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Synthesis, Identification and evaluation of antibacterial activity of some new substituted N-benzyl-5-Bromo Isatin

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Abstract

This research includes synthesis of new heterocyclic derivatives of N-benzyl-5-bromoisatin. New 1, 2, 4-triazole, oxazoline and thiazoline derivatives of [N-benzyl-5-bromo-3-(Ethyliminoacetate)-indole-2-one] (2) have been synthesized. The preparation process started by the reaction of 5-bromoisatin with sodium hydride in dimethylformamide (DMF) at 0°C, gave suspension of sodium salt of 5-bromoisatin and subsequent reaction with benzylchloride to give N-benzyl-5-bromoisatin (1). Compound (1) reacted with ethylglycinate (Schiff base) obtained the intermediate compound (2) which reacted with different reagents in two ways. The first way, compound (2) reacted with (hydrazine hydrate, semicarbazide, phenylsemicarbazide and thiosemicarbazide), then converted to (hydrazide, semicarbazide, phenylsemicarbazide and thiosemicarbazide) derivatives respectively to give compounds (3-6). After that compounds (4-6) cyclized in presence of alkaline media (4N-NaOH) to form substituted 1, 2, 4-triazole derivatives (7-9). In alkaline media (20%KOH) compound (3) reacted with CS_2 to give potassium salt (10) that reacted with excess of hydrazine hydrate to give compound (11). The second way includes reaction of compound (3) with (phenylisocyanate and phenylisothiocyanate) to give compound (5 and 12), which undergo cyclization with *p*-bromophenacylbromide to obtain oxazoline (13) and thiazoline (14). Newly synthesized compounds were identified via spectral methods; their [FTIR and some of them by ^{1}HNMR, ^{13}C-NMR] and measurements of some of its physical properties and also some specific reactions. Furthermore the effects of the synthesized compounds were studied on some strains of bacteria.

Keywords: N-benzyl-5-bromoisatin, 1, 2, 4-Triazole, Oxazoline, Thiazoline, antibacterial.

تحضير، تشخيص وتقييم الفعالية المضادة للبكتريا لعدد من المعوضات الجديدة لـ N-بنزايل-5-بروموايساتين

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الخلاصة

تضمن البحث تحضير مشتقات جديدة غير متجانسة الحلقة لـ N-بنزايل-5-بروموإيساتين. المشتقات الجديدة هي 4,2,1-ترايزول واوكسازولين وثايوزولين من [N-بنزايل-5-بروموـ3-(اثيل إمينو استيت) اندول-2-أون] (2) التي تم تحضيرها. عملية التحضير تبدأ بتفاعل 5-بروموايساتين مع هيدريدالصوديوم في DMFعند درجة الصفر المئوي ليعطي عالق ملح الصوديوم لـ5-بروموايساتين الذي فوعل لاحقا مع كلوريد

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البنزايل مكونا N–بنزايل–5–بروموإيساتين (1). المركب (1) فوعل مع اثيل كلايسينيت (قاعدة شيف) للحصول على المركب الوسطي (2). تضمن المسار الأول للبحث تفاعل المركب (2) مع (هيدرازين المائي، سمي كاربزايد، فنيل سميكاربزايد و ثايوسميكاربزايد) ليعطي مشتقات (هايدرازايد، سميكاربزايد، فنيل سميكاربزايد و ثايوسميكاربزايد) على التوالي (3–6). بعد ذلك المركبات (4–6) حولقت في وسط قاعدي (4N–NaOH) لتعطي مشتقات 4,2,1–ترايزولات معوضة المقابلة (7–9). في الوسط القاعدي (20%KOH) المركب (3) فوعل مع CS_2 ليعطي ملح البوتاسيوم (10). الذي تمت مفاعلته مع زيادة من هيدرازين مائي ليعطي المركب (11). تضمن المسار الثاني للبحث تفاعل المركب (3) مع (فنيل ازوسيانات و فنيل ثايوازوسيانات) ليعطي المركبين (5 و 12) التي حولقت مع بارا–بروموفيناسيل برومايد للحصول على مشتق اوكسازولين(13) ومشتق ثايوزولين(14). تم اثبات تراكيب المركبات الجديدة المحضرة بواسطة الطرق الطيفية [FTIR وبعض منها بواسطة ,^{13}C–NMR ^{1}H–NMR] وقياس بعض خواصها الفيزياوية وبعض الكشوفات الخاصة. فضلا عن ذلك تمت دراسة تأثر المركبات المحضرة على بعض سلالات البكتيريا.

Introduction

Isatin derivatives having several medicinal properties, it has distinct and discontinuous distribution of body fluid and peripheral tissue, having aroused excellent attention in recent year because of their bioactive properties [1]. And has thus been studied for anti-inflammatory, analgesic, antitubercular , anticonvulsant and antidepressant [2]. Isatin derivatives have got remarkable anti-fungal and antibacterial properties and great significance in medicinal chemistry [3], and also known to possess a vast spectrum of pharmacological properties, including antihelmintic, antitumoral antineoplastic, herbicidal, antiviral, antioxidant activity, cysticidal, hypotensive and enzymatic inhibition [4-6]. Newly anticancer drug to treat of gastrointestinal stromal tumors and advanced renal carcinoma [7]. Besides antimicrobial activity, the antioxidative capabilities of compounds are becoming more and more significant presently [8]. Derivatives of N-benzylisatin have been used as inhibitors of human rhinovirus (HRV) and antihypoxic agents, N-benzylisatin derivatives compounds were tested for pharmacological activity for central nervous system and toxic effects in mice, also studied cardiovascular response in cats, and anti-inflammatory potency [9]. 1, 2, 4-Triazole derivatives are characterized have a broad spectrum of biological activity, which include larvicidal activity, antiparasitic activity,cytostatic activity, herbicidal activity and antioxidant activity. Many compounds were developed as herbicides or commercial fungicides [10] and anti-HIV activity [11]. And also reported to have pharmacological, fungicidal, insecticidal, and herbicidal activities, in addition, have been used in medicine for treating breast cancer as nonsteroidal aromatase inhibitors [12]. Several compounds that contains 1, 2, 4-triazole rings are well known as drugs [13] and including CNS stimulants, H1/H2 histamine receptor blockers, sedatives, and antianxiety agents, their derivatives have attracted widespread attention.[14]. Differente derivatives oxazoline can be used in the industry including solution in the liquid scintilators in the optic applications [15], 2-Oxazoline used in polymerization as starting materials, and broad biological activity [16].

Experimental

Materials and Instruments

Chemicals used in this work are supplied from BDH, Fluka, Merck and Sigma Aldrich companies and used without further purification. Melting points were uncorrected and registered via digital Stuart scientific SMP3 melting point device .Thin layer chromatography (TLC) used to check purity and homogeneity of synthesis compounds. FTIR spectra of the compounds in the (4000-600) cm^{-1} spectral range were recorded on SHIMAZU FTIR-8400 Fourier transform Infrared spectrophotometer using KBr discs. ^{1}HNMR and ^{13}CNMR spectra were recorded on mar23ar 300MHz instrument using TMS as internal reference and DMSO-d_6 as a solvent.

Synthesis of N-benzyl-5-bromoisatin (1) [17]

A mixture of 5-Bromoisatin(Indole-2,3-dione) (2g, 0.0088mol) with (9ml) dimethylformamide (DMF) in 50 ml round bottomed flask had been coold to be of 0°C, as well as sodium hydride (0.192g, 0.0088mol) was cautiously added to the solution in little amounts with stirring. (0.92ml, 0.0088 mol) of benzylchloride was added to this solution, and also the reaction mixture was gradually heated to laboratory temperature degree, then refluxed for (8 hrs.). The reaction mixture has been

filtered in addition to poured on ice water, and the precipitate was recrystallized via ether. Physical properties of the products are listed in Table-1.

Synthesis of N-benzyl-5-bromo-[3-(Ethyl imino acetate)]-indole-2-one (2) [3]

To a solution of compound [1] (2.5g, 0.0079mol) with ethyl glycinate (1.054g, 0.0079mol) in (10ml) DMF and 4-5 drops of glacial acetic acid. This mixture was refluxed for (12 hrs.), trying to keep the heat of the range at (50-60) °C. The formed precipitate may be cooled off at room temperature before pouring into crushed ice, filtered with recrystalization from ethanol-water. Physical properties and FTIR spectral data of compound [2] are listed in Table-1.

Synthesis of N-benzyl-5-bromo-[3-(imino acetohydrazide)]-indole-2-one (3) [12]

In round bottomed flask 50 ml placed (0.5g, 0.0012mol) of compound [2], dissolved in dimethylformamide (5ml) and added excess of 80% hydrazine hydrate (0.0018mol) with continuous stirring, the solution was refluxed for (7-8 hrs.). The resulted, cooled off before pouring into crushed ice. The obtained precipitate was filtered, washed by distilled water and dried then was purified by recrystallization from ethanol. Physical properties are listed in Table-2.

Synthesis of N-benzyl-5-bromo-[3-(imino acetyl) hydrazinecarboxamide]-indole-2-one(4), N-benzyl-5-bromo-[3-(imino acetyl)-N-phenylhydrazinecarboxamide]-indole-2-on (5), and N-benzyl-5-bromo-[3-(imino acetyl)hydrazinecarbothioamide]-indole-2-one (6) [12]

Compound [2] (0.5g, 0.0012mol) with DMF (10ml) (semicarbazide, phenylsemicarbazide, thiosemicarbazide) (0.0012mol) was added with continuous stirring in round bottomed flask with to sodium acetate (0.0984g, 0.0012mol) in absolute ethanol (2ml), and refluxed for (10-12 hrs.). TLC (Thin Layer Chromatography) was used to check the end of reaction which showed that the starting materials were disappeared. The reaction mixture was slaked with water and filtered the solid, then purified by recrystallization from ethanol-water. Physical properties of compounds [4-6] are listed in table-2.

Synthesis of N-benzyl-5-bromo-[3-(methyl imino)-4H-1,2,4-triazol-5-ol]-indole-2-one (7), N-benzyl-5-bromo-[3-(methyl imino) 4-phenyl-1,2,4-triazol-5-ol]-indole-2-one (8) and N-benzyl-5-bromo-[3-(methyl imino)4H-1,2,4-triazol-5-thiol]-indole-2-one (9) [12]

Compounds [4-6] (0.0011mol) were refluxed in 4N sodium hydroxide solution (10ml) for (10-12 hrs). After cooling the mixture and neutralized with (1:1) hydrochloric acid. The solid product was filtered, and then recrystallized from ethanol. Physical properties of these compounds [7-9] are listed in Table-3.

Synthesis of potassium N-benzyl-5-bromo-[3-(imino acetyl) dithiocarbazate]-indole-2-one (10) [12]

Dissolved the mixture of hydrazide derivative [3] (0.5g, 0.0013mol) in stirred ethanolic solution of KOH (0.073gm, 0.0013mol) solute in absolute ethanol (10ml), and (0.1ml, 0.002mol) of CS_2 was lingeringly added to the solution and then the reaction mixture was stirred overnight. The orange ppt. filtered, washed with (10ml) of dry ether. In the next step, salt [10] which we got used without more purification. Physical properties of the compound obtained are listed in Table-3.

Synthesis of N-benzyl-5-bromo-[3-(methyl imino)-4-amino-1,2,4-triazol-5-thiol]-indole-2-one (11) [12]

In round bottomed flask (0.4gm, 0.0008mol) of potassium salt [10] were refluxed with (5ml) excess of 80% hydrazine hydrate until layover of the transmutation of hydrogen sulphide. During reflux the color was changed of the reaction mixture, then resulted a homogenous mixture, cooling the product obtained and acidified with hydrochloric acid 10% to yield pale brown precipitate. It was purified via recrystallization from ethanol to get crystals. Physical properties of compound [11] are listed in Table-3.

Synthesis of N-benzyl-5-bromo-[3-(imino acetyl) phenylsemicarbazide]-indole-2-one (5), and N-benzyl-5-Bromo-[3-(imino acetyl)phenylthiosemicarbazide]-indole-2-one (12) [18]

In round bottom flask (0.5gm, 0.0013mol) of compound [3], phenylisocyanate (0.078ml, 0.0013mol) and phenylthioisocyanate (0.154ml, 0.0013mol) in (8ml) absolute ethanol. The mixture was heated under reflux temperature for (5-6 hrs.).After Cooling, filtered, dried and recrystallized from acetone. Physical properties of the precipitate are listed in table-4.

Synthesis of N-benzyl -5-bromo-[3-imino- (5-*p*-Bromophenyl-2-hydroxy-3-phenyl-2, 3-dihydro-1, 3-oxazole-2-yl) acetohydrazide]-indole-2-one (13), N-benzyl-5-Bromo-[3-imino- (5-*p*-Bromophenyl)-2-mercapto-3-phenyl-2, 3-dihydro-1, 3-oxazole-2-yl) acetohydrazide]-indole-2-one (14) [18]

The compounds [5, 12] (0.00078mol) with (0.2gm, 0.00078mol) *p*-bromophenacyl bromide in (10ml) absolute ethanol was refluxed for (6-7 hrs.). Cooled, neutralized via solution of ammonium hydroxide. A solid product was filtered, washed with water and dried under vacuum. The product was recrystallized from dioxane. Physical properties of these compounds are listed in table-4.

Table 1-Physical properties and FTIR spectral data cm^{-1} of the synthesized compounds (1, 2).

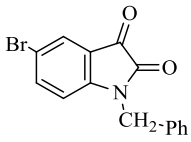
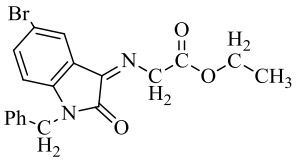
Com .No.	Physical Properties				Major FTIR Absorption cm^{-1}				
	Structures	M.P °C	Yield %	Color	ν(C-H) arom.	ν(C-H) aliph.	ν(C=O)	ν(C=C) arom.	Others
1		127-129	93	Deep Orange	3087	2923 2854	1747 ketone 1731 amide	1604 1494 1469	ν(C-Br) 698
2		96-98	90	Pale Orange	3062	2979 2923 2854	1733 EsterOver Lap with amid	1608 1481	ν(C=N) 1664

Table 2-Physical properties and FTIR spectral data cm^{-1} of the synthesized compounds (3-6).

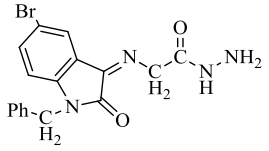
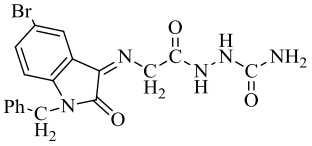
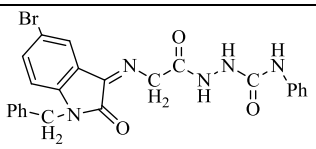
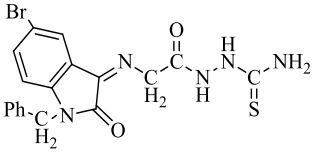
Com .No.	Physical Properties				Major FTIR Absorption cm^{-1}				
	Structures	M.P °C	Yield %	Color	ν(N-H)	ν(C-H) arom.	ν(C-H) aliph.	ν(C=O) Amid	Others
3		158-160	72	Brown	3228	3032	2921 2852	1703	ν(NH_2) asym. 3415, Sym. 3369 ν(C=N) 1652
4		108-110	80	Pale Yellow	3265	3033 3031	2979 2954 2925	1720 1689	ν(NH_2) asym. 3473, Sym. 3348
5		114-115	68	Pale Brown	3240	3062 3031	2923 2854	1731 1666	δ (N-H) 1608
6		119-120	85	Brown	3224	3066 3031	2977 2854	1716 1695	ν(NH_2) asym. 3364, Sym. 3245 ν(C=S) 1298

Table 3- Physical properties and FTIR spectral data cm^{-1} of the synthesized compounds (7-11).

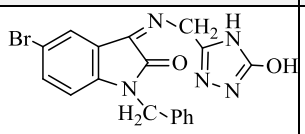
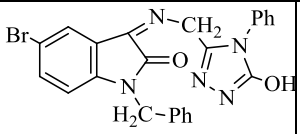
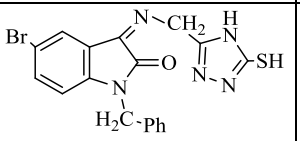
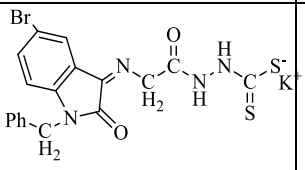
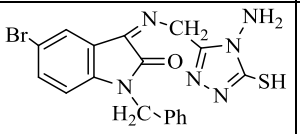
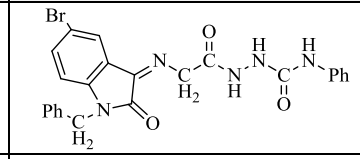
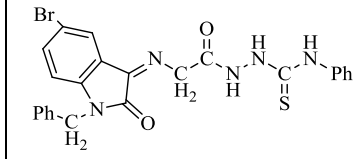
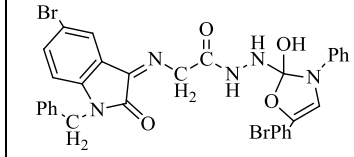
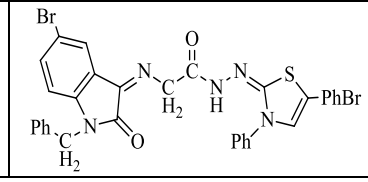
Com No.	Physical Properties				Major FTIR Absorption cm^{-1}					
	Structures	M.P °C	Yield %	Color	ν(N-H)	ν(C-H) arom.	ν(C-H) aliph.	ν(C=O) Amid	ν(C=N)	Others
7		121-122	75	Brown	3280	3064	2923 2852	1718	1666	ν(O-H) 3365
8		147-149	80	Black	-	3062 3029	2921 2854	1716	1651	ν(O-H) 3346
9		108-110	71	Deep Brown	3238	3062 3031	2923 2852	1735	1637	ν(S-H) 2700
10		180-182	85	Orange	3255	3060 3031	2979 2925	1718	1635	ν(C=S) 1255
11		117-118	74	Pale Brown	3234	3064 3031	2925 2854	1712	1606	ν(NH_2) asym. 3415, Sym. 3388

Table 4- Physical properties and FTIR spectral data cm^{-1} of the synthesized compounds (5,12-14).

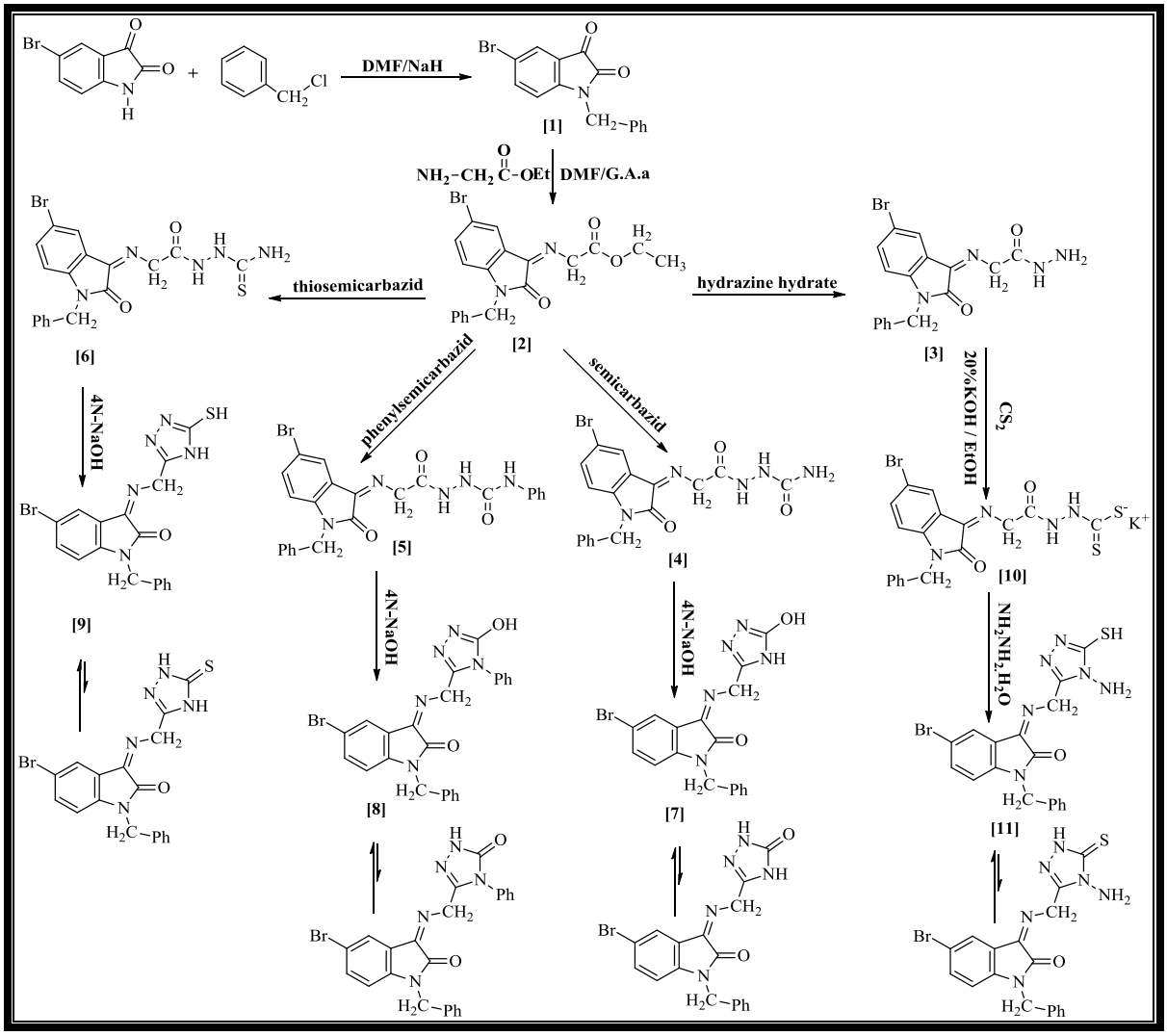
Com .No.	Physical Properties				Major FTIR Absorption cm^{-1}				
	Structures	M.P °C	Yield %	Color	ν(N-H)	ν(C-H) arom.	ν(C-H) aliph.	ν(C=O) Amid	Others
5		116-117	82	Pale Brown	3284	3064 3029	2950 2923 2852	1718 1666	δ (N-H) 1608
12		100-101	87	Brown	3348 3286 3190	3090	2948 2923 2854	1716	ν(C=N) 1652 ν(C=S) 1272
13		98-100	80	Off White	Over Lap with ν(O-H)	3088 3079	2978 2951	1716 1695	ν(O-H) 3367 ν(C-Br) 696 C-O-C 1197, 1072
14		88-90	82	Pale Yellow	3369	3050	2952 2923	1718 1695	ν(C-Br) 648 C-S-C 1278, 1197

Anti-bactrial activity test [19]

The test was performed according to the disk diffusion method. Some of the synthesized compounds were tested against two strain –ve bacteria (*Escherichia coli* and *pseudoman acruginosa*) and two strain gram +ve (*Bacilles* and *Staphylococcus aura*). Whattman no.1, 5mm diameter of filter paper disk was sterilized via autoclaving for 15 min. at 121°C. The sterile disks were impregnated with different compounds (800µg /disk). Agar plates were surface inoculated uniformly in 100°µL from both culture of tested microorganism. The impregnated disk was placed on the medium suitably spaced a part and the plates incubated at 5 °C for 1 hr. to permit good diffusion ,then transferred to an incubator at 37°C for 24 hrs.. The inhibition zones caused by various compounds on the microorganisms were examined.

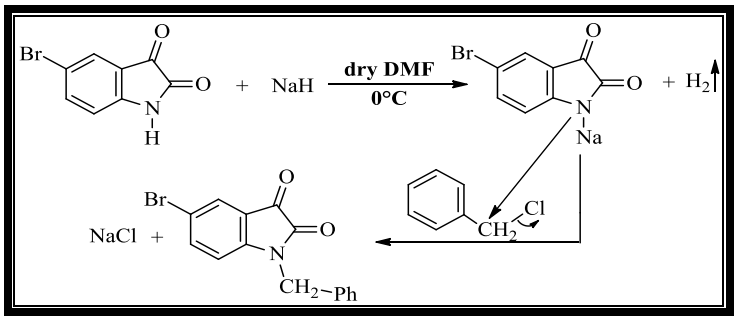
Results and Discussion

The synthetic sequences for preparation of series of new N-benzyl-5-bromoisatin, 1, 2, 4-triazoles as in sch**e**me-1.



Scheme 1- Synthesis of new derivatives of N-benzyl-5-bromosatin, 1,2,4-triazoles (1-11)

N-benzyl-5-bromoisatin was prepared by reaction of 5-bromoisatin with sodium hydride in DMF as a solvent at 0°C and subsequent reaction with benzylchloride as the following mechanism.Scheme-2:



Scheme 2- Mechanism of the prepared compound (1)

The FTIR spectrum of synthesized compound (1) indicated the disappearance of a ν(N-H) (3201cm^{-1}) while ν(C-H) aliphatic at (2923cm^{-1}, 2854cm^{-1}) was appeared. Compound(2) was synthesized by reaction of compound(1) with ethyl glycinate and dropes of glacial acetic acid in DMF, the FTIR spectrum of this compound indicated that ν(C=O) (1747cm^{-1}) of ketone group was disappeared from the spectrum while a ν(C=O) of ester overlap with ν(C=O) of amid at (1733cm^{-1}) also presence of ν(C-H) aliphatic at (2979cm^{-1}) spectrum[20], physical properties are listed in table-1. ^{1}HNMR spectrum showed triplet signal at δ=(0.87) ppm due to (-C<u>H</u>$_3$) protons, quartate signal at δ=(3.44) ppm due to (-O-C<u>H</u>$_2$) protons, singal signal at δ=(4.23) ppm due to (-C<u>H</u>$_2$-Ph) protons, singlet signal at δ=(4.99) ppm due to (=N-C<u>H</u>$_2$-) protons, and signals at δ=(6.89-7.71) ppm due to aromatic rings protons as shown in Figure-1. And listed in table-5. ^{13}C-NMR spectrum data of this compound (2) were shown in figure-2, and listed in table-6. Also, hydroxamic acid tested to improve the presence of ester group; it gave a positive test [21].

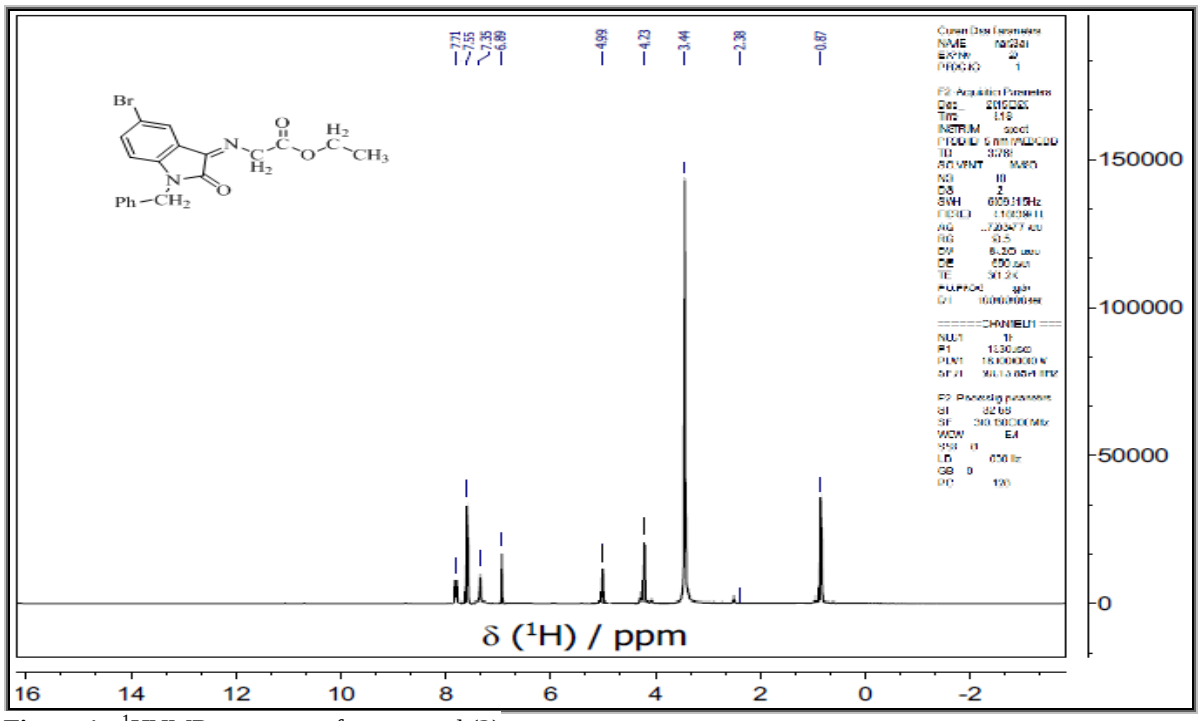
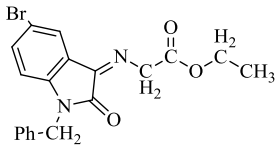
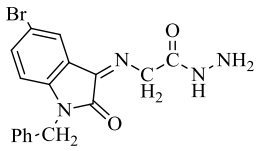
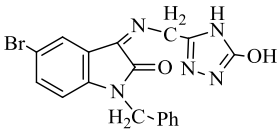
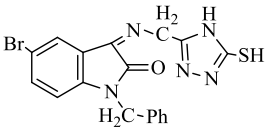


Figure 1 - ^{1}HNMR spectrum of compound (2)

Table 5 - ^{1}HNMR spectral data (ppm) for selected compounds.

Comp. No.	Structures	^{1}HNMR Spectral data(δppm)
2		0.87 (t,3H,CH_3); 3.44 (q,2H-O-CH_2); 4.23 (s,2H,-CH_2-Ph) ; 4.99(s,2H,=N-CH_2-); 6.89-7.71 (m,8H,Ar-H)
3		3.33(s,2H,NH_2); 4.20 (s,2H,-CH_2-Ph) ; 4.98(s,2H,=N-CH_2-); 7.35 (m,8H,Ar-H); 8.55 (s,1H,N-H)
7		4.44 (s,2H,-CH_2-Ph) ; 4.96(s,2H,=N-CH_2-); 6.64(s,1H,O-H); 6.97-7.86 (m,8H,Ar-H); 8.46 (s,1H,N-H)
9		3.40(s,1H,S-H); 4.46 (s,2H,-CH_2-Ph) ; 4.91(s,2H,=N-CH_2-); 6.90-7.85 (m,8H,Ar-H); 8.73 (s,1H,N-H)

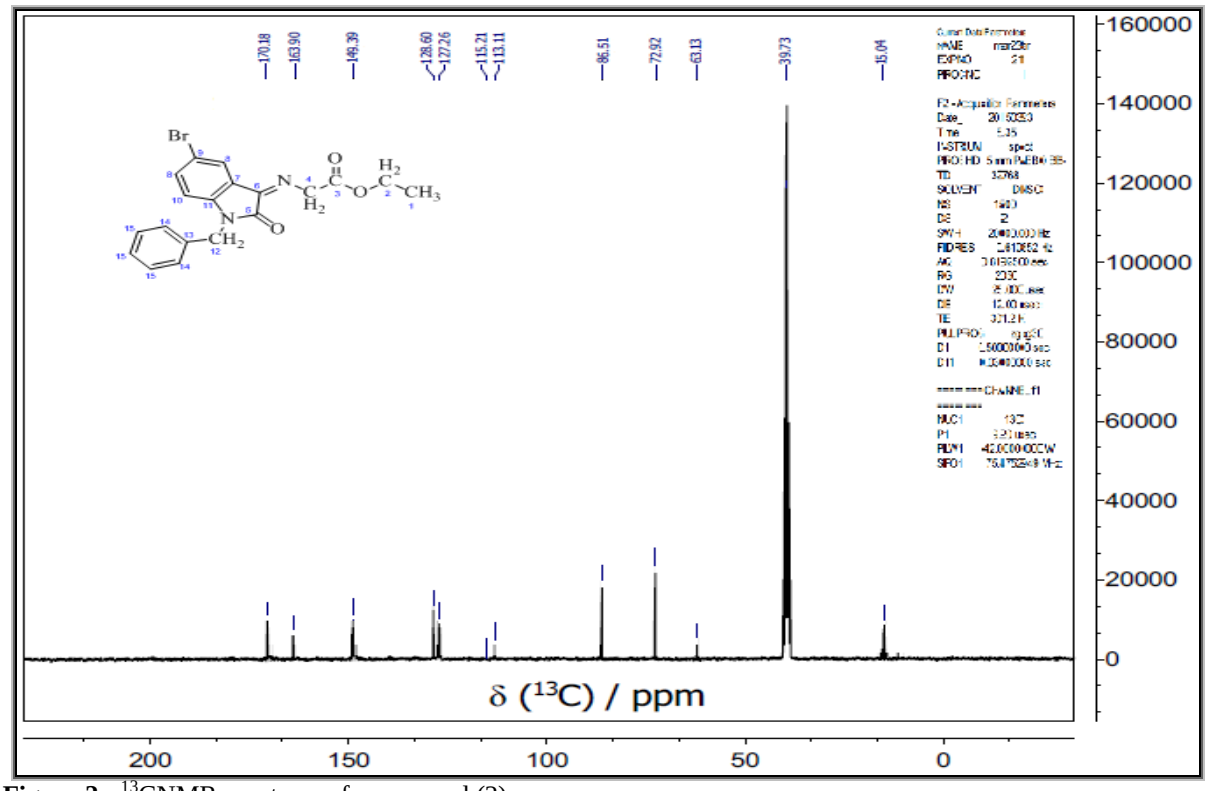
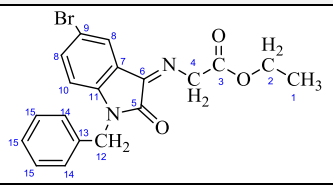
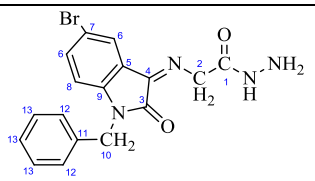
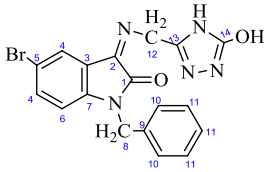
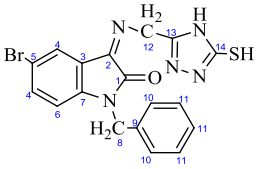


Figure 2 - ^{13}CNMR spectrum of compound (2).

Table 6 - ^{13}C-NMR spectral data (ppm) for selected compounds.

Com. No	structure	13CNMR Spectral data(δppm)
2		15.04(C1); 63.13(C2); 72.92(C12); 86.51(C4); 113.11-128.60 (C-7, 8, 9, 10, 11, 13, 14, 15); 149.39 (C6), 163.90(C5), 170.18(C3).
3		75.01(C10); 78.30(C2); 127.10-136.00(C- 5, 6, 7, 8, 9, 11, 12, 13), 154.95 (C4), 164.01(C- 1, 3).
7		75.50(C8); 86.95(C12); 113.96-138.95(C- 3, 4, 5, 6, 7, 9, 10, 11), 157.14 (C- 2, 13, 14), 163.37(C1).
9		76.11(C8); 80.26(C12); 113.11-128.60(C- 3, 4, 5, 6, 7, 9, 10, 11), 156.11 (C- 2, 13, 14), 164.00(C1).

Compound (2) was reacted with excess of hydrazine hydrate and gave compound (3) hydrazide. FTIR spectrum showed absorption of $-NH_2$ group asym. at(3415cm^{-1}) and sym. at(3369cm^{-1}), and –NH group stretching band respectively at (3228cm^{-1}). Also showed ν(C=O) band from (1703cm^{-1}) of amid. ^{1}HNMR spectrum showe in Figure-3 single signal at δ=(3.33) ppm due to (-N$\underline{H}_2$) protons, singlet signal at δ=(4.20) ppm due to (-C$\underline{H}_2$-Ph) protons, singlet signal at δ=(4.98) ppm due to (=N-C$\underline{H}_2$-) protons, signals at δ=(7.35) ppm due to aromatic rings protons, and singlet signal at δ=(8.55) ppm due to (-N-$\underline{H}$) proton as shown in table-5. ^{13}C-NMR spectrum data of this compound (3) were listed in Figure-4, table-6.

On the other hand the compound (2) reacted with (semicarbazide, phenylsemicarbazide and thiosemicarbazide) to obtain semicarbazide(4), phenylsemicarbazide(5) and thiosemicarbazide(6) derivatives by scheme-1, table-2 FTIR spectral data showed absorption at (3473cm^{-1}) asym. (3348cm^{-1}) sym. for ν-NH_2, (3265cm^{-1}) for ν(N-H) and (1720cm^{-1}, 1689cm^{-1}) ν(C=O) of amid in synthesis compound(4) .while in compound(5) showed absorption band at (3240cm^{-1}) for ν(N-H) and (1731cm^{-1}, 1666cm^{-1}) ν(C=O) of amid, and showed absorption at(3364cm^{-1}) asym. (3245cm^{-1}) sym. for ν-NH_2, (3224cm^{-1}) for ν(N-H), ν(C=O) of amid at (1716cm^{-1}, 1695cm^{-1}) and (1298cm^{-1}) for ν(C=S) in compound (6).

Cyclization of compounds (4-6) in alkaline media (4N-NaOH) to give the hydroxytriazole derivative (7), phenylhydroxytriazole (8) thiohydroxytriazole (9) which identified via FTIR spectra, that shows results in table-3. All the spectral data showed the presence of absorption band at ν(C=N) group at about (1666cm^{-1}-1637cm^{-1}) with appearance of ν(O-H) for compound (7 and 8) (3365cm^{-1},3346cm^{-1}) successively also show ν(S-H) at (2700cm^{-1}) for compound(9). ^{1}HNMR spectrum for compound(7) showed signals signal at δ=(4.44) ppm due to (-C$\underline{H}_2$-Ph) protons, singlet signal at δ=(4.96) ppm due to (=N-C$\underline{H}_2$-) protons, singlet signal at δ=(6.64) ppm due to (-O-H) protons, signals δ=(6.97-7.86) ppm due to aromatic rings protons, and singlet signal at δ=(8.46) ppm due to (-N-$\underline{H}$) proton as shown in table-5. ^{13}C-NMR spectral data of this were listed in table-6.For compound (9) ^{1}HNMR spectrum showed singlet signal at δ=(3.40) ppm due to (-S-H) protons ,signals signal at δ=(4.46) ppm due to (-C$\underline{H}_2$-Ph) protons, singlet signal at δ=(4.91) ppm due to (=N-C$\underline{H}_2$-) protons, signals δ=(6.90-7.85) ppm due to aromatic rings protons, and singlet signal at δ=(8.73) ppm due to (-N-$\underline{H}$) proton as shown in table-5. ^{13}C-NMR spectral data of this compound (7) were listed in table-6.

Hoggarth's method[22] has been used for synthesis of compound(11) in ethanolic KOH by reaction of hydrazide(3)with CS_2, gave the dithiocarbazate salt(10) in moderate yield with appearance of ν(C=S) at (1255cm^{-1}), then cyclized via refluxing with 80% hydrazine hydrate to give a little yield of triazole derivative(11). FTIR spectrum showed absorptions at (3234cm^{-1}) for N-H group and absorption of $-NH_2$ group at (3415cm^{-1} Asym. and 3388cm^{-1} Sym.), (1606cm^{-1}) for ν(C=N) group.

Derivatives of oxazoline are considered importance branch of heterocyclic compounds due to their biological activities. The reaction of compounds (5 and 12) with *p*-bromo phenacylbromide under refluxing, then cyclization through SN_2 mechanism and tetrahedral nucleophilic substitutions [19] as in scheme-3. FTIR spectral data showed absorption bands at (3348, 3286, 3284, 3190)cm-^{1} for ν(N-H) (1718,1716,1666)cm-^{1} for ν(C=O)Amide for compound (5' and 12) with appearance of a band at (1272cm-^{1}) for ν(C=S) of compound (12) and disappearance of νNH_2 at (3415cm^{-1}) Asym., (3369cm^{-1}) sym. the FTIR spectrum for Compound (13)showed ν(N-H) over lap with a broad band of ν(O-H) group at (3367cm^{-1}) and ν(C-O-C) of oxazoline ring at (1197cm^{-1}, 1072cm^{-1}), while compound (14) appearse strong sharp bands of ν(N-H) at (3369cm^{-1}), band of ν(C=O)amid at (1718cm^{-1}, 1683cm^{-1}), ν(C-S-C) at (1278cm^{-1}, 1197cm^{-1}) of thiazoline ring .

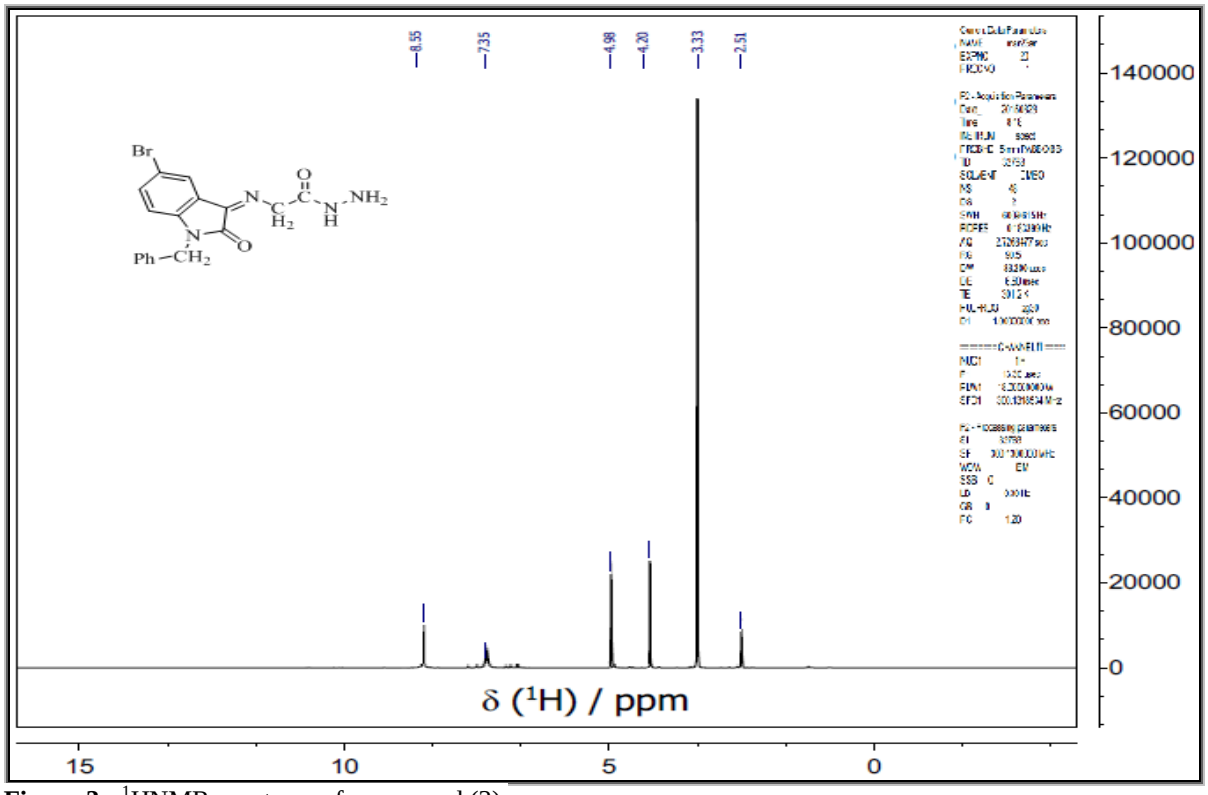


Figure 3 - ^{1}HNMR spectrum of compound (3).

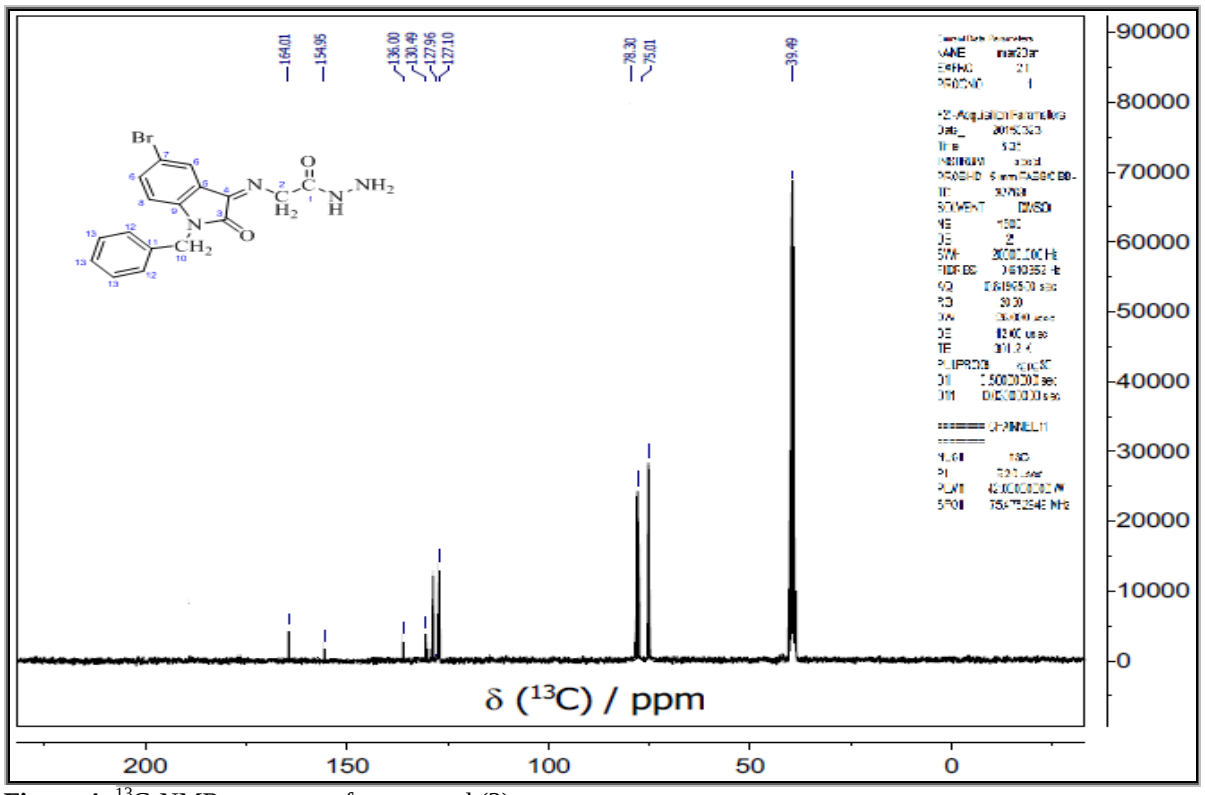
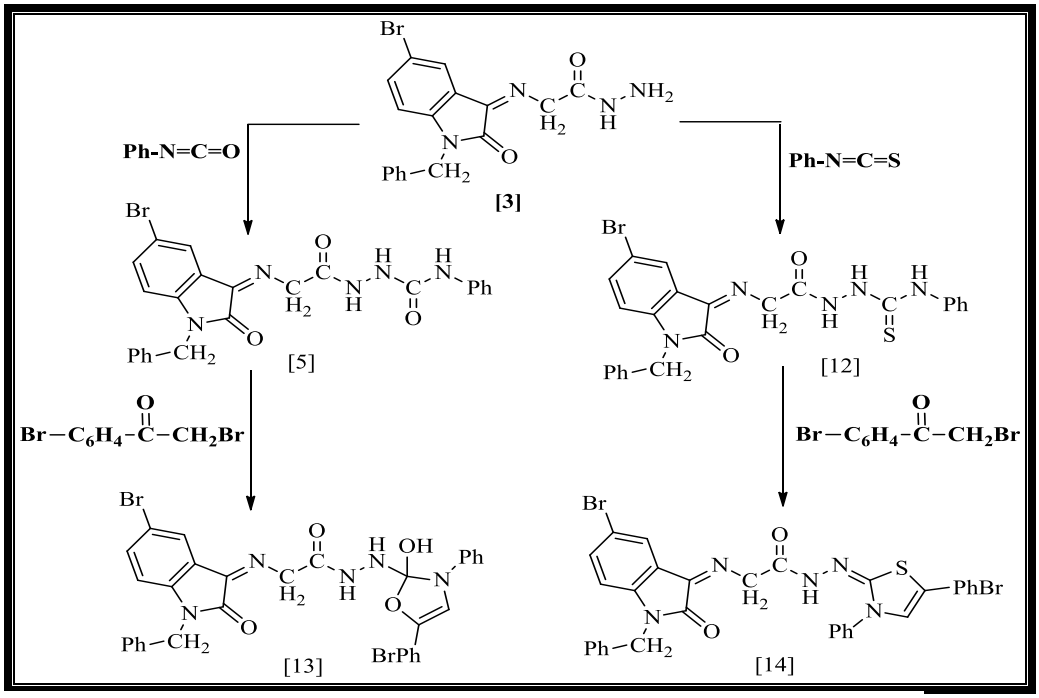


Figure 4- ^{13}C-NMR spectrum of compound (3).



Scheme 3- Synthesis of oxazoline and thiazoline derivatives for compounds (5,12-14)

Anti-bactrial activity

The results of antibactrial activity are listed in table-7. The results referred to, that all synthetic compounds possess moderate and strong activity against certain types of bacteria, while it did not possess any activity against others. compounds (2,3,9,11,13,14) possess strong activity against *Escherichia coli*, While compound (13,14) also possess strong activity against *Pseudomonas aeruginosa*. compound (2,3,7,9,5,11,12,13) possess strong activty against *Bacilliessubtilus* while *staphylococcus aureus* was inhibited by compounds (7,8,9,11,12,13 and 14).

Table 7- Anti-bactrial activity of the tested synthesized compounds

Comp. No.	*E. Coli*	*Pseu. Aure*	*Bacillies*	*Staph. Aure*
2	12	10	14	-
3	12	-	15	-
5	11	-	12	-
7	11	10	14	11
8	11	-	-	11
9	13	-	12	12
11	12	11	13	11
12	11	-	14	11
13	18	20	23	25
14	12	12	11	10

Solvent: DMSO: [C]: 800µg/ml.
Zone of inhibition: (-) no inhibition zone; (3-6) weak; (7-10) moderate; (11-15) strong.

Conculusion

Present research work involves synthesis of novel N-benzyl-5-bromoisatin derivatives to explore their antibacterial activity. Compound (13) exhibited highest antibacterial activity for *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacilliessubtilus* and *staphylococcus aureus*. Hence, it is conculuded that there is ample scope for further study in developing these as good lead compounds for the treatment of bacterial strain as well as fungal strain.

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