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Synthesis and Anticonvulsant Activity of Oxadiazole Derivatives Incorporating Phthalazin-1,4 (2H, 3H)-dione Scaffolds

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Abstract

In this present work, we prepared the 2- (2-mercapto oxadiazole phthalazin (2H, 3H) -1,4-dione (1) and its salt (2) from 2-hydrazino carbonylmethylphthalazine (2H, 3H) -dione which resulted from condensation of carbondisulfide and potassium hydroxide in ethanol. Also we prepared 2- (2-mercapto oxadiazole-6,7 –dichloro phthalazin (2H, 3H) -1,4-dione (3) and its salt (4). The two salts (2) and (4) reacted with different alkylchloroacetates to produce compounds (5 a-f) and (6 a-f) these compounds tested as anticonvulsant drugs, its revealed anticonvulsant activity compared with phenobarbitone as refrence drug.

Keywords: Oxadiazole • Phthalazindione • Anticonvulsant • Phenobarbitone

Introduction

The phthalazindione nucleus it is promising nucleus, where it used anticancer, anticonvulsant, antibacterial, antiviral, antihyperlipidemic, analgesics, etc. Also the phthalazindione is bioisostere for quinoxalindione and quinazolindione these compounds either have the dione or one or without i.e., may be phthalazine, quinoxaline and quinazoline [1-23]. These rings formed of benzene ring fused with diazine ring to for phthalazine, quinoxaline and quinazoline which bind with receptor via hydrogine bonds or by bi-bi stacking bond and may be hydrogine bond via carbonyl gp (s) if present in addition to oxadiazole ring which also bind with receptor via heteroatoms which containing it. All three nucleuses phthalazinedione, quinoxalinedione and quinazolinedione have many and more of biological uses in previous literature [1-7,12-19,23]. All three nucleuses phthalazindione, quinoxalindione and quinazolindione have many and more of biological uses in previous literature (Figures 1 and 2).

Firstly the starting materials are phthalicanhydrite and 4,5-dichlorophthalicanhydrite which refluxed with hydrazine hydrate in ethanol for six hours to produce phthalazinedione and 6,7 dichlorophthalazinedione which they treated with alcoholic potassium hydroxide gave the salts of phthalazinedione and 6,7-dichlorophthalazinedione they condensed with ethylchloroacetate to obtain on 2- (2-ethylcarbonylmethylphthalazinedione and 2- (2-ethylcarbonylmethyl-6,7-dichlorophthalazinedione. They are reacted with hydrazine hydrate to produce 2-hydrazino carbonylmethylphthalazine (2H, 3H) –dione and 2-hydrazino carbonylmethyl-6,7- dichlorophthalazine (2H, 3H) –dione [8-11,16,20-22].

Synthesis of 2- (2-mercapto oxadiazole methyl phthalazine-1,4 (2H, 3H) dione (1)

2- (2-hydrazino carbonyl methylphthalazinedione (0.01 mol) (2.34 g) refluxed in ethanol with carbon isulphide (0.01 mol) (0.76 ml) or excess and potassium hydroxide (0.01 mol) (0.56 g) for 12 hrs. then pour on (HCl – H_2O) (3:1) gave the compound (1) m.p. >300, yield 70% (1.95 g) (Figure 3 and Table 1).

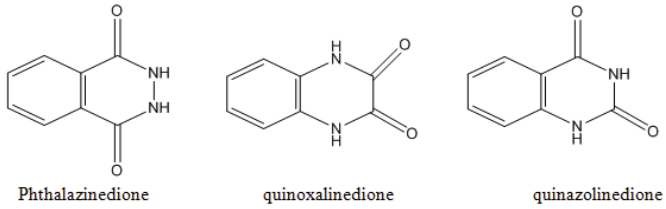

Figure 1. Schematic representation of Phthalazinedione, Quinoxalinedione and Quinazolinedione.

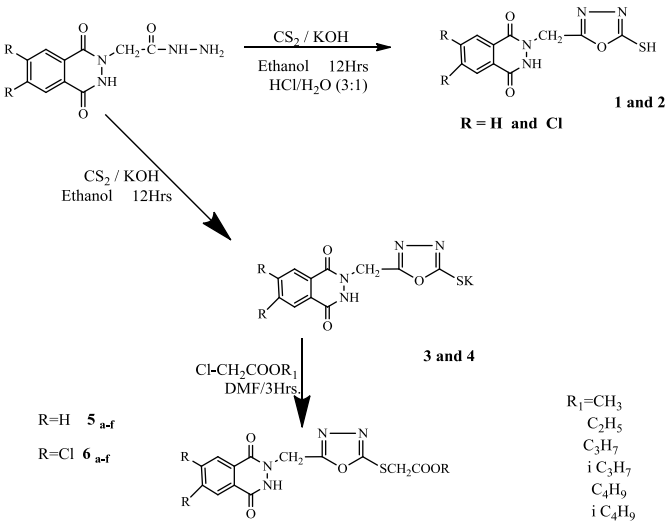

Figure 2. Schematic representation of all three nucleuses phthalazindione, quinoxalindione and quinazolindione and their biological reaction.

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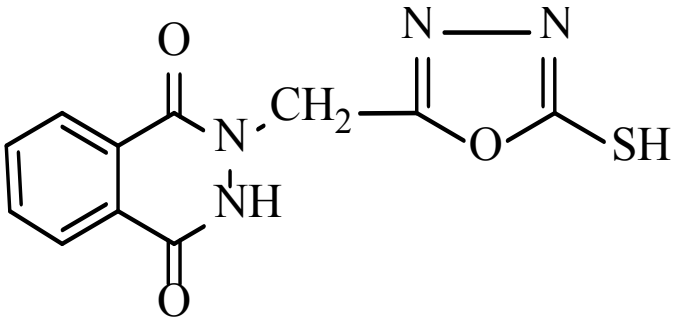

Figure 3. 2-(2-hydrazino carbonyl methylphthalazinedione.

Table 1. Synthesis of 2- (2-mercapto oxadiazole methylphthalazin (2H, 3H) -1, 4-dione (1).

VariablesC%		H%
Calculated	47.83	2.9
Found	47.36	3.16

Synthesis of 2- (2-mercapto oxadiazole methyl phthalazine-1,4 (2H, 3H)dione potassium salt (2)

2- (2-hydrazinocarbonylmethylphthalazinedione (0.01 mol) (3.34 g) refluxed in ethanol with carbon-disulphide (0.01 mol) (0.76 ml) or excess and potassium hydroxide (0.01 mol) (0.56 g) for 12 hrs. leave the reaction mixture to cool m.p. >300, yield quantitatively (Figure 4).

Synthesis of 2- (2-mercapto oxadiazole methyl-6,7-dichlorophthalazine (2H, 3H)-1,4-dione (3)

2- (2-hydrazino carbonyl methylphthalazinedione (0.01 mol) (3.03 g) refluxed in ethanol with carbon disulfide (0.01 mol) (0.76 ml) or excess and potassium hydroxide (0.01 mol) (0.56 g) for 12 hrs. then pour on (HCl – H_2O) (3:1) gave the compound (3), m.p. 288-289, yield 65% (2.26 g) (Figure 5 and Table 2).

Synthesis of 2- (2-mercapto oxadiazole methyl-6,7-dichlorophthalazine (2H, 3H)-1,4-dione potassium salt (4)

2- (2-hydrazinocarbonylmethyl-6,7- phthalazinedione (0.01 mol) (3.45 g) refluxed in ethanol with carbon disulfide (0.01 mol) (0.76 ml) or excess and potassium hydroxide (0.01 mol) (0.56 g) for 12 hrs. leave the reaction mixture to cool, m.p. >300, yield quantitatively (Figure 6).

2 (5-Alkoxycarbonylmethylthio-1,3,4-oxadiazol-2-yl-methyl) -1,4- (2H, 3H) phthalazinedione (5a-f) and 2 (5-Alkoxycarbonylmethylthio-1,3,4-oxadia-zol-2-yl-methyl)-6,7-dichloro-1,4- (2H, 3H) phthal-azinedione (6a-f)

A mixture of equimolar quantities 3.15 g, (0.01 mol) of 3 or 3.84 g, (0.01 mol) of 4 and the appropriate alkyl choroacetates in dimethylformamide (50 ml) was heated for two hours on water bath (Figure 7). The reaction mixture was then cooled, poured onto a stirred ice cold water (200 ml) for 30 minutes and the resulting solid was purified, washed with water, dried and recrystallized from ethanol (Tables 3 and 4).

Materials and Methods

Rats of either sex weighing 20-30 g were arranged in groups each of six animals. Phenobarbitone (Aldrich) was used as a reference drug and pentylenetetrazole (Aldrich) was used to induce convulsions in the experimental animals. Five compounds of phthalazinedione derivatives were selected for evaluation of anticonvulsant activity and their specifications are presented in Determination of the convulsive dose of pentylene-tetrazole Four graded doses of pentylenetetrazole (80, 160, 240 and 320 mg/kg) were injected to groups of six frogs. The animals were observed for 60 minutes. The

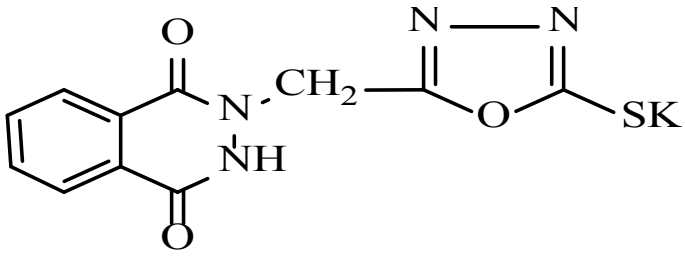

Figure 4. 2-(2-hydrazinocarbonylmethylphthalazinedione.

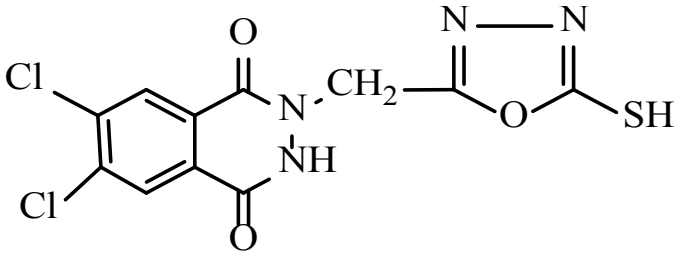

Figure 5. 2-(2-hydrazino carbonyl methylphthalazinedione.

Table 2. Synthesis of 2- (2-mercapto oxadiazole methyl-6, 7- dichloro phthalazine (2H, 3H) -1, 4-dione (3).

Variables	C%	H%
Calculated	38.26	1.74
Found	38.05	2.10

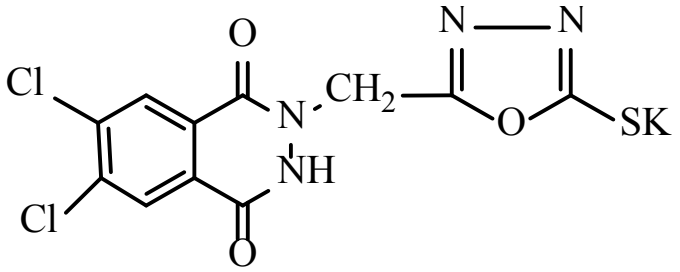

Figure 6. 2-(2-hydrazinocarbonylmethyl-6,7- phthalazinedione.

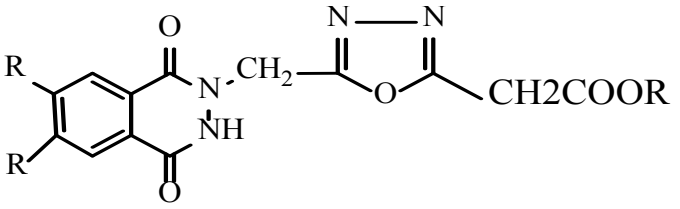

Figure 7. 2(5-Alkoxycarbonylmethylthio-1,3,4-oxadiazol-2-yl-methyl).

dose of 320 mg/kg was found to be the suitable convulsive dose that could induce a tonic convulsion in all injected animals within 30 minutes and without death during 24 hours.

Results and Discussion

Pharmacological testing

A variety of the newly synthesized phthalazinedione 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 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

Table 3: Spectral Data of Some of the Compounds and their elemental analysis.

Comp. No.	R	R_1	M.P. °C	Yield %	Molecular formula M. Wt	Elemental analyses		
						%	Calcd.	Found
5_a	H	CH_3	160-1	68	$C_{14}H_{12}N_4O_5S$ 348	C H N	48.28 3.45 16.09	47.95 3.67 16.03
5_b	H	C_2H_5	80-2	88	$C_{15}H_{14}N_4O_5S$ 362	C H N	49.72 3.87 15.47	49.55 4.10 15.13
5_c	H	C_3H_7	125-7	75	$C_{16}H_{16}N_4O_5S$ 376	C H N	51.06 4.26 14.89	50.85 3.90 14.55
5_d	H	Iso-C_3H_7	90-2	50	$C_{16}H_{16}N_4O_5S$ 376	C H N	51.06 4.26 14.89	50.77 4.06 15.10
5_e	H	C_4H_9	160-2	65	$C_{17}H_{18}N_4O_5S$ 390	C H N	52.31 4.62 14.36	51.95 4.35 14.11
5_f	H	Iso-C_4H_9	149-1	75	$C_{17}H_{18}N_4O_5S$ 390	C H N	52.31 4.62 14.36	51.95 4.36 13.88
6_a	Cl	CH_3	176-8	80	$C_{14}H_{10}Cl_2N_4O_5S$ 417	C H N	40.29 2.40 13.43	39.95 2.36 13.88
6_b	Cl	C_2H_5	158-9	90	$C_{15}H_{12}Cl_2N_4O_5S$ 431	C H N	41.76 2.78 12.99	42.04 2.55 12.65
6_c	Cl	C_3H_7	130-2	80	$C_{16}H_{14}Cl_2N_4O_5S$ 445	C H N	43.15 3.15 12.58	42.90 3.05 12.30
6_d	Cl	Iso-C_3H_7	122-4	72	$C_{16}H_{14}Cl_2N_4O_5S$ 445	C H N	43.15 3.15 12.58	43.07 3.01 12.90
6_e	Cl	C_4H_9	180-2	70	$C_{17}H_{16}Cl_2N_4O_5S$ 459	C H N	44.44 3.49 12.20	44.75 3.33 12.05
6_f	Cl	Iso-C_4H_9	170-2	78	$C_{17}H_{16}Cl_2N_4O_5S$ 459	C H N	44.44 3.49 12.20	44.04 3.09 12.10

Table 4: Spectral Data of Some of the newly Synthesized Compounds.

Comp. No.	Item	IR cm^{-1}, ^{1}HNMR, ppm, Ms (m/z) Spectral data
3	IR	3165 (NH of the ring), 3017 (CH aliphatic), 1660,1601 (carbonyls of phthalazindione nucleus)
	^{1}HNMR	5.67 (s, 2H, NCH_2CO), 7.90 (s,1H, aromatic protons), 8.29 (s,1H, aromatic protons) , 9.71 (s, 1H, NH of the ring), 12.06 (s,1H, SH of the oxadiazole group).
$mp5_a$	IR	3168 (NH of the ring), 3023 (CH,aliphatic), 1748 (ester carbonyl), 1655 (carbonyl of the ring).
	1HNMR	3.71 (s, 3H, COOCH3), 5.00 (s, 2H, NCH_2), 7.92-8.27 (m, 4H, aromatic protons), 11.97 (s, 1H, NH of the phthalazine ring)
5_b	IR	3169 (NH of the phthalazine ring , 2987 (CH, aliphatic), 1759 (ester carbonyl), 1658, 1593 (carbonyls of phthalazinedione nucleus)
	1HNMR	1.19 (t, 3H, COO-CH2-CH3), 3.37 (s, 2H, N-CH2), 4.15 (q, 2H, CO2CH2CH3), 4.96 (s, 2H, SCH2-CO), 7.94-8.30 (m,4H, aromatic protons), 11.98 (s, 1H, NH of the ring).
6_b	IR	3414 (my be SH of due to resonance), 3161 (NH of the ring), 2991 (CH, aliphatic), 1749 (ester carbonyl), 1652, 1603 (carbonyls of phthalazine ring)
	1HNMR	1.19 (t, 3H, COOCH2-CH3), 3.91 (s, 2H, N-CH2), 4.17 (q, 2H, COOCH2CH3), 4.97 (s,2H, SCH2-CO), 8.17-8.42 (2d,2H, aromatic protons of dichloro derivatives of phthalazinedione), 11.75 (s,1H, NH of the ring).
6_a	MS	417 (M) 419 (M+2)10%,15% Respectively ,344 (100%) (M – CH_3COO) and 358 (70%) these results indicate to presence of dichloro in the compounds where the mass spectroscopy revealed the isotopes.
6_c	MS	445 (M) 443(M-2)40%,60% and 29 (33%) Respectively ,358 (100%) these results indicate to presence of dichloro in the compounds where the mass spectroscopy revealed the isotops.
6_e	MS	457 (M-2) 459 (M) 7%,10%, 230 (30%) Respectively , 344 (100%) these results indicate to presence of dichloro in the compounds where the mass spectroscopy revealed the isotops.

and / or electroshock agents and inhibition of such convulsions by the drug under test. 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-Echaque and Lim [24].

Table 5: Anticonvulsant activity of some the newly synthesized compounds

Comp. No.	Dose mg/kg	Protection %	ED_{50} mg/kg	ED_{50} m mol/kg ±S.D	Relative Potency M ± S.D
5_a	50 100 200	33.33 50 100	90	0.259 ±0.08	0.120 ± 0.03
5_b	50 100 200	33.3 66.6 100	90	0.249 ±0.09	0.124 ± 0.02
5_c	75 150 250	33.3 66.6 100	100	0.266 ±0.07	0.116 ± 0.04
6_a	50 150 300	33.3 66.6 100	130	0.312 ±0.11	0.099 ± 0.02
6_b	75 150 300	33.3 66.6 100	125	0.290 ±0.05	0.106 ± 0.03
Phenobarbitone	75 125 175	3333 66.6 100	100	0.403 ±0.12	0.1 ± 0.021

The percent protection, ED50 (mg/kg) and or mmols/kg and the mean of the relative potency ± S.D. of the test compounds to phenobarbitone as reference drug

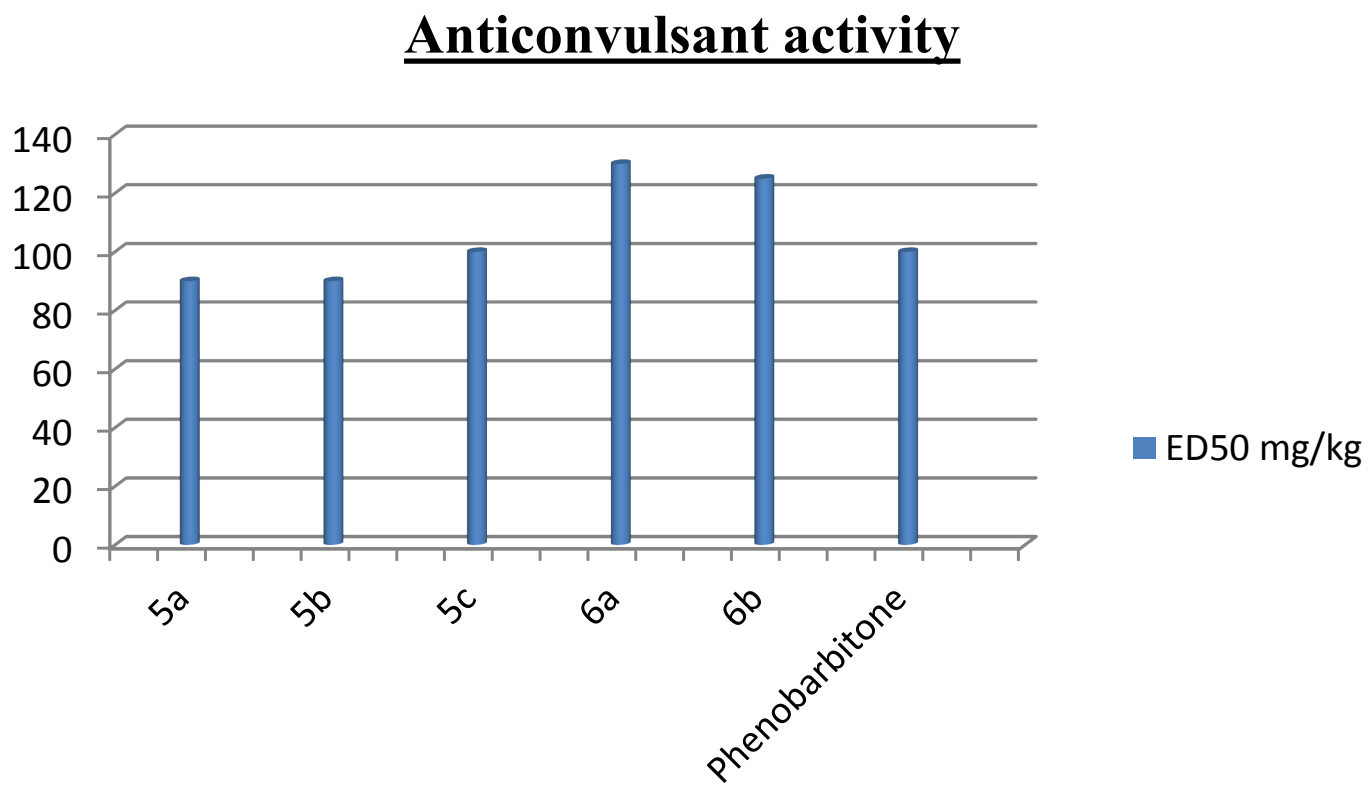

Figure 8. Activity of the new compounds due to its have more than aromatic and heteroatoms which these aromatic ring and heteroatoms.

Preliminary assessment of the anticonvulsant activity

The anticonvulsant activity of some phthalazinediones was assessed in frogs against pentylenetertrazole induced convulsion in comparison to phenobarbitone as a reference drug following the technique of Soaje-Echque 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 six Frogs 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 adminstration were considered to be protected. The percent protection, ED-50 (mg/kg) and or mmol/kg and the mean of the relative potency ± S.D. of the test compounds to phenobarbitone were calculated. The data are presented in Table 5 and Figure 8.

Conclusion

The new compounds which tested as anticonvulsant showed anticonvulsant activity compared with phenobarbitone as reference standard drug The activity of the new compounds due to its have more than aromatic and heteroatoms which these aromatic ring and heteroatoms have good binding with receptor so showed the anticonvulsant activity.

References

1. Rezk R. Ayyad, Ahmed M. Mansour and Ehab M. Mostafa design and synthesis of new compounds of phthalazindion and its anticonvulsant activity. *Med Chem* 10 (2020):8

2. Abdel-Ghany El-Helby, Helmy Sakr, Rezk Ayyad, and Hazem Mahdi, et al. Design, synthesis, molecular modeling, *in vivo* studies and anticancer activity evaluation of new phthalazine derivatives as potential DNA intercalators and topoisomerase II inhibitors." *Bioorganic Chemistry* 103 (2020): 104233.

3. Rezk R. Ayyad." Synthesis and biological evaluation of novel iodophthalazinedione derivatives as anticonvulsant agents." *Al-Azhar J Pharm Sci* (2012): 1-13.

4. Eldehna, Wagdy M, Sahar M. Abou-Seri, Ahmed M. El Kerdawy, and Rezk R. Ayyad, et al." Increasing the binding affinity of VEGFR-2 inhibitors by extending their hydrophobic interaction with the active site: Design, synthesis and biological evaluation of 1-substituted-4-(4-methoxybenzyl) phthalazine derivatives." *Eur J Med Chem* (2016): 50-62.

5. El-Helby, Abdel Ghany A, Rezk R. Ayyad, Helmy M. Sakr, and Adel S. Abdelrahim, et al." Design, synthesis, molecular modeling and biological evaluation of novel 2, 3-dihydrophthalazine-1, 4-dione derivatives as potential anticonvulsant agents." *J Mol Struct* (2017): 333-351.

6. El-Helby, Abdel-Ghany A, Rezk RA Ayyad, Helmy Sakr, and Khaled El-Adl, Mamdouh M. Ali, et al." Design, Synthesis, Molecular Docking, and Anticancer Activity of Phthalazine Derivatives as VEGFR-2 Inhibitors." *Archiv der Pharmazie* (2017): 1700240.

7. El-Helby, Abdel-Ghany A, Rezk RA Ayyad, Khaled El-Adl, and Hazem Elkady." Phthalazine-1, 4-dione derivatives as non-competitive AMPA receptor antagonists: design, synthesis, anticonvulsant evaluation, ADMET profile and molecular docking." Molecular Diversity 23 (2019): 283-298.

8. Eissa, Ibrahim H, Ahmed M. Metwaly, Amany Belal, and Ahmed BM Mehany, et al." Discovery and antiproliferative evaluation of new quinoxalines as potential DNA intercalators and topoisomerase II inhibitors." *Archiv der Pharmazie* 352 (2019): 1900123.

9. Ibrahim, Mohamed-Kamal, Ashraf A. Abd-Elrahman, Rezk RA Ayyad, and Khaled El-Adl, et al." Design and synthesis of some novel 2-(3-methyl-2-oxoquinoxalin-1 (2H)-yl)-N-(4-(substituted) phenyl) acetamide derivatives for biological evaluation as anticonvulsant agents." Bulletin of Faculty of Pharmacy, Cairo University 51 (2013): 101-111.

10. Elhelby, Abdelghany Aly, Rezk Rezk Ayyad, and Mohamed Fathalla Zayed." Synthesis and biological evaluation of some novel quinoxaline derivatives as anticonvulsant agents." Arzneimittelforschung 61 (2011): 379-381.

11. El-Helby, Abdel-Ghany A, Rezk RA Ayyad, Khaled El-Adl, and Alaa Elwan." Quinoxalin-2 (1H)-one derived AMPA-receptor antagonists: design, synthesis, molecular docking and anticonvulsant activity." *Med Chem Res* 26 (2017): 2967-2984.

12. El-Helby, Abdel-Ghany A, Rezk RA Ayyad, Mohamed F. Zayed, and Hamada S. Abulkhair, et al." Design, synthesis, *in silico* ADMET profile and GABA-A docking of novel phthalazines as potent anticonvulsants." *Archiv Der Pharmazie* 352 (2019): 1800387.

13. El-Helby, Abdel-Ghany A, Helmy Sakr, Rezk RA Ayyad, and Khaled El-Adl, et al." Design, Synthesis, *In vitro* Anti-cancer Activity, ADMET Profile and Molecular Docking of Novel Triazolo [3, 4-a] phthalazine Derivatives Targeting VEGFR-2 Enzyme." *Anti-Cancer Agent Med* 18 (2018): 1184-1196.

14. Mohd Nassar, Ekhlass, Fathy M Abdelrazek, Rezk R Ayyad, and Ahmed F. El-Farargy." Synthesis and some reactions of 1-aryl-4-acetyl-5-methyl-1, 2, 3-triazole derivatives with anticonvulsant activity." *Mini-Rev Med Chem* 16 (2016): 926-936.

15. Ayyad, Rezk." Synthesis and anticonvulsant activity of 6-iodo phthalazinedione derivatives." *Al-Azhar J Pharm Sci* 50 (2014): 43-54.

16. El-Helby, Abdel-Ghany A, M.K. Ibrahim, A.A. Abdel-Rahman, and R.R.A. Ayyad, M.A. Menshawy, and K. El-Adl." Synthesis, molecular modeling and anticonvulsant activity of benzoxazole derivatives." *Al-Azhar J Pharm Sci* 40 (2009): 252-270.

17. Rezk RA Ayyad, H Sakr, K El-Gamal. Synthesis, modeling and anticonvulsant activity of some phthalazinedione. *Am J Org Chem* (2016): 29-38.

18. Rezk RAAyyad. Synthesis and anticonvalsunt activity of tetrabromophthalazinedione. *AZ J Pharm Sci* (2008) 33-45.

19. El-Helby, Abdel-Ghany A, MK Ibrahim, MA Amin, and Rezk RA Ayyad. Synthesis and anticonvulsant activity of phthalazindione derivatives. *AZ J Pharm Sci* (2002): 22-35.

20. Ibrahim, M. K., A. A. Abdel-Rahman, R. R. A. Ayyad, K. El-Adl, F. Elsherbeny, and M. Rashed." Design and synthesis of some novel N-phthalimide derivatives with potential anticonvulsant activity." *Al-Azhar J Pharm Sci* 42 (2010): 305-22.

21. Alaa, A-M., Laila A. Abou-Zeid, Kamal Eldin H. El-Tahir, Rezk R. Ayyad, A-A. Magda, and Adel S. El-Azab." Synthesis, anti-inflammatory, analgesic, COX-1/2 inhibitory activities and molecular docking studies of substituted 2-mercapto-4 (3H)-quinazolinones." *Eur J Med Chem* 121 (2016): 410-421.

22. Mohamed, Menshawy A, Rezk R. Ayyad, Taghreed Z. Shawer, and A-M. Alaa, et al." Synthesis and antitumor evaluation of trimethoxyanilides based on 4 (3H)-quinazolinone scaffolds." *Eur J Med Chem* 112 (2016): 106-113.

23. Hall J.H., Hall E.S. and Wong O.T. Cumulated Index Medicus. *Anticancer Drug* (1992): 55-62.

24. Soje-Echaque, E. and Lim R.K.S. Inflammation and Anti-inflammatories. Spectrum, New York, USA. *J Pharmacol Exp Ther* (1962): 138-224.

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