convulsive dose of pentylenetetrazole (PTZ) in a dose of (100 mg/kg body weight) subcutaneously of 1% solution. The animals that showed no tonic convulsions within 60 minutes after PTZ injection were considered to be protected [18].

Most of these compounds produced anticonvulsant activity near that produced by diazepam since they considered 100% protection for the mice injected with pentylenetetrazole for the high doses as showed at **(Table2).**

In the medium doses it was reported that bearing of cyano group at the side chain of position 5 (comp.4), and primary alcoholic hydroxyl group at position 11 (comp.**7a**) increased the anti convulsant activity to higher level than of diazepam.

Table 2: The anticonvulsant effect of tested compounds comparing with that of diazepam

Relative Potency	Protection %	Dose mg/kg	Compound number
0.8	66.6	5	Diazepam
1	83.5	10	
1.2	100	15	
0	0	5	3
0.8	66,6	10	
1.2	100	15	
0.8	66.6	5	4
1.2	100	10	
1.2	100	15	
0.4	33.3	5	5
1	83.3	10	
1.2	100	15	
0	0	5	6a
0.8	66.6	10	
1.2	100	15	
0.6	50	5	6b
1	83.3	10	
1.2	100	15	
0	0	5	6d
0.4	33.3	10	
0.8	66.6	15	
0.8	66.6	5	7a
1.2	100	10	
1.2	100	15	
0.4	0	5	8a
0.8	66.6	10	
1	83.3	20	
0.4	33.3	5	9a
0.8	66.6	10	
1	83.3	20	
0.8	66.6	5	10a
1	83.3	10	
1	83.3	20	

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