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Design, Synthesis and Anticonvulsant Activity of Some New Acetanilide Derivatives Incorporating Phthalazine- 1,4 (2H, 3H) Dione Scaffolds

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Abstract

We prepared phthalazine -1,4 (2H, 3H) dione (1) from phthalic anhydride and hydrazine hydrate. The compound (1) reacted with alcoholic potassium hydroxide, we obtained on compound (2) (the potassium salt of phthalazine -1,4 (2H, 3H) dione. Also we synthesized acetanilide derivatives (3) from aniline derivatives with chloroacetyl chloride. Then we reacted the compound (2) with the compounds (3) resulted compounds (4a-q) which tested some of them (some new compounds acetanilides) against phenobarbitone as standard reference drug as anticonvulsant agents, some of these new compounds revealed promising anticonvulsant activity.

Keywords: Acetanilides • Phthalazinedione • Anticonvulsant • Phenobarbitone

Introduction

The acetanilides revealed many of biological medicinal uses, so we incorporate the acetanilide derivatives with phthalazine-1,4 (2H, 3H) dione which it (phthalazine-1,4 (2H, 3H) dione) have also many of biological medicinal uses e.g. anticancer, antoconvulsant, antimicorobial, antiinflamatory, analgesics, antiviral…etc. [1-7,8-12,13-16,17-20,21-26].

N.B. The phthalazinedione, phthalazinone and phthalazine resemble quinoxalinedione, quinoxalinone and quinoxaline also resembles quinazolinedione, quinazolinone and quinazoline in chemical structure where all of these structures have benzene ring fused with diazine ring either carry two carbonyls or one carbonyl or no carbonyl [1,8-12,16,21-25] Where the phthalazine-1,4 (2H, 3H) dione promising nucleus we synthesis new compounds from phthalazine-1,4 (2H, 3H) dione and acetanilides to testing as anticonvulsants.

A mixture of- 1,4 (2H, 3H) phthalazinedione potassium salt 2.01 g, (0.01 mol) and the appropriate N-chloroacetylphenylamino derivatives was refluxed in dimethyl formamide (DMF) (50 ml) for 3 hrs. On water bath then cooled. The reaction mixture was poured onto ice-cold water, filtered and recrystallized from ethanol or glacial acetic acid. The analysis of compounds (4a-q) present in Tables 1 and 2.

Elemental analysis were performed at the Microanalytical Center, Faculty of Science, Cairo University, Cairo, Egypt IR Spectra were carried out an a Pye Unicam SP 1000 IR spectrophotometer at Microanalytical Center, Cairo University. Using potassium bromide disc technique 1HNMR spectra were recorded on a varian (CCl4, 90 MHz were recorded on 9 spectrophotometer at Microanalytical Center, Cairo University, TMS was used as internal reference and DMSO-d6 was used as solvent, the chemical shifts values were measured in δ (ppm) (Figure 1 (a-c).The Mass spectra were recorded on HP-model-MS 5988 (EI,70ev) at the Microanalytical Center, Cairo University, Cairo, Egypt.

N.B. All melting points were carried out on a Griffin melting point apparatus at Faculty of Pharmacy, Al-Azhar University and were uncorrected.

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Materials and Animals

The animal studies were undertaken with approval from the ethics committee (approval #23PD/3/12/8R) of Al-Azhar University, Cairo, Egypt. All the trials were caried out according to the respective intrnationally valid guidelines. Anticonvulsant activity of our compounds was evaluated according to the method reported by soaje-Echaque and Lim, using swiss Albino adult male mice, weighing 20-25 g. They were obtained from an animal facility (Animal House, Deparment of pharmacology and Toxicology. Faculty of Pharamacy Al-Azhar Uneversity, Cairo, Egypt. Mice were housed in stainless steel wirefloored cages without any stressful stimuli. Animals were kept under will-ventilated conditions at room tempreture (25-30 Â °C)They were fed on an adequate standard laboratory chow (El-Nasr Co, Abou zabal, Egypt) and allowed to acclimatize with free access to food and water for a 24 hrs period before testing except the short time they were removed from the cages for testing. Albino mice were randomly arranged in groups each comprising 12 animals. Phenobarbital sodioum (Sigma-Aldrich chemical Co, Milwaukee, WI, USA) was used as a reference drug for comparison. Pentylenetetrazole (Sigma-Aldrich chemical Co, Milwaukee, WI, USA) was used to induce convulsions in the exepremintal animal. The tested compounds tested for evaluation of their anticonvulsant activities.

Pharmacological testing

A variety of the newly synthesized phthalazinediones were subjected to

Table 1. The melting points, yield and elemental analyses of new compounds

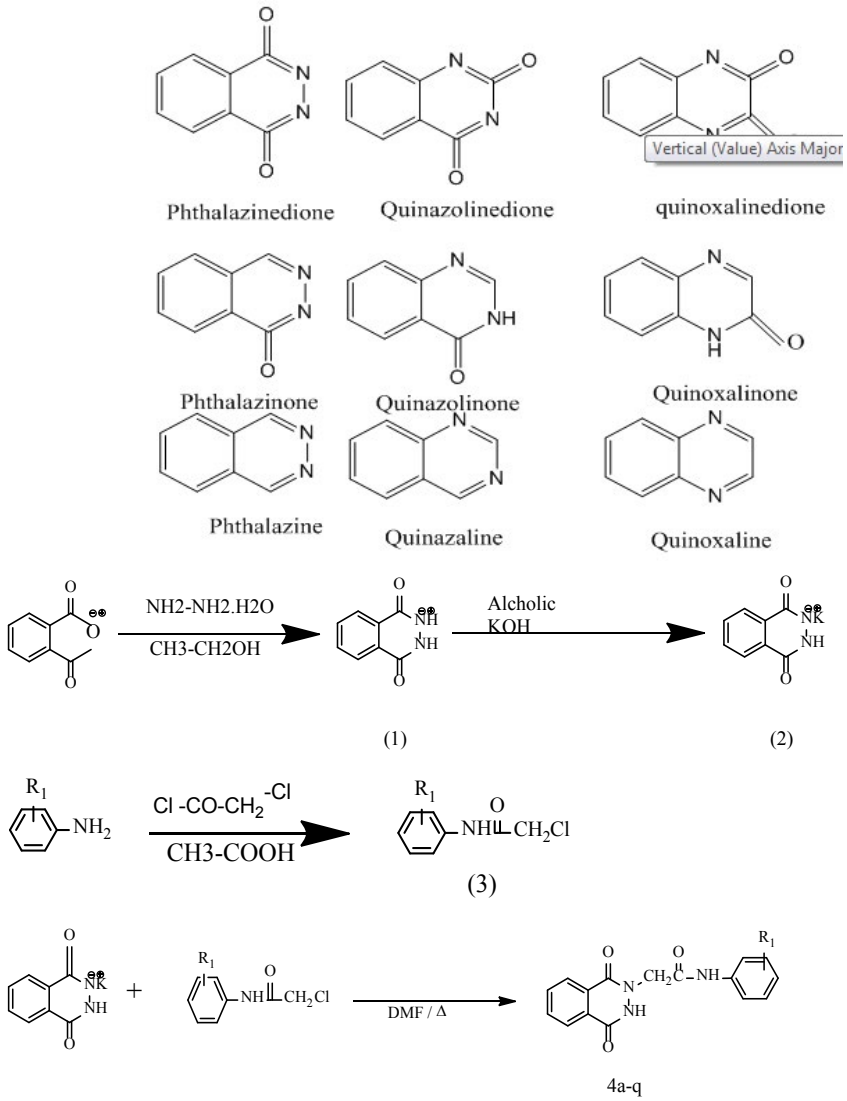
Comp. No.	R	M.P. (°C)	Yield (%)	Molecular formula (M. Wt)	Elemental analyses		
					%	Calcd.	Found
4a	H	277-9	95	$C_{16}H_{13}N_3O_3$ 295	C	65.08	65.52
					H	4.41	3.95
					N	14.24	14.09
4b	4-Cl	255-6	92	$C_{16}H_{12}ClN_3O_3$ 329.5	C	58.27	57.67
					H	3.64	3.75
					N	12.75	13.03
4c	4-F	260-2	80	$C_{16}H_{12}FN_3O_3$ 313	C	61.34	61.57
					H	3.83	4.03
					N	13.42	13.83
4d	4-Br	242-4	85	$C_{16}H_{12}BrN_3O_3$ 374	C	51.34	51.73
					H	3.21	3.11
					N	11.23	10.83
4e	2, 5-di-Cl	298-9	95	$C_{16}H_{11}Cl_2N_3O_3$ 364	C	52.75	53.11
					H	3.02	2.96
					N	11.54	12.01
4f	2-OH -4-Cl	210-11	65	$C_{16}H_{11}ClN_3O_4$ 345.5	C	55.57	55.22
					H	3.18	2.98
					N	12.16	12.47
4g	2.6-di-Cl	288-9	82	$C_{16}H_{11}Cl_2N_3O_3$ 364	C	52.75	53.07
					H	3.02	3.09
					N	11.54	11.40

Table 2. Some spectral data for some new derivatives as representative examples.

Comp No.	Items	IR cm^{-1}, ^{1}HNMR, ppm, Ms (m/z) Spectral data
4a	^{1}HNMR (DMSO-d_6)	4.96 (s, 2H, N-CH_2CO), 7.05-8.40 (m, 9H, aromatic protons), 10.21 (s, 2H, NH of the ring and amide group).
4b	^{1}HNMR	4.98 (s, 2H, N-CH_2CO), 7.37-7.97 (m, 8H, aromatic protons), 10.38 (s, 1H, NH of the amide group), 11.95 (s, 1H, NH of the ring).
4g	IR	3173 (NH), 1747 (carbamoyl group), 1664-1586 (carbonyls of the ring)
4h	^{1}HNMR (DMSO-d_6)	1.32 (t, 2H, $\underline{CH_2}$-CH_2-COOH), 4.29 (t, 2H, -CH_2-$\underline{CH_2}$-COOH), 7.64-8.27 (m, 8H, aromatic protons), 10.53 (s, 1H, NH amide), 10.58 (s, 1H, NH of the ring), 11.96 (s, 1H, OH of the COOH)
4m	^{1}HNMR (DMSO-d_6)	2.25 (s, 3H, p-CH_3), 4.94 (s, 2H, N-CH_2-CO), 7.09-8.30 (m, 8H, aromatic protons), 10.11 (s, 1 H amide NH)

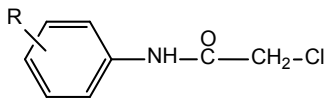
Table 3. The protection % of the chosen new compounds as anticonvulsant agents.

Comp. No.	Dose mg/kg	Protection %	ED_{50} mg/kg	ED_{50} m mol/kg ± S.D	Relative Potency M ± S.D
4a	50	33.3	90	0.305 ± 0.1	0.101 ± 0.03
	100	50			
	200	100			
4b	75	33.3	100	0.303 ± 0.08	0.102 ± 0.02
	150	66.6			
	250	100			
4g	100	33.3	160	0.440 ± 0.12	0.07 ± 0.015
	200	66.6			
	300	100			
4o	100	50	100	0.308 ± 0.08	0.1 ± 0.012
	200	66.6			
	400	100			
Phenobarbitone	75	3333	100	0.403 ± 0.12	0.1 ± 0.021
	125	66.6			
	175	100			



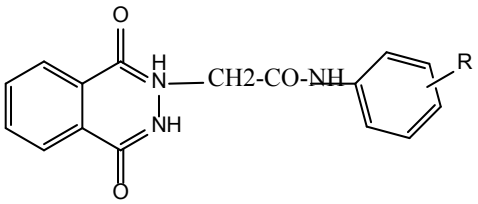
R = H, 4-Cl, 4-Br, 4-F, 2,5-di-Cl, 2-OH, 5-Cl, ,6-di-Cl, 4-CH_2-CH_2-OH, 2,6-di-CH_3, 2-CH_3, 4-CH_3, 2-NO_2, 4-Cl, 3-OCH_3, 4-NO_2, 2,4-di-OCH_3, 2,6-di-OCH_3, 2-COOH

1a. Chemistry and experimental



To aniline derivatives (0.01 mol) we add chloroacetyl chloride (0.01 mol) in glacial acetic acid (20ml) as solvent with stirring for 6 hours on ice bath, then filtered the product dried and crystallized from glacial acetic acid (See reference)

1b. Preparation of acetanilide derivatives (3)



1c. 2-(Arylaminocarbonylmethyl)-1,4-(2H,3H) phthala-zinedione (4 $_{a-q}$)

Figure 1. The chemical structures of Phthalazine quinazaline and quinoxaline and its dione and one.

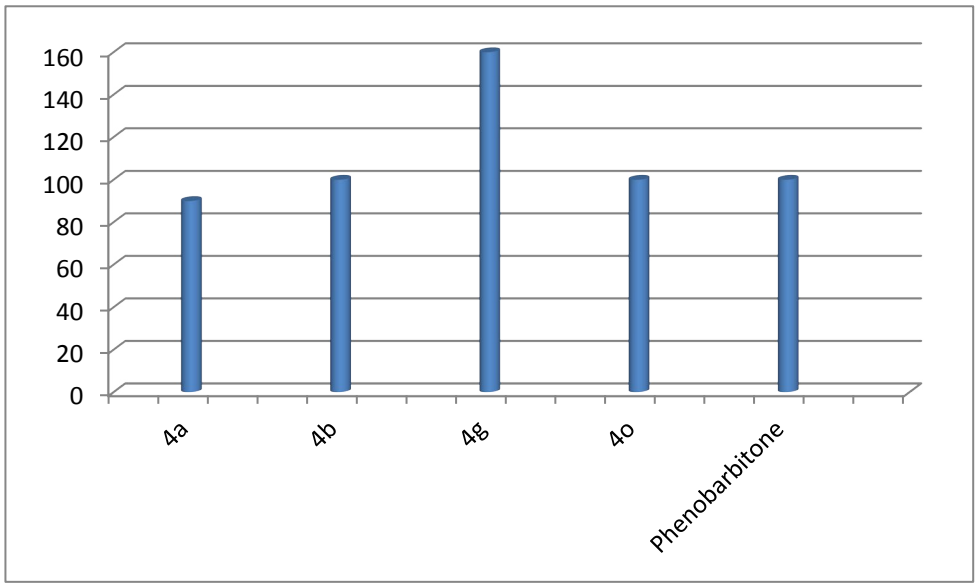


Figure 2. The relative activity between the chosen compounds as anticonvulsant and phenobarbitone. In addition to presence of carbonyl groups and-NH-groups which formed hydrogen bonds with the receptor which responsible for anticonvulsant drugs and the activity produced.

preliminary pharmacological testing with regard to their sedative hypnotic as well as anticonvulsant activities. CNS-depressant activity of many sedative-hypnotic agents are mainly evaluted using several screening methods including, loss of righting reflux corneal reflex, motor activity amphetamine antagonism and response to the various chemical stimulants. On the other hand most of the experimental methods for evaluation of the anticonvulsant activity of many drugs involve the artificial induction of convulsions by chemo and/or electroshock agents and inhibition of such convulsions by the drug under test (89,90). In this investigation the loss of righting reflex method was adopted for evaluation of the anticonvulsant activity of such compounds and screened by determining their ability to protect the experimental animals against pentylenetetrazole induced convulsation following the method reported by Soaje-Echague and Lim.

Preliminary assessment of the anticonvulsant activity

The anticonvulsant activity of some phthalazinediones was assessed in albino mice against pentylenetertrazole induced convulsion in comparison to phenobarbitone as a reference drug following the technique of Soaje-Echague and Lim. The test compounds and phenobarbitone were suspended in water with the aid of tween-80 to give suspension with 2% concentration. Pentylenetetrazole was also dissolved in water containing few drops of tween-80 to produce 2% solution. Groups of twelve mice were injected in the dorsal lymph sac with three graded doses of the test compounds or phenoparbitone. After 45 minutes, the animals were injected with the convulsive dose of phentylenetetrazole (320 mg/kg). The animals that showed no tonic convulsion within 60 minutes after pentylenetetrazole administration were considered to be protected. The percent protection, ED50 (mg/kg) and or mmol/Kg and the mean of the relative potency ± S.D. of the test compounds to phenobarbitone were calculated (Table 3 and Figure 2).

Discussion and Conclusion

All the tested compounds showed the anticonvulsant activity comparing with phenobarbitone as reference compounds. Compounds, 4a, 4b, 4g and 4o showed the most activity This indicate that CO-CH2-N-NH group responsible for anticonvulsant activity reflecting that the presence of the hydrogen atom on the nitrogen attached to the 2-position might play certain role in the mechanism of action of such compounds as anticonvulsant agents.

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