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Design and Synthesis of Some New Derivatives of 6,7-Dicholorophthalazine 1,4-(2H, 3H) dione for Pharmacological Testing as Anti-convulsant Agents

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Abstract

In the present work we synthesized some new compounds of Design and Synthesis of Some New Derivatives of 6,7-Dicholorophthalazine 1,4-(2H, 3H) dione via the reaction of 4,5-Dicholoro phthalicanhydride with hydrazine hydrate resulted 6,7-dicholorophthalazine 1,4-(2H, 3H) dione (I). The compound (I) reacted with alcoholic potassium hydroxide to obtain the potassium salt of 6,7- Dicholorophthalazine 1,4-(2H, 3H) dione (II). Also the acetanilide derivatives (III) condensed with compound (II) in dimethylformamide (DMF) on water bath for six hours, gave compounds (IV 1-12) which choose some of them to test as anti-convulsant activity compared with phenobarbitone sodium as standard reference drug. The choice new compounds which tested revealed anti-convulsant activity.

Keywords: 6,7- Dicholorophthalazine 1,4-(2H, 3H) dione • Anti-convulsant • Phenobarbitone sodium

Introduction

From the previous work of phthalazine 1,4-(2H, 3H) dione we encouraged to react the 4,5-Dicholorophthalicanhydrite with hydrazine hydrate to obtain 6,7-Dicholorophthalazine 1,4-(2H, 3H) dione and react it through the condensation of acetanilide derivatives in dimithylformamide (DMF) to obtain the compounds (IV 1-12) The acetanilide derivatives itself used in wide verities in biology and medicinal field. Also the phthalazinedione, phthalazinone and phthalazine resemble quinazolinedione, quinazolinone and quinazoline. Also resemble too quinoxalinedione, quinoxalinone and quinoxaline. All the previous chemical nucleuses have biological and medicinal uses e.g. anti-bacterial, anti-inflammatories, analgesics, anti-hypertensive, anti-hyperlipedeamics, ant-convulsants, anti-cancer, anti-viral, anti-fungal, etc. [1-7,9-12,13-16,17-20,21-26].

N.B. All the nucleuses phthalazine, quinazoline and quinoxaline either carry to carbonyls, one carbonyl or no carry any carbonyl. And acetanilide derivatives are intermediates [9-12,16,21-24,26] (Figures 1-5), (Scheme 1) The analysis of new compounds present at (Tables 1 and 2).

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

- 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 techique.
- 1HNMR spectra were recorded on a varian (CCl4 90 MHz) were recorded on 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 (ppm).
- The Mass spectra were recorded on HP-model-MS 5988 (EI 70 ev) at the Microanalytical Center, Cairo University, Cairo – Egypt.

Anti-convulsant activity

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

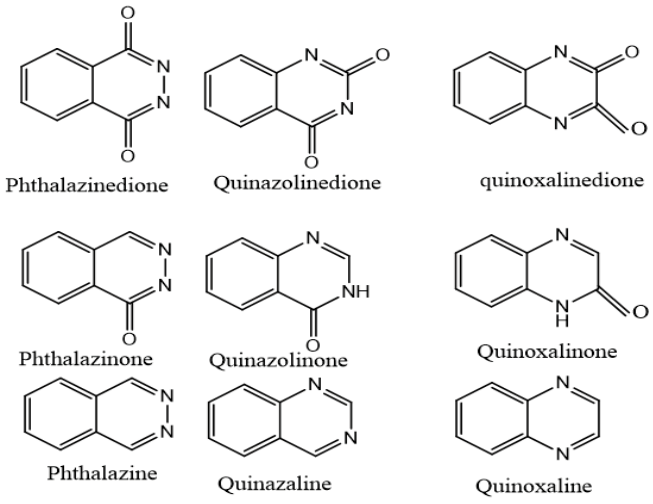

Figure 1. The Chemical Structures of Phthalazine quinazaline and quinoxaline and its dione and one.

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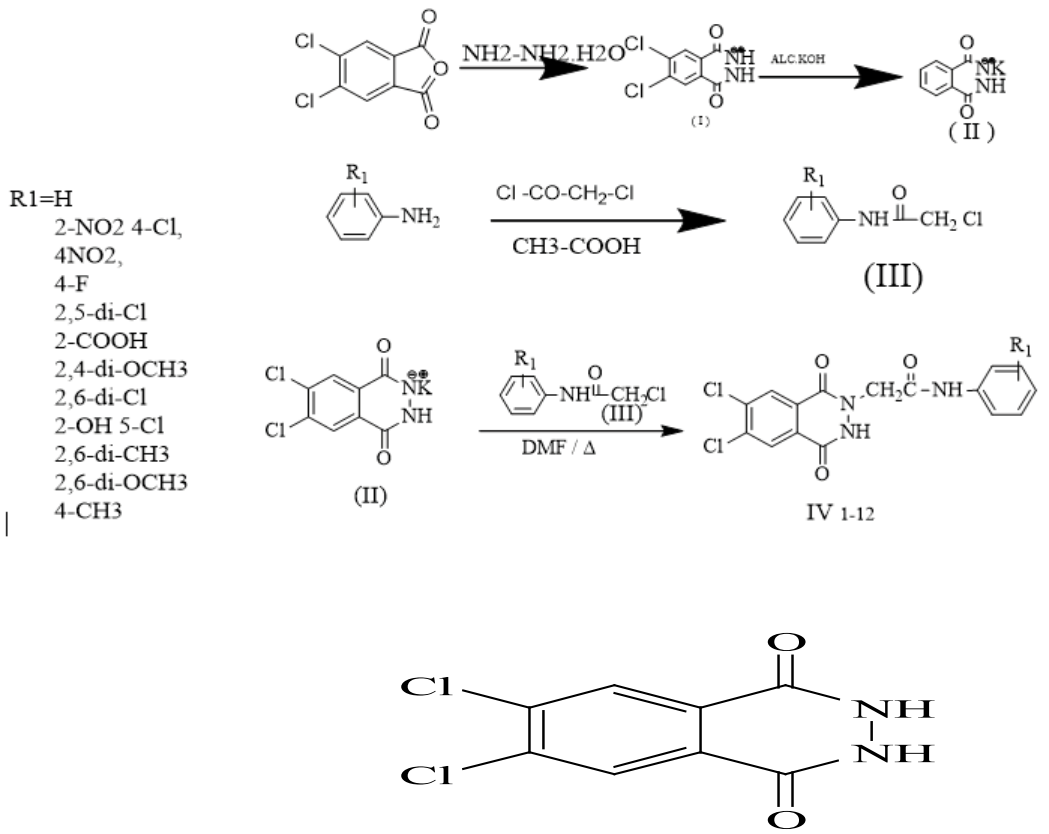

Figure 2. 6,7-Dichloro-1,4 (2H, 3H) phthalazinedione.

Note: A mixture of 4,5-dichlorophthalic anhydride 2.17 gs, (0.1 mol) and 0.5 ml, (0.1 mol) slight excess hydrazine hydrate in absolute ethyl alcohol (50 ml) was heated under reflux for four hours then cooled. The precipitate so obtained was filtered, crystallized from ethanol. **(M.P.** 328-330 (as reported) **Yield:** 2.26 gs (98%) as reported).

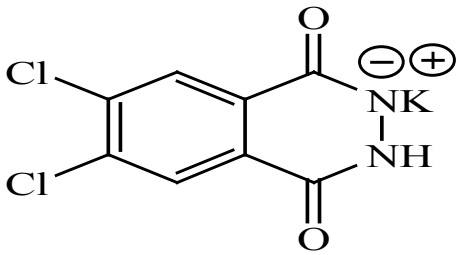

Figure 3. 6,7-Dichloro-1,4(2H,3H) phthalazinedione potassium salt.

Note: A solution of appropriate 6,7-dichloro-1,4-(2H,3H)phthalazinedione 2.31 gs, (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 yield was almost quantitatively. **Yield:** 2.57 gs (95%) as reported).

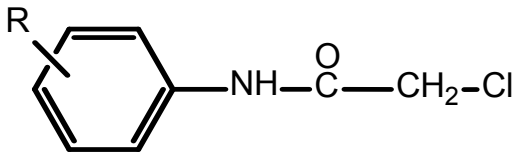

Figure 4. Preparation of acetanilide derivatives.

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

were caried out according to the respective intrnationally valid guidelines. Anti-convulsant activity of our compounds was evaluated according to the method reported by soaje-Echague and Lim, using swiss Albino adult male mice, weighing 20-25g. 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

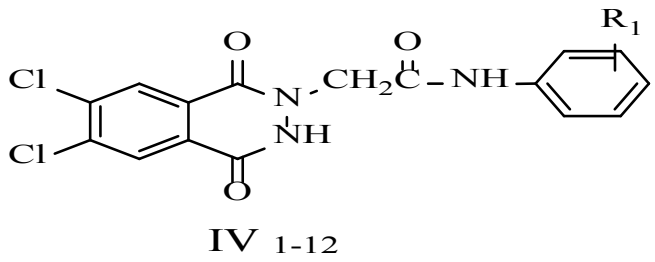

Figure 5. 2-(Arylaminocarbonylmethyl) 6,7-dichloro-1,4-(2H,3H) phthalazinediones IV_{1-12}

Note: A mixture of 6,7-dichloro-1,4-(2H,3H)phthalazinedione potassium salt 2.7 g, (0.01 mol) and the appropriate N-chloroacetylphenylamino derivatives was refluxed in dimethylformamide (DMF) (50 ml) for 3 hrs. on water bath then cooled. The reaction mixture was poured onto ice-cold water, filtered and crystallized from ethanol or glacial acetic acid.

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 anti-convulsant activities.

The test compounds were suspinded in normal saline with the aid of Tween 80 (Mwdical Union Pharmacuetical Co., Ismailia, Egypt). Test compounds were injected intraperitoneally (i.p.) in a dose ranging from 25-100 mg/kg animal eaight using the same dosing volume of 0.2 ml per 25 gm.

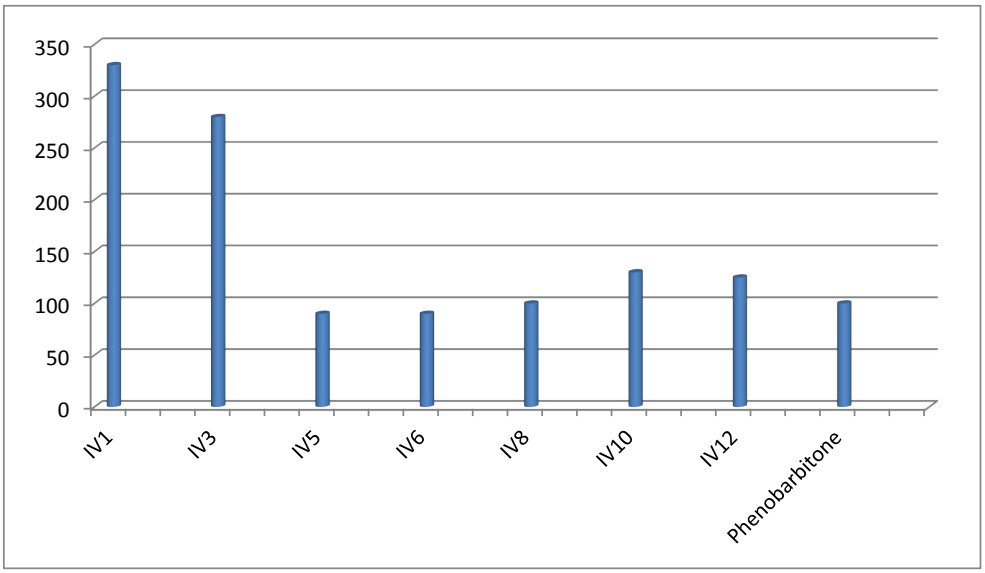

Figure 6. The relative activity between the choosed compounds as anticonvulsant and phenobarbitone (Graphically).

Pentylenetetrazole was desolved in normal saline in 2% concentration and was given i.p. in a dose of 100 mg/kg body mass. Phenobarbiton sodium was desolved in normal saline in 2% concentration and it was given i.p. in doses of 6.25,12.5 and 25mg /kg using the same dosing volume. All drugs were freshly prepared to the desired concentration just before use. The percentsge protection per each dose and the dose which makes protection for 50% of animals (ED50) was calculated using INSTAT 2 program (ICS, Philadelphia. PA, USA), Presented in Table 3 the activity of test compounds in comparison to phenobarbiton sodium or relative potency of the test compounds to phenobarbiton sodium was calculated and used for comparison among compounds under test as shown in Figure 6 and Table 3.

Discussion and Conclusion

All tested compounds showed anti-convulsant activity compared with phenobarbitone sodium maybe less, more or equal to activity of phenobarbitone. This indication to these compounds bind with the receptor which bind with phenobarbitone, why not, Due to presence of carbonyls and nitrogen in the compounds and aromatic system which facilitate the binding of tested compounds with the receptor which bind with phenobarbitone. So the tested compounds revealed anti-convulsant activity compared with phenobarbitone.

Conflict of Interest

The authors of this paper have no commercial associations that might pose a conflict of interest in connection with the submitted manuscript such as employment consultancies paid lecturing, financial involvement, patent ownership, etc.

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