REVIEW ARTICLE

Synthesis, Characterization of Isatin Dithiocarbamate Derivatives with Expected Biological Activities

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ABSTRACT

The present work demonstrates the synthesis of isatin dithiocarbamate derivatives in a satisfactory yield, involves the synthesis of the parent nucleus((Z)-3-((4-aminophenyl)imino)indolin-2-one)(A) by reaction of isatin with p-phenylenediamine (Schiff's base reaction) ,then will be reacted with carbon disulfide in basic media (triethylamine) and acetone as solvent to afford dithiocarbamate salt ((Z)-N,N,N-triethyl-S-(1-((4-((2-oxoindolin-3ylidene)amino) phenyl)amino) vinyl)thiohydroxylammonium) (L) compound, finally the dithiocarbamate salt reacted with different alkylating agents as(benzyl chloride ,methyl iodide, *p*-nitro benzyl chloride and phenacyl bromide) to get four final products named as (AL1, AL2, AL3, AL4).

All titled compounds were prepared screened for their *in vitro* preliminary antimicrobial activities against four bacterial strains, two of them are gram-positive bacteria include *Staph. aureas, Strep. Pneumonia,* and two gram-negative bacteria: *Escherichia oli* (*E.coli)*, *Pseud aeruginosa,* and two fungal strains*, Candida albicans* and *Candida glabrata* by well diffusion method. (AL1,AL2,AL4) compounds showed slightly antibacterial activity against both gram-positive and gram-negative bacteria while (AL3) showed moderate antibacterial activity against gram-positive bacteria only as well as, AL1 shows highly antifungal activity against (*C. Glabrata* and *albicans*), and a slight antifungal activity against by others using cefotaxime, amoxicillin, and ciprofloxacin as standard antibacterial drugs while used fluconazole as a standard antifungal drug.

Keywords: Dithiocarbamate salt, Isatin, p-phenylene diamine, Schiff base.

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Conflict of interest: None

INTRODUCTION

Isatin

Isatin is an indole derivative having keto group at position 2 and 3 of the ring, or 1H-indole -2,3-dione. Isatin ring system consists of benzene ring fused with pyrrole ring. Isatin was first synthesized by Erdman and Laurent in 1841. The compound is found in many plants, such as Isatis tinctoria, Couroupita guianensis and in Calanthe discolor. Substituted isatins are also found in plants, for example, the melosatin alkaloids (methoxy phenylpentyl isatins) in *Melochia tomentosa*. Isatin is also found in humans as it is a metabolic derivative of adrenaline.[1,2]

Isatin is a flexible chemical building block, able to form a large number of heterocyclic molecules. Isatin can share in a broad range of synthetic reactions, leading to its widespread use as an originator molecule in medicinal chemistry. The presence of numerous reaction centers in isatin and its derivatives render them capable of participating in a large number of reactions. The keto group at position 2 and particularly at position 3 can enter into addition reactions at the C-O bond also into condensation reactions. Compounds of the isatin series can enter into N-alkylation and N-acylation and into Mannich and Michael reactions through the primary amine group. Literature surveys reveal that various isatin derivatives possess various activities such as antibacterial, antiviral, antifungal, anti-HIV, anti-mycobacterial, anti-inflammatory anti-cancer, and anticonvulsant activities.[3]

Dithiocarbamate

Dithiocarbamates, (dtcs) are organo-sulfur ligands that with metals form stable complexes. Two types of dithiocarbamates are mono- and, dialkyl-dithiocarbamates; the two are formed, depending, on nature, of amines that are used during the synthesis of the compound.[4]

Dithiocarbamates chemistry starts in the early twentieth century, precisely, in 1930. Commercial application was used as a fungicide for the first time during, world war II. Other wide applications can be seen in the fields of accelerating, vulcanization, acting as flotation agents agriculture (pesticide), materials science, biology, medicine, Organic dithiocarbamates have received great attention

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owing to their interesting chemistry and wide value as radical originators and intermediates in organic synthesis. They also have antioxidants.[5,6]

They can act as, inhibitors of enzymes and have a deep effect on biological systems because they have strong metal binding capacity. Moreover, they have found, application the treatment of human immunodeficiency virus (HIV) and cancer [7]

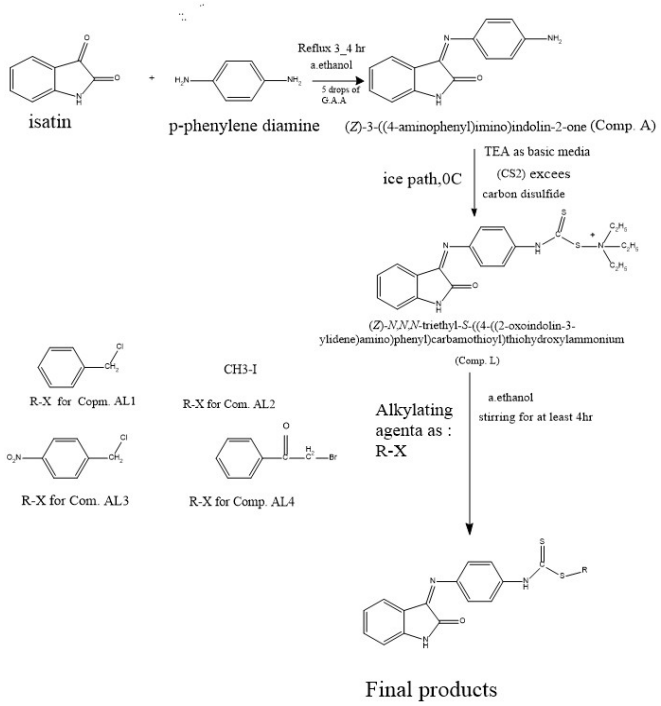
EXPERIMENTAL PART

Materials and Analytical Methods

All chemicals, solvents, and other reagents used in this investigation were either bought from a commercial source or from the chemicals store of the college of the pharmacy. The monitoring of the reactions was done by thin-layer chromatography (TLC), the mobile phase solvent systems used are A:(chloroform: methanol) (1:1) and B: toluene: ethyl acetate: ethanol) (1:1:0.5). Electronic melting point apparatus (Stuart SMP30) was used to determine all melting points in this study. Fourier-transform infrared spectroscopy (FTIR) spectrophotometer (Schimadzu, Japan), were done by thin-film technique. ^{1}HNMR spectra were obtained on BRUKER model Ultra shield 500 MHz spectrophotometer, using dimethyl sulfoxide (DMSO) as a solvent.

The pathway of synthesis for final compounds was illustrated below in Scheme 1:

A mixture of isatin (0.01 mol,1.47g) in 25 ml of absolute ethanol and p-phenylenediamine (0.01 mol,1.08g) in 10 mL of absolute ethanol was placed in a round bottom flask (5 drops of glacial acetic acid) and refluxed for 3-4 h. The reaction mixture was cooled, and solid separated was collected by filtration, dried, and recrystallized from ethanol.[8]



Scheme 1: Synthesis of(Z)-3-((4-aminophenyl)imino)indolin-2-one(A)

Yield = 90%, R*f* = 0.25 (A), IR: (3444 &3174 cm^{-1}) N-H stretching of 1º & 2º amine, (3039 cm^{-1}) C-H str. of Ar ring (1735 cm^{-1}) C=O stretching of amide, (1604 cm^{-1}) C=N stretching, (1651, cm^{-1}) C=C stretching of Ar ring (1195 & 833 cm^{-1}) in and out of plane of Ar ring. ^{1}HNMR: 5.38 (2H, s, NH2), 7.49-6.44 (8H, M, C-H aromatic), 10.83 (1H, s, -NH-amide).

Synthesis of (Z)-N,N,N-triethyl-S-((4-((2-oxoindolin-3-ylidene)amino)phenyl)carbamothioyl)thiohydroxylammonium (M.wt: 413.58) (L)

Take 0.001 mol, 0.237 g of compound (A) in dry acetone 10 mL and then (0.001 moles, 0.1011g,0.14 ml) of TEA was added as a basic medium with stirring. The reaction flask was placed later in an ice bath at 0ºC, and CS_2 (0.001 mol, 0.06 mL, excess by 5 fold) was then added in a dropwise fashion then the mixture was left for 2 hours and at room temperature 25ºC for 3 hr. the product was filtered and dried.[9]

Yield = 70%, R*f* = 0.22(A), IR: (3210 cm^{-1}) N-H str. of 2º amine, (3120 cm^{-1}) C-H str. of Ar ring, (2985,2877 cm^{-1}) C-H str. of alkane, (1728 cm^{-1}) C=O str. of amide, (1651 cm^{-1}) C=C str. of Ar ring, (1612 cm^{-1}) C=Nstr.,1087,1037 asym and sym. of (C=S) (1238 and 837 cm^{-1}) in and out of plane of Ar ring.(605 cm^{-1}) (C-S) ^{1}HNMR: 1.10-1.13 (9H, t, -CH_3), 2.91-2.96 (6H, q, -CH_2), 7.87-6.51 (8H, m, Ar C-H), 10.2 (1H, s, -NHCO).11.0(1H,s,NHCS)

Synthesis of Final Compounds (AL1,AL2,AL3,AL4):

Take 0.0005 mol, 0.206 gm of dtc salt (L) (Z)-N,N,N-triethyl-S-((4-((2-oxoindolin-3-ylidene)amino)phenyl)carbamothioyl)

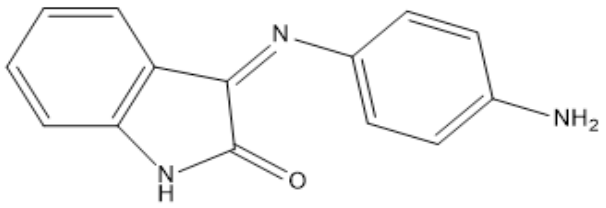


Figure 1: Chemical structure of compound (A)

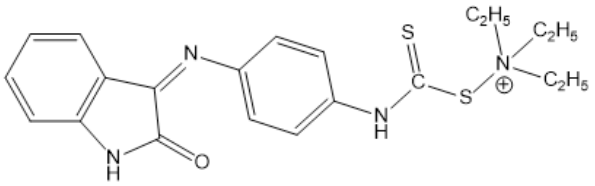


Figure 2: Chemical structure of compound (L)

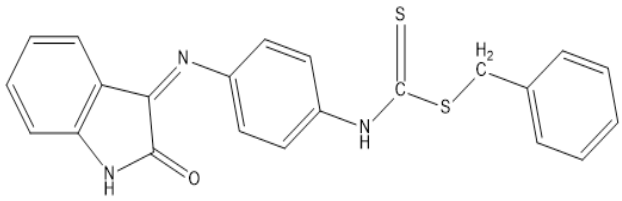


Figure 3: (Z)-(4-((2-oxoindolin-3 ylidene) amino)phenyl) carbamodithioate (AL1)

thiohydroxylammonium and dissolved in 15 mL of absolute ethanol in a rounded flask then add (0.0005 moles, 0.0575 mL) of benzyl chloride for the compound (AL1), (0.0005 mole, 0.07 gm, 0.03 mL) of methyl iodide for the compound (AL2), (0.0005 mole, 0.0857gm) of p-nitro benzyl chloride for the compound (AL3), 0.0005 mole, 0.099 gm of phenacyl bromide for the compound (AL4) and the mixture left sterring for 6 hours. at 25ºC the product was washed with water, filtered, dried and recrystallized from EtOH to give crystals[10].

Orange powder, yield = 75%, M.P. = (172-174) ºC, R*f* = 0.75 (B), IR: (3255 cm^{-1}) N-H str. of 2º amine, (3093 cm^{-1}) C-H str. of Ar ring, (2951 & 2970 cm^{-1}) C-H str. of alkane, (1735 cm^{-1}) C=O str. of amide (1662 cm^{-1}) C=C str.of Ar ring, (1589 cm^{-1}) C=N str., (1292 & 752 cm^{-1}) in and out of plane of Ar ring.

(1199,1091 cm^{-1}) asym and sym. of C=S

^{1}HNMR 3.1 (2H, s, -CH_2), 7.79-6.54 (13H, m, C-H aromatic), 10.0 (1H, s, N-H amide), 10.94 (1H,s, N-HCS).

Reddish brown powder, yield = 80%, M.P. = (165–168)ºC, R*f* = 0.25 (b), IR: (3275 cm^{-1}) N-H str. of 2º amine, (3059 cm^{-1}) C-H stretching of Ar ring, (2970 & 2858 cm^{-1}) C-H str. of alkane, (1716 cm^{-1}) C=O str. of amide, , (1666cm^{-1}) C=C str. of Ar ring (1612 cm^{-1}) C=N stretching, (1176,829 cm^{-1}) in and out of plane of Ar ring.(1029,995 cm^{-1}) C=S,(671 cm^{-1}) C-S

^{1}HNMR 3.1 (3H, s, -CH_3), 7.73-6.64 (8H, m, Ar C-H), 10,3 (1H, s, N-H amide), 11.0 (1H, s, NHCS),

Sandy color powder, yield = 70%, M.P. = (220–222)ºC, R*f* = 0.31 (B), IR: (3236 cm^{-1}) N-H str. of 2º amine, (3059 cm^{-1}) C-H str. of Ar ring, (3001 & 2881 cm^{-1}) C-H str. of alkane, (1720 cm^{-1}) C=O str. of amide, (1612 cm^{-1}) C=N stretching C=C str. of Ar ring (overlap) ,(1508& 1338 cm^{-1})asym& sym of NO2 (1095 and 752 cm^{-1}) in and out of plane of Ar ring.

^{1}HNMR 4.5 (2H, s, -CH_2), 7.58-6.5 (12H, m, Ar C-H), 10.1 (1H, s, N-H amide), 11.0 (1H, s, NHCS)

Orange powder, yield = 75%, M.P. = (260-264) ºC, R*f* = 0.28 (B), IR: (3222 cm^{-1}) N-H stretching of 2º amine, (3049 cm^{-1}) C-H stretching of Ar ring, (2991 and 2871 cm^{-1}) C-H stretching of alkane, (1710 cm^{-1}) C=O str. of amide, (1602 cm^{-1}) C=N str.C=C str. of Ar ring(overlap), (1323 & 752 cm^{-1}) in and out of plane of Ar ring.(1200 ,1095 cm^{-1}) asym. &sym. of C=S

^{1}HNMR 5.12 (2H, s, -CH_2), 7.56-6.53 (13H, m, Ar C-H), 10.66 (1H, s, N-H amide), 11.63 (1H, s, NHCS).

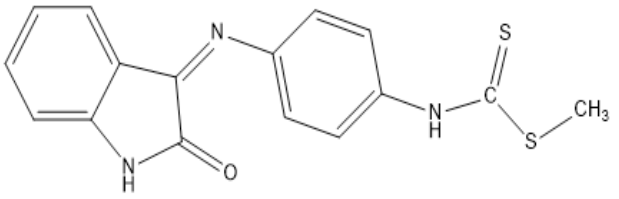


Figure 4: methyl (Z)-(4-((2-oxoindolin-3 ylidene) amino)phenyl) carbamodithioate (AL2)

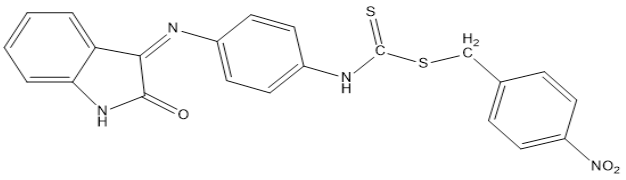


Figure 5: 4-nitrobenzyl (Z)-(4-((2-oxoindolin-3-ylidene)amino) phenyl) carbamodithio, (AL3)

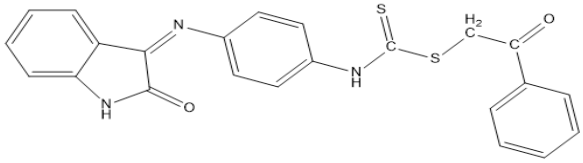


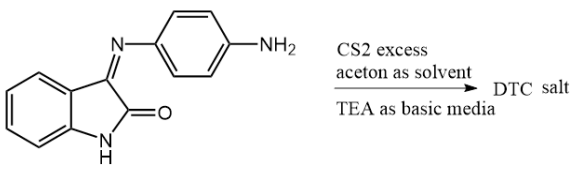
Figure 6: 2-oxo-2-phenylethyl (Z)-(4-((2-oxoindolin-3-ylidene)amino) phenyl)carbamodithioate (AL4)

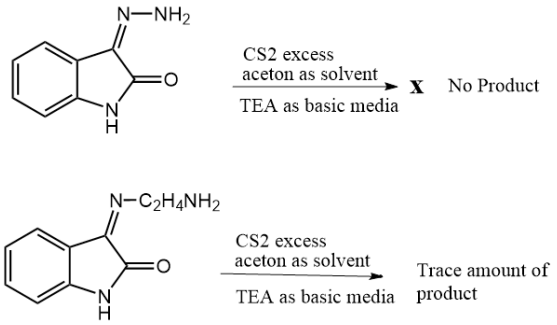
Antimicrobial Evaluation

The antimicrobial activities of the synthesized derivatives (AL1, AL2, AL3, AL4) were measured using well diffusion technique, using G (+ve) and G (-ve) bacteria, with a comparison to cefotaxime sodium, ciprofloxacin, and Amoxicillin as standard antibacterial agents, and fluconazole as a standard antifungal agent and using DMSO as a solvent and as a control, all the synthesized compounds had been screened for their antimicrobial activity against 2-gram-positive bacteria (*Staph Aureus, streptococcus*), and two gram-negative bacteria (*Pseud. aeruginosa,* and *E. coli*), and antifungal activity against two fungi species, (*C. glabrata,* and *Candida albicans*). A minimum inhibitory concentration (MIC) of 100µg/mL was used for all derivatives, followed by using MIC of 100 µg/mL for all derivatives in DMSO. It had been found that (AL1, AL2, AL4) showed a moderately active against gram-positive and gram-negative bacteria except AL3 showed moderate activity against gram-positive bacteria only, As well as, (AL1)shows *highly* antifungal activity against (*C. Glabrata* and *albicans*), and a *slight* antifungal activity against by others.

CONCLUSION

- Diathiocarbamte easily prepared from CS_2 and real amines as anilin, p-phenylenediamine, diethylamine and Morpholine by simple reaction, but it is difficult to prepare from CS_2 and imine (Schiff's base), which need special conditions and more time
- Dithiocarbamate cannot prepare from the reaction of CS2 with Schiff,s base of isatin and hydrazine; this may be due to the steric effect of carbonyl no.2 of isatin on terminal -NH_2 group. So it is prepared from the reaction of CS_2 with Schiff,s base of isatin and p-phenyl diamine or ethylenediamine which yield trace amount (hydrazine replaced by above amines linkers which have significant role in this reaction) as shown below:





- Dithiocarbamate from Schiff base reaction prepared by using aceton as a solvent while no produce with absolute ethanol on other hand, dithiocarbamate from real amine can be prepared by using absolute ethanole or aceton
- Dithiocarbamate cannot be recrystallized by hot method due to decomposition by heat
- A novel isatin dithiocarbamates derivatives were successfully synthesized, characterized, and evaluated for their antimicrobial, antifungal activities. All the synthesized compounds showed slight to moderate activity against any of the tested gram positive and gram negative bacteria, while they showed good antifungal activity against *C. albicans* and *C. glabarta*.

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