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Design and Synthesis of New Compounds of Phthalazindion and its Anticonvulsant Activity

Rezk R. Ayyad[1]*, Ahmed M. Mansour[2] and Ehab M. Mostafa[3,4]

[1]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt*
[2]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt*
[3]*College of Pharmacy, Jouf University, Sakaka, Saudi Arabia*
[4]*Department of Pharmacognosy, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt*

Abstract

In this work we synthesized 6,7-Dichloro-1,4-(2H,3H) phthalazinedione (I) [1] and its salt (II) which react with different alkylchloroacetates, afforded compounds III_{1-6}. When reacted, the compound III_2 with ammonia and different amines we obtained on IV and V_{1-7} respectively. The compound III_2 also react with Hydrazine hydrated, result the compound VI, afforded compound (hydrazide) Hydrazied condensed with different aldehydes, we obtained on compounds $VIII_{1-10}$. The compounds III_1, III_2, III_3, III_4, III_5, IV, V_1,V_2, V_3, VI, VII_1, VII_5, VII_6,VII_9, $VIII_1$, $VIII_2$, $VIII_7$ and $VIII_8$ tested as anticonvulsant against phenobarbitone as reference drug. The compounds III_{1-3}, IV, V_3, VI, $VIII_{1,2}$ showed the most activity while the compounds V_2, $VII_{6,9}$ revealed moderate Introduction, finally compound VII_5 was the lowest activity.

Keywords: Phathalazinedione • Phenobarbitone • Anticonvulsant activity

Introduction

The phthalazinedione nucleus and its derivatives used in wide range of biological activity where it used as phosphodiasterase inhibitory activity [2] cytotoxic activity [3] antianexiety [4] tuberoclostatic [5] hypolepidemic effect [6] antihelmintics [7] antioxidative activity [8]. Insectidal and nematocidol activity [9] prophage induction in lysogenic (antimflammatory and antibacterial activity [10], antiviral activity [11], and *E. coli* [12] antineoplastic activity [13-16] and anticonvulsant activity [17-23].

All melting were carried out on a griffin melting point apparatus at Faculty of Pharmacy Al-Azhar the analysis were performed at the microanalytical Center Faculty of Science, Cairo, University IR spectra were carried out on a pye unicam SP 1000 IR spectrophotometer at microanalytical center Cairo University using potassium Bromide basic technique.

^{1}HNMR spectra were recorded on a variant 90 MHz were recorded on spectrophotometer at micro analytical center Faculty of Science, Cairo University TMS was as internal reference and DMSO-d6 was used as solvent the chemical shift values were measured in δ (prm).

The mass spectra were recorded on HR-MS model 5088 (70ev) carried previous center (Scheme 1).

Chemistry and Experimental Section

6,7-Dichloro-1,4-(2H,3H)phthalazinedione

A mixture of 4,5-dichlorophthalmide 2.18 g (0.01 mol) and 50 ml (0.01 mol) hydrazine hydrate in absolute ethyl alcohol (50 ml) was heated under reflux for 6 hrs then cooled. The precipitate so obtained was filtered, crystallized from ethanol m.p. 328-330 (reported) the yield 98% as reported.

6,7-Dichloro-1,4-(2H,3H) phthalazinedione potassium salt II

A solution of appropriate 6.7 Dichlorophthalazinedione 2.31 g (0.01 mol in absolute ethanol (50 ml) was treated with alcoholic potassium hydroxide solution 0.56 g (0.01 mol). The mixture was heated for 30 minutes with stirring at 40°C then allowed to cool whereby the potassium salt was separated. The crude product was collected washed several times with ethanol then dried m.p. >330°C the yield almost quantitatively yield 2.57 g (95%).

2-(Alkaoxy-carbonylmethyl) 6,7-dichloro-phthalazinedione III_{1-6}:

A mixture of equimolar quantitates 2.7 g (0.01 mol) of the 6,7-dichlorophthalazinedione potassium salt and appropriate alkylchloroacetates in dimethylformamide (DMF) (50 ml) was heated under reflux for two hours on a water bath. The reaction mixture was than cooled, poured onto ice-cold water (200 ml) and stirred for 30 minutes. The resulting solid was filtered washed with water, dried and crystallized from ethanol.

2-[Amino-carbonymethyl-6,7-dichloro-1,4-(2H,3H)-phthalazinedione IV

A solution of 3.17 g (0.01) mole of compound III_2 was treated with ammonia gas (excess) the reaction was stirred over night at room temp in absolute ethanol (50 ml). the mixture was poured onto cold water with stirring, the precipitate so obtained was filtered and crystallized from ethanol m.p. 300-301. The yield 2.02 g (70%)

Variables	C%	H%	N%
Calculated	41.67	2.43	14.58
Found	41.82	2.61	14.36

2-[Alkylamino-Carbonymethyl-6,7-dichloro-1,4-(2H,3H)-phthalazinedione V_{1-7}

A mixture of equimolar quantities 2.7 g (0.01 mol) and excess of appropriate alkylamines was heated under reflux in absolute ethanol (50 ml) for 3 hrs, the reaction mixture was cooled poured onto ice-cold water (200 ml) and the precipitate formed washed with water, filtered and crystallized from ethanol.

***Address for Correspondence:** Rezk R. Ayyad, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt, E-mail: rezek_ayad@yahoo.com*

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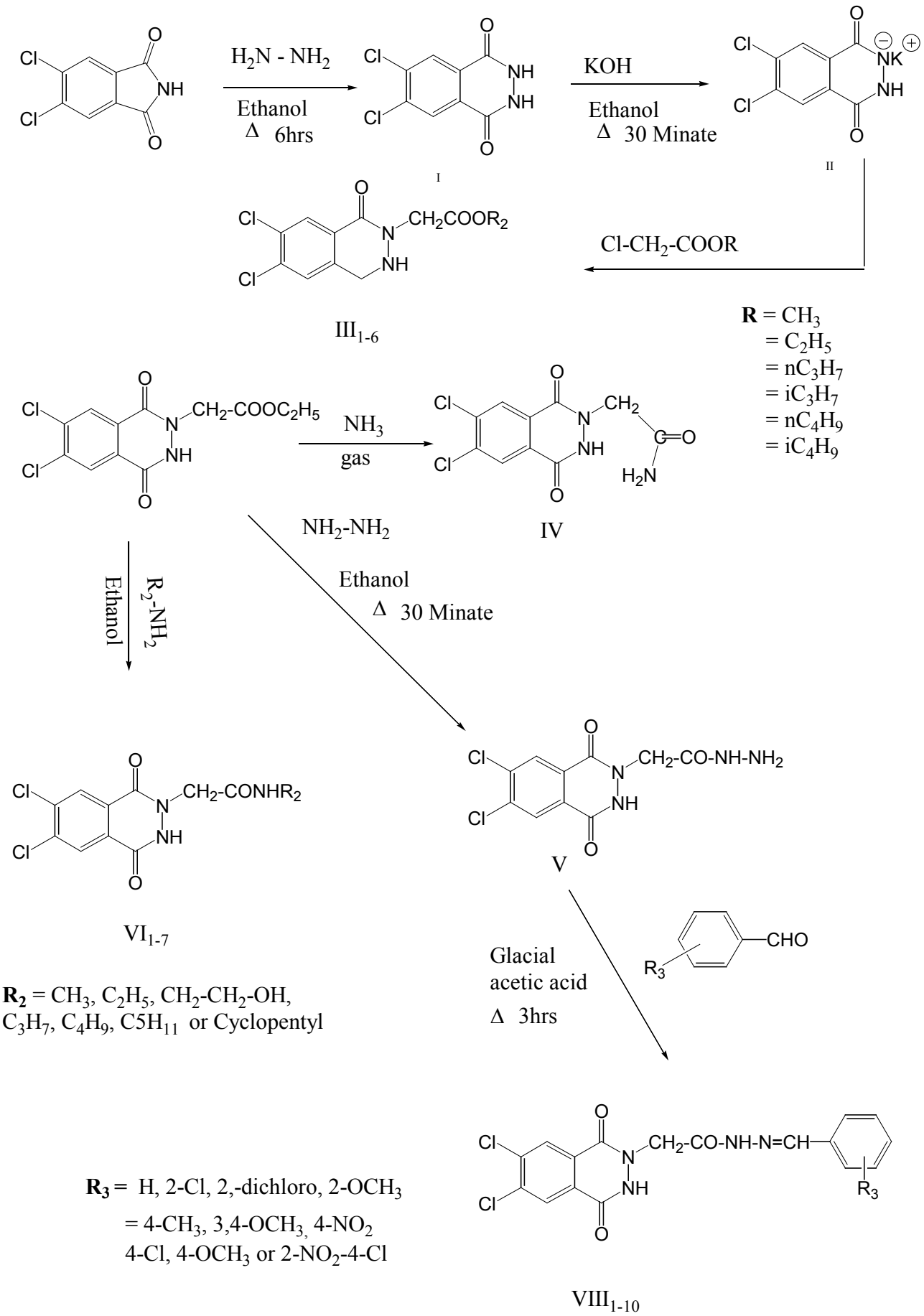


Scheme 1. Mass spectra recorded on HR-MS model 5088 (70ev).

6,7-Dichloride-2-Hydrazino Carbonymethyl-1,4-(2H,3H) Phthalazinedione VI

Compound III_2 3.2 g (0.01 mol) dissolve in absolute ethanol (50 ml) and then treated with excess of hydrazine hydrate in excess (10 ml), the mixture heated for 30 minutes, cooling the solid was filtered and crystallized from glacial acetic acid m.p. 280-282°C the yield 2.79 g (92%)

Variables	C%	H%	N%
Calculated	39.60	2.64	18.48
Found	39.34	2.21	18.61

2-(Arylidenchydrazinocarbonylmethyl)-6,7-Dichloro-1,4 (2H,3H) Phthalazinedione VII_{1-10}

A mixture of 6,7-dichloro-2 (hydrazinocarbonylemthyl)-1,4 (2H,3H) phthalazinidione 3.03 g (0.01 mol) and appropriate aromatic aldehydes (0.01 mol) was refluxed in glacial acetic acid (50 ml) for 3 hrs, then cooled. The reaction mixture was poured onto ice-cold water filtered and crystallized from glacial acetic acid.

The pharmacological testing

Some of the newly synthesized compounds were subjected to preliminary pharmacological testing with regard to their sedative, hypnotic as well as anticonvulsant activities. CNS-depressant activity of many sedative hypnotic agents are mainly evaluated using several screening methods including loss of righting reflux, corneal reflux, motor activity amphetamine antagonism and response to the various chemical stimulant. On the other hand most of the experimental methods for evolution of the anticonvulsant activity of many drugs involve the artificial induction of convulsion by chemo and/ or electroshock agents and inhibition of such convulsion by drug under test, in this investigation the loss of righting reflux method was adopted for evolution of the anticonvulsant activity of such compounds and screened by determining their ability to protect the experimental convulsion following the method reported by Soaje-Echague and Lim.

Results and Discussion

The pharmacological testing carrying on rats male arranged in groups each of six. Phenobarbitone (Aldrich) was used as reference drug and pentylenetetrazole (Aldrich) was used to induce convulsion in experimental animals Fourteen (14) compounds of dichlorophthalazine dione derivatives were selected for evaluation of anticonvulsant activity and their specification are present in Tables 1-3.

Determination of convulsive dose of pentylenetetrazole

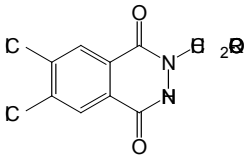
Four graded dose of pentylenetetrazole (80, 160, 240, 30 mg/kg) were injected to groups of six rate. The animals were observed for 60 minutes. The dose of 320 mg/kg was found to be the suitable convulsive dose that without death during 24 hrs.

Preliminary assessment of the anticonvulsant activity

The anticonvulsant activity of some phthalazinediones were assessed in rats against pentylenetetrazole induced convulsion to phenobarbitone as a reference drug following the technique of Soaje-Echague and Lim [24].

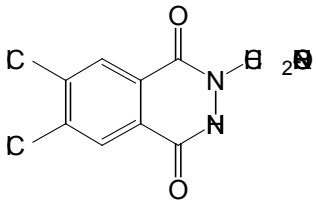
The test compounds and phenobarbitone 80 to give suspension with 2% concentration, pentylenetetrazole was also dissolvent in water containing few drops of tween 80 to produce 2% solution. Groups of six rat injected in the dorsal lymph sac with three graded dose of the test compounds or phenobarbitone. After 45 minutes, the animals were injected with the convulsive dose of phenylenetratazole (320 mg/kg). The animals that showed no tonic convulsion within 60 minutes after pentylenetetrazole administration were considered to be protected. The percent protection ED_{50} mg/kg) and or mmol/kg and the mean of the relative potency ± SD of the test compounds to phenobarbitone were calculated. The data are presented in Tables 4 and 5, Figures 1a and 1b.

Table 1. 2-[Amino carbonymethyl-6, 7-dichloro-1, 4- (2H, 3H) -phthalazinedione IV.



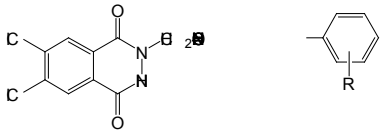
Comp. No.	*R*	*M, p.*	Yield %	Mol. Formula Mol. Wt	Elemental analyses		
					%	Calc	Found
III_1	CH_3	179-180	76	$C_{11}H_8Cl_2N_2O_2$ 303	C	43.56	43.72
					H	2.64	2.91
					N	9.24	9.44
III_2	C_2H_5	183-185	90	$C_{12}H_{10}Cl_2N_2O_4$ 317	C	45.43	45.61
					H	3.15	3.29
					N	8.85	9.04
III_3	C_3H_7	169-179	80	$C_{13}H_{12}Cl_2N_2O_4$ 331	C	47.13	47.35
					H	3.63	3.95
					N	8.46	8.13
III_4	iC_3H_7	185-187	78	$C_{13}H_{12}Cl_2N_2O_4$ 331	C	47.13	47.08
					H	3.63	3.87
					N	8.46	8.83
III_5	C_4H_9	117-119	85	$C_{14}H_{14}Cl_2N_2O_4$ 345	C	48.70	48.93
					H	4.06	3.70
					N	8.12	7.79
III_6	iC_4H_9	99-100	90	$C_{14}H_{14}Cl_2N_2O_4$ 345	C	48.70	48.56
					H	4.06	4.46
					N	8.12	8.34

Table 2. 6, 7-Dichloro -2-Hydrazino Carbonymethyl- -1, 4- (2H, 3H) P hthalazinedione VI.



Comp. No.	R	M, p.	Yield %	Mol. Formula Mol. Wt	Elemental analyses		
					%	Calc	Found
V_1	CH_3	155-157	70	$C_{11}H_9Cl_2N_2O_3$ 302	C	43.71	43.50
					H	2.98	3.31
					N	13.01	12. 91
V_2	C_2H_5	201-203	80	$C_{12}H_{11}Cl_2N_2O_3$ 316	C	45.56	45.43
					H	3.48	3.29
					N	13.29	13.42
V_3	C_2H_5OH	243-245	95	$C_{12}H_{11}Cl_2N_2O_4$ 332	C	43.37	43.61
					H	3.31	2.83
					N	12.65	12.42
V_4	C_3H_7	178-179	75	$C_{13}H_{13}Cl_2N_2O_3$ 330	C	47.27	47.42
					H	3.94	4.15
					N	12.73	12.95
V_5	C_4H_9	180-181	85	$C_{14}H_{15}Cl_2N_2O_3$ 344	C	48.84	48.61
					H	4.36	4.64
					N	12.21	12.15
V_6	C_5H_{11}	181-183	90	$C_{15}H_{17}Cl_2N_2O_3$ 358	C	50.28	50.04
					H	4.25	4.64
					N	11.75	11.89
V_7		268-269	85	$C_{15}H_{15}Cl_2N_2O_3$ 356	C	50.56	50.72
					H	4.21	4.51
					N	11.80	11.98

Table 3. 2- (Arylidenchydrazinocarbonylmethyl) -6, 7-Dichloro-1, 4 (2H, 3H) Phthalazinedione VII1-10..



Comp. No.	R	M, p.°C	Yield %	Mol. Formula Mol. Wt	Elemental analyses		
					%	Calc	Found
VII_1	H	255-257	90	$C_{17}H_{12}Cl_2N_4O_3$ 391	C	52.17	52.35
					H	3.07	2.71
					N	14.32	14.11
VII_2	2-Cl	173-174	65	$C_{17}H_{11}Cl_3N_4O_3$ 425.5	C	47.94	48.13
					H	2.59	2.69
					N	13.16	13.42
VII_3	2, 4-di-Cl	250-251	60	$C_{17}H_{10}Cl_4N_4O_3$ 460	C	44.35	44.11
					H	2.17	2.53
					N	12.17	12.24
VII_4	$2\text{-}OCH_3$	140-141	95	$C_{18}H_{14}Cl_2N_4O_3$ 421	C	51.31	51.61
					H	3.33	3.51
					N	13.30	13.12
VII_5	4-CH3	275-277	90	$C_{18}H_{14}Cl_2N_4O_4$ 405	C	53.33	53.64
					H	3.46	3.19
					N	18.83	18.61
VII_6	3, 4-di OCH_3	252-253	85	$C_{19}H_{16}Cl_2N_4O_5$ 451	C	50.55	50.22
					H	3.55	3.33
					N	12.42	12.22

VII_7	4-NO_2	268-269	75	$C_{17}H_{11}Cl_3N_4O_3$ 436	C	46.79	47.11
					H	2.52	2.22
					N	16.06	15.90
VII_8	4-Cl	275-277	80	$C_{17}H_{11}Cl_3N_4O_3$ 425.5	C	47.94	48.22
					H	2.59	3.03
					N	13.16	13.33
VII_9	4-OCH_3	256-258	75	$C_{18}H_{14}Cl_2N_4O_4$ 421	C	51.31	50.99
					H	3.33	3.66
					N	13.30	13.33
VII_{10}	2-NO_2 4-Cl	235-236	86	$C_{17}H_{10}Cl_3N_5O_5$ 470.5	C	43.36	42.99
					H	2.13	1.90
					N	14.88	15.11

Table 4. Spectral data of some of the newly synthesized compounds.

Comp. No	Item	IRcm^{-1} ^{1}HNMR and MS (m/z) spectral data
III_1	IR	3163 (NH), 3020 (CH aliphatic), 1733 (CO of ester moiety), 1673, 1589 (CO phthalazine ring)
	MS	302, 304 (M. M^{+2}, 90.70, 60.52%) respectively 243 ($C_8H_4Cl_2N_2O_2$ 100%)
III_2	^{1}HNMR DMSO- d6	1.2 (t, 3H, O-CH_2CH_3), 4.20 (q, 2H, OCH_2-CH_3) 4.97 (s, 2H, -N-CH_2-CO), 8.15-8.39 (m, 2H, aromatic protons) 12.2 (s, 1H, NH) .
III_4	^{1}HNMR DMSO- d6	1.22 (d, 6H, CH $(CH_3)_2$), 4.92 (s, 2H, N-CH_2CO) . 5 (m, 1H, CH $(CH_3)_2$, 8.15-8.34 (m, 2H aromatic protons), 12.20 (s, 1H NH in phthalazine ring)
IV	IR	3389, 3178 (NH, NH_2) of the ring and side chain), 290 (CH aliphatic), 1694 (carbonyl group), 1652 (CO of the ring) .
V2	IR	3167 (NH) (of the phthalazine ring) 2986 (CH-aliphatic), 1778 (carbonyl gp), 1664, 1589 (CO of the ring)
	Ms	315, 317 (M, M+2) (100%, 70.74%) respectively.
V_3	^{1}HNMR	1.23 (t, 2H, NCH_2CH_3), 4.18 (t, 2H, NCH_2CH_2-OH), 4.97 (s, 2H, N-CH_2-CO), 8.2 (s, 1H, aromatic proton), 8.40 (s, 1H, aromatic proton), 12.21 (s, 1H, NH of ring)
V_4	^{1}HNMR DMSO- d6	1.18 (t, 3H, N-CH_2-CH_2-CH_3), 4.14 (m, 4H, N-CH_2-CH_2-CH_3), 4.93 (s, 2H, -N-CH_2-CO), 7.75-8.11 (2d, 2H, aromatic protons), 11.9 (s, 1H, NH of the ring.
	Ms	343, 345 (M$^+$, M^{+1}) (40%, 28% respectively), 243 (m/z $C_6H_2Cl_2$ 100%)
VI	IR	3284, 3164 (NH, NH_2), 1662 (carbonyl gp.), 1500, 1543 (carbonyl of the ring) .
	^{1}HNMR DMSO- d6	4.37 (s, 2H, NH_2), 4.7 (s, 2H, N-CH_2-CO), 8.35 (s, 1H aromatic proton at C_5), 8.60 (s, 1H, NH of the ring) .
VII_1	^{1}HNMR DMSO- d6	4.8 (s, 2H, -N-CH_2-CO), 7.23-7.29 (m, 5H aromatic protons, 8.41 (s, 1H aromatic proton at C_5), 8.71 (s, 1H aromatic at C_8), 4.37 (s, 1H, N=CH-)
VII_3	^{1}HNMR DMSO- d6	4.8 (s, 2H, N-CH_2-CO), 7.11 (s, 1H, N=CH), 7.17 (s, 1H, aromatic proton), 7.51-7.54 (d, 2H, aromatic protons of the side chain), 8.3-8.34 (d, 2H aromatic protons), 10.18 (s, 1H, NH of the arylidene) 12, 20 (s, 1H, NH of ring) .
Comp. No	**Item**	**IRcm^{-1} ^{1}HNMR and MS (m/z) spectral data**
VII_5	IR	3165 (NH), 1740 (carbonyl gp), 1661, 1601 carbonyl gps of ring.
	^{1}HNMR DMSO- d6	2.35 (s, 3H, p-CH_3), 5.3a (s, 2H, H-CH_3CO), 7.25 (d, 2H, aromatic protons at C_2 and C_3), 7.20 (d, 2H aromatic protons of C_5, C_6 moiety), 7.58 (s, 1H, N=CH-Ph), 8.20 (s, 1H, aromatic at C_5 of the ring), 8.4 (s, 1H, aromatic at C_6 of the ring), 11.64 (s, 1H, NH of the NH arylidene), 11.57 (s, 1H)
VII_7	^{1}HNMR DMSO- d6	5.39 (s, 2H, N-CH_2-CO), 7.25-8.37 (m, 7H, aromatic protons and CH of arylidene), 11.57 (s, 1H, NH of the arylidene gp.), 12.13 (s, 1H, NH of the ring) .
VII_8	^{1}HNMR DMSO- d6	5.4 (s, 3H, N-CH_2-CO), 7.23-8.36 (m, 7H, aromatic protons and CH of arylidene gp.)
VII_9	^{1}HNMR DMSO- d6	3.87 (s, 3H, p-OCH_3), 7.01-8.95 (m, 7H aromatic protons and CH of the gp.), 11.62 (s, 1H, NH of the arylidene), 11.94 (s, 1H, NH of the ring

Table 5. Anti-convulsant activity of some newly synthesized compounds.

Comp. No	Dose mg/kg	Protection	ED_{50} kg	ED_{50} mmol/kg ±S.D.	Relative potency M ±S.D.
III_1	50	33.3	90	0.297 ± 0.1	0.1 ± 0.01
	100	50			
	200	100			
III_2	50	33.3	90	0.284 ± 0.09	0.109 ± 0.008
	100	66.6			
	200	100			
III_3	75	33.3	100	0.302 ± 0.08	0.102 ± 0.03
	150	66.6			
	250	100			
III_4	50	33.3	130	0.393 ± 0.12	0.078 ± 0.02
	150	66.6			
	250	100			

III_5	75	33.3	125	0.313 ± 0.11	0.085 ± 0.02
	150	66.6			
	300	100			
IV	50	33.3	90	0.313 ± 0.11	0.099 ± 0.03
	100	50			
	200	100			
V_1	50	33.3	100	0.331 ± 0.08	0.093 ± 0.02
	100	66.6			
	200	100			
V_2	100	33.3	160	0.506 ± 0.16	0.061 ± 0.01
	200	66.6			
	300	100			
V_3	50	33.3	100	0.301 ± 0.01	0.103 ± 0.02
	100	66.6			
	200	100			
VI	50	33.3	90	0.297 ± 0.13	0.104 ± 0.03
	100	50			
	200	100			
VII_1	100	33.3	170	0.436 ± 0.16	0.07 ± 0.02
	200	66.6			
	400	100			
VII_5	200	33.3	280	0.815 ± 0.21	0.038 ± 0.01
	400	66.6			
	450	100			
VII_6	200	33.3	280	0.621 ± 0.2	0.05 ± 0.015
	400	66.6			
	600	100			
VII_9	200	33.3	100	0.66 ± 0.23	0.04 ± 0.013
	400	66.6			
	600	100			
Penabarbitol	75	33.3	100	0.403 ± 0.12	0.1± 0.021
	150	66.6			
	175	199			

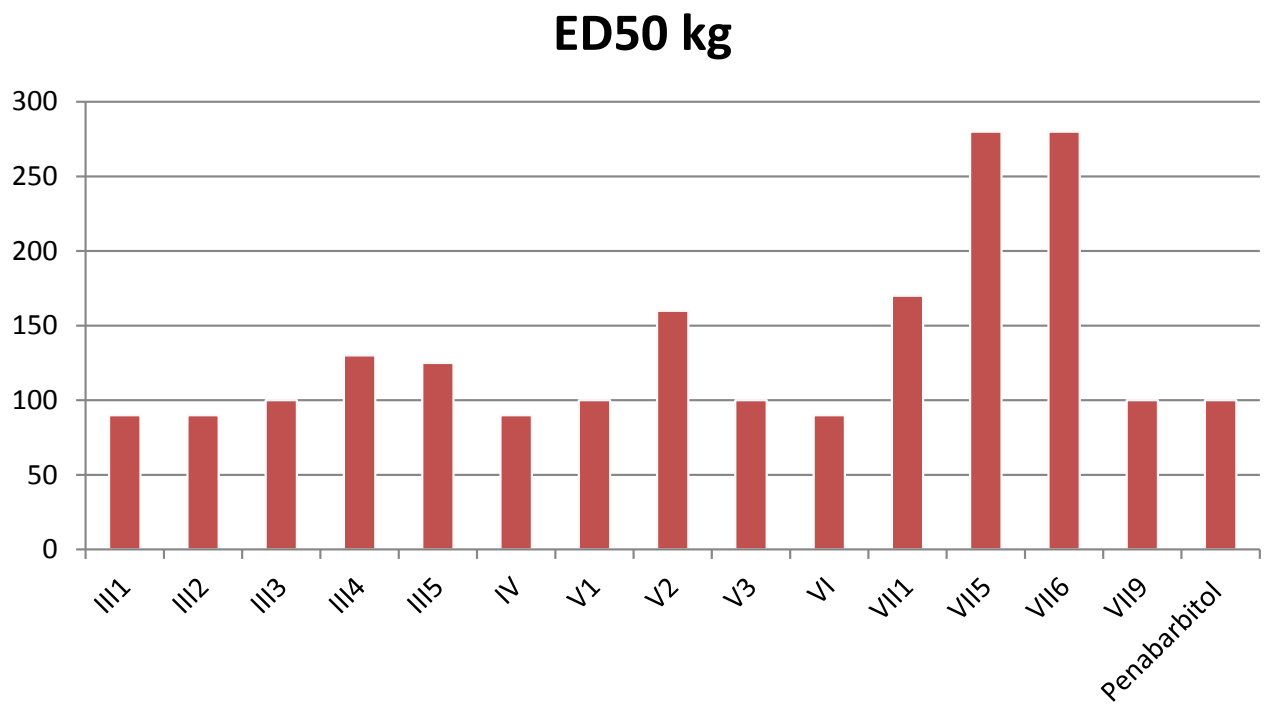


Figure 1a. The new compounds tested against phenobarbital.

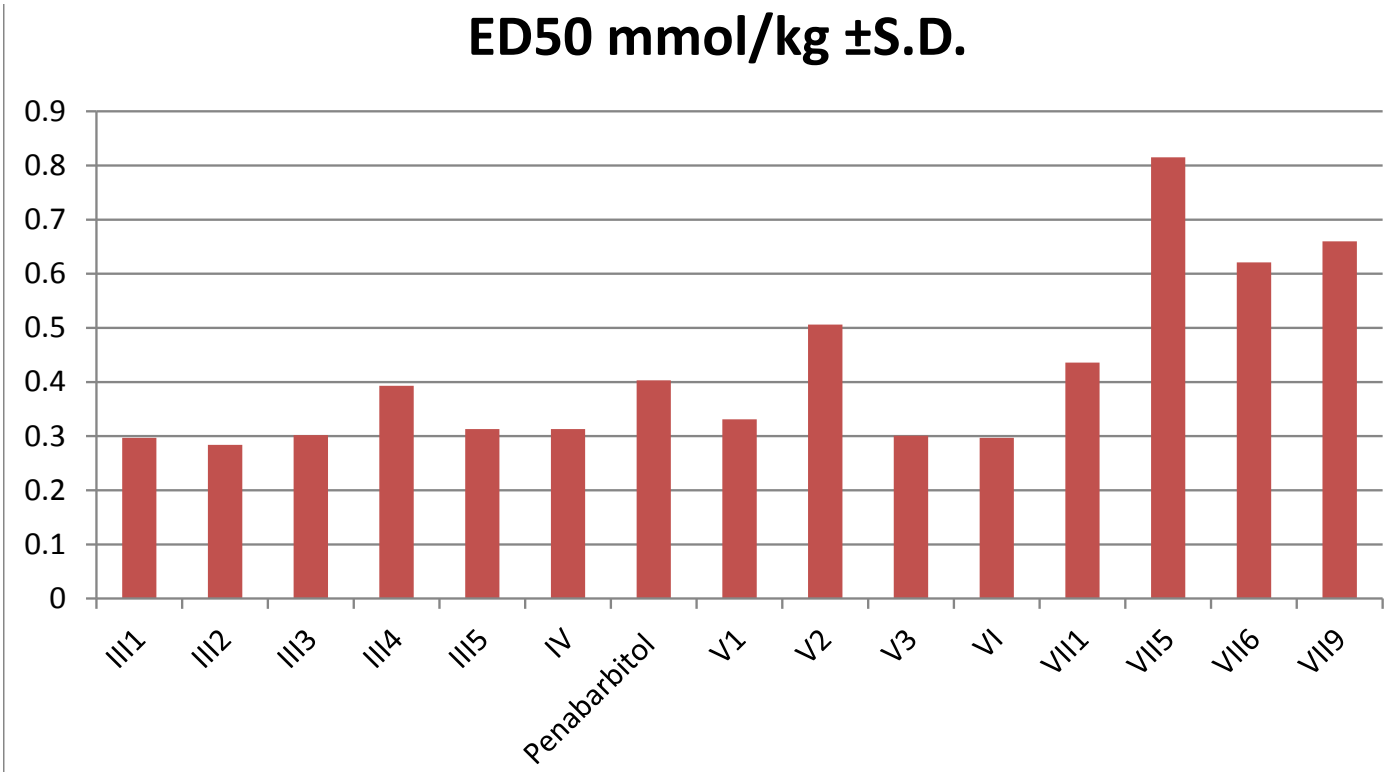


Figure 1b. The new compounds tested against phenobarbital.

Conclusions

All the tested compounds showed the anticonvulsant activity comparing with phenobarbitone as reference compounds.

- Compounds $III_{1,3}$-IV –V_3-VI $VIII_{1,3}$ showed the most activity comparing while the compounds V_2 and $VII_{6,9}$ revealed moderate activity.
- Finally compound VII_5 shaving lowest activity.

This indicates the –CO-CH_2-N-NH group, responsible for anticonvulsant activity reflecting that the presence of the hydrogen bonds between the phthalazinedione plays certain role in the mechanism of action of such compounds as anticonvulsant agents. Also the presence of nitrogen and oxygen atoms in the phthalazinedione compounds make the hydrogen bonds between the phthalazibedione and the receptors which formed of protein (Amino acids). So the phthalazinedione compounds bind with the receptor easier and having potency as anticonvulsant agents.

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