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Synthesis and Characterization of New Derivatives of Metformin with Expected Anti-diabetic Effects

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Abstract

Metformin considered as a drug that widely used in the treatment of diabetes type-2 patients, and it is recommended for management of hyperglycaemia as the first-line agent. This research included the preparation of new derivatives of metformin 1-8 which contain in their composition both cyclic imide and metformin components with expected anti-diabetic effects, via two methods, the first involved reacting metformin with different anhydrides (maleic, succinic, citraconic, phthalic, pyridinic, , pyromillitic) in the presence of glacial acetic acid as a solvent and dehydrating agent. The second involved smelting of metformin with equimolar amount of anhydrides (1,8-naphthalicanhydride and 1,4,6,8-naphthalicdianhydride).The compositions of the synthesized compounds 1-8 were confirmed using FT-IR spectroscopy, ^{1}HNMR spectroscopy and elemental analysis (C, H, N, O), and the practical results were in agreement with the expected results.

Keywords: Cyclic imide, Metformin, Dimethylbiguanide, Diabetic, Anhydride

Introduction:

Diabetes is a common disease that affects large numbers of people around the world, numbering up to 45 million. It is associated with a heart disease and leads to chronic kidney disease [1- 4]. The high level of sugar in the blood (hyperglycemia) leads to the common symptoms of polyphagia polyuria, polydipsia, increase in heart attack or stroke, nerve problems and sexual dysfunction. Metformin has been used since ancient times as a first stage glucose-lowering drug in treatment of diabetes type (II).

By regulating the level of sugar in the blood, metformin reduces the production of the liver, reduces the absorption process in the stomach and small intestine, and helps reduce interferences and protect the body's sensitivity to insulin [5, 6].

Metformin considered as afirst line and backbone and recommended for treatment of diabetes type (II), where the level of absorption of this drug in the small intestine reaches its maximum level within an hour to three hours after oral use. And it is excreted at a high speed through the kidneys, where the elimination rate is four times of the elimination rate of creatinine when the functions of the urinary system are normal. [7-9]

In addition to its use in treatment of diabetes type(II), it was found that metformin has other therapeutic uses, such as treating cardiovascular disease, diabetic nephropathy, polycystic ovary syndrome, and gestational diabetes, anti –aging, and treatment of several type of cancer [10-15].

On the other hand, it was found that cyclic imides possess a wide spectrum of biological and pharmaceutical properties and activities such as analgesic, antibacterial, anticancer, anti-inflammatory and antifungal, and these encouraged researchers to prepare compounds containing this important part in their composition [16].

Experimental

Material and Methods

All chemicals used in the research were produced by sigma aldrich company, purchased from the market and used without additional purification.

The melting points of the prepared compounds were measured using a Gallenkamp apparatus and were uncorrected. SHIMADZN FTIR-8400 spectrophotometer was used to determine the infrared spectra using potassium bromide disk. Bruker ultrasheild 300 MHz apparatus was used for recording ^{1}HNMR spectra using trimethylsilane (TMS) as a reference (internal standard) and (DMSO-d_6) duterated dimethyl sulfoxide as a solvent.

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Synthesis of N-(N, N-dimethylcarbamimidoyl)-carbox- imidamide [1-5]

The titled compounds 1-5 were prepared according to the literature procedures [17, 18], with some modifications. A mixture of (succinic, maleic, straconic, phthalic, pyridinic) anhydride (0.01 mol) and metformin (A) (1.66g, 0.01 mol) in glacial acetic acid (50 mL), were refluxed for 8 hours at 140-160 ^{o}C. The obtaining solution was cooled to R.T. and then poured onto frozen distilled water (D.W.). The solid formed was filtered, washed by using sodium bicarbonate solution (25mL, 5%), dried and then recrystallized from ethanol. Physical properties that observed for compounds 1-5 are listed in Table (1).

Synthesis of N-(N, N-dimethylcarbamimidoyl)-1, 3-dioxo-1H-benzo[de]isoquin- oline -2(3H)-carbox-imidamide [6]

Equivalent molar quantities of 1,8-naphthalic anhydride (0.01 mol, 1.98g) and metformin (A)(0.01 mol, 1.66g) were smelted in a large pyrex tube on an oil bath for 2 hr. The product was poured hot into a wide watch glass, then it was ground , washed with a solution of sodium bicarbonate (25 mL, 5%) and then with distilled water and finally recrystallized from EtOH. Yield%; 83%, off white crystals, (MP = >300 ^{o}C), (500 MHz, using DMSO-d_6) ^{1}H-NMR; 6.67 ppm (s, 2H, -NH-), 7.21 ppm (s, 4H, C=NH), 3.10 ppm (s, 12H, -N(CH_3)$_2$), (8.04-8.80) ppm (m, 4H, Ar-H).

Synthesis of N2,N6-bis(N,N-dimethylcarbamimid-oyl)-1,3,5,7-tetraoxo-5,7-dihydropyrrolo[3,4-f]iso-indole-2,6(1H,3H)-bis(carboximidamide)[7]

Compound 7 was prepared via same method that used in preparation of compounds 1-5 by reaction of (0.0l mol) of pyromillitic anhydride and (0.02 mol) of metformin. Yield%; 87%, Yellow crystal, (MP = >300), (500 MHz, using DMSO-d_6) ^{1}H-NMR; 7.16 ppm (s, 1H, -NH-), 6.70 ppm (s, 2H, C=NH), 3.13 ppm (s, 6H, -N(CH_3)$_2$), (7.44-7.99) ppm (m, 6H, Ar-H).

Synthesis of N2,N7-bis(N,N-dimethylcarbamimidoyl)-1,3,6,8-tetraoxo-1,3,6,8-tetrahydrobenzo[lmn] [3,8]phenanthroline-2,7-bis(carboximidamide)[8]

The compound 8 was prepared via same method that used in preparation of compounds 6 by reaction of (0.0l mol) of 1,3,6,8-Naphthalenetetracarboxylicdianhydride and (0.02 mol) of metformin. Yellow crystal, Yield%; 68%, (MP = >300), (500 MHz, using DMSO-d_6) ^{1}H-NMR; 7.20 ppm (s, 2H, -NH-), 6.73 ppm (s, 4H, C=NH), 2.93 ppm (s, 12H, -N(CH_3)$_2$), (7.31- 8.02) ppm (m, 4H, Ar-H).

Physical properties of prepared compounds are listed in Table (1).

Result and Discussion

It is also known that both metformin and cyclic imides possess a wide range of biological activity and pharmaceutical applications. Therefore, the trend was towards preparing new compounds containing these two important parts, with the aim of restricting compounds that combine both characteristics of the two parts and improving their effectiveness. These compounds were prepared in two ways: either by direct reaction in a medium of glacial acetic acid with reflux or by smelting of metformin and the various anhydrides, as shown in the Scheme (1).

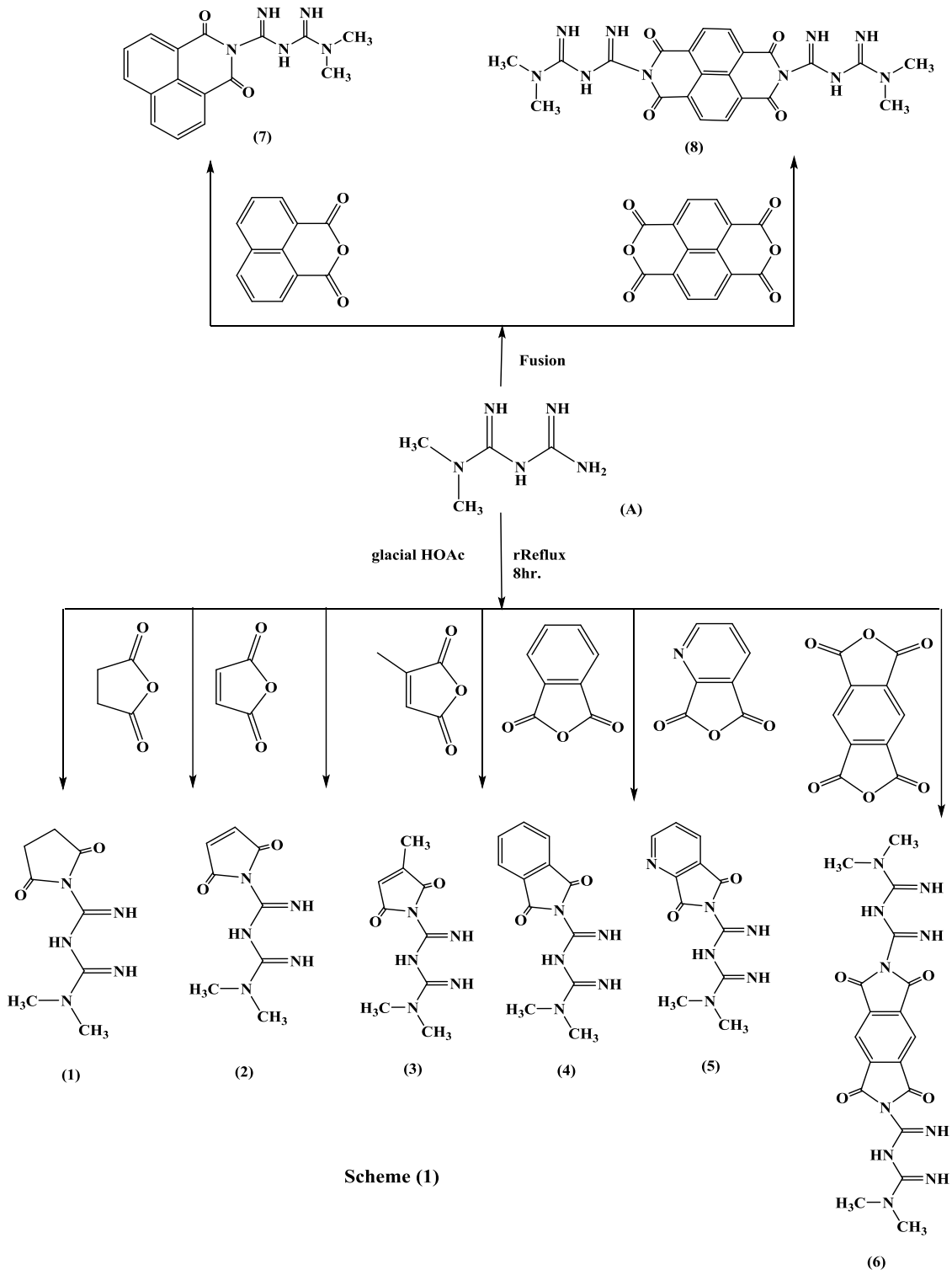
The infrared spectra of prepared compounds 1-8 showed distinct bands at (1697-1713) cm^{-1}, (332-392) cm^{-1}, (2914-2974) cm^{-1}, (3164-3187) cm^{-1}, (1475-1628) cm^{-1}, (1625-167) cm^{-1}, (1062-1078) cm^{-1} belong to ν(C=O), ν(N-H), ν(aliphatic C-H), ν(aromatic C-H), ν(C=C aromatic), ν(C=N), ν(C-N) respectively, with the disappearance of the package belonging to the amino group (NH_2) of metformin. This indicates definitely the composition of the desired compounds, as describe in Table 2.

^{1}HNMR spectrum of prepared compound (1) showed clear signals at δ = 2.93 ppm belong to two methylene groups (CH_2), δ = 3.12 ppm belong to (N(CH_3)$_2$), δ = 7.21 ppm belong to (NH) proton and δ = (6.67-6.69) ppm belong to (=NH) protons. On the other hand ^{1}HNMR spectrum of compound (2) showed characteristic signals at δ = 6.22 ppm due to two vinyl protons (-CH=CH-), δ = (3.07-3.16) ppm belong to (N(CH_3)$_2$), δ = 7.33 ppm belong to (NH) proton and δ = (6.84) ppm belong to (=NH) protons.[19,20]

^{1}HNMR spectrum of compound (3) showed signals at δ = 1.87 ppm due to (-CH_3) protons, δ = 5.89 ppm belong to vinylic proton (C=CH), δ = 3.20 ppm belong to (-N(CH_3)$_2$), δ = 7.61 ppm belong to (NH) proton and δ = (6.80-6.69) ppm belong to (=NH) protons.

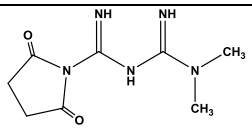
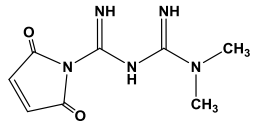
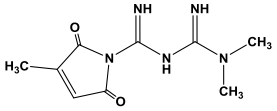
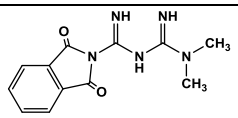
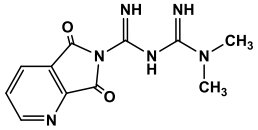
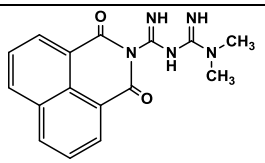
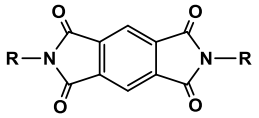
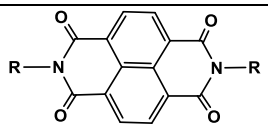
^{1}HNMR spectra of compounds (4-8) showed signals ranging between δ = (2.93-3.21) ppm, δ = (7.16-7.56) ppm, δ = (6.70- 6.67) ppm and δ = (7.44- 7.82) ppm belong to (-N(CH_3)$_2$), (NH), (=NH) and (Ar-H), respectively as shown inTable3.

Furthermore, the elemental analyses indicate that the results calculated in practice match with the theoretically calculated, and this indicates the accuracy of the prepared compounds, (see Table 4).



Scheme (1)

Table 1. Names, structure and physical data of the synthesized compounds 1-8.

Com. Numb.	Comp. Structure	Comp. name	Comp. color	%Yield	M p.
1		N-(N,N-dimethylcarbamimidoyl)-2,5-dioxopyrrolidine-1-carboximidamide	white	65	224-226
2		N-(N,N-dimethylcarbamimidoyl)-2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboximidamide	Off white	73	165-168
3		N-(N,N-dimethylcarbamimidoyl)-3-methylene-2,5-dioxopyrrolidine-1-carboximidamide	Faint yellow	67	170-172
4		N-(N,N-dimethylcarbamimidoyl)-1,3-dioxoisoindoline-2-carboximidamide	yellow	80	260-263
5		N-(N,N-dimethylcarbamimidoyl)-5,7-dioxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboximidamide	white	75	250-253
6		N-(N,N-dimethylcarbamimidoyl)-1,3-dioxo-1H-benzo[de]isoquinoline-2(3H)-carboximidamide	Off white	83	>300
7		N2,N6-bis(N,N-dimethylcarbamimidoyl)-1,3,5,7-tetraoxo-5,7-dihydropyrrolo[3,4-f]isoindole-2,6(1H,3H)-bis(carboximidamide)	yellow	87	>300
8		N2,N7-bis(N,N-dimethylcarbamimidoyl)-1,3,6,8-tetraoxo-1,3,6,8-tetrahydrobenzo[lmn][3,8]phenanthroline-2,7-bis(carboximidamide)	yellow	68	>300

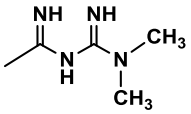
R = 

Table 2. Characteristic absorption bands of FT-IR for prepared compounds (1-8)

Com. Number.	υ (C=O) Carbonyl	υ (N-H)	υ (N-H) aliphatic	υ (C-H) Aromatic	υ (C=C) Aromatic	υ (C=N)	υ (C-N)
1	1699	3371	2937 2974	3170	1481 1568	1627	1064
2	1685	3367	2974	3178	1481 1585	1629	1062
3	1679	3392	2950 2970	3164	1475 1568	1629	1062
4	1679	3332	2802 2914	3095	1488 1606	1627	1072
5	1687	3345	2938 2925	3165	1477 1611	1625	1075
6	1712	3336	2945	3172	1484 1628	1630	1078
7	1693	3354	2972	3187	1482 1608	1634	1067
8	1713	3348	2968	3173	1479 1617	1637	1073

Table 3. ^{1}HNMR data (ppm) of the prepared compounds.

Chemical Shift (ppm)					
Com. No.	Ar-H(m)	=NH (s)	-$(CH_3)_2$ (s)	NH (s)	other
1	---	6.67-6.69	3.12	7.21	$C\underline{H}_2$(m) 2.93
2	---	6.84	3.07-3.16	7.33	C=$\underline{C}$H (d)
3	---	6.80-6.69	3.20-3.43	7.61	=C-$C\underline{H}_3$(s) 1.87-1.96 C=C$\underline{H}$ (s) 5.89-5.98
4	7.82-8.65	7.19-7.38	3.12-3.21	7.49	---
5	8.26-9.07	7.09-7.23	2.93-3.03	7.54	---
6	8.04-8.80	6.67-6.75	3.03-3.06	7.48	---
7	7.44-7.99	6.70	2.63-3.13	7.34	---
8	7.31-8.02	6.73	2.75-2.93	7.20	---

Table 4. Elemental analysis for prepared compounds (1-8)

No. comp.	Molecular formula / Molecular Weight	% C		% H		% O		%N	
		Cal. %	Found%	Cal. %	Found%	Cal. %	Found%	Cal. %	Found%
1	$C_8H_{13}N_5O_2$ 211.23	45.49	45.53	6.20	6.53	15.15	14.41	33.16	33.53
2	$C_8H_{11}N_5O_2$ 209.21	45.93	46.42	5.30	5.74	15.29	13.89	33.48	33.86
3	$C_9H_{13}N_5O_2$ 223.24	48.42	48.93	5.87	6.26	14.33	13.07	31.37	31.74
4	$C_{12}H_{13}N_5O_2$ 259.27	55.59	56.23	5.05	5.91	12.34	10.74	27.01	27.39
5	$C_{11}H_{12}N_6O_2$ 260.26	50.77	51.22	4.65	5.23	12.29	10.99	32.29	32.56
6	$C_{16}H_{15}N_5O_2$ 309.33	62.1	62.72	4.89	5.26	10.34	10.51	22.64	22.87
7	$C_{18}H_{20}N_{10}O_4$ 440.42	49.09	49.65	4.58	4.87	14.53	13.27	31.80	32.21
8	$C_{22}H_{22}N_{10}O_4$ 490.48	53.87	54.12	4.52	4.74	13.05	12.25	28.56	28.89

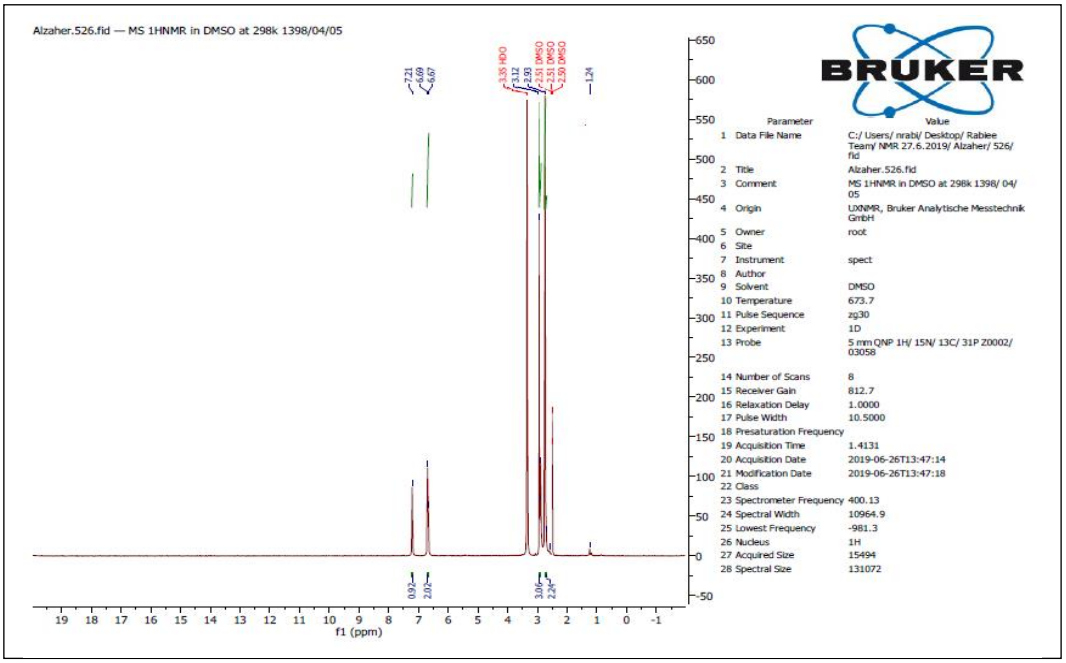


FIGURE.1 ^{1}HNMR spectrum for compound (1)

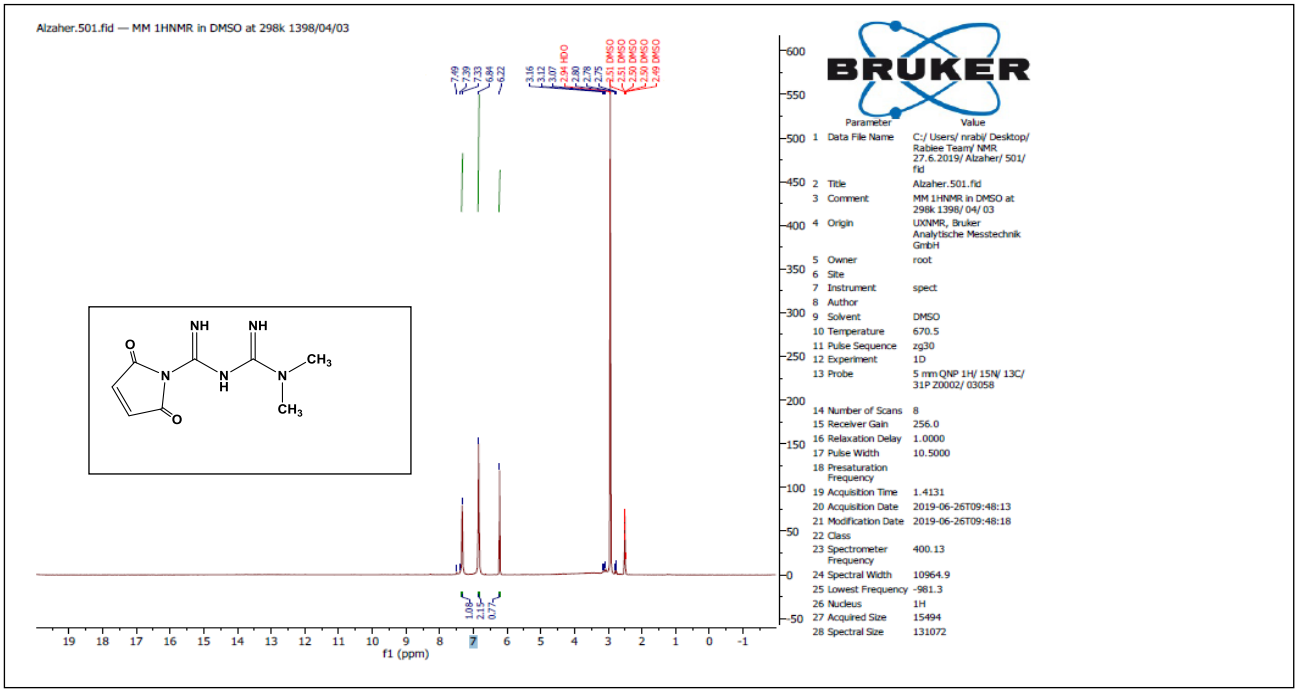


FIGURE.2 [1]HNMR spectrum for compound (2)

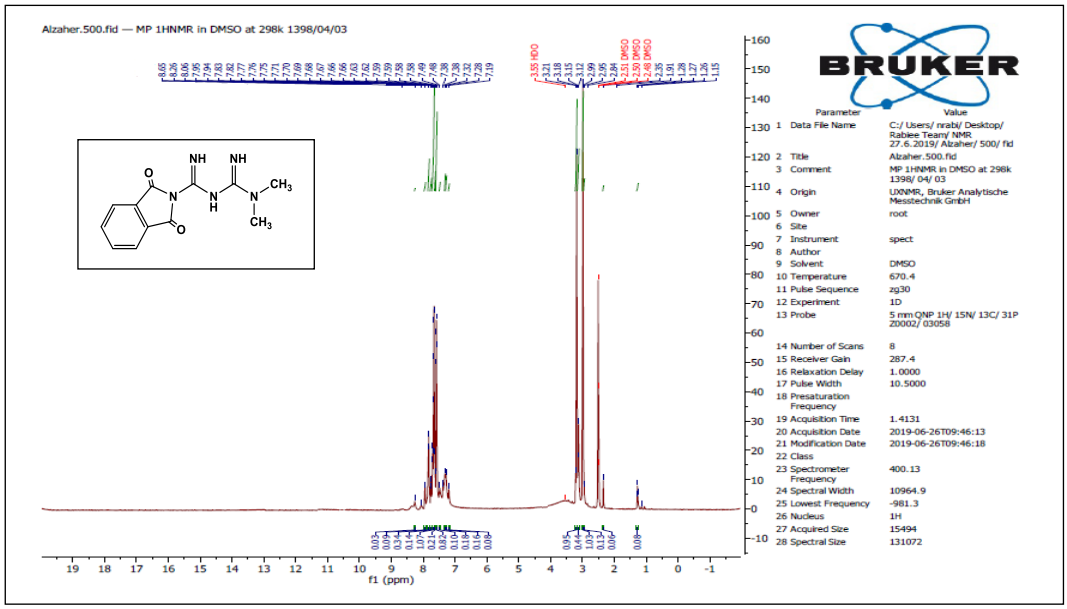


FIGURE.3 [1]HNMR spectrum for compound (4)

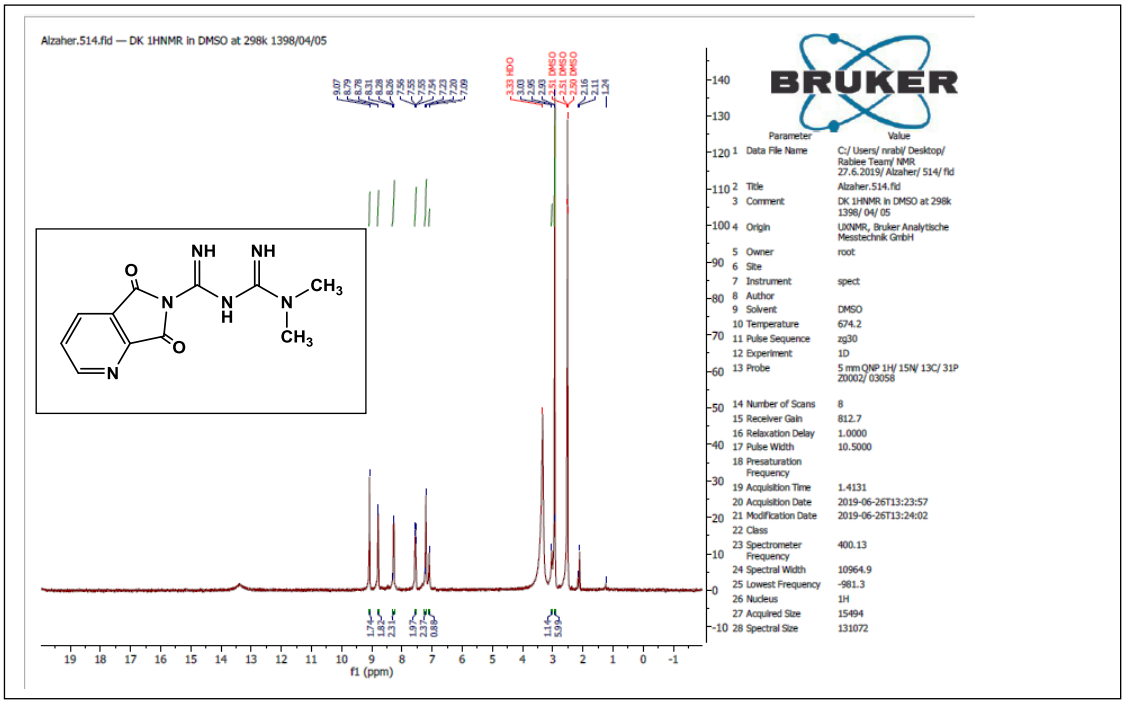


FIGURE.4 [1]HNMR spectrum for compound (5)

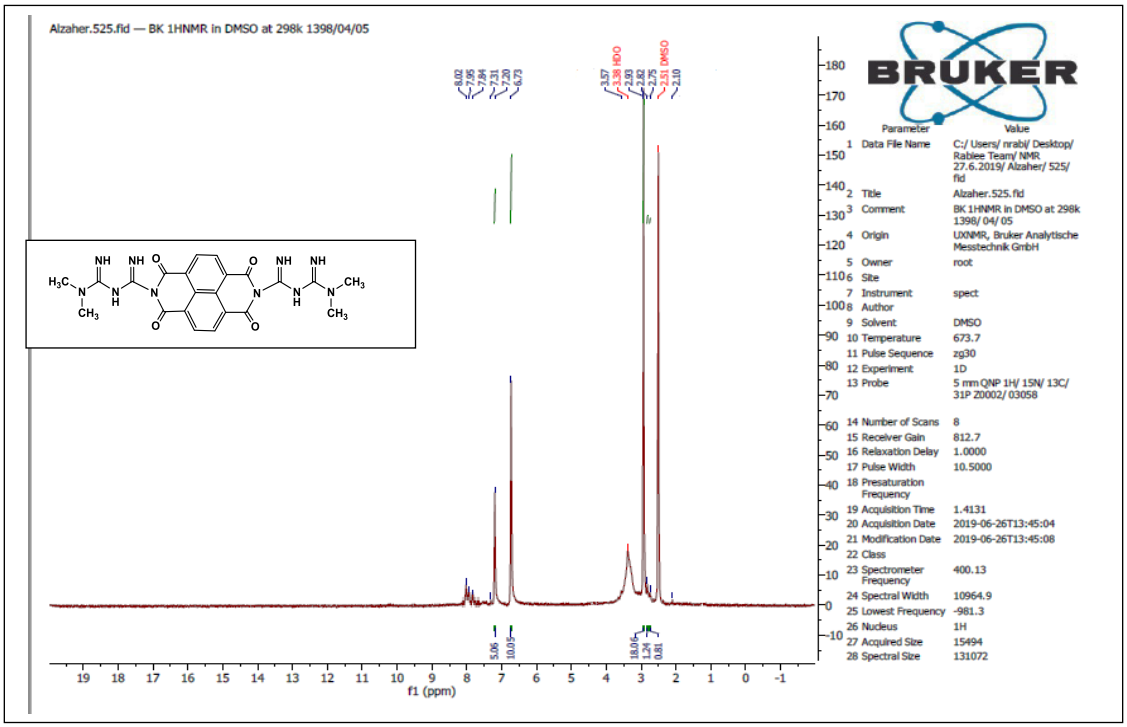


FIGURE.5 [1]HNMR spectrum for compound (8).

Conclusion

New compounds were prepared from the interaction of metformin with different anhydrides in the aim of obtaining compounds bearing both moieties of metformin and cyclic imide to obtain a variety of activity. The validity of the prepared compounds was verified by measuring melting points and using infrared and nuclear magnetic resonance spectroscopy in addition to elemental analysis. The study revealed the correctness of the composition of the prepared compounds.

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تحضير وتشخيص مشتقات جديدة للمتفورمين ذات فعالية متوقعة مضادة لمرض السكر

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الخلاصة

يعتبر الميتفورمين من الادوية المهمة حيث يستخدم على نطاق واسع في علاج مرضى السكري من النوع الثاني ، ويوصى به لعلاج ارتفاع السكر في الدم كعلاج للخط الأول. تضمن هذا البحث تحضير مشتقات جديدة من الميتفورمين (1-8) تحتوي في تركيبتها على كل من مكونتي الإيميد الحلقي والميتفورمين التي يتوقع ان تكون لها فعالية مضادة لمرض السكري ، عبر طريقتين :

تضمنت الطريقة الأولى تفاعل الميتفورمين مع أنهيدريدات مختلفة (الماليك، السكسينيك ، السيتراكونيك ، الفتاليك، البايريدينيك، البايروميليتيك) باستعمال حمض الخليك التلجي كمذيب وعامل مجفف.

اما الطريقة الثانية فتضمنت صهر كميات مولية متكافئة من الميتفورمين و أنهيدريدات (1،8- انهيدريد النفثاليك و 1،4،6،8- ثنائي انهيدريد النفثاليك). تم التأكيد من صحة تراكيب المركبات المحضرة (1-8) باستخدام مطيافيتي الاشعة تحت الحمراء(FT-IR) و الرنين النووي المغناطيسي (^{1}HNMR) وتحليل العناصر (C، H، N، O) ، وكانت النتائج العملية متوافقة مع النتائج المحسوبة المتوقعة.