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DESIGN, SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NEW ISATIN-MOXIFLOXACIN BASED 1,2,3-TRIAZOLE COMPOUND

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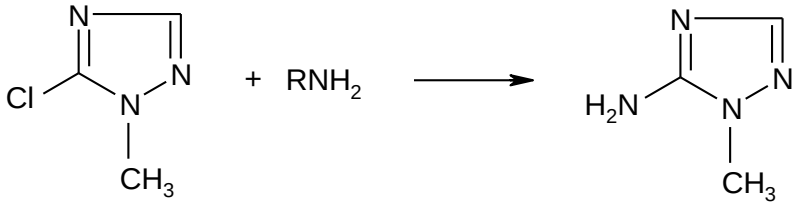
INTRODUCTION

Tuberculosis (TB) which is caused mainly by Mycobacterium tuberculosis (MTB), led to 1.3 million deaths and 10 million (5.8 million men, 3.2 million women, and 1.0 million children) newly clinical cases in the year of 2017 according to the World Health Organization (WHO) 2018 report. Moreover, the numbers are in continual increase, especially in developing countries. There are several reasons responsible for this situation, and the wide spread of drug-resistant TB (DR-TB), multidrug-resistant TB (MDR-TB), and coinfection with HIV, as well as the emergence of extensively drug-resistant TB (XDR-TB) and totally drug-resistant TB (TDR- TB) are the major reasons.

Normally it attacks thelungs (pulmonary TB) but can attack other organs as well (extrapulmonary TB) and spreads in the air when patients expel bacteria by coughing, sneezing, or spit. According to World Health Organization (WHO) report, 9.6 million new TB caseswere estimated and claiming the lives of 1.5 million people in the year 2014 despite the great advances in chemotherapy and the Bacille-Calmette-Guérin (BCG) vaccine.3 The current standard therapy attributed for TB is a six month regimen, termed DOTS (Directly Observed Therapy, Short-course) in which the initial 2 months include isoniazid (INH), rifampicin (RIF), pyrazinamide(PZA), and ethambutol (E), followed by a 4 month continuation phase of RIF and INH.

Furthermore, TB attracts numerous interests of the scientific community due to high weakness of human immunodeficiency virus (HIV)-infected persons to this disease and the global emergence of multidrug resistant (MDR) defined as resistant to the two most efficient TB drugs, rifampin and isoniazid, and extensively drug-resistant (XDR) strains thatare further resistant to the fluoroquinolones and one of the second-line injectable drugs (i.e. amikacin, kanamycin, or capreomycin). The confines of long-term oral chemotherapyand scarce compliance to the current treatment regimen, thediscovery of bedaquiline in the end of 2012, build a new hope for the treatment of TB and especially MDR-TB. Nevertheless the side effects of bedaquiline such as nausea, joint pain and headache create a risk in clinical use. Therefore, there is a still need for the development of new and effective antimycobacterials with reduced toxicity, synthetically feasible, stronger efficacy that function by novel mechanisms of action against emerging MDR and XDR TB bacteria and latent diseases in shorter treatment duration.



Acidity of Triazole: The acidity of five parent compounds is compared with that of pyrrole. The acidity of the ring system is increased as the number of nitrogens increases. The acidity of pyrrole is increases for each successive addition of a nitrogen atom. 1,2,3-triazoles is slightly more acidic than 1,2,4-triazoles.

Mechanism of action of Triazole

Triazoles act by inhibiting the fungal cytochrome P-450 enzyme lanosterol 14-demethylase and thus impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to the accumulation of 14-a-methylsterols. These methylsterols may disrupt the close packing of acyl chains of phospholipids, impairing the functions of certain membrane-bound enzyme systems such as ATPase and enzymes of the electron transport system and thus inhibiting growth of the fungi. The lower toxicity of triazoles compared to imidazole has been correlated with their lower affinity for mammalian Cytochrome P-450 and lesser propensity to inhibit mammalian sterol synthesis. However, because they are active against certain bacteria as well (which do not have ergosterol) other mechanism also appear to be involved.

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REVIEW OF LITERATURE

Prevention of diseases continues to be a challenge for the society and mankind as a whole due to some or other reasons, with respect to the development of the living conditions of human being and total mankind. There are number of diseases which spread due to one or other reasons. Some are communicable diseases eg. Tuberculosis. One of the main condition or factor responsible for the spread of disease(s) is the sanitary condition or hygiene. An increasing morbidity and mortality from tuberculosis (TB) in the near future is forecast for the world at large, with the number of newly occurring cases predicted to increase from 7.5 million a year in 1990 to 8.8, 10.2 ,11.9 and 31.8 million in the years 1995, 2002, 2005, 2006 respectively.

Tuberculosis (TB) is still a major health concern worldwide and the main cause of death by a single infectious agent, namely *Mycobacteriumtuberculosis*. The disease spreads more easily in overcrowded settings and in the conditions of malnutrition and poverty; characteristics typical of developing countries. India contributes nearly 25 percent of the global burden of tuberculosis, India recorded 1.9 million new cases in 2006 and an estimated 70,000 people detected with multi-drug resistant tuberculosis (MDR-TB) require quality second-line treatment in India. An increasing prevalence of multidrug resistance (MDR) in several parts of the world including India has been one of the major reasons for declaring tuberculosis (TB) control as a global emergency by WHO.

The reasons for these problems are numerous. Compliance with even the best available regimen is poor, and treatment failure is all too common. This regimen comprises daily isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) treatment for 2 months followed by 4 months of daily doses of INH and RIF To overcome this, the World Health Organization is encouraging widespread implementation of its DOTS (directly observed therapy, short course) strategy. Although existing drugs an often cure TB, the treatment is lengthy, and requires taking a combination of drugs for at least 6 months. However, the therapy is not always successful and often results in patient relapsing. Further, poor patient compliance has led to the emergence of drug-resistant TB, which is even more difficult to treat. The situation is further exacerbated by the emergence of HIV/AIDS, which is a serious risk factor for TB. The above facts indicate an urgent need for the development of novel, more effective drugs with potent sterilizing activity that would shorten the current treatment, and act on persistent and drug-resistant TB.

MATERIALS AND METHODS

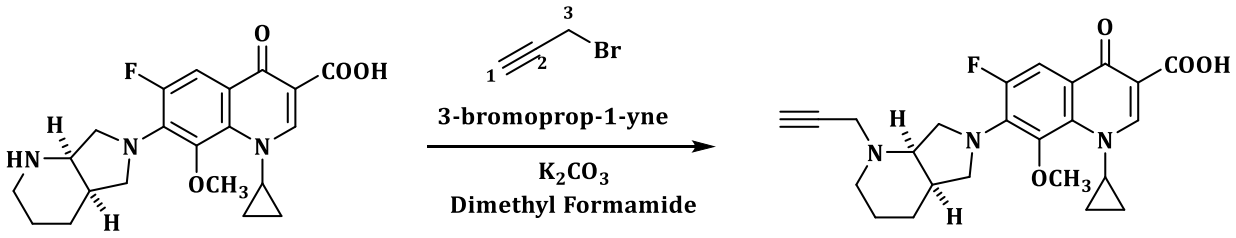
SYNTHESIS AND CHARACTERIZATION

REAGENT AND SOLVENT

The drugs Moxifloxacin, Isoniazid and Rifampicin was procured from Taj Pharmaceutical Pvt. Ltd, Mumbai. The 3-bromopropyne, Potassium carbonate and Dimethyl formamide was purchased from CDH, New Delhi. The 6-chloroindoline-2,3-dione, 6-bromoindoline-2,3-dione, 6-nitroindoline-2,3-dione, 6-methyloindoline-2,3-dione, 6-methoxyindoline-2,3-dione, 6-ethylindoline-2,3-dione and Sodium azide was purchased from Sigma Aldrich, Delhi.

SYNTHESIS

Synthesis Scheme-I



Moxifloxacin [1] **Propargyl Moxifloxacin [2]**

Table : List of the chemicals and their quantity used in Synthesis Scheme-I

S. No.	Chemical	Mol. wt. (g/mol)	Quantity taken (g)
1.	Moxifloxacin	401.18	4.01
2.	3-bromopropyne	118.60	1.18
3.	Potassium carbonate	138.20	1.38
4.	Dimethyl Formamide	73.10	0.73

Procedure

The moxifloxacin (0.01 M) was reacted with 3-bromopropyne (0.01 M) in the presence of potassium carbonate solution in water and Dimethyl formamide (DMF). The solution was refluxed for 45 minutes at 60˚C. The resultant was poured to ice cold water to precipitate the resultant product and filter out the product. The synthesized compound was further washed several times with distilled water.[56] The synthesized compounds propargyl moxifloxacin (Yield 72%) was recrystallized from ethanol and water (7:3%v/v). The List of chemical and quantity used in synthesis scheme-I was represented in Table 1.

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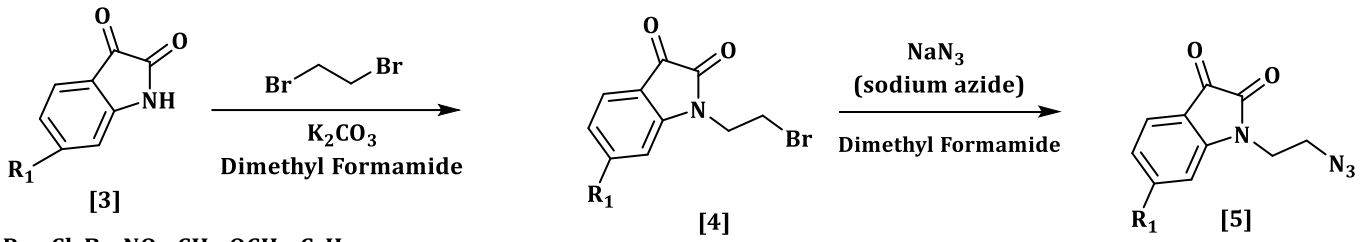
Synthesis Scheme-II



R_1= Cl, Br, NO_2, CH_3, OCH_3, C_2H_5,

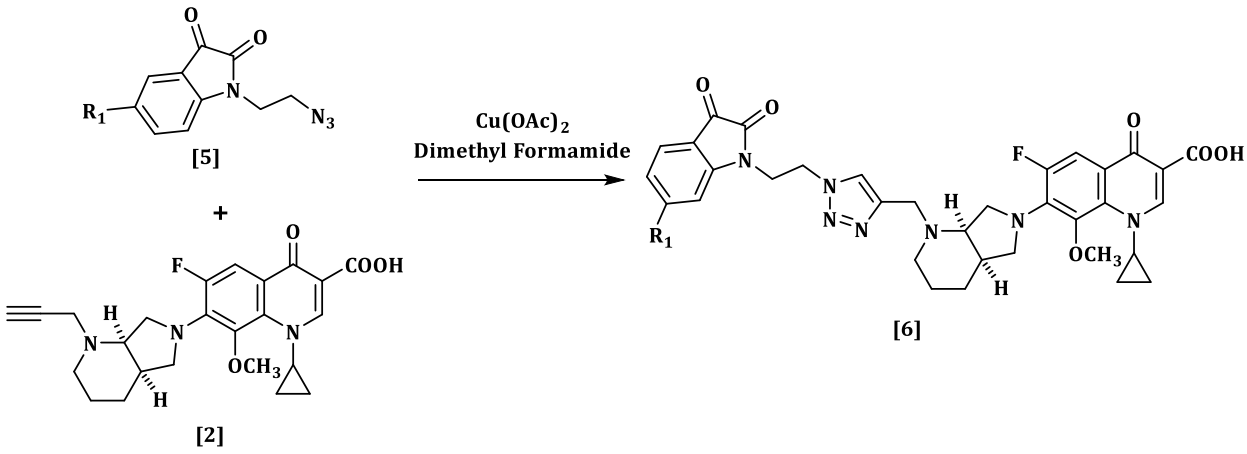
Table 1: List of the chemicals and their quantity used in Synthesis Scheme-II

S. No.	Chemical	Mol. wt. (g/mol)	Quantity taken (g)
1.	6-chloroindoline-2,3-dione	181.58	1.81
2.	6-bromoindoline-2,3-dione	226.03	2.26
3.	6-nitroindoline-2,3-dione	192.13	1.92
4.	6-methyloindoline-2,3-dione	147.18	1.47
5.	6-methoxyindoline-2,3-dione	177.17	1.77
6.	6-ethylindoline-2,3-dione	175.19	1.75
7.	Potassium carbonate	138.20	1.38
8.	Dimethyl Formamide	73.10	0.73
9.	Sodium azide	65.01	0.65

Procedure

The substituted indoline-2,3-dione derivatives [Compound 3, yield 62%] was reacted with the 1,2-dibromo methane in the presence of potassium carbonate solution and dimethyl formamide to form 1-(2-bromoethyl)-6-substituted indoline-2,3-dione [Compound 4, yield 55%]. The reaction was carried out at 60˚C. [57] The result product was filter and washed with cold water. The compounds 4, was further reacted with sodium azide and dimethyl formamide at 60˚C to form compound 5, 1-(2-azidoethyl)-6-substitutedindoline-2,3-dione, yield 78%) was filtered out and washed with cold water.The List of chemical and quantity used in synthesis scheme-II was represented in Table 2.

Synthesis Scheme-III



Procedure

To a mixture of N-(2-azidoethyl)-isatin (1-(2-azidoethyl)-6-substitutedindoline-2,3-dione) (0.01 M; 5) and propargyl moxifloxacin (0.01 M; 2) in Dimethyl formamide (50 ml), $Cu(OAc)_2$ (10 mg) was added under nitrogen atmosphere. The 1,2,3-triazole derivatives 6A to 6F (yield: 53-72%) via Cu-promoted azide–alkyne cycloaddition reaction in the presence of Cu(OAc)2 in dimethyl formamide (DMF).The mixture was allowed to react for 48 hrs. at room temperature and after removal of the solvent, the residual product [6] was purified by silica gel column chromatography eluted with DCM: MeOH (10:1). The List of chemical and quantity used in synthesis scheme-III was represented in Table 3.

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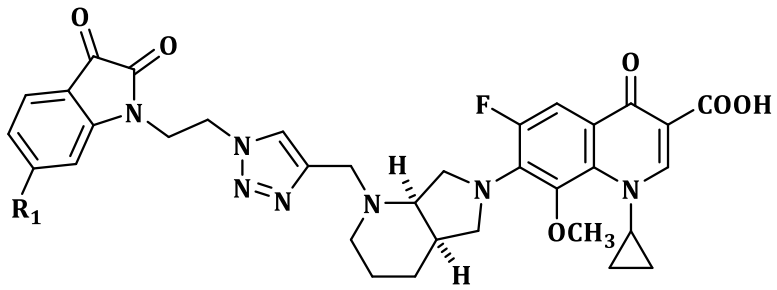
Table 4.3: List of the chemicals and their quantity used in Synthesis Scheme-III

S. No.	Chemical	Mol. wt. (g/mol)	Quantity taken (g)
1.	Propargyl Moxifloxacin	439.49	4.39
2.	1-(2-azidoethyl)-6-chloroindoline-2,3-dione	250.64	2.50
3.	1-(2-azidoethyl)-6-bromoindoline-2,3-dione	295.10	2.95
4.	1-(2-azidoethyl)-6-nitroindoline-2,3-dione	261.20	2.61
5.	1-(2-azidoethyl)-6-methylindoline-2,3-dione	230.23	2.30
6.	1-(2-azidoethyl)-6-methoxyindoline-2,3-dione	246.23	2.46
7.	1-(2-azidoethyl)-6-ethylindoline-2,3-dione	244.25	2.44

List of Final Synthesized Compounds



R_1= Cl, Br, NO_2, CH_3, OCH_3, C_2H_5

List of the synthesized compounds with chemical name

1. **6A:**7-((4aR,7aR)-1-((1-(2-(6-chloro-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-1-cyclopropyl-6-fluoro-8- methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
2. **6B:**7-((4aR,7aR)-1-((1-(2-(6-bromo-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl) methyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
3. **6C:**1-cyclopropyl-6-fluoro-8-methoxy-7-((4aR,7aR)-1-((1-(2-(6-nitro-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
4. **6D:**1-cyclopropyl-6-fluoro-8-methoxy-7-((4aR,7aR)-1-((1-(2-(6-methyl-2,3-dioxo indolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
5. **6E:**1-cyclopropyl-6-fluoro-8-methoxy-7-((4aR,7aR)-1-((1-(2-(6-methoxy-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
6. **6F:**1-cyclopropyl-7-((4aR,7aR)-1-((1-(2-(6-ethyl-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

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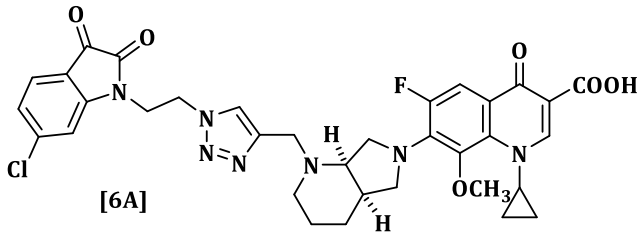
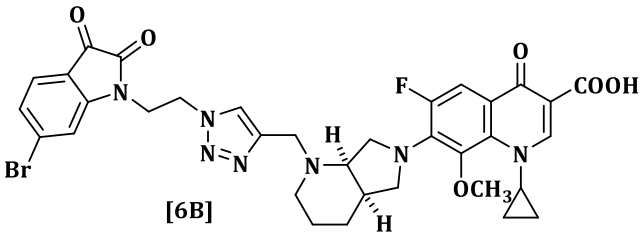
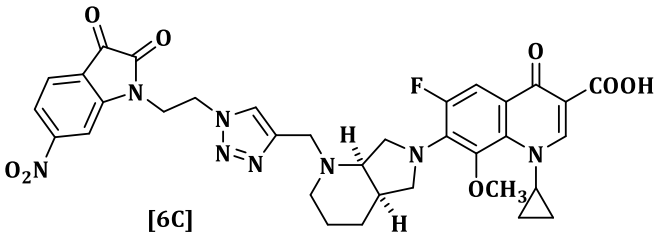


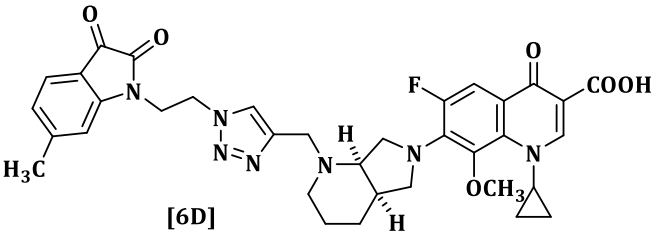
[6A]



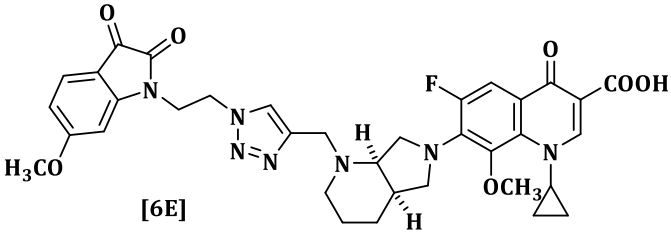
[6B]



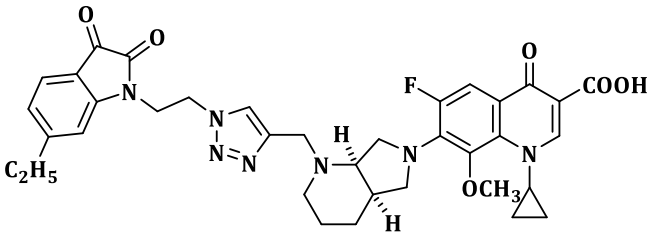
[6C]



[6D]



[6E]



[6F]

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Physicochemical Characterization

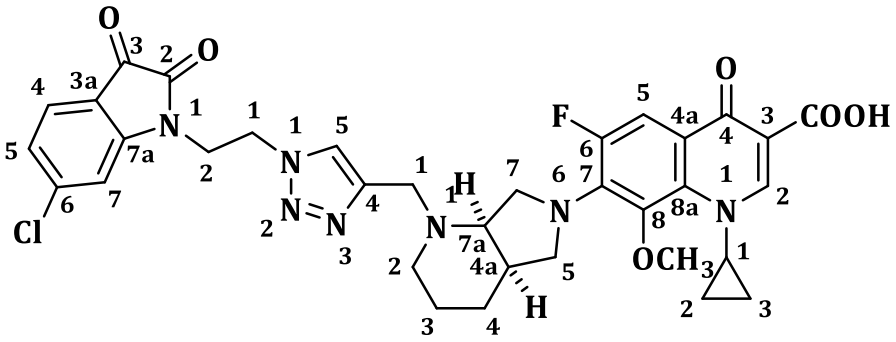
Table : Physicochemical properties of the synthesized compounds

Comp.	% Yield	Physical Appearance		Melting Point (˚c)	Rf Value
		Color	State		
6A	72	Light yellow solid	Solid	170-172°C	0.62
6B	53	Yellow	Solid	143-145°C	0.58
6C	60	Deep Yellow	Solid	160-162°C	0.55
6D	65	Light Yellow	Solid	174-176°C	0.64
6E	68	Yellow	Solid	156-158°C	0.52
6F	58	Yellow	Solid	160-162°C	0.33

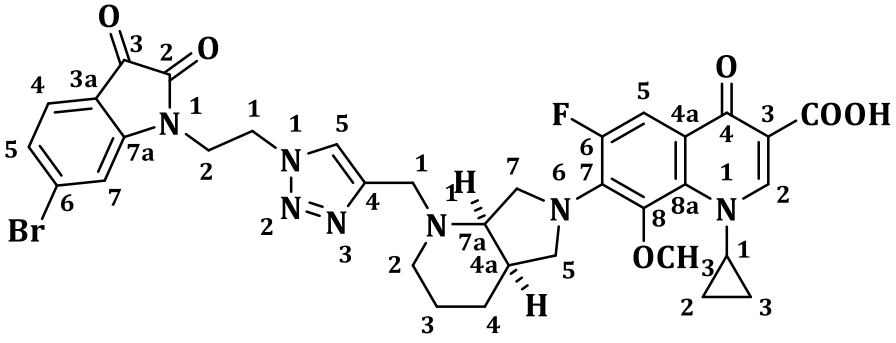
Table : Solubility studies of the synthesized compounds

Compound	Water	Alcohol	Acetone	Glacial Acetic Acid	Benzene	Dimethyl Sulfoxide
6A	-	+++	+	++	-	++
6B	-	+++	+	++	-	++
6C	-	+++	+	++	-	++
6D	-	+++	+	++	-	++
6E	-	+++	+	++	-	++
6F	-	+++	+	++	-	++

- Insoluble; + = Slightly soluble; ++ = soluble; +++ = Freely soluble
- **Spectroscopic analysis of Compounds by IR and ^{1}HNMR**
- **Compound 6A**



- **IUPAC name:** 7-((4aR,7aR)-1-((1-(2-(6-chloro-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
- **Chemical Formula:** $C_{34}H_{33}ClFN_7O_6$
- **Molecular Weight:** 690.13; m/z: 689.22 (100.0%)
- **Elemental Analysis:** C (59.17%); H (4.82%); N (14.21%); O (13.91%)
- **Log P:** 3.04
- **^{1}HNMR (400 MHz; DMSO-d6, ppm):** 2.65–2.70 (m, 1H), 2.77–2.79 (m, 1H), 3.55–3.81 (m, 8H), 4.12–4.15 (m, 3H), 4.25 (s, 3H, NOCH3), 4.66–4.68 (m, 2H), 6.88 (d, 1H, Ar–H), 7.12 (d, 1H, Ar-H), 7.58–7.60 (m, 2H, Ar–H), 7.88 (1H, s, triazole-H), 8.64 (1H, s, C2–H), 15.20 (1H, brs, COOH).
- **Compound 6B**



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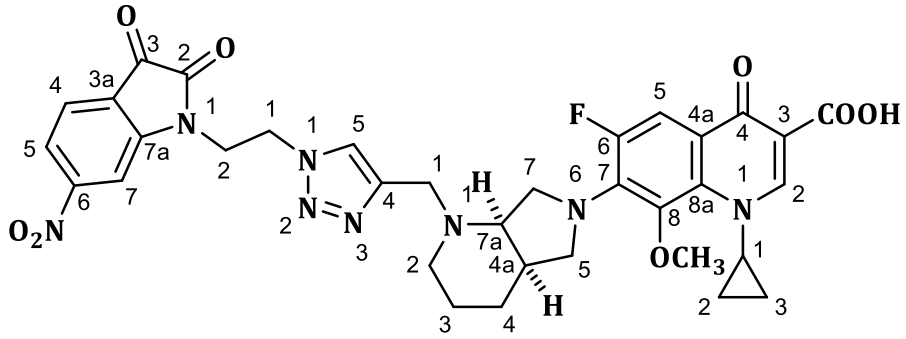
- **IUPAC NAME:** 7-((4aR,7aR)-1-((1-(2-(6-bromo-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
- **Chemical Formula:** $C_{34}H_{33}BrFN_7O_6$
- **Molecular Weight:** 734.58**; m/z: 733.17 (100.0%)**
- **Elemental Analysis:** C (55.59%); H (4.53%); N (13.35%); O (13.07%)
- **Log P:** 3.31
- **^{1}HNMR (400 MHz; DMSO-d6, ppm):** δ 0.96–1.62 (m, 9H), 2.03–2.09 (m, 1H), 2.38–2.40 (m, 1H), 2.56–2.58 (m, 1H), 2.76–2.79 (m, 1H), 3.56–3.88 (m, 11H), 4.11–4.13 (m, 3H), 4.60–4.62 (m, 2H), 6.80 (d, 1H, Ar–H), 7.10 (d, 1H, Ar–H), 7.61–7.62 (m, 1H, Ar–H), 7.69 (d, 1H, Ar–H), 7.87 (1H, s, triazole-H), 8.66 (1H, s, C2-H), 13.52 (1H, brs, NOH), 15.29 (1H, brs, COOH).

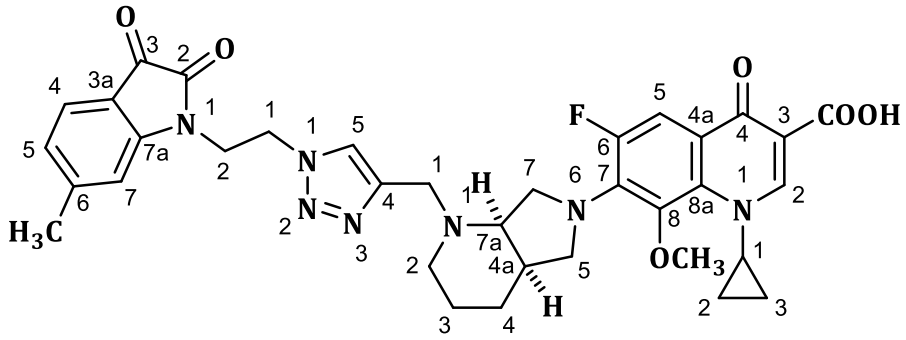
Compound 6C



IUPAC NAME: 1-cyclopropyl-6-fluoro-8-methoxy-7-((4aR,7aR)-1-((1-(2-(6-nitro-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
Chemical Formula: $C_{34}H_{33}FN_8O_8$
Molecular Weight: 700.68; m/z: 700.24 (100.0%)
Elemental Analysis: C (58.28%); H (4.75%); N (15.99%); O (18.27%)
Log P: 3.97

^{1}HNMR (400 MHz; DMSO-d6, ppm):δ 1.00–1.57 (m, 9H, 2.07–2.09 (m, 1H), 2.38–2.39 (m, 1H), 2.64–2.66 (m, 1H), 2.72–2.76 (m, 1H), 3.58–3.83 (m, 8H), 4.10–4.13 (m, 3H), 4.60–4.62 (m, 2H), 6.90 (s, 1H, Ar–H), 7.27 (s, 1H, Ar–H), 7.54 (d, 1H, Ar–H), 7.88 (1H, s, triazole-H), 8.64 (1H, s, C2–H), 8.68, 9.01 (s, 1H, CONH2), 12.17 (s, 1H, NNHCO), 15.21 (1H, brs, COOH).

Compound 6D



IUPAC NAME: 1-cyclopropyl-6-fluoro-8-methoxy-7-((4aR,7aR)-1-((1-(2-(6-methyl-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
Chemical Formula: $C_{35}H_{36}FN_7O_6$
Molecular Weight: 669.71; m/z: 669.27 (100.0%)
Elemental Analysis: C (62.77%); H (5.42%); N (14.64%); O (14.33%)
Log P: 2.97
^{1}HNMR (400 MHz; DMSO-d6, ppm): δ1.03–1.55 (m, 9H), 2.04–2.06 (m, 1H), 2.36–2.39 (m, 17H), 2.51 (s, 3H, CH_3); 2.66–2.68 (m, 1H), 2.75–2.78 (m, 1H), 3.55–3.81 (m, 11H), 4.11–4.14 (m, 3H), 4.61–4.62 (m, 2H), 6.88 (s, 1H, Ar–H), 7.34 (s, 1H, Ar–H),

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Volume: 10| Issue: 3| March 2024|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2024: 8.402 || ISI Value: 1.188

7.65 (d, 1H, Ar–H), 7.83 (1H, s, triazole-H), 8.67 (1H, s, C2–H), 8.69, 9.00 (s, 1H, CONH2), 12.16 (s, 1H, NNHCO), 15.26 (1H, brs, COOH).

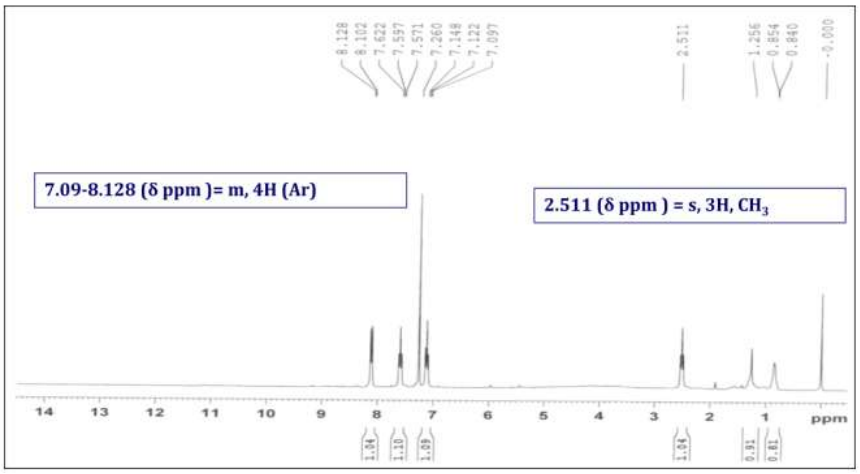
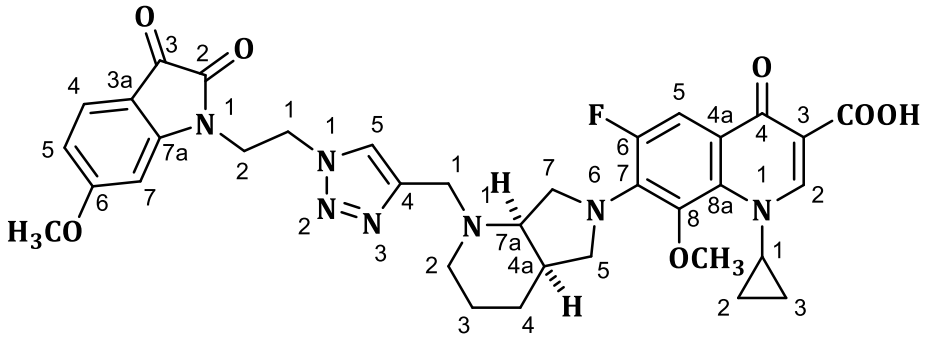


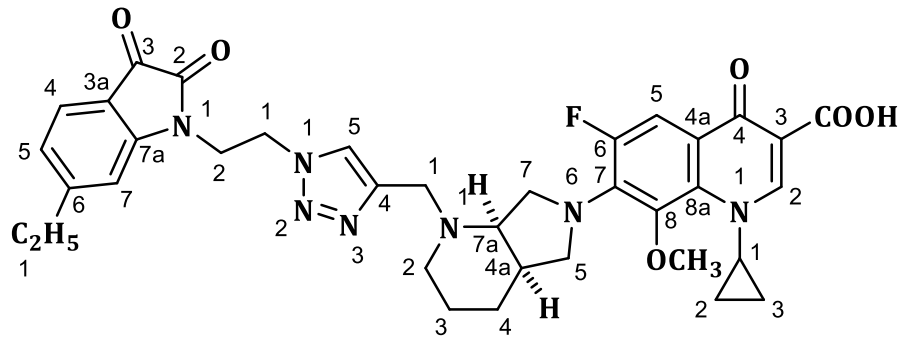
Figure 4.1: IR spectrum of compound 6D

Compound 6E



IUPAC NAME: 1-cyclopropyl-6-fluoro-8-methoxy-7-((4aR,7aR)-1-((1-(2-(6-methoxy-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
Chemical Formula: $C_{35}H_{36}FN_7O_7$
Molecular Weight: 685.71; **m/z: 685.27 (100.0%)**
Elemental Analysis: C (61.31%); H (5.29%); N (14.30%); O (16.33%)
Log P: 2.36
^{1}HNMR (400 MHz; DMSO-d6, ppm): δ 1.01–1.64 (m, 9H), 2.11–2.13 (m, 1H), 2.36–2.38 (m, 1H), 2.65–2.74 (m, 1H), 2.83–2.85 (m, 1H), 3.59–3.85 (m, 11H), 4.14–4.17 (m, 3H), 4.24 (s, 3H, NOCH3), 4.65–4.67 (m, 2H), 6.79–7.04 (m, 2H, Ar–H), 7.47 (d, 1H, Ar–H), 7.71 (d, 1H, ArH), 7.91; (1H, s, triazole–H), 8.71 (1H, s, C2–H), 15.28 (1H, brs, COOH).

Compound 6F



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Volume: 10| Issue: 3| March 2024|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2024: 8.402 || ISI Value: 1.188

IUPACNAME:1-cyclopropyl-7-((4aR,7aR)-1-((1-(2-(6-ethyl-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
Chemical Formula: $C_{36}H_{38}FN_7O_6$
Molecular Weight: 683.74; m/z: 683.29 (100.0%)
Elemental Analysis: C (63.24%); H (5.60%); N (14.34%); O (14.04%)
Log P: 3.39
^{1}HNMR(400MHz;DMSO-d6,ppm):δ0.95–1.57(m,9H),2.06–2.08(m,1H),2.31–2.34 (m, 1H), 2.58–2.60 (m, 1H), 2.82–2.84 (m, 1H), 3.54–3.79 (m, 8H), 4.09–4.12 (m, 3H), 4.59–4.61 (m, 2H), 6.93 (d, 1H, Ar–H), 7.42–7.47 (m, 2H, Ar–H), 7.61 (d, 1H, Ar-H), 7.98 (1H, s, triazole-H), 8.65 (1H, s, C2-H), 15.26 (1H, brs, COOH).

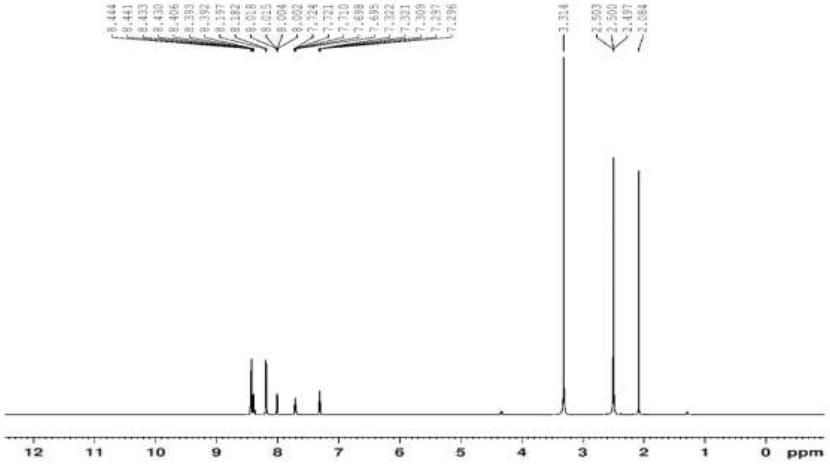

Figure 4.2: IR spectrum of compound 6F

DISCUSSION

The six new derivatives of 1,2,3-triazole derivatives has been synthesized and characterized by Proton Nuclear Resonance Spectrophotometer (^{1}HNMR). ^{1}HNMR spectrum of the synthesized compounds has shown the peaks at ppm δ 0.95–1.57 (m, 9H), 2.06–2.08 (m, 1H), 2.31–2.34 (m, 1H), 2.58–2.60 (m, 1H), 2.82–2.84 (m, 1H), 3.54–3.79 (m, 8H), 4.09–4.12 (m, 3H), 4.59–4.61 (m, 2H), 6.93 (d, 1H, Ar–H), 7.42–7.47 (m, 2H, Ar–H), 7.61 (d, 1H, Ar-H), 7.98 (1H, s, triazole-H), 8.65 (1H, s, C2-H), 15.26 (1H, brs, COOH). The melting point was in the ranges of 140 ˚C to 176˚C of Thin layer chromatography was performed for every individual process and has shown the Retention factor less than 0.7. These all the characterized parameter depicted that compound were synthesized as per expected and confirmed by ^{1}HNMR analysis.

ANTIMICROBIAL EVALUATION

Microbiology is the study of microscopic organisms such as bacteria, viruses, fungi and protozoa. This discipline includes fundamental research on the biochemistry, physiology, cell biology, ecology, evolution and clinical aspects of microorganisms, including the host response to these agents. Bacterial resistance to existing drugs is a growing problem in the world. Considerable researches have been performed on the synthesis of new quinazolinone derivatives with potent antimicrobial activity. These derivatives possess antibacterial activities, especially against the gram-positive strains, and fungi through their interaction with the cell wall and DNA structure. The term chemotherapeutic agents were initially restricted to antibiotics, but now since microbial metabolites have been isolated for their antimicrobial activity. Hence both synthetic and microbiologically produced drugs need to be included together. However, it would be more meaningful to use the term Anti-microbial agent (AMA) to designate synthetic as well as naturally obtained drugs that attenuate microorganisms.

The antimicrobial drugs occupy uniqueness in the history of medicine. During the entire proceeding history of medicine, less than a handful of drugs had been submitted to systemic laboratory investigation. The exponential development in the antibacterial field is the inevitable result of the momentum created by sulfonamides and penicillin [96]. The term microbe is sometimes applied only to the unicellular microphytes. However, in its broader sense it includes multicellular microphytes and microbes as well therefore antimicrobial studies include antibacterial, antifungal, antiprotozoal and antimycotic studies. After the development of desired new drug molecules with different structure an antimicrobial screening program is necessary to uncover the interesting activity of the

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compounds. The inhibition of the microbial growth under standardized condition may be utilized for demonstrating the therapeutic efficacy of the synthesized compounds.

Microorganisms inhabit various sites of the human body, including the skin, nose, mouth and digestive gut. Drugs which are helpful in combating the infectious disease caused by microbes are known as antimicrobial agent. Therefore, it was thought worthwhile to explore out the possibility of the compounds of the present series to be effective antimicrobial agent.

Table 5.1: List of Fungal Strains

S. No.	Fungal strain	MTCC* No.	Incubation Temperature (ºC)	Incubation period
1.	*Aspergillus Niger*	281	25	5 days
2.	*Candida albicans*	227	25	2 days

*Procured from IMTECH Chandigarh.

EXPERIMENTAL

Preparation of Solution of Standard Drug

A stock solution of Fluconazole (1 mg/ml) was prepared in DMF and further diluted as reported for antibacterial studies.

Preparation of solution of the synthesized compounds

The solutions were prepared in the same way as mentioned under antibacterial screening. All those compounds screened earlier for antibacterial activity were also tested for their antifungal activity. The fungi employed for the screening were *Aspergillus Niger* and *Candida albicans*. Fluconazole (2-(2,4-difluorophenyl)-1,3-di(1H-1,2,4-triazol-1-yl)propan-2-ol) (Figure 5.1) was employed as standard to compare the results. The test organisms were sub-cultured using Potato-DextroseAgar (PDA) medium

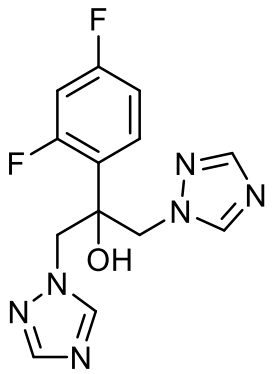

Figure 5.1: Chemical structure of Fluconazole

The tubes containing sterilized medium were inoculated with test fungi and kept at room temperature for obtaining growth. After that, they were stored at 4ºC in a refrigerator. The activity of the derivatives was performed by Agar diffusion-based cup plate method at different concentration level. Fluconazole was used as standard drug at concentration remains same. Fluconazole solution prepared at a concentration of 1000 g/ml in sterilized distilled water.

RESULT AND DISCUSSION

Antifungal Activity

The antifungal activity result stated that all synthesized compounds (6A-6F) of isatin-moxifloxacin based 1,2,3-triazole derivatives have shown good to moderate activity against tested organisms and was shown in Table 5.1.

Antifungal activity of synthesized 1,2,3-triazoles derivatives.

COMPOUND	Zone inhibition (mm)			
	C. Albicans		*A. Niger*	
Concentration	**50**	**100**	**50**	**100**
6A	14.75±0.53	27.65±0.43	23.34±0.28	28.25±0.32
6B	8.32±0.33	12.72±0.34	14.52±0.26	17.64±0.32
6C	16.72±0.34	29.32±0.26	19.62±0.23	29.72±0.18
6D	10.45±0.28	22.20±0.22	22.23±0.43	24.35±0.25
6E	9.22±0.65	25.25±0.34	18.42±0.46	21.55±0.12
6F	9.64±0.88	15.32±0.44	16.65±0.16	20.52±0.12
DMSO (Control)	-	-	-	-
Fluconazole	25.30 ±0.32	30.25±0.26	24.25±0.32	29.20±0.23

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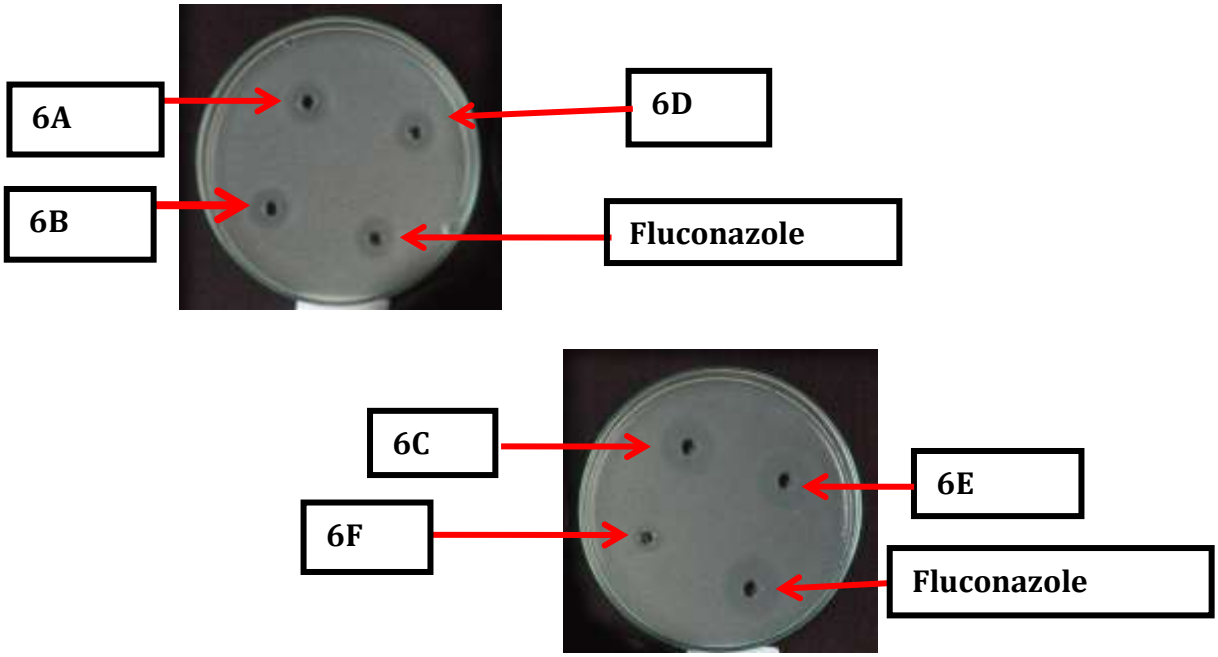

Figure 5.2: Zone inhibition against *C. Albicans*

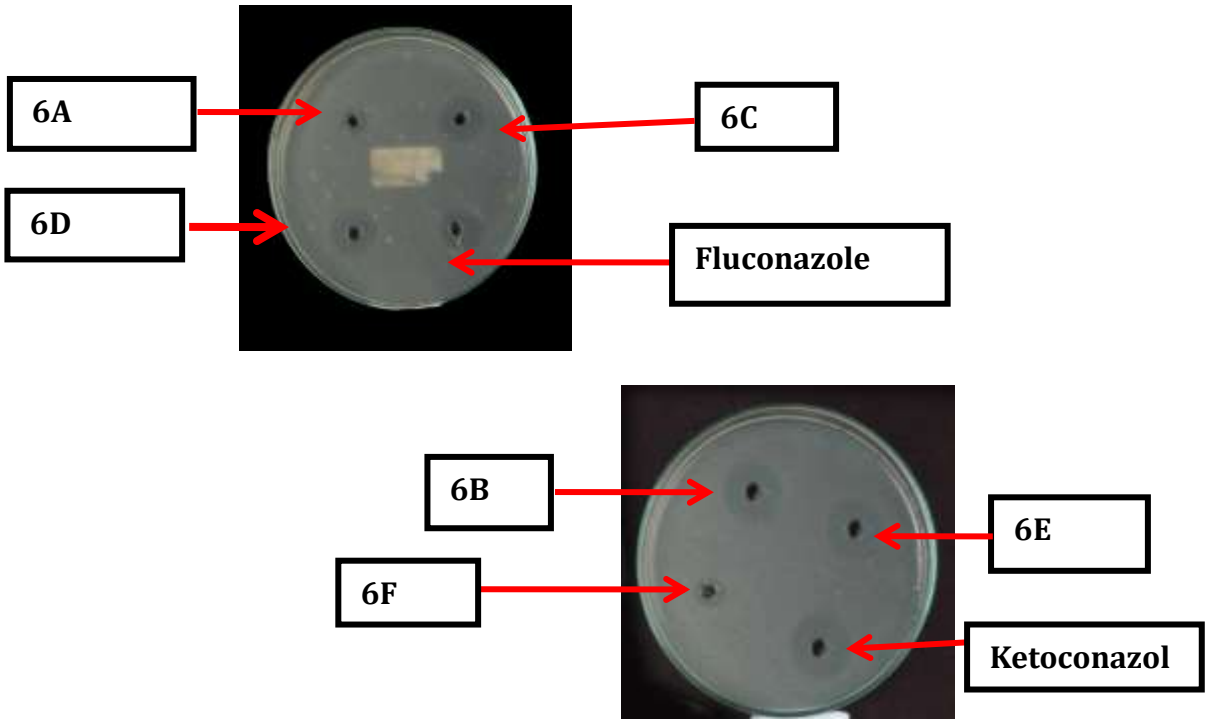

Figure: Zone inhibition against *A. Niger*

Discussion

The six new derivatives of 1,2,3-triazoles derivatives has been synthesized and evaluated for their antifungal activity against two fungal strains using Agar diffusion method. The Fluconazole was used as standard to compare the antifungal potency of the synthesized compounds. The antifungal activity data of 1,2,3-triazoles derivatives (6A-6F) signifies that inhibitory action on fungal strains at 50 µg and 100 µg drug concentration as compared with standard. The compounds 6A and 6C possessed maximum activity in fungal strains.

SUMMARY AND CONCLUSION

The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating disease. Most of the activity in this discipline is directed to the new natural or synthetic organic compounds, organic compounds have a major place in

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therapy and they being with increasingly specific pharmacological activities are clearly the dominant force. Thousands of organic chemicals are prepared annually throughout the world, and many of them enter into pharmacological screening to determine if they have useful biological activity. Among these organic chemicals, heterocyclic nucleus containing compounds occupy a major portion.

The thesis work is broadly classified into two section. In this section, detailed methods and procedures for synthesis of various 1,2,3-triazole derivatives along with their purification and physicochemical parameters had given. Literature is flooded with reference to show the efficacy of substituted 1,2,3-triazole with N-(2-azidoethyl)-isatin (1-(2-azidoethyl)-6-substitutedindoline-2,3-dione) and propargyl moxifloxacin was used to synthesized the compound,1-cyclopropyl-6-fluoro-8-methoxy-7-((4aR,7aR)-1-((1-(2-(6-nitro-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl) octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid as potent medicinal agents for various pharmacological activities like antibacterial, antifungal and antitubercular etc.

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