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Original Research Article

Synthesis and Antimicrobial Evaluation of Some Novel Isatin Derivatives

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Abstract

Present day challenge of managing microbial infection is ever increasing on account of many factors, out of which emergence of microbial resistance is topmost. Microorganisms are responsible for a number of diseases in human and other animals. As per a report, infectious disease is responsible for 16 million deaths every year worldwide and a lot of these are avoidable. The high level of antimicrobial resistance is a global public health concern. Resistance to potent and effective drugs such as cephalosporins, fluoroquinolones, and carbapenems is a particular concern, as is multidrug resistance. India occupies highest position in the world, in infectious disease list. Antimicrobial agents are considered to be ‒miracle drugs‖ that are the leading weapons in combating infectious disease caused by microbes like bacteria, viruses, and fungi. Antimicrobial resistance (AMR), or drug resistance, is the ability of microbes, including bacteria, fungi, parasites, and viruses, to grow in the presence of antimicrobial agent that previously treated them effectively‖. Statistics of World Health Organisation (WHO), show that 490000, people developed MDR-TB, in 2016, globally. The drug resistance is also causing hindrance in fight against HIV and malaria. The study also indicates that people with methicillin resistance Staphylococcus aureus‖ is 64% more proven to death than people infected with non-resistant microbes.

Experts are constantly working hard to devise newer compounds to meet this challenge.Many pharmacophore have the potential as antimicrobial and anticancer agent. Pyrimidine, like Isatin also reported to possess versatile activity such as antimicrobial, anticancer, antifungal, anti-malarial, antiviral and anti-tubercular

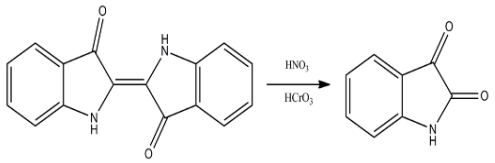
Introduction

Medicinal chemistry is the branch of science which deals with the discovery and development of new drug molecules for the treatment of disease. [1] More than 20 millions chemical compounds currently registered, majority of compounds are either fully or partially aromatic, besides half of the compounds are heterocycles (Dua et al., 2011). A large number of biologically active agrochemical entity are heterocyclic while countless additive and modifier used in cosmetics, material science, information storage, plastic and polymer industry are also heterocyclic in nature. Many natural drugs such as morphine, reserpine, alkaloids, glycosides (digoxin), hyoscimine etc are heterocyclic. Majority of the synthetic drugs such as rosuvastatin, esomeprazole, diazepam, 5-fluorouracil etc are heterocyclic. The

heterocyclic chemical compounds constitute the largest part of chemical division of organic chemistry. 2-5] These are important not because of their abundance but also because of their chemical and biological significance. One distinguished feature lies in heterocycles are their ability to modify substituent around a core nucleus to get better representative (Dabiri et al., 2006). Among a wide range of heterocycles explored to develop in to pharmacologically active molecules, isatin has an important place in medicinal chemistry.

Isatin:

Chemically, Isatin is 1H-Indole-2, 3-dione, possessing an indole scafold substituted with carbonyl groups at 2nd and 3rd position. In 1841, ‑Erdman and Laurent‖ obtained isatin by nitric and chromic acid oxidation of indigo. It is also known as oxindole. It is an endogenous compound reported to be present in many organisms (Prakash et al., 2013)



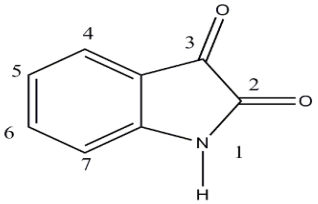
Indigo Isatin

Physical properties of Isatin:

Isatin

Chemical Name: Isatin; 1H-Indole-2, 3-dione; Indoline-2, 3-dione; 2, 3-Indolinedione;Indole-2, 3-Dione

Molecular Formula: $C_8H_5NO_2$;

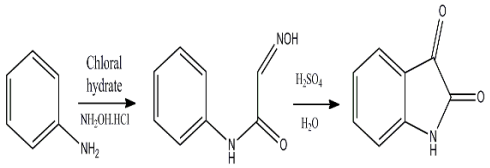


Molecular Weight: 147.133 g/mol

Isatin is a yellow to red needle crystalline substance, which melt at 200 °C (392 °F; 473 K). It has variable solubility in different solvents. It is soluble in methanol, hot ethanol, ethyl ether, hot water, benzene and acetone, dissolve in alkali metal hydroxide (Baluja et al., 2013).

Method of synthesis:

2.1. The Sandmeyer synthesis



Aniline Isonitroso acetanilide Isatin

This is one of the most efficient synthetic procedures for preparation of isatin and derivatives. this method involving reaction between aniline, chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulphate solution, to accord isonitrosoacetinilide, which on cyclization either in the presence of concentrated H_2SO_4or in $BF_3.ET_2O$ at 90^0C yield Isatin (da silva, 2001).

Material and Methods

Chemicals, Reagents and Solvents

The chemicals employed in the synthetic work were purchased from, SD Fine Chemicals, Mumbai (Anhydrous sodium sulfate, Hydroxylamine hydrochloride, Chloral hydrate), Spectrochem, Mumbai (Substituted aniline), CDH New Delhi (Substituted Methyl benzoate), SAS Chemicals Co, Mumbai (Substituted Benzyl chloride). Rolex Laboratory, Mumbai (Anthranilic acid, Benzoyl chloride). The invitro biological activity was carried out at Scientific and Applied Research Centre, Meerut.

Methods

All chemicals were weighed on a single pan analytical balance of Donna Pvt. Ltd. The reagents were of L.R/ A.R. Grade and were purified and dried before use in different reactions. Open capillary tubes was used for determining the Melting point (m.p) of newly synthesized compounds. Diffuse reflectance technique was employed for

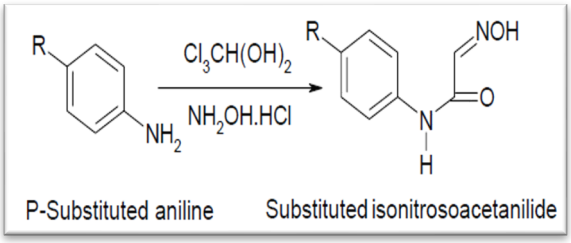
FTIR spectra for the confirmation of functional groups of newly synthesized compounds by using KBr powder using JASCO, V460 IR spectrophotometer by. ^{1}H-NMR spectra were measured in $CDCl_3$ and d^{6}DMSO at δppm on Bruker Ultraspec spectrometer, 400 MHz spectrophotometer. Tetra methyl silane (TMS) was taken as an internal standard to report the chemical shift of various protons on δ scale. Mass spectra (LCMS) were also recorded on Shimadzu with the LCMS-2010-A data report. Thin layer chromatography (TLC) using silica gel G coated glass plates taking mobile phase $CHCl_3$:CH_3OH(9:1) is used to monitor the reaction and purity of synthesized derivatives. The spots were visualized in U.V chamber or exposure to iodine vapours.

The reactions were carried out following reported methods. TLC (Thin layer chromatography) was carried out at different time intervals to monitor the reaction. After the confirmation of product formation the reaction mixture was processed as usual to get the desired/expected solid product. It was purified/crystallized/ recrystallized with suitable solvent for removing any impurities present. It was observed that no minor product(s) were obtained during the experiments.

Experimental work

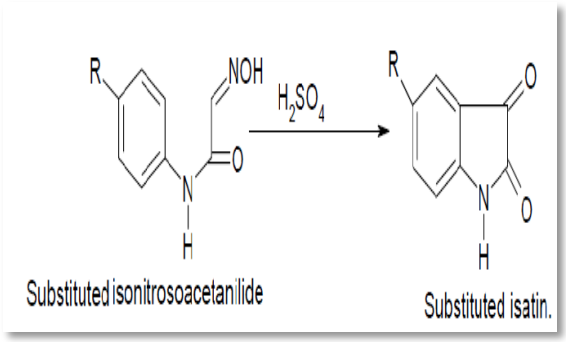
Synthesis of 5-substituted-indole-2,3 dione (isatin)

Synthesis of Substituted isonitroso acetanilide from substituted aniline



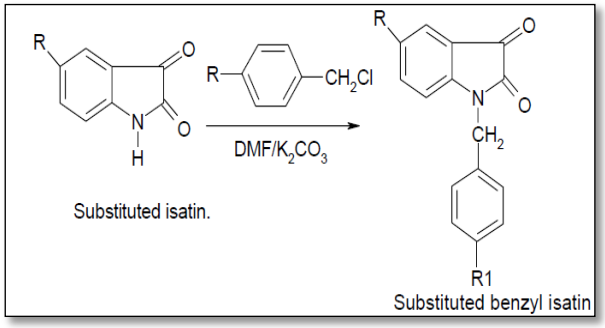
Where R= H, Cl, CH_3.

Synthesis of 5-substituted isatin from substituted isonitrosoacetanilide



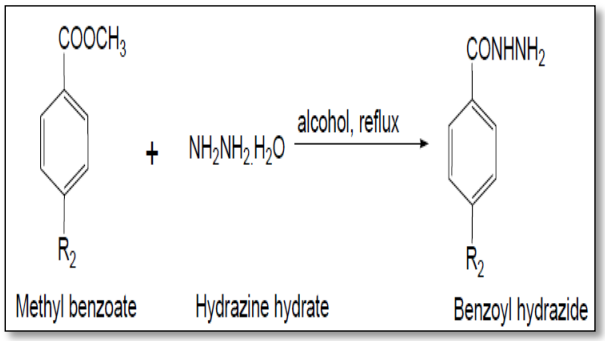
Where R= H, Cl, CH_3.

Synthesis of 1-(4-substituted benzyl)-5-substituted-indoline-2,3-dione from substituted indolin-2,3-dione



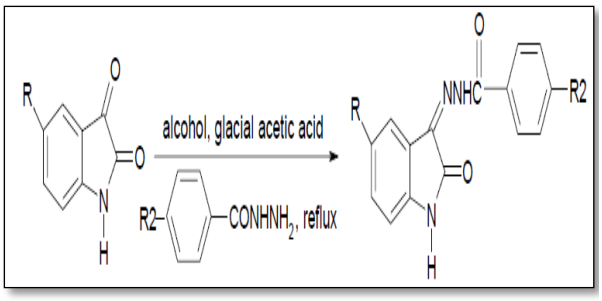
Where R= H, Cl, CH_3.
R1= H, Cl, CH_3

Synthesis of Benzoyl hydrazide from Methyl benzoate.



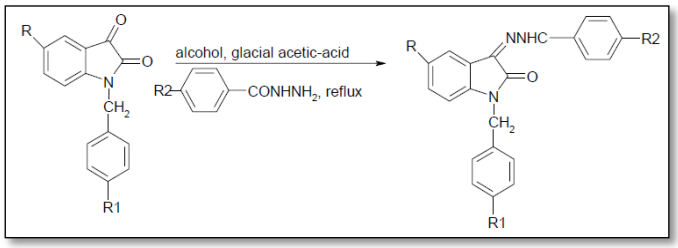
R_2= H, Cl, Br, NH_2, NO_2

Synthesis of 5-substituted-2-oxoindolin-3-ylidene]-4-substituted benzohydrazide(3a-c).



Where R= H, CH_3, Cl
R2= H, Cl, Br, NO_2, NH_2

Synthesis of N^1-[1-(4-substituted benzyl)-5-substituted-2-oxoindolin-3-ylidene]-4-substituted-benzohydrazide (4a-z,z')



Where R= H, Cl, CH_3R1= H, Cl, CH_3
R2= H, Cl, Br, NO_2, NH_2

Table 1: Physical data of compound 4a- N^1-(1-benzyl-2-oxoindolin-3-ylidine)-4-chlorobenzohydrazide

Physical characteristics	Yield %	Molecular Formula	Rf value	M. P. (°C)	R	R_1	R_2
Yellow fluffy solid	84	$C_{22}H_{16}N_3O_2Cl$	0.68	220	H	H	Cl

Spectral data:

IR (ν, cm^{-1}): 3359 (NH); 3051 (CH, Ar); 1683 (C=O);

^{1}H NMR (δ, ppm/ DMSO-d_6): 4.98 (s, 2H, CH_2), 7.03-8.15 (m, 13H, Ar-H), 13.73 (s, 1H, NH)

Table 2: Physical data of compound 4b- N^1-(1-benzyl-5-chloro-2-oxoindolin-3-ylidine)-4-chlorobenzohydrazide

Physical characteristics	Yield %	Molecular Formula	Rf value	M. P. (°C)	R	R_1	R_2
Pale yellow fluffysolid	81	$C_{22}H_{15}N_3O_2Cl_2$	0.74	223-225	Cl	H	Cl

Spectral data:

IR (ν, cm^{-1}): 3237 (NH); 3044 (CH, Ar); 1703 (C=O);

^{1}H NMR (δ, ppm/ DMSO-d_6): 4.94 (s, 2H, CH_2), 6.78-7.91 (m, 12H, Ar-H), 13.94 (s, 1H, NH)

MS: $[M/]^+$ at m/z 422.

Table 3: Physical data of compound 4c- N^1-(1-benzyl-5-methyl-2-oxoindolin-3-ylidine)-4-chlorobenzohydrazide

Physical characteristics	Yield %	Molecular Formula	Rf value	M. P. (°C)	R	R_1	R_2
Creamy crystallinesolid	78	$C_{23}H_{18}N_3O_2Cl$	0.76	211-213	CH_3	H	Cl

Spectral data:

IR (ν, cm^{-1}): 3217 (NH); 3073 (CH, Ar); 2884 (CH, Ali); 1671 (C=O);

^{1}H NMR (δ, ppm/ DMSO-d_6): 2.32 (s, 3H, CH_3), 4.96 (s, 2H, CH_2), 6.68-8.04 (m, 12H, Ar-H), 14.08 (s, 1H, NH)

Table 4: Physical data of compound 4d- N^1-[1-(4-chlorobenzyl)-2-oxoindolin-3-ylidine]-4-chlorobenzohydrazide

Physical characteristics	Yield %	Molecular Formula	Rf value	M. P. (°C)	R	R_1	R_2
Yellow fluffy solid	74	$C_{22}H_{15}N_3O_2Cl_2$	0.70	208-210	H	Cl	Cl

Spectral data:

IR (ν, cm^{-1}): 3228 (NH); 3055 (CH, Ar); 1682 (C=O);

^{1}H NMR (δ, ppm/ DMSO-d_6): 4.90 (s, 2H, CH_2), 6.73-8.02 (m, 12H, Ar-H), 14.00 (s, 1H, NH)

Table 5: Physical data of compound 4e- N^1-[1-(4-chlorobenzyl)-5-chloro-2-oxoindolin-3-ylidine]-4-chlorobenzohydrazide

Physical characteristics	Yield %	Molecular Formula	Rf value	M. P. (°C)	R	R_1	R_2
Dark yellow solid	81	$C_{22}H_{14}N_3O_2Cl_3$	0.74	242	Cl	Cl	Cl

Spectral data:

IR (ν, cm^{-1}): 3236 (NH); 3046 (CH, Ar); 1704 (C=O);

^{1}H NMR (δ, ppm/ DMSO-d_6): 4.76 (s, 2H, CH_2), 6.55-7.89 (m, 11H, Ar-H), 13.84 (s, 1H, NH, exchangeable with D_2O).

Table 6: Physical data of compound 4f- N^1-[1-(4-chlorobenzyl)-5-methyl-2-oxoindolin-3-ylidine]-4-chlorobenzohydrazide

Physical characteristics	Yield %	Molecular Formula	Rf value	M. P. (°C)	R	R_1	R_2
Pale yellow fluffy solid	83	$C_{23}H_{17}N_3O_2Cl_2$	0.69	218-220	CH_3	Cl	Cl

Spectral data:

IR (ν, cm^{-1}): 3213 (NH); 2894 (CH, Ar); 2828 (CH, Ali); 1728 (C=O);

^{1}H NMR (δ, ppm/ DMSO-d_6): 2.26 (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 6.57-7.96 (m, 11H, Ar-H), 13.95 (s, 1H, NH)

MS: $[M/]^+$ at m/z 437.

Biological Evaluations

General

Pharmacological evaluation involves testing the microbial susceptibility of the synthesized title compounds towards chemotherapeutic agents. Determination of the antimicrobial effectiveness against specific pathogens i.e. bacterial and fungal is determined by applying proper therapy. Findings can reveal information about the agents whose are more effective against a selective pathogen and give an estimate of proper therapeutic dose. Some ideas of the effectiveness of amino therapeutic agent a pathogen can be obtained from the minimum inhibitory concentration (MIC).

Antimicrobial activity of synthesized compounds (Zone of Inhibition)

The synthesized compounds 3a-c, 4a-f were evaluated for antifungal and antibacterial

activity using cup plate method method and MIC for potent compounds were calculated by serial dilution method. Parez et al (1990); Rohini et al (2010)

Test organism fungi

Aspergillus niger (ATCC 16404) Candida albicans (ATCC 10231) Trichoderma viridae (IAM 5061)

Test organism gram-positive bacteria Staphylococcus aureus (ATCC 25923) Bacillus subtilis (ATCC 9372) Streptococcus pyrogens (ATCC 19615)

Test organism gram-negative bacteria Salmonella typhimurium (ATCC 14028) Escherichia coli (ATCC 25922) Klebsiella pneumoniae (ATCC 3882)

Table 7: MIC values of potent isatin derivatives and standard drugs. (Scheme 2)

Compd.	MIC @µg/ml								
	Fungi			Gram positive bacteria			Gram negative bacteria		
	A. n	T. v	C. a	S. a	S. p	B. s	S. t	K. pn	E. coli
3a	20±2.4	30±1.5	30±1.1	20±2.6	35±0.6	25±03	15±0.4	20±0.2	20±0,3
3c	20±3.5	30±2.4	25±1.8*	15±2.5	30±1.5	25±3.5	20±1.5	15±2.6	20±1.6
4a	25±1.4	25±2.1	35±1.5	153.5±1.9	35±2.7	25±0.4	15±0.5	20±0.4	15±2.1*
4c	20±2.5	25±1.7	30±1.5	15±0.3	35±1.9	30±2.0	20±1.1	15±2.0	20±1.0
4d	20±1.9	25±2.9	30±2.7	15±1.8	35±2.5	25±1.7	15±2.8	20±1.7	20±2.7
4e	15±1.8*	25±3.2	30±3.1	15±2.0	30±1.6	25±2.5	20±1.8	10±2.0*	20±2.4
4f	25±1.2	30±2.7	30±2.8	10±1.6*	30±1.9	252.4±	15±3.8	20±2.1	25±2.9
Std	15±1.4[a]	20±2.5[a]	25±1.9[a]	10±1.1[b]	25±0.4[b]	20±0.9[b]	10±0.7[b]	10±0.71[b]	15±0.75[b]

[a] Ketoconazole, [b] Ampicillin

Value are mean ± SD, n=3, [a]P<0.05 versus isatin derivatives, [b]P<0.05 versus isatin derivatives, * Results are comparable to standard indicating non-significant difference, Remaining all are significantly different from standard.

A.n	=	Aspergillus niger
C.a	=	Candida albicans
T.v	=	Trichoderma viridae
S.a	=	Staphylococcus aureus
B.s	=	Bacillus subtilis
S.p	=	Streptococcus pyrogens
S.t	=	Salmonella typhimurium
E.c	=	Escherichia coli
K.pn	=	Klebsiella pneumoniae

Results and Discussion

Spectral analysis of N^1-[1-(4'-substituted benzyl)-5-(substituted-2-oxindolin-3- ylidine)-4-substituted benzohydrazide derivatives. [6,7]

The treatment of 5-substituted-indoline-2,3-dione (isatin) (1) with 4-substitutedbenzyl chloride in presence of Na_2CO_3 and dimethyl formamide (DMF) as a solvent yielded 1-(4-substituted benzyl)-5-substituted-indoline-2,3-dione (2). Different benzoyl hydrazides were reacted with compound (1) and (2) in presence of glacial acetic acid and ethanol as asolvent furnished the title compounds; 5-substituted-2-oxoindolin-3-ylidene]-4-substituted-benzohydrazide and N^1-[1-(4-substituted-benzyl)-5-substituted-2-oxoindolin-3-ylidene]-4-substituted-benzohydrazide (3a-c, 4a-f). It was noticeable that ketonic group (C=O) present at 3rd position of isatin is more compatible with the fusion of primary amine group (-NH_2) of hydrazide and the reaction is followed by elimination of water molecule, while the ketonic group (C=O) present at 2nd position is not usually involved for the fusion with amine group (-NH_2) because it acts as typical amide due to

the closer to nitrogen atom present in the indole ring. The structure elucidation of final derivatives was done by IR, ^{1}H-NMR and Mass spectroscopy. IR spectral peaks of the compound were recognized from 1708-1695 cm^{-1} for C=O stretching, 3360-3247 cm^{-1} for N-H stretching, 3086-2846 cm^{-1} for C-H aliphatic and aromatic. [8,9] In ^{1}H-NMR spectra typical proton signals for CH_3, CH_2, aromatic and N-H were observed around δ 2.2, 4.9, 6.6-8.0, 14, respectively. [10,11] In the mass spectral analysis of compound 4b, the Mass fragmentation pattern showed the appearanceof m/z peaks at 422[M+]. [12]

Spectral analysis of N^1-[1-(4'-substituted benzyl)-5-(substituted-2 xindolin-3- ylidineamino)-2,3-dihydro-2-phenylquinazolin-4-(4aH)-one derivatives. A new series of 5-(substituted-2-oxoindolin-3-ylidineamino)-2,3-dihydro-2-phenylquinazolin-4- (4aH)-one/ Synthesis of N^1-[1-(4'-substituted benzyl)-5-(substituted-2-oxoindolin-3-yli dineamino)-2,3-dihydro-2-phenylquin azolin-4-(4aH)-one, were designed and synthesized. In the reaction, the keto group of compound (1) and (2) reacted with the primary amine of quinazoline, at 3rd position with the elimination of water. This reaction also involved 3rd ketonic position (C=O) of isatin with the fusion of amine group (-NH_2) of quinazoline as ketonic group present at 2nd position act as typical amide. All final compounds (3a-c, 4a-f) were pure and stable. IR, ^{1}H-NMR and Mass spectroscopic techniques were used for the structure elucidation of the final compounds. IR spectral peaks of the compound were recognized from 1720-1705 cm^{-1} for C=O stretching, 3400-3200 cm^{-1} for N-H stretching, 3100-2850 cm^{-1} for C-H aliphatic and aromatic correspondently. In ^{1}H-NMR spectra typical proton signals for C-H aliphatic, aromatic and N-H were observed near 3.50-2.25, 8.10-6.25, 11.30-10.15 δ ppm and N-H protons were exchangeable with D_2O. [13-16]

Antibacterial and antifungal activity of N^1-[1-(4'-substituted benzyl)-5-(substituted-2-oxindolin-3-ylidine)-4-substituted benzohydrazide derivatives (3a-c, 4a-f)

All the newly synthesized 1,3,5-trisubstituted-2-oxindole derivatives incorporated with chemotherapeutic pharmacophores were examined for antibacterial and antifungal activities using invitro model. Screening at the Preliminary level was taken out for all the compounds amounting the antifungal activity in sabouraud agar medium against three fungal strains and antibacterial activity in the nutrient agar medium against six bacterial (three gram positive and three gram negative) strains by cup plate method at a fixed concentration of 1000 µg/ml. The zone of inhibition (mm) of each derivative was ascertained and compared with ketoconazole and ampicillin taken as a standard drug for fungi and bacteria respectively. DMSO was used to prepare stock solutions of tested derivatives. The findings of antimicrobial evaluation presented that most of the compounds have comparable activity against the bacterial and fungal strains. [17-20]

Antibacterial and antifungal activity of N^1-[1-(4'-substituted benzyl)-5-(substituted-2-oxindolin-3-ylidineamino)-2,3-dihydro-2-phenylquinazolin-4-(4aH)-one derivatives (3a-c,4a-f)

In scheme 2 all the newly synthesized 5-substituted-oxindole-3-amino-2-phenyl quinazoline derivatives (3a-c, 4a-f) were reported for their antifungal and antibacterial activity against some selected fungal and bacterial strains. The results of antimicrobial evaluation exerted that most of the compounds have significant activity against both fungal and bacterial strains. While performing the antimicrobial screening it was noticeable that among tested compounds, compound 3c and 4e containing electron withdrawing groups at 5th position (5-Fluro) andelectron donating group (-CH_3) at N-[(1-4th)] position were

marked the most active derivative against fungal strains in comparison to standard drug ketoconazole. Whereas 4f with electron withdrawing groups (-F, NO_2) at 5^{th} position and N-[(1-4^{th})] position was marked active derivative against gram (+) bacterial strains and 4a was pointed the most active derivative against gram (-) bacterial strains with the presence of electron withdrawing group (-NO_2) at 5^{th} position and electron donating group at N-[(1-4^{th})] position, in comparison to standard drug ampicillin. Compound 4c, 4d and 4e showed moderate antibacterial and compound 4d showed moderate antifungal activity against selected bacterial and fungal strains. [21]

MIC

Liquid dilution method was adopted to evaluate the minimum inhibitory concentration (MIC) of influential derivatives against all fungal and bacterial strains, the comparison of the derivatives which are tested was made against ampicillin and ketoconazole and measured as growth of microorganism in the form of turbidity. The tested derivatives revealed their MIC closer to standard drugs are known as potential derivatives.

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