RESEARCH ARTICLE

Synthesis and Characterization of the Novel Compounds Containing Imidazole, Thiadiazole, Schiff Base, and Azetidinone Chromospheres as a New Antibacterial Agents

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Received: 10th September, 2020; Revised: 22th October, 2020; Accepted: 21th November, 2020; Available Online: 25th Decemeber, 2020

ABSTRACT

In this study, a novel series of of 1-(4-substituted)-N-(5-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl) methanimine and 3-chloro-4-(4-substituted)-1-(5-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one derivatives were synthesized *by* the reaction of benzil with benzaldehyde in presence of ammonium acetate to get the imidazole derivatives. The imidazole intermediate then reacted with methyl chloroacetylchloride, thiosemicarbazide and sodium hydroxide respectively, to obtain 5-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine intermediate. Then, it will be converted into Schiff base derivatives which will be treated with chloroacetyl chloride to obtain the final products. The structures of the synthesized compounds were confirmed by the aid of ^{1}HNMR, ^{13}CNMR, mass spectroscopy and elemental analysis. In our conclusion, the antibacterial effects were tested with the use of tow Gram positive (*S. aureus* and, Enterococcus facaels,), two gram negative [*Escherichia coli* (*E. coli*), Klebsiella pneumonia], and anaerobic (*S. pyogen*) bacteria. Many synthesized compound concentrations were used and the findings were compared with expectations (cefixime and metronidazole). Some of the synthesized compounds demonstrate a considerable activity compared to the standards.

Keywords: Imidazole, Thiadiazole, Schiff Base, Azetidinone, antibacterial

International Journal of Drug Delivery Technology (2020); DOI: 10.25258/ijddt.10.4.16

How to cite this article: Mosa MN, Baiwn RS, Mohammed AK. Synthesis and Characterization of the Novel Compounds Containing Imidazole, Thiadiazole, Schiff Base, and Azetidinone Chromospheres as a New Antibacterial Agents. International Journal of Drug Delivery Technology. 2020;10(4):602-607.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Antibacterial is one of the greatest discoveries in medical history[1]. They are used to treat many life threatening bacterial diseases worldwide.[2,3] Unfortunately, the misuse and overuse of these medications has resulted in the emergence of bacterial resistance. This danger phenomenon threats the efficacy of antibiotics that saved millions of lives for many decades.[4] Furthermore, there is a noticeable decrease in the development of new antibiotics by the pharmaceutical industry over the past three decades.[4,5] Therefore, the need for new effective antibiotics against resistant bacteria continues to grow. One approach to achieve that is through targeting the resistant microorganism with a new agent having more than one mechanism of action.[6,7] On the basis of various literature, many antimicrobial agents are available; however, each of them has a different mechanism depending on its chemical structure. For example, 2,4,5- triphenyl-1H-imidazole derivatives have shown a varying range of antimicrobial activity.[7-9] The heterocyclic imidazole ring moiety in those derivatives shows various pharmacological activities such as antimicrobial, anti-inflammatory, analgesic and anticancer.[10-13]

Furthermore, β- lactam (azetidinone) antibiotics like penicillin, cephalosporin, monobactams and carbapenems are powerful wide spectrum antibacterial agents. All have a beta-lactam ring as a core structure, which is essential for their antibacterial activity.[14] In addition, The 1, 3, 4-thiadiazole is an established heterocyclic nucleus that is associated with antibacterial and antifungal activity. It is a fundamental scaffold of many antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, and antitubercular agents.[15,16] Moreover, many Schiff bases compounds have been reported to exhibit a promising antibacterial activity.[17] Accordingly, it is reasonable to synthesize agents with expected multiple mechanism of action through the combining of two or more of the mentioned functional groups in order to overcome the bacterial resistance.

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EXPERIMENTAL

Chemical Synthesis

Synthesis of 2,4,5-triphenyl-1H-imidazole (1)

Benzil (4.2 gm, 20 mmole), benzyldehyde (2.1gm, 20 mmole) and excess amount of ammonium acetate (2.3gm, 30 mmole) in 50 mL of acetic acid where refluxed for 4 hours. The mixture was cooled and filtered to remove the uncreated compounds. The filtrate was added to crush ice.

Saturated sodium carbonate solution was added to make the pH around 8. White precipitate was formed. This precipitate was collected by filtration and recrystallized from ethanol. Yield 65%; mp 290–292°C.

Synthesis of methyl 2-(2,4,5-triphenyl-1H-imidazol-1-yl) acetate (2)

Compound 1(2.9gm, 10 mmole) was dissolved in acetone (30ml). Methyl chloroacetate (1.3gm, 12mmole) was added slowly. The reaction was stirred for 8 hr at room temperature. Crystals was formed and collected by filtration. The product was recrystallized from (ethanol: water). Yield 70%; mp 124-127°C.

Synthesis of 2-(2-(2,4,5-triphenyl-1H-imidazol-1-yl)acetyl) hydrazine-1-carbothioamide (3)

Compound 2(2.2 gm, 6 mmole) and thiosemicarbazide (0.5 gm, 6 mmole) in ethanol (30 ml) were refluxed for 8 hr. The mixture was cooled and the precipitate was formed. This product was isolated by vacuum filtration and washed with water. Recrystallization from (ethanol: water) was taken place. Yield 76%; mp 160–163°C.

Synthesis of 5-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine (4)

Compound 3 (1.7 gm, 4 mmole) was dissolved in 0.5N Na0H (30 ml). The mixture was stirred at room temp for 48hr. The reaction was acidified with 0.5N HCl till white precipitate was formed. The product was filtered and recrystallized from ethanol. Yield 68%; mp 190–192°C.

Synthesis of 1-(4-substituted)-N-(5-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)methanimine (5)

Compound 4 (0.2gm, 0.5mmole) was dissolved in ethanol (30 mL) with few drops of acetic acid. Benzaldehyde derivatives (0.6 mmole) were added. The mixture was refluxed for 8 hrs. Subsequently, it was cooled. Crystals was formed and collected by filtration. Recrystallization from ethanol was taken place. Yield and melting points were summarized in Table 1.

1-phenyl-N-(5-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)methanimine (5a)

1HNMR (250 MHz , CDC l3),δ(ppm)=4.99(s,2H,-CH2-), 8.99(s,1H,-CH=N-), 7.23–8.28(m,20H, phenyl).

4-(((5-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2 yl)imino)methyl)phenol (5b)

1HNMR (250 MHz , CDC l3),δ(ppm)=4.99(s,2H,-CH2-), 8.99(s,1H,-CH=N-), 7.23–8.28(m,19H, phenyl), 9.68(s,1H-OH).

1-(4-methoxyphenyl)-N-(5-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)methanimine (5c)

1HNMR (250 MHz , CDC l3),δ(ppm)=4.99(s,2H,-CH2-), 8.99(s,1H,-CH=N-), 7.23–8.28(m,19H, phenyl), 3.81(s,3H, -CH3).

1-(4-chlorophenyl)-N-(5-((2,4,5-triphenyl-1H-imidazol-1-yl) methyl)-1,3,4-thiadiazol-2-yl)methanimine (5d)

1HNMR (250 MHz , CDC l3),δ(ppm)=4.99(s,2H,-CH2-), 8.99(s,1H,-CH=N-), 7.23–8.28(m,19H, phenyl).

1-(4-nitrophenyl)-N-(5-((2,4,5-triphenyl-1H-imidazol-1-yl) methyl)-1,3,4-thiadiazol-2-yl)methanimine (5e)

1HNMR (250 MHz , CDC l3),δ(ppm)=4.99(s,2H,-CH2-), 8.99(s,1H,-CH=N-), 7.23–8.28(m,19H, phenyl).

Synthesis of 3-chloro-4-(4-substituted)-1-(5-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl) azetidin-2-one (6)

0.3 mmole of Schiff base derivatives (compound 5) and excess triethylamine (0.05 gm, 0.5 mmole) were dissolved in THF. α-chloroacetyl chloride was added dropwise over 30 minutes on ice bath. The mixture was stirred at room temperature for 24 hours. Finally, this mixture was poured on iced water with stirring. The precipitate was formed and collected by filtration. Recrystallization from ethanol was taken place. Yield and melting points were summarized in Table 1.

3-chloro-4-phenyl-1-(5-((2,4,5-triphenyl-1H-imidazol-1-yl) methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one (6a)

1HNMR (250 MHz , CDC l3),δ(ppm)=4.99(s,2H,-CH2-), 5.05 (d,1H, -CH-N-), 5.44 (d,1H, -CHCl), 7.27–8.28(m,20H, phenyl).

13C-NMR(125M Hz):47.3, 62, 67.8, 126.7, 127.5, 129.2, 130, 133.2, 138, 141.2, 143.3, 153, 162, 168

m/z: 573.14 (100.0%), 574.14 (35.7%), 575.14 (32.0%), 576.14 (11.4%), 575.13 (4.5%), 575.15 (3.5%), 575.15 (2.7%), 574.14 (1.8%), 576.14 (1.6%), 577.13 (1.4%), 577.14 (1.1%)

Table 1: Physicochemical properties of the prepared compounds

Compound	*Melting point°C*	*% of yield*	*Appearance*
1	290-292	65	White precipitate
2	124-127	70	White crystals
3	160-163	76	White crystals
4	190-192	68	White precipitate
5a	152-153	78	Yellow crystalline powder
5b	167-170	72	Yellow-orange crystalline powder
5c	159-161	65	Yellow crystalline powder
5d	178-180	81	Yellow crystalline powder
5e	155-158	74	Orange crystalline powder
6a	162-163	65	White crystals
6b	157-160	61	White crystals
6c	180-181	55	White crystals
6d	158-160	63	White crystals
6e	175-178	59	White crystals

Elemental Analysis: C, 69.04; H, 4.21; Cl, 6.17; N, 12.20; O, 2.79; S, 5.58

3-chloro-4-(4-hydroxyphenyl)-1-(5-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one (6b)

1HNMR (250 MHz , CDC l3),δ(ppm)=4.99(s,2H,-CH2-), 5.05 (d,1H, -CH-N-), 5.44 (d,1H, -CHCl), 7.27–8.28(m,19H, phenyl),9.06 (s,1H, OH).

13C-NMR(125M Hz):47.3, 62, 67.8, 126.7, 127.5, 129.2, 130, 133.2, 138, 141.2, 143.3, 153,156, 162, 168

m/z: 589.13 (100.0%), 590.14 (35.7%), 591.13 (32.0%), 592.13 (11.4%), 591.14 (6.2%), 591.13 (4.5%), 590.13 (1.8%), 592.13 (1.6%), 593.13 (1.4%), 593.14 (1.1%)

Elemental Analysis: C, 67.17; H, 4.10; Cl, 6.01; N, 11.87; O, 5.42; S, 5.43

3-chloro-4-(4-methoxyphenyl)-1-(5-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one (6c)

1HNMR (250 MHz, CDC l3),δ(ppm)=3.81 (s,3H, -CH3), 4.99(s,2H,-CH2-), 5.05 (d,1H, -CH-N-), 5.44 (d,1H, -CHCl), 7.27–8.28(m,19H, phenyl).

13C-NMR(125M Hz):47.3,56.3, 62, 67.8, 126.7, 127.5, 129.2, 130, 133.2, 138, 141.2, 143.3, 153, 162, 168

m/z: 603.15 (100.0%), 604.15 (36.8%), 605.15 (32.0%), 606.15 (11.8%), 605.15 (4.5%), 605.16 (3.9%), 605.16 (2.7%), 606.15 (1.7%), 604.15 (1.5%), 607.14 (1.4%), 607.15 (1.2%)

Elemental Analysis: C, 67.60; H, 4.34; Cl, 5.87; N, 11.59; O, 5.30; S, 5.31

3-chloro-4-(4-chlorophenyl)-1-(5-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one (6d)

1HNMR (250 MHz , CDC l3),δ(ppm)= 4.99(s,2H,-CH2-), 5.05 (d,1H, -CH-N-), 5.44 (d,1H, -CHCl), 7.27–8.28(m,19H, phenyl).

13C-NMR(125M Hz):47.3, 62, 67.8, 127.5, 129.2, 130, 131.2, 133.2, 138, 141.2, 143.3, 153, 162, 168

m/z: 607.10 (100.0%), 609.10 (63.9%), 608.10 (35.7%), 610.10 (22.8%), 611.09 (10.2%), 609.10 (4.5%), 612.10 (3.6%), 609.11 (3.5%), 611.09 (2.9%), 609.11 (2.7%), 611.10 (2.2%), 611.10 (1.7%), 610.10 (1.6%), 608.10 (1.1%), 612.10 (1.0%)

Elemental Analysis: C, 65.13; H, 3.81; Cl, 11.65; N, 11.51; O, 2.63; S, 5.27

3-chloro-4-(4-nitrophenyl)-1-(5-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one (6e)

1HNMR (250 MHz , CDC l3),δ(ppm)= 4.99(s,2H,-CH2-), 5.05 (d,1H, -CH-N-), 5.44 (d,1H, -CHCl), 7.27–8.28(m,19H, phenyl).

13C-NMR(125M Hz):47.3, 62, 67.8, 127.5, 129.2, 130, 133.2, 138, 141.2, 143.3, 145.9, 153, 162, 168 m/z: 618.12 (100.0%), 619.13 (35.7%), 620.12 (32.0%), 621.12 (11.4%), 620.13 (6.2%), 620.12 (4.5%), 619.12 (2.2%), 622.13 (2.0%), 621.12 (1.6%), 622.12 (1.4%)

Elemental Analysis: C, 64.02; H, 3.74; Cl, 5.73; N, 13.57; O, 7.75; S, 5.18

Antibacterial Activity

The antimicrobial activities of the synthesized compounds (4, 5a-e, 6a-e) have been screened and evaluated. *In-vitro* antimicrobial activity was carried out through a disk-diffusion method against (*S. aureus*, MTCC3160), Enterococcus facaels, (E. coli MTCC), Klebsiella pneumonia (*K. pneumonia*, MTCC), and anaerobic bacteria (*S. pyogen*). The diameters of inhibition growth zones have been measured.

The anaerobic bacteria (*S. pyogen*) was distributed on the agar of Muller Hinton in the same way as mentioned above, except that the petri dishes were kept in anaerobic conditions via using of a tightly closed glass container that is evacuated from oxygen by placing a candle inside the closed jar. The flame of the candle will put out after the oxygen consumption. The jar then place in the incubator at a temperature of 37°C for 24 hours [18].

The antimicrobial activities of both Cefixime and Metronidazole were tested beside the synthesized compounds to be used as a reference. The results were summarized in Table 2.

RESULTS AND DISCUSSION

Generally, compounds 4, 5a-e, and 6a-e showed different antibacterial activities against the tested bacterial species compared to the standard antibiotics. Compound 4 showed less activity against both Gram-positive and Gram-negative species compared to the standard cefixime. However, it can be seen that it had no activity against the anaerobic bacteria. Both compounds 5a and 6a showed less activity against gram-positive and gram-negative bacteria than cefixime. Additionally, their activities against *S. pyogen* have seemed to be less than the activity of metronidazole. Regarding compounds 5b and 6b, an improvement in the activity have been seen against gram-positive species compared to cefixime, while their activities against gram-negative bacteria was found to be somewhat less than that have been seen by cefixime. Despite of that, both appeared to have less antibacterial activity against *S. pyogen* compared with metronidazole. Regarding compounds 5c and 6c, their activities against S. aureus were found to be similar to the standard cefixime in 0.250 gm/mL concentration, however, with 0.125 gm/mL, the activity was slightly better. Additionally, both showed higher activity against E. Fecalis than cefixime only with 0.250 gm/mL concentration. Furthermore, 5c seemed to have slightly lower activity than cefixime against *E. coli*, while the activity of 6c was better in 0.250 mg/ml concentration. The activity of both 5c and 6c against *K. pneumonia* was found to be less than cefixime. Despite of that, neither 5c nor 6c showed any activity against *S. pyogen*. After all, compounds 5d, 5e, 6d, and 6e showed clearly lower activity than cefixime against both gram-negative and Gram-positive species. Whereas their activities against *S. pyogen* were slightly less than what has be seen with metronidazole, except 6e, which showed the best antibacterial activity against S. pyogen among all the synthesized compounds

Table 2: Antibacterial activity of the synthesized compounds

Compound	*Concentration mg/ml*	*Inhibition zone result diameter mm*				
		S. aureus	*E.Fecalis*	*E.coli*	*K.pneumoniae*	*S. pyogen*
Standard Cefixime	0.250	9	8	15	13	2
	0.125	4	5	12	12	0
Standard Metronidazole	0.250	0	0	0	0	7
	0.125	0	0	0	0	5
4	0,250	3	3	2	4	0
	0.125	1	0	0	2	0
5a H	0.250	4	3	2	3	3
	0.125	2	0	0	0	2
5b OH	0,250	10	10	13	9	2
	0.125	6	5	9	8	0
5c OCH3	0.250	9	10	14	10	0
	0.125	5	4	9	7	0
5d Cl	0.250	4	3	3	4	6
	0.125	1	0	0	1	3
5e NO2	0,250	3	3	4	3	6
	0.125	1	1	1	0	4
6a H	0.250	5	3	4	3	3
	0.125	2	1	1	0	2
6b OH	0,250	11	11	13	122	2
	0.125	6	5	8	8	0
6c OCH3	0.250	9	11	16	10	0
	0.125	6	5	9	6	0
6d Cl	0,250	4	3	3	4	6
	0.125	2	1	0	0	4
6e NO2	0.250	4	3	4	3	8
	0.125	1	0	1	0	5

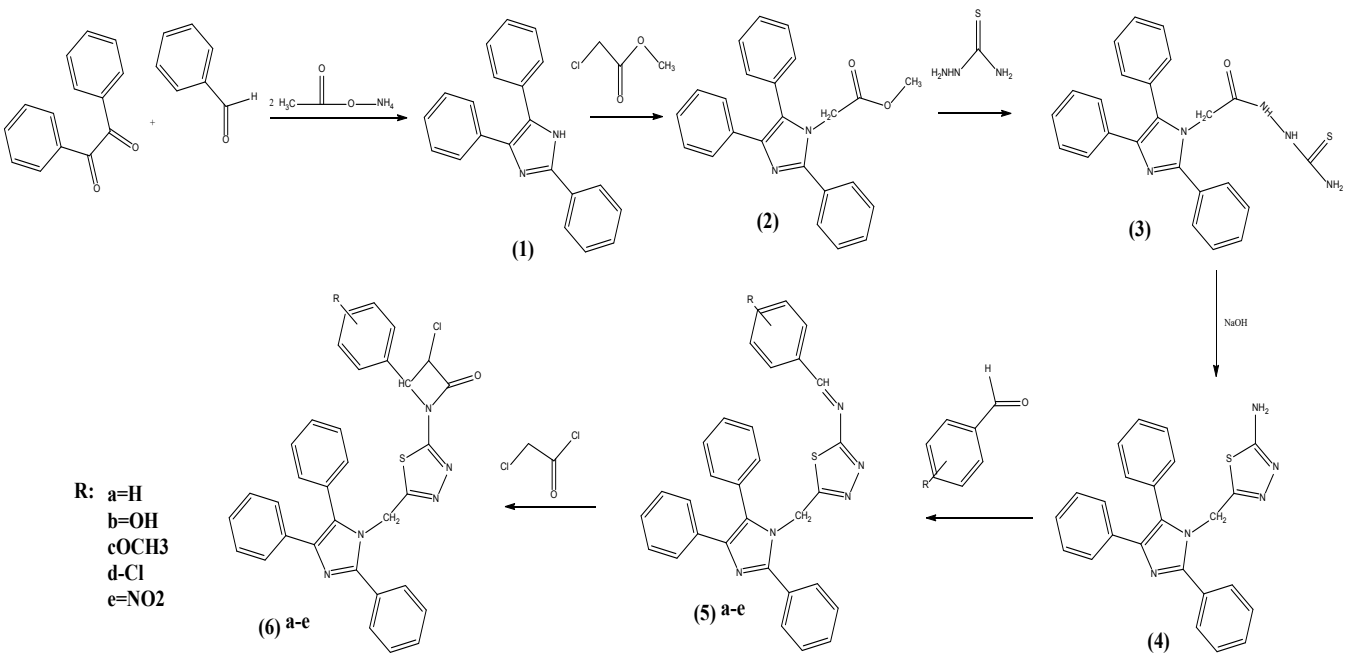

Figure 1: Chemical synthesis of the target compounds

As seen in Figure 1, the entire synthesized compound have the same core structure, which contains 2, 4, 5- triphenyl-1H-imidazole and 1, 3, 4-thiadiazole. The differences are in the substituted groups at position 2 of the 1, 3, 4-thiadiazole. Regarding the aerobic bacteria, when this group is amine (compound 4), the antibacterial activity was relatively low. This might be due to the high basicity of the primary amine. Furthermore, the small size of this group might not be helpful in enhancing the antibacterial activity.[19]

Series of five Schiff bases were synthesized using five benzaldehyde derivatives with different para substitutions. However, only two of them showed a significant improvement in the antibacterial activity (compounds 5b and 5c). This indicates that converting the amine group to Schiff base is not necessarily enhancing the antibacterial activity as seen with compounds 5a, 5d and 5e. However, the activity is seemed to be affected by the para-substituted group at the phenyl group. Furthermore, modification of the Schiff bases to beta-lactam moiety is not necessarily improving the activity as seen with compounds 6a, 6d and 6e. However, both 6b and 6c showed remarkable improvement. This supports the effect of the para-substitution at the phenyl group on the antibacterial activity. From the results above, it is clear that the best antibacterial activity against the aerobic species was related to the compounds which have a hydroxyl (5b and 6b) or methoxy (5c and 6c) groups attached at the phenyl group. This might be related to the electron donating effect of both hydroxy and methoxy functional groups.[20] However, electron-withdrawing groups like nitro and chloride decrease the antibacterial activity.[21]

Regarding the anaerobic bacteria, the standard metronidazole activity is thought to be related to the reduced 5-nitro group intermediate. This intermediate is responsible for the lethal effect since it covalently binds to the DNA of the microorganism. The highest activity against S.pyogen was seen by compounds 5d, 5e, 6d, and in particular 6e. This might be related to the electron-withdrawing effect of both chloride and nitro groups.[18]

However, the significant activity of 6c could be related to the microbial reduction of the nitro group as expected with metronidazole.

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