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Synthesis and some Hetero cyclic compounds containing O,N from benzidine

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Abstract

In this research, a multistep reaction path produced a number of new heterocyclic derivatives. First, the appropriate thiourea derivatives (G1, G2) were condensed from substituted aryl isothiocyanates (R = 4-CH_3, 4-OCH_3) with benzenidine. Then, in dry toluene under reflux, yellow mercury (II) oxide (HgO) was applied on these intermediates, producing the carbodiimide derivatives (G3, G4). Treatment of G3 and G4 with anthranilic acid in acetic acid to generate quinazoline-4-one derivatives (G5, G6) followed cyclization reactions; reaction with salicylic acid in ethanol produced benzo-1,3-oxazin-4-one derivatives (G8, G9). At last, appropriate hydrolysis of G5 and G8 under basic conditions (NaOH/H_2O) resulted in the synthesis of quinazoline-3,4-dione (G7) and a novel benzo-1,3-oxazine-4-one (G10), respectively. FT-IR, $^1H/^{13}C$ NMR, and mass spectrometry characterization of all produced compounds confirmed their structural identities. This study offers an effective pathway to biomedically pertinent heterocycles, with possible uses in materials chemistry and medicine.

Keywords: Benzenidine, carbodiimide, quinazoline-4-one, benzo-1,3-oxazine-4-one, heterocyclic synthesis

تكوين بعض المركبات الحلقية غير المتجانسة المحتوية على O,N من البنزيدين

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الملخص

في هذا البحث، أنتج مسار تفاعل متعدد الخطوات عددًا من مشتقات حلقية غير متجانسة جديدة. أولًا، تم تكثيف مشتقات الثيويوريا المناسبةG1) ، (G2من إيزوثيوسيانات الأريل المستبدلة(R = 4-CH_3 ، 4-OCH_3)مع البنزينيدين. بعد ذلك، في التولوين الجاف تحت تأثير الارتجاع، طُبّق أكسيد الزئبق الأصفر (HgO)على هذه المركبات الوسيطة، مما أدى إلى إنتاج مشتقات الكاربوديميدG3) ، .(G4تبع معالجة المركبين G3 و G4بحمض الأنثرانيليك في حمض الأسيتيك لتوليد مشتقات الكينازولين-4-ونG5) ، (G6 تفاعلات حلقية؛ وأدى التفاعل مع حمض الساليسيليك في الإيثانول إلى إنتاج مشتقات البنزو-3،1-أوكسازين-

4-ون(G8) ، .(G9وأخيرًا، أدى التحلل المائي المناسب للمركبين G5 و G8في ظل ظروف قاعدية (NaOH/H₂O)إلى تكوين الكينازولين-4،3-ديون (G7) وبنزو-3،1-أوكسازين-4-ون جديد(G10) ، على التوالي. وقد أكدت توصيفات جميع المركبات الناتجة باستخدام تقنية تحويل فوربيه للأشعة تحت الحمراء (FTIR)، والرنين المغناطيسي النووي $^{1}H/^{13}C$، ومطياف الكتلة، هوياتها البنيوية. تُقدم هذه الدراسة مسارًا فعالًا لتطوير حلقات غير متجانسة ذات صلة بالطب الحيوي، مع استخدامات محتملة في كيمياء المواد والطب. الكلمات المفتاحية: بنزينيدين، كاربوديميد، كينازولين-4-ون، بنزو-3،1-أوكسازين-4-ون، تكوين حلقي غير متجانس

Introduction

The biological activities which contribute to the medical value of quinazolin-2,4-diones and pyrimidines include antihypertensive effects and anti-inflammatory properties in addition to roles in vasodilatory actions [1–6]. Research indicates that quinazolin-2,4-dione compounds can block Wnt-β/catenin pathway activation which makes them potential treatments for aggressive cancer manifestations such as glioblastoma multiforme [7] . The structural malleability of these compounds makes them suitable for interacting with important biological receptors like serotonin, dopamine, adrenergic receptors and enzymatic targets aldose reductase and carbonic anhydrase [8]. .

Traditional synthesizing methods for quinazolin- 2,4 -diones and benzooxazine- 4 -ones encounter multiple-step procedures and methods using expensive materials while requiring restrictive conditions which produces minimal final yields [9,10]. Their therapeutic value in treating hypertension [11] and bacterial diseases [12] leishmaniasis [13], epilepsy [14], depression [15]and diabetes [16,17]. maintains quinazolin- 2,4 -diones and benzooxazine- 4 -ones under constant medical research focus. Modern scientific studies indicate that these organic compounds possess inhibitory properties toward α-glucosidase and α-amylase enzymes which could help develop new type 2 diabetes treatment methods [18,19].

Benzo-1,3-oxazine-4-one derivatives were produced during our research (G5, G6) through the reaction of salicylic acid with bis-thiourea biphenyl intermediates (G3, G4). The preparation pathway utilizes classic reflux conditions of dry benzene for 20 hours followed by ethanol recrystallization yet recent research demonstrates advancing sustainability by employing environmentally friendly methods such as isocyanate cyclization[20] and microwave-based solventless reactions[21] as well as acyl chloride activators. [22].

Experimental

Synthesis of substituted of thiourease(1,2) [23]

A solution of 1-butyl isothiocyanate (0.2 mol, 23 g) or 1-phenyl isothiocyanate (27 g) in 100 mL of diethyl ether was prepared. To this solution, a mixture of benzidine (0.2 mol, 36.8 g) dissolved in 50 mL of diethyl ether was added. The reaction mixture was stirred at room temperature for 5 hours. Upon completion, the solvent was evaporated under reduced pressure to yield the desired product. The physical constants are shown in Table(1).

Table (1): physical constants for compounds(G1-G2)

Comp. No.	Molecular Formula	Molecular Weight	M.P. (°C)	Yield	Color
G1	$C_{22}H_{30}N_4S_2$	414.64	280	90%	Light Green
G2	$C_{26}H_{22}N_4S_2$	454.61	<300 (dec.)	92%	White

Synthesis of substituted of Carbodiimide(3,4) [23]

A solution of compound G39-40 (0.062 mol) was prepared in 90 mL of dichloromethane (DCM). Yellow mercuric oxide (0.25 mol, 54 g) was added to the solution and the reaction mixture was stirred for 20 hours. An additional portion of yellow mercuric oxide (0.25 mol, 13.4 g) was added and stirring continued for another 12 hours. The mixture was filtered and the solvent was removed under reduced pressure to afford the desired product. The physical constants are shown in Table(2).

Table (2): physical constants for compounds(G3-G4)

Comp. No.	Molecular Formula	Molecular Weight	M.P. (°C)	Yield	Color
G3	$C_{22}H_{26}N_4$	346.48	162–164	88%	Brown
G4	$C_{26}H_{18}N_4$	386.46	128–130	89%	Light Brown

3. Bis[2,N(substituted)imino quinazoline-2,4dione]-3-3'-biphenyl(5,6)[24]

Anthranilic acid (0.05 mol, 7 g) was added to compound G3 or G4 (0.133 mol, 19.6 g) in 25 mL of dry benzene. The mixture was left at room temperature for 3 hours, then refluxed for 20 hours. After cooling, the solution was filtered and the filtrate was evaporated under reduced pressure. The obtained product was recrystallized from ethanol. The physical constants are shown in Table(3)

Table (3): physical constants for compounds(G5-G6)

Comp. No.	Molecular Formula	Molecular Weight	M.P. (°C)	Yield	Color
G5	$C_{36}H_{36}N_6O_2$	584.72	140	94%	Light Green
G6	$C_{40}H_{28}N_6O_2$	624.70	171–173	87%	Light Yellow

Bis[quinazoline-2,4dione]-3- 3'-biphenyl(7) [24]

Compound(G5)was fluxed for 5 hours in 10% sulfuric acid in ethanol. The reaction mixture was concentrated using a rotary evaporator and the residue was washed with hot 1% sodium carbonate solution to obtain the desired product, The physical constants are Molecular Formula: $C_{28}H_{16}N_2O_6$,M.wt:476.44, M.P. (°C)= 190 , 93% , Color: Green

Bis[2,N(substituted)imino quinazoline-1,3 benzoxazine2,4-one]-3-3'-biphenyl(8,9) [25]

Salicylic acid (0.05 mol, 7 g) was added to compound G3 or G4 (0.133 mol, 19.6 g) in 25 mL of dry benzene. The mixture was left at room temperature for 3 hours, then refluxed for 20 hours. After cooling, the solution was filtered and the filtrate was evaporated under reduced pressure. The obtained product was recrystallized from ethanol., the corresponding compounds were obtained. The physical constants are shown in Table(4).

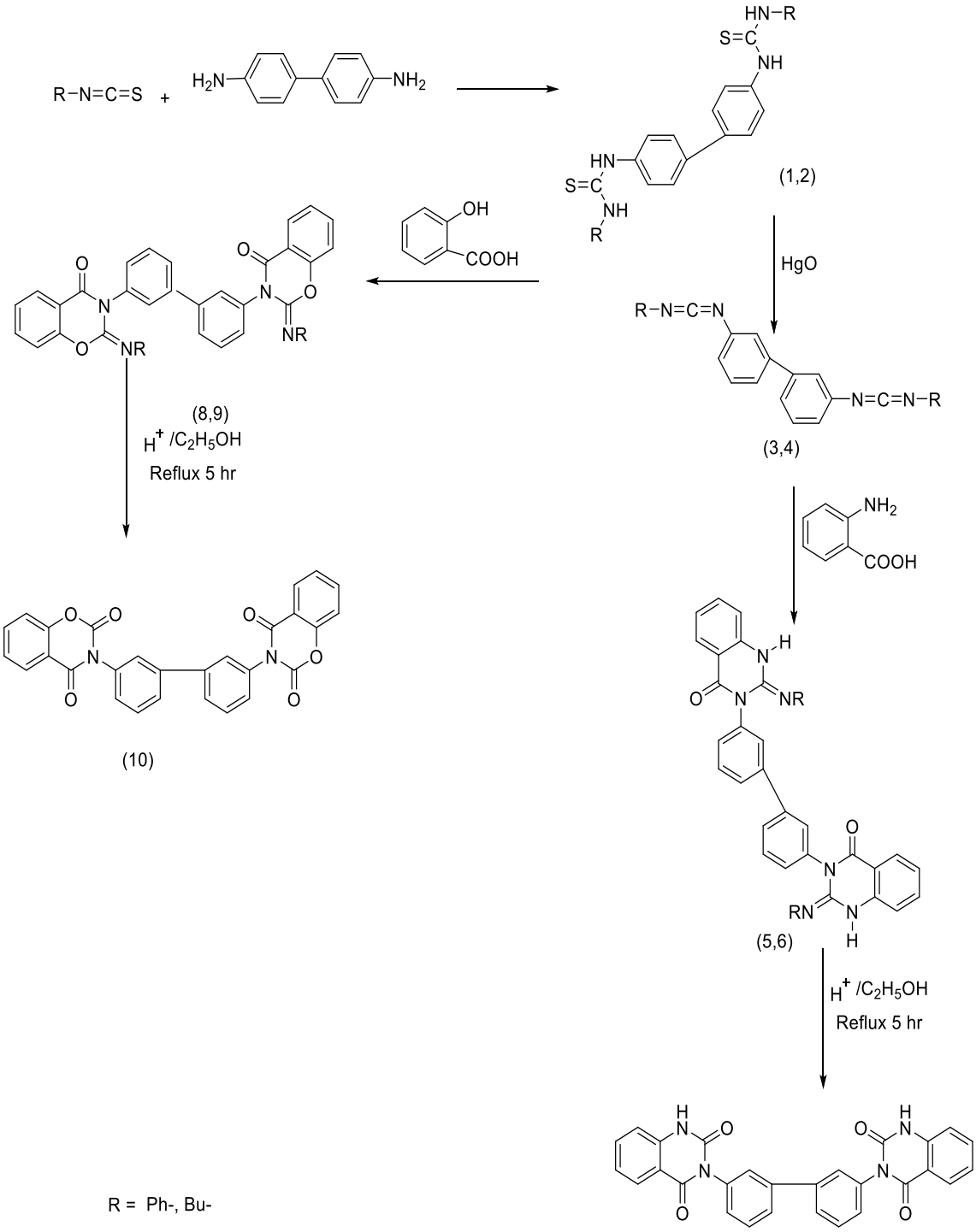
Table (4): physical constants for compounds(G8-G9)

Comp. No.	Molecular Formula	Molecular Weight	M.P. (°C)	Yield	Color
G8	$C_{36}H_{34}N_4O_4$	586.69	285	90%	Light Yellow
G9	$C_{40}H_{26}N_4O_4$	626.67	<300 (dec.)	91%	White

Bis[1,3 benzoxazine2,4-one]-3-3'-biphenyl(10) [25]

Compound (G8)was refluxed in 100 mL of water for 5 hours. The reaction mixture was then concentrated using a rotary evaporator, and the residue was filtered to

afford the target compound. The physical constants are Molecular Formula: $C_{28}H_{18}N_4O_4$,M.wt: 474.48, M.P. (°C)= 160, 86% , Color: White



Results and Discussion

Scheme(I): Synthesis Compounds (G1-G10)

In this research thiorase (G1,G2) substitutes were prepared from isothiocyanate substitutes reactor with gasoline and were diagnosed using the IR spectrum where the C = S insistent mat was obtained)) at range (1248-1241) cm-1 as well as insistent duct frequency (C = C) at range (1496-1652) and frequency (C-H) alphatist at range (3009-3010) cm^{-1} and insistent frequency (N-H) at range) 3197-3242) cm^{-1} and hence these compounds were reduced using yellow mercury oxide to create corresponding carbodiemide substitutes (G3,G4) which were diagnosed with the IR spectrum for the following frequency values are shown in Table(5).

Table(5) The (IR) spectral for compounds(G3-G5)

No.	R	C=C Aromatic	C=N (Carbodiimide)
G3	$CH_3(CH_2)_2CH_2$	1489,1540	2126
G4	Phenyl	1487-1585	2101

Hence the reactivity of these compounds with anthranlic acid for compounds (G5,G6) was diagnosed using infrared spectrometry (IR), where spectrometry showed an absorption strip in range 1715- 1698cm^{-1}which is due to vibration of the bond (C = O). IR spectrum data summarized in the following table(6)

table(6) The (IR) spectral for compounds(G5-G6)

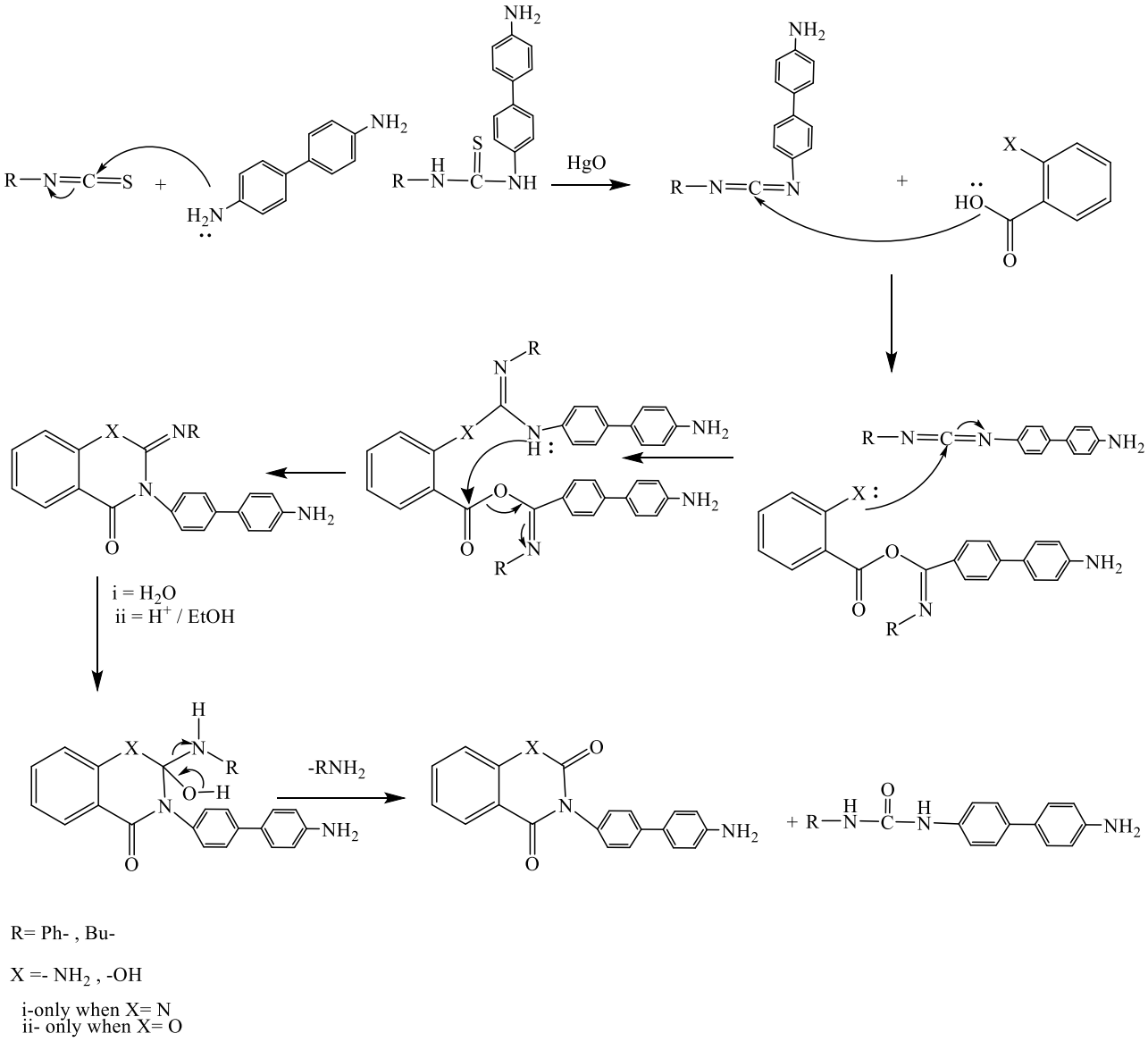
IR								
Compound	C-N	C-O	C=C Aromatic	C=N	C=O	C-H Aliphatic	C-H Aromatic	N-H
G5	1004	1112	1454-1540	1652	1715	3030	-	-
G6	1035	-	1488-1558	1652	1698	2931	3030	3566

IR							
No.	R	C-N	C-O	C=C Aromatic	C=N	C=O	C-H Aromatic
G8	$CH_3(CH_2)_2CH_2$	1061	1154	1540-1647	1647	1661	3050
G9	Phenyl	1054	1050	1489-1540	1620	1678	3032

table(7) The (IR) spectral for compounds(G8-G9)

Hence the reactivity of these compounds (G3,G4) with salalic acid for compounds (G8,G9) IR spectrum data is summarized in the following table(7)

the mechanism it explained through the following steps.



R= Ph- , Bu-

X =- NH_2 , -OH

i-only when X= N
ii- only when X= O

Scheme(II): mechanism of Compounds (G1-G10)

Then the acid hydrolysis of the compounds (G5) was performed to obtain the compounds (G7) as the disappearance of the package (C = N) was obtained the IR data as follows:

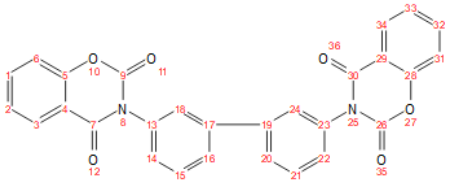
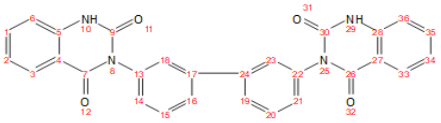
C-N =1040,C-O =1156,C=C =Aromatic1495-1540, C=O =1652,C-H Aromatic=3010.and Measured (^{1}H-NMR) for compound: 6.84-8.88(m, 16H) 4Ar-H.

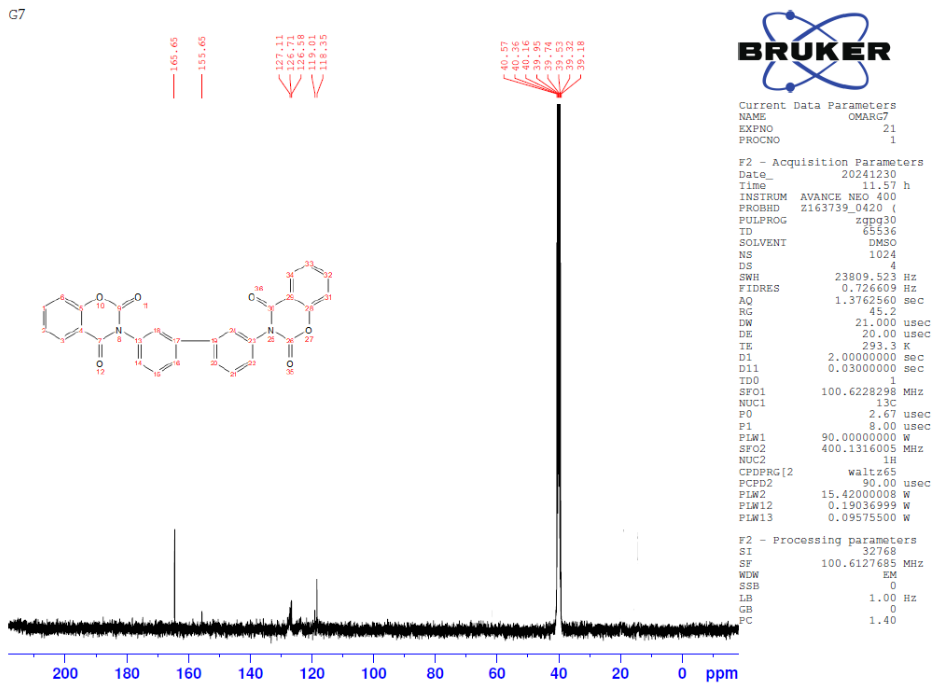
Then the acid hydrolysis of the compounds (G9) was performed to obtain the compounds (G10) as the disappearance of the package (C = N) was obtained the IR data as follows:

C-N =1031, C=C =Aromatic1488-1540, C=O =1698, C-H Aliphatic =2840,C-H Aromatic=3031, N-H=3212.

And Measured (^{1}H-NMR) for compound: 6.97-7.71(m, 16H) 4Ar-H ; 9.89 (s, 2H) NH.

Table (9) : C^{13}NMR compounds (G7-G10)

G7		4,6,29,31:118.35 , 2,16,18,20,24,32,33:119.01 , 3,14,15,17,19,21,22,34:126.58 , 13,23:126.71 , 5,28:127.11 , 9,26:155.65 , 7,30:165.56
G10		4,7:124.06 , 6,36:124.30 , 16,18,19,23:124.85 , 2,34:126.45 , 3,14,21,33:126.79 , 15,20:128.81 , 1,35:128.90 , 13, 22:129.26 , 17,24:130.40 , 5,28:139.94 , 9,30:154.09 , 7,26:168.70


G7
165.65
155.65
127.11
126.71
126.58
119.01
118.35
40.57
40.36
40.16
39.95
39.74
39.53
39.32
39.18
BRUKER
Current Data Parameters
NAME OMARG7
EXPNO 21
PROCNO 1
F2 - Acquisition Parameters
Date_ 20241230
Time 11.57 h
INSTRUM AVANCE NEO 400
PROBHD Z163739_0420 (
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 23809.523 Hz
FIDRES 0.726609 Hz
AQ 1.3762560 sec
RG 45.2
DW 21.000 usec
DE 20.00 usec
TE 293.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6228298 MHz
NUC1 13C
P0 2.67 usec
P1 8.00 usec
PLW1 90.00000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.42000008 W
PLW12 0.19036999 W
PLW13 0.09575500 W
F2 - Processing parameters
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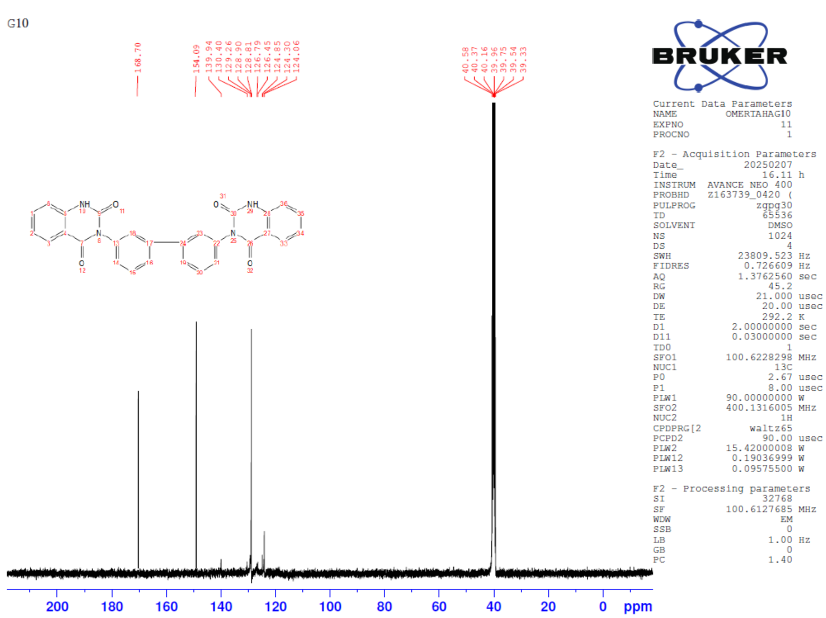
SF 100.6127685 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200
180
160
140
120
100
80
60
40
20
0
ppm

Fig(1)


G10
168.70
154.09
139.94
130.40
129.26
128.90
128.81
126.79
126.45
124.95
124.30
124.06
40.58
40.37
40.16
39.96
39.75
39.54
39.33
BRUKER
Current Data Parameters
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EXPNO 11
PROCNO 1
F2 - Acquisition Parameters
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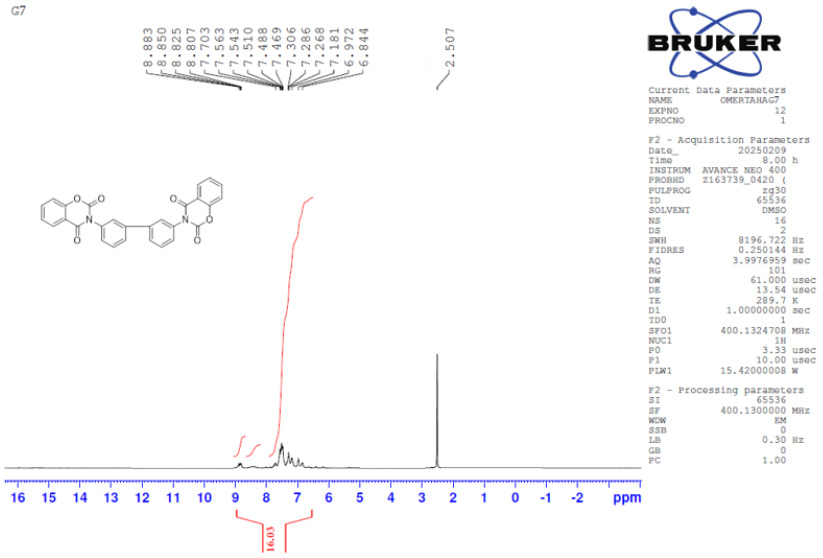
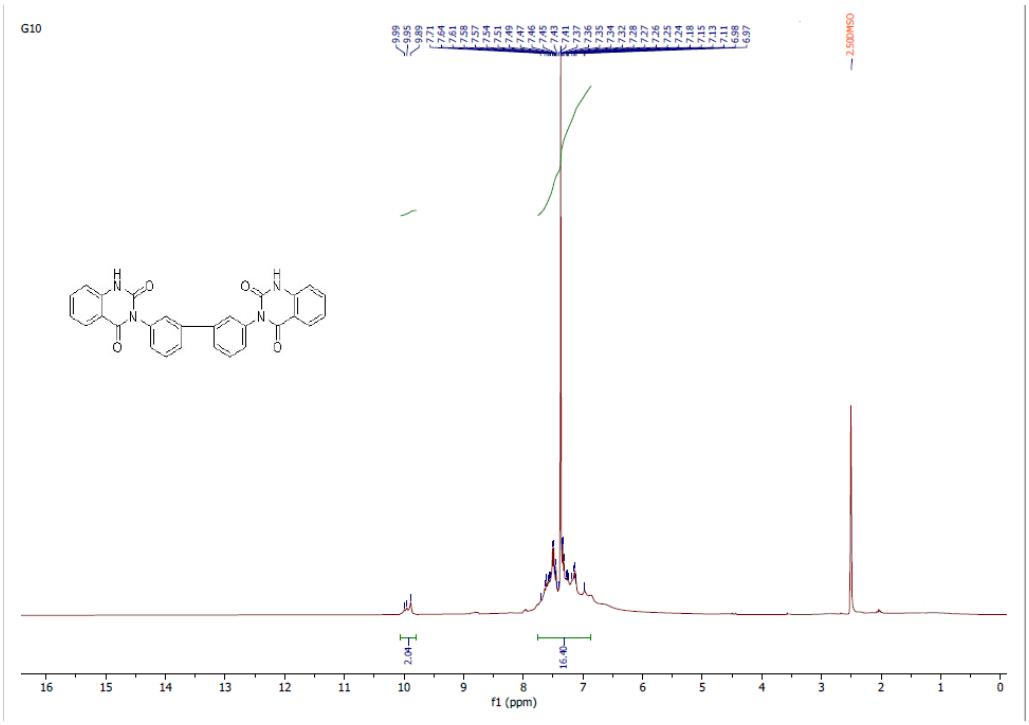
SOLVENT DMSO
NS 1024
DS 4
SWH 23809.523 Hz
FIDRES 0.726609 Hz
AQ 1.3762560 sec
RG 45.2
DW 21.000 usec
DE 20.00 usec
TE 292.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6228298 MHz
NUC1 13C
P0 2.67 usec
P1 8.00 usec
PLW1 90.00000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.42000008 W
PLW12 0.19036999 W
PLW13 0.09575500 W
F2 - Processing parameters
SI 32768
SF 100.6127685 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200
180
160
140
120
100
80
60
40
20
0
ppm

Fig(2)



Fig(3)



Fig(4)

Conclusions

In this study, a series of heterocyclic compounds was successfully synthesized using benzidine as the central scaffold. The synthetic route involved stepwise transformations starting from isothiocyanate derivatives to thioureas (G1, G2), followed by oxidation to carbodiimides (G3, G4), and subsequent condensation with anthranilic acid and salicylic acid to produce benzo-1,3-oxazine-4-one and quinazoline-2,4-dione derivatives (G5–G10).

The structural integrity and identity of the synthesized compounds were confirmed through comprehensive spectroscopic analyses including **IR**, **^{1}H-NMR**, and **^{13}C-NMR**, which revealed characteristic signals consistent with the proposed structures. The IR spectra in particular showed diagnostic bands for functional groups such as C=N, C=O, and aromatic C=C, confirming successful transformations across each reaction stage.

Among the synthesized derivatives, compounds G7 and G10 demonstrated distinct spectroscopic features following acid hydrolysis, indicating successful ring closure and loss of imine functionality. Additionally, the high melting points and good yields observed throughout the series underscore the efficiency and robustness of the adopted synthetic pathways.

This work highlights the synthetic versatility of benzidine-based scaffolds in producing bioactive heterocyclic systems such as quinazolinones and benzoxazines, which are widely recognized for their pharmacological relevance. These findings open avenues for further exploration of these derivatives in pharmaceutical applications, particularly in the development of antibacterial, anti-inflammatory, and anticancer agents.

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References

1. Hassan MA, et al. Synthesis and spectral characterization of some heterocyclic nitrogen compounds. Eur J Chem. 2013;4(2):121-123.
2. Younes AMM, Taha MM, Abdel-Monsef ABH. (2,4-Dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetic acid hydrazide: synthesis and reactions. J Asian Sci Res. 2013;3(8):800.
3. Jin HZ, et al. A new quinazolinedione alkaloid from the fruits of Evodia officinalis. Fitoterapia. 2008;79(4):317-318.
4. Zhao L, et al. Practical one-pot protocol for the syntheses of 2-chloro-pyrrolo[3,2-d]pyrimidines. Tetrahedron. 2011;67(15):2803-2806.
5. Wenzel DG. Anticonvulsant activity of some uracils and related compounds. J Am Pharm Assoc Sci Ed. 1955;44(9):550-553.
6. Connolly D, et al. Synthesis of quinazolinones and quinazolines. Tetrahedron. 2005;61:10153-10202.
7. Hansen P, Pedersen E. Simple synthetic route to silylated methyl 3-azido-2,3-dideoxy-α,β-D-erythro-pentofuranoside. ChemInform. 1990;21(37):no-no.
8. El-Sheshtawy HS, et al. Synthesis, structural, and theoretical studies of quinazoline-2,4-dione derivatives. Polycycl Aromat Compd. 2019.
9. Hassan MA, et al. Synthesis and reactions of 3-aminotetrachloroquinazolin-2,4-dione. Eur J Chem. 2011;2(4):514-518.
10. Li Z, et al. Microwave-assisted efficient and convenient synthesis of 2,4(1H,3H)-quinazolinediones and 2-thioxoquinazolines. J Comb Chem. 2008;10(3):484-486.
11. Hayao S, et al. New sedative and hypotensive 3-substituted 2,4(1H,3H)-quinazolinediones. J Med Chem. 1965;8(6):807-811.
12. Tran TP, et al. Synthesis and structural–activity relationships of 3-hydroxyquinazoline-2,4-dione antibacterial agents. Bioorg Med Chem Lett. 2004;14(17):4405-4409.
13. Ryu CK, et al. 6-Arylamino-5,8-quinazolinediones as potent inhibitors of endothelium-dependent vasorelaxation. Eur J Med Chem. 2002;37(1):77-82.
14. Usifoh CO, Scriba GK. Synthesis and anticonvulsant activity of acetylenic quinazolinone derivatives. Arch Pharm. 2000;333(8):261-266.
15. Fujimori H, Cobb DP. Central nervous system depressant activity of ma1337, 3-[3-(4-M-chlorophenyl-1-piperazyl)propyl]-2,4(1H,3H)quinazolinedione hydrochloride. J Pharmacol Exp Ther. 1965;148(2):151-157.
16. Clauss A, et al. Quinazolinedione derivatives, preparation thereof and various therapeutic uses thereof. Google Patents; 2014.

17. Defossa E, et al. Urea- and urethane-substituted acylureas, process for their preparation and their use. Google Patents; 2012.
18. Zeng YF, et al. Towards alpha-glucosidase folding induced by trifluoroethanol: kinetics and computational prediction. Process Biochem. 2012;47(12):2284-2290.
19. Moreland RJ, et al. Species-specific differences in the processing of acid α-glucosidase are due to the amino acid identity at position 201. Gene. 2012;491(1):25-30.
20. Gao S, Wang Z, Li J. Synthesis and anticancer activity of novel benzo[e][1,3]oxazin-4-one derivatives. Eur J Med Chem. 2013;67:58-66.
21. Patel RV, Thakkar VR, Dadhania HA. Solvent-free synthesis of benzo[e][1,3]oxazine derivatives under microwave irradiation. Bioorg Med Chem Lett. 2015;25(18):4071-4076.
22. Zhang Y, Liu Q, Chen X. Efficient synthesis of benzo[e][1,3]oxazin-4-ones via acyl chloride activation. Synth Commun. 2020;50(7):995-1001.
23. Sheehan JC, Cruickshank PA, Boshart GL. J Org Chem. 1961;26:2525.
24. Loev B, Kormendy M. A novel reaction of carbodiimides. J Org Chem. 1962;27(9):3365-3366.
25. Busch M, Blume G, Pungs E. Zur Kenntnis der Carbodiimide. J Prakt Chem. 1909;79(1):513-546.