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Synthesis and antimycobacterial evaluation of novel 5,6-dimethoxy-1-oxo-2,5-dihydro-1*H*-2-indenyl-5,4-substituted phenyl methanone analogues

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ABSTRACT

In present investigation, a series of substituted phenyl-5,6-dimethoxy-1-oxo-2,5-dihydro-1*H*-2-indenyl-methanone analogues were synthesized and were evaluated for antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$ and INH resistant *M. tuberculosis*. All the newly synthesized compounds were showing moderate to high inhibitory activities. The compound 5,6-dimethoxy-1-oxo-2,5-dihydro-1*H*-2-indenyl-4-fluorophenylmethanone (**5g**) was found to be the most promising compounds active against *M. tuberculosis* $H_{37}Rv$ and isoniazid (INH) resistant *M. tuberculosis* with Minimum inhibitory concentration 0.10 and 0.10 μM.

Tuberculosis or TB is a dreadful life threatening disease caused by the bacteria *Mycobacterium tuberculosis*. This infectious disease affects many parts of the body; the lungs are the most commonly infected organ. The disease is highly contagious, transmitted by the droplets from the throat and lungs of the infected people. Globally there are 9.2 million cases of TB every year. The TB epidemic is getting worsened and kills more than 2 million people around the world annually.[1] There were an estimated 1.57 million new cases of tuberculosis among HIV-infected people and 456,000 deaths in 2007 as per the WHO survey. TB is shown to be the top cause of death in HIV-positive people. According to the 2009 global TB control report one out of four TB deaths is related to HIV infection.[2]

The current treatment for TB is not satisfactory as the therapy involves risk of treatment failures, relapses, severe side effects and some times leads to drug resistant TB. The treatment failure and relapses occur in patients who fail to strictly follow the treatment regimen. Also the treatment is not patient compliant. The drugs used for curing TB shows potential side effects including thrombocytopenia, neuropathy, rashes, fever, drug induced hepatitis. The most common drugs used for TB are rifampicin, isoniazid, ethambutol, pyrazinamide which are the first line drugs. The second line drugs include ethionamide, kanamycin, amikacin, capreomycin, ciprofloxacin, etc.[3,4]

A recent threat to TB is the development of drug resistant strains. The drug resistant TB is classified in to two categories such as multi drug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB). The MDR-TB is defined as TB that is resistant to isoniazid and rifampicin. In 2007, an estimated 500,000 people had multidrug-resistant TB (MDR-TB), has a mortality rate of up to 80%. The XDR-TB is resistant to quinolones and also to any one of kanamycin, capreomycin, or amikacin. The drug resistant TB also can be spread from one person to another person which is a dangerous situation. Hence it is considered to be a global threat for public health.

The global mortality rate for TB is very high and the development of new kinds of TB like MDR and XDR-TB alarming for the discovery of new drugs to reduce the potential hazards caused by the fatal disease. Objective of the present work is to develop new chemical entities that show good effect against the drug resistant strains of TB. The current work describes the synthesis of novel diketone moiety with encouraging antimycobacterial activity against INH resistant *M. tuberculosis*. We have recently reported the synthesis and AChE inhibitory activity of novel diketones.[5]

The physiological values of diketones have resulted in a tremendous activities and their function is quite stable which has inspired chemists to utilize this stable fragment in bioactive moieties to synthesize novel compounds possessing different biological activities. This prompted us to synthesize various substituted diketone derivatives using acidic (or) basic media. Therefore in the current work we have focused on the synthesis of some novel diketones and their biological evaluation against strains of *M. tuberculosis*.

The analogues of 5,6-dimethoxy-1-oxo-2,5-dihydro-1*H*-2-indenyl-5,4-substiutedphenylmethanone **5a**–**n** described in this study are shown in Table 1 and a reaction sequence for the preparation is outlined in Scheme 1. In the initial step, the 5,6-dimethoxy-2-

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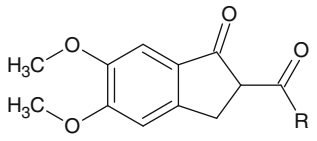
Table 1
Physical constants and antimycobacterial activity of the synthesized compounds



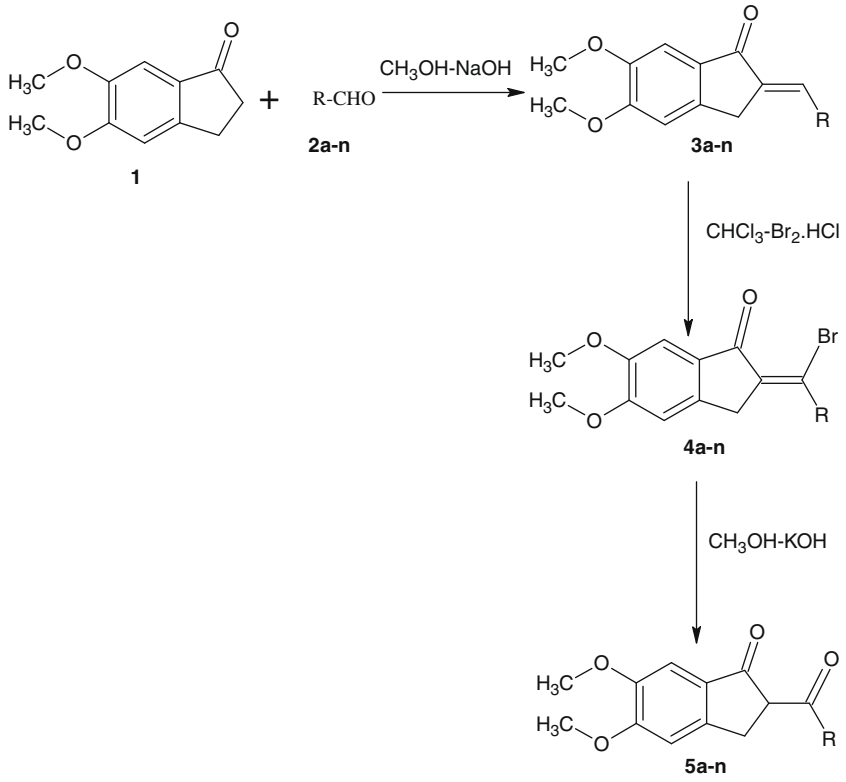
5a-5n

Compound	R	Yield (%)	Mp (°C)	(MIC) μM	
				MTB[a]	MTB[b]
5a	4-Methoxy phenyl-	74	164	>6.25	>6.25
5b	4-Chloro phenyl-	70	142	1.52	8.20
5c	4-Dimethylamino phenyl-	72	114	5.94	8.78
5d	Phenyl-	80	151	6.62	11.56
5e	3,4-Dimethoxy phenyl-	82	118	>6.25	>6.25
5f	3,4,5-Trimethoxy phenyl-	85	155	>6.25	>6.25
5g	4-Fluoro phenyl-	92	146	0.10	0.10
5h	2-Chloro phenyl-	85	125	1.82	3.72
5i	2,6-Dichloro phenyl-	77	154	2.48	4.96
5j	3-Nitro Phenyl-	82	104	3.46	8.72
5k	Furyl-	90	98	6.59	6.58
5l	Thiophenyl	56	198	6.25	6.25
5m	4-Bromo phenyl-	81	184	4.94	11.74
5n	4-Cyano phenyl-	76	202	>6.25	>6.25
INH	—	—	—	0.75	11.57

[(*E*)-1-phenylmethylidene]-1-indanone derivatives were synthesized by condensing 5,6-dimethoxy-1-indanone with appropriate aromatic aldehydes in dilute methanolic sodium hydroxide solution at room temperature. Then the resulting products 5,6-dimethoxy-2-[(*E*)-1-phenylmethylidene]-1-indanone were brominated in minimum quantity of chloroform followed by hydrolysis with methanolic potassium hydroxide to get titled compounds. The yields of titled compounds were ranging from 56% to 92% after recrystallization with ethanol. The purity of the compounds was checked by TLC and elemental analyses. Both analytical and spectral data (^{1}H NMR, IR) of all the synthesized compounds were in full agreement with the proposed structures. In general, infra red spectra (IR) revealed CH, C=O, and C–F peak at 1640, 1520, and 786 cm^{-1}, respectively. In the Nuclear Magnetic resonance spectra (^{1}H NMR) the signals of the respective protons of the prepared titled compounds were verified on the basis of their chemical shifts, multiplicities and coupling constants. The spectra showed a triplet at δ 3.20–3.55 ppm corresponding to CH group; doublet at δ 3.41–3.44 ppm corresponding to CH_2 group; singlet at δ 3.82, 3.86 ppm corresponding to OCH_3 multiplet at δ 6.48–7.20 ppm corresponding to aromatic protons. The elemental analysis results were within ±0.4% of the theoretical values.

The synthesized compounds **5a**–**n** were tested for their in vitro antimycobacterial activity against MTB and INHR-MTB by agar dilution method using double dilution technique similar to that recommended by the National Committee for Clinical Laboratory Standards.[6] The INHR-MTB clinical isolate was obtained from Tuberculosis Research Center, Alwar, India. The MIC was defined as the minimum concentration of compound required to inhibit 90% of bacterial growth and MIC of the compounds were reported in Table 1 with standard drug INH for comparison.

Among the fourteen compounds synthesized ten compounds were found to be most active compounds with minimum inhibitory concentration of less than 1 μM and were more active than INH against MTB. Compounds with electron withdrawing group substituted phenyl group were showing more activity. Among the fourteen newly synthesized compounds, the compound 5,6-dimethoxy-1-oxo-2,5-dihydro-1*H*-2-indenyl-4-fluoroyphenylmethanone (**5g**) was found to be most active against *M. tuberculosis* H_{37}Rv (MTB) and INH resistant *M. tuberculosis* (INHR-MTB) with mini-



Scheme 1. Protocol for synthesis.

mum inhibitory concentration of <0.10 μM. When compared to INH, the compound (**5g**) was found to be 9.12-fold and 115.7-fold more active against MTB and INHR-MTB. Following compounds 2-chlorophenyl (**5h**), 4-chlorophenyl (**5b**), and 2,6-dichlorophenyl (**5i**) substituents were found to be more active against MTB[a] and MTB[b] with MIC of 1.82 μM, 3.72 μM, and 1.52 μM, 8.20 μM, 2.48 μM, 4.96 μM, respectively. The 4-fluoro group substituted (**5g)** derivative displayed relatively higher inhibitory activity in general. However the electron withdrawing group such as 4-cholrophenyl, 2-chlorophenyl, 2,6-dichlorophenyl, thiophenyl, furyl, and 4-nitrophenyl substituted analogues showed moderate to good inhibitory activity against *M. tuberculosis* ($H_{37}Rv$) and INH resistant *M. tuberculosis* (INHR-MTB). On the other hand the electron donating group containing analogues like (OCH_3) group substituted 4-methoxy phenyl (**5a**), 3,4 dimethoxy phenyl (**5e**), and 3, 4, 5 trimethoxy phenyl (**5f**) functional groups showed low antitubercular activity. These reports clearly show that the substitution of electron withdrawing group like 4-fluoro substitution causes remarkable improvement in antimycobacterial activity.

All the compounds were tested for cytotoxicity (IC_{50}) in VERO cells at concentrations of 62.5 μg/mL or 10 times. After 72 h exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 Non-radioactive Cell proliferation method. Most of the active compounds were found to be non-toxic till 62.5 μg/mL.[7] The screening of diketone derivatives identified novel compounds that were endowed with antimycobacterial activity, exhibiting MIC values less than 1 μM. It is conceivable that derivatives showing more potency, selectivity and low toxicity make them excellent leads for synthesizing novel derivatives for antimycobacterial activity against MTB and INHR-MTB. Also these derivatives can be further modified to exhibit better potency than the standard drugs. Further studies will be performed to acquire more information about Quantitative Structure–Activity Relationships (QSAR) and MDR which are in progress in our laboratory. The diketone derivatives discovered in this study may provide valuable therapeutic intervention for the treatment of anti-tubercular diseases.

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Reference and notes

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7. Gundersen, L. L.; Nissen-Meyer, J.; Spilsberg, B. *J Med.Chem*, **2002**, *45*, 1383. Compound (**5g**): 5,6-dimethoxy-1-indanone with 4-fluorobenzaldehyde in dilute methanolic sodium hydroxide solution at room temperature to get 2-[(*E*)-1-(4-fluorophenyl)methylidene]-5,6-dimethoxy-1-indanone then brominated in minimum quantity of chloroform to get 2-[(*Z*)-1-bromo-1-(4-fluorophenyl) methylidene]-5,6-dimethoxy-1-indanone followed by hydrolysis with methanolic potassium hydroxide to get (**5g**) 5,6-dimethoxy-1-oxo-2,5-dihydro-1*H*-2-indenyl-4-fluorophenylmethanone. IR: (KBr) cm^{-1}: 3042 (CH), 1642 (C=O), 786 (C–F). ^1H NMR (DMSO-d_6) ppm: 3.20–3.35(1H, t, CH), 3.41–3.44 (2H, d, CH_2), 3.86 (6H, s, OCH_3), 6.68–7.20 (6H, m, aromatic); mass (*m*/*z*) 315 (M^{+1}); Calcd/Anal. [C (68.78) 68.79, H (4.81) 4.82, O (20.36) 20.37].