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Original Article

Synthesis and Characterization of New Amide Drug from Cromoglicic Acid and Study of Their Possible Biological Activity

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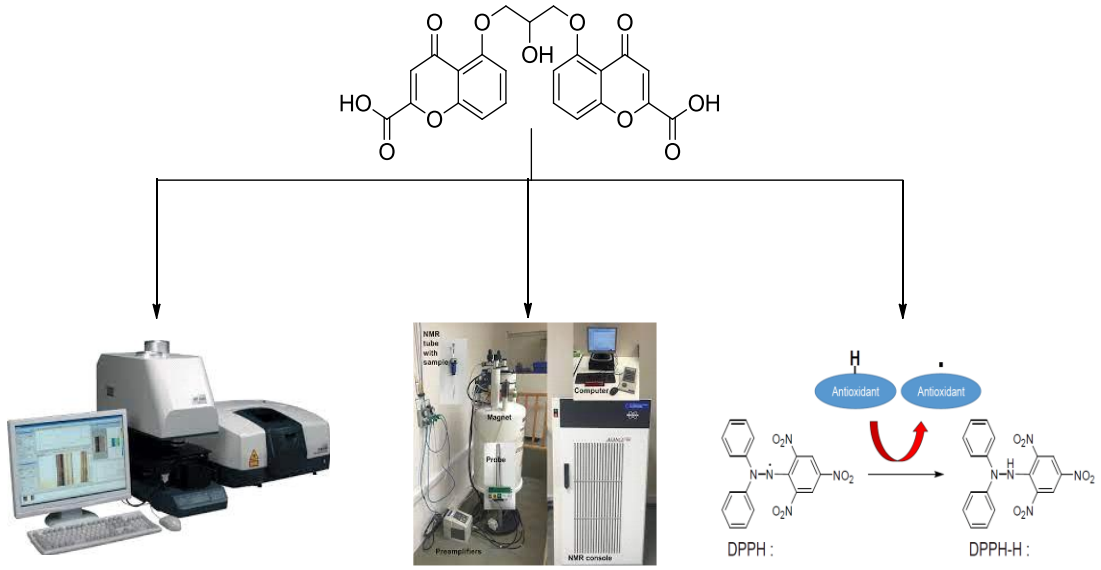
ABSTRACT

The research included preparing a high yield of new derivatives of cromoglicic acid have been created with new properties. Cromoglicic acid constitutes a major type of pharmaceutical organic compound. Its derivatives can be utilized in the manufacture of new types of drugs, possess a wide range of biological activity, and reduce side effects. The work included direct interaction for eight amino drugs (amoxicillin, ampicillin, folic acid, Mefenamic acid, Paracetamol, Theophenyl, cephalexin, and 4-aminoantipyrine) after converting acid into chloride using $SOCl_2$ and DCM and the addition of (tri methylamine), T LC to control the chemical reaction and to characterize the new derivatives using FT-IR, ^{13}CNMR and ^{1}HNMR techniques. The antioxidant activity of the prepared compounds was examined by DPPH method and the results showed an excellent antioxidant activity of all these prepared compounds, much higher than that of ascorbic acid.

GRAPHICAL ABSTRACT



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Introduction

Cromoglicic acid is a mastocyte stabilizer (Figure 1). Its common maximum amount makes use of this drug with inside the remedy of bronchial allergies and conjunctivitis. Cromoglycate formulations consist of an amphoteric surfactant and an alkylated cetyl alcohol as vital components for the remedy of atopic dermatitis. A composition comprises cromoglicic acid, or salts thereof, in addition to hydrophilic macromolecular material. The composition is beneficial with inside the remedy of pores and skin wounds and accidents that produce secretions, including the ones resulting from dermatitis. Discloses cromoglicic acid esters which can be beneficial with inside the remedy of dermatitis in which a hypersensitive reaction, inflammation of the nasal mucosa (cromoglicic acid) and infrequently candidiasis (corticosteroids) take place [1]. Some sufferers with AR, however, decide upon non-pharmacological therapies. These remedies are targeted both on eliminating allergens and secretions from the nasal mucosa, along with saline nasal irrigation [2].

Cromoglicic acid is a mastocyte stabilizer. Its common maximum amount makes use of this drug are with inside the remedy of bronchial allergies and conjunctivitis. Cromoglycate formulations encompass an amphoteric surfactant and an alkylated acetyl alcohol as crucial components for the remedy of atopic dermatitis. A composition comprises cromoglicic acid, or salts thereof, in addition to hydrophilic macromolecular material. The composition is beneficial with inside the remedy of pores and skin wounds and accidents that produce secretions, which includes the ones as a result of dermatitis. Discloses cromoglicic acid esters which are beneficial with inside the remedy of dermatitis where hypersensitivity takes place [3]. Heterocyclic compounds are the cyclic natural compounds which include at the least one hetero atom, the maximum not unusual place heteroatoms are the nitrogen, oxygen, and sculpture. However, heterocyclic jewelry containing different hetero atoms are also broadly known. Carbocyclic compound is a cyclic natural compound containing all carbon atoms in ring formation. Heterocyclic are the opposite numbers of monocyclic compounds. Thus, incorporation of oxygen, nitrogen, sulfur, or an atom of an associated detail into a natural ring shape in region of a carbon atom offers upward push to a heterocyclic compounds [4].

In the latest years, the prevalence of fungal and bacterial infections has accelerated dramatically. The huge use of antifungal and antibacterial pills in resistance to drug remedy towards fungal and antibacterial infections which brought about extreme fitness hazards [5] of new Oxadiazole incorporated with Imidazole and Pyrazole. It is famous that heterocyclic compounds having azole nucleus are critical pharmacophore which seem significantly in diverse forms of pharmaceutical agents, extensively implicated in biochemical procedures and show a range of pharmacological activities. These heterocyclic compounds shape a prime a part of natural chemistry; they may be extensively dispensed in nature and play an essential position in metabolism of residing cells. For their realistic programs variety from huge medical use to fields as numerous as medicine, agriculture, photochemistry, biocidal system, and polymer science [6].

Heterocyclic compounds were taken into consideration as one of the critical lessons of natural compounds that are used in lots of organic fields, because of it is miles pastime in a couple of illnesses. Biological molecules including DNA and RNA, chlorophyll, hemoglobin, nutrients, and a plenty of extra ones consists of the heterocyclic ring in the primary skeleton. There are lots of heterocyclic compounds that are have software in lots of unusual place sicknesses inclusive of tri-azine derivatives were used as antimicrobial herbicides, urinary antiseptics, and anti-inflammatory agents. Benz imidazole derivatives were reviews to own extensive variety of organic sports consisting of antibacterial, antifungal, antiviral, and anthelmintic [7]. Chromones are benzoanelated γ-pyrone ring (4*H*-chromen-4-one, 4*H*-1-benzopyran-4-one) heterocyclic which are broadly allotted in nature. They were used due to the historic instances in conventional medicine 1

and are famous through their variety of pharmacological ownership, consisting of anti-allergic, anti-inflammatory, anti-diabetic, antitumor, and antimicrobial [8].

Chromones (nedocromil sodium and sodium cromoglycate) used as mast mobileular stabilizer, having an appropriate protection profile, however low efficacy. They are covered in tips as the second-line medicinal drugs in preliminary remedy steps and prevention of exercise-precipitated bronchial allergies [9]. Cromolyn sodium administered with inside the first few days of lifestyles has now no longer been proven to save you continual lung sickness in preterm infants. This is due, in part, to irritation with inside the lungs. Theoretically, Cromolyn sodium is a drug that could assist save you this irritation. It is fairly secure and aspect outcomes are rare. It may be given through nebulizer or aerosol inhaler with inside the first few days of lifestyles to try and save you continual lung sickness [10].

The early experiments [11-13] caused the idea that those pills acted especially on mast cells to suppress histamine release, however in addition, they inhibit cytokine generation [14]. The Chromones are further powerful in different fashions of irritation [15] and have an impact on many aspects of the inflammatory manner in vivo [16] or in vitro, *e.g.,* eicosanoid generation [17], [18] which might be unrelated to mast mobileular activation. Any putative mechanism of motion ought to include this various pharmacology.

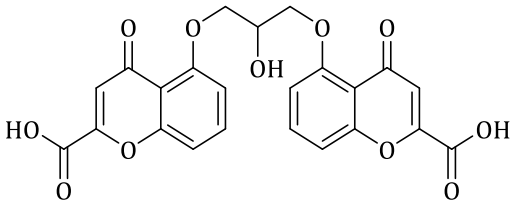


Figure 1: Structure of cromoglicic acid

Materials and Methods

After any other technology, chemicals were extracted from Merck and BDH was used. By SMP30 melting point instrument, the melting points of the prepared compounds were selected, though the degrees of melting were not corrected. The "Testseon Shimadzu (FTIR 8400Series Japan)" with KBr disk, and the ^{1}HNMR spectra were obtained with DMSO as solvent and TMS with "Bruker, Ultra Shield 500 MHZ Switzerland" as the internal standard.

*One pot Procedure of synthesis of compound (**A1-A8**)*

1 mmol (0.46 g) of cromoglicic acid is delivered to two mmol of amine and 3 mmol (0.30 g) of triethylamine (Et_3N) in dichloromethane, then 2 mmol (2.3 g), and 0.14 mL of $SOCl_2$ is introduced at room temperature. The aggregate is stirred for 5–20 minutes at room temperature. The restoration of the response product is done through evaporating the solvent. The ensuing residue is taken up in dichloromethane and washed with 1 N HCl after which with 1 N NaOH TLC became used to test the response's development [19].

Biological Activity

Antibacterial activity

Antimicrobial susceptibility tests of a few synthesized compounds have been accomplished in line with the “nicely diffusion technique”. Synthesized compounds were evaluated on bacterial strains, one gram-positive bacterium (staphylococcus aureus) and one gram-negative bacterium (Klebsiella pneumonia*).* All samples were dissolved in DMSO. Samples have been cultured on Muller Hinton agar medium at a temperature of 37 °C for 24 hours, at 0.1 mg/ml concentration and the consequences have been precise for a few compounds, as proven in table [20].

Antioxidants activity

The changed answer included from mild through overlaying the check tubes with aluminum foil. DPPH (4 mg) turned into dissolved in 100 mL of methanol. Some of the produced compounds have

been used to make numerous concentrations of (25, 50, and 100) ppm. It was made by means of dissolving 1 milligram of the chemical in 10 mL of methanol to make one hundred elements according to million, then diluting it to 50 and 25 components in keeping with million. The concentrations had been made with inside the equal way. 1 mL of the diluted or ordinary answer (25, 50, and 100) ppm turned into brought to at least one mL of DPPH answer in a check tube. After 30 minutes of incubation at 37 °C, the absorbance of every answer was measured the use of a spectrophotometer at 517 nm. The following equation turned into use to decide the capacity to scavenge DPPH radicals [21].

I % = (Absorption control – Absorption sample) /Absorption blank x 100

*Synthesis and identification of compound (**A1-A8**)*

For **A1**, the FT-IR spectrum showed the following values (V max., cm^{-1}): 3416- 3398 (OH), 1720 (C = O Ketone), 1651 (N-C=O amid), 1604 (C=C Aromatic), and 1247-1398 (C-O, C-N). ^{1}H-NMR (500 MH, δ ppm): 2.66 (CH_3), 2.5 (DMSO), 4.6 (CH), 4.07 (CH_2), 5.77 (OH, Cromo.), 6.82 -7.5 (CH, Benzene), and 9.44 (OH, Para.). ^{13}C-NMR (125 MH, δ ppm): Singlet 182.7 (C=O, Carbonyl), Singlet 170.49, Singlet 175.4 (C=O amide), 158.2-107.6 (1-benzene), Triplet 68.7 (CH), Doublet 71.1 (CH_2), Septet 40.4(DMSO), and Singlet 26.1 (CH_3) (Table 1).

For **A2**, the FT-IR spectrum revealed the following values (V max., cm^{-1}): 3404-3421 (H-OH, Phenol), 1732 (C=O, Ketone), 1651 (N-C=O amid), 1602 (C=C, Arom), and 1265-1334 (C-N, Aryl). ^{1}H-NMR (500 MH, δ ppm): 2.51 (DMSO), 3.28-3.35 (CH_3), 4.4-3.9 (CH_2), 4.7 (CH), 5.87 (OH, Alcohol) 6.82-7.8 (CH, Benzene), and 8.75 (H, imidazol). ^{13}C-NMR (125 MH, δ ppm): Doublet 182.1, Singlet 164.7 (C=O, Carbonyl), Singlet 150.4 (C=O amide), Singlet 136.8(CH, imidazol), Singlet 138.6, Singlet 114.7 (C, imidazol), Doublet 151.3 (C-N, Urea), Doublet 173.6 (1-ethylene), Singlet 127.5 (1-ethylene), Triplet 69.0 (CH aliphatic), Septet 40.2 (DMSO), Doublet 70.01 (CH_2 aliphatic), Singlet 30.7, and Singlet 29.0 (CH_3 aliphatic) (Table 1)..

For **A3**, the FT-IR spectrum indicated the following values (V max., cm^{-1}):

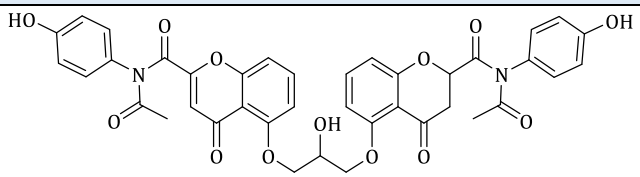
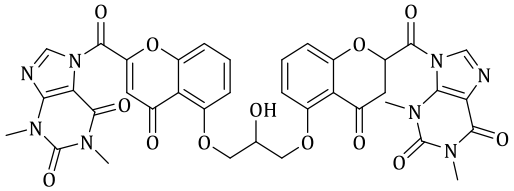
3338 (H-OH, Phenol), 1716(C=O, Ketone), 1612 (N-C=O amid), 1602 (C=C, Arom), and 1230-1309 (C-N, Aryl). ^{1} H-NMR (500 MH, δ ppm): 2.26 (CH_3), 2.51 (DMSO), 3.9 (NH, Sec. Amine), 4.07 (CH_2), 4.6 (CH), 5.7 (OH, cromo.), 6.82-7.5 (CH, Benzene), and 10.06 (NH, Sec. Amide). ^{13}C-NMR (125 MH, δ ppm): Doublet 182.3 (C=O, Carbonyl), Singlet 162.2 (C=O amide), 158.7- 115.3 (1-benzene), Singlet 118.1 (1-ethylene), Singlet 163.7, Singlet 133.6, Singlet 103.2 (1-ethylene), Septet 40.4(DMSO), Triplet 69.0 (CH aliphatic), and Doublet 70.1 (CH_2 aliphatic) (Table 1).

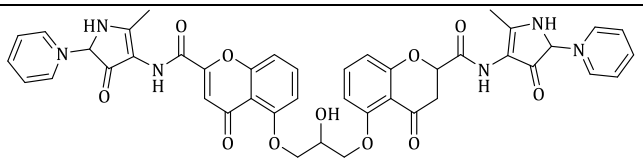
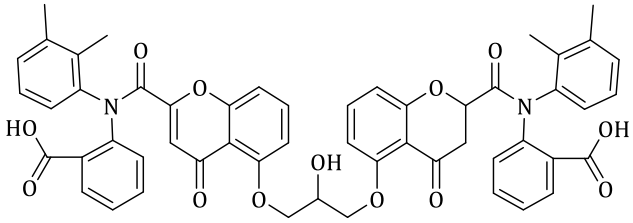
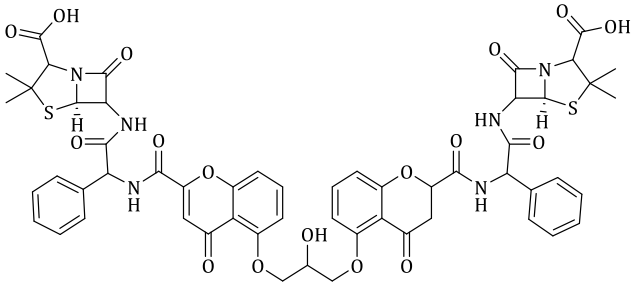
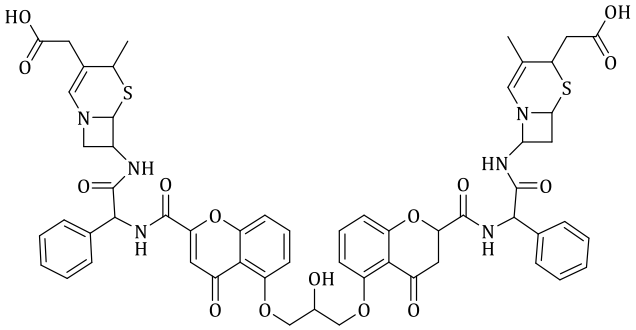
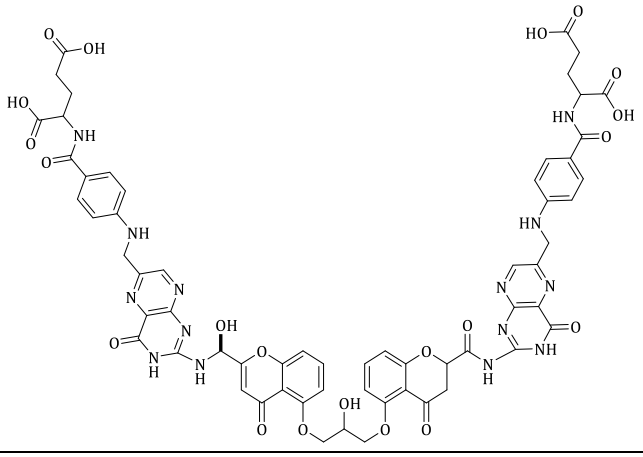
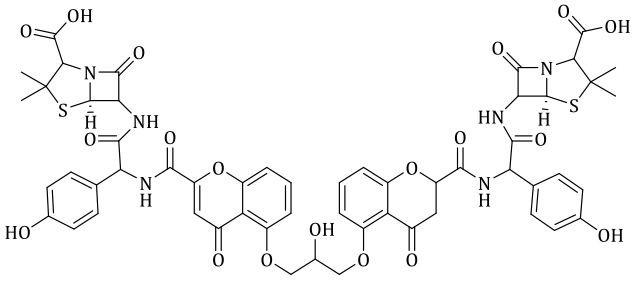
For **A4**, the FT-IR spectrum showed the following values (V max., cm^{-1}): 2492-3416 (OH, carb. Acid+ Phenol Overlap), 2995 (CH str.), 1716 (C = O Ketone), 1661 (N-C=O amid), 1601 (C=C, Ar), 1209.4-1307.7 (C-N, Aryl). ^{1}H-NMR (500 MH, δ ppm): 1.6-2.12 (CH_3), 2.49 (DMSO), 4.07 (CH_2), 4.6 (CH), 5.7 (OH, Alcohol), 6.82-8.09 (CH, Benzene), and 13.1 (OH, Carb. acid). ^{13}C-NMR (125 MH, δ ppm): Doublet 182.0(C=O, Carbonyl), Singlet 169.7 (C=O, Carboxyl), Singlet 159.5 (C=O amide), 159.3-107.7 (1-benzene), Doublet 163.7 (1-ethylene), Singlet 69.02 (CH aliphatic), Septet 40.4 (DMSO), Doublet 70.1 (CH_2 aliphatic), Singlet 13.3, and Singlet 18.4 (CH_3 aliphatic) (Table 1).

For **A5**, the FT-IR spectrum demonstrated the following values (V max., cm^{-1}): 3400 (NH), 2362-3346 (OH, Carb. acid and Phenol Overlap), 2945(CH str.), 1716 (C=O, Ketone), 1654 (N-C=O amid), 1606 (C=C, Arom.), and 1217 (C-N, Aryl). ^{1}H-NMR (500 MH, δ ppm): 1.55(CH_3), 2.5 (DMSO), 2.07 (CH_2), 4.22-5.56 (CH), 5.77 (OH, Alcohol), 6.82-7.5 (CH, Benzene), 8.73 (NH, sec. amide), 9.48 (NH, sec. amine), and 12.39 (OH, Carb. acid). ^{13}C-NMR (125 MH, δ ppm): Doublet 182.1(C=O, Carbonyl), Triplet 169.7 (C=O, Carboxyl), Doublet 174.5, Doublet 166.8 (C=O amide), 163.3-108.6 (1-benzene), Doublet 163.9 (1-ethylene), Octet 64.3, Doublet 72.7, Doublet 60.07, Doublet 79.9, Doublet 60.05, triplet 69.0 (CH aliphatic), Septet 40.3 (DMSO), Doublet 70.1 (CH_2 aliphatic), and Singlet 29.8 (CH_3 aliphatic) (Table 1).

For **A6**, the FT-IR spectrum revealed the following values (V max., cm^{-1}):
2400-3338 (H-OH, Carboxyl and Phenol overlap), 3080(C=CH), 2989 (CH str.), 1716 (C=O, Ketone), 1612 (N-C=O amid), 1602 (C=C, Arom.), and 1230-1309 (C-N, Aryl). ^{1}H-NMR (500 MH, δ ppm): 1.22, 3.32(CH_3), 2.5 (DMSO), 2.9, 3.6, 3.8, 4.07 (CH_2), 4.6, 5.2, 5.6, 5.8 (CH), 5.7 (OH, Alcohol), 6.8-7.5 (CH, Benzene), 8.1-9.1(NH, Amid.), and 12.2 (OH, Carb. acid). ^{13}C-NMR (125 MH, δ ppm): Doublet 181.1 (C=O, Carbonyl), quartet 177.2 (C=O, Carboxyl), triplet 169.2, Doublet 168.5, singlet 166.8 (C=Oamide), 158.0-115.7 (1-benzene), Doublet 74.9, triplet 64.2, quartet 73.5, quartet 48.5 (CH,Azetidine), Doublet 56.8, triplet 33.0 (CH_2, Azetidine), singlet 163.7, triplet 114.7 (1-ethylene), singlet 136.2 , singlet 118.8 (1-ethylene), Septet 40.4 (DMSO), triplet 69.06(CH aliphatic), Doublet 70.01 (CH_2 aliphatic), and Doublet 25.9 (CH_3 aliphatic) (Table 1).
For **A7**, the FT-IR spectrum indicated the following values (V max., cm^{-1}): 3590 (NH), 2362-3346 (OH, Carb. acid and Phenol Overlap), 2995 (CH str.), 1720 (C=O, Ketone), 1658 (N-C=O amid), 1606 (C=C, Arom.), and 1213-1307 (C-N, Aryl). ^{1}H-NMR (500 MH, δ ppm): 2.5 (DMSO), 2.09-4.54 (CH_2), 4.55-4.6 (CH) ,5.7 (OH, Alcohol), 6.28, 8.7 (NH, Sec. Amin.), 6.82-7.59 (CH, Benzene), 8.24 (NH, Sec. Amid.) ,9.2 (pyrazine), 10.25, 2.0(NH, quaindine), 12.66, and 12.01 (OH, Carb. acid). ^{13}C-NMR (125 MH, δ ppm): Doublet 182.1 (C=O, Carbonyl), quartet 178.2, triplet 174.6 (C=O, Carboxyl), Doublet 157.1, Doublet 167.5 (C=O amide), triplet 147.6 (C-imine), singlet 150, singlet 147.7, singlet 129(C-pyrazine), triplet 112.9, triplet 122.3, triplet 130.0, quartet 152.7 (Fo. Benzene), Doublet 107.2, Doublet 109.3, singlet 115.6, Doublet 157.5, Doublet 138.7 (Cro. Benzene), Doublet 163. (1-ethylene), singlet 118 (1-ethylene), Septet 40.2 (DMSO), quartet 56.1, triplet 69.0 (CH aliphatic), Doublet 70.01, Doublet 47.2, triplet 30.8, and quartet 26.1 (CH2 aliphatic) (Table 1).
For **A8**, the FT-IR spectrum revealed the following values (V max., cm^{-1}): 3510(NH), 2495-3435 (OH, Carb. Acid, and Phenol Overlap), 2906 (CH str.), 1720 (C=O, Ketone), 1640 (N-C=O amid), 1612 (C=C, Arom.), 1220-1301 (C-N, C-O). ^{1}H-NMR (500 MH, δ ppm): 1.55 (CH_3), 2.5 (DMSO), 4.07 (CH_2), 4.32, 4.44-5.56 (CH), 5.77, 9.06 (OH, Alcohol), 8.63 (NH, Sec. Amin.), 6.82-7.5 (CH, Benzene), 9.48 (NH, Sec. Amid.), and 12.39 (OH, Carb. acid).^{13}C-NMR (125 MH, δ ppm): Doublet 182 (C=O, Carbonyl), triplet 169.7 (C=O, Carboxyl), triplet 171.9 (NH-C=O amide), Doublet 166.8 (N-C=O amide), triplet 174.6 (C-imine), triplet 129 (C-pyrazine), Doublet 158.6, Doublet 107.7, Doublet 109.1, triplet 138.3 (Cro. Benzene), triplet 135.7, Doublet 115.7, quartet 156.5 (Amp. Benzene), singlet 118 (1-ethylene), Septet 40.2 (DMSO), Doublet 72.2, triplet 60.7, singlet 79.5, Doublet 69.6, (CH aliphatic), Doublet 70.01 (CH_2 aliphatic), and singlet 29.8 (CH_3 aliphatic) (Table 1).

Table 1: Some of physical properties of (**A1-A8**) compounds

No. of Compound	Structural formula	Color	M.P. (°C)	Yield (%)	R_f [a] (Cm)
A1		Orange	146-148	70	0.74
A2		Off White	208-210	89	0.96

A3		Orange	118-120	80	0.81
A4		Light brawn	146-148	71	0.76
A5		Reddish Brawn	109-111	90	0.60
A6		Brawn	104-106	79	0.68
A7		Dark Yellow	123-125	84	0.40
A8		Dark Red	103-105	88	0.45

[a] (9:1) (acetone/hexane)

Results and Discussion

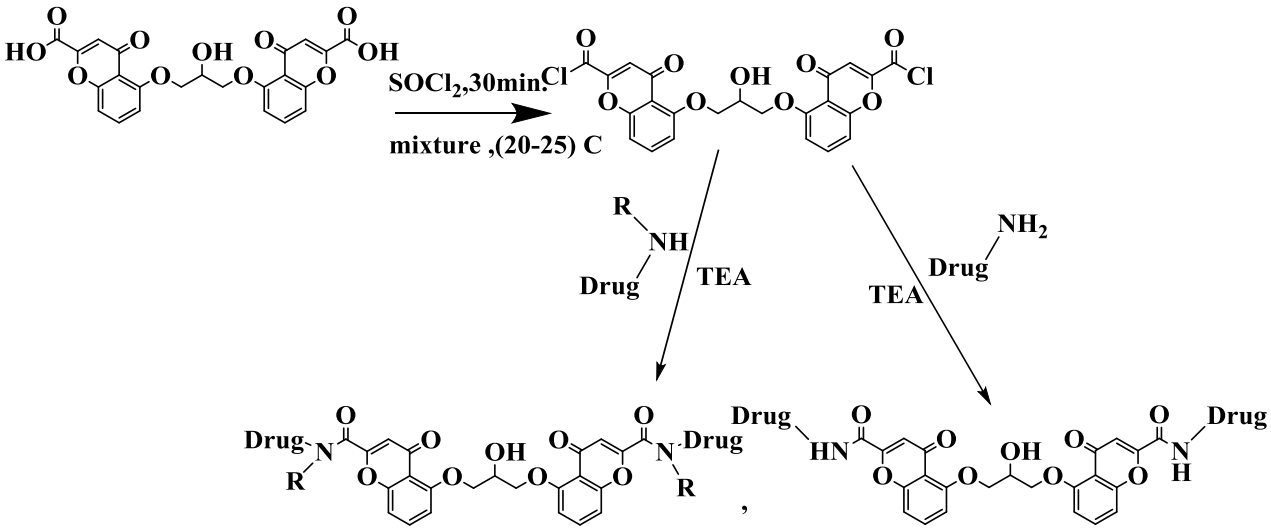
The solubility

The solubility for synthesized compounds was studied by using different polarity solvents, all prepared compounds are partially soluble in water due to the relatively high molecular weight and they are completely soluble in each of DMSO and ethanol. All synthesized compounds are insoluble in each diethyl ether, petroleum ether and ethyl acetate because the polarity for prepared compounds is higher than the polarity of these solvents (Table 2).

Table 2: The solubility of prepared derivatives in different solvents

Solvent / Compound	DMSO	Water	Ethanol	Acetone	Methanol	Hexane	1,4-dioxane	DCM	DMF	Diethyl ether	Petroleum ether	Ethyl acetate
A1	+	-	+	+	partial	-	+	partial	+	-	-	-
A2	+	-	-	+	partial	-	-	-	+	-	-	-
A3	+	-	partial	+	partial	partial	partial	-	+	partial	-	partial
A4	+	-	+	+	+	-	+	+	+	-	-	+
A5	+	partial	+	+	+	-	partial	partial	+	-	-	partial
A6	+	+	-	-	+	-	partial	-	+	-	-	-
A7	+	partial	-	partial	-	-	-	-	-	partial	-	-
A8	+	partial	+	+	+	partial	+	partial	+	partial	-	partial

To enhance the properties of cromoglicic acid (CGA) and reduce its side effects, new amino-containing drugs were synthesized by the formation of amide bonds. The compounds (**A1-A8)** were prepared by one pot reaction of a Cromoglicic acid with amino drug in $SOCl_2$ and TEA (Scheme 1).



R-NH-Drug, Drug-NH_2: (R1.Paracetamol-R2.Theophylline-R3.4-Aminoantipyrine-R4.Mefenamic acid-R5.Amoxicillin-R6Cephalexin-R7.Folic acid-R8.Ampicillin.

Scheme 1: Synthesis of compounds **A1-A8**

Biological Activity

Antibacterial activity

The findings revealed that the majority of the tested compounds have a good antibacterial activity. These bacteria were chosen because of their wide importance in the clinical field, as they cause a variety of diseases in addition to their various antibiotic and chemical drug resistances. The experiment was done 3 times with different concentrations and the best concentration at 0.1 mg /mL. Table 3 reveals that the produced compounds have biological activity against the bacteria because they may suppress the bacteria by varying the amounts of the compounds. This difference in toxicity is due to change in functional group or structures, as depicted in Figures 2 and 3.

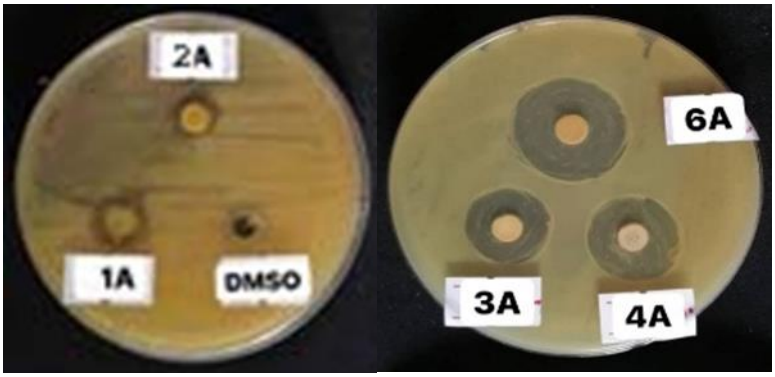


Figure 2: Klebsiella pneumonia activity test

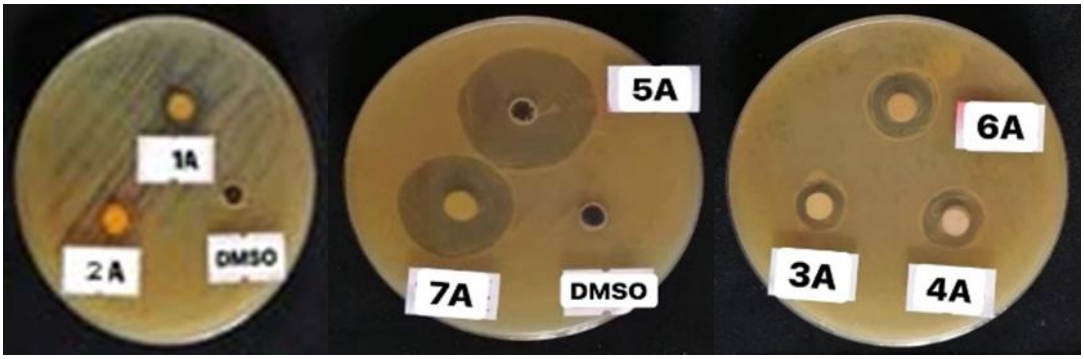


Figure 3: Staphylococcus aureus activity test

Table 3: Antibacterial activity for compounds (A1-A8)

No. of Compound	Antibacterial activity test	
	klebsiella pneumonia (Gram-negative bacterium)	*Staphylococcus aureus (Gram-positive bacterium)*
Control	6	14
A1	11	15
A2	14	11
A3	20	15
A4	22	17
A5	15	30
A6	26	19
A7	14	28
A8	13	22

Antioxidants activity

Compounds antiradical test was carried out using the standard DPPH method.

Figure 4 and Table 4 indicated the comparison with normal (ascorbic acid) activity (IC50=28.72 mg/mL), and the majority of compounds offered moderate to high antioxidant activity. The maximum activity was attributable to the OH group in compounds (**A1-A8**) with a considerable activity, and ascorbic acid, a generic medication,

with an IC50 of 28.72 mg/mL. The forces for the antioxidant activity of the test substances are in the following sequence when compared with the reference: **A5>A2>A1>A6>A4>A3>A8>A7**.

Table 4: Antioxidants activity for compounds (**A1-A8**)

No. of Comp.	Inhibition %			IC50 mg/mL
	25 mg/mL	50mg/mL	100mg/mL	
A1	54.67	55.83	60.77	27.92
A2	49.05	55.12	58.6	24.45
A3	46.13	52.11	60.02	43.5
A4	48.04	53.05	57.12	36.36
A5	48.06	58.56	60.91	21.33
A6	49.46	53.02	59.16	30.08
A7	44.22	51.44	61.03	50.38
A8	49.01	50.01	55.21	42.23
Ascorbic acid(STD)	46.12	60.14	65.01	28.72

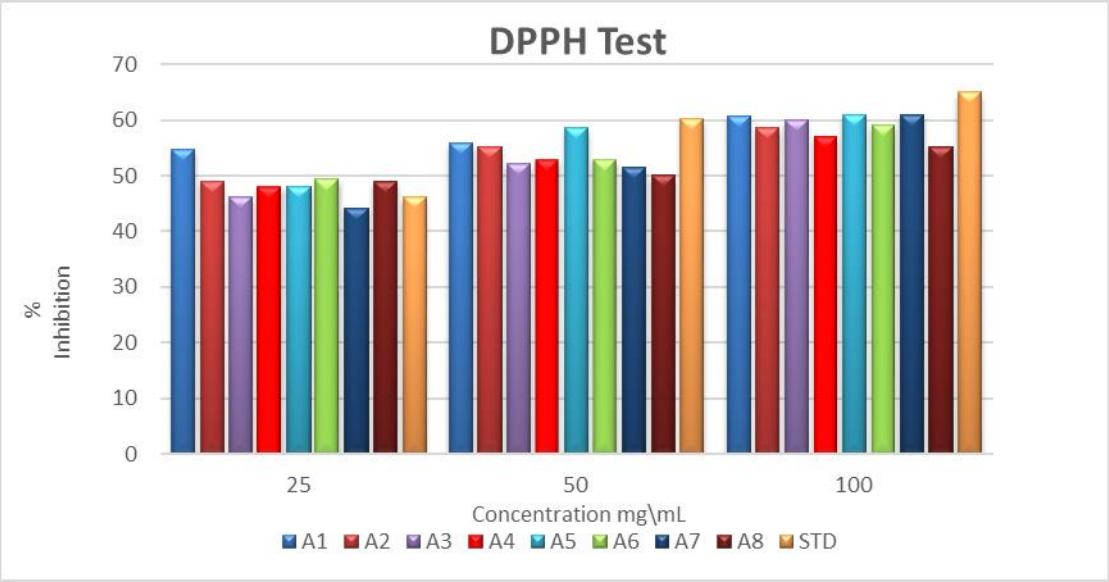


Figure 4: Standard DPPH method

Conclusion

In this study, it is possible to prepare new, developed, and suitable drug derivatives in the treatment of infection prevention, because most of the prepared derivatives gave good results for biological activity and anti-oxidant. The prepared compounds gave a large proportion of the output and were prepared from simple and available materials. All prepared compounds were stable in various conditions.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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