Baraa H. Latief et al /J. Pharm. Sci. & Res. Vol. 10(12), 2018, 3047-3051

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Synthesis of New Cyclic Imides Comprising Antipyrine and Thiazole Cycles

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Abstract:
In this work a variety of new cyclic imides bearing both antipyrine and thiazole moieties were synthesized. Synthesis of the new imides was based on the key compound [2] 2-amino-4-(antipyrine-4-yl-amino)thiazole which was prepared via reaction between 4-(2-chloro acetamido)antipyrine [1] and thiourea. The target imides were synthesized by two steps in the first one compound [2] was introduced in reaction with different cyclic anhydrides affording amic acids [3-6] and these inturn were dehydrated by fusion in the second step affording the target imides [7-10]. Naphthalimide [11] is the only imide that was synthesized by direct fusion of key compound [2] with napthalic anhydride.

Keywords; Cyclic imides, antipyrine, thiazole, amic acids, key compound.

1. Introduction

Cyclic imides and their derivatives have received considerable attention owing to their effective biological importance [1,2] including anti-inflammatory [3], antibacterial [4,5], anticancer [3] and analgesic [6] activities, thus they are used as versatile building blocks in synthesis of many drugs and pharmaceuticals. On the other side heterocycles in particular azoles [7,8] form the basis of different pharmaceuticals, drugs and agrochemical products due to their wide spectrum of biological activities such as anticancer, antiviral, antimicrobial and anti-inflammatory activities [9,10]. According to all these points it seems worthy to build new molecules by combination of both cyclic imide and azoles in the same molecule which may exert potentially biological activities.

The present work involved synthesis of new molecules containing two azole moieties, namely (antipyrine and thiazole) beside different imide cycles. The newly synthesized molecules are expected to exhibit biological activity due to the presence of three biologically active segments in their structures.

2. Materials And Methods

The used chemicals in this work were purchased by Aldrich, BDH, Fluka and Merk companies.

Synthesis of 4-(2-chloro acetamido) antipyrine [1] [11]

A mixture of (0.01mol, 2.03g) of 4-aminoantipyrine and (0.01 mol, 0.56 gm) of chloro acetyl chloride in (25 mL) chloroform was refluxed in the presence of K_2CO_3 (0.01mol, 0.69 gm) for about 12 hrs. After removing of excess solvent the residue was stirred with water (25 mL). The formed precipitate was filtered, washed with sodiumbicarbonat solution (5%) and subsequently with distilled water, dried and purified by recrystallization from ethanol to afford Yellow crystals in (84%) Yield and m.p (139-141) $^{\circ}$C.

Synthesis of 2-amino-4- (antipyrine-4-yl-amino) thiazole [2] [12]

To a methanolic solution of compound [1] (0.01 mol, 2.79 gm) in (25 mL) methanol, thiourea (0.01 mol, 0.76 gm) was added then the mixture was refluxed for (12 hrs). After distillation of methanol the residue was poured into crushed ice with stirring and the obtained solid was filtered, dried then recrystallized from methanol to furinsh a pale yellow solid. Yield (81%), m.p (73-75) $^{\circ}$ C.

Synthesis of N-[4-(antipyrine-4-yl- amino) thiazole-2-yl] amic acids [3-6] [8]

The titled amic acids [3-6] were synthesized via addition of (0.01mol, 3.01gm) of compound [2] dissolved in (30 mL) dry acetone to (0.01mol) of cyclic anhydride (maleic, phthalic, citraconic or tetrachloro phthalic anhydrides) dissolved in (20 mL) dry acetone with cooling and stirring. After completion of addition the mixture was stirred at room temperature for additional two hours then the obtained solid was filtered, washed with diethyl ether twice, dried then recrystallized from a suitable solvent. Physical properties of amic acids [3-6] are shown in Table (1).

Synthesis of N-[4-(antipyrine-4-yl-amino) thiazole-2-yl] imides [7-10] [5]

The titeld imides [7-10] were synthesized via dehydration of amic acids [3-6]. Amic acid was heated until fusion then temperature was kept at ten degrees above melting point of amic acid for two hours. The resulted product was left at room temperature and the obtained solid was purified by recrystallization from a suitable solvent.

Synthesis of N-[4-(antipyrine-4-yl- amino) thiazole-2-yl] naphthalimide [11] [13]

The titled imide [11] was synthesized via heating the mixture of (0.01 mol, 3.01 gm) of compound [2] with (0.01 mol, 1.98 gm) of naphthalic anhydride until complete fusion. The mixture was kept at fusion temperature for two hours, then cooled and the resulted solid was purified by recrystallization.

Physcial properties of the prepared imides are shown in Table (2).

Antibacterial activity study

The cup plate method was used in studying the antibacterial activity of the prepared cyclic imides against many types of bacteria using gentamicin as the reference compound. Nutrient agar medium was used beside DMSO as sample solution and sample volume for all the studied compounds was fixed as (0.1 mL) . Cups were scooped out of agar medium contained in a petridish which was previously incubated with the microorganisms. The test compound solution (0.1mL) was added in the cups and the petridishes were incubated at 37°c for 48 hrs. Zones of inhibition caused by each compound was measured in mm and the results are listed in Table (5).

3- Result And Discussion

In continuation of our interest in synthesis of different cyclic imides bearing different heterocycles the present work involved building of new molecules by combination of two azole cycles namely (antipyrine and thiazole) with different imide cycles together in the same molecule. The new target molecules were expected to exhibit high biological activity since they contain three known biologically active components.

Synthesis of the target compounds involved many steps which are summarized in scheme (1).

In the first step 4-amino antipyrine was introduced in nucleophilic substitution reaction with chloro acetyl chloride producing compound [1] 4-(2-chloro acetamido) antipyrine which in turn was introduced in the second step in nucleophilic reaction with thiourea followed by ring closure producing compound [2] 2-amino-4-(antipyrine-4-yl-amino) thiazole.

By these two steps we build a new molecule that contains two heterocycles antipyrine linked to thiazole ring through (NH) group.

In compound [2] the presence of amino group at position two in thiazole ring gives the opportunity for introducing this compound in reaction with different cyclic anhydrides in the third step producing the corresponding amic acids [3-6] N-[4-(antipyrine-4-yl-amino) thiazole-2-yl] amic acids.

Dehydration of amic acids [3-6] in the fourth step by fusion method afforded the corresponding N-[4-(antipyrine-4-yl-amino) thiazole-2-yl] imides [7-10].

In the case of N-[4-(antipyrine-4-yl-amino) thiazole-2-yl] naphthalimide [11] the synthesis is performed by fusion the mixture of compound [2] with naphthalic anhydride [13].

Characterization of the synthesized compounds was performed by depending on FTIR and NMR spectral data.

FTIR spectrum of compound [1] showed absorption band at 3188 cm^{-1} due to υ (N-H) amide and other bands at 3039, 2929 and 2873 cm^{-1} which are due to υ (C-H) aromatic, asym. and sym. υ (C-H) aliphatic respectively [14]. The spectrum showed also clear absorption bands at 1691 cm^{-1}, 1639 cm^{-1}, 1614 cm^{-1} and 788 cm^{-1} which are attributed to υ (C=O) amide, υ (C=O) in antipyrine ring, υ (C=C) and υ (C-Cl) respectively [15].

FTIR spectrum of compound [2] showed disapperance of υ (C=O) amide and υ (C-Cl) absorption bands and apperance of two bands at 3429 and 3386 cm^{-1} due to asym. and sym. υ (NH_2). Other bands appeared at 1660 cm^{-1}, 1589 cm^{-1} and 636 cm^{-1} which are due to υ (C=O) in antipyrine ring, υ (C=C) and υ (C-S) respectively [14], while bands due to υ (C-H) aromatic and υ (C-H) aliphatic appeared at 3045 cm^{-1}, 2975 cm^{-1} and 2815 cm^{-1}.

^{1}H-NMR spectrum of compound [2] showed signals at δ = (2.09-2.2) ppm and (3.12-3.2) ppm belong to CH_3 and (-N-CH_3) protons, signals at δ = 3.89 ppm and 4.22 ppm belong to (NH) amine proton and vinylic proton and signals at δ = 7.16 and (7.30-7.54) ppm belong to (NH_2) protons and aromatic protons [14]. ^{13}C-NMR spectrum of compound [2] showed signals at (δ = 11.09 and 35.8) ppm belong to (CH_3) and (-NCH_3) carbons and signals at (δ = 103.79- 154.39) belong to aromatic carbons. Signals belong to vinylic carbons in antipyrine ring appeared at (δ = 156.44-162.14) ppm, signals belong to vinylic carbons in thiazole ring appeared at (δ = 171.10) ppm and signals belong to (C=N) and (C=O) carbons appeared at (δ = 181.84 – 184.34) ppm and (187.93- 188.23) ppm respectively [15].

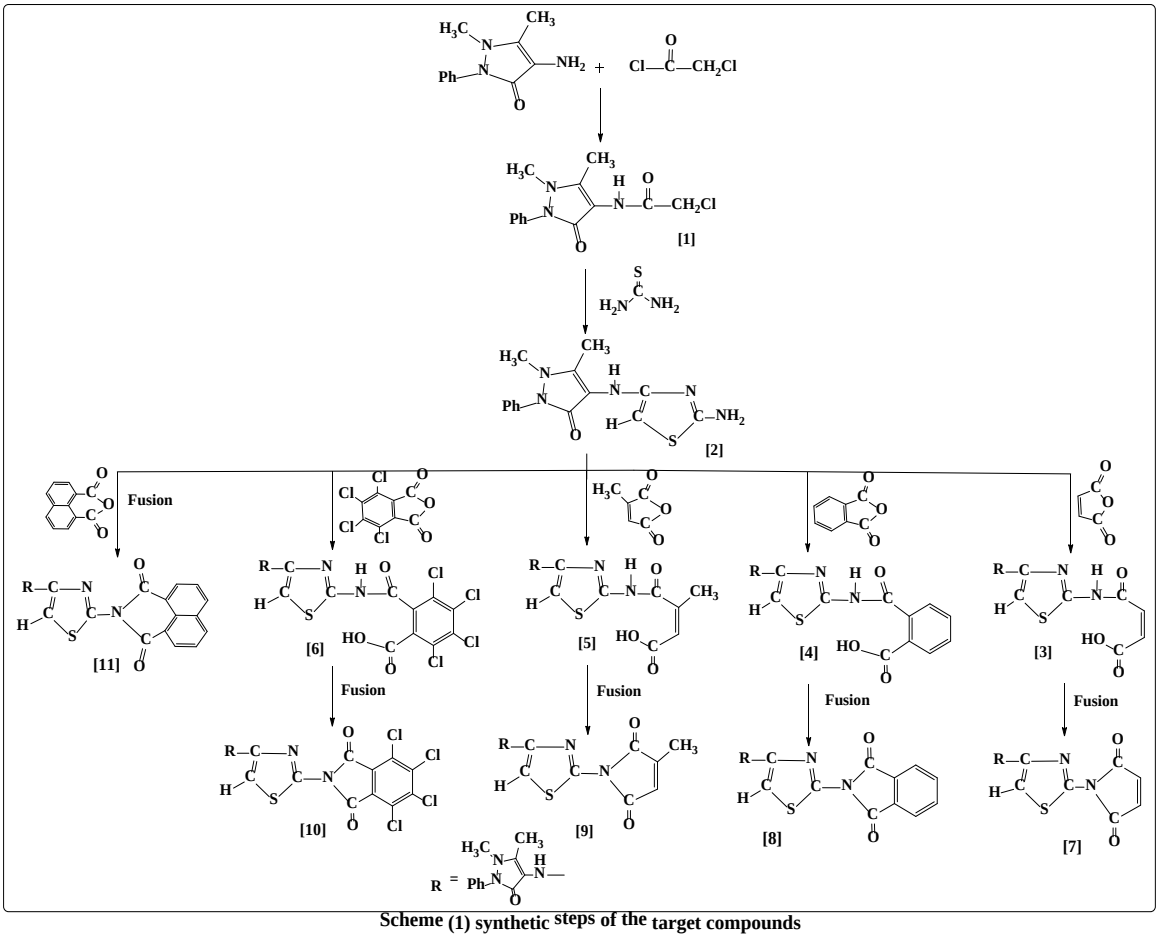
FTIR spectra of amic acids [3-6] showed clear absorption bands at (3436- 3477) cm $^{-1}$ and (3197-3413) cm^{-1} due to υ (O-H) and υ (N-H).

Also other clear strong bands appeared at (1718-1735) cm^{-1} , (1660-1699) cm^{-1}, (1620- 1637) cm^{-1} and (1548-1583) cm^{-1} which are attributed to υ (C=O) carboxyl, υ (C=O) amide, υ (C=N) in thiazole ring and υ (C=C) respectively. Absorbtion bands due to υ (C-S), υ (C-H) aromatic and asym., sym. υ (C-H) aliphatic appeared at (638- 696) cm^{-1}, (3002-3060) cm^{-1}, (2935- 2983) cm^{-1} and (2831-2880) cm^{-1} respectively.

FTIR spectra of the newly synthesized imides [7-11] showed absorption bands at (3172- 3446) cm^{-1}, (3045-3064) cm^{-1}, (2931-2987) cm^{-1} and (2808- 2880) cm^{-1} due to υ (N-H) amine, υ (C-H) aromatic and asym., sym. υ (C-H) aliphatic.

Strong absorption bands appeared at (1706-1733) cm^{-1} due to υ (C=O) imide beside the appearance of shoulder bands at (1772-1778) cm^{-1} in FTIR spectra of imides [10] and [11] due to asym. υ (C=O) imide and this is a characteristic band for imides.

The spectra showed also other clear bands at (1660-1699) cm^{-1} , (1622-1658) cm^{-1} , (1577-1595) cm^{-1} , (1353-1402) cm^{-1} and (696-698) cm^{-1} which are attributed to υ (C=O) in antipyrine ring, υ (C=N), υ (C=C), υ (C-N) imide and υ (C-S) respectively [14].



Scheme (1) synthetic steps of the target compounds

FTIR spectral data of amic acids [3-6] and imides [7-11] are listed in Tables (3) and (4). ^{1}H-NMR spectrum of imide [7] N-[4-(antipyrine-4- yl- amino) thiazole-2-yl] maleimide showed signals at (δ = 2.22 and 3.18) ppm belong to CH_3 protons and (-N-CH_3) protons. Other signals appeared at (δ = 3.47) ppm, (7.21-7.22) ppm and (7.32-7.55) ppm which are belong to (NH) proton, vinylic protons and aromatic protons.

^{13}C-NMR spectrum of imide [7] showed signals at (δ = 10.74 and 36.3) ppm belong to (CH_3) carbon and (-N-CH_3) carbon. Signals belong to aromatic carbons and vinylic carbons appeared at (δ = 124.79-134.89) ppm and (154.02) ppm while signals belong to (C=N) and (C=O) carbons appeared at (δ = 173.58) and (174.34) ppm.

^{1}H-NMR spectrum of imide [9] N-[4-(antipyrine-4-yl-amino) thiazole-2-yl] citraconimide showed signals at (δ = 2.07-2.22) ppm belong to two CH_3 protons and at (δ = 3.2) ppm belong to (-N-CH_3) protons.

Signal belong to (NH) proton appeared at (δ = 3.39) ppm, signals belong to vinylic protons appeared at (δ = 6.5, 6.85) ppm and signals belong to aromatic protons appeared at (δ = 7.20-7.73) ppm.

^{13}C-NMR spectrum of imide [9] showed signals at (δ = 10.72, 19.02) ppm belong to two CH_3 carbons and signals at (δ = 35.54-36.30) ppm belong to (-N-CH_3) carbon. Other signals appeared at (δ = 123.99-134.73) ppm , (153.98-160.46) ppm and (171.22-171.62) ppm which are belong to aromatic carbons and vinylic carbons in antipyrine, thiazole and citraconimide cycles. Signals belong to (C=N) and (C=O) carbons appeared at (δ = 173.58) ppm and (174.34) ppm. ^{1}H-NMR spectrum of imide [11] N-[4-(antipyrine-4-yl-amino) thiazole-2-yl] napthalimide showed signals at (δ = 2.01-2.25) ppm and (3.24) ppm belong to CH_3 protons and (-N-CH_3) protons. The spectrum showed also signals at (δ = 3.41) ppm, (δ = 7.20) ppm and (7.26- 8.52) ppm which are belong to (NH) proton, vinylic proton and aromatic protons respectively [15].

^{13}C-NMR spectrum of imide [11] showed signals at (δ = 10.76-12.28) ppm and (35.77-36.30) ppm belong to CH_3 carbon and (-N-CH_3) carbon.

Signals for aromatic carbons appeared at (δ = 103.79-136.52) ppm, signals for vinylic carbons appeared at (δ = 155.03 and 161.75) ppm while signals belong to (C=N) and (C=O) carbons appeared at (δ = 164.05) ppm and (164.56) ppm respectively.

Table (1) Physical properties of amic acids [3-6]

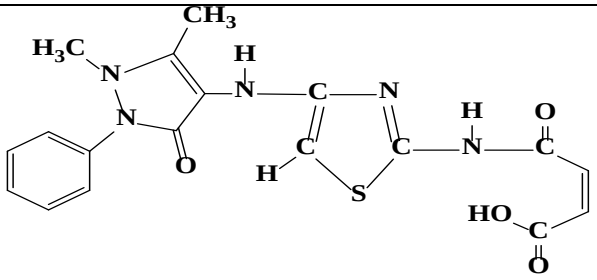
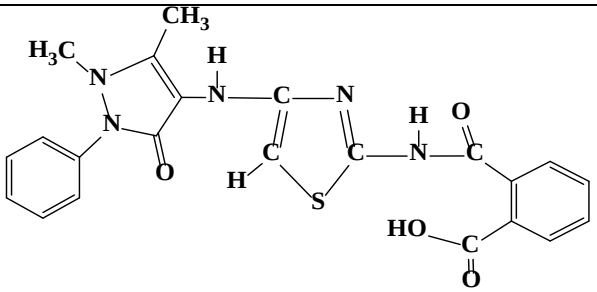
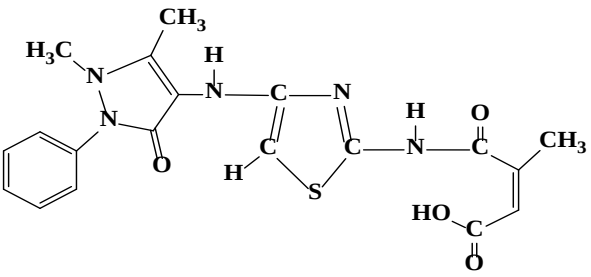
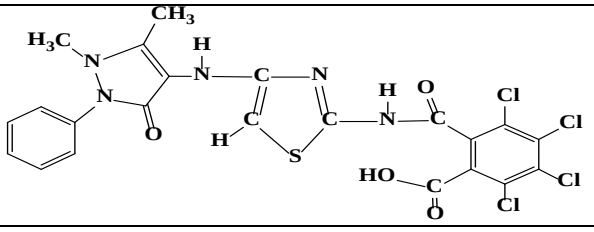
Comp. No	Compound Structure	Color	Melting Point c°	Yield %	Recrystallization Solvent
3		Orange	80-82	60	Ethanol
4		Redish brown	88-89	76	acetone
5		Deep red	gummy	81	acetone
6		Orange	110-112	93	Ethanol

Table (2) Physical properties of cyclic imides [7-11]

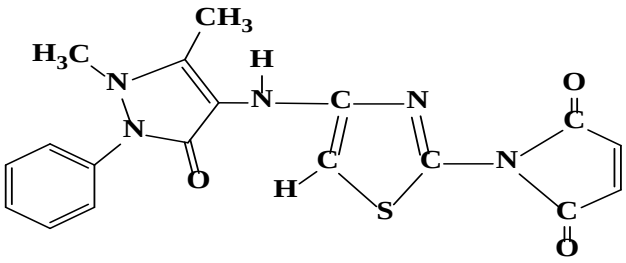
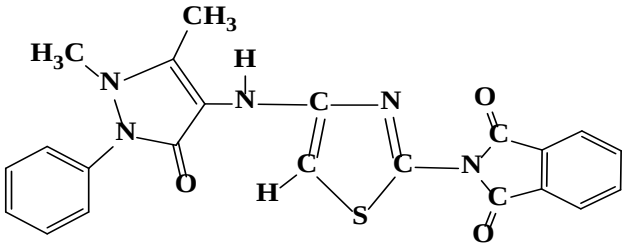
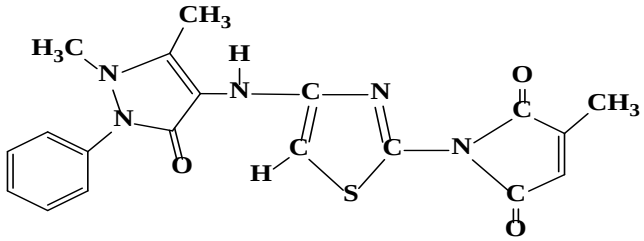
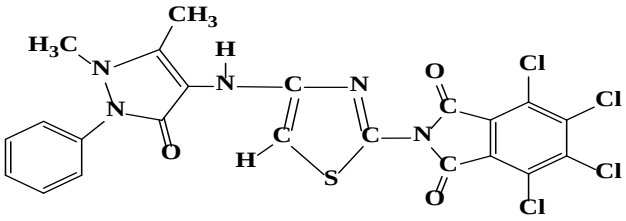
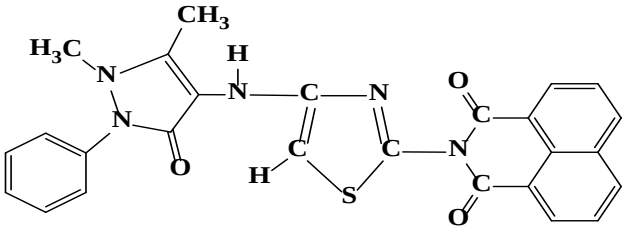
Comp. No	Compound Structure	Color	Melting Point c°	Yield %	Recrystallization Solvent
7		Brown	162-165	83	acetone
8		Dark red	248-250	81	Ethanol- acetone
9		Pale orange	193-195	68	acetone
10		Shine black	180-182	83	Ethanol - acetone
11		Deep brown	140-141	62	Ethanol - acetone

Table (3) FTIR spectral data (cm^{-1}) of amic acids [3-6]

Comp. No	υ (O-H) υ (N-H)	υ (C-H) Aromatic	υ (C-H) Aliphatic	υ (C=O) Carboxyl	υ (C=O) Amide	υ(C=N)	υ(C=C)	υ(C-S)	Others
3	3444 3382	3051	2935 2867	1722	1697	1625	1579	651	-
4	3477 3197	3060	2935 2831	1720	1660	1629	1577	638	-
5	3446 3384	3002	2937 2880	1718	1697	1637	1583	696	-
6	3436 3413	3040	2983 2860	1735	1699	1620	1548	644	υ(C-Cl) 1014

Table (4) FTIR spectral data (cm^{-1}) of cyclic imides [7-11]

Comp. No	υ (N-H)	υ (C-H) Aromatic	υ (C-H) Aliphatic	υ (C=O) Imide	υ (C=O) Antipyrine	υ(C=N)	υ(C=C)	υ(C-N) Imide	υ(C-S)
7	3446 3388	3049	2980 2808	1720	1689	1658	1591	1402	698
8	3400 3350	3045	2933 2860	1722	1699	1622	1577	1384	698
9	3444 3410	3064	2987 2880	1716	1660	1649	1595	1388	696
10	3444 3406	3045	2985 2819	1778 (sh.) 1733	1695	1637	1589	1369	696
11	3415 3172	3058	2931 2815	1772 (sh.) 1706	1677	1630	1587	1353	696

Table (5) Inhibition Zones of antibacterial activity of cyclicimides

Comp. No	*staphylococcus aureus*	*staphylococcus epidermidis*	*E.Coli*	*pseudomonas*
2	++	++	++	++
7	+++	+++	++	++
8	+++	+++	++	++
9	++	++	+++	+++
10	+++	+++	+++	+++
Gentamicin	+++	+++	+++	+++

Moderately active = ++ = inhibition zone 9-12 mm ; Highly active = +++ = inhibition zone > 13 mm

Anti bacterial Activity

Antibacterial activities of compound 2- amino-4- (antipyrine-4-yl-amino) thiazole [2] and the newly synthesized cyclic imides [7-10] were tested against four types of becteria including *staphylococcus aureus*, *staphylococcus epidermidis*, *Eshreshia coli* and *pseudomonas*. Inhibition Zones resulted from each tested compound are listed in Table (5). The resultes indicated that compounds [7], [8] and [10] showed high activity against *staphylococcus aureus and staphylococcus epidermidis* while compounds [9] and [10] are highly active against *Eshreshia coli* and *pseudomonas.* Other compounds showed moderate activity against the tested bacteria.

REFERENCES

[1] Al- Azzawi, A. M. and Hassan, A. S. Synthesis and antimicrobial activity of new succinimides bearing different heterocycles. International Journal of Research in pharmacy and chemistry. 2014, 4 (4), 755- 762.

[2] 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 hypoglycemic, anti-hyperlipidemic agents. European Journal of Medicinal Chemistry. 2011, 46 (9) , 4324-4329.

[3] Sondhi, S. M. , Rani, R. , Roy, P. , Agrawal, S. K. and Saxena, A. K. Microwave – assisted synthesis of N- Substituted cyclic imides and their evaluation for anticancer and anti-inflammatory activities. Bioorganic and Medical Chemistry Letters. 2009, 19, 1534-1538.

[4] Al-Azzawi, A. M. and Raheem, A.A. Synthesis and antibacterial screening of new Schiff bases based on N-(4-acetophenyl) succinimide. Iraqi Journal of Science. 2017, 58 (4A), 1790- 1800.

[5] Latief, B. H. and Al-Azzawi, A. M. Synthesis and antibacterial activity screening of new trimethoprime derivatives containing bis cyclic imides. International Journal of Science and Research. 2018 , 7 (5), 82- 85.

[6] Borchhardt, D. and Andricopulo, A. COMFA and COMSIA 3D QSAR models for a series of cyclic imides with analgesic activity. Medical Chemistry. 2009, 5, 66-73.

[7] Al- Azzawi, A. M. and Hamd, A. S. Synthesis, characterization and evaluation of biological activity of novel cyclic imides containing heterocycles based on 2,5- disubstituted- 1,3,4- thiadiazoles. Al-Anbar Journal of Veternary Science. 2011, 4 (2), 152-164.

[8] Al- Azzawi, A. M. and Mehdi, S. A. Synthesis and evaluation of antimicrobial activity of several new maleimides linked to benzothiazole moiety. Journal of Baghdad for Science. 2013, 10 (3), 658- 672.

[9] Al- Azzawi, A. M. and Hamed, A. S. Synthesis and antimicrobial screening of new naphthalimides linked to oxadiazole, thiadiazole and triazole cycles. International Journal of Research in Pharmacy and Chemistry. 2014, 4 (2) , 283- 290.

[10] Cherala, S. , Lingbathula, H. , Ganta, R. , Ampati, S. and Manda, S. Synthesis and anti- inflammatory activity of a novel series of diphenyl- 1,2,4- triazoles and related derivatives. E- Journal of Chemistry . 2012, 9 (4), 2510- 2515.

[11] Al- Azzawi, A. M. Synthesis , Characterization and evaluation of antibacterial activity of several new 3,4- dimethyl maleimides and 1,8-naphthalimides containing 1,3,4- oxadiazole ring. Journal of Al-Nahrain University. 2011, 14 (1), 15-29.

[12] Singh, I. , Kaur, H. , Kumar, S. , Kumar, A. , Lata, S. and Kumar, A. Synthesis of new coumarin derivatives as antibacterial agents. International Journal of ChemTech Research. 2010, 2 (3), 1745-1752.

[13] Al- Azzawi, A.M. and Faiq, E. Synthesis and modification of new phenolic resins bearing pendant 1,8- naphthalimides. International Journal of Science and Research. 2017, 6 (8), 1498- 1504.

[14] Sliverstine, R.M. , Bassler, G.C. and kiemle, D.J. Spectroscopic Identification of organic compounds, 2005. Seventh Edition. John Wiley and Sons. NewYork.

[15] Aruldhas, G. Molecular structure and spectroscopy. 2014. Second Edition. P.H.I. Learning private limited, Delhi.