Synthesis, characterization and antimicrobial activity of some new N-substituted-oxindole derivatives

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تحضير وتشخيص والفعالية البايولوجية لبعض مشتقات الاوكسيندول

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قسم الكيمياء /كلية العلوم /جامعة بغداد

المستخلص

يهدف البحث لتحضير مشتقات جديدة لمركب الاوكسيندول تتضمن حلقات الثايوزلدين والتترازول واوكسوازتدين. اختير مركب الاوكسيندول [1] كمركب أولي لتحضير مشتق الفاكلورواوكسيندول استمايد[2] والذي حضر بطريقتين. الطريقة الأولى من تكاثف الاوكسيندول مع كلورواستيل كلورايد بوجود ثلاثي اثيل امين والايثانول. الطريقة الثانية بتفاعل كلورواستيل كلورايد مع ملح الصوديوم للاوكسيندول. تفاعل الفاكلورواوكسيندول استمايد[2] مع الهيدرازين المائي لينتج الفاهيدرازينواوكسيندول استمايد[3] والذي بتفاعله مع الديهايدات اروماتية مختلفة يعطي قواعد شيف مختلفة[4a-d]. الغلق الحلقي لقواعد شيف باستخدام حامض مركبتواستيك وأزيد الصوديوم وكلورواستيل كلوريد لينتج المشتقات الاوكسوثايازوليدين[5a-d] وتترازول [6a-d] و اوكسوازيتيدين [7a-d] على التوالي. شخصت المركبات المحضرة باستخدام الاشعة تحت الحمراء وطيف الرنين النووي المغناطيسي للبروتون ولنظير الكربون. أظهرت بعض المركبات المحضرة (الاوكسوثايازوليدين[5a,b] و التترازول [6b]) فعالية مضادة لثلاثة أنواع من البكتريا.

Abstract

The aim of this research is the synthesis of new heterocyclic derivatives containing 4-oxo-thiazolidines, tetrazol or oxoazetidin ring from oxindole. To obtain these derivatives, oxindole [1] was chosen as the starting material to synthesize α-chloro-N-oxindole acetamide [2] which was prepared by two methods. The first method by direct condensation of oxindole with chloroacetylchloride in presence of triethylamine and absolute ethanol as solvent. The second method by reaction of chloroacetylchloride with sodium salt of oxindole. Treatment of α-chloro-N-oxindole acetamide [2] with hydrazine hydrate gave α-hydrazino-N-(oxindole)acetamide [3] which is the desired chiron. Compound [3] was reacted with different aromatic aldehydes which gave the corresponding Schiff base derivatives [4a-d]. 4-Oxothiazolidines [5a-d], tetrazole [6a-d] and 2-oxoazetidine [7a-d], were obtained from cyclization of Schiff base derivatives [4a-d] using mercaptoacetic acid, sodium azide and chloroacetylchloride respectively. The synthesized compounds were characterized by spectral methods FTIR, ^{1}H-NMR,and ^{13}C-NMR . Biological activities of prepared compounds were tested against three types of bacteria, which showed promising antibacterial activity of 4-oxothiazolidines [5a, b] and tetrazole [6b].

Keywords: Oxindole, Schiff base, 4-oxothiazolidine, tetrazole, 2-oxoazetidine

Introduction

The oxindole skeleton has been found in numerous natural products, for example there are two groups of oxindole alkaloids in the cat's claw plant: pentacyclic oxindole alkaloids (POAs) and tetracyclic oxindole alkaloids (TOAs) (1). Oxindole is used as a synthetic intermediate for the preparation of numerous heterocyclic compounds with interesting

biological property (2). The derivatives of oxindole have found very wide biological and pharmacological applications; as anti-oxidants (3), inhibit differentiation of promyelocytic leukemia cells HL-60 (4), inhibit inflammatory cytokines (5), cytotoxicity human leukemia K562 (6), antifungal (7), anti-cancer (8) and also act as human growth hormone secretagogue (9). Furthermore the oxindole is found in the blood vessels because it was helped to relaxation the blood vessels (10).

Heterocyclic compounds containing nitrogen, sulfur (or both) are common features incorporated in the structures of numerous natural products and pharmaceutical compounds and the development of simple and effective methods for their preparation is a point of major concern in medicinal chemistry. Four or five members heterocyclic like 2-oxoazetidin, tetrazole and 4-oxothiazolidines constitute potential class of compounds which posses a broad field of biological activity (11, 12). Considerations of all these factors lead to synthesize some new N-substituted-oxindole derivatives, which can be expected to have biological activities.

Experimental

General

Melting points were determined on Gallen Kamp melting point apparatus and are uncorrected. Fourier transform infrared (FTIR) spectra were recorded on Shimadzu FTIR-8400 Spectrophotometer, Department of Chemistry, College of Science, Baghdad university as KBr disc. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Burker model ultra shield at 300MHz, Al al-Bayt University, Jordan, using DMSO-d^{6} as solvent and TMS as internal reference. All data are given as chemical shifts δ (ppm) downfield from tetramethylsilane.

The purity of compounds was checked routinely by TLC which was performed on aluminum sheets protected with silica gel supplied by Merck. Spots were detected with iodine vapors. Yields, physical properties and spectroscopic data for the products are listed in Tables (1- 3).

Preparation of α-chloro-N-(oxindole) acetamide [2]

Method (I)

To a solution of oxindole (4 g, 0.03 mol) in absolute ethanol(30 mL) was added with continues stirring chloroacetylchloride (2.5 mL, 0.03 mol) in absolute ethanol (20 mL) and triethylamine (2 mL) , the mixture was refluxed for 10hours. The solvent was evaporated and the residue was washed with 5% $NaHCO_3$. The precipitate was filtered and recrystallized from (toluene:ethylacetate 1:1).

Method (II)

A solution of oxindole (4 g, 0.03 mol.) in DMF (10 mL) was cooled to 0°C, sodium hydride (0.8 g, 0.03 mol, 60% in mineral oil) was then added dropwise with continues stirring. Chloroacetylchloride (2.5 mL, 0.03 mol, 80% in toluene) was added to the slurry via syringe, and the reaction mixture was slowly warmed to room temperature. The reaction was quenched with water after 14hours the resulting solid was removed via filtration. The filtrate was concentrated under reduced pressure and crude product was recrystalized from (toluene:ethylacetate 1:1).

2.2. Preparation of α-hydrazino-N-(oxindole) acetamide [3]

To a solution of compound [2] (3 g, 0.01 mol) in absolute ethanol (30 mL), hydrazine hydrate (1.5 mL, 0.02 mol) was added with continuous stirring and the resulting mixture was refluxed for 4hours after cooling the mixture, yellow

precipitate was formed. The precipitate was filtered and recrystalized from ethanol.

General procedure for preparation Schiff base derivatives of α-hydrazino-N-(oxindole) acetamide [4a-d]

To a hot stirred solution of compound [3] (2.24 g, 0.01 mol) in methanol (10 mL), the appropriate aromatic aldehyde (0.01 mol) with 3-4 drops of glacial acetic acid in methanol was added, and the reaction mixture was heated at (60-70)°C for (2-5)hours. The separated solid was filtered and recrystalized from methanol.

2-[(4-nitrophenyl)-3-(acetylamino)-1,3-thiazolidine-4-ones]-N-oxindole [5a]

To a solution of compound 4a (3.57 g, 0.01 mol) in ethanol (20 mL) , mercaptoacetic acid (0.92 mL, 0.01 mol) and pinch of $ZnCl_2$ as a catalyst was added and the mixture was refluxed for 8hours. The solvent was evaporated to give product **5a**. The solid product was filtered, dried and recrystallized from ethanol/water.

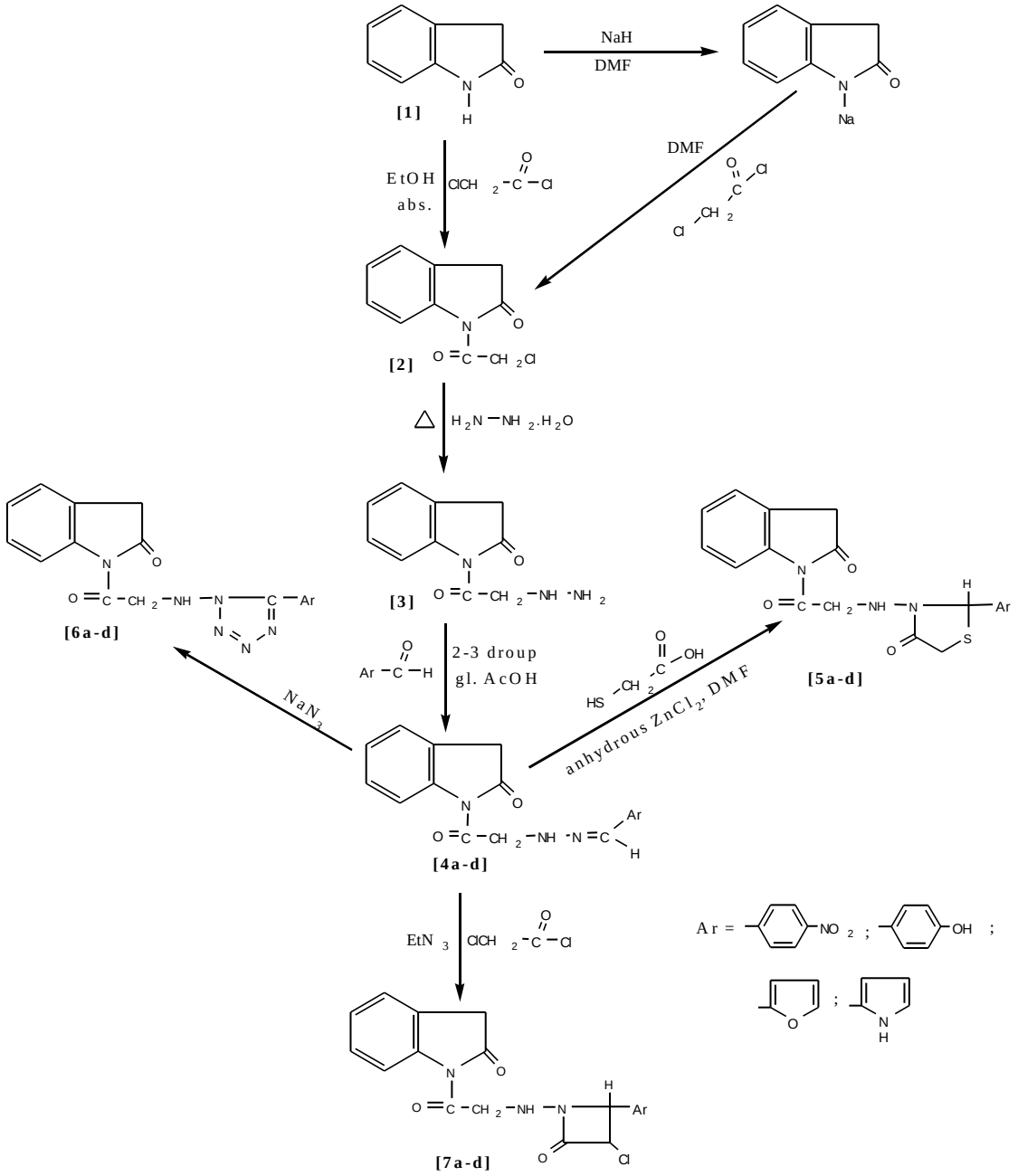
Other compounds [5b-d] were prepared by the same method, using [4b-d].

2-[5-substituted-tetrazole-1-yl)-N-acetylaminooxindol [6a-d]

A mixture of appropriate Schiff base (0.002 mol), and sodium azide (0.15 g, 0.002 mol) in dry acetone (20 mL) was stirred at 50°C overnight. The reaction mixture was filtered and evaporated to furnish the tetrazole [6a-d].

N-(3-chloro-4-substituted-2-oxoazetidin-1-yl) acetylamino-N-oxindole [7a-d]

Chloroacetylchloride (2.26 g, 0.02 mol) in dioxane (10 mL) cooled at (0-5)°C, triethylamine (2.78 mL, 0.02 mol) was added, and Schiff base (4a-d) (0.02 mol) dissolved in dioxane (10 mL) was slowly added and refluxed for 12hours. After completion of the reaction as mentioned by TLC, the reaction mixture poured into ice-cold water, the precipitate was filtered and dried.



Scheme (1): Synthesis steps of oxindole derivatives

Table (1): Physical properties and FTIR spectral data of α-substituted-N-(oxindole) acetamide and 4-oxothiazolidine derivatives of oxindole [5a-d]

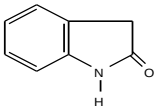
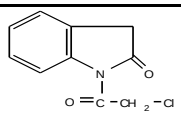
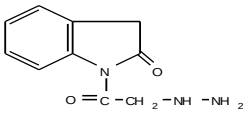
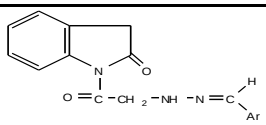
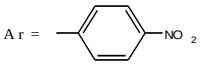
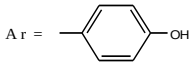
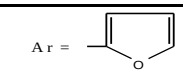
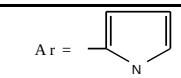
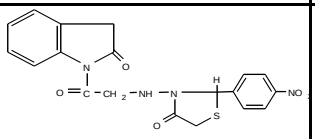
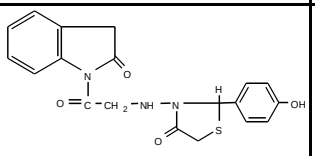
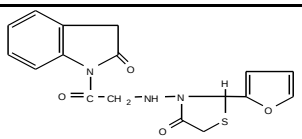
Comp. No.	Compound structure	Color	Yield %	Melting point °C	Major FTIR absorptions cm^{-1}			
					ν(N-H)	ν(C-H) alph.	ν(C=O)	Other bands
1		Light brown	-	125	3209	2839	1705	δ(N-H) 1689
2		Brown	70	78	-	2839 2764	1705 1697	ν(C-Cl) 655
3		Yellow	85	168	3198			$\nu(NH_2)$ 3407asym and 3238 sym.
4								
4a		Red	80	96-96	3195	2840	1698	$\nu(NO_2)$ 1527asym 1334sym
4b		Brown	68	255	3200	2860	1698	ν(O-H) 3420
4c		Brown	60	265d	3198	2900	1700	ν(C-O-C) 1235
4d		Violet	65	244d	3204	2998	1695	
5a		Deep brown	70	172	3198	2980	1700	$\nu(N=O_2)$ 1525 asym 1332 sym
5b		Pale brown	75	185	3197	2985	1702	ν(O-H) 3395
5c		Brown	68	202	3195	2975	1705	ν(C-O-C) 1240

Table (2): Physical properties and FTIR spectral data of tetrazole derivatives of oxindole [6a-d] and azetidin-2-one derivatives of oxindole [7a-d]

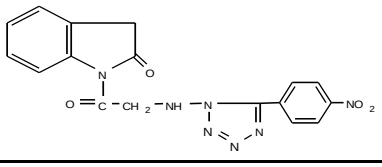
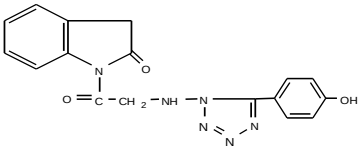
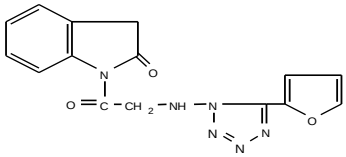
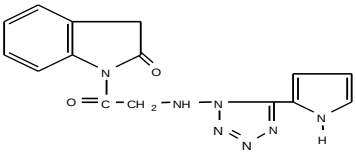
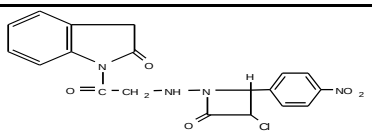
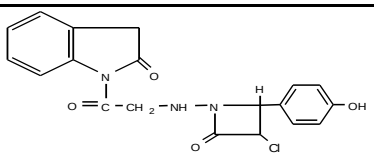
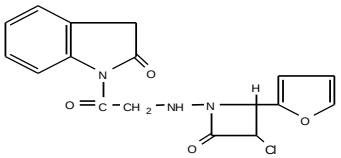
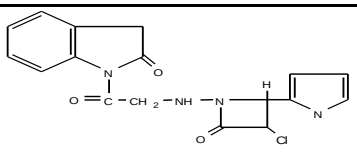
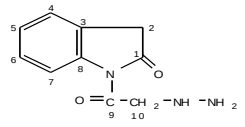
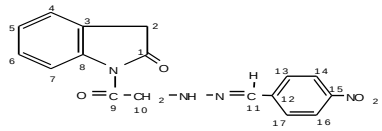
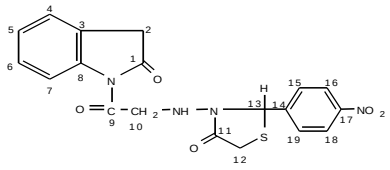
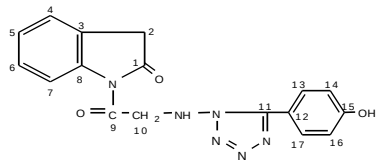
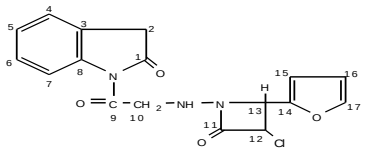
Comp. No.	Compound structure	Color	Yield %	Melting point °C	Major FTIR absorptions cm^{-1}				
					ν(N-H)	ν(C=O)	ν(C=N)	ν(tetrazol)	Other bands
6a		Brown	75	163	3205	1700	1605	1089	ν($N=O_2$) 1520 asym 1012 sym
6b		Deep yellow	80	202	3204	1702	1610	1114	ν(O-H) 3410
6c		Deep yellow	65	302d	3205	1700	1608	1120	ν(C-O-C) 1145
6d		Pale brown	68	255	3210	1705	1608	1112	
7a		Deep orange	75	138	3201	1695 1740	**ν(C-Cl)** 680	-	ν(NO_2) 1525 asym 1335 sym
7b		Deep yellow	80	187	3195	1698 1735	**ν(C-Cl)** 682	-	ν(O-H) 3415
7c		Pale brown	60	198	3205	1700 1738	**ν(C-Cl)** 680	-	ν(C-O-C) 1240
7d		Pale brown	65	178	3201	1700 1740	**ν(C-Cl)** 685	-	

Table (3):^{1}H- NMR and ^{13}C-NMR spectral data for some of the prepared compounds

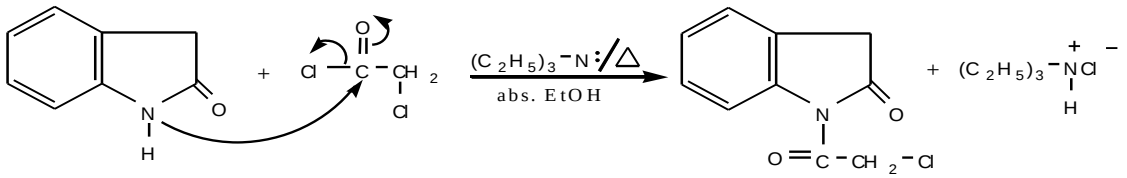
Comp. no.	Compound structure	^{1}H-NMR (δ ppm) in DMSO-d^{6} solvent	^{13}C-NMR (δ ppm) in DMSO-d^{6} solvent
3		2.83(s, 2H, -CH_2-oxindole); 4.36(d, 2H, $-C(=O)-CH_2-N$); 4.47(s, 2H, -NH_2); 6.89-7.6(m, 4H, Ar-H); 7.76(b, 1H, -NH-)	182(^{1}C); 57.3(^{2}C); 127.6-140.2(^{3}C, ^{4}C, ^{5}C, ^{6}C, ^{7}C, ^{8}C); 170.2(^{9}C); 80.6(^{10}C)
4a		2.81(s, 2H, -CH_2-oxindole); 4.34(d, 2H, $-C(=O)-CH_2-N$); 4.92(s, 1H, =CH-ph); 6.9-7.92(m, 8H, Ar-H); 7.8(b, 1H, -NH-)	181.6(^{1}C); 57.4(^{2}C); 127.8-139.2(^{3}C, ^{4}C, ^{5}C, ^{6}C, ^{7}C, ^{8}C); 171.6(^{9}C); 80.7(^{10}C); 156(^{11}C); 130(^{12}C); 26.2(^{13}C, ^{17}C); 129(^{14}C, ^{16}C); 150.8(^{15}C)
5a		2.82(s, 2H, -CH_2-oxindole); 3.16(s, 1H, $N-CH-S$); 3.59(s, 2H, $O=C-CH_2-S$); 4.41(d, 2H, $-C(=O)-CH_2-N$); 6.92-7.62(m, 8H, Ar-H); 7.82(b, 1H, -NH-)	178.3(^{1}C); 58.1(^{2}C); 127.8-140.1(^{3}C, ^{4}C, ^{5}C, ^{6}C, ^{7}C, ^{8}C); 170.2(^{9}C); 81(^{10}C); 172(^{13}C); 57.2(^{12}C); 140.8(^{13}C); 126.3(^{15}C, ^{19}C); 128.6(^{15}C, ^{16}C); 151(^{17}C)
6b		2.78(s, 2H, -CH_2-oxindole); 4.42(d, 2H, $-C(=O)-CH_2-N$); 6.94-7.72(m, 8H, Ar-H); 8.10(b, 1H, -NH-); 12.85(s, 1H, -OH)	178.3(^{1}C); 58.2(^{2}C); 128.2-140.2(^{3}C, ^{4}C, ^{5}C, ^{6}C, ^{7}C, ^{8}C); 172(^{9}C); 81.2(^{10}C); 133.3(^{11}C); 130.2(^{12}C); 127.4(^{13}C, ^{17}C); 129.6(^{14}C, ^{16}C); 155(^{15}C)
7c		2.81(s, 2H, -CH_2-oxindole); 4.41(d, 2H, $-C(=O)-CH_2-N$); 4.96(d, 1H, -CH-azetidin); 6.65(m, 1H, -CHCl-); 6.92-7.41(m, 7H, Ar-H and furane); 7.81(b, 1H, -NH-)	178.4(^{1}C); 58.3(^{2}C); 128.8-141.2(^{3}C, ^{4}C, ^{5}C, ^{6}C, ^{7}C, ^{8}C); 172.2(^{9}C); 81.2(^{10}C); 184(^{11}C); 52(^{12}C); 58.3(^{13}C); 141.2(^{14}C, ^{17}C); 126.3(^{15}C, ^{16}C)

Results and discussion

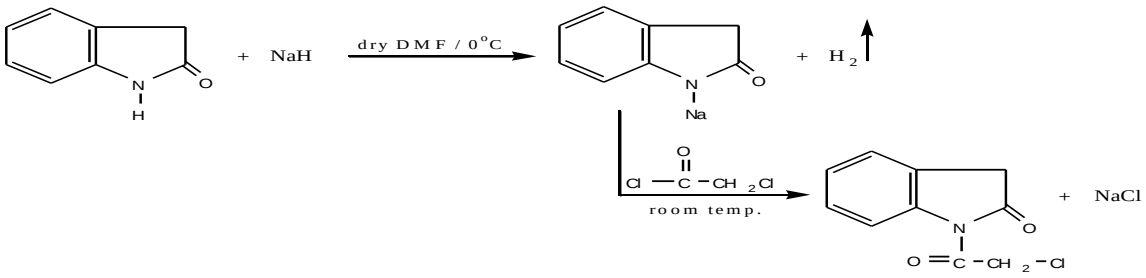
In this work we aimed to synthesize some different heterocyclic systems on substituted-N-oxindole,α-chloro-N-(oxindole) acetamide [2], which was seen as a suitable chiron for this synthetic approach (Scheme 1).

The second method by reacting oxindole with sodium hydride in dimethylformamide at 0°C to have sodium salt. of oxindole and subsequent reaction addition of the chloroacetylchloride to α-Chloror-N-(oxindole)acetamide [2] was prepared by two methods, in the first method condensing of oxindole with chloroacetylchloride in absolute ethanol containing triethylamine as a catalyst according to the following equation:

obtain compound [2] according to the following equation:



[2]



[2]

The second method was of choice because it gives compound [2] in good yield and in high purity.

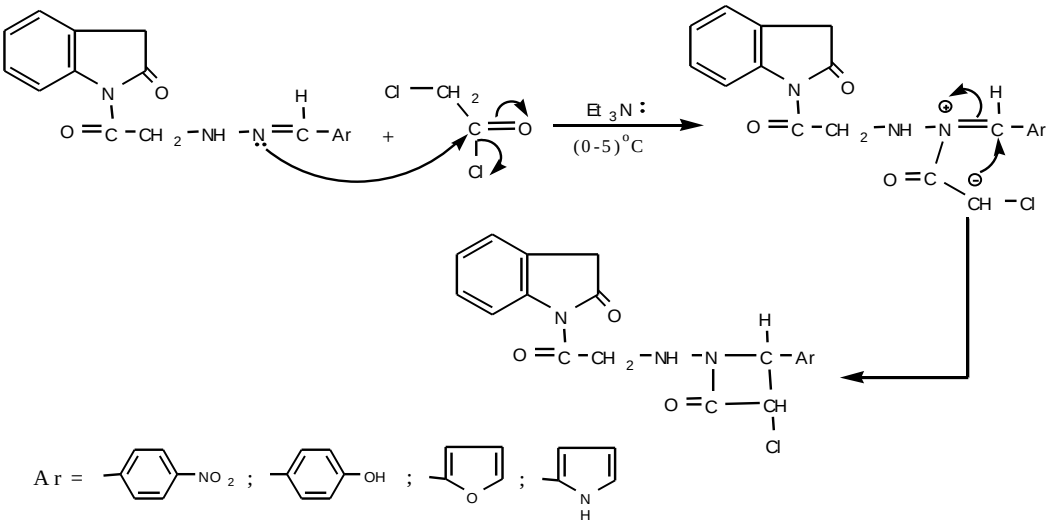
The structure of compound [2] was confirmed by physical properties which are listed in Table (1). FTIR spectra showing the absorption at 3040 and 2839, 2764 cm^{-1} for νC-H arm. and νC-H alp. respectively; (1705 and 1697) cm^{-1} for (νC=O oxindol and νC=O amide) respectively; 655 cm^{-1} for (νC-Cl) and disappearance the absorption of (νN-H cyclic). Other chemical test was carried out to characterize compound [2] such as alcoholic sliver nitrate test that confirmed the presence of chlorine group (13).

The reaction of compound [2] with hydrazine hydrate gave α-hydrazino-N-(oxindole)acetamide [3]. FTIR spectrum of compound [3] showed absorption bands at (3407, 3238 and 3198) cm^{-1} which could be attributed to νNH_2 asym., νNH_2 sym. and νN-H respectively, while νC-Cl band was disappeared. The ^{1}H-NMR spectrum of compound [3] (14) in DMSO-d^6 solvent showed signals at δ2.83(s, 2H, -CH_2- oxindole); δ4.36(d, 2H, $-\overset{O}{\overset{\|}{C}}-CH_2-N$); δ4.47(s, 2H, -$NH_2$); δ6.89-7.6(m, 4H, Ar-H) and broad signal at δ7.76ppm for NH proton. ^{13}C-NMR results were listed in Table (3). The Schiff bases [4a-d] were obtained in good yield through the reaction of hydrazine [3] with different aromatic aldehydes (scheme 1). The FTIR spectrum of compounds [4a-d] are listed in Table (1). All the spectral data showed disappearance the absorption of νNH_2 group. While ^{1}H-NMR for compound [4a], in DMSO-d^6 solvent showed signals at δ2.81(s, 2H, oxindol); δ4.34(d, 2H, $-\overset{O}{\overset{\|}{C}}-CH_2-N$); δ4.92(s, 1H, =CH-ph); δ6.9-7.92(m, 8H, Ar-H) and δ7.8ppm(b, 1H, -NH-). ^{13}C-NMR spectra results are listed in Table (3).

The 4-oxothiazolidines [5a-d] derivatives were synthesized by the intramolecular cyclization of Schiff bases [4a-d] with mercaptoacetic acid and $ZnCl_2$ as a catalyst in ethanol. The prepared [5a-d] derivatives were identified by FTIR, results are listed in Table (2). FTIR spectrum of compounds [5a-d] showed absorption bands at

3198-3212 for (N-H), 2980-2987 for C-H alp., 1700-1710 cm^{-1} for C=O group. The ^{1}H-NMR of compound [5a] in DMSo-d^6 solvent showed the singlet signals at δ2.82(s, 2H, -CH_2- oxindole); δ3.16(s, 1H, -CH-S); δ3.59(s, 2H, $-\overset{O}{\overset{\|}{C}}-CH_2-S$); and doublet signal at δ4.41(d, 2H, $-\overset{O}{\overset{\|}{C}}-CH_2-N$); while the aromatic ring protons appeared at δ6.92-7.62(m, 8H, Ar-H); and a broad signal at 7.82 ppm for NH proton. ^{13}C-NMR results are listed in Table (3). Schiff bases [4a-d] were converted to tetrazole derivatives [6a-d] by the reaction with sodium azide in dry acetone. The structures of tetrazole derivatives [6a-d] were confirmed by FTIR, results are listed in Table (2). ^{1}H-NMR of compound [6b] in DMSO-d^6 solvent showed signals at δ2.78(s, 2H, -CH_2- oxindole); δ4.42(d, 2H, $-\overset{O}{\overset{\|}{C}}-CH_2-N$); δ6.94-7.72(m, 8H, Ar-H); δ8.10(b, 1H, -NH-) and δ12.85ppm(s, 1H) for OH proton. ^{13}C-NMR results of compound [6b] are listed in Table (3).

On the other hand, the preparation of N-(3-chloro-4-substituted-2-oxoazetidin-1-yl)-acetylamino-N-oxindol [7a-d] were achieved by the reaction of Schiff bases [4a-d] with chloroacetyl chloride and triethylamine at (0-5)°C (scheme 1). The mechanisms (15) of the prepared compounds [7a-d] are shown below:



The compounds [7a-d] were identified by FTIR spectra and the results are listed in Table (2). FTIR spectrum of compounds [7a-d] showed absorption bands at 3195-3201 for N-H, 1695-1740 for C=C, 680-685 cm^{-1} for C-Cl. The ^{1}H-NMR of compound [7c] in DMSO-d^6 solvent showed the singlet signal at δ2.81ppm for -CH_2- oxindole; and doublet signals at δ4.41(d, 2H) and δ4.96(d, 1H) for $-\overset{O}{\overset{\|}{C}}-CH_2-N$ and -CH- azetidin respectively, while the proton of -CHCl- appeared at δ6.65ppm as multiplet. Protons of phenyl and furane rings appeared as multiplet at δ6.92-7.41 ppm, while the proton of NH group appeared as broad signal at δ7.81ppm. The results of ^{13}C-NMR are listed in Table (3).

Antibacterial Activity

The prepared compounds were screened for their antibacterial activity against of Gram +ve *Staphyloccus*, and two strain Gram -ve *Escherichia coli*, and *Serratia* , by paper disc diffusion method (16) at a concentration (600 µg/ mL) using DMSO as solvent and blank.

Inhibition zones were measured in mm, and are listed in Table (4).

Table (4): Antibacterial activities of the tested compounds

sample	*Staphyloccus*	*Serratia*	*Escherichia coli*
Control (DMSO)	_	_	_
5a	+	+	+++
5b	_	+	+++
5c	_	_	++
5d	_	_	++
6a	++	_	++
6b	++	+	++++
6c	++	+	++
6d	+	_	++
7a	++	_	++
7b	+++	_	++
7c	+++	_	++
7d	+++	_	++

Very highly active = ++++ (inhibition zone 21-30mm)
Highly active = +++ (inhibition zone 15-20mm)
Moderately active = ++ (inhibition zone 10-14mm)
Slightly active = + (inhibition zone 6-9mm)
Inactive = -(inhibition zone < 6mm)

References

1. **Ziarani, G. M.,Gholamzadeh, P., Negar L. and Hajiabbasi, P. (2013)**.Oxindole as starting material in organic synthesis. Arkivoc (I):470-535.
2. **Goehring, R.R.,Sachdeva, Y.P., Pisipati, H. S., Sleevi, M.C. and Wolfe, J.F.** (**1985**). Photoinduced cyclizations of mono and dianions of N-Acyl-o-chloroanilines and N-Acyl-o-chlorobenzylamines as general methods for the synthesis of oxindoles and 1,4-dihydro-3(2H)-isoquinolones. J. Am. Chem. Soc., 107:435-443.
3. **Takao, T., Kitatani, F., Watanabe, N., Tagi, A. and Sakata, K.** (**1994**).Simple screening method for antioxidants and isolation of several antioxidants produced by marine bacteria for first and shellfish. Biosci. Biotech. Biochem., 58: 1780-1783.
4. **Kamano, Y., Zhang, H.P., Tchihara, Y., Kizu, H., Komiyma, K. and Pettit, G.R.** (**1995**). Covolutamydines A, a novel bioactive hydroxyl oxindole alkaloid from marine bryozoan Amathia convolute. Tetrahedron Lett., 36: 2783-2784.
5. **Komakine, N., Takaishi, Y., Honda, G., Ito, M., Takeda, Y., Kodzhimatov, O. K. and Ahurmetov, O.**(**2005**). Indol alkaloids from rheum maxi-mowiczii. Nat. Med.,59: 45-48.
6. **Tang, Y.O., Sattler, I.,Thiericke, R., Grabley, S. and Feng, X. Z.** (**2001**). Diketo-piperazines, and maremycins e and f, novel polycyclic spiro-indole

metabolites isolated from streptomyces. Eur. J. Org. Chem: 261-267.

7. **Lin, S., Yang, Z. O.,Kwok, B. H., Koldobskiy, M., Crews, C. M. and Danishefsky, S. J.** (**2003**). Simplified synthetic tms-95a/b analogues retain the potency of protea some inhibitory activity. Chem. Biochem., 4: 508-513.
8. **Satyamaheshwar, P.**(**2009**).3Substituted-3-hydroxy-2-oxindole, and emerging new scaffold for drug discovery with potential anti-cancer and other biological activities. Current Bioactive Comp., 5: 20-38.
9. **Tokunaga, T., Hume, W. E., Nagamine, J., Kawamura, T., Taiji, M. and Nagata, R.** (**2005**).Structure-activity relationships of the oxindole growth hormone secretagogues. Bioorg. Med. Chem. Lett., 15: 1789-1792.
10. **Matloubi, M.F.,Hojabri, L., Taheri, S. and Pirani, P.** (**2010**). A Tandem Aldol-Diels-Alder reaction accelerated water: Approach to the catalyst-free one-pot synthesis of spiro thio-oxindoles. J. Iran. Chem. Soc., (3): 781-790.
11. **Yadav, R., Srivastava, S. D., and Srivastava,S.K.**(**2005**).Synthesis, antimicrobial and anti-inflammatory activies of 4-oxo thiazolidines and their 5- arylidenes. J. Ind. Chem., 44B: 1262-1266.
12. **Jignesh, P. R., Hemul, V. P., Pradip, S.P., Nilesh, H. P. and Kishor, R. D.** (**2009**). A rapid, convenient microwave assisted and conventional synthesis of novel azetidin-2-one derivatives as potent antimicrobial agents. Asian J. Research Chem., 2(2):171-177.
13. **Ralph, L., Shriner, L., Rehnold, C., and David, Y.** (**1980**).In the systematic identification of organic compounds.6th Ed., John Wiley and Sons, New York.
14. **Silverstein, R. M., and Websters, X.** (**1998**).Spectrometic identification of organic compounds. 6th Ed., John Wiley and Sons, New York.
15. **Isaacs, N.S.** (**1976**). Reductive ring contraction of meso ionic thiazole-4-ones to azetidin-2-ones. chem..Soc. Rev.: 255-256.
16. **Vigmolo, G.M., Surian, F., Hogado, A.P., and Oliver, G.** (**1993**). Antibacterial activity of *Iactobacillus* strains isolated from fermented sausage. J. App., Bac., 75: 344-349.