Synthesis, Characterization and Spectroscopic Study of Some Heterocyclic Compounds (2,3-Dihydroquinazolin, Dzetidin-2-one) Derived from Schiff Bases and Evaluation Their Bacterial Activity

Khamaael M. Fayyadh[*1] and Inam H. Khudhair[2]**

[1] Department of Chemistry - College of Education pure sciences - University of Tikrit
[2] Middle Technical University - Ba'aquba Medical Technical Institute

[*]khamaael@yahoo.com
[**]inaamh722@gmail.com

Received: 27 December 2017 Accepted: 16 April 2018

Abstract

This search includes preparation of Schiff Bases (R_1 - R_4) from the reaction 2, 4- diamino-5-(3, 4, 5-trimethoxy benzyl) pyrimidine with some of aromatic aldehydes. Then preparation the compounds of tetracyclic ring as derivatives of 1, 1- (3, 4, 5-trimethoxybenzyl) pyrimidine-2, 4 diyl) bis (3-chloro-4-(substituted phenyl) azetidin-2-one) (R_5-R_8), from reaction of Schiff bases (R_1-R_4) with chloro acetyl chloride in presence of tri ethyl amine in 1, 4-dioxane. And also, preparation of hexacyclic as derivatives 3, 3-(3, 4, 5-trimethoxybenzyl) pyrimidine-2,4diyl)-bis(2(substitutedphenyl)-2,3-dihydroquinazolin-4 (1H) one) (R_9-R_{12}) with 2-amino-benzoic acid by using 1, 4- dioxane as a solvent. The structure of the synthesized compounds was confirmed by (I.R) and (^{1}H-NMR) spectrum, as well as, the physical means such color and melting point, the biological activity was studied against of some kind of bacteria.

Keywords: 2, 4-diamino-5-(3, 4, 5-trimethoxy benzyl) pyrimidine, azetidin-2-one, dihydroquinazolin-4, Schiff base

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تحضير وتشخيص ودراسة بعض المركبات الحلقية (3، 2- داي هايدروكونازولين، ازيتيدين 2-اون) المشتقة من قواعد شف وتقييم فعاليتها البكتيرية

خمائل محمد فياض[1] و انعام حسين خضير[2]

[1]جامعة تكريت – كلية التربية – قسم الكيمياء
[2]جامعة التقنية الوسطى- المعهد التقني الطبي- بعقوبة

الخلاصة

تضمن هذا البحث تحضير مشتقات قواعد شف (R_1-R_4) من تفاعل 2, 4- ثنائي امينو -5-(5,4,3-ثلاثي ميثوكسي بنزيل) بايرميدين مع بعض الالديهايدات الاروماتية, من ثم حضرت مركبات الحلقة الرباعية كمشتقات1, 1-(3, 4, 5– ثلاثي ميثوكسي بنزيل) (بايرميدين-4,2 –دايل) بس (-3– كلورو (فنيل) ازيتدين-2- اون) (R_5-R_8) من تفاعل قواعد شف مع كلورو استيل كلورايد بوجود ثلاثي امين في 4,1 - دايوكسان. وايضا تحضير الحلقة السداسية كمشتقات 3, 3 (3, 4, 5 – ثلاثي ميثوكسي بنزيل) (بايرميدين-4,2– دايل) بس (2 (فنيل)3,2- ثنائي هايدروكونازولين-4–(1H) اون (R_9-R_{12}) مع 2- امينو حامض البنزويك باستخدام 4,1- دايوكسان كمذيب. ثم شخصت المركبات المحضرة بالطرق الطيفية مثل أطياف الاشعة تحت الحمراء(I.R) والرنين النووي المغناطيسي (^{1}H-NMR) ، فضلاً عن الطرق الفيزيائية مثل اللون ودرجات الانصهار، كما تمت دراسة الفعالية ضد البكتريا .

الكلمات المفتاحية: 2, 4-داي امينو -5-(5,4,3- تراي مبثوكسي بنزيل) بايرميدين-ازيتيدين-2-اون. داي هايدروكونازولين-4-, قواعد شف.

Introduction

Schiff bases are compounds which contain imine or azomethine (-C=N-) group. They obtained by condensation primary amines with carbonyl compounds and prepared for the first time by the chemist Hugo Schiff in 1864 [1, 2]. Schiff bases have huge importance in medical fields, pharmacological activities and medicines and a wide range of biological activities such as anti-inflammatory [3, 4], analgesic [5, 6], anti-microbial [7, 8], anti-convulsant [9], anti-tubercular[10], anti-cancer [11,12], anti-oxidant[13], as for the parasites it is biological activities to Schiff bases are anti-amoebic [14], anti-giardia [15], anti- Trypanosoma [16], anti-malarial [17], anti-Echinococcusgranulosus [18], Pharmacologically, Trimethoprim 2, 4-

diamino-5-(3,4,5- tri methoxy benzyl) pyrimidine (TMP) is known as folic acid antagonist and is commonly used in combination with sulfonamides to treat gastrointestinal and respiratory tract infections power full bacteriostatic agent. Trimethoprim has bacteriostatic effect with broad-range of gram positive and Gram-negative bacteria and generally is ineffective to anaerobe. Its main uses now are in Pneumocystis carinii pneumonia, toxoplasmosis, and nocardiosis. Gastrointestinal disturbances (mainly nausea and vomiting) [19]. Structure of trimethoprim is 5- (3, 4, 5-trimethoxybenzyl) pyrimidin-2,4-diyldiamine. White and yellowish white colored crystal or crystallized powder. Alternative names are Proloprim, Trimpex, Monotrim, Trimexazole and 5- (3, 4, 5- Trimethoxtbenzyle) [20]. The azetidin-2-one compounds are present in antibiotics such as penicillin (I) and cephalosporin's (II), which was used as an anti-inflammatory and anticonvulsant and microbes and fungi, anti-cancer and tuberculosis is also working to kill pathogenic micro organisms pathogenesis [21]. The compounds 2, 3-dihydroquinazolin -4 (1 H) one) great importance and pharmacological and is used in the preparation of many pharmaceutical drugs and antibacterial [22]. Derivatives 2, 3 dihydroquinazolin -4 (1 H) one) used in pesticide inhibitor for the bacteria even more than the standard norfloxacin for anti-bacterial and calming the central nervous system (CNS) and the anti-cancer [23].

Material and Methods

Infrared Spectrophotometer model Shimadzu 8400, Type (KBr) Scale [400-4000 cm^{-1}], Melting Point Electro thermal 9300 melting point Apparatus, and ^{1}H- NMR spectrometer for proton (^{1} H-NMR) Bruker400MHz, has measurements using DMSO-d_6 as a solvent was to measure in Ahl– Albate University in Jordan. by a device Ultra shield 400 MHz. Bruker 2003. Chemical Materials Of the following companies: (Fluka, BDH, Aldrich, Merck) and materials used directly without recrystallization.

Preparation methods

1-Synthesis of N^2, N^4- diarylidene-6-(3,4,5trimethoxybenzyl) pyrimidine-2,4-diamine(R_1-R_4)

2,4-diamino-5-(3,4,5-trimethoxy benzyl) pyrimidine (0.01 mole) dissolved in(30ml) of absolute ethanol and mixed with different aromatic aldehydes (0.02 mole) dissolved in (15 ml) of absolute ethanol. was added (0.02g) *p*-toluene sulfonic acid. After the addition was completed the reaction mixture was refluxed in water bath for (12 hr). Recrystallized by benzene [24]. Physical properties of the prepared compounds are shown in Table (1).

2 - Synthesis of 1,1^1-(3,4,5-trimethoxybenzyl) pyrimidine-2,4diyl) bis (3-chloro-4-(substituted phenyl) azetidin-2-one) (R_5-R_8)

(0.02 mole) of chloro acetyl chloride dissolved in (10ml) of cold 1,4-dioxane at (0 -5 ^{0}C) with (0.02 mole) tri ethyl amine dissolved in (10ml) 1,4-dioxane were mixed. Then add (0.01 mole) of synthesized Schiff bases dissolved in (10 ml) 1,4-dioxane. The mixture was stirred for (24 hr) at room temperature. After completion of the reaction, the contents were poured in stirred ice-cold water and stirring was continued for (1 hr). The solid material separated,washed with water, filtered, dried and Recrystallized from ethanol or benzene[25] . Physical properties of the prepared compounds are shown in Table (2).

3 - Synthesis of 3,3^1-(3,4,5-trimethoxybenzyl) pyrimidine-2,4diyl)-bis (2 (substituted phenyl)-2,3-dihydroquinazolin-4(1 *H)* one) (R_9-R_{12})

Reaction of (0.01 mole) of the synthesized Schiff bases dissolved in (10 ml) of 1,4-dioxane, with (0.02 mole) 2-aminobenzoic acid dissolved in (10 ml) of 1,4-dioxane were mixed. the reaction mixture was refluxed for (16 hr). After cooling the resulting solid at room temperature and equivalent of using a sodium bicarbonate solution (10%). Then the contents were poured in ice cold water, the solid material separated, washed with water, filtered, dried and Recrystallized 1,4-dioxane or benzene [26]. Physical properties of the prepared compounds are shown in Table (3).

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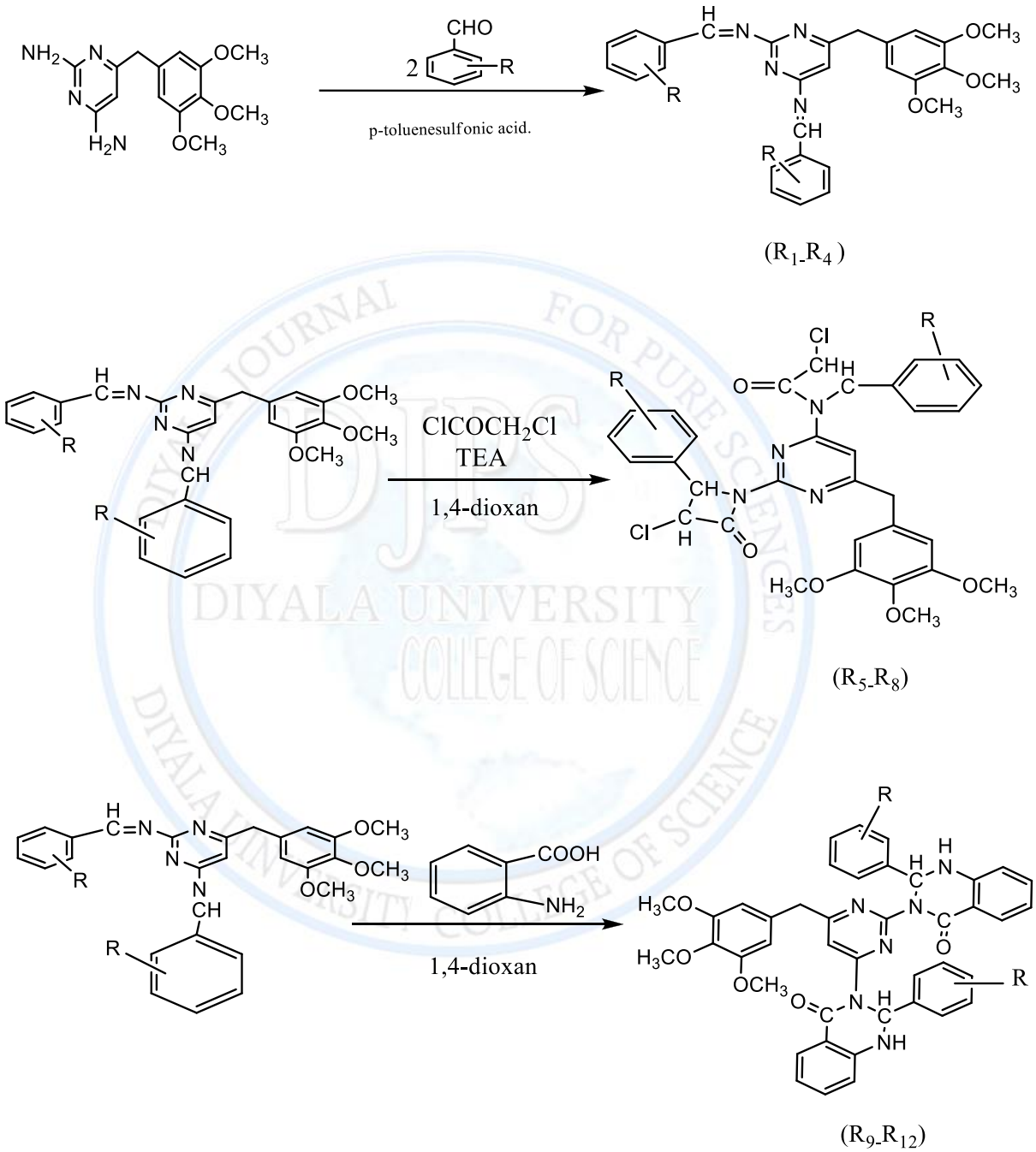

Scheme 1: Path ways for synthesized compounds

Biological activity

Antibacterial activity of these compounds was determined by the ager diffusion method. Using *Escherichia Coli (G-)* and *Streptococcus Pyogene (G+)*, 10mM and 5mM of synthesized compounds were placed on an agar seeded with the test organism. The plate was incubated at the appropriate temperature at (37 ^{0}C) for (24hr) and read the score after (24 hr) by limiting the diameters of inhibition zones and that compared with standard tables installed by (NCCLS.1993) to determine whether the isolates were sensitive or resistant life to antibiotics, as the increase in the diameter damping means an increase in effectiveness biological compounds [27].

Results and Discussion

1-Synthesis of N^2, N^4- diarylidene-6-(3,4,5trimethoxybenzyl) pyrimidine-2,4-diamine.

New Schiff bases were synthesized from the reaction of 2, 4-diamino-5-(3, 4, 5-trimethoxy benzyl) pyrimidine with different aromatic aldehyde (R_1-R_4) are shown in scheme (1) After follow-up change the physical properties (melting point, color) we sure got on the reaction. And then were identified by FT-IR, and ^{1}HNMR. FT-IR spectra of Schiff bases (R_1-R_4) stretching absorption bands at (3242cm^{-1}) due to (OH) and showed clear absorption bands at range of (3032-3061cm^{-1}), and (2811-2945 cm^{-1}) which belong to both (C-H) aromatic and aliphatic respectively. While (C=N) appeared at (1612-1646 cm^{-1}), beside that the (C=C aromatic) appeared at range of (1435– 1594 cm^{-1}), and at (1278-1366 cm-^{1}) due to (C-N). As shown in the table (4) and Figure (1).

On the other hand of ^{1}H-NMR in DMSOd6, showed, at δ= (2.50) ppm (C – H Aliph), at δ = (3.36) ppm (OCH_3), at δ = (7.11-8.07) ppm (C=C) of aromatic ring, at δ = (8.72) ppm (CH-N), and δ (13.12) ppm (OH). the Compound (R_4), [28] .as shown in Figure (4).

2-Synthesis of 1,1^1-(3,4,5-trimethoxybenzyl) pyrimidine-2,4diyl) bis (3-chloro-4-(substituted phenyl) azetidin-2-one)

New azetidin-2-one were synthesized from the reaction of chloro acetyl chloride with Schiff bases (R_5-R_8), shown in scheme (1) FT-IR spectra of azetidin-2-one (R_{5-8}) showed clear absorption

bands at range of (3035-3051cm^{-1}), and (2756-2930 cm^{-1}) which belong to both (C-H) aromatic and aliphatic respectively, While (C=O) appeared at (1682-1713 cm^{-1}) , beside that the (C=N) appeared at range of (1600– 1620 cm^{-1}),While (C=C aromatic) appeared at (1429-1545 cm^{-1}), and at (1270-1374 cm-^{1}) due to (C-N), and at (748-962cm^{-1}) due to (C –Cl), As shown in the table (5) and Figure (2).

On the other hand of ^{1}H-NMR in DMSOd6, showed, at δ= (3.34) Ppm (C – H Aliph), at δ = (3.82) ppm (OCH_3), at δ = (7.00-7.98) ppm (C=C) of aromatic ring, and δ = (8.41) ppm (CH-N) the Compound (R_5). as shown in Figure (5).

And the Compound (R_6) showed, at δ= (2.65) Ppm (C – H Aliph), at δ = (3.73) ppm (OCH_3), at δ = (6.11-7.72) ppm (C=C) of aromatic ring and δ= (8.01) ppm (CH-N) the Compound (R_6), [28]. as shown in Figure (6).

3-Synthesis of 3,3^{1}-(3,4,5-trimethoxybenzyl) pyrimidine-2,4diyl)-bis (2 (substituted phenyl)-2,3-dihydroquinazolin-4(1 *H)* one)

New 2, 3-dihydroquinazolin-4(1 H) one) were synthesized from the reaction of 2-aminobenzoic acid with Schiff bases(R_9-R_{12}), shown in scheme (1)

FT-IR spectra dihydroquinazolin (R_{9-12}) showed clear absorption bands at (3450-3380cm^{-1}) due to (NH) ,and showed clear absorption bands at range of (3040-3072cm^{-1}) ,and (2806-2933 cm^{-1}) which belong to both (C-H) aromatic and aliphatic respectively, While (C=O) appeared at (1655-1723 Cm^{-1}) , beside that the (C=N) appeared at range of(1602– 1622 cm^{-1}) ,While (C=C aromatic) appeared at (1435-1580cm^{-1}) ,and at (1241-1345 cm-^{1}) due to (C-N) . As shown in the table (6) and Figure (3). On the other hand of ^{1}H-NMR in DMSOd6, showed, at δ= (2.50) ppm (C – H Aliph), at δ = (3.37) ppm (OCH_3), at δ = (6.76-7.75) ppm (C=C) of aromatic ring, at δ = (8.04) ppm (CH-N), and δ (10.12) ppm (NH). the Compound (R_9). as shown in Figure (7) znd the Compound (R_{11}) showed, at δ= (2.50) ppm (C – H Aliph), at δ = (3.38) ppm (OCH_3), at δ = (6.83-8.12) ppm (C=C) of aromatic ring, at δ= (8.13) ppm(CH-N), and δ (10.12) ppm (NH), [28] .as shown in Figure (8).

Biological activity

The synthesized compounds showed different biological activities against two types of bacteria gram positive and gram-negative bacteria including *Streptococcus Pyogene* and

Escherichia Coli. The test results showed that the most of synthesized compounds showed moderate activity against two types of bacteria, while the compounds (R_1, R_{12}) showed Highly active against two types of bacteria, the compounds (R_8) showed no activity against two types of bacteria. All these results are shown in Table (7).

Table 1: Physical properties of the prepared compounds: (R_1-R_4)

Comp. No.	R	Molecular formula	Color	M.P(^{0}C)	Yield (%)	Recryst. Solvent
R_1	4-NO_2	$C_{28}H_{24}N_6O_7$	Dark Yellow	188-190	92	1,4-Dioxane
R_2	2-Br	$C_{28}H_{24}Br_2N_4O_3$	Pale Yellow	180-182	55	Benzene
R_3	3-OCH_3	$C_{30}H_{30}N_4O_5$	Dark Yellow	171-173	62	Benzene
R_4	3-OH	$C_{28}H_{26}N_4O_5$	Bright yellow	165-167	83	Benzene

Table 2: Physical properties of the prepared compounds:(R_5-R_8)

Comp. No.	R	Molecular formula	Color	M.P(^{0}C)	Yield (%)	Recryst. Solvent
R_5	4-NO_2	$C_{32}H_{26}Cl_2N_6O_9$	Dark Yellow	200-202	87	Benzene
R_6	2-Br	$C_{32}H_{26}Br_2Cl_2N_4O_5$	Pale Brown	140-142	61	Ethanol
R_7	3-OCH_3	$C_{34}H_{32}Cl_2N_4O_7$	Orang	165-167	70	Ethanol
R_8	3-OH	$C_{32}H_{28}Cl_2N_4O_7$	Yellow	184-182	65	Benzene

Table 3: Physical properties of the prepared compounds: (R_9-R_{12})

Comp. No.	R	Molecular formula	Color	M.P(^{0}C)	Yield (%)	Recryst. Solvent
R_9	4-NO_2	$C_{42}H_{34}N_8O_9$	Dark Yellow	245-247	90	Benzene
R_{10}	2-Br	$C_{42}H_{34}Br_2N_6O_5$	Brown	162-164	80	1,4-Dioxane
R_{11}	3-OCH_3	$C_{44}H_{40}N_6O_7$	Orang	181-179	76	1,4-Dioxane
R_{12}	3-OH	$C_{42}H_{36}N_6O_7$	Yellow	195-197	75	1,4-Dioxane

Table 4: Wave numbers in cm^{-1} of I.R spectrum for prepared compounds: (R_1-R_4)

Comp. No.	R	IR, (KBr), cm^{-1}						
		Fixed bands in structure					Changed bands in structure	
		ν(=CH)Ar	νC – H Aliph	ν C=N.	νC=CAr	ν C – N		
R_1	3-NO_2	3050	2870	1612	1435,1571	1287	ν(NO_2) 1347	
R_2	2-Br	3032	2863,2890	1620	1477,1568	1320	ν (C – Br) 795	
R_3	3-OCH_3	3056	8011,2945	1612	1490,1588	1366	ν (C–O–C) 1163	
R_4	3-OH	3061	2850	1646	1546-1594	1350	ν(OH) 3242	ν (C–OH) ,1050

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Table 5: Wave numbers in cm^{-1} of I.R spectrum for prepared compounds :(R_5-R_8)

Comp. No.	R	IR, (KBr), cm^{-1}								
		Fixed bands in structure							Changed bands in structure	
		ν(=CH) Ar	νC – H Aliph	ν C = O	ν C=N.	νC=CAr	νC– N	ν C-Cl		
R_5	4-NO_2	3080	2802,2930	1713	1600	1496,1545	1345	815	ν(NO_2) 1545	-----
R_6	2-Br	3065	2855	1690	1620	1480,1592	1374	748	ν (C – Br) 780	-----
R_7	3-OCH_3	3051	2800	1695	1600	1429,1535	1284	962	ν (C–O–C) 1095	-----
R_8	3-OH	3035	2756,2894	1682	1608	1482,1513	1270	901	ν (O – H), 3400	ν (C–OH) ,1185

Table 6: Wave numbers in cm^{-1} of I.R spectrum for prepared compounds:(R_9-R_{12})

Comp. No.	R		IR, (KBr), cm^{-1}							
			Fixed bands in structure						Changed bands in structure	
		ν N –H	ν(=CH)Ar	νC – H Aliph	ν C = O	ν C=N.	νC=CAr	ν C – N		
R_9	4-NO_2	3450	3072	2933	1723	1622	1511,1580	1341	ν(NO_2) 1560	
R_{10}	2-Br	3380	3057	2890	1663	1602	1500,1569	1336	ν (C – Br), 784	
R_{11}	3-OCH_3	3392	3040	2806,2923	1670	1602	1435,1570	1291	ν (C–O–C), 1155	
R_{12}	3-OH	3437	3051	2856	1655	1612	1490,1580	1345	ν (O – H), 3312	(COH),1147

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Table 7: Biological activity of some prepared compounds.

Comp. No.	R	G-Escherichia oli (G-),		Streptococcus Pyogene(G+),	
		5mM	10mM	5mM	10mM
R_1	4-NO_2	+	+++	+++	+
R_3	3-OCH_3	++	+	-	- +
R_6	2-Br	++	++	-	++
R_8	3-OH	-	-	+	-
R_{10}	3-OCH_3	++	-	+	+
R_{12}	3-OH	+	+++	++	+++

Key (-) Inactive (<5mm), (+) Slightly active (10-12mm), (++) Moderately active (15-20mm) (+++) Highly active (>20mm)

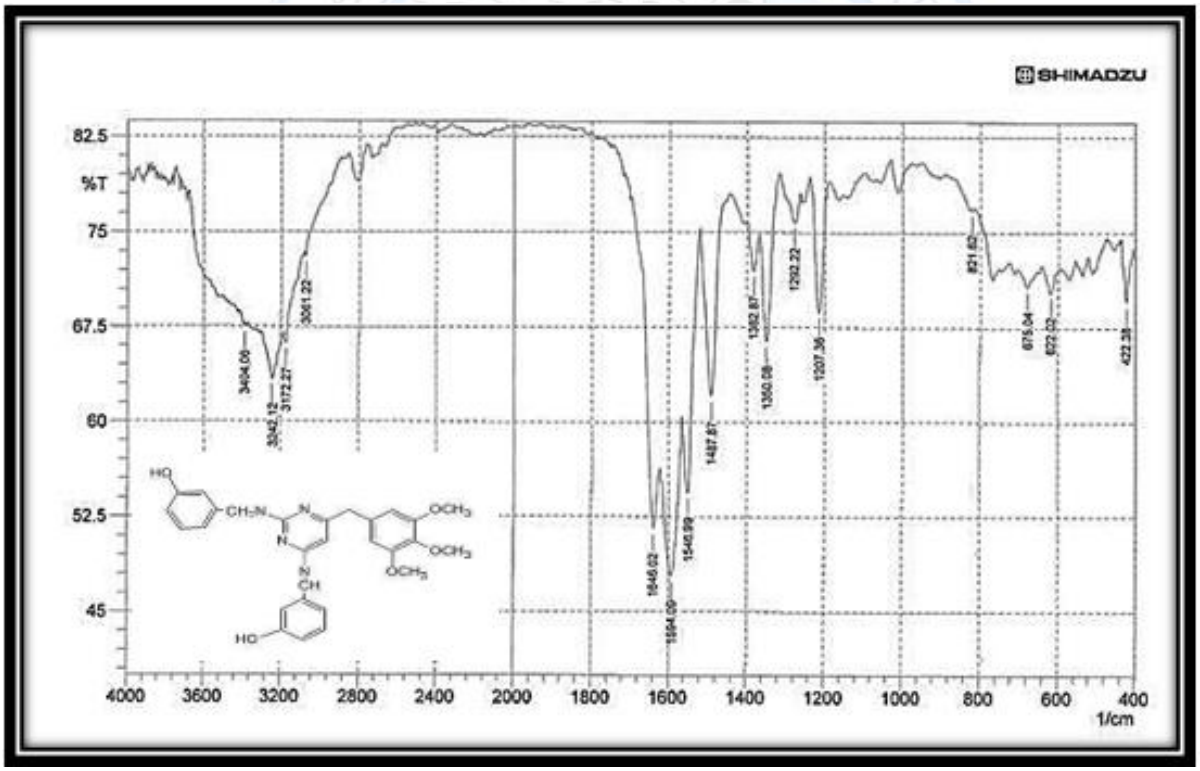

Figure1: IR spectrum of synthesized compound (R_4)

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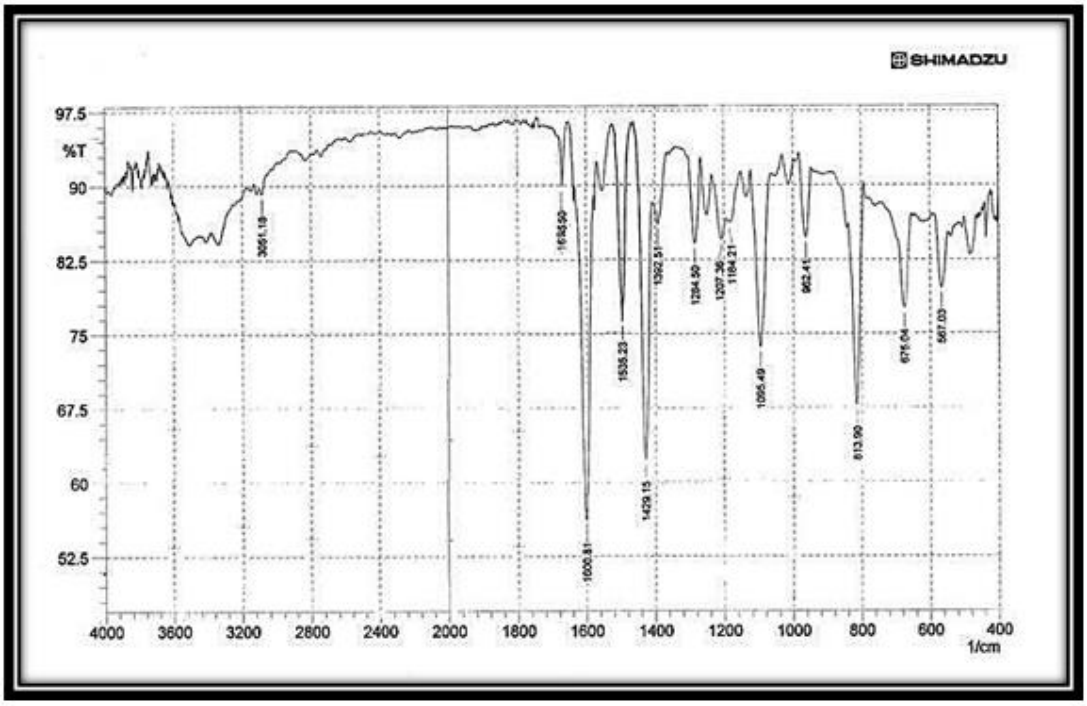

Figure 2: IR spectrum of synthesized compound (R7)

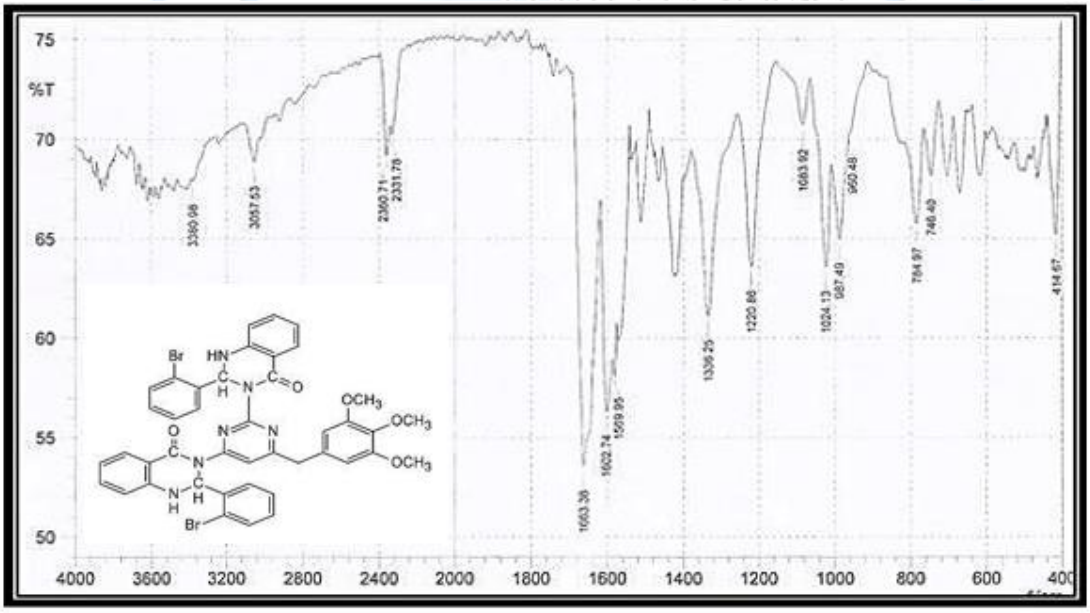

Figure3: IR spectrum of synthesized compound (R_{10})

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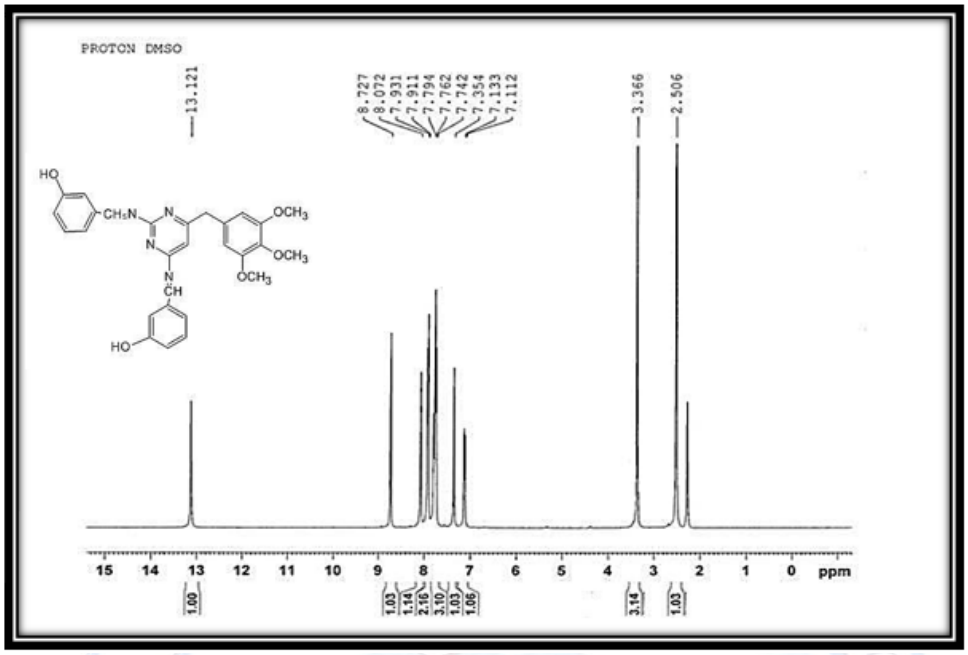

Figure 4: ^{1}H-NMR. spectrum of synthesized compound (R_4)

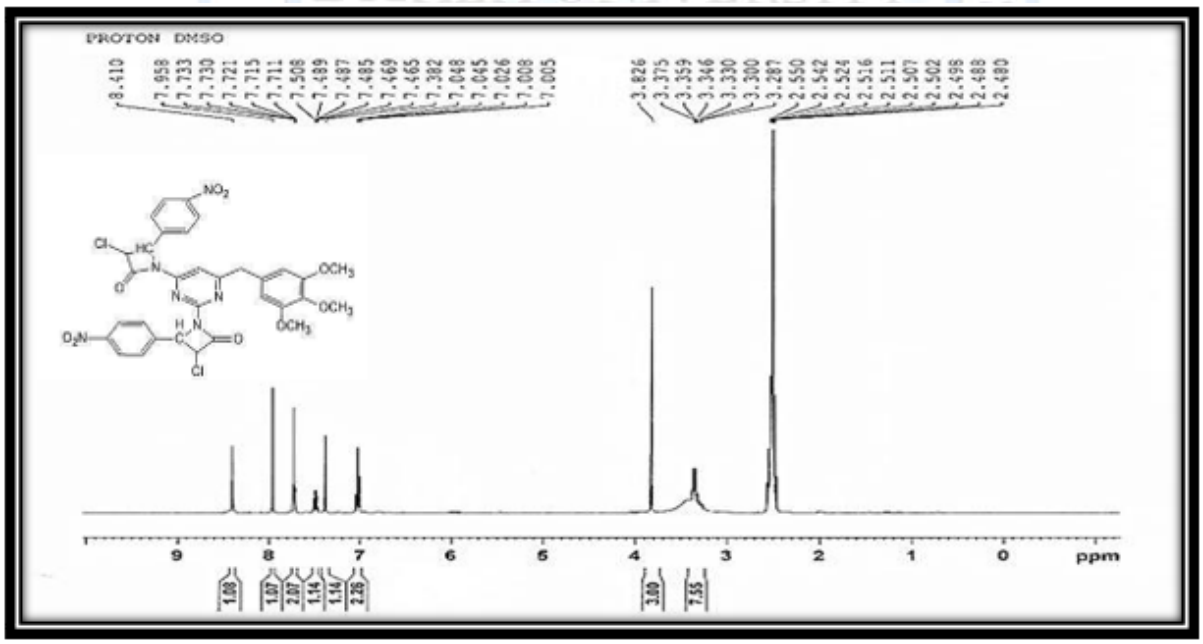

Figure 5: ^{1}H-NMR. spectrum of synthesized compound (R_5)

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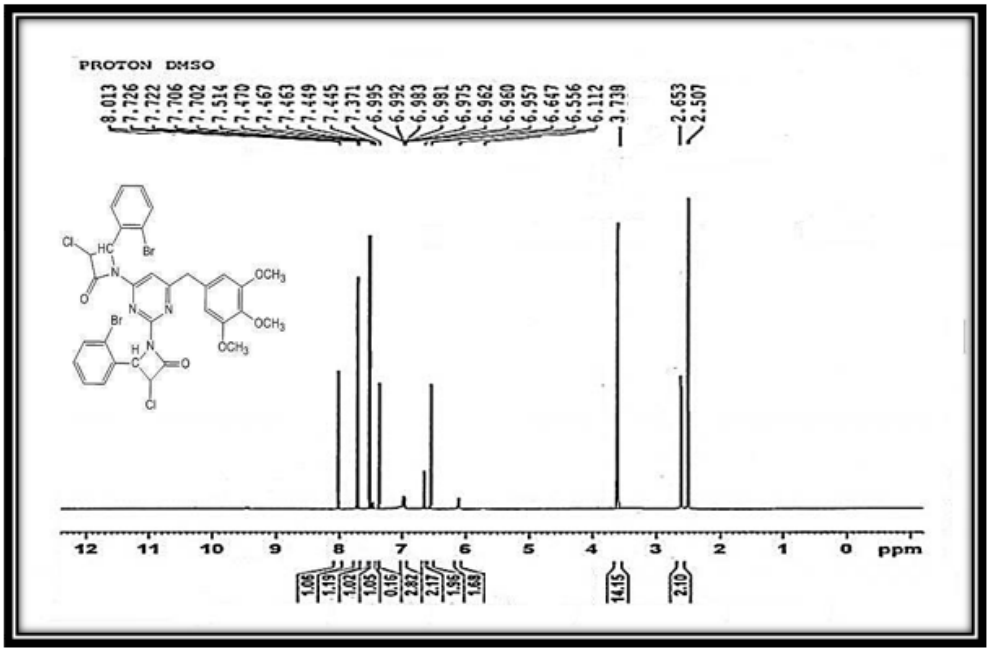

Figure 6: ^{1}H-NMR. spectrum of synthesized compound (R_6)

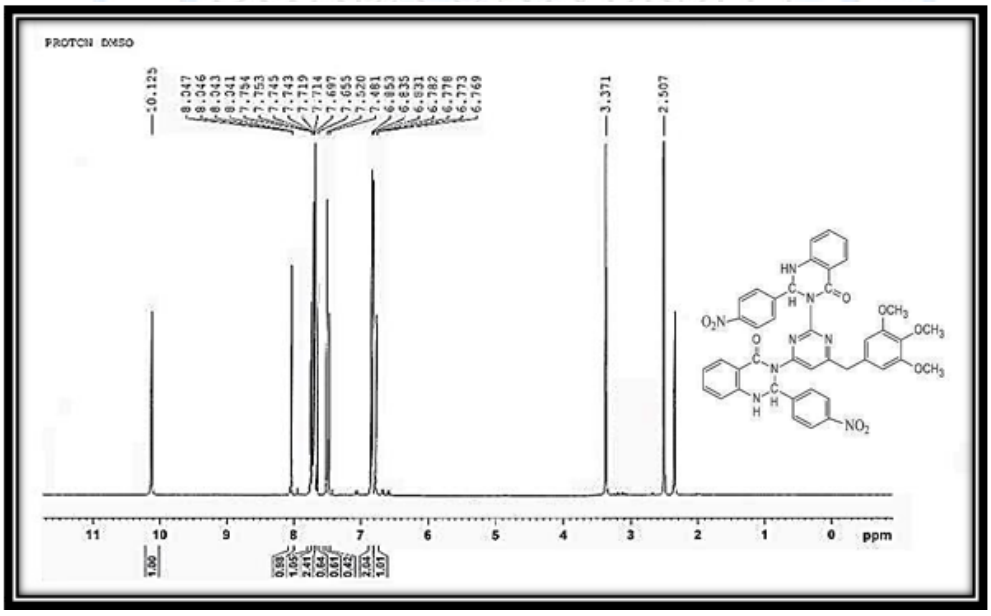

Figure 7: ^{1}H-NMR. spectrum of synthesized compound (R_9)

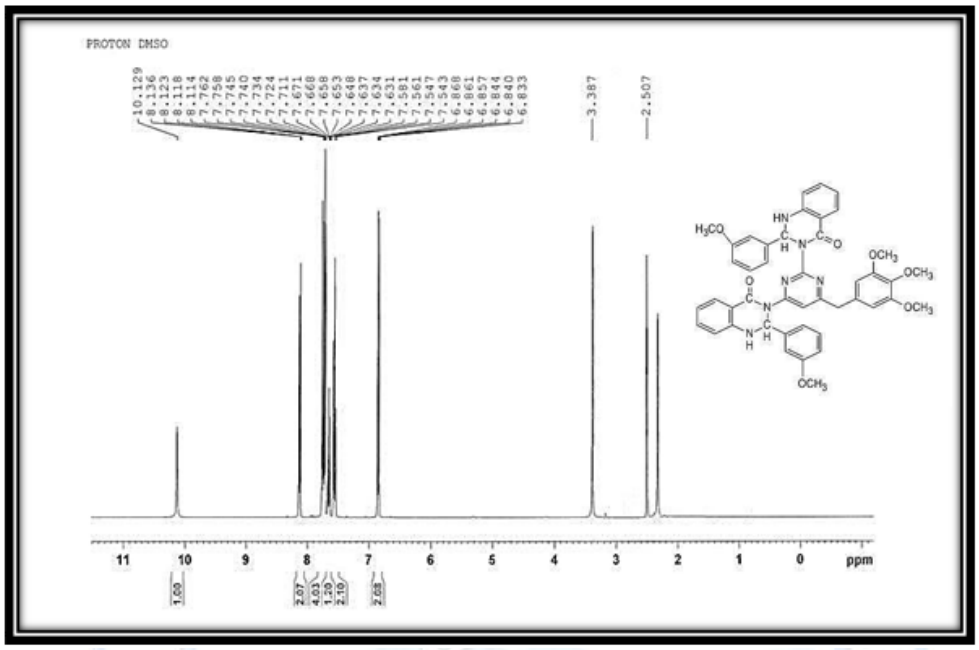

Figure 8: ^{1}H-NMR spectrum of synthesized compound (R_{11})

Conclusion

Schiff Bases (R1- R 4) were Synthesized successfully from the reaction 2,4-diamino-5-(3,4,5-trimethoxy benzyl) pyrimidine with aromatic aldehyde. Successful preparation azetidin-2-one (R5- R 8) from reaction of Schiff bases (R1- R 4) with chloro acetyl chloride in presence of drops of tri ethyl amine in 1,4-dioxane. Preparation of hexacyclic as derivatives 3, 3- (3, 4, 5-trimethoxybenzyl) pyrimidine-2, 4 diyl) – bis (2 (substitutedphenyl)-2, 3- dihydroquinazolin-4(1H) one) (R9- R 12) with 2-amino-benzoic acid by using 1, 4 - dioxane as a solvent. The structures of the synthesized compounds were confirmed by (IR) and (^{1}H-NMR) spectrum.

Acknowledgements

Author gratefully acknowledges to the Department of Chemistry - University of Tikrit, to the Department of Chemistry - University of Diyala for help and support.

References

1. Cimerman, Z.; Miljanic, S.; Galic, N. Croatica Chemica Acta 2000. 73(1), 81-95.
2. Ergenç, N.; Günay, N.S.; Eur. J. Med. Chem. 1998, 33(2), 143-148.
3. Sathe, B. S. Int J Pharm Res Dev 2011, 3(3), 164-169.
4. Pandey, A. Int J Chem Tech Res 2011, 3(1),178-184.
5. Udupi, R. H. Journal of Chemical and Pharmaceutical Research 2012, 4(2),1151-1159.
6. Chinnasamy, R. P.; Sundararajan, R.; Govindaraj, S. Journal of advanced pharmaceutical technology & research 2010, 1(3), 342-347.
7. Mounika, K.; Pragathi, A.; Gyanakumari, C. Journal of scientific research 2010, 2(3), 513-524.
8. Venkatesh, P. Asian J Pharm Hea Sci 2011. 1(1), 8-11.
9. Kumar, C.A.; Pandeya, S.N. International Journal of Pharm Tech Research 2012, 4(4), 590-598.
10. Aboul-Fadl, T. F.; Mohammed, A. H.; Hassan, E. A. S. Archives of pharmacal research 2003, 26(10), 778-784.
11. Miri, R.; Razzaghi-asl, N.; Mohammadi, M.K. Journal of molecular modeling 2013, 19(2), 727-735.
12. Ali, S. M. M. Asian Pacific journal of tropical biomedicine 2012, 2(6), 438-442.
13. Wei, D. Science in China Series B 2006, 49(3), 225-229.
14. Saxena, A. K.; Koacher, J. K.; Tandon, J. P.; Das, S. R. Journal of Toxicology and Environmental Health, Part A Current Issues 1982, 10(4-5), 709-715.
15. Saadeh, H.A. Medicinal Chemistry Research 2012, 21(10), 2969-2974.
16. Iakovidis, I.; Delimaris, I.; Piperakis, S.M. Molecular biology international, 2011
17. Brodowska, K.; Lodyga-Chruscinska, E. Chem Inform 2015, 46(11).
18. Nasr, Wafa' A. T.; Haythem A. Saadeh; Mohammad S. Mubarak; Sami K. Abdel-Hafez Jordan Journal of Biological Sciences 2014, 187-194.
19. Refat, M. S.; Refat, S. A.; El-Deen, I. M.; El- Sayed, S. M. J. Mol. Struct 2010, 980, 124-136.

20. Laurence, D. R.; Bennett, P. N. Clinical Pharmacology 7th Ed.: Singapore, 1992 Publishers (Pte) Ltd., Singapore, pp169 –170.

21. Shah, S. H.; Ptel, P.S. Research Journal of Chemical Sciences 2012, 2(7), 62-68.

22. Wayadande, J. A.; Dubey, R.; Bhusari, V. K.; Dhaneshwar, S. R. Pharm. Sinica. 2011, 2(4), 286-294.

23. Hunoor, R. S.; Patil, B. R.; Badiger, D. S.; Vadavi, R. S.; Gudasi, K. B. Der. Pharm 2010, 2(2), 116-128.

24. Dhahir, S. A.; Al-Sahib, S. A.; Al-Razaq, W. A.; Kadhim N. J. Baghdad Science Journal 2010, 7(1).

25. Jamal, M. Y.; Aowda, S. A. Diyala Journal for Pure Sciences 2014, 10(3), 14-31.

26. Majeed, I. Y. Ph. D. Thesis, University of Baghdad, Baghdad, Iraq, 2011.

27. Ronald, M. A. Experimental microbiology 6th Ed., Mosby.

28. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. Spectrometnic Inntification of organic Compound 4th Ed.; John Wiley and Sons, Inc.: New York, 1981.