SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL IODOPHTHALAZINEDIONE DERIVATIVES AS ANTICONVULSANT AGENTS

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ABSTRACT:

In view of their expected anticonvulsant activity, some new derivatives of phthalazine (**I, II, III$_{a-f}$, IV, V, VI$_{a-f}$ and VII$_{a-h}$**) were designed and synthesized by condensation of Iodophthalic anhydride with hydrazine hydrate to produce iodophthalazindione **I** which heating with Alc. KOH to give compound **II**. The compounds **III$_{a-f}$** resulted from condensation of compound **II** with different alkylcholoroacetates. Compound **II$_b$** reacted with ammonia, hydrazinehydrate and different alkyl amines resulted compounds **IV, V** (hydrazide) and **VI** respectively. Compound **V** (hydrazide) react with different aromatic aldehydes to produce compounds **VII$_{a-h}$**. the final compounds were structurally elucidated basis of IR , ^{1}HNMR, Ms Carbon, hydrogen and nitrogen analysis. The final compounds were evaluated for anticonvulsant activity using pentylenetetrazole (ptz) to induce convulsion and phenobarbital as reference standard. The compounds **I, II, IV, V, VI$_a$, VI$_b$, VI$_c$, VI$_d$, VI$_f$, VII$_a$, VII$_b$, VII$_c$** and **VII$_g$** were active than Phenobarbital as standard reference the remain compounds less active than Phenobarbital. To under stand the molecular significant of these results we compared the binding modes of these compounds.

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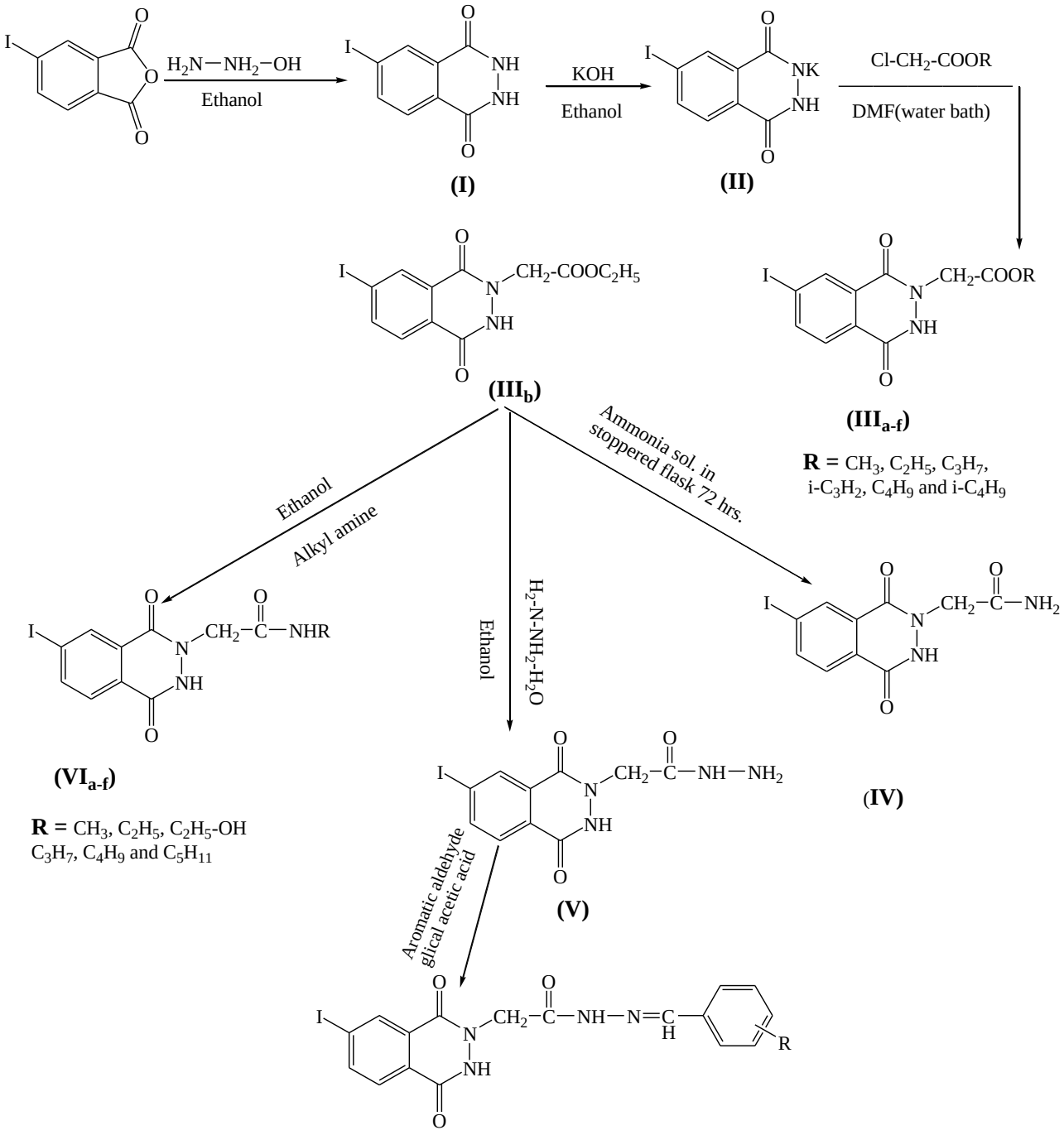
Keywords: phthalazine, phthalazinedione and anticonvulsant agent

INTRODUCTION

Phthalazine derivatives received much attention in recent years a wing to both their biological significance and pharmaceutical applications **(Napoletano, *et al.*, 2001; Napoletano, *et al.*, 2001; Napoletano, *et al.*, 2000; Curia, *et al.*, 2002; Imamura, *et al.*, 2003)**. Many phthalazine derivatives have been reported as anticonvulsants **(Siva, et al., 2002; Ayyad, 2008; El-Helby, *et al.*, 2001**; **El-Helby, *et al.*, 2002)** Some phthalazines were reported to possess anticonvulsant activity against minimal electrical sock (MES) and exhibited significant decrease in elevated motor activity **(Siva, et al., 2002)**. On the other hand, it has been reported that a lot of compounds containing arylidene moiety possess good anticonvulsant activity and have a big role in MAO inhibitory action **(Eid, *et al.*, 1991)**. On the light of these findings, we decided to design and synthesize novel derivatives of iodophthalazine containing arylidene moiety and other derivatives (ester, amide) to evaluate their anticonvulsant activity and to compare the difference in the pharmacological effects. As a result, we found that the synthesized compounds (**I, II, III$_{a-f}$, IV, V, VI$_{a-f}$** and **VII$_{a-h}$**) have appreciable anticonvulsant activity.

. The following scheme illustrate our experimental work.


H2N—NH2—OH
Ethanol
KOH
Ethanol
Cl-CH2-COOR
DMF(water bath)
(I)
(II)
(IIIb)
(IIIa-f)
R = CH3, C2H5, C3H7, i-C3H2, C4H9 and i-C4H9
Ethanol
Alkyl amine
Ammonia sol. in stoppered flask 72 hrs.
H2-N-NH2-H2O
Ethanol
(VIa-f)
R = CH3, C2H5, C2H5-OH C3H7, C4H9 and C5H11
(IV)
(V)
Aromatic aldehyde glical acetic acid
(VIIa-h)
R = H, 2-OH, 4-OH,4-NO2, 2-NO2, 2-CH3,4-CH3,4-F

Scheme

Chemistry

1) 6 – Iodophthalazine (2H, 3H) – 1, 4 – dione I.

4-Iodophthalic anhydride (2.78 gm) (0.01 mol) is refluxed with hydrazine hydrate (excess) in ethanol for 4hours. The product resulted in compound **I**. m.p. 313-315^{o}C, yield 90% (2.63 gm), Mol wt. 292, Mol. Formula $C_8H_5IN_2O_2$. IR: showed 1598 cm^{-1} for carbonyl group of ring 3920 cm^{-1}, NH- of ring. ^{1}HNMR(ppm.) (dmso) : reveled signal at 8 ppm (S, NH-) which indicate for –NH of ring. and (7.5 and 8.51) (m, 3H aromatic). Ms: (M 292, 91%), 262 ($C_8H_3IO_2$,11%) and 206 (C_6H_3I)100%.

Calc.	C: 3.29	H: 1.71	N: 9.59
Found	3.19	2.05	9.30

2) Potassium salt of 7-iodophthalazine (2H,3H)-1,4-dione II.

In 50 ml ethanol dissolve 2.93 gm (0.01 mol) compound **I** and (0.56 gm KOH) (0.01 mol) dissolved in ethanol (10 ml) add the latter solution to the former to give the potassium salt of 6-iodophthalazine (2H,3H) 1,4-dion (**II**) which crystallized from ethanol. m.p. > 350, yield 95% (3.10 gm), mol. Formula, $C_8H_4IN_2O_2K$., mol, wt 331 and yield quantitative.

3) 2-Akyloxycarbonylmethyl-6-idophthalazine (2H,3H)-1,4-dione (III_{a-f})

In a conical flask (250 ml) (3.3 gm) (0.01 mol) of Compound **II** moistened with appropriate amount (0.01 mol) of alkylchloroacetate in 100 ml dimethylformamide (DMF) refluxed for two hours, then cooled, poor on crushed ice. The crystals collected by filtration, resrystallized from ethanol (table 1).

Table1. Physical data

Comp. No.	M.P. ^{o}C	Yield (gm)%	Molecular formula M. Wt	Elemental analyses		
				%	Calcd.	Found
III_a	195-6	80% (2.91)	$C_{11}H_9IN_2O_4$ 364	C% H% N%	36.26 2.43 7.69	35.87 2.33 8.05
III_b	170-2	93% (3.52)	$C_{12}H_{11}IN_2O_2$ 378	C% H% N%	38.10 2.91 7.41	37.82 2.93 7.55
III_c	205-6	72% (2.82)	$C_{13}H_{13}IN_2O_2$ 392	C% H% N%	39.80 3.32 7.14	40.11 3.01 6.79
III_d	201-3	92% (3.61)	$C_{13}H_{13}IN_2O_2$ 392	C% H% N%	39.80 3.32 7.14	39.93 3.47 6.83
III_e	217-9	65% (2.64)	$C_{14}H_{15}IN_2O_2$ 406	C% H% N%	41.38 3.69 6.90	40.99 3.81 7.11
III_f	213-4	77% (3.13)	$C_{14}H_{15}IN_2O_2$ 406	C% H% N%	41.38 3.69 6.90	41.09 3.48 6.65

Spectra data of compounds III_{a-f}

IR cm^{-1} (example **IIIa**) 3263 (NH), 3020 (CH_2-), 1717 (CO-) of the ester moiety and (1671, 1610) for carbomyl moiety of ring.

^{1}HNMR, ppm (dmso) **IIIa** (3.4, s,-CH_3-,(3.2-d,j=8 Hz-CH_2-), 8-s, NH- and 7.5, 8.51 m, aromatic)

III_b (1.1,s,-CH_3-, (3.41, d,j=8 Hz -CH_2), (3.23,d, j=8 Hz-,CH_2-), 8.25,s-, NH, 7.53-8.45 m, aromatic)

III_c (0.97, s,CH_3, (1.60-d, j =8 Hz CH_2-CH_3), (2.45,d, j=8 Hz-O-CH_2-CH_2-), (4.11-d,j=8 Hz CH_2-COO-), 8.35, NH and 7.46, 8.53, aromatic).

III_f (1,s, CH_3,CH_3, 2,m,CH, (2.4d, j= 8 Hz-CH_2-CH), (4.3,d,j=8 Hz CH_2-), 9s, NH,(7-7.41), 8.3,m, aromatic).

Ms(M/z) comp. **III_a** [M364 (6%)][349 M-CH_3,(21%), [M-OCH_3, 333(33%)] [206, C_6H_3I(100%)].

Comp**. III_b** [M-378 (3%)], 349 M-C_2H_5(5%)], [287$C_8H_4IN_2O_2$ (51%)], [206, C_6H_3I, 100%].

Comp. **III_e** [M-406(17%)], [376, M-2CH_3- (70%)] , [$C_9H_6IN_2O_2$, 391, (35%)], 287 $C_8H_4IO_2N_2$ (74%)], [206-C_6H_3I, (100%)]

4. (2-Aminocarbohylmethyl)-6-Iodophthalazin (2H,3H)-1,4-dione IV.

Excess ammonia solution is added to ethanol solution of **III_b** (0.01 mol) (3.78 gm) in stappered flask and stirring at room, compound **IV** is precipitated, then recystallized from ethanol.

m.p. 231-2, yield 55% (1.92 gm), mol. Formula $C_{10}H_8IN_3O_3$, mol wt. 349.

Calc.	C: 34.38	H: 2.29	N: 12.03
Found	34.67	2.13	11.88

IR cm^{-1}, 3730 , NH, 1610 and 590 carbonyl of ring, 1745-carbonyl of amide, 4200 NH_2.

^{1}HNMR. ppm. (dmso) 6, -NH_2, (4.1,d,j=8Hz-CH_2), 6,s-NH, 7.9, 8.48 m aromatic)

Ms (m/z) M-349(6%), 287, $C_8H_4IN_2O_2$(13%),206, C_6H_3I(100%).

5) (2-Hydrazinocarbonylmethyl)-6-Iodophthalazine (2H,3H)-1,4-dion V.

A mixture of ethanolic solution from **III_b** (0.01 mol) (3.78 gm) and excess (1 ml) of hydrazine hydrate heated and stirring at 100C for 30 minutes, then the mixture is filtered, washed with ethanol and crystallized from ethanol the m.p. 247-9 yield 90% (3.28 gm) mol. Formula, $C_{10}H_9IN_4O_3$, mol wt. 364, elemental analyses.

Calc.	C: 32.97	H: 2.47	N: 15.38
Found	32.61	2.63	15.3

^{1}HNMR,ppm (dmso)[2,s, NH_2], [8-s,NH, side chain of ring], [4,d, j=8Hz -CH_2] and 7.9 and 8.51)m-aromatic.

Ms(m/z)[M,364 (20%)],[M-NH_2, 348 (7%)],[391 $C_9H_6IN_2O_2$ (55%)],[287 $C_8H_4IN_2O_2$,(75%),] and[206, C_8H_3I (100%)].

6) (2-Alkylaminocarbonylmethyl)-6-Iodophthalazin (2H,3H)-1,4-dion VI_{a-f}.

In conical flask (250 ml) have ethanolic solution of **III_b** (0.01 mol) (3.78 gm) and appropriate amount (0.01 mol) of different alkyl amine refluxed at 120^{o}C for 3 hrs. The product collect by filtration crystallized by ethanol (table 2).

Table 2. Physical data

Comp. No.	R	M.P. oC	Yield % (gm)	Molecular formula M. Wt	Elemental analyses		
					%	Calcd.	Found
VI_a	CH_3	251-3	65% (2.36)	$C_{11}H_{10}IN_3O_3$ 363	C% H% N%	36.36 2.75 11.57	35.98 2.63 11.48
VI_b	$-CH_2-CH_3$	242-3	68% (2.56)	$C_{12}H_{12}IN_3O_3$ 377	C% H% N%	38.20 3.18 11.14	38.11 3.15 11.51
VI_c	CH_2-CH_2-OH	193-5	77% (3.03)	$C_{12}H_{12}IN_3O_4$ 393	C% H% N%	36.64 3.05 10.69	36.71 2.15 10.31
VI_d	$n-CH_2-CH_2CH_3$	248-49	85% (3.34)	$C_{13}H_{14}IN_3O_3$ 391	C% H% N%	39.32 3.58 10.74	39.53 3.71 10.55
VI_e	$n-(CH_2)_3CH_3$	238-39	55% (2.28)	$C_{14}H_{16}IN_3O_3$ 405	C% H% N%	41.48 3.95 10.37	41.77 3.98 10.33
VI_f	$n-(CH_2)_4CH_3$	256-8	60% (2.51)	$C_{15}H_{18}IN_3O_3$ 419	C% H% N%	42.96 4.32 10.02	42.88 4.68 10.24

Spectra data of compounds VI_{a-f}.

IR cm^{-1}, 4100 , NH, 3940, NH_2, 1740, $C(=O)-C-NH$,1610, 1595 carbonyl of ring

^{1}HNMR, ppm (dmos). Comp. **VIa.** [2.5s.CH_3-NH-], [8,s-, NH], [4,d,j =8Hz CH_2] and [7.9and 8.5m, aromatic].

VI_b (1.2-s,CH_3), (3.1-q, j=7.8 Hz $-CH_2-CH_3$), (4-d, $-CH_2-COO$),(8-s,-NH), (7.7 and 8.4 m aromatic)

VI_c (2-s, OH), (3.9-q, j=7.8 Hz-CH_2-OH), (3.3-q, j=7.8 Hz CH_2-CH_2), (4.1-d, j=8 Hz CH_2-COO), (8-s,-NH) and (7.6 and 8.5-m, aromatic)

VI_d (1-s, CH_3)(2-q, j=7.8Hz-CH_2-CH_3), (3.1-q,j=7.8 Hz CH_2-CH_2), (4-d,j=8Hz CH_2-COO), (8-s,-NH) and (7.75 and 8.35-m, aromatic)

VI_f (1-s, CH_3), (1.3-q, ,j=7.6Hz $-CH_2-CH_3$, over loped), (1.6-q, j=7.6Hz $CH_2-(CH_2)2CH_3$), (3.1-q, j=7.8Hz -NH-CH_2), (8-s,-NH) and (7.8 and 8.55-m, aromatic)

Ms(M/z) **VI_a** [M-363(11%)], [M-CH_3, 349, (32%)],[$C_9H_6IN_2O_2$, 391 (17%)],206 [C_6H_3I(100%)].

VI_a [417-M (21%)], [348$C_{10}H_7IN_3O_3$ (9%)], [291 $C_9H_6IN_2O_2$ (76%)], [206C_6H_3I (100%)]

7) (2-Arylidenocarbonylmethyl)-6-iodophthalazine(2H,3H)-1,4-dionVII_{a-h}.

Dissolve (0.01 mol) (3.64 gm) of compound **V** in 100 ml of glacial acetic acid and add to acetic acid solution appropriate amount of aromatic aldehyde and refluxed at 150^{o}C for 3hrs. Then, cooled, the crystals of compounds **VII_{a-h}** are collected and recrystalized from glacial acetic acid the physical data at table 3.

Table 3. Physical data

Comp. No.	R	M.P. °C	Yield % (gm)	Molecular formula M. Wt	Elemental analyses		
					%	Calcd.	Found
VII_a	H	278-9	90% (4.07)	$C_{17}H_{13}IN_4O_3$ 452	C% H% N%	45.13 2.88 12.39	44.87 2.92 12.53
VII_b	Orth- OH	283-5	75% (3.51)	$C_{17}H_{13}IN_4O_4$ 468	C% H% N%	43.69 2.78 11.97	43.83 2.43 11.62
VII_C	Para-OH	297-8	87% (4.07)	$C_{17}H_{12}IN_4O_4$ 468	C% H% N%	43.59 2.78 11.97	43.57 2.63 12.23
VII_d	Para-NO_2	281-2	65% (3.23)	$C_{17}H_{12}IN_5O_5$ 497	C% H% N%	41.05 2.41 14.08	40.86 2.37 14.03
VII_e	Ortho-NO_2	273-5	60% (2.98)	$C_{17}H_{11}IN_5O_5$ 497	C% H% N%	41.05 2.41 14.08	41.10 1.87 14.09
VII_f	Ortho-CH_3	268-9	55% (2.56)	$C_{18}H_{14}IN_4O_3$ 465	C% H% N%	46.45 3.01 12.04	46.76 2.93 11.93
VII_g	Para-CH_3	273-4	50% (2.32)	$C_{18}H_{14}IN_4O_3$ 465	C% H% N%	46.45 3.01 12.04	46.62 2.91 12.27
VII_h	Para-F	257-9	55% (2.59)	$C_{17}H_{12}IN_4O_3F$ 470	C% H% N%	43.40 2.55 11.91	43.21 2.33 11.97

Spectra data of compounds VII_{a-h}.

IR (cm^{-1}), 650 for CH aromatic, 4100-NH-, 1755, -CO- of amid, 1625, 1610 -CO- of ring.

^{1}HNMR, ppm.(dmso) VII_a (7.2-7.4,7.9 and 8.55 m, aromatic), (6. CH-C_6H_5), (5.5-s, -NH-N=), (4-d,j=8Hz CH_2-COO-), (8-NH of ring).

VII_b (7.1-7.3, 7.9 and 8.4, m of aromatic), (8-s,NH), (5.5-s, OH), (4-d, -CH_2-COO).

VII_c(7.1-7.3, 7.75 and 8.6, m, aromatic), (5-s,OH), (6-m,CH-C_6H_5), (4-d, j=8Hz CH_2-COO-), (8-s,NH).

VII_d (7.5-8.1, 7.9 and 8.6-m, of aromatic), (6-m, of CH-C_6H_5), (4-d, j=8Hz -CH_2-COO-) and (8-s,NH).

VII_e (7.5-8.15, 7.8 and 8.55-m, of aromatic), (7-m, of CH-C_6H_5), (4-d,j=8Hz -CH_2-COO-) and (8-s,NH).

VII_f (2.3-s, CH_3-C_6H_5), (7-7.2, 7.8 and 8.45-m, of aromatic), (6.9-m,CH-C_6H_5), (4-d,j=8Hz CH_2-COO-) and (8-s,NH).

$VIII_g$ (2.33-s, CH_3-C_6H_5), (7-7.3, 7.9 and 8.55-m, of aromatic), (6.9-m,CH-C_6H_5), (4-d ,j=8Hz CH_2-COO-) and (8-s,NH).

$VIII_h$ (7-7.33, 7.75 and 8.55-m, of aromatic), (6.8-m,CH-C_6H_5), (4-d,j=8HzCH_2-COO-) and (8-s,NH).

Ms M/z **VII_a** [M-452(11%)], [M+1(453),(9%)], [347 $C_{10}H_6IN_3O_3$(31%)], [245 C_9H_6I(73%)], [206C_6H_3I(100%)].

VII_b [M-467(23%)], [M-1(466),(27%)], 347 [$C_9H_6IN_3O_3$(19%)], 245 [C_9H_6I(7%)], 271[$C_8H_4IN_2$ (23%)], 206[C_6H_3I(100%)].

RESULTS AND DISCUSSION

The synthesized compounds **I, II , III_{a_f} , IV , V , $VI_{a–f}$** and **VII_{a_f}** were confirmed by melting point spectral data and C , H , and N analysis . Also anticonvulsant activities of the synthesized compounds (**I -VII_{a_f}**) were determined using the pentylenetetrazole (ptz). Seizure threshold test **(Swinyard, *et al.*, 1982)** preliminary screening results showed that all compounds (**I -VII_{a_f}**) exhibit anticonvulsant activity the compounds are divided into two groups all of them are evaluated at three different dose levels the first at 25, 50 and the second at 50, 100 and 200 mg using Phenobarbital sodium at three different dose levels (50, 100 and 200 mg) as positive control. The test compounds were injected intrapretoneal (ip) followed by subcutaneous (sc) (ptz) at 70 mg / kg aminimal dose that produce threshold seizures in approximately 100% of control animals (the compounds **I , II , III_{a-d} , VI_{d-f}** and **VII_{f-h}** are tested at three different dose levels (25 , 50 , and 100 mg) and revealed anticonvulsant activity equal to or more than Phenobarbital as positive control , while the compounds **III_e , III_f , IV , V , VI_a , VI_b , VI_c , VII_d , VII_e** tested at three different dose levels (50 , 100 and 200mg) and revealed anticonvulsant activity less than Phenobarbital. In general, there is no one of all tested compounds less than 80% active as Phenobarbital. The activity of tested compounds due to Phormocophoric group in phthalazine nucleolus which have CO – N – N – CO which different in there positions in quinoxaline and qiunazoline N – CO – CO – N and CO – N – CO- N, respectively which have anticonvulsant activity **(Ossman *et al.*, 1986; Aziza, *et al.*, 1996)**. Some of the ester groups have activity less than Phenobarbital due to the ester functional group which undergo esterase enzyme but the other groups have amide which is difficult to breakage by amidase enzyme comparing with esterase enzyme.

All tested compounds showed 33.3% protection at the dose (25mg, 50mg), 66,6% protection at the dose(50mg ,100mg) and 100% protection at the dose (100mg, 200mg) . This kind of protection is an indication for the potential anticonvulsant activity of the tested compounds particularly against absence seizures. Anticonvulsant activity **(While, *et al.*, 1995)** could be associated with some undesirable effects such as sedation. N.B. GABA is the major inhibitory transmitter in the mammalian CNS, which controls the excitability of many central pathways. The GABA is the receptor complex mediates the flux of chloride ions across nerve membranes and may be related to the anticonvulsant action of GABA – mimetic drugs **(Reddy, *et al.*, 1997; Wood, *et al.*, 1980)** the principal mode of action of this transmitter occurs by modulation of the GABA – chloride ion channel complex as attempt explore the possible GABA- mimetic activity of the active compounds.

Anticonvulsant activity

The animals were under taken with approval from ethics committee approval (23PD/3/12/18R) of Al-Azhar University, Cairo, Egypt. All the trials were carried out according to the respective internationally valid guidelines. Anticonvulsant activity of our compounds was evaluated according to the method reported by **Soaje-Echaque and-Lim (1962)** using Swiss albino adult male mice, weighing 20-59 gm. They were obtained from an animal Facility (Animal house. Department of pharmacology and toxicology, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt. Mice were housed is stainless steel wire floored cages without any stressful stimuli. Animals were kept under well- ventilated conditions at room temperature (25-30^{o}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 24 hrs period before testing except during the short time they were removed from the cages for testing. Albino mice were randomly arranged in groups each comprising 12 animals. Phenobarbital sodium (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 convulsion in the experimental animals. All

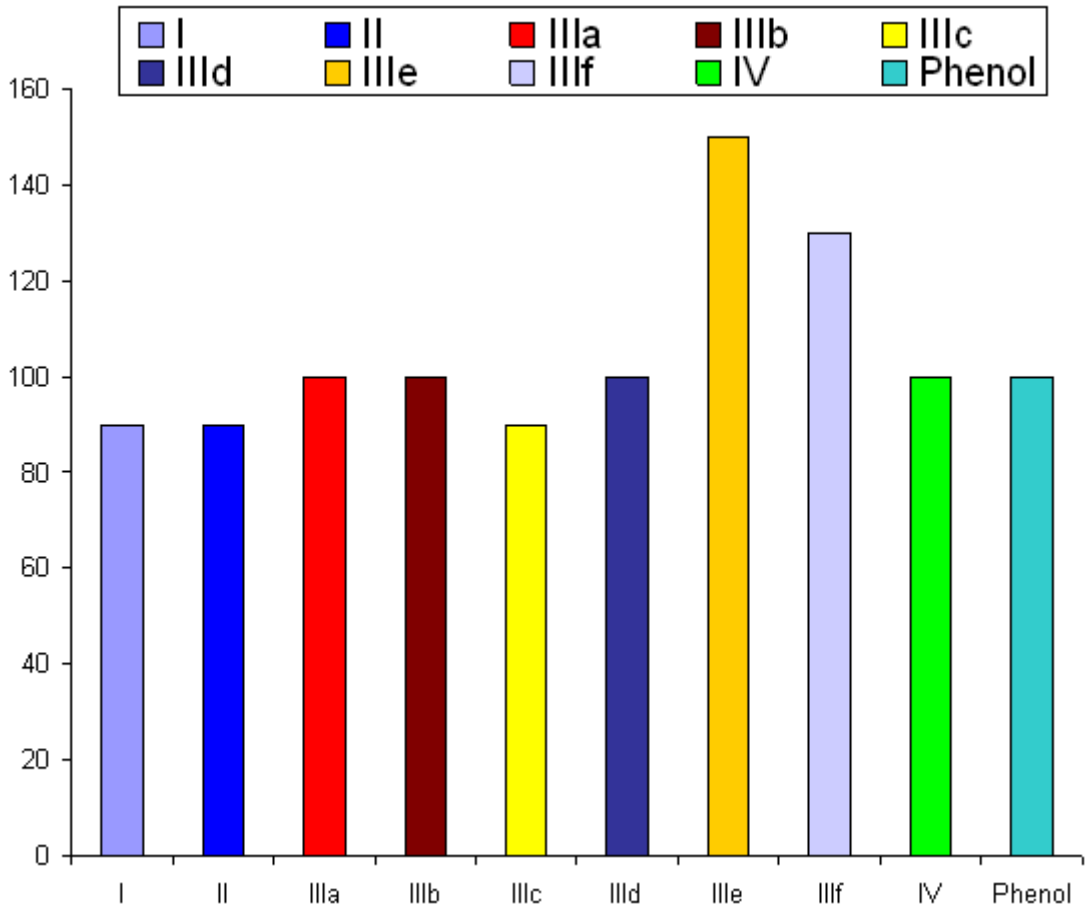
synthesized phthalazine were tested for evolution of their anticonvulsant activities. The test compounds were suspend in normal saline with the aid of Tween 80 (Medical union Pharmaceuticals Co., Ismailia, Egypt)test compounds were intraperitoneally (i.p) injected in dose ranging from 25-200 mg/kg animal weight using the same dosing volume of (0.2 ml per 25 gm. Pentylenetetrazole was dissolved in normal saline in 2% concentration and was given (sc) in dose 50-200 mg/kg (70 mg/kg as a minimal dose that produce threshold seizure in approximately 100% of control animals) using the same dosing volume. All drugs were freshly prepared to the desired concentration just before use. The percentage protection per each dose and the dose which makes protection for 50% of animals (ED_{50}) was calculated using INSTAT2 program (ICS Philadelphia, PA, USA) presented in table (4) the activity of test compounds in comparison to Phenobarbital or relative potency of the test compounds to Phenobarbital was calculated and used for comparison among compounds under test as shown in table (4).

Table (4): Anticonvulsant activity of synthesized compounds

Comp. No.	Dose (mg/kg)	Protection %	ED_{50} mg/kg	ED_{50} m ml/kg± S.D.	Relative potency M± S.D.
I	25 50 100	33.33 50 100	90	0.288 ± 0.1	0.1 ± 0.01
II	25 50 100	33.33 66.66 100	90	0.326 ± 0.09	0.109 ± 0.008
III_a	25 50 100	33.33 66.66 100	100	0.364 ± 0.12	0.078 ± 0.02
III_b	25 50 100	33.33 66.66 100	100	0.374 ± 0.1	0.085 ± 0.02
III_c	25 50 100	33.33 66.66 100	90	0.391 ± 0.09	0.099 ± 0.03
III_d	25 50 100	33.33 66.66 100	100	0.391 ± 0.09	0.093 ± 0.02
III_e	50 100 200	33.33 66.66 100	150	0.406 ± 0.12	0.061 ± 0.01
III_f	50 100 200	33.33 66.66 100	130	0.406 ± 0.16	0.074 ± 0.014
IV	50 100 200	33.33 66.66 100	100	0.349 ± 0.1	0.103 ± 0.02
V	50 100 200	33.33 66.66 100	90	0.364 ± 0.13	0.104 ± 0.03
VI_a	50 100 200	33.33 66.66 100	90	0.363 ± 0.1	0.101 ± 0.03
VI_b	50 100 200	33.33 66.66 100	100	0.377 ± 0.1	0.102 ± 0.02

Cont. table

Comp. No.	Dose (mg/kg)	Protection %	ED_{50} mg/kg	ED_{50} m ml/kg± S.D.	Relative potency M± S.D.
VIc	50 100 200	33.33 50 100	160	0.393 ± 0.12	0.07 ± 0.015
VId	25 50 100	33.33 66.66 100	100	0.391 ± 0.08	0.1 ± 0.012
VI_e	25 50 100	33.33 66.66 100	90	0.406 ± 0.13	0.104 ± 0.03
VI_f	25 50 100	33.33 66.66 100	100	0.421 ± 0.1	0.103 ± 0.02
VII_a	25 50 100	33.33 66.66 100	100	0.451 ± 0.08	0.1 ± 0.012
VII_b	25 50 100	33.33 66.66 100	90	0.467 ± 0.08	0.120 ± 0.03
VII_c	25 50 100	33.33 66.66 100	90	0.467 ± 0.09	0.124 ± 0.02
VII_d	50 100 200	33.33 66.66 100	170	0.496 ± 0.13	0.074 ± 0.014
VII_e	50 100 200	33.33 66.66 100	200	0.496 ± 0.11	0.067 ± 0.02
VII_f	25 50 100	33.33 66.66 100	100	0.464 ± 0.07	0.116 ± 0.04
VII_g	25 50 100	33.33 66.66 100	90	0.464 ± 0.08	0.106 ± 0.03
VII_h	25 50 100	33.33 66.66 100	125	0.459 ± 0.11	0.0999± 0.03
Phenobarbital	50 100 200	33.33 66.66 100	100	0.403 ± 0.12	0.1 ± 0.021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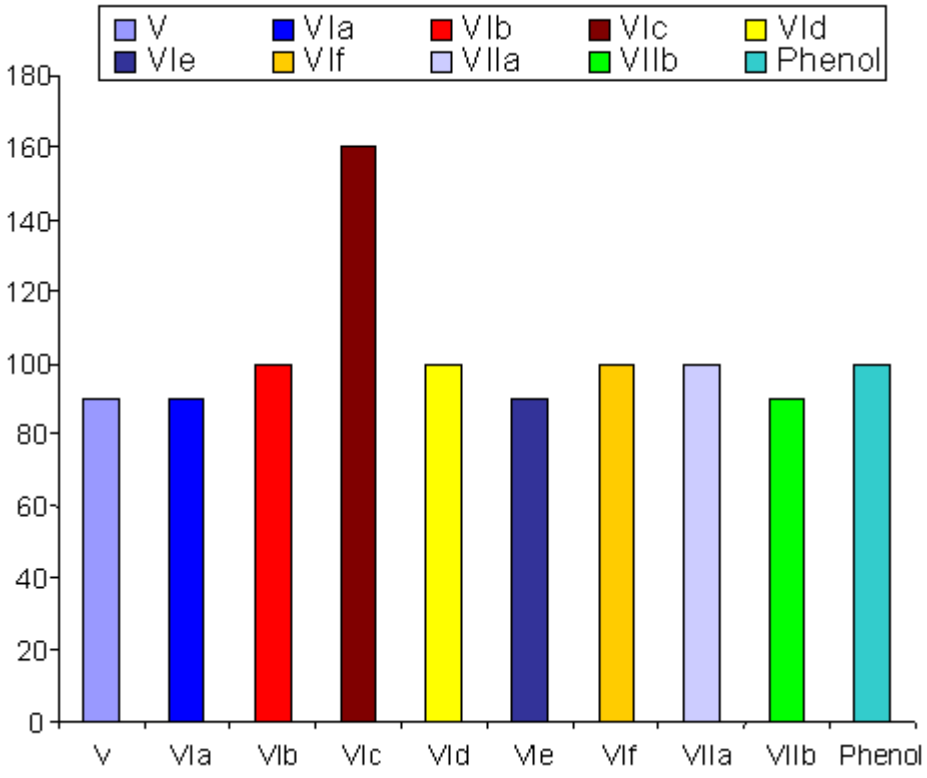
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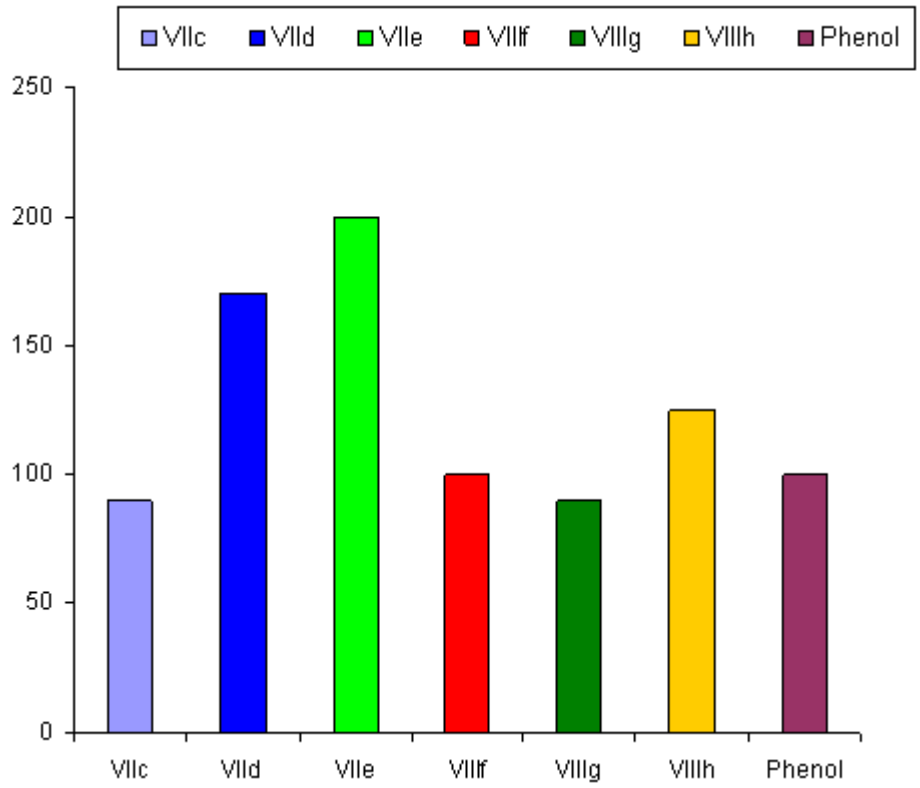

Figure 1. Compounds **II , IV , V , VI_a , VI_b , VI_e VI_f , VII_b , VII_c , VII_f** , and **VII_g** showed anticonvulsant activity more than Phenobarbital. While compounds **I**, **VI_d ,** and **VII_a** revealed activity equal to Phenobarbital. The rest compounds are anticonvulsant activity less than Phenobarbital but not less than 80% of its activity.

Experimental Section

All melting points were measured on a griffin melting point apparatus (Griffin, Valdosta, GA, USA) and are corrected. The infrared spectra were recorded asKBr discs on a nicolet IR 200 (thermo fisher scientific, Barrington, USA) at the pharmaceutical analytical unit, Faculty of Pharmacy, Al-Azhar University, Cairo Egypt. The ^{1}HNMR spectra were ran using TMS as an internal standard (Aldrich Chem. CO., Milwaukee, Wi, USA) on varian Mercury VXr-300 NMR (Varian Palo., Alto, CA, USA) at the Micro Analytical Center, Faculty of Sciences Cairo, University Giza, Egypt.

Mass spectra were performed on varian MAT 311-A (70eV) (Varian, San Fernando, GA, USA) at the Micro analytical center of Cairo University Giza, Egypt, Elemental analyses (C,H,N) were performed on a Perkin-Elmer 2400.

Analyzer (Perkin-Elmer, Nor walk, C.T., USA) at the Micro analytical unit of Cairo University, Giza, Egypt. All compounds were within ± 0.4% of the theoretical. All chemicals used for synthesis were purchased from Sigma- Aldrich Chemical Co. Milwaukee, WI, USA.

Anticonvulsant activity

The animal were under taken with approval from ethics committee approval #23PD/3/12/18R) of Al-Azhar University, Cairo, Egypt. All the trials were carried out according to the respective internationally valid guidelines. Anticonvulsant activity of our compounds was evaluated according to the method reported by Soaje-Echaque and-Lim[(11)] using Swiss albino adult male mice, weighing 20-59 gm. They were obtained from an animal Facility (Animal house. Department of pharmacology and toxicology, Faculty of Pharmacy,

Al-Azhar University, Cairo, Egypt. Mice were housed is stainless steel wire floored cages without any stressful stimuli. Animals were kept under well- ventilated conditions at room temperature (25-30^{o}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 24 hrs period before testing except during the short time they were removed from the cages for testing. Albino mice were randomly arranged in groups each comprising 12 animals. Phenobarbital sodium (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 convulsion in the experimental animals. All synthesized phthalazine were tested for evolution of their anticonvulsant activities. The test compounds were suspend in normal saline with the aid of Tween 80 (Medical union Pharmaceuticals Co., Ismailia, Egypt)test compounds were intraperitoneally (i.p) injected in dose ranging from 25-200 mg/kg animal weight using the same dosing volume of (0.2 ml per 25 gm. Pentylenetetrazole was dissolved in normal saline in 2% concentration and was given (i.p) in dose 50-200 mg/kg using the same dosing volume. All drugs, were freshly prepared to the desired concentration Just before use. The percentage protection per each dose and the dose which makes protection for 50% of animals (ED_{50}) was calculated using INSTAT2 program (ICS Philadlphia, PA, USA).

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تشييد وتقييم بيولوجى لمشتقات ايودو الفثالازين كمضادات للتشنجات العصبية

الدكتور / رزق رزق عبدالله عياد

من قسم الكيمياء الصيدلية ـ كلية الصيدلة (بنين) ـ جامعة الأزهر بالقاهرة

فى هذا البحث تم تشييد ثلاثة وعشرون مركبا جديد من نواة الأيودو فيثالازين وتم أختبارها بيولوجيا كمضادات للتشنجات العصبية مستخدما البنتلين تترازول كعامل يؤدى للتشنج وقد ثبت للمركبات الجدية فاعلية كمضادة ضد التشنجات مقارنة بالفينوباربيتال كعقار مرجع