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New Derivatives of 3-Substituted 5,5-Diphenyl-2,4-imidazolidinedione as Anticonvulsant and Antiepileptic Candidates

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ABSTRACT

New reliable synthetic method for the preparation of 3-substituted-5,5-diphenyl-2,4-imidazolidinedione derivatives, through Mannich reaction of phenytoin, small aldehydes or ketones, and amines. In this procedure it is possible to attach known biologically active molecules to the molecule of 5,5-diphenyl-2,4-imidazolidinedione through methylene bridge to give products with good yields. Many amines having straight or branched chain alkyl, or substituted aromatic ring, were found to follow this procedure, and the products were identified following available techniques such as ^{1}H and ^{13}C NMR, UV-visible and FT-IR absorption techniques, as well as elemental analysis. In all the cases paraformaldehyde was used as Mannich aldehyde of moderate reactivity, and the products obtained were white to yellow stable solids with good yields. These derivatives are good anticonvulsant and antiepileptic candidates.

Keywords: 3-substituted-5,5-diphenyl-2,4-imidazolidinedione derivatives, Mannich reaction, phenytoin, biologically active molecules to the molecule, methylene bridge, anticonvulsant and antiepileptic candidates.

INTRODUCTION

Dreyfus summarized the story of the discovery, and the use of phenytoin, 5,5-diphenyl-2,4-imidazolidinedione, in his book entitled "The Story of a Remarkable Medicine." **[1]**. Aside from seizures, it is an option in the treatment of *trigeminal neuralgia* as well as certain cardiac *arrhythmias* **[1-4]**. It was first synthesized by German physician Blitz in 1908 **[5]**, and sold it to Parke-Davis, which did not find an immediate use for it. In 1938, Merritt and Putnam discovered phenytoin's usefulness against electrically induced seizures in cats, without the sedative effects **[6]**.

More than 60 years since Merrit and Putnam demonstrated that phenytoin, the compound is still the drug of choice for the treatment of generalized tonic-clonic seizures (so-called grand mal epilepsy) and focal motor seizures [**2]**. Nowadays, phenytoin has found new applications due to the neuro-and cardioprotective properties **(3-4)**. This heterocycle is present in a wide range of biologically active compounds including antiarrhytmics **[7]**, anticonvulsant **[8]** and antitumor **[9]**. According to the results of recent studies, 5,5-diphenylhydantoin inhibits binding of human immunodeficiency virus (HIV) to lymphocytes **[10]**, affects hepatic hyroxine **[11]**, selectively enhances vincristine cytotoxicity **[12]**, affects myocardial contractivity

and hemodynamics **[13]**, and reduces pesticide residue in human adipose tissue **[14]**. Recently, new synthetic methods for several 5,5-diphenyl hydantoins were published, some have been prepared by microwave-assisted synthesis **[15]**, and the other were prepared in one pot procedure **[16]**. This work includes even much reliable synthesis of 3-substituted-5,5-diphenyl hydantoins through nucleophilic substitution, and Mannich reaction**[17,18]**. The aim of this study is to prepare new derivatives of 3-substituted-5,5-diphenyl-2,4-imidazolidinedione through Mannich reaction with few amines, which were not mentioned in our previous work. The investigation of their biological activities on local Iraqi bacteria species, as high study project, is already investigated **[19]**.

MATERIALS AND METHODS

Chemicals: Chemicals such as: paraformaldehyde from Ferfax, thiourea, Hydrazine sulfate, and hydroxylamine hydrochloride from Ferak, Berlin; ethanol amine from Koch Ltd, England; diphenylamine and sulfamic acid from R.D.H, 4-aminoantipyrine from Prolabo, France. Solvents and chemicals were used without purification.

Instruments: Products were characterized by U.V-visible, IR, NMR, TLC, and m.p.). Melting points were measured by Electrothermal melting point (BÜCHI 535) without correction. I.R spectra were recorded by using Pye-Unicom SP3-100 spectrophotometer as KBr discs, U.V-visible spectra were recorded with double beam scanning spectrophotometer Shimadzu U.V-Visible-1650. Elemental analysis were performed with Perkin Elmer C.H.N Elemental Analysis. ^{1}H and ^{13}C NMR spectra were recorded using Ultra Shield 300 MHz, Bruker, Switzerland, by using DMSO as solvent and TMS as reference. Shimadzu GC-Mass QP 1000 A Spectrometer was used for the determination of phenytoin mass spectrum.

Starting material and general methods: Benzoin, benzil, and phenytoin were prepared following the literature procedures **[20]**. The pale yellow product of benzoin was obtained in 90 % yield, m.p 137.1 °C (lit. 137 °C), benzil was then recrystallized from ethanol to give yellow crystals in 95 % yield, m.p 93-97 °C (lit. 94-96 °C), and phenytoin as white crystals 47.0 % yield, m.p 298-299 °C (literature 297-298 °C **[20]**.

General procedure for Mannich reaction: A mixture of 5,5-Diphenyl-2,4-imidazalidindione (5.0 g, 19.84 mmol), paraformaldehyde (0.58 g, 21.8 mmol), 50 mL of 95 % ethanol, and 21.8 mmol of one of the following amines (hydroxylamine hydrochloride, thiourea, diphenylamine, Hydrazine sulfate, 4-aminoantipyrine, sulfamic acid, procaine hydrochloride, 2-aminethanol) was refluxed for 2 h. Half of the solvent volume was removed by distillation, and distilled water was added (50 mL), and then the mixture was cooled to room temperature. The precipitate formed was filtered on sintered filter funnel under vacuum and washed with cold distilled water (two portion of 10 mL). The products were dried in an oven at 80 °C, and their physical properties were presented in tables1 and 2. All ^{1}H, and ^{13}C NMR data were recorded in $CDCl_3$, or DMSD-d_6 using a Bruker DMK-500 NMR Spectrophotometer 300-MHz spectrometer. Chemical shifts were reported in ppm (δ) using TMS as internal reference as the following:

Phenytoin (5,5-Diphenyl-imidazolidine-2,4-dione)(I): ^{1}H NMR (DMSO-d_6) δ: 10.7 (s, 1H, N-H), 8.9 (s, 1H, N-H), 7.2-7.8 (b, 10H, ArH); ^{13}C NMR (DMSO-d_6) δ: 156 (C_2=O), 173.7 (C_4=O), 75.52 (C_5), 150.22 (C_{Ar}), 129.56 (C_{Ar}), 128.41(C_{Ar}), 126.35(C_{Ar}),. Mass spectrum**:** m/z (% relative intensity) 252 ($M^{+\cdot}$ 3 %), 176 (30 %), 154 (100 %), 128 (3 %), 77 (15 %), 51 (8 %), and 39 (10 %).

3-[(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylamino)-ethyl]-,5-diphenyl-imidazolidine-2,4-dione (II): ^{1}H NMR (DMSO-d_6) δ: 6.4 (s, 1H, N-H), 2.2 (s, 2H, N-H), 1.72 (s, 3H, CH_3-Ar), 2.47 (s, 3H, CH_3-N), 6.7-7.2 (m, 15H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 160.5 (N-N-C=O), 57.4 (C_{CH2}), 15.2 (C_{CH3}), 35.5 (C_{CH3}-N), 161 (C_2=O), 169 (C_4=O), 73.2 (C_5=O), 143.22 (C_{Ar}), 129.41 (C_{Ar}), 129.2 (C_{Ar}), 128.56 (C_{Ar}), 126.35 (C_{Ar}), 142 (C_{Ar}), 112 (C_{Ar}), 119 (C_{Ar}), 116.4 (C_{Ar}).

(2-{4-[2,5-Dioxo-4,4-diphenyl-imidazolidin-1-ylmethyl)-amino]-benzyolamino}-ethyl)-diethyl-ammonium chloride (III): ^{1}H NMR (DMSO-d6) δ: 6.0 (s, 1H, N_1-H), 4.1 (s, 1H, N-H), 8.1 (s, 1H, N-H), 2.7, 3.32, and (q, 2H, CH_2), 2.4 (q, 4H, CH_2), 1.0 (t, 6H, CH_3), 6.6-7.2 (m, 14H, Ar-H).

3-[(2-Hydroxy-ethyl-amino)-methyl]-5,5-diphenyl-imidazolidine-2,4-dione (IV): DMSO-d6) δ: 10.7 (s, 1H, N-H), 8.9 (s, 1H, N-H), 7.2 (m, 10H, ArH); ^{13}C NMR (DMSO-d6) δ: 161.2 (C_2=O), 170 (C_4=O), 73.1 (C_5=O), 143.2 (C_{Ar}), 128.5 (C_{Ar}), 129.2 (C_{Ar}), 126.1(C_{Ar}), 60, 50, 64.5 (C_{CH2}).

3-[(Diphenylamino)-methyl-imidazolidine-2,4-dione (V): (DMSO-d_6) δ: 4.9 (s, 2H, CH_2), 6.0 (s, 1H, N-H), 6.6-7.2 (b, 20H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 161.3(C_2=O), 169.3 (C_4=O), 73.0 (C_5=O), 59.9 (CH_2), 49.5 (CH_2-N), 65.0 (CH_2-O), 143.2, 129.1, 128.5, 126.1 (C_{Ar}).

3-Hydrazinomethyl-5,5-diphenyl-imidazolidine-2,4-dione (VI): (DMSO-d_6) δ: 6.05 (s, 1H, N_1-H), 2.09 (s, 3H, N-N-H), 4.55 (s, 2H, CH_2), and 7.07-7.2 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 161.15 (C_2=O), 169.2 (C_4=O), 73.05 (C_5=O), 143.2 (C_{Ar}), 129.2 (C_{Ar}), 128.4 (C_{Ar}), 126.1(C_{Ar}), 63.9 (C_{CH2}).

(2,5-Dioxo-4,4-diphenyl-midazolidin-1-ylmethyl)-thiourea (VII): (DMSO-d_6) δ: 6.05 (s, 1H, N_1-H), 2.0 (s, 3H, N-C=S), 4.5 (s, 2H, CH_2), and 7.06-7.17 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 161.2 (C_2=O), 169.0 (C_4=O), 73.14 (C_5=O), 143.0 (C_{Ar}), 129.02 (C_{Ar}), 128.4 (C_{Ar}), 126.11(C_{Ar}), 60.09 (C_{CH2}).

3-Hydroxyaminomethyl-5,5-diphenyl-imidazoldine-2,4-dione (VIII): (DMSO-d_6) δ: 6.05 (s, 1H, N_1-H), 2.03 (s, 2H, NH-O), 2.00 (s, 1H, N-OH), 4.55 (s, 2H, CH_2), and 7.06-7.2 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 161.2 (C_2=O), 169.2 (C_4=O), 73.05 (C_5), 143.0 (C_{Ar}), 129.0 (C_{Ar}), 128.4 (C_{Ar}), 126.01(C_{Ar}), 62.8 (C_{CH2}).

(2,5-Dioxo-4,4-diphenyl-imidazolin-1-ylmethyl)-sulfamic acid (IX): (DMSO-d_6) δ: 6.0 (s, 1H, N_1-H), 2.0 (s, 1H, NH-S), 2.0 (s, 1H, HO-S), 4.53 (s, 2H, CH_2), and 7.06-7.14 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 161.2 (C_2=O), 169.2 (C_4=O), 73.05 (C_5), 143.0 (C_{Ar}), 129.0 (C_{Ar}), 128.4 (C_{Ar}), 126.01(C_{Ar}), 62.8 (C_{CH2}).

The FT-IR of these compounds were presented in table 3.

Table 1. Physical properties of the new derivatives of 3-substituted 5,5-diphenyl-2,4-imidazolidinedione prepared from Mannich reaction.

No.	Formula	Mol. Wt.	U.V		M.p (˚C)	Yield (%)
			λ (nm)	Є (l.mol^{-1})		
I	$C_{15}H_{12}N_2O_2$	252.27	247	3042	298-299 ℃	47.0
II	$C_{29}H_{33}N_5O_3$	499.60	247, 304	4838.6, 4383.2	232.5-234.5	75.0
III	$C_{18}H_{19}N_3O_3$	325.36	234	3042	184.5-186.0	60.0
IV	$C_{17}H_{16}N_4O_2S$	340.40	239	3381.4	243.5-245.0	73.5
V	$C_{16}H_{15}N_3O_3$	297.31	247	3023	164.5-166.0	55.5
VI	$C_{28}H_{23}N_3O_2$	433.50	244	4649.2	212.0-213.5	78.0
VII	$C_{16}H_{16}N_4O_2$	296.13	252	3013.2	256.0-256.5	61.0
VIII	$C_{27}H_{25}N_5O_3$	467.52	299, 240	4500, 4885.7	210.5-213.0	76.5
IX	$C_{16}H_{15}N_3O_5S$	361.37	246	3739.5	264.0-264.5	66.0

Table 2. Elemental analysis of the new derivatives of 3-substituted 5,5-diphenyl-2,4-imidazolidinedione prepared from Mannich reaction.

No.	Formula	Mol. Wt.	C %		H %		N %	
			Meas.	Calc.	Meas.	Calc.	Meas.	Calc.
I	$C_{13}H_{12}N_2O_2$	252.27	71.78	71.42	4.91	4.79	10.05	11.10
II	$C_{29}H_{33}N_5O_3$	467.52	69.54	69.72	6.23	6.66	14.14	14.02
III	$C_{29}H_{38}ClN_5O_3$	325.36	65.07	64.98	6.24	6.39	12.85	13.06
IV	$C_{17}H_{16}N_4O_2S$	340.40	59.65	59.98	4.56	4.74	16.46	16.46
V	$C_{16}H_{15}N_3O_3$	297.31	64.51	64.64	5.10	5.09	14.12	14.13
VI	$C_{28}H_{23}N_3O_2$	433.50	77.23	77.58	5.40	5.35	9.70	9.69
VII	$C_{16}H_{16}N_4O_2$	296.13	64.80	64.85	5.56	5.44	18.95	18.91
VIII	$C_{27}H_{25}N_5O_3$	467.52	69.58	69.36	5.43	5.39	14.35	14.98
IX	$C_{16}H_{15}N_3O_5S$	361.37	53.22	53.18	4.23	4.18	11.55	11.63

Table 3. The FT-IR absorption bands of the functional groups for 3-substituted 5,5-diphenyl-2,4-imidazolidinedione.

#	$\upsilon_{C=O}$ (cm^{-1})	υ_{N-H} (cm^{-1})	υ_{C-H} (cm-1) (Aromatic)	$\upsilon_{C=C}$ (cm^{-1}) (Aromatic)	υ_{C-H} (cm^{-1}) (Aliphatic)	Others υ cm^{-1}
I	1772 (imido) 1741(amido)	3270 (imido) 3204 (amido)	3050	1597, 1541, and 1508	2850	-
II	1700(amido)	-	3050	1440	2850	$\upsilon_{(N-N)}$ $\upsilon_{(C=C)}$
III	1750, 1700 (amido)	-	3000	1500 1450	2800	$\upsilon_{(C=O)}$: 1715 $\upsilon_{(C-O)acid}$: 1220 $\upsilon_{(O-H)out\ of\ plan}$: 930
IV	1700(amido)	3275	3050	1600 1550	2960 2850	$\upsilon_{(O-H)}$: 1430-1340 $\upsilon_{(C=O)ester}$: 1740, $\upsilon_{(C-O)ester}$: 1220
V	1700(amido)	3260	3050	1600 1500	2860 2850	$\upsilon_{(O-H)}$: 1420-1330 $\upsilon_{(-CH2-)}$: 720
VI	1690 (amido)	3240	3020	1600 1580	2850	$\upsilon_{(C=O)ketone}$: 1720
VIII	1740(amido)	3230	3040	1600 1500	2840	$\upsilon_{(C-Br)}$: 660 $\upsilon_{(-CH2-)}$: 722
IX	1700(amido)	3250	3050	1600 1550	-	$\upsilon_{(Ar-Cl)}$:1096-1086, 800

RESULTS AND DISCUSSION

The most straight forward condition for the synthesis of phenytoin, 5,5-diphenyl-2,4-imidazolidinedione, is the base-catalyzed condensation using benzil and urea, as shown in figure 1, known as the Biltz synthesis of phenytoin **[5]**. It consists of the condensation of benzil with urea in much step preparation to end with phenytoin. Bucherer–Bergs procedure is one of the general methods which are usually used for the synthesis of hydantoin **[20]**, in particular for the preparation of 5-substituted hydantoin derivatives containing a nonaromatic or one phenyl group. Unfortunately this is not the only product obtained; glycoureide was obtained from the condensation of one molecule of benzilic acid with two molecule of urea, as shown in Figure-2. The formation of glycoureide, a sparingly soluble molecule in water and alcohol, which posse's unknown biological activity, reduces the yield of the desired products, and complicate the purification procedure. The optimal ratio being 1:2 in order to minimize the formation of the side product, the glycolureide. Poupaert *et al*, previously reported that the use of a two-phase system

such as aqueous KOH/*n*-BuOH and Polyethylene glycol (PEG 600) as phase transfer catalyst drastically reduced the quantity of side product increasing the yield of phenytoin (87 - 93 %) **[22]**. The glycolureide was obtained as a single diastereomer possessing *cis* configuration **[14]**.

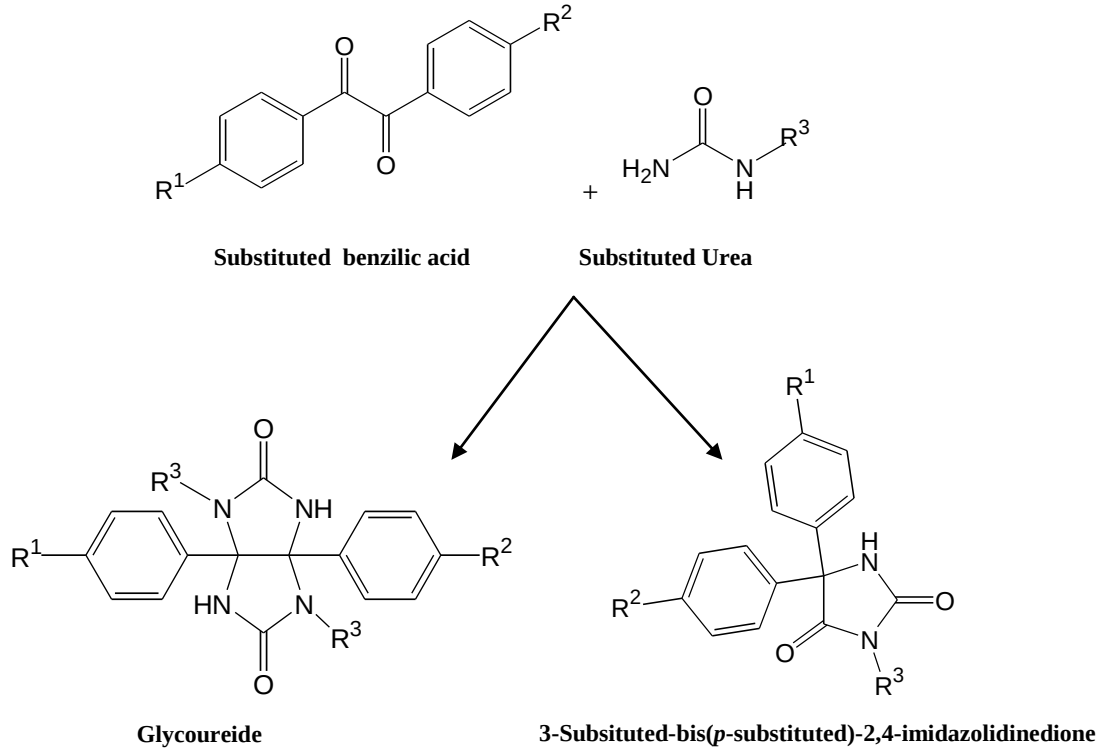


Figure 1. The common route for the preparation of 3-substituted 5,5-aryl substituted derivatives hydantoins such as 5,5-diphenyl-2,4-imidazolidinedione is through the condensation of one molecule of benzilic acid with one molecule of monosubstituted urea **[11, 16-18]**.

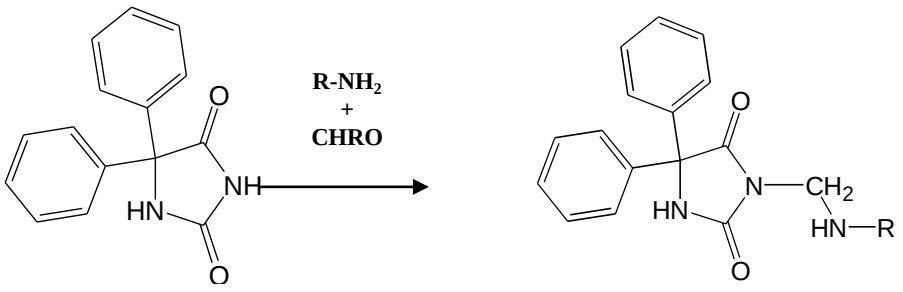
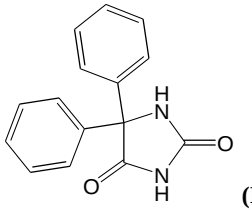


Figure 2. Preparation of many derivatives of the 3-substituted 5,5-diphenyl-2,4-imidazolidinedione through Mannich reaction.

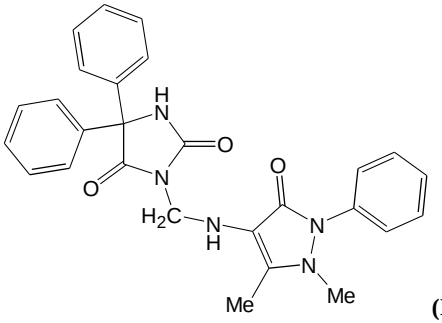
The most common reaction used to prepare 5,5-aryl substituted derivatives hydantoins such as 5,5-diphenyl-2,4-imidazolidinedione is through the condensation of one molecule of benzilic with one molecule of monosubstituted urea as shown in Figure-1 **[11, 16-18].**

The main objective of this work is the preparation of many derivatives of the 3-substituted 5,5-diphenyl-2,4-imidazolidinedione through Mannich reaction according to the following equation shown in Figure-2. This type of substitution will offer new compounds having the same main structure of the original

biologically active compound, with variety of side chains that can contribute different pharmacokinetic behavior. The procedure described in this work give a reliable synthesis of eight derivatives of 3-substituted-5,5-diphenyl-2,4-imidazolidinediones, in similar manner described in earlier work by our group **[17]**. Monosubstitution obtained on position-3 of the five-membered hydantoin ring, and no substitution took place at the nitrogen atom at position-1. The derivatives prepared by following this procedure were identified by their physical and chemical properties, such as elemental analysis, U.V-visible spectrophotometry presented in tables1 and 2. The chemical structures of these derivatives were presented in figure 3. Most of these derivatives were obtained as white crystals in a moderately good yield, and they are stable compounds at room temperature with relatively high melting points. According to the literature molecules having such structures were good candidates to be an antiarrhytmics , anticonvulsant and antitumor . It is worth mentioning that most of these preparations include products substituted at the phenyl functional groups, far away from the hydantoin ring connected with the biological activities. Such substitutions will dramatically change the nature of phenytoin. In our opinion that it will be much better to improve the activity of phenytoin by introducing side chains substitution for the many reasons. It will be possible to direct the phenytoin moiety towards different body organs by changing the type of substitutions on the hydantoin ring at the position of nitrogen-3.



(I)



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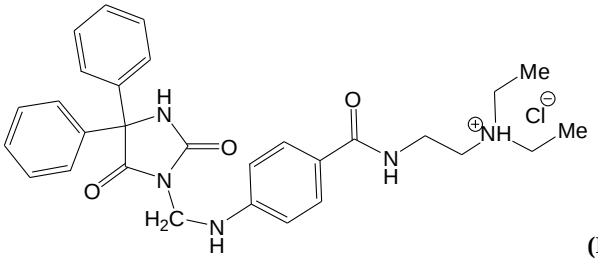

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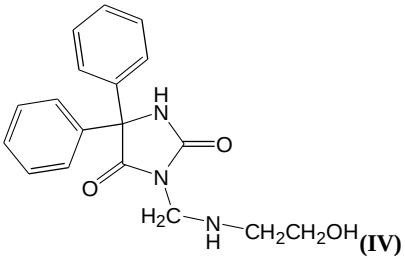

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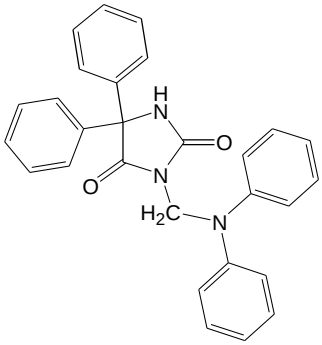

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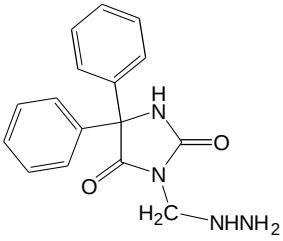

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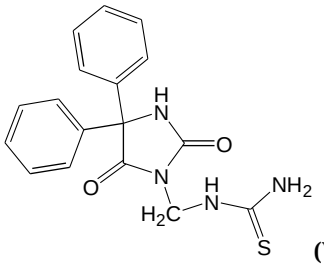

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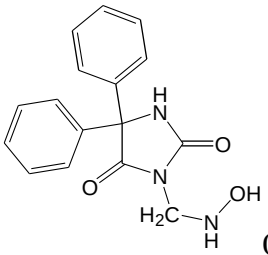

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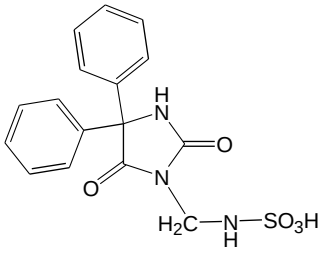

(IX)

Figure 3. The chemical structure of the new derivatives of 3-substituted 5,5-Diphenyl-imidazolidine-2,4-dione.

It will be possible to tune the pharmacokinetic behavior of phenytoin such as solubility, bioavailability, execration, and so on by changing the type of substitutions on the hydantoin ring. There will be no change concerning the structure of the diphenyl- substituted hydantoin ring, hence most of the well exanimate biologically activities will not be lost.

APPLICATIONS

The beneficiaries from this research will be the patients suffering from different symptoms of epilepsy, by reserving new pharmacological preparations of new 3-substituted-5,5-diphenyl-2,4-imidazolidinedione. The aim of this work is establish a procedure that can be used for industrial production.

CONCLUSIONS

New reliable synthetic method for the preparation of 3-substituted-5,5-diphenyl-2,4-imidazolidinedione derivatives, through Mannich reaction of phenytoin, small aldehydes or ketones, and amines. Many amines having straight or branched chain alkyl, or substituted aromatic ring, were found to follow this procedure. These derivatives are good anticonvulsant and antiepileptic candidates.

REFERENCES

[1] J.Jack Dreyfus, "*The Story of a Remarkable Medicine*.", Lantern Books, 2nd edition, **2000**.
[2] M.G.Chapman, M. Smith, N.P.Hirsch, *Anaesthesia*, **2001,**56(7),648-59.
[3] E.M.Manno, *Mayo Clin. Proc.*, **2003**, 78(4), 508-18.
[4] Nemanja Trisovic, Tamara Timic, Jovana Divljakovic, Jelena Rogan, Dejan Poleti, Miroslav M. Savic, Gordana and Uscumlic, *Monatsh Chem* ,**2012,** 143,1451-1457
[5] H. Biltz, *Ber*., **1908,** 41, 1379.
[6] T.J.Putnam, H.H.Merritt, *Science*, **1937,** 85, 525-526.
[7] J.Knabe, J. Baldauf, A. Ahlhem, *Pharmazie*, **1997,** 52, 912–919.
[8] S.Sholl, A. Koch, D. Henning, G. Kempter, E. Kleinpeter, *Struct. Chem*., **1999,** 10, 355–366.
[9] T.R.Rodgers, M.P. LaMontagne, A.Markovac, A.B.Ash, *J., Med. Chem.*, **1977,** 20, 591–594.

[10] W.M.Cloyd, S.W. Lynn, K. Ramsey,S. Baron, *Virology*, **1989,** 173(2), 581–590.
[11] O.S.Goussis, T.J. Theodropoulos, *Horm. Metab. Res.*, **1990,** 22, 42-344.
[12] K.L.Kawamura, D. Grabowski, K. Weizer, R. Bukowski, R.Ganapathi, *Brit. J. Cancer*, **1996,** 73(2), 183–188.
[13] S.P.Pvri, *Am. Heart. J*., **1971,** 82(10), 62–68.
[14] J.E.Davies, W.F. Edmundson, A. Macec, G.L. Irvin, J. Cassady,A. Barquet, *Food Cosmet. Toxicol*., **1971,** 9(3), 413–423.
[15] G.G.Muccioli, J.H. Poupaert, J. Wouters, B. Norberg, G.K.E. Wolfgang Poppitz, Scriba, D.M.Lambert, *Tetrahedron*, **2003** ,59,1301–1307.
[16] N.O. Mahmoodi,S. Emadi, *Russian J. of Organic Chem*., **2004**, 40(3), 377–382.
[17] Al-Shaia, O. N., "Synthesis, spectroscopic and Biological Activity Studies of Some New Phenytoin Derivatives.", *M. Sc. Thesis*, Al-Mustansiryah University, Baghdad, Iraq, **2001**.
[18] Al-Nemi, M. A-L., "Synthesis, spectroscopic and Biological Activity Studies of Some New 5,5-Diphenyl-2,4-imidazolidinedione Derivatives.", *M. Sc. Thesis*, Baghdad University, Baghdad, Iraq, **2002**.
[19] Saadi M. D. Al-Nuzal, S. S. Hussain, A. K. Khuder, and K. K. Gergees. *Journal of Al-Mustansiriya University*, **2007,** 2(1).
[20] A.I.Vogel, "*Text book of Practical Organic Chemistry*.", *5th Ed.*, Longman Scientific & Technical, **1989**.