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FULL PAPER

Synthesis, characterization, and evaluation of antibacterial and antioxidant activity of 1, 2, 3-triazole, and tetrazole derivatives of cromoglicic aid

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The present work includes preparing new compounds of 1, 2, 3-Triazole, and Tetrazole based on Cromoglicic Acid and using them as anti-bacterial and ant-oxidant agents. The mentioned compounds were prepared using click chemistry; triazole rings were reacted with azide (terminal alkyne of cromoglicic acid) in the presence of copper as a catalyst. The modified compounds were characterized using different techniques such as FTIR, ^{1}H-NMR, and ^{13}C-NMR. Then, the antioxidant and antibacterial activities of the synthesized compounds were experimentally examined *in vitro* versus two kinds of bacteria (*Escherichia coli* (gram-negative bacteria) and *Staphylococcus aureus* (gram-positive bacteria)).The DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) free radical method was used to measure the antioxidant activity of the prepared compounds, while the antibacterial activity was examined using the diffusion method. The obtained results for all prepared compounds were good as an antioxidant in comparison with ascorbic acid.

KEYWORDS

Azide; triazole rings; anti-oxidant; antibacterial activity.

Introduction

Cromoglicic acid (INN), also known as cromolyn (USAN), cromoglycate (old BAN), or cromoglicate, is often marketed as the sodium salt sodium cromoglicate. It is typically characterized as a mast cell stabilizer. Because of its convenience, leukotriene receptor antagonists have essentially taken the place of cromoglicic acid, which was once the non-corticosteroid medication of choice for treating asthma (and perceived safety). Inhaled corticosteroids do not bring any benefits when used with cromoglicic acid, which administered orally four times daily. Cromoglicic acid is used to treat allergies and conjunctivitis, a surfactant and as atopic dermatitis therapy. It helps heal skin wounds and reduces the risk of pulmonary irritation [1,2]. Because cromoglicic acid is a highly ionized, water-soluble substance, it cannot pass through cell membranes and should be inhaled to be delivered efficiently [2,3].

Although the specific mechanism of action of cromoglicic acid (cromolyn), a medication that is thought to stabilize mast cells, is considerably more complex, it is still thought to have this effect. According to the recent findings, cromolyn inhibits glycogen synthase kinase 3β, which suggests that it may be useful in treating insulin-induced lipoatrophy as well as diabetes, obesity, and other

conditions. Agonizing GPR35 has also been reported to have possible anti-fibrotic effects [4-6].

Heterocyclic compounds are natural cyclic compounds with different heteroatoms, including triazole derivatives, which are used in wide fields as herbicides, anti-bacterials, disinfectants, and anti-inflammatory agents [7]. Triazoles are five-member rings that have many important applications such as anti-virus, microbial, and antihistamine. Likewise, have industrial uses such as dyes, agricultural chemicals, and the pharmaceutical industry [8-12]. Cyclic addition reactions are one of the most important types of cyclic reactions used in the synthesis of triazoles from the [2 + 3] cyclic reaction, via two or more unsaturated molecules that are combined to form the triazoles [13-15].

In the present work, we prepared new derivatives having effective groups of 1, 2, 3-triazoles and tetrazole derivatives based on cromoglicic acid, and also their biological activities as antibacterial, and antioxidant were studied.

Experimental part

Materials

The chemical compounds used are from Merck & BDH. The melting point was measured with, "tests eon & Shimadzu (FTIR 8400, Series Japan)" instrument, and also ^{13}C-NMR, ^{1}H-NMR spectra utilizes DMSO-*d6* solvent and with "Bruker, Ultra Shield 500-M.HZ Switzerland."

Synthesis of compounds (S1) & (S2)[16]

Cromoglicic Acid (S) (0.01 mol, 4.72 gm) dissolved in 50 ml round bottom flask with 25 mL of thionyl chloride and the mix stirred for 15.0 min at room condition. Next, (25 mL) of ethanol and (2 drops) of H_2SO_4 were added with reflux for 3 h, and then the solution was concentrated by rotary evaporator and collected to get oil product (S1) and (S2) white off precipitate compounds, respectively (Scheme 1 and Table 1).

Synthesis of compound (S3) [17,18]

(0.01 mol, 4.44 gm) of compound (S2) was added in a round bottom flask and the mixture of hydrazine (0.02 mol, 0.64 gm) and ethanol (40 mL) was added, and then the mixture has been refluxed with stirring for six hours. After that, the precipitate was collected and recrystallized from absolute ethyl alcohol to afford (S3) compound as orange color precipitate (Scheme 1 and Table1).

Synthesis of compound (S6, S7) [19]

In 50 ml round bottom flask, (0.02 mol, 7.0 gm, an 7.75 gm) of 3-chlorobenzaldehyde and vanillin were mixed separately with (0.01 mol, 3.56 gm) of S3, and then 20 mL of ethanol and two drops of glacial acetic acid were added to the mixture. After that, the mix was refluxed for 4 h, and then the mix was filtered and the precipitation was collected. TLC technique was applied to follow the reactions. The precipitate recrystallized from absolute ethyl alcohol to afford compounds S6 and S7 as orange and dark yellow respectively (Scheme 1 and Table 1).

Synthesis of azide derivative (S8 and S9) [18]

NaN_3 (5 g) was mixed with compound S6 and S7 (0.02 mol.) separately, DMSO (150 mL), and D.W (50.0 mL) in a round bottom flask and stirred at room temperature for 24 hours. The mix was diluted with (200 mL) of D.W, and extracted with diethyl ether (3.0 x 100 mL), the organic layer was collected and dried with $MgSO_4$ to get a clear liquid. The solvent was removed using rotary evaporator and the precipitate was purified by recrystallization using ethanol as a solvent to get dark red and white yellow precipitate compounds S8 and S9 respectively (Scheme 1 and Table 1).

Synthesis of terminal alkynes [S4] [20]

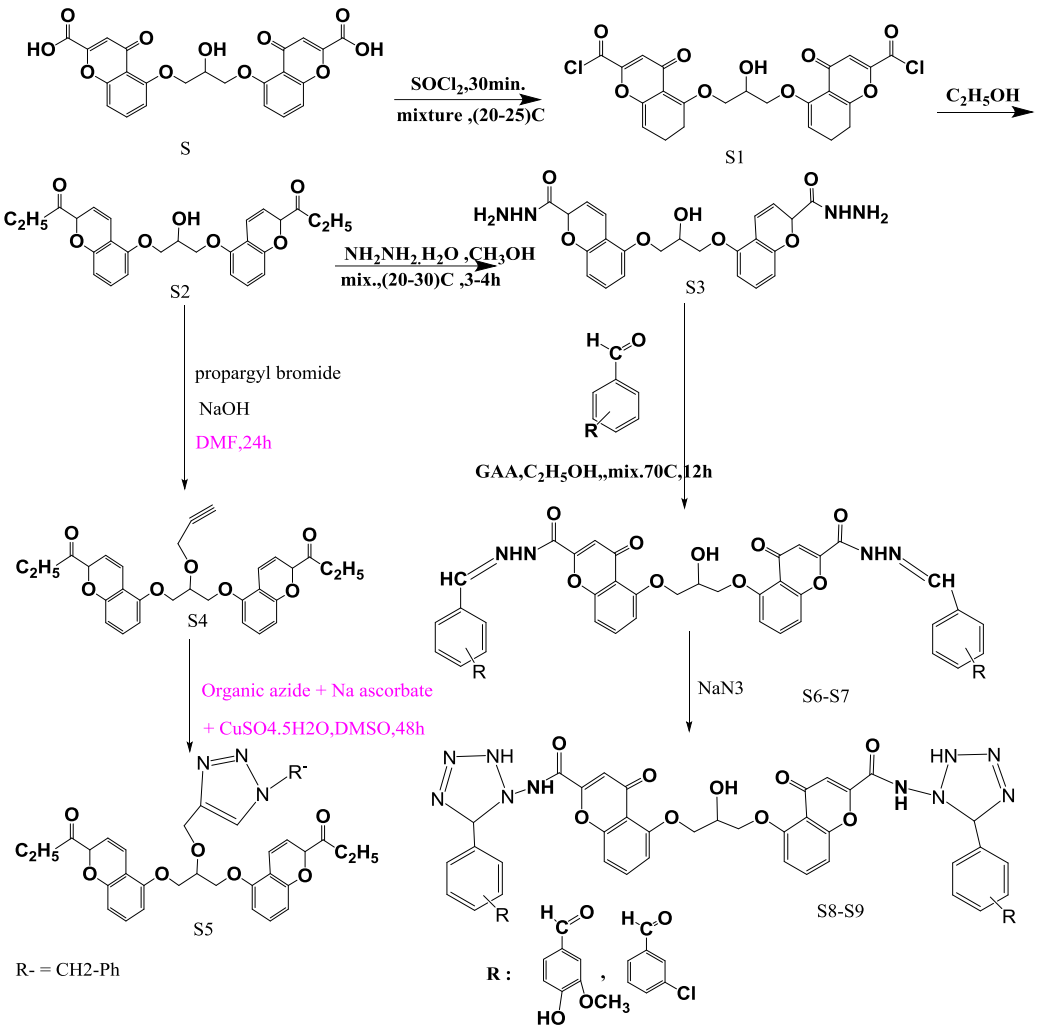
(20 mmol) of compound (S2) was dissolved in solvent -DMF (60.0 mL), and then K_2CO_3 (4.0 g), propargyl bromide (2 mL) were added to the mix with stirring and cooling ice bath for 20 minutes. After that, the mixture was stirred for 24 h at 25 C. D.W (120.0 mL) was added to the mixture and extracted by diethyl ether (3.0 x 70 mL). The organic layer was collected and dried with $MgSO_4$ to get a clear liquid. The solvent was removed by utilizes rotary evaporator to get yellow liquid compound S4 (Scheme 1 and Table 1).

Synthesis of 1, 2, 3-Triazoles derivatives [S5] [21]

Compound [S3] (5.30 mmol) was mixed with sodium ascorbate (0.09540 g) and copper sulfate pentahydrate (0.05830 g) in DMSO (5.0 mL). The mixture was stirred for 10 minutes at 60 °C, benzyl azide (5.3 mmol) was added while being heated and stirred for 48 hours. Water (80 mL) was added to the solution and extracted with ethyl acetate three times. The mixture was washed twice in 40 mL of H_2O, dried with MgSO4. The solvent was removed using rotary evaporator and the precipitate was purified by recrystallization using ethanol as a solvent to get reddish brawn precipitate compound S5 (Scheme 1 and Table 1).

TABLE 1 Physical characteristic of derivative (S1-S9)

No.	Color	M. formula	M.Wt	M.P (°C)	Yield %	*Rf*
S1	Orange	$C_{23}H_{18}Cl_2O_9$	508.08	146-148	70%	0.74**(2:8)** DCM:Hexane
S2	Off White	$C_{27}H_{28}O_7$	464.18	208-210	89%	0.96**(2:8)** DCM:Hexane
S3	Orange	$C_{23}H_{24}N_4O_7$	468.47	118-120	80%	0.81(3:7**)** DCM:Hexane
S4	Yellow	$C_{30}H_{30}O_7$	502.56	Liquid	71%	0.76**(2:8)** DCM:Hexane
S5	Reddish Brawn	$C_{37}H_{37}N_3O_7$	635.6	179-181	90%	0.60(1:9**)** DCM:Hexane
S6	Orange	$C39H_{23}N_4O_{13}$	764.7	104-106	79%	0.68**(2:8)** DCM:Hexane
S7	Dark Yellow	$C_{37}H_{26}Cl_2N_4O_9$	741.5	Dec>160	84%	0.40(1:9**)** DCM:Hexane
S8	Dark Red	$C_{39}H_{34}N_9O_{13}$	850	303-305	88%	0.45(1:9**)** DCM:Hexane
S9	White yellow	$C_{38}H_{27}Cl_2N_{10}O_9$	872	380<	65%	0.56(3:7**)** DCM:Hexane



SCHEME 1 Synthesis of compounds (S1-S9)

Biological activity

Antibacterial activity

The diffusion method was used to examine the antimicrobial characterization of the prepared compounds and two kinds of bacteria (*Staphylococcus aureus* and *Klebsiella pneumonia*). The test compounds was doubly diluted across the range of 0.39-50 g/mL after being fully dissolved in dimethyl sulfoxide (DMSO) and placed to a plate (agar medium) at 37.0°C for 24 hours, showed good results (Table 3) [22].

Antioxidants activity

DPPH (4.0 mg) was utilities by dissolving it in 100.0 mL of CH_3OH different concentrations (25.0, 50.0, and 1.0 hundred) ppm were attended. It was soluble in (10.0 mL) of methanol, 3.0 mL of the sample was taken, and 1.0 mL of DPPH was added to it in a tube and left for 30.0 minutes in the dark at 37.0°C, the wave length of antioxidants at 517 nm. The inhibition ratio was calculated using the equation below [23-25].

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

Results and discussion

A new compounds contain functional groups (1, 2, 3-triazoles and tetrazole) based on cromoglicic acid compound have been synthesized (Scheme1) and studied their activity as antibacterial and antioxidant. These compounds were characterized by different techniques.

Synthesis and characterization of compounds (S3-S9)

The FT-IR spectra for S1revealed these values (*Vmax*, cm^{-1}): It indicated that the –OH of carboxylic acid was disappeared and the following bands were appeared, 3338 (OH, aliphatic), 3090 (C=CH), 2869 (CH str.), 1765 (C=O), 1612 (C=C),1230-1309 (C-O ,C-N), 780 (Cl-C=O) .^{1}H-NMR (δ ppm): 2.50 (DMSO), 3.83 (CH_2), 8.9 (OH) , 6.9 -7.5 (CH, Ar.). Compound S2, the FT-IR spectrum showed the following values ($V_{max.}$, cm^{-1}): 3418- 3362 (OH), 3091 (C=CH), 2943 (CH str.), 1651 (C = O), 1565 (C=C Aromatic), 1215-1394 (C-N, Aryl) .^{1}H-NMR (500 MH, δ ppm): 3.8 (CH_2) , 6.9-7.9 (C, Ar.) , 7.17 (H, Ethylene), 2.51 (CH_3, ethane), 3.95 (OH, aliphatic), 2.5 (DMSO). The FT-IR spectrum for S3 shows these values (V_{max}, cm^{-1}): appeared new bands at 3298 (NH) and 3398 (NH_2), in addition to 3416 (OH), 3091 (C=CH), 2943 (CH str.), 1651 (N-C=O amid), 1604 (C=C), 1247-1398 (C-O, C-N). ^{1}H-NMR (δ ppm): 2.50 (DMSO), 4.60 (NH_2), 4.07 (CH_2), 5.77 (OH), 6.82 -7.50 (CH, Ar), 9.44 (NH). ^{13}C-NMR (125 MHz, δ ppm): 170.49, 175.40 (C=O), 158.2-107.60 (C-Ar), 68.70 (CH), 71.10 (CH_2), 40.40 (DMSO). The FT-IR spectrum for S٤ revealed these values (V_{max}, cm^{-1}): 3090 (C=CH), 2945 (CH str.), 1732 (C=O ester), new band at 2342 (HC≡CH), 1602 (C=C), 1265-1334 (C-N). ^{1}H-NMR (δ ppm): 2.51 (DMSO), 3.31 (CH_3), 4.4-3.9 (CH_2), 4.7 (CH), 5.87 (OH) 6.82-7.50 (CH, Ar), 3.32 (HC≡CH). ^{13}C-NMR (125 MH, δ ppm): 182.1, 164.7 (C=O), 138.6- 108.7 (C, Ar.), 151.3 (C-O), 69.0(CH), 40.2 (DMSO), 70.01 (CH_2), 30.7, 29.0 (CH_3). The FT-IR spectrum of S5 showed these values (V_{max}, cm^{-1}): 3090 (C=CH), 2983 (CH str.), 1647(C=O), 1570 (C=C), 1230-1309 (C-N), disappear of HC≡CH and appearance a new band at 1435(N=N). ^{1}H-NMR (δ ppm): 2.26 (CH_3), 2.51 (DMSO), 3.9 (NH), 4.07 (CH_2), 4.6 (CH), 5.7 (OH), 6.82-7.5 (CH,Ar.), 10.06 (NH).^{13}C-NMR (125 MHZ, δ ppm): 185.4 (C=O), 137.6- 109.1 (C-Ar) , 40.4 (DMSO), 69.0 (CH), 72.7 (CH_2), 31.3 (CH_3).

The FT-IR spectrum for S6 revealed these values (V_{max}, cm^{-1}): 2492-3416 (OH, NH), 2995 (CH str.), appearance new band at 1661 (C=N), 1601 (C=C, Ar), 1716 (C = O), 1209.40-1307.70(C-N). ^{1}H-NMR (δ ppm): 3.90 (OCH_3), 2.490 (DMSO), 4.40, 4.70 (CH_2), 8.70 (CH=N), 5.80, 9.540 (OH), 6.82-7.80 (CH, Benzene), 11.20 (NH). The FT-IR spectrum for S٧ shows these values (V_{max}, cm^{-1}): 3494, 3214 (OH, NH), 2914 (CH str.), 3042 (CH, Ar.), 1691 (C=O), appearance new band at 1651 (C=N), 1549 (C=C, Ar), 1209.4-1307.7 (C-N). ^{1}H-NMR (δ ppm): 2.49 (DMSO), 4.5, 4.6 (CH_2), 8.8 (CH=N), 5.7 (OH), 6.8-7.9(CH, Benzene), 10.09 (NH). The FT-IR spectrum for S٨ revealed these values (V_{max}, cm^{-1}): 3394, 3390 (OH, NH), 2995 (CH str.), 1718(C=O), 1608 (C=C, Ar), appearance new band at 1660 (C=N), 1217.4-1419.7 (C-N). ^{1}H-NMR (δ ppm):3.9 (OCH_3), 2.49 (DMSO), 4.5, 4.6 (CH),4.04 (CH_2), 5.7 (OH, aliphatic), 9.4(OH, phenol) , 6.8-7.5 (CH, Benzene), 12.3 (NH), 4.30 (NH tetrazole).^{13}C-NMR (125 MH, δ ppm): 182.9,147.2 (C=O, Carbonyl),138.3-108.6 (C-benzene), 156, 158 (C-OH), 40.4 (DMSO), 69.06 (CH, aliphatic), 70.09, 72.2 (CH_2 aliphatic), 60 (OCH_3). The FT-IR spectrum for S9 revealed these values (V_{max}, cm^{-1}): 3416 ,3346 (OH, NH), 2995 (CH str.), 1716 (C=O), 1601 (C=C, Ar), appearance new band at 1665 (C=N), 1209.4-1307.7(C-N).^{1}H-NMR (δ, ppm): 2.49 (DMSO), 4.04 (CH_2), 4.67 (CH), 5.3 (OH), 6.82-8.1 (CH, Benzene), 13.14 (NH), 4.2 (NH tetrazole). ^{13}C-NMR (125 MHZ, δ ppm): 182.1 (C=O, Carbonyl), 138.3-103.7 (C-benzene), 156, 158 (C-OH), 40.4 (DMSO), 69.06 (CH aliphatic), 70.01 (CH_2 aliphatic).

The prepared compounds insoluble in hexane, petroleum ether, diethyl ether, and acetone but shows a good solubility in solvent DMF &DMSO. Some of them have partial solubility in water, ethanol, and ethyl acetate. Solubility properties of prepared compounds in different solvents (H_2O, petroleum ether, ethanol, CH_2Cl_2, ether, DMSO, hexane, ethyl acetate, acetone, and DMF) are listed in Table 2.

TABLE 2 Solubility for compounds S1-S9 using different solvents

Compound	DMSO	DMF	DCM	Pet. ether	Ethyl acetate	Acetone	Di ethyl ether	H_2O	Hexane	EtOH
S1	+	+	-	Partial	Partial	partial	-	+	Partial	+
S2	+	+	+	-	+	-	-	Partial	-	Partial
S3	+	+	-	Partial	Partial	Partial	-	+	-	+
S4	+	+	-	-	+	+	-	+	-	Partial
S5	+	+	+	-	Partial	+	-	Partial	Partial	+
S6	+	+	Partial	Partial	+	Partial	-	+	Partial	Partial
S7	+	+	+	-	-	+	-	Partial	-	+
S8	+	+	Partial	Partial	Partial	+	-	Partial	Partial	Partial
S9	+	+	+	Partial	+	Partial	-	+	Partial	Partial

Biological activity

Anti-bacterial

The biological efficiency effect of bacteria *(E-coli)* and *(Staph. Aureu.)* was studied. The derivatives (S4-S9) have a good effectiveness in inhibiting the growth of (G-), the compounds (S3, S5-S9)) have a good effectiveness in inhibiting bacteria (*G+*) with compared of Cefotaxime Table 3 [24,26]. The prepared compounds possess good antibacterial activity, due to having functional groups and it has a wide importance in the clinical field, because of their resistance to chemical drugs and various antibiotics (Figures 1 and 2 and Table 3).

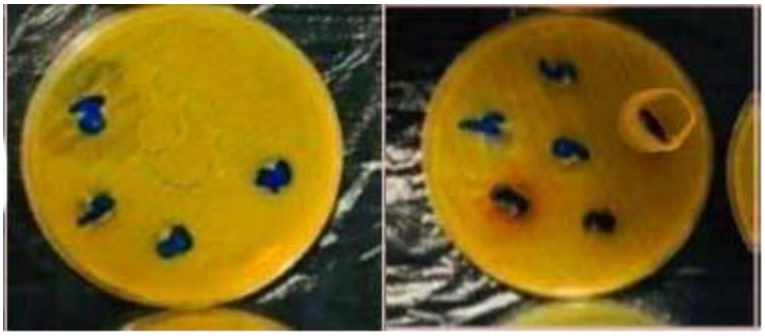


FIGURE 1 *Staphylococcus aureus* activity test of the prepared compounds

FIGURE 2 *Klebsiella pneumonia* activity test of the prepared compounds

TABLE 3 Anti-bacterial activity for (S3-S9)

No. of Compound	Anti-bacterial activity test	
	***Klebsilla pneumonia* (G-)**	***Staphylcoccus aureus* (G+)**
Cefotaxime (Antibiotic) Standard	8	12
S3	7	13
S4	10	9
S5	22	17
S6	26	14
S7	12	24
S8	22	21
S9	11	23

Antioxidant activity

The DPPH method is used to study the activity of the synthesized compounds as antioxidant. Figure 3 and Table 4 show the results in comparison with ascorbic acid as control using 25, 50, and 100 mg/mL concentrations, the results shows that the 100 mg/mL concentration gave a good inhibition zone compared to control. Compound S8 is the best one due to inhibiting the bacteria with IC_{50} mg/mL 21.33. The existence of functional groups in the structure of synthesized compounds (S1-S9) might have an effect on the inhibition process. The order of compounds ordered compared to reference as follows:

S8>S2>S6>S5>S4>S9>S1>S7.

TABLE 4 Anti-oxidants activity for (S1-S9)

Compound No.	Inhibition %			IC50 mg/mL
	25 mg/mL	50 mg/mL	100 mg/mL	
S1	49.01	50.01	55.21	42.23
S2	49.05	55.12	58.6	24.45
S3	46.13	52.11	60.02	43.5
S4	48.04	53.05	57.12	36.36
S5	49.46	53.02	59.16	30.08
S6	54.76	55.83	60.77	27.92
S7	44.22	51.44	61.03	50.38
S8	48.06	58.56	60.91	21.33
S9	47.04	54.05	57.12	36.35
Ascorbic acid(STD)	46.12	60.14	65.01	28.72

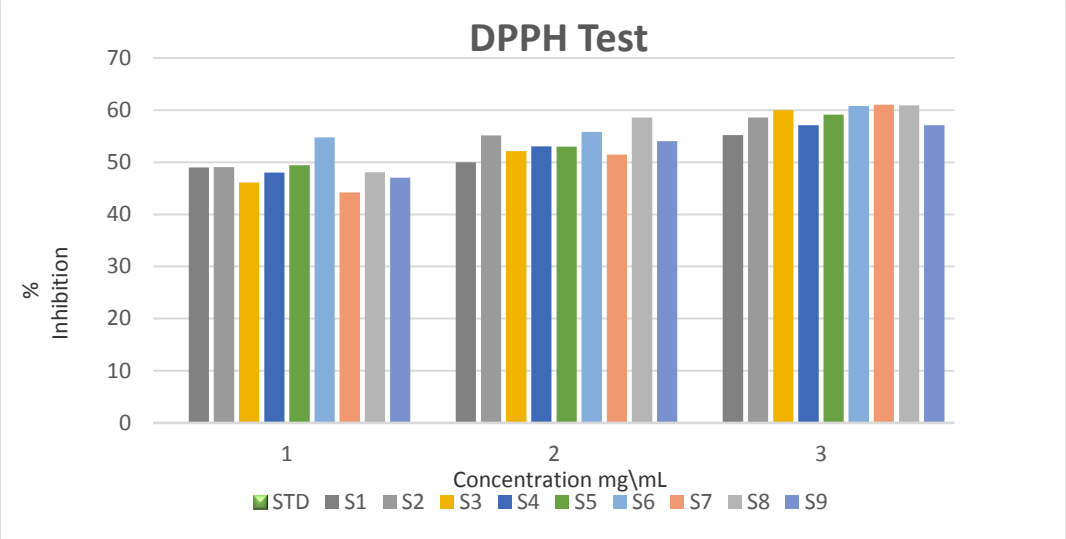


FIGURE 3 Standard DPPH method for synthesized derivatives S1-S9

Conclusion

Series of new compounds containing 1, 2, 3-triazoles and tetrazole groups have been synthesized based on Cromoglicic Acid and characterized using various techniques. In addition, the antibacterial activity of these compounds was tested against some pathogenic bacteria species and the obtained results showed a good activity. Furthermore, the activity as antioxidant was studied using DPPH method, the results show that most of these compounds have good activity as antioxidant agent compared to the control.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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