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Research Article

CONVENTIONAL SYNTHESIS AND CHARACTERIZATION OF NOVEL ISATIN DERIVATIVES CONTAINING 1,3 THIAZOLE-4-ONE MOIETIES WITH ANTIMICROBIAL ACTIVITY

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ABSTRACT

The present work which involve reaction between subtituted aniline with Chloral hydrate and hydroxylamine and Con.Sulphuricacide to get substituted Isatin which on reaction with substituted benzyl chloride to get intermediates N-benzyl isatin derivatives, which on rectting with Thiosemicarbazide to give schiff's bases. Then which can reaction with Chloroacetic acid in presence of glacial acetic acid to give respective title compounds. The structures of all the newly synthesized compounds were characterized as ***5a-5l*** *on the basis of satisfactory analytical and spectral data including IR, LC-MASS, ^{1}H NMR data. Antibacterial activity against various grams positive and gram negative bacterial strains by measuring zone of inhibition by agar diffusion method. Streptomycinwas used as a standard drug and also screened for antifungal activity by taking Gresiofulvin as standard. The synthesized compounds* ***5j*** *have shown highest activity.*

KEYWORDS: *Subtituted aniline, Benzyl chloride, Isatin, Chloroacetic acid, antimicrobial activity.*

INTRODUCTION

Heterocycles bearing nitrogen sulphur and thiazole moieties constitute the core structure of a number of biologically interesting compoundsThe chemistry of 1,3 Thiazole-4-one and its derivatives is particularly interesting because of their potential application in medicinal chemistry.

Literature survey shows that thiazole derivatives play a very important role in biological fildes such as Antimicrobial [1], antidiabetic[2], antiviral [3], antiinflammotory[4], antituberculosis[5], and anticancer [6] activities. 1,2,4-Triazole is among the various heterocycles that have received the most attention during the last two decades as potential antimicrobial agents.

MATERIALS AND METHODS: [7-8]

The synthesized compounds werescreenedfor anthelmentic activities. Fourier Transform IR spectrometer (model Shimadzu 8700) inthe range of 400-4000 cm^{-1} Using KBr pellets and values are reported in cm^{-1}andthe spectra were interpreted. ^{1}H-NMRspectrawererecordedonDPX-200MHzNMRspectrometerusingDMSO-$d_6$andchemicalshifts(δ)arereportedinpartspermilliondown field frominternal reference Tetramethylsilane (TMS) and the Spectra were interpreted. Massspectra were recorded on Mass spectrophotometer (model Shimadzu) by LC- MS and the spectra wereinterpreted.Precoated Silica gel G plates were used to monitor the progress of reaction as well as to check the purity of the compounds: n-Hexane: Ethyl acetate (7:3).

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General procedures:

Steps 1: Synthesis of nitrosoacetanilide from Aniline:

9 gm of Chloral hydrate was taken into the round bottom flaskand dissolved in 120 ml water. To that 13 gm of sodium sulphate, a solution of 5.4 gm of Aniline in 30 ml of water containing 5.12 gm of concentrated hydrochloric acid (4.34 ml) to dissolve the amine and solution of 11 gm of hydroxylamine hydrochloride in 50 ml of water were added. Flask was then heated vigorously until the reaction was completed. After it, the solution containing beaker was cooled in running water followed by the filtration of reminder crystallized product with suction pump and air dried.

Step 2: Synthesis of substituted Isatin from nitrosoacetanilide:

18.4 gm of concentrated sulphuric acid (10.0 ml) was warmed to 50^{0}C and 2.5 gm of dry nitrosoacetanilide was added in such a rate so as to keep the temperature between 60-70^{0}C but not higher. External cooling was applied at this stage so that the reaction could be carried out more rapidly after the addition of isonitroso compound was finished. The solution was heated to 80^{0}C and kept at this temperature for about 10 min to complete the reaction. Then the reaction mixture was cooled to room temperature and poured it into ten times its volume of cracked ice. After standing for 90mint, the final product was filtered with suction pump followed by washing with cold water to remove sulphuric acid and dried in air.

Step III: N-Benzyl indole 2, 3- dione (N-Benzyl Isatin):

In the round bottomed flask take indole-2,3-dione (Isatin) 0.8gm (3.37mM) and equimolar quantity of benzyl chloride i.e. 6.5ml (3.7mM), mix with 20ml of DMF and to this mixture add 2gm of K_2CO_3. After gentle mixing of this reaction mixture, reflux for 2 hr, cool and pour to 100 ml of ice cold water. The resultant orange red ppt. collected wash with water and dried and recrystallized from acetonitrile.

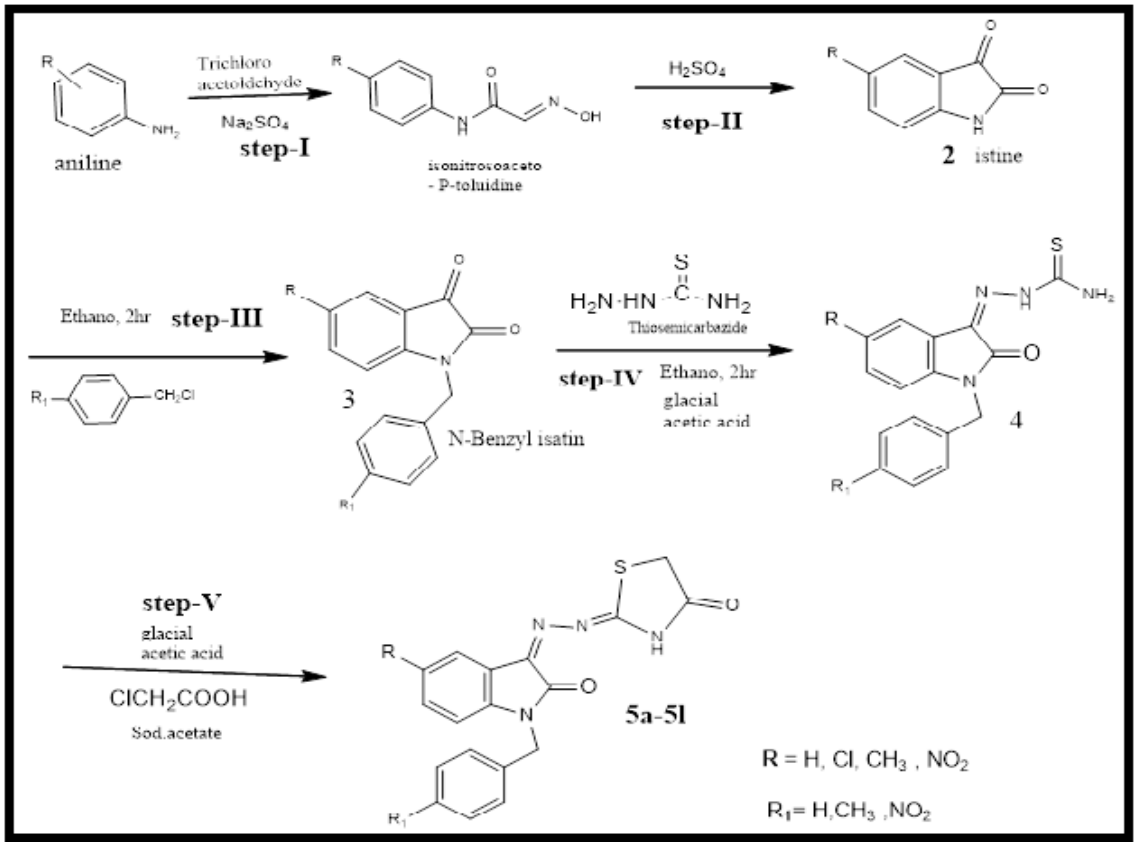
Step IV: Synthesis of Schiff's bases (4):

Equimolar quantities (0.01mol) of N-Benzyl Isatin and Thiosemicarbazide (0.01mol) were dissolved in warm ethanol and glacial acetic acid (1:1%, 30ml). The reaction mixture was refluxed for 2hrs and then kept in refrigerator for overnight. The resultant solid was filtered, dried and recrystallized from suitable solvent to afford compounds.

Step V: Synthesis of novel Isatin derivatives containing 1,3 Thiazole-4-one moieties:

A mixture of compound (4) (0.01mol) and chloroacetic acid (0.01) in glacial acetic acid 30ml containing anhydrous sodium acetate (0.04mol) was refluxed for 7hrs.The reaction mixture was monitored by TLC. The reaction mixture was cooled and the obtained precipitate was filtered off, dried and recristallized from ethanol. The physical data are reported in **Table1.**

Scheme of synthesis:



Spectral Data:

5a-IR Cm⁻¹ (KBr):3467(-NH Str, indole), 3096(-CH Str, Aromatic), 2961(-CH 2Str, alphatic), 2895(-CH2 Str, Thiazoline), 1709(C=O Str), 1676(C=O Str), 1576(C=N Str), 1317(C-N Str), 1216(C-N Str), 1058(N-N Str). ***1H-NMR (DMSO δ ppm):*** 10.44(1H,-NH Thiazolidine), 8.04-7.39(9H, Ar-H), 4.80-4.78(2H, benzyl),3.84--3.82(2H, CH2in Thiazoline). ***Mass (EI-MS):*** 350(M), 351(M+1,100%), 349(M-1, 100%).

5b-IR Cm⁻¹ (KBr):3415(-NH Str, indole), 3098(-CH Str, Aromatic), 2977(-CH 2Str, alphatic), 2861(-CH2 Str, Thiazoline), 1724(C=O Str), 1697(C=O Str), 1586(C=N Str), 1371(C-N Str), 1230(C-N Str), 1097(N-N Str), 863(C-Cl Str).***¹H-NMR (DMSO δ ppm):***1HNMR (DMSO, δppm): 10.82(1H,-NH Thiazolidine), 8.33-7.02(8H, Ar-H), 4.76-4.71(2H, benzyl), 3.83-3.81(2H, CH2in Thiazoline).***Mass (EI-MS):***384(M), 385(M+1,100%), 383(M-1, 100%).

5c-IR Cm⁻¹ (KBr):3424(-NH Str, indole), 3054(-CH Str, Aromatic), 2937(-CH 2Str, alphatic), 2891(-CH2 Str, Thiazoline), 1743(C=O Str), 1697(C=O Str), 1576(C=N Str), 1317(C-N Str), 1216(C-N Str), 1058(N-N Str).***¹H-NMR (DMSO δ ppm):***10.46(1H,-NH Thiazolidine), 7.44-7.00-7.02(8H, Ar-H), 4.55-4.53(2H, benzyl), 3.85-3.83(2H, CH_2in Thiazoline), 3.85-3.83(3H, -CH_3).***Mass (EI-MS):*** 364(M), 365(M+1,100%), 363(M-1, 100%).

5d-IR Cm⁻¹ (KBr): 3443(-NH Str, indole), 3070(-CH Str, Aromatic), 2954(-CH_2 Str, alphatic), 2895(-CH_2 Str, Thiazoline), 1702(C=O Str), 1682(C=O Str), 1647(NO_2 Str), 1546(C=N Str), 1317(C-N Str), 1258(C-N Str), 1063(N-N Str).***¹H-NMR (DMSO δ ppm):***10.12(1H,-NH Thiazolidine), 7.77-6.92(8H, Ar-H), 4.55-4.54(2H, benzyl), 3.75-3.74(2H, CH_2 in Thiazoline).***Mass (EI-MS):*** 395(M), 396(M+1,100%), 394(M-1, 100%).

5e- IR Cm⁻¹ (KBr):3403(-NH Str, indole), 3042(-CH Str, Aromatic), 2998(-CH_2 Str, alphatic), 2890(-CH2 Str, Thiazoline), 1710(C=O Str), 1697(C=O Str), 1565(C=N Str), 1364(C-N Str), 1234(C-N Str), 1052(N-N Str).***¹HNMR (DMSO, δppm):*** 10.15(1H,-NH Thiazolidine), 7.55-6.85(8H, Ar-H), 4.72-4.71(2H, benzyl), 3.81-3.80(2H, CH_2in Thiazoline), 2.40-2.31(3H, -CH_3). ***Mass (EI-MS):*** 364(M), 365(5M+1,100%), 363(M-1, 100%).

5f- IR Cm⁻¹ (KBr):3402(-NH Str, indole), 3033(-CH Str, Aromatic), 2989(-CH_2 Str, alphatic), 2890(-CH_2 Str, Thiazoline), 1721(C=O Str), 1690(C=O Str), 1554(C=N Str), 1337(C-N Str), 1298(C-N Str), 1018(N-N Str), 823(C-Cl Str).***¹HNMR (DMSO, δppm):*** 10.95(1H,-NH Thiazolidine), 7.71-6.91(7H, Ar-H), 4.89-4.88(2H, benzyl), 3.73-3.72(2H, CH_2in Thiazoline), 2.41-2.31(3H, -CH_3).***Mass (EI-MS):*** 398(M), 399(5M+1,100%), 397(M-1, 100%).

5g- IR Cm⁻¹ (KBr):3412(-NH Str, indole), 3032(-CH Str, Aromatic), 2986(-CH_2 Str, alphatic), 2893(-CH_2 Str, Thiazoline), 1701(C=O Str), 1696(C=O Str), 1576(C=N Str), 1362(C-N Str), 1288(C-N Str), 1099(N-N Str).***¹H-NMR (DMSO δ ppm):***10.46(1H,-NH Thiazolidine), 7.44-7.00-7.02(8H, Ar-H), 4.55-4.53(2H, benzyl), 3.85-3.83(2H, CH_2 in Thiazoline), 3.85-3.83(3H, -CH_3).***Mass (EI-MS):*** 378(M), 379(5M+1,100%), 377(M-1, 100%).

5h- IR Cm⁻¹ (KBr):3412(-NH Str, indole), 3036(-CH Str, Aromatic), 2986(-CH 2Str, alphatic), 2890(-CH_2 Str, Thiazoline), 1730(C=O Str), 1695(C=O Str), 1623(NO_2 Str), 1563(C=N Str), 1334(C-N Str), 1226(C-N Str), 1063(N-N Str), 863(C-Cl Str).***¹HNMR (DMSO, δppm):*** 10.16(1H,-NH Thiazolidine), 7.75-6.90(7H, Ar-H), 4.73-4.72(2H, benzyl), 3.72-3.71(2H, CH_2in Thiazoline), 2.39-2.35(3H, -CH_3). ***Mass (EI-MS):*** 409(M), 410(M+1,100%), 408(M-1, 100%).

5i-IR Cm⁻¹ (KBr):3423(-NH Str, indole), 3023(-CH Str, Aromatic), 2978(-CH_2 Str, alphatic), 2894(-CH_2 Str, Thiazoline), 1718(C=O Str), 1690(C=O Str), 1643(NO_2 Str), 1554(C=N Str), 1328(C-N Str), 1246(C-N Str), 1054(N-N Str). ***¹H-NMR (DMSO δ ppm):***10.65(1H,-NH Thiazolidine), 8.02-6.98(8H, Ar-H), 4.23-4.02(2H, benzyl), 3.98-3.76(2H, CH_2 in Thiazoline).***Mass (EI-MS):*** 395(M), 396(M+1,100%), 394(M-1, 100%).

5j- IR Cm⁻¹ (KBr):3408(-NH Str, indole), 3054(-CH Str, Aromatic), 2979(-CH_2 Str, alphatic), 2883(-CH_2 Str, Thiazoline), 1715(C=O Str), 1695(C=O Str), 1634(NO_2 Str), 1578(C=N Str), 1328(C-N Str), 1262(C-N Str), 1078(N-N Str), 873(C-Cl Str). ***¹H-NMR (DMSO δ ppm):***10.78(1H,-NH Thiazolidine), 7.98-6.90(7H, Ar-H), 4.68-4.60(2H, benzyl), 3.78-3.73(2H, CH_2 in Thiazoline).***Mass (EI-MS):*** 429(M), 430(M+1,100%), 428(M-1, 100%).

5k-IR Cm⁻¹ (KBr):3414(-NH Str, indole), 3028(-CH Str, Aromatic), 2973(-CH_2 Str, alphatic), 2872(-CH_2 Str, Thiazoline), 1708(C=O Str), 1689(C=O Str), 1634(NO_2 Str), 1558(C=N Str), 1329(C-N Str), 1247(C-N Str), 1080(N-N Str). ***¹H-NMR (DMSO δ ppm):***10.28(1H,-NH Thiazolidine), 8.02-7.12(7H, Ar-H), 4.68-4.58(2H, benzyl), 3.98-3.92(2H, CH_2 in Thiazoline), 3.53-3.48(3H, -CH_3).***Mass (EI-MS):*** 409(M), 410(M+1,100%), 408(M-1, 100%).

5l-IR Cm⁻¹ (KBr):3419(-NH Str, indole), 3046(-CH Str, Aromatic), 2973(-CH_2 Str, alphatic), 2867(-CH_2 Str, Thiazoline), 1743(C=O Str), 1689(C=O Str), 1634(NO_2 Str), 1548(C=N Str), 1328(C-N Str), 1234(C-N Str), 1089(N-N Str).***¹H-NMR (DMSO δ ppm):***10.38(1H,-NH Thiazolidine), 8.02-6.98(7H, Ar-H), 4.82-4.80(2H, benzyl), 3.68-3.60(2H, CH_2 in Thiazolin). ***Mass (EI-MS):*** 440(M), 441(M+1,100%), 439(M-1, 100%).

Anmicrobial activity: [10-12]

The medium was prepared by dissolving all the ingredients in distilled water and subjected to sterilization in an autoclave at 121 °C/15lbs for 15 minutes. The Petri plates were washed thoroughly and sterilized in hot air oven at 160 °C for 1 ½ hours. 30 ml of sterile SDA was seeded by organisms (about 2ml according to Mc Far land's standard), in semi hot conditions (40 °C) was poured aseptically in sterile Petri plate and allowed to solidify at room temperature. Bores were made on the medium using sterile borer and 0.1 ml of the solution of synthesized compounds at 50µg/mL concentration in DMSO were added to respective bores and 0.1ml of the standard Streptomycine at a concentration of 50µg/mL was used as standard. The Petri plates seeded with fungal organisms, containing solution of synthesized compounds and the standard drug were kept in a refrigerator at 4 °C for 30mints to facilitate the diffusion of the compounds and the standard in to the media. After diffusion the Petri plates were incubated at 28 °C for one week and later the zone of inhibition was observed and measured using a scale. **Table No.2.**

RESULTS AND DISCUSSION

Synthesis:

The characterization data of all compounds **5a-5l** are given the experimental section. All the synthesized compounds gave satisfactory analysis for the proposed structures, which were confirmed on the basis of their elemental analysis by FT-IR, LC-MASS and ^{1}H-NMR data. The present work which involve reaction between subtituted aniline with Chloral hydrate and hydraxilamine and Con.sulphuricacide to get substituted Isatin which on reaction with substituted benzyl chloride to get intermediates N-benzyl isatin derivatives, which on rectting with Thiosemicarbazide to give schiff's bases. Then which can reaction with Chloroacetic acid in presence of glacial acetic acid to give respective title compounds.

Spectroscopy:

The structures of all the newly synthesized compounds were characterized as **5a-5l** on the basis of satisfactory analytical and spectral data including IR, LC-MASS, ^{1}H NMR data

Antibacterial activity:

The antibacterial activity of the synthesized compounds was studied by cup plate method. The standard drug used was Streptomycin. Antibacterial activity among the test compounds is presented in **Table 3**. All the test compounds **[5a-5l]** showed a varied degree of antibacterial activity with broad spectrum of activity against the entire Gram negative and Gram positive bacterial strains employed. However, among this series of compounds 5h and 5i showed high activity, where as the test compounds 5a,5b, and 3e exhibited moderate activity (**Figure 1**).

Antifungal activity:

The antifungal activity of newly synthesized novel Isatin derivatives containing 1,3 Thiazole-4-one derivatives evaluated against three organisms *Asperigillusnigrum,Pencilliumnotatum, C.Coffeanum.* The test compounds are comparable with the standard i.e., Gresiofulvin in their antifunal activity. From the results it was found that compounds showing zone of inhibition values between 09-32mm. Antifungal activity among the test compounds was represented in **Table 4**. The newly synthesized novel Isatin derivatives containing 1,3 Thiazole-4-one derivatives 5j and5i exhibited the highest activity (**Figure 2**).

Table No. 1: Physical data of (5a-5l)

Code	R	R_1	Mol. Formula	Mol. wt (g.mol^{-1})	M.P (^{0}C)
5a	-H	-H	$C_{18}H_{14}N_4O_2S$	350	223-225
5b	-Cl	-H	$C_{18}H_{13}N_4O_2SCl$	384	216-218
5c	-CH_3	-H	$C_{19}H_{16}N_4O_2S$	364	220-222
5d	-NO_2	-H	$C_{18}H_{13}N_5O_4S$	395	242-244
5f	-Cl	-CH_3	$C_{19}H_{15}N_4O_2SCl$	398	272-274
5g	-CH_3	-CH_3	$C_{20}H_{18}N_4O_2S$	378	234-236
5h	-NO_2	-CH_3	$C_{19}H_{15}N_5O_4S$	409	216-218
5i	-NO_2	-NO_2	$C_{18}H_{12}N_6O_6S$	440	227-229
5j	-Cl	-NO_2	$C_{18}H_{12}N_5O_4SCl$	429	198-200
5k	-CH_3	-NO_2	$C_{19}H_{15}N_5O_4S$	409	256-268
5l	-H	-NO_2	$C_{18}H_{13}N_5O_4S$	395	229-231
5f	-Cl	-CH_3	$C_{19}H_{15}N_4O_2SCl$	398	272-274

Table No.2:Antibacterial activity by zone of inhibition (in mm)

Compound	Zone of Inhibition (in mm)			
	L.Bacillus	*Pseudomonas*	*E.Coli*	*P.Vulgares*
Streptomycin	**31**	**30**	**34**	**34**
5a	11	17	-	19
5b	20	-	19	21
5c	19	12	10	23
5d	20	12	24	15
5e	12	13	24	22
5f	23	20	10	10
5g	20	19	-	12
5h	-	-	22	20
5i	24	20	19	10
5j	**26**	18	**27**	**26**
5k	24	25	-	23
5l	**27**	20	**28**	20

*All values are expressed as Zone of Inhibition in mm, Bore size = 6mm;*Compounds showed maximum activity against respective bacteria; Zone size 9-11 = Poor activity; Zone size 12-18 = Moderate activity,Concentrationof test compounds is 50µg/ml.*

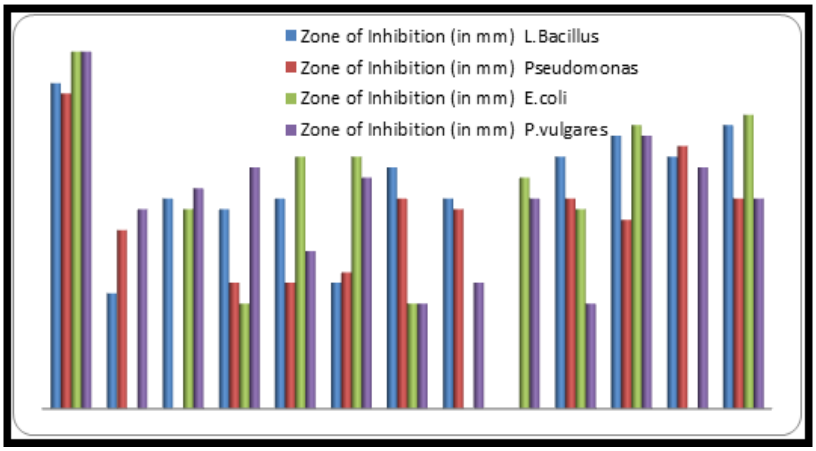


Fig.1: Graphical representation of antibacterial activity of compounds (5a-5h) – Zone of Inhibition(mm)

Table No.3: Antifungal activity by Zone of Inhibition (in mm)

Microorganism	Zone of Inhibition (in mm)												
	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**	**3l**	**Gresiofulvin**
A.Nagram	-	14	19	-	18	19	12	-	20	10	23	**25**	28
P.Notatum	10	16	14	22	24	13	-	-	22	**28**	10	**27**	32
C.Coffeanum	09	-	12	19	23	-	-	09	18	**32**	29	22	36

*All values are expressed as Zone of Inhibition in mm, Bore size = 6mm; *Compounds showed maximum activity against respective Fungal; Zone size 9-11 = Poor activity; Zone size 12-18 = Moderate activity, Concentrationof test compounds is 50µg/mL,*

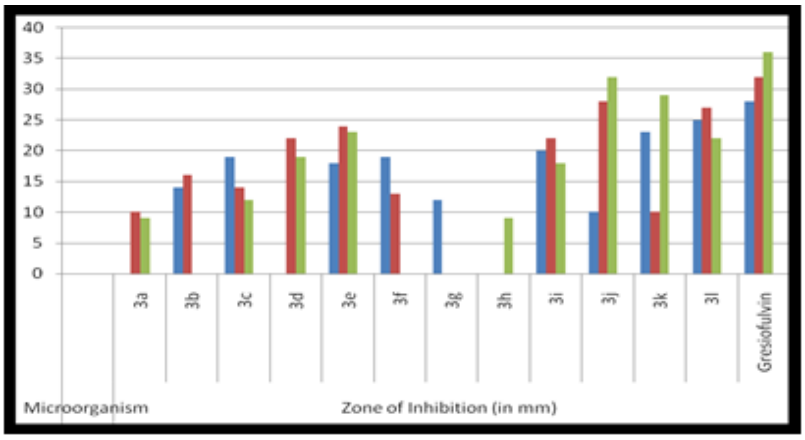


Fig :2: Graphical representation of antifungal activity of compounds (5a-5h) - Zone of Inhibition (in mm).

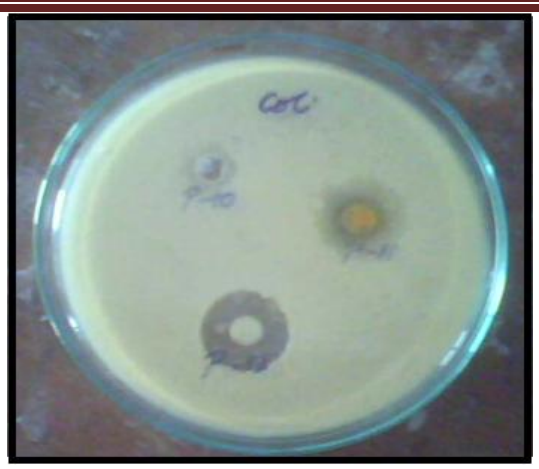


Fig.3: Photographs of various Novel 1,3 Thiazole-4-one derivatives - Antibacterial activity.

CONCLUSION

The objective of the present work was to synthesize, purify, characterize and evaluate the biological activity of newly synthesized structural analogs of 1,3 Thiazole-4-one . The yield of the synthesized compound was found to be in the range from 70-87%. All these molecules were characterized by FTIR, $H^{1,}$ ^{13}C-NMR and Mass spectral analysis along with physical data. The functional groups in the title compounds (5a,5b and 5c) are indicated by their IR,1H NMR and MASS spectra.

All the synthesized compounds were screened for their antibacterial activity against various gram positive and gram negative bacterial strains by measuring zone of inhibition by agar diffusion method. Streptomycin was used as a standard drug. 5j and 5i has shown highest activity. The synthesized compounds (5a-5l) were also screened for antifungal activity by taking Gresiofulvin as standard. The synthesized compounds 5j have shown highest activity. In conclusion, the present study highlights the importance of 1,3 Thiazole-4-one derivatives having various heterocyclic moiety features responsible for the antibacterial, antifungal, anthelmintic and antioxidant activities and may serve as a lead molecule for further modification to obtain clinically useful novel entities. A series of novel Isatin derivatives containing 1,3 Thiazole-4-one compounds were synthesized and evaluated for antimicrobial, antifungal activities.

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