RESEARCH ARTICLE

Synthesis of New Tetrazole and Azitidenen Compounds with Evaluating of its Antibacterial Effects

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ABSTRACT

4-((4-chlorobenzoyl)oxy) benzoic acid was used to synthesize new thiazole heterocycles. The antimicrobial, anti-inflammatory, and analgesic activities of the synthesized compounds Schiff base. Then we derive from Schiff base 4-oxoazetidine and 4-oxothiazolidin heterocycles.

Keywords: 1,3,4-Triazole, Antibacterial, Oxazetidin, Schiff base, Tetrazole.

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INTRODUCTION

Heterocyclic chemistry is a major branch of organic chemistry that accounts for roughly a third of all modern publications. Heterocyclic compounds are among the organic compounds. Carbocyclic compounds are cyclic organic compounds with carbon atoms arranged in a ring. A heterocyclic ring system is one in which at least one atom is not carbon and forms a component of the ring system.[1]

Many biological molecules[2] incorporate heterocyclic compounds as building blocks, with five- and six-member rings being the most prevalent.[3] Potential biological and industrial applications cause the creation of heterocyclic molecules. The heterocyclic compounds revealed a wide range of pharmacological properties, including antibacterial,[4] antiviral,[5] and anti-inflammation properties.

A schiff base is an aldehyde or ketone analog in which the carbonyl group is substituted with a (C=N) group. It's commonly made by combining an aldehyde or ketone with a primary amine.[6] Hunch Weber was the first to prescribe thiazoles in 1887. Bob validated its structure in 1889. From the sulfur atom, the numbering in the thiazole begins. Thiazoles have been investigated extensively as components of B vitamins, antimicrobial penicillins, and thiazoles.

Few thiazoles are utilized to research peptides and proteins found as structural units in biologically important substances.[7]

1,3,4-thiadiazoles are important heterocyclic compounds with a wide range of applications in medicinal, agricultural, and materials chemistry. Their amino or imino group derivatives have a wide range of pharmaceutical and biological properties, including antimicrobial, antitubercular, anticancer, anti-inflammatory/analgesic, antidepressant, antioxidant activities, and antimicrobial properties.[8]

Tetrazoles are synthetic heterocyclic compounds with a five-member ring consisting of four nitrogen, one carbon, and two hydrogen atoms. Tetrazole has the chemical formula CN_4H_2. Tetrazole is a crystalline solid that is white to pale yellow, has a faint odor, and is soluble in water or alcohol. Due to the presence of four nitrogen atoms, it is acidic.[9]

METHODS

Synthesis of 4-chlorobenzoyl Chloride

Compound (1) syntheses for a mixture of 4-chlorobenzoic acid (5 g, 0.031 mole), (15 mL) thionyl chloride and (2-4) drops DMF was refluxed for (1.5 hours) (Figure 1).[10]

Synthesis of 4-((4-chlorobenzoyl)oxy)benzoic acid

P-chloro benzoic acid (0.057 mole, 7 g) was dissolved in dry pyridine, then cooled 4-chloro benzoylchloride (0.057 mole, 15 mL) was added dropwise for 4 hours while stirring. TLC was used to monitor the reaction. With diluted HCL, the reaction mixture is poured onto crushed ice. Filtration was used to collect the precipitate, which was then dried and recrystallized using ethanol (Figure 2).[11]

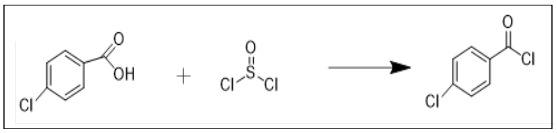

Figure 1: Synthesis of acid chloride compound (1)

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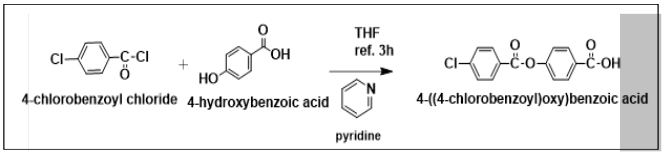


Figure 2: Synthesis of compound (2)

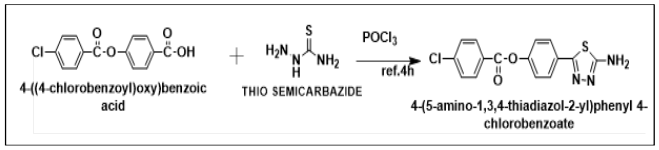


Figure 3: Synthesis of compound (3)

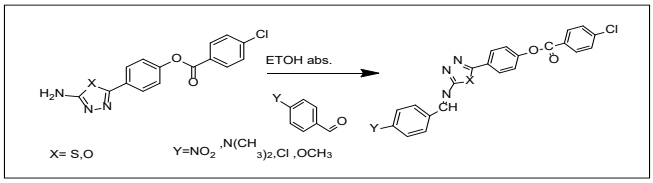


Figure 4: Synthesis of compound (4-7)

Synthesis of 4-(5-amino-1,3,4-thiadiazol-2-yl)phenyl 4-chlorobenzoat

For 5 hours, a combination of compond (3) (0.037 mole, 5 gm), thiosemicarbazide (0.074 mole, 6.7 gm), and $POCl_3$ (20 mL) was refluxed. Dropwise additions of cold water (15 mL) cooled the mixture, which was then refluxed for another 2 hours. The mixture was neutralized with sodium hydroxide, yielding a deep yellow precipitate that was filtered and dried (Figure 3).[12]

Synthesis of Schiff's Bases (4-7)

The components of the compound are (3), (1 gm, 0.005 mole) and (0.7 gm.) of 4- chloro benzaldehyde, (0.8 gm.) of 4-nitro benzaldehyde, and (0.6 gm.) of methoxy benzaldehyde (0.5 gm) of 4-(dimethylamino)benzaldehyde were refluxed for 4 hours in full ethanol (15 mL) with 3–4 drops of glacial acetic acid. The mixture is then cooled, and the solid is recrystallized using ethanol and gathered by filtration (Figure 4).[13]

Synthesis of 4-oxazetidin (10,11)

The aforementioned compounds of Schiff's bases (6,7) were improved by mixing 0.01 mole of chloroacetyl chloride to a combination of selected derivatives [16,17, or 18] (0.01 mole) of [16-18] and Et3N (10 mL) at °C and stirring for 4 hours, and then refluxed for 1 hour. To obtain the intended compound the result was cooled and dumped on crushed ice, filtered, rinsed with water, and lastly, allowed to dry (Figure 5).[14]

Synthesis of Tetrazole [8, 9]

A mixture of Schiff base [4-5] (0.1 gm, 0.0005 mole) dissolved in tetra hydro furan (20 mL) (0.03 gm,0.0005 mole) sodium azide and methylamine (0.04 gm, 0.0005 mole) were put under heat reflux of (55–60)ċ for (4–6) hours, filtered, and recrystallized from ethanol (Figure 6) (Scheme 1).[15]

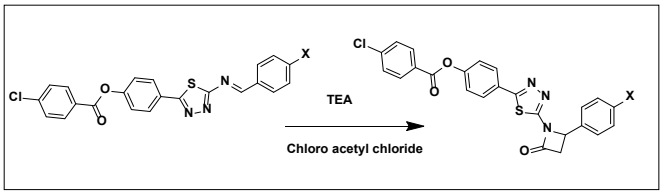


Figure 5: Synthesis of Ox azetidine compounds (10,11)

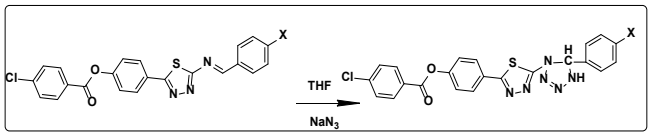
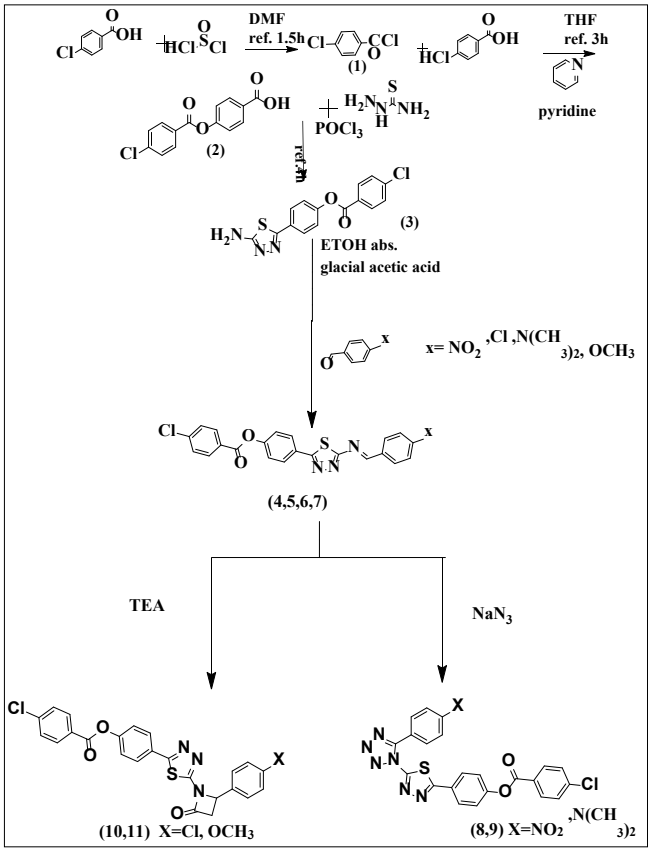


Figure 6: Synthesis of tetrazole compounds (8,9)

RESULTS AND DISCUSSION



Scheme 1: Synthesis and characterization of compound (1) to the formation (10,11) and compound (8,9)

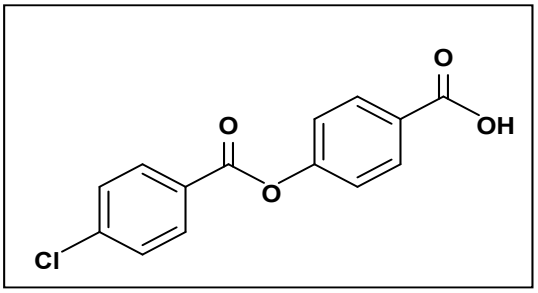


Figure 7: Compound(2)

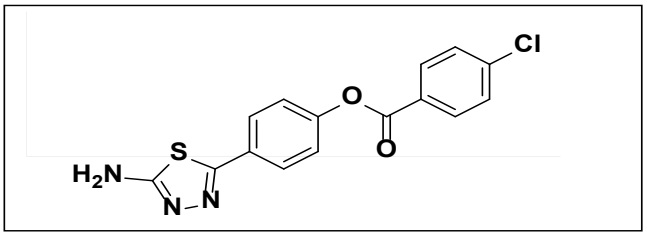


Figure 8: Compound (3)

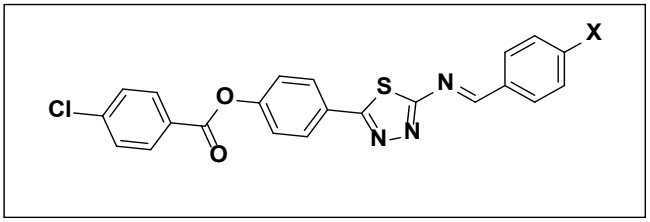


Figure 9: Compound (4-7)

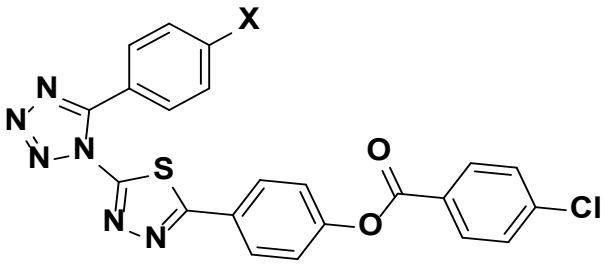


Figure 10: Compound (8-9)

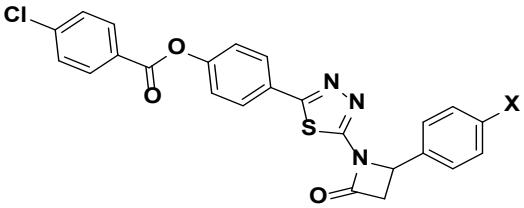


Figure 11 : Compound (10-11)

Characterization of 4-((4-chlorobenzoyl)oxy)benzoic acid (2)

The reaction of 4-chlorobenzoyl chloride with p-hydroxy benzoic acid in the presence of pyridine yielded this chemical. The melting point of the product was used to determine its structural assignment. Spectral characteristics and other physical properties of fourier-transform infrared spectroscopy (FTIR) (Figure 7).

Apart from the band at (1165–1215 cm^{-1}) for (C-O) aster group, at (1427 cm^{-1}) for (O-H) carboxylic acid, and at (1215–1323 cm^{-1}) for (C-O) carboxylic acid, there are bands at (3005 cm^{-1}) for (CH) aromatic, (1735 cm^{-1}) for (C=O) ester group, and (1593 cm^{-1}) for (C=C) aromatic.

Compound (1) displayed multiplet signals in the area (7.08–8.6) ppm due to four aromatic protons for the benzene ring, as well as a singlet signal at (9.45) ppm due to protons for O-H in the proton nuclear magnetic resonance (^{1}HNMR) spectrum.

Characterization of 4-(5-amino-1,3,4-thiadiazol-2-yl) phenyl 4-chlorobenzoate (3):

The reaction of compound (3), thiosemicarbazone, and $POCl_3$ was refluxed 2 hours yielded this chemical. The product's melting point was used to determine its structural assignment. Spectral characteristics and other physical properties FTIR.

The FTIR spectrum for compound (3) indicates that all peaks of (OH), (C=O) for the carboxylic acid have vanished, revealing the distinctive sucking twists in the regions (3070 cm^{-1}). Because of aromatic (C-H), the FTIR spectra additionally display absorption bends in the region (1593) cm^{-1} due to (C=N) of thiadiazol ring, (C-O) band at (1168–1215 cm^{-1}) ester bond, (C=C) stitching in benzene ring at (1477, 1508 cm^{-1}), and a new band at (2981 cm^{-1}) due to (C-S), at (1273 cm^{-1}) for (C-N) (Figure 8).

Characterization of Schiff base [4-7]

Compounds (4-7) were created by combining chemical [3] with 4-nitrobenzaldehyde made from 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-methoxybenzaldehyde,and N, N-dimethyl benzaldehyde in 100% ethanol. The main approach for preparing schiff bases is to compensate an equimolar amount of primary amine with appropriate aromatic aldehydes.

The FTIR spectrum of compound (4) expose to us (C=N) stretching band at (1600 cm^{-1}), (C-H) aromatic at (3074 cm^{-1}), (N-H) at (3105 cm^{-1}), (CH_2) band at (1454 cm^{-1}), (C=C) at (1458, 1508 cm^{-1}), (C-N) at (1350 cm^{-1}), (C-O-C) at (1157, 1203 cm^{-1}), (C-NO_2) at (1508,1373 cm^{-1}).

Shows the ^{1}H-NMR spectrum of chemical [4], including signals at 8.58 (1H,NH). Several signals at 7.23–8.3 ppm (1H) may be assigned to benzene ring protons. ^{1}H-NMR spectrum of chemical [7], including signals at 8.4 (1H, NH). And a number of signals between 7.22 and 8.71 ppm (1H) that could be assigned to benzene ring protons (Figure 9).

Synthesis and Characteristics of Tetrazole Compounds (8,9)

A mixture of Schiff base [4-5] dissolved in tetra hydro furan sodium azide and methylamine were put under heat reflux.

The stretching vibration bands of (C=N) for schiff bases have vanished, with new bands appearing in the range (1415-1404 cm^{-1}) due to the (N=N) group of the tetrazole ring. The spectra also revealed bands belonging to the (N-H) and (C-H) aromatic rings in the range (3116-3087 cm^{-1}), respectively. Table 1 lists all of the major bands (3.7)

The ^{1}H-NMR spectrum of the compound [8], reveals aromatic protons as multiple at (7.3–8.9) and the proton of (N-H) at (10.11) ppm.

Table 1: Antibacterial activities of some prepared compounds.

	Comp.No.	*Enterobacter cloacae (G-)*	*Staphylococcus aureus (G+)*
A3	4	11	14
A6	7	12	12
A4N	10	11	17
control		0	0
Amoxicillin		11	20

Table 2: The physical properties, FTIR and ^{1}HNMR spectral data synthesis compounds [2-11]

Cm. No.	*m.p. °C*	*Color*	*Yield%*	*IR(ν , cm^{-1}) KBr*	*^{1}H-NMR (DMSO) (δ ,ppm)*
[2]	158–160	light beige	60	1735 (C=O aster), 1165-1215 (C-O aster), 1427, 1323 (C=O, C-O carboxylic acid)	9.45 (s, H, OH), 7.01–8.6(dd, 8H, Ar-H)
[3]	193–195	Gray-yellow	76	1593(N-H), 1273 (C-N), 1593 (N=N thiadiazol ring).	-
[4]	128–130	orange	80	1651 (C=N endo cyclic), 1508 (C-NO2.)	8.58 (s, H,NH), 7.23–8.3 (m, 16H, Ar-H),
[5]	162–164	white	60	1651 (C=N endo cyclic), 1597 (C=C arom.), 3078 (N-CH_3 arom.)	
[6]	198–200	pale yellow	64	3271 ,3086(NH2asy.,sy.& NH), 1658 (C=N endo cyclic), 765(C-Cl).	
[7]	130–132	goldenyellow	68	3483 (OH), 3406 (NH), 1640 (C=N), 1620 (C=Cimidazol ring), 759(C-S)	7.13–7.51 (m, 10H, Ar -H), 8.25 (s, 1H, NH),
[8]	196–198	white	70	1508 (C=C arom.),1600 (C=N), 1415 (N=N), 3178 (N-H),	7.3–8.9 (m,Ar-H) 10.11 (s,1H,NH)
[9]	184–186	yellow	66	1516 (C=C arom.), 1600 (C=N), 1404 (N=N), 3101 (N-H),	
[10]	200–202	browen	80	1685 (C=O, oxoazetidin ring), 1446 (C-N), 3155(N-H).	7.23–8.2(m, Ar-H), 3.5–4.7 (m,H ,C-H)
[11]	167–169	orang	86	1581 (C=O oxoazetidin ring), 1450 (C-N), 3186 (N-H).	

Synthesis and Characteristic of 4-oxoazetidin Derivatives (10,11)

Compounds (11) were synthesized from compounds (7) reaction with chloroacetyl chloride in ET_3N as a base and solvent. The compounds were characterized by their melting points and FTIR spectra.

The FTIR spectrum of compounds (11), shows the appearance of a band at (1681cm^{-1}) attributed to υ (C=O) of ring and band at (3186 cm^{-1}) assigned to stretching frequency of υ (N-H) , υ (C-N) stretch (aryl) (1450).

^{1}H-NMR spectrum of compound (10) shows an aromatic proton as multiple at (δ 7.23–8.2) and the proton as multiple of (H, C-H) appeared at (δ 3.5–4.77) ppm (Figure 11).

Biological Activity Evaluation

This section examines the antibacterial properties of several of the produced chemicals. The activity against two pathogenic bacteria, *Staphylococcus aureus* (G+) and *Enterobacter cloacae*, was assessed *in-vitro* using the well diffusion method (G-). As stated in Table 1, the collected data revealed that several of these compounds had quantifiable action Table 2 shows the physical activities.

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