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Synthesis and Evaluation of N^1-(Aryl methylene)-2-(naphthalen-2-yloxy) acetohydrazides as antimicrobial and antimycobacterial Agents

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ABSTRACT: Naphthalenes are used as anti-fungal, anti-inflammatory, anti-cancer,anti-microbial, anti-tubercularagents etc.Naphthalene derivative (Bedaquiline) shows anti mycobacterial activity by inhibiting ATP synthase enzyme of Mycobacterium tuberculosis.[1]
Naphthalenes have been identified as new range of potent antimicrobials effective against wide range of human pathogens. They occupy a central place among medicinally important compounds due to their diverse and interesting antibiotic properties with minimum toxicity. Several naphthalene containing drugs antimicrobial agents are available at present in market such as bedaquiline, naftifine , tolnaftate , terbinafine, etc., which play vital role in the control of microbial infection[2]. Naphthalene is a basic framework in several natural products namely, rumexneposides A and B, naphthalenones, naphthoquinones, naphthalecin, naphthaquinones like 3,3-plumbagin and maritinone[3].
Objective: To Synthesize and Evaluate of N^1-(Aryl methylene)-2-(naphthalen-2-yloxy) acetohydrazides derivatives recrystallized, characterized by m.p, R_f, FTIR, H^1 NMR Data.
Methods: The molecular property prediction of all the synthesized compounds by using Lipinski's rule of 5, PASS, OSIRIS molecular property explorer, Mol soft.The all compounds were synthesized by conventional method. The synthesized compounds were evaluated antibacterial activity by using cup plate method, MIC & Antifungal activity. Results: All the compounds show the good percentage yields. All the compounds obeys the Lipinski's rule, non-toxic, drug likeness. All the compounds shows antibacterial, antifungul activity.Conclusion: compound 7b with 2-furanyl group exhibited highest potency against E.coli with zone of inhibition of 14mm compared to 16mm shown by the standard Moxifloxacin at 50µg/ ml concentration. Compound 7c with 2-thienyl group next in the order of potency with 13mm zone of inhibition.Compound 7d with phenyl substitution (Ar=phenyl) has been found to be the least potent (zone of inhibition=10mm at 50 µg/ ml,Compound 7b is also found to be the most potent against K. pneumonia, B. substilis and S. aureus with zones of inhibition of 14, 10 and 12 mm against 16,14 and 14 mm shown by the standard Moxifloxacin at 50 µg/ ml concentration.The compounds (7a-7e) show 8–12 mm poor antifungal activity, 13–16 mm moderate antifungal activity and 18-23 mm significant antifungal activity.
Key words:2-(naphthalen-2-yloxy) acetohydrazide derivatives, Antibacterial activity, Anti fungal activity, Ketoconazole, Moxifloxicin, Schiff base.

I.INTRODUCTION:

Tuberculosis is a contagious disease transmitted through the air caused by the bacterium Mycobacterium tuberculosis. It is important worldwide public health problem, which was declared as a global health emergency in 1993 by the WHO.According to statistics 1/3rd of the world's population is currently infected with the TB bacillus.Each year 8 million people get infected worldwide developing active TB (1.7 million deaths)Currently important problem in TB treatment is the Development of multi drug resistant tuberculosis.MDR (multidrug resistance), XDR (extensively drug resistance) in TB treatment. Hence,There is a need to develop new drugs and strategies to treat this drug resistant TB effectively.[4]Recently published studies and a systematic review have shown that XDR-TB is associated with higher probability of failure and death, and lower probability of treatment success than MDR-TB[5].

Heterocyclic compounds are widely distributed in nature and play a diverse and important role in the field of Pharmaceutical chemistry. Heterocyclic chemistry has now become

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a separate field of chemistry with long history, present society and future prospects. The earliest compounds known to mankind were of heterocyclic origin. Life, like ours, is totally dependent on the heterocyclic compounds, it takes birth with purine /pyrimidine bases, nourishes on carbohydrates and in case of disease, is cured from medicines, many of which are heterocyclic in nature. Today, the heterocyclic chemistry delivers reagents and synthetic methods of its own traditional activity in synthesis of drugs, pesticides and detergents as well as into the related fields such as biochemistry, polymers and material sciences. They are also used as optical brightening agents, antioxidants, co-polymers, solvents, photographic sensitizers, corrosion inhibitors and additives, dye stuffs and pigments. Heterocyclic compounds are also finding an increasing use as intermediates in organic synthesis. Heterocyclic compounds and aromatic organic compounds like heterocyclic aldehydes and naphthalene with several of its derivatives exhibited diversified biological activity.

Politicians and public health officials have joined specialist professionals in recognizing antibiotic resistance as a threat to modern medicine. Their response has centered on minimizing unnecessary antibiotic prescribing, aiming to reduce selection pressure for resistance. Despite a few hopeful trends, established resistance is proving hard to displace; moreover, new resistances continue to emerge and to proliferate at new sites. There consequently remains a strong need for new antibiotics, particularly those directed against multiresistant Gram-negative bacteria in hospitals. Already some non-fermenters of the genera Acinetobacter and Pseudomonas are resistant to all good antibiotics and many Enterobacteriaceae are resistant to all except carbapenems. There is also a growing need for new agents against community-acquired pathogens, including the agents of tuberculosis, gonorrhoea and urinary tract infections. Unless antibacterial development is re-energized, there is a serious risk that a growing proportion of infections, especially in hospitals, will become effectively untreatable[6].

Generally, TB therapy is based on the combination of four drugs, rifampicin, isoniazid, ethambutol (EMB) and pyrazinamide (PZA) for 2 months, followed by rifampicin and isoniazid for 4 months. Unfortunately, poor patient compliance, as well as inadequate health care specialized structures, favored the selection of MDR-TB treatment that includesusage of second line drugs (bedaquilin, fluoroquinolones, amikacin, kanamycin and capreomycin) for at least 20 months, which are more toxic and less efficient, with cure rates are in the range of 60–75%.MDR-TB are strains resistant to the most potent first-line drugs, rifampicin and isoniazid. In 2012, 4,50,000 people developed MDR-TB in the world. It is estimated that about 9.6% of these cases were extensively-drug-resistant (XDR-TB), showing additional resistance to at least one fluoroquinolone and one injectable drug (bedaquilin, amikacin, kanamycin or capreomycin).For patients affected by XDR-TB, the therapeutic efficacy is quite limited. Therefore, new anti-tubercular drugs, as well as novel TB targets, are urgently required to overcome the problem of drug resistance and to finally eradicate TB[7]

Naphthalene is a basic framework in several natural products namely,rumexneposides A and B, naphthalenones,naphthoquinones, naphthalecin, naphthaquinones like 3,3’-plumbagin and maritinone[8].

Synthetic naphthalene based compounds manifests a number of importantand therapeutically useful biological activities like antimicrobial, cytotoxicity, antimycobacterial, antimalarial, anticonvulsant, anti-inflammatory, cardiovascular agent, non-steriodal oestrogen. Some of the synthetic compounds containingnaphthalene moiety are propranolol, naphazoline(cardiovascular agent), naproxen , nabumetone (an anti-inflammatory agent), methallenestril**,** nafacilline(non-steroidal oestrogen).[9]

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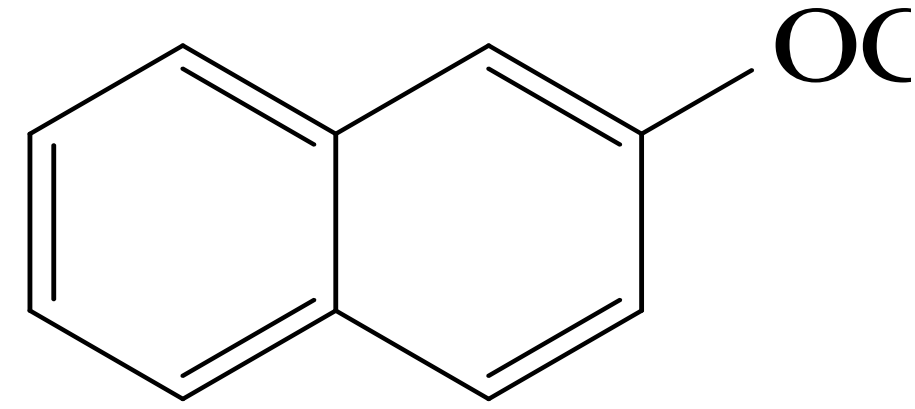
II.MATERIALS AND METHODS:

In view of the biological importance of the naphthalene and heterocyclic aldehydes it was planned to synthesize 2-(naphthalen-2-yloxy)-N-(substituted aldehydes) aceto-hydrazides and to screen them for antimicrobial activity. [10,12]

STEP -1: Preparation of ethyl 2-(naphthalen-2-yloxy) acetate

STEP -2: Preparation of 2-(naphthalen-2-yloxy) acetohydrazide



STEP -3: Preparation of 2-(naphthalen-2-yloxy) acetohydrazide derivatives

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Table-1: Physical data of 2-(naphthalen-2-yloxy) acetohydrazide derivatives

COMPOUND	Molecular weight	Molecular formula	Melting Point range (°C)	% yield	R_f (hexane: ethyl acetate 7:3)
7a	338.79	$C_{19}H_{15}ClN_2O_2$	154-156 °C	45	0.45
7b	294.30	$C_{17}H_{14}N_2O_3$	135-138 °C	60	0.46
7c	310.37	$C_{17}H_{14}N_2O_2S$	160-161 °C	55	0.44
7d	304.34	$C_{19}H_{16}N_2O_2$	177-179 °C	48	0.28
7e	**364.39**	**$C_{21}H_{20}N_2O_4$**	**160-161 °C**	**52**	**0.47**

III. RESULTS AND DISCUSSION

The synthesized compounds are purified by column chromatography. All new compounds are characterized by the analytical and spectral (IR, ^{1}H NMR and Mass) data. The compounds synthesized are evaluated for anti microbial activity.

When the two moieties are fused or combined and screened for antibacterial studies they showed moderate to strong antibacterial activity against Gram positive and Gram negative bacteria. It is clearly concluded that the synthesized compounds with substitution of 2-(naphthalen-2-yloxy) acetohydrazide and heterocyclic aldehyde conjugation showed potent antibacterial activity against Gram positive and Gram negative bacteria.

Among the series, compound 7b with 2-furanyl group exhibited highest potency against E.coli with zone of inhibition of 14mm compared to 16mm shown by the standard Moxifloxacin at 50µg/ ml concentration. Compound 7c with 2-thienyl group next in the order of potency with 13mm zone of inhibition.Compound 7d with phenyl substitution (Ar=phenyl) has been found to be the least potent (zone of inhibition=10mm at 50 µg/ ml.

Compound 7b is also found to be the most potent against K. pneumonia, B. substilis and S. aureus with zones of inhibition of 14, 10 and 12 mm against 16,14 and 14 mm shown by the standard Moxifloxacin at 50 µg/ ml concentration.

The compounds (7a-7e) show 8–12 mm poor antifungal activity, 13–16 mm moderate antifungal activity and 18-23 mm significant antifungal activity.

Antibacterial activity:

Antibacterial activity of substituted **2-(naphthalen-2-yloxy)-N-(aldehyde-2-yl methylene) acetohydrazide** against Gram-negative bacteria at various concentrations on different strains of bacteria.[11]

Table-2: Antibacterial activity against E. coli - (Zones of inhibition in mm

Compounds	50µg/ml (in mm)	100µg/ml (in mm)	300µg/ml (in mm)
7a	12	16	20
7b	14	18	22
7c	13	17	21
7d	10	12	16
7e	11	13	18
MXN	16	20	24

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Table-3: Antibacterial activity against Klebsiella pneumonia- (Zones of inhibition in mm)

Compounds	50µg/ml (in mm)	100µg/ml (in mm)	300µg/ml (in mm)
7a	10	12	16
7b	14	16	18
7c	12	14	20
7d	08	10	15
7e	09	11	14
MXN	16	20	24

Table-4: Antibacterial activity against Bacillus substilis - (Zones of inhibition in mm)

Compounds	50µg/ml (in mm)	100µg/ml (in mm)	300µg/ml (in mm)
7a	06	08	11
7b	10	14	16
7c	08	12	14
7d	04	07	10
7e	05	08	12
MXN	14	18	20

Table-5: Antibacterial activity against Staphylococcus aureus- (Zones of inhibition in mm)

Compounds	50µg/ml (in mm)	100µg/ml (in mm)	300µg/ml (in mm)	Compounds
7a	07	10	12	7a
7b	12	14	16	7b
7c	10	12	14	7c
7d	05	08	10	7d
7e	03	06	08	7e
MXN	14	18	20	MXN

Antifungal activity:

Antifungal activity of compounds 7a-7e (Zone of inhibition in mm)

Compounds	C. albicans	A. niger	S. cervisiae
7a	12	10	14
7b	**18**	**15**	**17**
7c	**17**	**13**	**15**
7d	13	10	12
7e	11	10	13
Ketoconazole	23	18	21

Note: 8-12 mm poor activity, 13-16 mm moderate activity, 18-23 mm significant activity

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Spectral Analysis

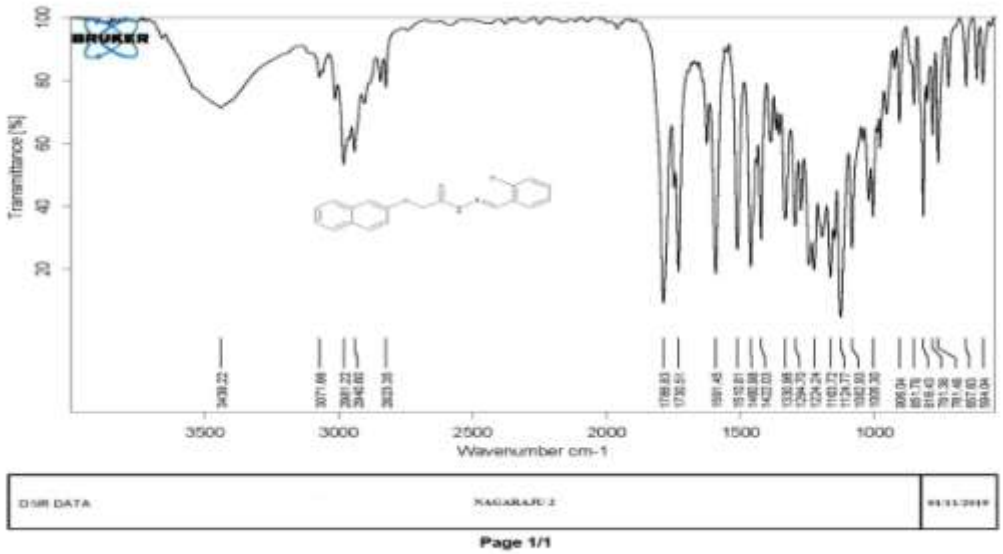
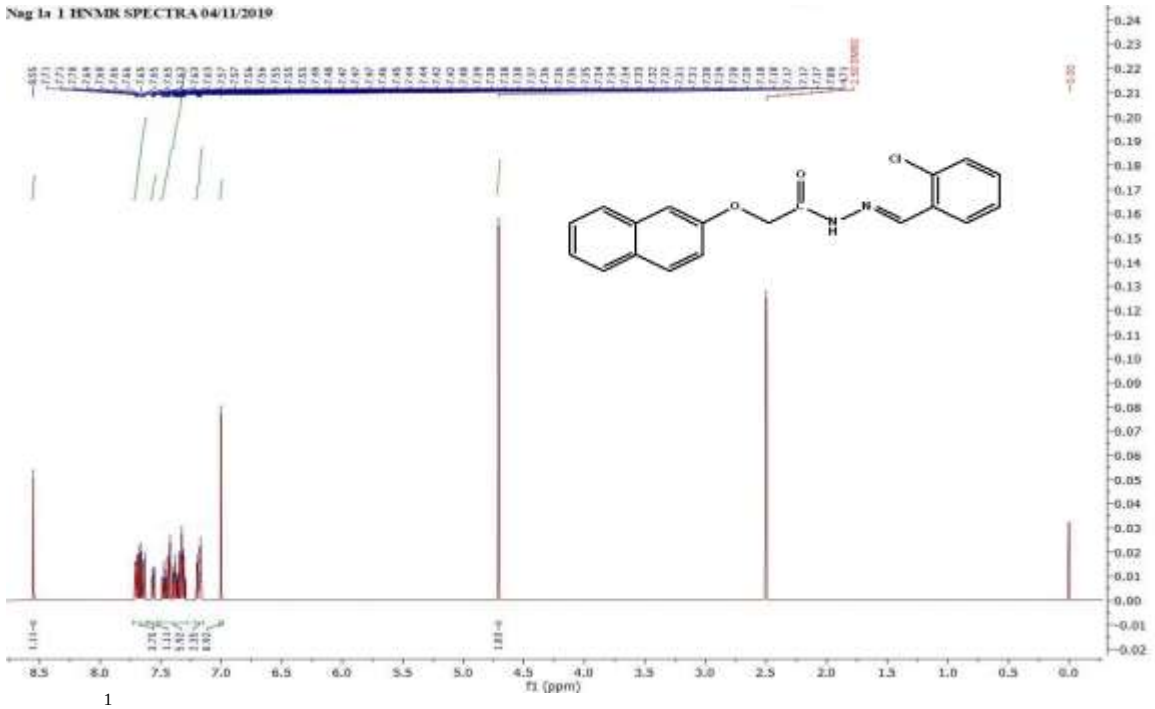


Fig.1: Infra Red spectrum of N'-(2-chlorobenzylidene)-2-(naphthalen-2-yloxy) acetohydrazide (7a)
IR (KBr, cm^{-1}) : 3439.22 (-NH), 3071.66 (C-H-Aromatic), 2981.22 (C-H, Aliphatic), 1786.83 (C=O), 1730.51(C=N), 1591 (C=C).



^{1}H NMR spectrum ofN'-(2-chlorobenzylidene)-2-(naphthalen-2-yloxy) acetohydrazide (7a)

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm**):** 8.55 (s, 1H, -NH), 7.71-7.17 (m, 10H, -Ar-H), 7.70 (s, 1H, -CH=N), 4.71 (s, 2H, $-CH_2$).

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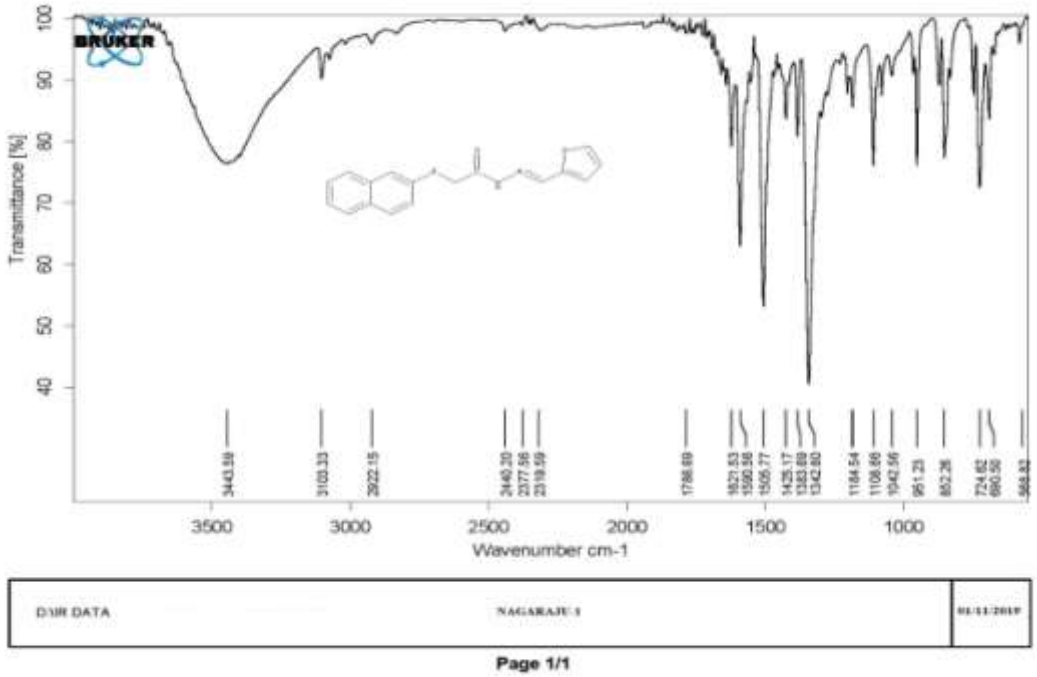
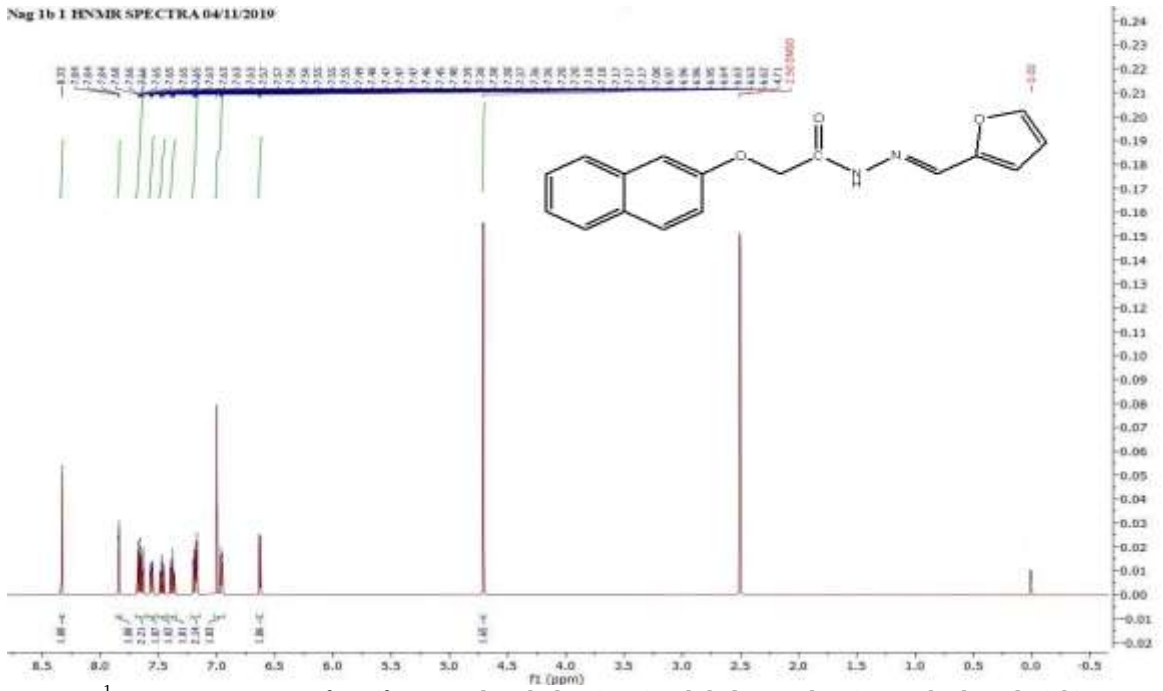


Infra Red spectrum of N'-(furan-2-ylmethylene)-2-(naphthalen-2-yloxy) acetohydrazide (7b)

IR (KBr, cm^{-1}): 3443.59 (-NH), 3103.33 (C-H Aromatic), 2922.15 (C-H, Aliphatic), 1786.69 (C=O), 1621.53 (C=C), 1590.56 (C=N).



^{1}H NMR spectrum of N'-(furan-2-ylmethylene)-2-(naphthalen-2-yloxy) acetohydrazide (7b)

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm) : 8.33 (s, 1H, -NH), 7.89-6.62 (m, 10H, Ar-H), 7.62-7.64 (d,1H, Ar-H), 4.71 (s, 2H, -CH2).

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