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Short communication

Synthesis and antimycobacterial evaluation of 3a,4-dihydro-3*H*-indeno [1,2-c] pyrazole-2-carboxamide analogues

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ABSTRACT

In the present investigation, a series of 3a,4-dihydro-3*H*-indeno [1,2-c] pyrazole-2-carboxamide analogues were synthesized and were evaluated for antitubercular activity by two fold serial dilution technique. All the newly synthesized compounds showed low to good inhibitory activities against *Mycobacterium tuberculosis* $H_{37}Rv$ and multi-drug resistant *M. tuberculosis* (MDR-TB). 3-(4-fluorophenyl)-*N*-(4-chlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno [1,2-c] pyrazole-2-carboxamide (**4c**) was found to be the most promising compound active against *M. tuberculosis*, $H_{37}Rv$ and MDR-TB with minimum inhibitory concentrations 0.83 μM and 3.32 μM respectively.

1. Introduction

Tuberculosis or TB is a dreadful life threatening disease caused by the bacteria *Mycobacterium tuberculosis* and to a lesser degree by *Mycobacterium Bovis* and *Mycobacterium Africana*. There are one-third of world's population which are currently infected with TB, with about 9.4 million worldwide and 1.6–2.4 million cases in India [1,2]. An estimated 1.7 million people died from TB in 2009 as per WHO survey. There are estimated 1.3 million multi-drug/extensively drug resistant tuberculosis (M/XDR-TB) cases which will need to be treated between 2010 and 2015 [2]. The development of multi-drug resistant tuberculosis (MDR-TB; resistant to isoniazid and rifampicin) and extensively drug resistant tuberculosis (XDR-TB; resistant to quinolones and also to any one of kanamycin, capreomycin or amikacin) are alarming for the discovery of new drugs to reduce the potential hazards caused by TB. The current strategies to cure the diseases are very complicated as they take several months of chemotherapy to eliminate persistent bacteria. Also the treatment of TB with the frontline drugs is associated with severe side effects including hepatotoxicity, ocular toxicity, thrombocytopoenia, neuropathy, rashes, fever, drug induced hepatitis. Nowadays there is an apparent need for fast acting drugs with less toxicity, which are capable to eliminate infection within a few weeks.

The azole group of heterocyclic compounds possess significant pharmacokinetic property, lipophilicity that influence the ability of drug to reach the target by transmembrane diffusion and showed promising activity against resistant TB by inhibiting the biosynthesis of lipids [3,4]. Pyrazoline is an important class of heterocyclic compounds, and were found to have various biological activities including antiamoebic, anticonvulsant, antimicrobial, anti-inflammatory, antiviral, antiarrhythmic, antidepressant, anti-cancer, antidiabetic, and antitubercular, etc [5–13]. Earlier we have reported the antimycobacterial activity of diketones and pyrazolines [14,15]. The present investigation is the continuation of the previous work. In this investigation we have focussed on the design and synthesis of some novel 3a,4-dihydro-3*H*-indeno [1,2-c] pyrazole-2-carboxamide analogues based on the structure of the known antitubercular agent, thiacetazone (Fig. 1) in which the "S" atom of the thiacetazone was replaced with isosteric "O" atom in the title compounds (**4a**–**r**). All the synthesized compounds were evaluated for their anti tubercular activity.

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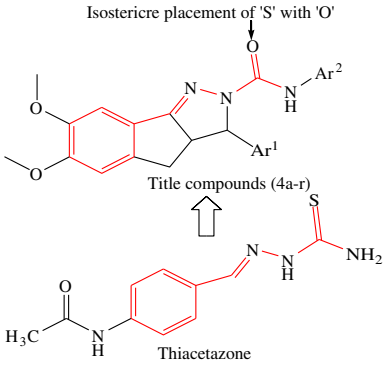


Fig. 1. Design of the title compounds based on known antitubercular drug.

2. Chemistry

The 3a,4-dihydro-3*H*-indeno [1,2-c] pyrazole-2-carboxamide analogues (**4a**–**r**) described in this study are shown in Table 1 and the reaction sequence for the synthesis is summarised in Scheme 1. In the initial step 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (0.01 mol) and appropriate aromatic aldehydes (0.01 mol) in diluted methanolic sodium hydroxide solution stirred at room temperature (Claisen–Schmidt condensation) giving the 2-substituted-5,6-dimethoxy-2,3-dihydro-1*H*-indene-1-one derivatives (**3a**–**f**). In the subsequent step 2-substituted-5,6-dimethoxy-2,3-dihydro-1*H*-indene-1-one derivatives treated with appropriate substituted phenyl semicarbazide/semicarbazide furnished the titled compounds (**4a**–**r**). The substituted phenyl semicarbazides were synthesized as per reported method [16]. The yields of the titled compounds were ranging from 62% to 88% after recrystallization with absolute ethanol. The purity of the compounds was checked by TLC using eluant benzene:acetone (9:1) and elemental analyses. Both the analytical and spectral data (IR, ^{1}H NMR and MS) of all the synthesized compounds were in full accordance with the proposed structures.

3. Biology

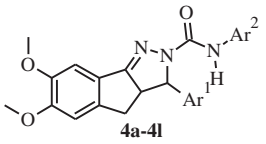
All the compounds were screened for their in vitro antimycobacterial activity against MTB and MDR-TB. The primary screening was carried out by agar dilution method using double dilution technique recommended by the National Committee for Clinical Laboratory Standards [17]. Isoniazid was used as standard drug. The observed data on the antimycobacterial activity of the title compounds (**4a**–**r**) and standard drug are given in Table 1.

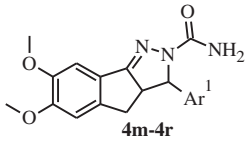
All the active compounds were tested for cytotoxicity (IC_{50}) in VERO cells at concentrations of 62.5 μg/mL or 10 times the MIC as per reported method [18].

4. Results and discussion

In the present work, a series of eighteen 3a,4-dihydro-3*H*-indeno [1,2-c] pyrazole-2-carboxamide analogues were synthesized. The synthesis of pyrazolines might be followed by cyclization of semicarbazone. In general, the IR spectra of the compounds afforded pyrazoline C=N stretching at 1501–1576 cm^{-1}, C–H deformation at 1362–1464 cm^{-1}, C_2–N_1 stretching at 1069–1189 cm^{-1}, and carbamoyl group N–H stretching at 3112–3481 cm^{-1} and C=O stretching at 1675–1687 cm^{-1} bands. The spectra showed singlet at δ 2.34–2.92 ppm corresponding to CH_3; multiplet at δ 3.27–3.35 ppm corresponding to CH; a doublet at δ 3.43–3.49 ppm corresponding to CH_2 group; a singlet at

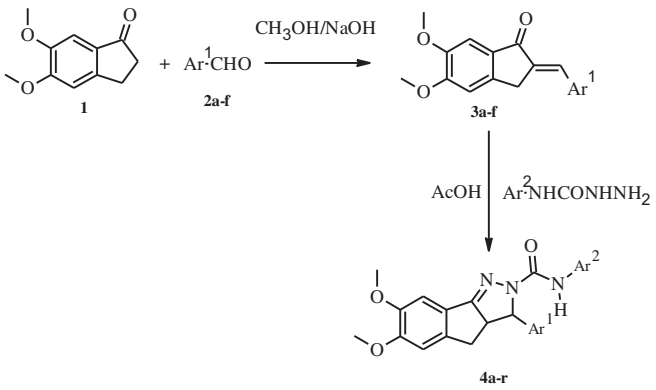
Table 1
Physical constant, antimycobacterial activity and cytotoxicity of the title compounds (**4a**–**r**).


4a-4l


4m-4r

Compound	Ar^1	Ar^2	Yield (%)	Mp (°C)	IC_{50} (μM)	MIC (μM)	
					Vero	MTB[a]	MTB[b]
4a	4-pyridinyl-	4-chlorophenyl-	72	116	>139.2	6.96	10
4b	2-chlorophenyl-	4-chlorophenyl-	76	124	NT	13.92	>13.92
4c	4-fluorophenyl-	4-chlorophenyl-	70	128	>133.6	0.83	3.32
4d	3,4-dimethoxyphenyl-	4-chlorophenyl-	84	136	NT	9.8	>9.8
4e	Phenyl-	4-chlorophenyl-	82	166	>139.4	6.97	10.46
4f	4-methoxyphenyl-	4-chlorophenyl-	76	188	NT	10.46	>10.46
4g	4-pyridinyl-	4-nitrophenyl-	62	168	68.0	6.80	>13.6
4h	2-chlorophenyl-	4-nitrophenyl-	68	130	NT	12.67	>12.67
4i	4-fluorophenyl-	4-nitrophenyl-	72	144	94.8	3.16	6.32
4j	3,4-dimethoxyphenyl-	4-nitrophenyl-	88	168	NT	12.05	>12.05
4k	Phenyl-	4-nitrophenyl-	72	160	51.08	6.81	13.62
4l	4-methoxyphenyl-	4-nitrophenyl-	66	164	NT	12.78	>12.78
4m	4-pyridinyl-	–	72	224	NT	11.79	>11.79
4n	2-chlorophenyl-	–	68	242	NT	10.75	>10.75
4o	4-fluorophenyl-	–	70	238	176.85	8.44	6.62
4p	3,4-dimethoxyphenyl-	–	78	216	NT	10.05	>10.05
4q	Phenyl-	–	72	220	NT	11.83	>11.83
4r	4-methoxyphenyl-	–	68	226	NT	10.86	>10.86
INH	–	–	–	–	>456	0.56	45.57

NT = not tested.
[a] *M. tuberculosis* H_{37}Rv.
[b] MDR-TB.



Scheme 1. Protocol for the synthesis.

δ 3.79–3.83 ppm corresponding to OCH_3 group; a doublet at 4.9–5.4 ppm corresponding to CH; multiplet at δ 6.51–8.38 ppm corresponding to aromatic protons; broad singlet at δ 8.88–10.02 ppm corresponding to $CONH_2$. The mass spectra of the compounds revealed in each case, a peak corresponding to their molecular ion peaks. The elemental analysis results were within ±0.4% of the theoretical values.

Among the eighteen synthesized compounds, six compounds were found to be active with minimum inhibitory concentration of 0.83–6.97 μM. The compound **4c** was found to be active against MTB and MDR-TB at a MIC of 0.83 and 3.32 μM respectively. When compared with isoniazid (INH) the compound, **4c** was less potent against MTB, while 13.6 folds more active against MDR-TB. In the title compounds (**4a**–**r**), both the C_3 aryl group and the *N*-aryl group influenced the antitubercular activity. The 3-substituted compounds with electron withdrawing groups such as 4-flourophenyl, 4-pyridyl produced more inhibitory activity than 2-chlorophenyl and the electron releasing groups such as 4-methoxyphenyl, 3,4-dimethoxyphenyl showed less inhibitory activity. The 4-chlorophenyl substitution on *N*-aryl group showed maximum inhibitory activity than 4-nitrophenyl substitution or when there was no substitution. The compound, **4i** showed good inhibitory activity against MTB at MIC 3.12 μM, while the compounds **4g**, **4k**, **4a** and **4e** showed moderate inhibitory activity against MTB at MIC 6.80 μM–6.97 μM (Table 1).

All the active compounds were tested for cytotoxicity (IC_{50}) in VERO cells at concentrations of 62.5 μg/mL or 10 times the MIC. The title compounds having *N*-aryl substitution with 4-nitrophenyl group showed more toxicity than 4-chlorophenyl group. The compounds showed IC_{50} ranging from 51.08 to >176.85 μM (Table 1). The compound **4c** was non-toxic up to >133.6 μM and showed selective index (IC_{50}/MIC) of more than 161 for MTB and more than 81 for MDR-TB.

The synthesized novel series of pyrazoline were synthesized in satisfactory yields. The antimycobacterial activity showed promising results. The SAR studies confirmed the compound **4c** is the potent lead compound for drug discovery with negligible cytotoxicity. The pyrazoline derivatives discovered in this study may provide valuable therapeutic intervention for the treatment of tubercular disease.

5. Experimental

5.1. Chemistry

The entire chemicals were supplied by E. Merck (Germany) and S. D. Fine Chemicals (India). Melting points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked on TLC plates (silica gel G) using eluants benzene–acetone (9:1), the spots were located under iodine vapours or UV light. IR spectra were obtained on a Schimadzu 8201 PC, FT-IR spectrometer (KBr pellets). ^{1}H NMR spectra were recorded on a Bruker AC 300 MHz spectrometer using TMS as internal standard in DMSO. Mass spectra were recorded on a Bruker Esquire LCMS using ESI and elemental analyses were performed on Perkin–Elmer 2400 Elemental Analyzer.

5.2. General method for the synthesis of 2-substituted-5,6-dimethoxy-2,3-dihydro-1H-indene-1-one derivatives (*3a–f*)

5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (0.001 mol) with appropriate aldehyde (0.001 mol) in diluted methanolic sodium hydroxide solution was stirred under room temperature for 4 h. The resulting solution was allowed to stand overnight and then the reaction mixture was poured into cold water and neutralized with dilute HCl. The solid was filtered, dried and recrystallized with ethanol furnished the 2-substituted-5,6-dimethoxy-2,3-dihydro-1*H*-indene-1-one.

5.3. General method for the synthesis of 3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2-carboxamide analogues (*4a–r*)

To a 2-substituted-5,6-dimethoxy-2,3-dihydro-1*H*-indene-1-one (**3a**–**g**) (0.01 mol) and substituted phenyl semicarbazide (0.01 mol) in 20 ml glacial acetic acid was refluxed for 12 h. The excess of solvent was removed under reduced pressure and then the reaction mixture was poured into the crushed ice. The solid mass was filtered dried and recrystallized with ethanol furnished the 3-substituted-*N*-aryl-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno [1,2-c] pyrazole-2-carboxamide.

5.3.1. 3-(Pyridin-4-yl)-N-(4-chlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2-carboxamide (*4a*)

IR: (KBr) cm^{-1}: 3334 (NH), 1680 (C=O), 1563 (C=N), 1110 (C–N). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.29–3.35 (1H, m, CH), 3.41–3.43 (2H, d, J = 6.2 Hz, CH_2), 3.81 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.1 (1H, d, J = 6.4 Hz, CH), 6.98–8.31 (10H, m, Ar), 8.89 (1H, s, CONH); m/z = 449 $(M+1)^+$.

5.3.2. 3-(4-Fluorophenyl)-N-(4-chlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2-carboxamide (*4c*)

IR: (KBr) cm^{-1}: 3331 (NH), 1681 (C=O), 1565 (C=N), 1144 (C–N) 787 (C–F). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.29–3.33 (1H, m, CH), 3.41–3.44 (2H, d, J = 6.3 Hz, CH_2), 3.80 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.1 (1H, d, J = 6.5 Hz, CH), 6.98–8.29 (10H, m, Ar), 9.19 (1H, s, CONH); m/z = 466 $(M+1)^+$.

5.3.3. 3-(3,4-Dimethoxyphenyl)-N-(4-chlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2-carboxamide (*4d*)

IR: (KBr) cm^{-1}: 3336 (NH), 1685 (C=O), 1565 (C=N), 1174 (C–N). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.29–3.33 (1H, m, CH), 3.40–3.44 (2H, d, J = 6.7 Hz, CH_2), 3.80 (6H, s, OCH_3), 3.83 (6H, s, OCH_3), 5.2 (1H, d, J = 6.4 Hz, CH), 6.78–8.19 (9H, m, Ar), 9.39 (1H, s, CONH); m/z = 439 $(M+1)^+$.

5.3.4. 3-Phenyl-N-(4-chlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2-carboxamide (*4e*)

IR: (KBr) cm^{-1}: 3331 (NH), 1681 (C=O), 1565 (C=N), 1144 (C–N). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.27–3.31 (1H, m, CH), 3.41–3.43 (2H, d, J = 6.0 Hz, CH_2), 3.81 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.1

(1H, d, $J = 6.3$ Hz, CH), 6.98–8.33 (11H, m, Ar), 9.49 (1H, s, CONH); $m/z = 448$ $(M+1)^+$.

*5.3.5. 3-(Pyridin-4-yl)-N-(4-nitrophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2-carboxamide (**4g**)*

IR: (KBr) cm^{-1}: 3334 (NH), 1685 (C=O), 1560 (C=N), 1121 (C–N). ^1H NMR (DMSO-d_6) ppm: 3.29–3.34 (1H, m, CH), 3.41–3.43 (2H, d, $J = 6.8$ Hz, CH_2), 3.81 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.1 (1H, d, $J = 6.0$ Hz, CH), 6.88–8.19 (10H, m, Ar), 10.19 (1H, s, CONH); $m/z = 459$ (M^{+1}).

*5.3.6. 3-(4-Fluorophenyl)-N-(4-nitrophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2-carboxamide (**4i**)*

IR: (KBr) cm^{-1}: 3331 (NH), 1680 (C=O), 1565 (C=N), 1145 (C–N), 786 (C–F). ^1H NMR (DMSO-d_6) ppm: 3.29–3.33 (1H, m, CH), 3.39–3.42 (2H, d, $J = 6.3$ Hz, CH_2), 3.81 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.1 (1H, d, $J = 6.1$ Hz, CH), 7.02–8.28 (10H, m, Ar), 9.09 (1H, s, CONH); $m/z = 477$ $(M+1)^+$.

*5.3.7. 3-Phenyl-N-(4-nitrophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2-carboxamide (**4k**)*

IR: (KBr) cm^{-1}: 3331 (NH), 1680 (C=O), 1561 (C=N), 1134 (C–N). ^1H NMR (DMSO-d_6) ppm: 3.23–3.25 (1H, m, CH), 3.39–3.40 (2H, d, $J = 6.2$ Hz, CH_2), 3.81 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.1 (1H, d, $J = 6.1$ Hz, CH), 6.98–8.31 (11H, m, Ar), 9.59 (1H, s, CONH); $m/z = 458$ (M^{+1}).

*5.3.8. 3-(4-Fluorophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2(3H)-carboxamide (**4o**)*

IR: (KBr) cm^{-1}: 3331 (NH), 1680 (C=O), 1561 (C=N), 1134 (C–N). ^1H NMR (DMSO-d_6) ppm: 3.21–3.23 (1H, m, CH), 3.37–3.39 (2H, d, $J = 6.2$ Hz, CH_2), 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 5.1 (1H, d, $J = 6.1$ Hz, CH), 5.49 (2H, s, $CONH_2$), 7.08–7.68 (6H, m, Ar); $m/z = 338$ $(M+1)^+$.

5.4. In vitro antimycobacterial activity

All the compounds were screened for their in vitro antimycobacterial activity against MTB and MDR-TB. MTB H37Hv was grown in Middlebrook 7H11 broth medium supplemented with 10% OADC (oleic acid, albumin, dextrose and catalase, 1, 10, 100 mg/L). In brief, 10^3 and 10^4 colony forming unit (CFU) were inoculated into 7H11 medium. The MTB and MDR-TB clinical isolate was obtained from Tuberculosis Research Center, Alwar, India. The minimum inhibitory concentration (MIC) was defined as the minimum concentration of compound required to 99.9% inhibition of bacterial growth.

All the active compounds were tested for cytotoxicity (IC_{50}) in VERO cells at concentrations of 62.5 μg/mL or 10 times the MIC by serial double dilution technique. 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 up to 62.5 μg/mL.

The molecular docking simulation for possible action on *InhA* are currently under investigation. Also studies to acquire more information about Quantitative Structure Activity Relationships (QSAR) and MDR are in progress in our laboratory.

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