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Synthesis and Antibacterial Activity Screening of New Trimethoprim Derivatives Containing Bis Cyclic Imides

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Abstract: ***The present work involved synthesis of new trimethoprim derivatives containing bis cyclic imides. Synthesis of the new derivatives containing maleimide, citraconimide, succinimide, phthalimide and tetrachloro phthalimide cycles was performed by reaction of trimethoprim with cyclic anhydrides producing bisamic acids which inturn were dehydrated to the corresponding bis cyclic imides by fusion method, while synthesis of trimethoprim linked to bis 1, 8- naphthalimides was made by direct fusion of trimethoprim with 1, 8- naphthalic anhydride in glacial acetic acid. The new derivatives were characterized on the basis of their FTIR, ^{1}HNMR and ^{13}C-NMR spectra and the results of their antibacterial activity screening showed that they exhibit good antibacterial activity.***

Keywords: Trimethoprim, bisamic acids, biscyclicimide

1. Introduction

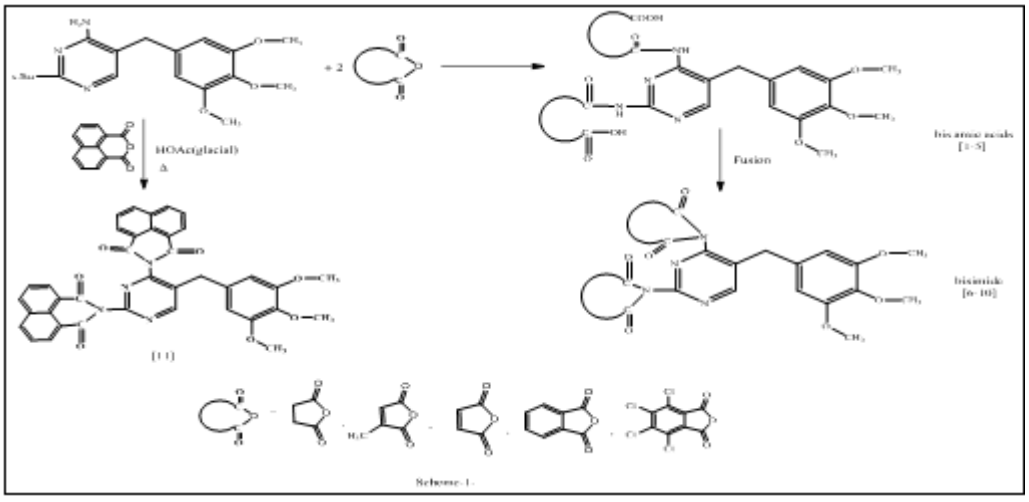
Cyclic imides are a valuable group of bioactive compounds which exhibit a variety of biological activities like antibacterial [1, 2], anticancer [3], analgesic[4], hypoglycemic[5], antimicrobial [6, 7] and anti inflammatory activities [3]. Besides they are important building blocks for synthesis of advanced materials, drugs and polymers [8, 9]. In the other side trimethoprim (TMP): 2, 4-diamino-5-(3, 4, 5-trimethoxy benzyl) pyrimidine is one of the most important synthetic antibiotics used in human and veterinary medicine world wide [10, 11].

Moreover (TMP) have a diversity of pharmaceutical uses like in treatment of bladder and middle ear infections, chemotherapy treatment, travelers diarrhea and as antimicrobial agent [12, 13]. Keeping in mind all these points we thought it is worthwhile to synthesize new molecules containing these two biologically active components (TMP and cyclic imide) together followed by screening their antibacterial activity.

2. Experimental

Melting points were determined on Thomas Hoover apparatus and were uncorrected.FTIR spectra were recorded on SHIMADZU FTIR- 8400 Fourier Transform Infrared spectrophotometer using KBr disc. ^{1}HNMR and ^{13}C-NMR spectra were recorded on Bruker 500MH$_Z$ instrument using DMSO-d_6 as solvent and TMS as internal standard.

1) Preparation of trimethoprim bis amic acids [1-5]
The titled compounds were prepared according to literatures [8, 9] via dropwise addition of (0.02 mol) of cyclic anhydride (Succinic, maleic, citraconic, phthalic and tetrachlorophthalic) anhydride dissolved in (25mL) of acetone to the mixture of (0.01 mol, 2.78 g) of trimethoprim dissolved in (20 mL) of acetone with cooling and stirring. After completion of addition the mixture was stirred for two hours and the formed precipitate was filtered, washed with acetone, dried and finally recrystallized from a suitable solvent. Physical properties of bis amic acids [1-5] are listed in Table -1.



2) Preparation of trimethoprim bis imides [6-10]
The titled compounds [6-10] were synthesized via dehydration of bis amic acids [1-5] by fusion method through heating (1gm) of bis amic acid in oil bath until melting then the temperature was raised for ten degrees above melting point for 2hrs [8]. The resulted solid product was recrystallized from a suitable solvent. Physical properties of bisimides [6-10] are listed in Table -2.

3) Preparation of trimethoprim bis naphthalimide [11]
The titled imide [11] was prepared by mixing and grinding (0.02 mol, 3.96 g) of naphthalic anhydride and (0.01 mol, 2.78 g) of trimethoprim then (25 mL) of glacial acetic acid was added and the mixture was heated in oil bath for 2hrs. The resulted product was recrystallized from cyclohexane. Physical properties of compound [11] are listed in Table-2.

4) Antibacterial activity study
The cup plate method was used in studying the antibacterial activity of the prepared bis imides against many types of bacteria. Nutrient agar medium was used beside DMF 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 ℃ for 48 hrs. Zones of inhibition caused by each compound was measured in mm and the results are listed in Table-5

3. Results and Discussion

Since both trimethoprim and cyclic imides are important biologically active components that exhibit wide spectrum of biological activities and applications the core of the present work is synthesis of new derivatives that contain these two active components linked together in the same molecule then evaluate their antibacterial activity. Performing this target is done by two steps in the first step a series of five bis amic acids linked to trimethoprim [1-5] are prepared via direct reaction between trimethoprim and cyclic anhydrides including: (succinic, maleic, citraconic, phthalic and tetrachlorophthalic) anhydrides. The reaction was proceeded through nucleophilic attack of two amino groups present in trimethoprim molecule on electron-defficient carbon of carbonyl groups present in cyclic anhydride. The resulted bisamic acids were dehydrated in the second step via fusion method producing the corresponding bis cyclic imides [8]. On the other hand trimethoprim derivative linking to 1, 8- naphthalimide was prepared via fusion the mixture of 1, 8- naphthalic anhydride, trimethoprime and glacial acetic acid for two hours. In this case the first product of reaction is bisnaphthalamic acid which was not separated but instead converted directly under the influence of heat and glacial acetic acid to the corresponding bisnaphthalimide. Synthetic route of the newly synthesized compounds was shown in scheme -1 while their physical properties are listed in Tables -1 and 2.

Chemical structures of the prepared compounds were cofirmed in the basis of their FTIR, ^{1}H-NMR and ^{13}C-NMR spectral data.

FTIR spectra of amic acids [1-5] showed clear absorption bands at (3400-3421) cm^{-1} and (3159-3365) cm^{-1} due to υ (O-H) carboxylic and υ (N-H) amide. Absorption bands due to υ (C=O) carboxyl and amide appeared at (1658-1733) cm^{-1} while absorption bands due to υ (C=N), υ (C=C), asym. and sym. υ (C-O-C) ether appeared at (1589-1622) cm^{-1}, (1506- 1595) cm^{-1}, (1234-1261) cm^{-1} and (1126-1130) cm^{-1} respectively [14].

On the other hand FTIR spectra of the prepared bisimides [6-11] showed disappearance of υ (O-H) carboxyl and υ (N-H) amide absorption bands and appearance of strong clear absorption band at (1710-1741) cm^{-1} beside sholder absorption band at (1764-1791) cm^{-1} due to sym. and asym. υ (C=O) imide. These two points are clear proofs for success of bis imide formation. Other absorption bands appeared at (1587-1672) cm^{-1}, (1548-1593) cm^{-1}, (1332-1373) cm^{-1}, (1238-1242) cm^{-1} and (1124-1126) cm^{-1} which are attributed to υ (C=N), υ (C=C), υ (C-N) imide, asym. υ (C-O-C) ether and sym. υ (C-O-C) ether respectively [14]. All details of FTIR spectral data of bis amic acids [1-5] and bis imides [6-11] are listed in Tables-3 and 4.

^{1}H-NMR spectrum of trimethoprim bis succinamic acid [1] showed two clear signals at (δ = 2.73 and 2.86-2.89) ppm belong to eight protons present in two succinamic moieties (-CO-CH_2CH_2CO-), beside clear signal at (δ = 3.40-3.42) ppm belong to (-CH_2-) benzylic protons. The spectrum showed also two signals at (δ = 3.63 and 3.73) ppm belong to nine protons of three methoxy groups. Signals belong to aromatic protons and pyrimidine ring proton appeared at (δ = 6.38, 7.95 and 8.32) ppm respectively while signals belong to (NH) amide protons and (OH) carboxyl protons appeared at (δ = 9.34 and 11.93) ppm respectively [14].

^{1}H-NMR spectrum of trimethoprim bismaleamic acid [2] showed singlet signal at (δ = 3.34)ppm belong to (CH_2) benzylic protons and two signals at (δ = 3.85-3.89) ppm belong to nine protons of three methoxy groups. Other signals appeared at (δ = 5.14, 5.17, 5.31) ppm belong to four vinylic protons, signals at (δ = 7.69 and 7.99) ppm belong to aromatic protons and proton in pyrimidine ring and signals at (δ = 10.30 and 11.83) ppm belong to (NH) amide protons and (OH) carboxyl protons. ^{1}H-NMR spectrum of trimethoprim bissuccinimide [6] showed two strong signals at (δ = 2.72 and 2.88) ppm belong to aliphatic protons in succinimide rings. The spectrum showed also two signals at (δ = 3.40 and 3.56) ppm belong to (CH_2) benzylic protons and nineprotons of three methoxy groups beside signals at (δ = 7.33, 7.95) and 8.36 ppm which belong to aromatic protons and proton in pyrimidine ring.

^{13}C-NMR spectrum of compound [6] showed signals at (δ = 31.19, 31.26 and 36.24) ppm belong to aliphatic carbons in succinimide rings and benzylic carbon. Other signals appeared at (δ = 66.79, (127-127.52), (162.67-162.85) and 179.39) ppm which are belong to (OCH_3) carbons, aromatic carbons, (C=N) carbons and (C=O) imide carbons respectively.

^{1}H-NMR spectrum of trimethoprim bismaleimide [7] showed signals at (δ = 3.55 and 3.63, 3.74) ppm belong to benzylic protons and protons of three methoxy groups. Signal belong to vinylic protons appeared at (δ = 6.62) while signals belong to aromatic protons and pyrimidine ring proton appeared at (δ = 7.45- 7.63) ppm and 8.11 ppm respectively.

^{1}H-NMR spectrum of trimethoprim biscitraconimide [8] showed singlet signal at (δ = 1.86) ppm belong to two methyl groups protons and signal at (δ = 3.60) ppm belong to (CH_2) benzylic protons. Two signals appeared at δ = 3.63 and (3.71-3.74) ppm belong to nine protons of three methoxy groups. Other signal appeared at δ = (6.08-6.09) ppm, (6.62-7.52) and 7.96 ppm which belong to vinylic protons, aromatic protons and pyrimidine ring proton respectively.

^{13}C-NMR spectrum of compound [8] showed signals at (δ = 23.25- 23.41) ppm and (32.59) ppm belong to methyl carbons and benzylic carbon.

Other signals appeared at δ = (55.76- 60.90), (106.24-109.29) ppm, (133.56- 144.52) ppm, (153.31- 154.97) ppm, (164.39) and (167- 168.) ppm which are belong to OCH_3 carbons, vinylic carbons, aromatic carbons, pyrimidine ring carbons, (C=N) carbons and (C=O) carbons respectively.

^{1}H-NMR spectrum of trimethoprim bis 1, 8- naphthalimides [11] showed signals at δ = 3.60, (3.69- 3.81) ppm belong to benzylic protons and proton of three methoxy groups. Other signals appeared at (δ = 5.97- 6.68) ppm and (7.46- 7.95) ppm belong to aromatic protons and signal at (δ = 8.18) ppm belong to pyrimidine ring proton. ^{13}C-NMR spectrum of compound [11] showed signals at (δ = 32.60) ppm and (55.73- 62.40) ppm belong to benzylic carbon and OCH_3 carbons. Other signals appeared at (δ = 106.12- 140.74), (153.28- 155.55), (164.38- 164.65) and (167.25- 167.39) ppm which are belong to aromatic carbons, pyrimidine ring carbons, (C=N) carbons and (C=O) carbons respectively.

Anti bacterial Activity

Antibacterial activity of the newly synthesized bisimides [6-11] were tested against four types of bacteria including *staphylococcus aureus, pseudomonas aeruginosa, Escherichia coli and streptococcus pneumonia*. Inhibition Zones resulted from each tested compound are listed in Table-5. The results indicated that compounds [6, 7, 8 and 10] showed very high activity against *pseudomonas aeruginosa*. Also compounds [6, 7, 8, 10 and 11] showed very high activity against *E-coli*. Compound [9] showed high activity against *staphylococcus aureus* and *streptococcus pneumonia* and compounds [7 and 10] showed high activity against *streptococcus pneumonia*. Other compounds showed moderate or weak activity against the tested bacteria.

Table 1: Physical properties of bis amic acids [1-5]

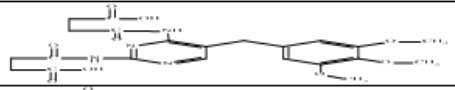
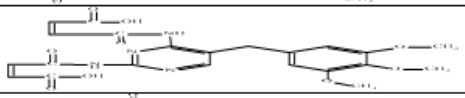
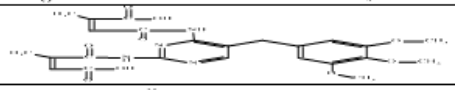
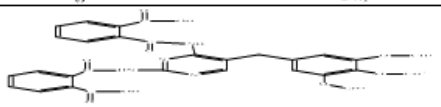
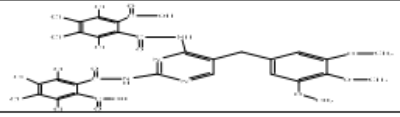
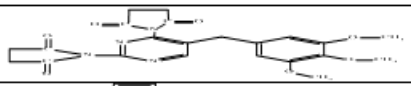
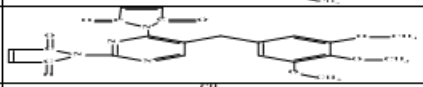
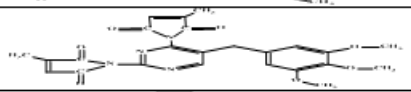
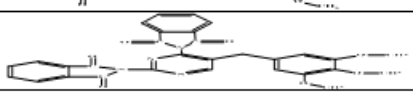
Comp. No	Compound Structure	Color	Melting Point ć	Yield %	Recrystallization Solvent
1		White	172-174	66	Ethanol
2		White	170-172	60	Ethanol
3		Pale yellow	180-181	82	Ethanol
4		White	194-196	74	Ethanol
5		White	100-102	85	Acetone

Table 2: Physical properties of bisimides [6-11]

Comp. No	Compound Structure	Colore	Melting Point ć	Yield %	Recrystallization Solvent
6		Off White	78-81	84	Ethanol
7		Black	81-83	70	Ethanol
8		Black	98-100	94	Dioxane
9		Dark Brown	88-90	88	Acetone

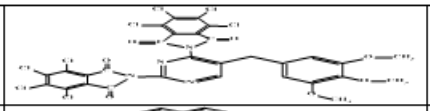
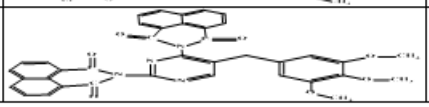
10		Black	278-280	75	Acetone
11		Brown	158-160	65	cyclohexane

Table 3: FTIR spectral data (cm-1) of bis amic acids [6-11]

Comp. No	υ (O-H) υ (N-H)	υ (C-H) Aromatic	υ (C-H) Aliphatic	υ (C=O)	υ (C=N)	υ (C=C)	υ(C-O-C) ether
1	3413, 3278 3159	2991	2939 2839	1658	1593	1506	1236 1128
2	3400, 3178	2990	2937 2821	1681 1688	1591	1564	1234 1126
3	3406, 3338 3180	3000	2935 2837	1681 1664	1589	1527	1240 1130
4	3421, 3350 3182	3000	2939 2839	1666	1591	1541	1242 1130
5	3410, 3365	3070	2977 2839	1733 1660	1622	1595	1261 1126

Table 4: FTIR spectral data (cm-1) of bis imide [6-11]

Comp. No	υ (C-H) Aromatic	υ (C-H) Aliphatic	υ (C=O)	υ (C=N)	υ (C=C)	υ (C-N)	υ (C-O-C) ether
6	2999	2943 2825	1718	1656 1631	1593	1332	1240 1124
7	2991	2939 2839	1774 1712	1622	1593	1332	1238 1126
8	3040	2937 2837	1718	1654 1622	1593	1332	1238 1124
9	3080	2939 2837	1764 1731	1623	1591	1367	1240 1124
10	3080	2939 2840	1791 1741	1587	1548	1373	1242 1124
11		2929 2880	1710	1672 1623	1589	1348	1240 1124

Table 5: Inhibition zones of antibacterial activity of bisimides in (mm)

Comp. No	*Stap. aureus*	*Pseudomonas aeruginosa*	*E.Coli*	*Streptococcus*
6	10	30	30	14
7	12	31	32	16
8	10	36	33	12
9	18	15	15	20
10	14	32	28	18
11	8	12	30	9

References

[1] Al- Azzawi, A. M. and Abd Al- Razzak, M. S. 2013. Synthesis, characterization and antibacterial screening of new Schiff bases linked to phthalimide. International Journal of Research in pharmacy and chemistry, 3(3): 682-690.

[2] Al- Azzawi, A. M. and Raheem, A. A. 2017. Synthesis and antibacterial screening of new Schiff bases based on N-(4-acetophenyl) succinimde. Iraqi Journal of science, 58-(4A): 1790-180.

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

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

[5] Abdel Aziz A., El-Azab A., Attia S., Al- Obaid A., Al-Omar M. and El- Subbagh H. 2011. Synthesis and biological evaluation of some novel cyclic imides as hypoglycemic, anti- hyperlipidemic agents. European Journal of Medicinal Chemistry, 46 (9): 4324-4329

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

[7] Al- Azzawi A. M. and Al-Obiadi K.K. 2016. Synthesis and antimicrobial screening of new bis Schiff bases and their acetyl oxadiazole, azetidinone derivatives derived from pyromelliticdiimide. International Journal of research in pharmacy and chemistry, 6(1): 1-8.

[8] Al- Azzawi A. M. and Yaseen H. K. 2017. Synthesis and copolymerization of several new N- (allyloxy phenyl) tetrachlorophthalimides. International Journal of Science and Research, 6(11): 1000- 1008.

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

[10] Kim S.H., Shon H.K. and Ngo H. H. 2010. Adsorption Characteristies of antibiotics trimethoprim on powdered and granular activated carbon. Journal of Industrial and Engineering chemistry, 16; 344-349.

[11] Al-Saidi K. H. and Yonis M. S. 2015. Simultaneous determination of sulphamethoxazole and trimethoprim in binary mixtures and in tablet using derivative spectrophotometry. Journal of Al- Nahrain university, 18 (1) : 46- 54.

[12] Joaquin R. Dominguez-Vargas. Valentine Carrillo-Perez. Teresa Gonzalez-Montero. Eduardo M. Cuerda-Correa. 2012. Removal of Trimethoprim by a Low-Cost Adsorbent: Influence of Operation Conditions. Water Air Soil Pollut, 223:4577-4588.

[13] Eiam- ong S., Kurtzman N.A. and Sabatini S. 1996. Studies on the mechanism of trimethoprim – induced hyperkalemia. Kidney International, 49: 1372- 1378.

[14] Pappas G., Athanasoulia A.P., Matthaiou D. K. and Falagas M. E. 2009. Trimethoprim – Sulfamethoxazole for methicillin- resistant staphylococcus aureus. Journal of Chemotherapy, 21: 115- 126.

[15] Sliverstine R., Bassler G. and kiemle D. Spectroscopic Identification of organic compounds, John Wiley and Sons, New Jersey, 2005. 7th Ed