INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

SYNTHESIS AND ANTIMICROBIAL SCREENING OF NEW BISSCHIFF BASES AND THEIR ACETYL OXADIAZOLE AZETIDINONE DERIVATIVES DERIVED FROM PYROMELLITICDIIMIDE

Ahlam Marouf A Azzawi[1] and Kafa Khalaf Hammud Al-Obiadi[2*]

[1]Department of Chemistry, College of Science,
University of Baghdad, Baghdad, Iraq.
[2]Ministry of Science and Technology, Baghdad, Iraq.

ABSTRACT

In this work, new Schiff bases, their acetyl oxadiazole, and azetidinone derivatives derived from pyromelliticdiimide were synthesized via multistep synthesis. In the first step, pyromelliticdiimide [1] was prepared via reaction of pyromelliticdianhydride with urea either under conventional heating or microwave irradiation.

In the second step, compound [1] was converted into its potassium salt [2] by treatment with alcoholic KOH solution.Inthe third step compound [2] was introduced in reaction with ethyl chloroacetate producing compound [3] ethyl -2- (N-pyromelliticdiimidyl) acetate. Compound [3] was introduced in reaction with hydrazine hydrate as a fourth step affording compound [4] 2- (N-(pyromelliticdiimidyl)) acetohydrazide.

Acid – catalyzed condensation reaction of compound [4] with aromatic aldehydes afforded new three Schiff bases [5-7]. The newly synthesized Schiff bases [5] and [6] were introduced in reaction with chloroacetyl chloride producing new two azetidinones derivatives [8] and [9]. Introducing of the newly prepared Schiff base [6] in reaction with acetic anhydride afforded new acetyl oxadiazole derivatives [10]. Antimicrobial activity of some prepared compounds against different types of bacteria and fungi were evaluated and showed promising results.

Keywords: Synthesis, Antimicrobial, BisSchiff bases, Acetyl OxadiazoleAzetidinone.

INTRODUCTION

Cyclic imides represent an important class of bioactive molecules that showed a wide range of biological - pharmacological activities such as androgen receptor antagonistic, anti-inflammatory, anxiolytic, antiviral, antibacterial, , and antitumor properties[1-7].

On the other hand, Schiff bases containing heterocyclic scaffolds have been known to possess a wide range of application human treatment from diseases and infections for a long time [8, 9]. Recently, these above mentioned compounds have been gained significant interest in the drug research and development as a main target field owing to their broad bioactivities such as antimicrobial, anti-inflammatory, anticonvulsant, antioxidant, and anticancer actions[10-12].Besides that, azetidinones are part of the antibiotic structureknown to exhibit promising antibacterial, anticonvulsant, anti-inflammatory, antitubecular efficacies[13-16].

Depending on the previously mentioned facts, our thought was directed to synthesize new molecules by incorporating both cyclic imide and Schiff base, their azetidinone, or / and acetyl oxadiazole derivatives in interest

molecular framework and screen their antimicrobial influences.

EXPERIMENTAL

-Instruments and apparatus

Melting points were determined on Gallenkamp capillary melting point apparatus.FTIR spectra were recorded using KBr discs on Shimadzu FTIR-8400 Fourier Transform Infrared spectrophotometer in Ministry of Science and Technology, Iraq and in IbnSina General Company, Ministry of Industry and Minerals, Iraq. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on near magnetic resonance Bruker, Ultrashield 300 MHz in Jordan, using tetramethylsilane as internal standard and deuterated dimethyl sulfoxide (DMSO-d_6) as solvent.Domestic microwave oven, SHOWNIC, China.

- Preparation ofpyromelliticdiimide [1]

Compound [1] was prepared by two methods (A and B)[17].

A. Conventional method

Pyromellitic anhydride (0.02 mol, 4.36 g), urea (0.05 mol, 3g) were mixed, homogenized in a flask, and heated in an oil bath and slowly brought to 260°C until it completely turned into liquid. The white crystals were appeared after cooling and dispersed by adding water (250 mL), recrystallized with water repeatedly, filtered, and dried. Yield (77%), m.p. (> 320^{o}C).

B. Microwave irradiation method

Pyromelliticdianhydride (0.02 mol, 4.36 g) and urea (0.05 mol, 3g) were mixed then heated in domestic microwave oven for ten minutes with 90% power. The resulted crystals were cooled, dispersed by adding water, recrystallized with water, filtered, and dried to get white crystals. Yield (92%), m.p. (> 320^{o}C).

-Preparation of pyromelliticdiimide Potassium Salt [2]

Pyromelliticdiimide (0.01 mol) was dissolved in (5 mL) of N,N-dimethyl formamide then the clear solution was added to alcoholic potassium hydroxide solution [(0.01 mol) in (25 mL) of absolute ethanol] with stirring. The obtained precipitate was filtered and dried.

-Synthesis of ethyl-2-(N-(pyromelliticdiimidyl)) acetate [3][17]

(5 mL) of ethyl chloroacetate was added to a solution of potassium salt [2] (1g) and (10 mL) of pure dimethyl sulfoxidewith thoroughly mixing then the obtained mixture was heated for one hour. After cooling, (10 mL) water was added and the product was collected by filtration, dried, and recrystallized from glacial acetic acid.

-Synthesis of 2-(N-(pyromelliticdiimidyl))acetohydrazide [4] [17, 18]

A solution of the prepared ester [3] (0.01mol, 3.88g) in ethanol (150 mL) was mixed with hydrazine hydrate (98%, 0.02 mol, 1g, 1mL). The reaction mixture was refluxed for ten hours then was added to ice-water with stirring and left to stand for 10 hrs. The resulted product was filtered and washed with water then with petroleum ether. Physical properties of compounds [1-4] are listed in Table 1.

-Synthesis of 2-(N-(pyromelliticdiimidyl))-N'-substituted benzylidineacetohydrazides [5-7][17, 18]

A mixture of aromatic aldehyde (0.004 mol) and a solution of (0.002 mol, 0.72 g) of the hydrazide [4] in absolute ethanol containing few drops of glacial acetic acid was refluxed for three hours. The formed precipitate was filtered, washed with petroleum ether, and recrystallized from ethanol.

-Synthesis of 1-(N-(N-pyromellitdiimidyl)acetamido)-2- oxo-3-chloro-4-phenyl azetidine [8, 9] [17, 18]

Chloroacetyl chloride (0.02 mol) was added dropwiseto a solution of Schiff base [5 or 6] (0.01 mol) in benzene (3 mL) with constant stirring below 15 ^{o}C temperature then triethyl amine (0.02mol) was added and the reaction mixture was refluxed for ten hours. The product was isolated by filtration, dried, and recrystallized from methylene dichloride.

-Synthesis of 3-acetyl -5-(N-pyromelliticdiimide)-2-phenyl-2,3-dihydro-1,3,4- oxadiazole [10] [17, 18]

A mixture of Schiff base [6] (0.003 mol) and acetic anhydride (10 mL) was heated under reflux for four hours. After the reaction mixture attained room temperature, excess acetic anhydride was decomposed by adding water and the mixture was stirred for further thirty minutes. The separated product was filtered, washed with water, dried, and recrystallized from ethanol. Physical properties of compounds [5-10] are listed in Table 2.

-Biological activity

Several prepared compounds were tested for their in vitro growth inhibitory activity against, *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Klebsiella pneumonia*, and *Proteus merabilus* bacteria and against *Candida albicans*, *Cryptococcus albidus*,

Candida guilliermondii, *Rhodotorulamucilaginosa*, *Candida krusei*, and *Candida utilis* fungi by applying cup plate method using nutrient agar medium and dimethyl sulfoxide that used as a sample solution.

The test organisms were first cultured in nutrient broth and incubated for 24 hours at 37°C and then freshly prepared bacterial cells were spread onto the Nutrient Agar while fungal spores onto Potato Dextrose Agar in laminar flow cabinet. The tested compounds were previously dissolved in dimethyl sulfoxide then (0.1 mL) of each compound (known concentration) was added in the cups and the Petri dishes were subsequently incubated at 37°C for 24 hours. Inhibition zone produced by each compound was measured in (mm). Inhibition zones in (mm) are listed in Table (3).

RESULTS AND DISCUSSION

Sincecyclic imides, Schiff bases, azetidinones, and acetyl oxadiazoles are represent in all important biological active components, we planned in this work to synthesize new molecules containing biscyclic imides linked to Schiff base or their derivatives followed by antimicrobial screening. Performing this target was made by multistep synthesis based on pyromelliticdiimide and all these synthetic steps were summarized in Scheme 1.

The first step involved preparation of unsubstitutedpyromelliticdiimide [1] through the reaction of pyromelliticdianhydride with urea following two methods either by heating the mixture to high temperature or by irradiation the mixture with microwave for few minutes.

FTIR spectrum of compound [1] clear absorption bands at (3448 and 3197) cm^{-1} due to v(N-H) imide, 1770 cm^{-1} due to asym. v(C=O) imide, (1716 and 1693) cm^{-1} due to sym. v(C=O) imide, and at 1566 cm^{-1} due to v(C=C) aromatic[19]. Compound [1] represented the parent compound in this work from which all the target derivatives were synthesized, thus in the second step compound [1] was converted to its potassium [2] by mean of alcoholic KOH in order to increase nitrogen atom nucleophilicity and prepare it to the next step.

The third step involved introducing of compound [2] in reaction with ethyl chloroacetate. The reaction was proceed through nucloephilic attack of negative nitrogen in compound [2] on electron – deficient carbon in ethyl chloroacetateproducingpyomelliticdiimidyl acetate ester [3] confirmed with positive results in characteristic test for esters.

FTIR spectrum of compound [3] showed absorption bands at (1774, 1720, and 1392) cm^{-1}due to v(C=O) ester, v(C=O) imide, and v(C-N) imide respectively. Other bands appeared at (1215 and 1118) cm^{-1} belong to v(C-O) ester[19].

^{1}HNMR of compound [3] showed triplet signal at δ=1.2ppm belong to (CH_3) protons, quartet signal at δ=(4.2-4.4)ppm belong to (-OCH_2CH_3) protons, signal at δ=4.5ppm belong to (-N-CH_2-CO-) protons and signal at δ=8.3ppm belong to aromatic protons[19].

^{13}CNMR spectrum of compound [3] showed signals at (13.9, 48.4, and 61.5) ppm belong to (CH_3, (-OCH_2-), and (-N-CH_2-)) carbons. Signals for aromatic carbons appeared at (118.1-137.2) ppm and signals for (C=O) imide and (C=O) ester appeared at 165.5ppm and (167.1-168.4) ppm respectively[19].

Compound [3] was converted subsequently in the fourth step to the corresponding acetohydrazide [4] via treatment with hydrazine hydrate. The reaction involved replacement of ethoxy ester group with ($NHNH_2$) group throughnucleophilic substitution reaction including the attack of the strong nucleophile (-NH_2 hydrazine) on carbonyl group.

FTIR spectrum of compound [4] showed disappearance of absorption bands belong to v(C=O) and v(C-O) ester and instead appearance of two absorption bands at (3321 and 3267) cm^{-1} belong to v(NH-NH_2). Other absorption bands appeared at (1666, 1639, 1566, and 1377) cm^{-1} which belong to v(C=O) imide, v(C=O) amide, v(C=C) aromatic, and v(C-N) imide respectively[19].

In the fifth step of this work, compound [4] was introduced in condensation reaction with different aromatic aldehydes in absolute ethanol under reflux condition giving three new Schiff bases [5-7].

FTIR spectrum of compound [5] showed absorption bands at (3414 and 3390) cm^{-1}due to v(O-H) and v(N-H). Other bands appeared at (1743, 1693, 1620, 1581, and 1354) cm^{-1} which belong to v(C=O) imide, v(C=O) amide, v(C=N) imine, v(C=C) aromatic, and v(C-N) imide respectively[19].

FTIR spectra of compounds [6] and [7] showed absorption bands at ((3174-3159), 1658, (1624-1600), 1562, and (1361-1357)) cm^{-1} which belong to (NH) amide, (C=O) imide and amide, (C=N), (C=C) aromatic, and (C-N) imide respectively[19].

^{13}CNMR spectrum of compound [62] showed signals at (41.8, (100-135), 157.6, 161.4, and 169.9) ppm belong to (CH_2) carbon, aromatic carbons, (C=N), (C=O)amide, and (C=O) imide carbons respectively[19].

^{1}HNMR spectrum of compound [6] showed signals at δ=(7.51-7.89) ppm belong to aromatic protons and signals at δ =(8.72 and 11.9) ppm belong to imine proton and NH proton respectively.^{13}CNMR spectrum of the same compound [6] showed signals at 55.7 ppm belong to (-CH_2-) carbon, signals at (128.3-133.7) ppm belong to aromatic carbons, and signal at 161.4 ppm belong to (C=N) and (C=O) carbons[19].

^{1}HNMR spectrum of compound [7] showedsignal at 2.77 ppm belong to (N-CH_3) protons, signals at δ =(3.06, (6.45-7.51), and 8.27) ppm belong to (CH_2) protons, aromatic protons, and imine proton respectively.^{13}CNMR spectrum of compound [7] showed signals at (31-36) ppm belong to (N-CH_3) carbons, signal at 42 ppm belong to (CH_2) carbon, signals at (124.4-149.8) ppm belong to aromatic carbons, and signals at ((162.4-162.7) and (165.4-165.5)) ppm belong to (C=N) and (C=O) carbons respectively[19].

Schiff bases are known important compounds that serve as key intermediate in organic synthesis and can successfully introduced in reactions with many reagents through active imine group. Thus the prepared Schiff bases [5] and [6] were introduced in reaction with chloroacetyl chloride producing two new heterocyclic derivatives [8] and [9] which contain pyromelliticdiimide moiety linked to azeitidine ring through acetoamido group.

FTIR spectrum of compound [8] showed strong absorption band at 3417 cm-1 due to (O-H) and (N-H). Other absorptions appeared at (1724, 1685, 1624, 1531, and 1350) cm-1 due to v(C=O) imide, v(C=O) amide in lactam ring, v(C=O) amide, v(C=C) aromatic, and v(C-N) imide respectively.FTIR spectrum of compound [9] showed strong absorption bands at (3441, 3394) cm^{-1} due to v(N-H), absorption at (1739, 1658, 1562, and 1357) cm^{-1} due to v(C=O) imide, v(C=O) amide, v(C=C) aromatic, and v(C-N) imide respectively[19].

^{1}HNMR spectrum of compound [9] showed signals at δ=(1.2, 4.4, and 4.6) ppm belong to aliphatic proton in lactam ring, (-CH_2-) protons, and aliphatic proton (-CH-Cl) in lactam ring. Signals at δ=(7.3-7.45) and 9.55) ppm belong to aromatic protons and (NH) proton.^{13}CNMR spectrum of the same compound [9] showed signals at (8.5, 45.5, and 79.4) ppm belong to aliphatic carbon (-CH_2-Ph) in lactam ring, (-CH_2-), and aliphatic carbon (-C-Cl) respectively. Signals belong to aromatic carbons appeared at (112-152) ppm while signals for (C=O) amide and (C=O) imide appeared at ((160.5-165) and (168.5)) ppm respectively[19].

The present work also involved synthesis of new acetyl oxadiazole derivative [10] by introducing of the newly prepared Schiff base [7] in reaction with acetic anhydride under reflux. This reaction was proceed by nucleophilic attack by imine nitrogen in Schiff base on carbonyl group in acetic anhydride followed by another nucleophilic attack and ring closure.

FTIR spectrum of compound [10] showed absorption bandsat (1778, 1666, 1647, and 1562) cm^{-1} due to asym. and sym. v(C=O) imide, v(C=O) amide, v(C=N) oxadiazole, and v(C=C) aromatic respectively. Absorption bands due to v(C-N) imide and v(C-O-C) oxadiazole appeared at ((1350), and (1273, 1188)) cm^{-1} respectively[19].

^{13}CNMR spectrum of compound [10] showed signals at ((20.4), (67-69), and (79.5)) ppm belong to methyl, methylene carbons, and carbon in oxadiazole ring. Aromatic carbons signalsappeared at (101-130.9) ppm, signals for (C=N) and (C=O) amide appeared at ((158.6) and (159.7)) ppm, and finally signals for (C=O) imide appeared at (169) ppm[19].

Biological activity study

In this study, three of the newly synthesized compounds were chosen including Schiff base [7], azetidinone [8] and acetyl oxadiazole [10] derivatives to put in antimicrobial testing against different species of bacteria and fungi using hole- cup plate method.

The results indicated that compound [7] showed moderate antibacterial activity against *B. subtilus*, slight activity against *A. bowmanil*, and no activity against other microorganisms. Compound [10] showed moderate antibacterial activity against *A. bowmanil* and *C. albidus*, slight activity against *E. coli* and *P. merabilis*, and no activity against other microorganisms.On the other hand, compound [8] showed high antibacterial activity against all tested bacteria and fungi, and very high activity against *C. krusei*.

Table 1: Physical properties of compounds[1-4]

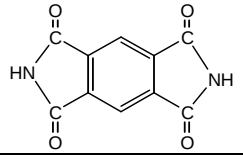
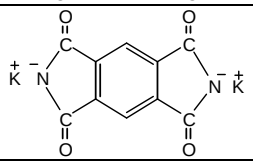
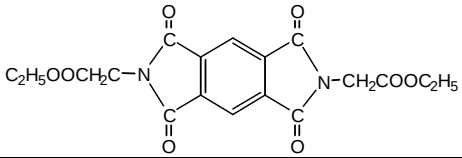
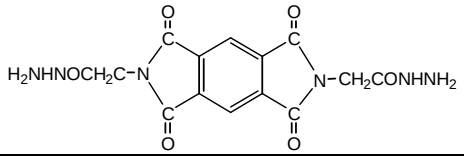
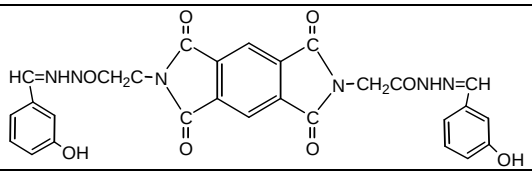
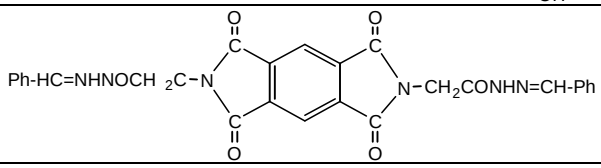
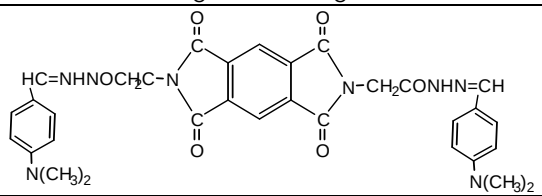
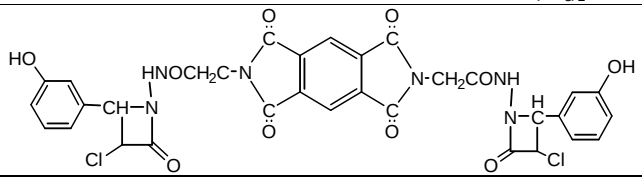
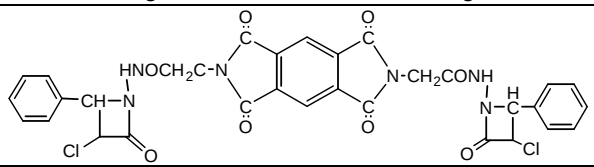
Comp. No.	Compound Structure	Colour	Melting point, °C	Yield, %	Recrystallization Solvent
1		White	>300	75-92	Ethyl acetate
2		Off white	>300	80	Acetone
3		Yellow	>300	68	Glacial acetic acid
4		Yellow	>300	60	Petroleum ether

Table 2: Physical properties of compounds [5-10]

Comp. No.	Compound Structure	Colour	Melting point, °C	Yield, %	Recrystallization Solvent
5		Yellow	>300	72	Ethanol
6		Yellow	208-210	70	Ethanol
7		Orange	>300	74	Ethanol
8		Black	>300	71	Methylene dichloride
9		Black	>300	76	Methylene dichloride

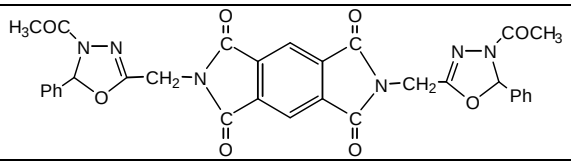
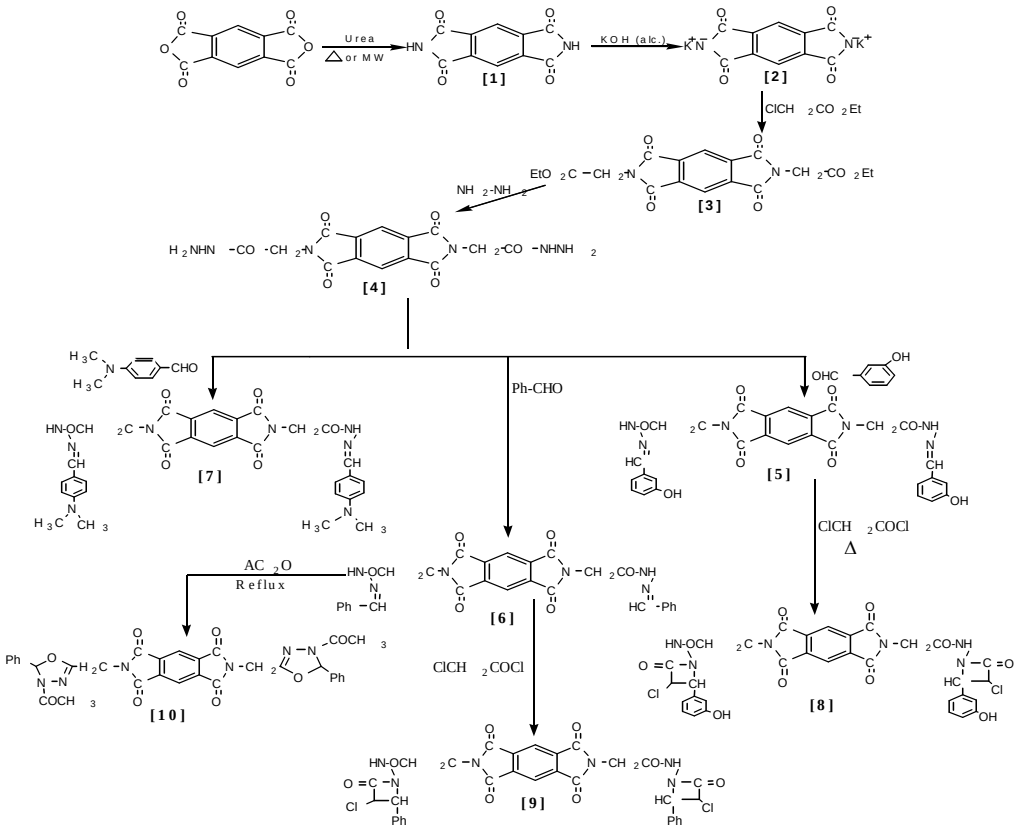
Comp. No.	Compound Structure	Colour	Melting point, °C	Yield, %	Recrystallization Solvent
10		Yellow	>300	60	Dioxane

Table 3: Biological activity of different compounds against different microorganisms

Species	Inhibition zone for 24 hrs., mm							
	Comp. [66]			Comp. [64]	Comp. [65]	Comp. [71]	Comp. [73]	Comp. [74]
	0.005 g/mL	0.01 g/mL	0.02 g/ mL	0.02 g/ mL	0.02 g/ mL	0.02 g/ mL	0.02 g/ mL	0.02 g/ mL
Serratiamarcescens	18	22	22	-	-	-	-	-
Klebsiellapneumonia	24	18	22	-ve	10	28	9	11
Pseudomonas aeruginosa	19	19	25	-ve	-ve	-ve	-ve	-ve
Bacillus subtilus	16	18	21	15	-ve	30	-ve	14
Actinobacterbowmanii	19	18	18	8	12	-ve	-ve	-ve
Proteus merabilis	-ve	-ve	22	-ve	10	12	-ve	-ve
Escherichia coli	19	20	22	-ve	8	15	6	10
Crytococcusalbidus	-ve	26	28	-ve	12	20	18	20
Candida guilliemondii	21	23	29	-ve	-ve	-ve	ve	-ve
Candida utilis	24	34	24	-ve	-ve	-ve	20	20
Candida gulliermondii	26	26	29	-ve	-ve	-ve	-ve	-ve
Candida krusei	-ve	34	39	-ve	-ve	-ve	-ve	-ve
Rhodorulamucilaginosa	-ve	28	27	-ve	-ve	-ve	-ve	-ve



Scheme (1): Synthetic route of the prepared derivatives (1-10).

REFERENCES

1. Zhou Q and Gallo JM. Quantification of sunitinib in mouse plasma, brain tumor and normal brain using liquid chromatography-electrospray ionization-tandem mass spectrometry and pharmacokinetic application. J Pharm Biomed Anal. 2010;51(4):958-964.
2. Andricopulo A Borchhardt D and Castilho M. Classical and Fragment-Based Hologram Structure-Activity Relationships for a Series of Analgesic Cyclic Imides. Lett Drug Des Discov. 2008;5(1):57-64.
3. Li J. Synthesis, Characterization and Antibacterial Activity of N-(N-Acetic Acid-yl-Phthalimide-5-yl) Maleamic Acid Dihydrate. J ChemCrystallogr 2010; 40(5), 428-431.
4. Abdel Aziz A, El-Azab A, Attia S, Al-Obaid A, Al-Omar M and El-Subbagh H. Synthesis and biological evaluation of some novel cyclic-imides as hypoglycaemic, anti-hyperlipidemic agents. Eur J Med Chemistry. 2011;46(9):4324-4329.
5. Hammud K. Science of imide with study case in Iraq: A mini review. Der Chemica Sinica, 2015;6(7):14-21.
6. Sharma S, Jain A, Aggarwal A and Gill N. Synthesis, Characterization and Pharmacological Evaluation of Novel Schiff Bases of Imide Moiety. J Med Sci. 2012;12(3):61-69.
7. Borchhardt D and Andricopulo A. CoMFA and CoMSIA 3D QSAR Models for a Series of Cyclic Imides with Analgesic Activity. Med Chem. 2009;5:66-73.
8. Sondhi S, Rani R, Roy P, Agrawal S and Saxena A. Microwave-assisted synthesis of N-substituted cyclic imides and their evaluation for anticancer and anti-inflammatory activities.Bioorg Med ChemLett. 2009;19(5):1534-1538.
9. Zhang Y, Zou B, Chen Z, Pan Y, Wang H, Liang H and Yi X. Synthesis and antioxidant activities of novel 4-Schiff base-7-benzyloxy-coumarin derivatives. Bioorg Med Chem Lett. 2011;21(22):6811-6815.
10. Belwal C and Joshi K. Pharmacological examination and synthesis of some Schiff bases and thiazolidinone derivatives of 5-amino-1H-imidazole-4-carboxamide. Der PharmaChemica. 2012; 4(5):1873-1878.
11. Patel N and Patel J. Synthesis and antimicrobial activity of Schiff bases and 2-azetidinones derived from quinazolin-4(3H)-one . Arabian J Chem. 2011;4(4):403-411.
12. Panneerselvam P, Reddy R, Murali K and Kumar N. Synthesis, analgesic, anti-inflammatory and antimicrobial activities of some novel Schiff's bases of 5-subsituted Isatin. Der PharmaChemica. 2010;2(1):28-37.
13. Zhang Y, Fang Y, Liang H, Wang H, Hu K, Liu X, Yi X and Peng Y.Synthesis and antioxidant activities of 2-oxo-quinoline-3-carbaldehyde Schiff-base derivatives. Bioorg Med ChemLett. 2013;23(1):107-111.
14. Parikh K, Oza P, Bhatt S and Parikh A. A synthesis of some new 2-azetidinones as potential antitubercular agents. Indian J Chem-Section B Org Med Chem. 2000;39(9):716-718.
15. Vashi B, Mehta D, and Shah V. Synthesis and biological activity of 4-thiazolidinones, 2-azetidinones, 4-imidazolinone derivatives having thymol moiety. Indian J Chem- Section B Org Med Chem.1995;34:802-808.
16. Patel K and Mehta A. Synthesis and antifungal activity of azetidinone and thiazolidinone derivatives of 2-amino-6-(2- naphthaleneyl) thiazolo [3,2-d] thiadiazole. Eur J Chem. 2006;3: 267-273.
17. Singh G, Mbukwa E and Pheko T. Synthesis and antimicrobial activity of new 2-azetidinones from N-(salicylidene)amines and 2-diazo-1,2-diarylethanones. ARKIVOC. 2007;ix:80-90.
18. Al-Azzawi A and Hammud K. Synthesis and Characterization of Some New 1,3,4-Oxadiazole and 1,2,4- Triazole Derivatives Based on 3,4,5,6 Tetrachlorophthalimide. Iraqi. J Sci. 2013; 54(4):782-788; Al-AzzawiA. and Hamd A., Synthesis, Characterization, and Antimicrobial Activity Evaluation of New Cyclic Imides Containing 1,3,4-Thiadiazole and 1,3,4- Oxadiazole Moieties. Int J Res Pharm Chem. 2013;3(4):890-897.
19. Al-Obaidi K. Synthesis, characterization of new heterocyclic derivatives, and studying the possibility for their applications as surfactants, antimicrobial agents and corrosion inhibitors, Department of Chemistry, College of Science,

Baghdad University, Baghdad, Iraq. 2013.
20. Silverstein R, Bassler G and Kiemle D. Spectroscopic Identification of Organic Compounds, John Wiley & Sons, New Jersey, 2005, 7thEdn.