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Fused Heterocycles: Synthesis of Some New Imidazopyridines as Anti-Mycobacterial Agents

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The reaction of semicarbazones bearing an imidazo[1,2-*a*]pyridine ring system with mercaptoacetic acid was investigated. The anti-mycobacterial activity of the compounds thus obtained were evaluated against *Mycobacterium tuberculosis* $H_{37}Rv$, using rifampin as the standard. Only **IVe** showed activity at 6.25 μg mL^{-1}.

Key Words: Imidazo[1,2-*a*]pyridine, semicarbazones, 4-thiazolidinone, antituberculous activity.

Introduction

Tuberculosis (TB) remains a major cause of death worldwide. The emergence of multi-drug resistant TB (MDR-TB) is most alarming. Up to 4% of all TB cases worldwide are resistant to more than one anti-tubercular drug because of incomplete or partial therapy.[1,2] Isonicotinic acid hydrazide (INH) is one of the primary drugs, in combination with ethambutol, rifampin and streptomycin, for treating TB, but the treatment of the disease is still a major health problem due to multi-drug resistant bacterial strains. New anti-mycobacterial agents, different from currently available first-line drugs, are urgently needed. This is an additional reason why many laboratories are seeking new anti-tubercular agents that could confer greater selectivity and lower toxicity.[3] We recently reported the synthesis of some imidazo[1,2-*a*]pyridine-3-carboxylic acid hydrazides as structural analogues of INH, related compounds, and their anti-mycobacterial activity.[4,5] Continuing our search for new anti-tubercular agents we have now synthesized some new semicarbazones (**IVa-f**) and 4-thiazolidinones (**Va-d**) incorporating an imidazo[1,2-*a*] pyridine moiety. These compounds were characterized by their elemental and spectral analyses (IR, ^{1}H-NMR, and mass spectra).

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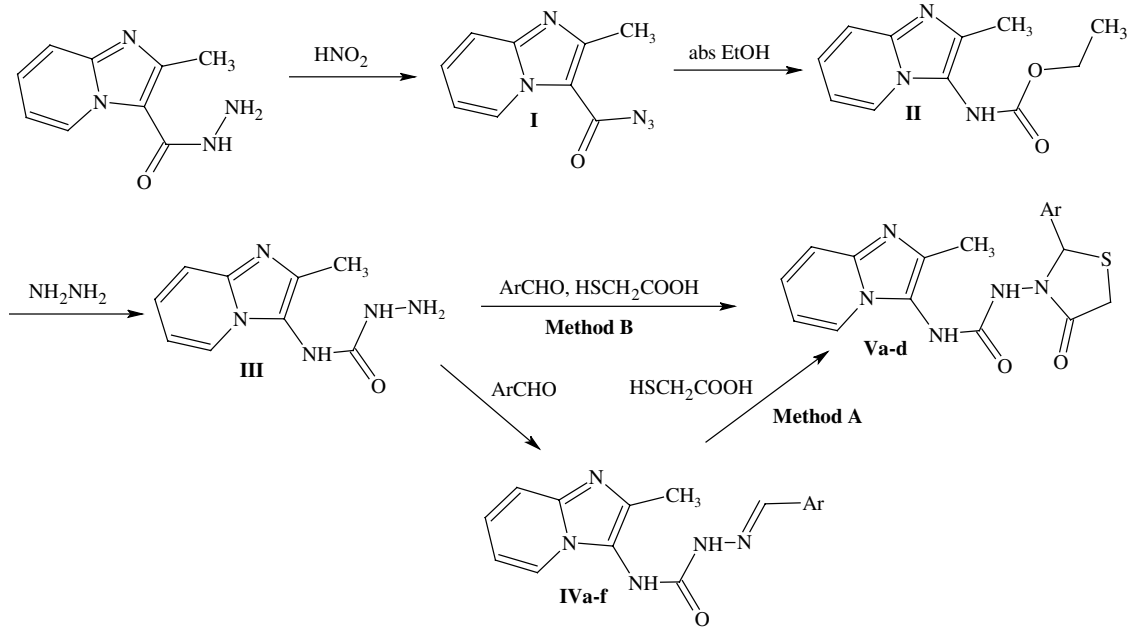
Experimental

Melting points were determined with an Electrothermal 9200 apparatus in open capillary tubes and are uncorrected. IR spectra were recorded on KBr disks, using a Perkin Elmer 1600 FT-IR spectrophotometer. ^{1}H-NMR spectra were obtained in DMSO-d_6, with Bruker AC 200 and Inova (500 MHz) spectrophotometers using TMS as the internal standard. EI and APCI mass spectra were determined with VG Zab Spec and LC/MSD Diod-Array instruments. Elemental analyses were performed on a Leco 932 CHNS-O elemental analyzer. The starting materials were either commercially available or synthesized according to the references cited.



Ar= C_6H_5 (**IVa**), p-C_6H_4Cl (**IVb**), p-$C_6H_4CH_3$ (**IVc**), p-$C_6H_4OCH_3$ (**IVd**), p-$C_6H_4NO_2$ (**IVe**), 5-nitro-2-furyl (**IVf**)
Ar= C_6H_5 (**Va**), p-C_6H_4Cl (**Vb**), p-$C_6H_4CH_3$ (**Vc**), p-$C_6H_4OCH_3$ (**Vd**)

Scheme. Synthetic pathway for the preparation of **I-V**.

2-Methylimidazo[1,2-*a*]pyridine-3-carbonyl azide (I)

In 80 mL of cold water were dissolved 0.02 mol of 2-methylimidazo[1,2-*a*]pyridine-3-carbohydrazide[4] and 0.02 mol of $NaNO_2$. Dropwise, 20 mL of HCl (25%) was added, maintaining the temperature below 15 °C. The solution was stirred for 15 min, neutralized with Na_2CO_3, and then the solid thus obtained was filtered, and dried and recrystallized from $CHCl_3$.

Yield: 85.67%, m.p.: 102-5 °C. IR ν_{max} (cm^{-1}): 2149 (N≡N), 1646 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.50 (3H, s, CH_3); 7.27 (1H, dd, $J_{5,6}$=$J_{6,7}$= 7 Hz, C_6-H); 7.68 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.74 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 9.34 (1H, d, $J_{5,6}$= 7 Hz, C_5-H). EIMS (%): 201 ($M^{+\cdot}$, 21.01), 144 (base peak). Anal. for $C_9H_7N_5O$: Calc. C: 53.73, H: 3.51, N: 34.81. Found C: 53.48, H: 3.98, N: 34.37.

Ethyl (2-methylimidazo[1,2-*a*]pyridine-3-yl)carbamate (II)

In 25 mL of absolute EtOH was refluxed 0.02 mol of **I** for 2.5 h; then EtOH was removed in vacuo. The product thus obtained was recrystallized from EtOH (96%).

Yield: 84.61%, m.p.: 72-8 °C. IR ν_{max} (cm^{-1}): 3273 (NH), 1694 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 1.23 (3H, t, $OCH_2\mathbf{CH}_3$); 2.37 (3H, s, CH_3); 4.12 (2H, q, $O\mathbf{CH}_2CH_3$); 6.87 (1H, dd, $J_{5,6}$=$J_{6,7}$= 7 Hz, C_6-H); 7.20 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.43 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.96 (1H, d, $J_{5,6}$= 7 Hz, C_5-H); 9.12 (1H, s, NH). EIMS (%): 219 ($M^{+\cdot}$, 83.17), 119 (base peak). Anal. for $C_{11}H_{13}N_3O_2.H_2O$: Calc. C: 55.69, H: 6.37, N: 17.71. Found C: 55.00, H: 5.86, N: 17.96.

N-(2-Methylimidazo[1,2-*a*]pyridine-3-yl)hydrazinecarboxamide (III)

In 20 mL of hydrazine (98%) was refluxed 0.02 mol of **II** for 2 h. The precipitate formed after cooling was filtered, washed with water, dried and recrystallized from EtOH (96%).

Yield: 43.70%, m.p.: 222-5 °C. IR ν_{max} (cm^{-1}): 3304, 3161 (NH), 1643 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.22 (3H, s, CH_3); 4.35 (2H, s, NHCONHN$\mathbf{H}_2$); 6.84 (1H, dd, $J_{5,6}$=$J_{6,7}$= 7 Hz, C_6-H); 7.16 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.59 (1H, s, N**H**CONHNH_2); 7.74 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.89 (1H, d, $J_{5,6}$= 7 Hz, C_5-H); 8.31 (1H, s, NHCON**H**NH_2). EIMS (%): 205 ($M^{+\cdot}$, 46.18), 144 (base peak). Anal. for $C_9H_{11}N_5O$: Calc. C: 52.67, H: 5.40, N: 34.13. Found C: 52.81, H: 5.39, N: 34.39.

General procedure for the preparation of aromatic aldehyde N-(2-methyl imidazo [1,2-*a*]pyridin-3-yl)semicarbazones (IVa-f)

For 2-6 h, 0.01 mol of **III**, 0.011 mol of appropriate aromatic aldehyde, and 25 mL of EtOH (96%) were refluxed. The solid that separated was filtered and recrystallized from EtOH or washed with EtOH (96%).

IVa. Yield: 60.00%, m.p.: 223-5 °C. IR ν_{max}(cm^{-1}): 3304, 3161 (NH), 1689 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.27 (3H, s, CH_3); 6.88 (1H, dd, $J_{5,6}$= 6 Hz, $J_{6,7}$= 7 Hz, C_6-H); 7.21 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.39-7.45 (4H, m, C_8-H and phenyl 3,4,5-H); 7.86-7.89 (2H, m, phenyl 2,6-H); 7.99-8.01 (2H, m, C_5-H and N=CH); 9.07 (1H, s, **NH**CONHN); 10.99 (1H, s, NHCO**NH**N). EIMS (%): 293 ($M^{+\cdot}$, 66.45), 78 (base peak). Anal. for $C_{16}H_{15}N_5O$: Calc. C: 65.52, H: 5.15, N: 23.88. Found C: 65.51, H: 4.92, N: 23.51.

IVb. Yield: 81.34%, m.p.: 242-4 °C. IR ν_{max} (cm^{-1}): 3369, 3170 (NH), 1685 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.26 (3H, s, CH_3); 6.87 (1H, dd, $J_{5,6}$= $J_{6,7}$= 7 Hz, C_6-H); 7.33 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.44 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.46 (1H, d, J= 8 Hz, phenyl 3,5-H); 7.90 (2H, d, J= 8 Hz, phenyl 2,6-H); 7.96-7.99 (2H, m, C_5-H and N=CH); 9.07 (1H, s, N**H**CONHN); 10.97 (1H, s, NHCON**H**N). EIMS (%): 329 (M^{+2}, 14.69), 327 ($M^{+\cdot}$, 39.62), 173 (base peak). Anal. for $C_{16}H_{14}ClN_5O$: Calc. C: 58.63, H: 4.31, N: 21.37. Found C: 58.70, H: 3.89, N: 21.51.

IVc. Yield: 84.25%, m.p.: 202-7 °C. IR ν_{max} (cm^{-1}): 3369, 3201(NH), 1687 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.26 (3H, s, CH_3); 2.33 (3H, s, phenyl 4-CH_3); 6.86 (1H, dd, $J_{5,6}$= 6 Hz, $J_{6,7}$= 7 Hz, C_6-H); 7.15-7.24 (3H, m, C_7-H and phenyl 3,5-H); 7.33 (2H, d, J= 8 Hz, phenyl 2,6-H); 7.44 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.96-7.98 (2H, m, C_5-H and N=CH); 8.92 (1H, s, N**H**CONHN); 10.76 (1H, s, NHCON**H**N). EIMS (%): 307 ($M^{+\cdot}$, 54.31), 134 (base peak). Anal. for $C_{17}H_{17}N_5O$: Calc. C: 66.43, H: 5.58, N: 22.79. Found C: 66.07, H: 5.51, N: 22.39.

IVd. Yield: 87.09%, m.p.: 188-92 °C. IR ν_{max} (cm^{-1}): 3307, 3194 (NH), 1690 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.26 (3H, s, CH_3); 3.80 (3H, s, phenyl 4-OCH_3); 6.85 (1H, dd, $J_{5,6}$=$J_{6,7}$= 7 Hz, C_6-H); 6.96 (2H, d, J= 9 Hz, phenyl 3,5-H); 7.18 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.44 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.78 (2H, d, J= 9 Hz, phenyl 2,6-H); 7.93-7.98 (2H, m, C_5-H and N=CH); 8.90 (1H, s, N**H**CONHN); 10.69 (1H, s, NHCON**H**N). EIMS (%): 323 ($M^{+\cdot}$, 27.48), 150 (base peak). Anal. for $C_{17}H_{17}N_5O_2$: Calc. C: 63.15, H: 5.30, N: 21.66. Found C: 63.34, H: 4.93, N: 21.48.

IVe. Yield: 73.41%, m.p.: 228-33 °C. IR ν_{max}(cm^{-1}): 3379, 3197 (NH), 1684 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.27 (3H, s, CH_3); 6.87 (1H, dd, $J_{5,6}$= $J_{6,7}$= 7 Hz, C_6-H); 7.21 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.45 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.99 (1H, d, $J_{5,6}$= 7 Hz, C_5-H); 8.08 (1H, s, N=CH); 8.10 (2H, d, J= 9 Hz, phenyl 2,6-H); 8.25 (2H, d, J= 9 Hz, phenyl 3,5-H); 9.22 (1H, s, N**H**CONHN); 11.26 (1H, s, NHCON**H**N). EIMS (%): 338 ($M^{+\cdot}$, 39.30), 173 (base peak). Anal. for $C_{16}H_{14}N_6O_3.H_2O$: Calc. C: 53.92, H: 4.52, N: 23.58. Found C: 54.24, H: 4.33, N: 24.65.

IVf. Yield: 56.50%, m.p.: 206 °C. IR ν_{max} (cm^{-1}): 3364, 3213 (NH), 1694 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.24 (3H, s, CH_3); 6.79 (1H, dd, $J_{5,6}$=$J_{6,7}$= 7 Hz, C_6-H); 7.14 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.22 (1H, d, J= 4 Hz, furan 3-H); 7.36 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.70 (1H, d, J= 4 Hz, furan 4-H); 7.83 (1H, s, N=CH), 7.92 (1H, d, $J_{5,6}$= 7 Hz, C_5-H); 8.99 (1H, s, **NH**CONHN); 11.25 (1H, s, NHCO**NH**N). APCI MS (%): 329 ($[M+H]^+$, 53.6), 79 (base peak). Anal. for $C_{14}H_{12}N_6O_4.1.5H_2O$: Calc. C: 47.98, H: 4.31, N: 23.98. Found C: 47.48, H: 4.17, N: 24.26.

General procedure for the preparation of 1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)-3-(4-oxo-2-aryl-1,3-thiazolidin-3-yl)ureas (Va-d)

Method A

A mixture of **IVa-d** (0.01 mol) and $HSCH_2COOH$ (0.25 mol) was heated under reflux for 4 h in dry benzene (30 mL) using a Dean-Stark trap. Excess benzene was evaporated in vacuo. The residue was triturated with saturated $NaHCO_3$ until CO_2 evaluation ceased and was then left to stand overnight. The solid thus obtained was filtered and washed with H_2O.

Method B

The appropriate aromatic aldehyde (0.011 mol) was added to a solution of **III** (0.01 mol) in dry benzene (30 mL) and the mixture was heated under reflux for 4 h using a Dean-Stark trap. After cooling, $HSCH_2COOH$ (0.15 mol) was added dropwise to the solution and the resulting mixture was refluxed for 2-4 h. The compounds were purified using the procedure described in Method A.

Va. Yield: 13.08% (Method A), 34.50% (Method B), m.p.: 233-6 °C. IR ν_{max} (cm^{-1}): 3295, 3154 (NH), 1700, 1674 (C=O). ^{1}H-NMR (500 MHz) δ (ppm): 2.13 (3H, s, CH_3); 3.76, 3.85 (2H, dd, J= 16 Hz, thiazolidinone CH_2); 5.83 (1H, s, thiazolidinone CH); 6.86 (1H, d, $J_{5,6}$= 6 Hz, C_6-H); 7.18 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 8 Hz, C_7-H); 7.38-7.48 (6H, m, C_8-H and phenyl 2,3,4,5,6-H), 7.76 (1H, s, C_5-H); 8.41 (1H, s, **NH**CONH); 8.94 (1H, s, NHCO**NH**). APCI MS (%): 368 ($[M+H]^+$, base peak). Anal. for $C_{18}H_{17}N_5O_2S.0.5H_2O$: Calc. C: 57.42, H: 4.81,N: 18.60. Found C: 57.27, H: 4.38, N: 18.49.

Vb. Yield 55.00% (Method A), 51.68% (Method B), m.p.: 244 °C. IR ν_{max} (cm^{-1}): 3395, 3263 (NH), 1700, 1674 (C=O). ^{1}H-NMR (500 MHz) δ (ppm): 2.25 (3H, s, CH_3); 3.86, 3.88 (2H, dd, J= 16 Hz, thiazolidinone CH_2); 5.86 (1H, s, thiazolidinone CH); 6.86 (1H, dd, $J_{5,6}$= 6 Hz, $J_{6,7}$= 7 Hz, C_6-H); 7.19 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 8 Hz, C_7-H); 7.41 (1H, d, $J_{7,8}$= 8 Hz, C_8-H); 7.48-7.53 (4H, m, phenyl 2,3,5,6-H); 7.76

(1H, s, C_5-H); 8.64 (1H, s, **NH**CONH); 9.09 (1H, s, NHCO**NH**). APCI MS (%): 404 ($[M+H]^{+2}$, 16.85); 402($[M+H]^+$, 49.44), 174 (base peak). Anal. for $C_{18}H_{16}ClN_5O_2S$: Calc. C: 53.80, H: 4.01, N: 17.43. Found C: 53.22, H: 4.11, N: 17.32.

Vc. Yield 17.04% (Method A), 40.00% (Method B), m.p.: 272 °C. IR ν_{max} (cm^{-1}): 3307, 3268 (NH), 1700, 1675 (C=O). ^{1}H-NMR (500 MHz) δ (ppm): 2.13 (3H, s, CH_3); 2.34 (3H, s, phenyl 4-CH_3); 3.75, 3.84 (2H, dd, J= 15 Hz, thiazolidinone CH_2), 5.81 (1H, s, thiazolidinone CH); 6.86 (1H, s, C_6-H); 7.19 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.23 (2H, d, J= 8 Hz, phenyl 3,5-H); 7.37 (2H, s, phenyl 2,6-H); 7.41 (1H, d, J= 9 Hz, C_8-H); 7.76 (1H, s, C_5-H); 8.37 (1H, s, **NH**CONH); 8.90 (1H, s, NHCO**NH**). APCI MS (%): 382 ($[M+H]^+$, 3.6%), 79 (base peak). Anal. for $C_{19}H_{19}N_5O_2S.0.5H_2O$: Calc. C: 58.59, H: 5.18, N: 17.68. Found C: 58.61, H: 4.66, N: 18.09.

Vd. Yield 22.22% (Method A), 38.75% (Method B), m.p.: 242 °C. IR ν_{max} (cm^{-1}): 3256, 3213 (NH), 1704, 1674 (C=O). ^{1}H-NMR (500 MHz) δ (ppm): 2.14 (3H, s, CH_3); 3.73-3.83 (5H, m, phenyl 4-OCH_3 and thiazolidinone CH_2); 5.81 (1H, s, thiazolidinone CH); 6.85 (1H, s, C_6-H); 6.97 (2H, d, J= 8 Hz, phenyl 3,5-H); 7.19 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 8 Hz, C_7-H); 7.36-7.42 (3H, m, C_8-H and phenyl 2,6-H); 7.75 (1H, s, C_5-H); 8.43 (1H, s, **NH**CONH); 8.94 (1H, s, NHCO**NH**). APCI MS (%): 398 ($[M+H]^+$, base peak). Anal. for $C_{19}H_{19}N_5O_3S$: Calc. C: 57.42, H: 4.82, N: 17.62. Found C: 56.95, H: 4.73, N: 17.76.

Antituberculous Activity

Anti-mycobacterial screening was conducted at 6.25 μg mL^{-1}against *M. tuberculosis* H_{37}Rv using the BACTEC 460 radiometric system at the National Institute of Allergy and Infectious Diseases, USA. Compounds resulting in inhibition < 90% (MIC > 6.25 μg mL^{-1}, MIC rifampin 0.031 μg mL^{-1}) were not evaluated further.[6] Only **IVe** showed anti-tuberculous activity (8% inhibition) at the tested concentration.

Results and Discussion

The synthetic pathway followed in the preparation of the compounds is outlined in the Scheme. The starting material, 2-methylimidazo[1,2-*a*]pyridine-3-carboxylic acid hydrazide, was obtained by a previously described method.[4]

In the first stage of the study 2-methylimidazo[1,2-*a*]pyridine-3-carbonyl azide (**I**) was obtained by reacting 2-methylimidazo[1,2-*a*]pyridine-3-carbohydrazide with nitrous acid. Compound **I** was refluxed in absolute ethanol to gain ethyl 2-(methylimidazo[1,2-*a*]pyridin-3-yl)carbamate (**II**), which was then reacted with hydrazine to afford N-(2-methylimidazo[1,2-*a*]pyridin-3-yl)hydrazinecarboxamide (**III**). Condensation of **III** with the appropriate aromatic aldehydes in ethanol yielded the corresponding aldehyde semicarbazones **IVa-f**. The semicarbazones were reacted with mercaptoacetic acid in dry benzene (Method A) to give cyclocondensation products **Va-d**. On the other hand, refluxing a mixture of **III** and the appropriate aromatic aldehydes, together with mercaptoacetic acid in dry benzene (Method B), also produced the target compounds, **V,** but in higher yields, except **Vb**.

The IR spectrum of **I** displayed a strong band at 2149 cm^{-1} due to N_3 stretching. Characteristic N-H and C=O absorptions at 3271 cm^{-1} and 1694 cm^{-1}, and loss of N_3 absorption at 2149 cm^{-1} supported the formation of **II**. The N-H and C=O absorption peaks were observed in the 3304-3161 cm^{-1} region and at 1643 cm^{-1} in the spectrum of **III**. The IR spectra of **IVa-f** exhibited C=O bands in the 1684-1694 cm^{-1} region. A new strong band in the 1700-1704 cm^{-1} region in the spectra of **Va-d** provided firm support for

the cycloaddition reaction. ^{1}H-NMR spectra of compounds **Va-c** displayed 2 doublets at about 3.76-3.88 ppm (except **Vd**, a multiplet together with OCH_3 resonance) due to the inequivalance of the SCH_2 protons. The singlet of N=CH at about 7.83-8.05 ppm in the spectra of **IVa-f** was shifted upfield to 5.81-5.86 ppm by the loss of the sp^2 character of the involved C atom. The mass spectra of all the compounds were relatively simple and showed their peaks due to molecular ions. All attempts to obtain the nitro derivatives (**V**) failed. This can be explained by the electronic effects of the nitro group (negative resonance and inductive effects) making the benzylic carbon atom more nucleophilic for the reaction with the sulfhydryl group.

All the compounds were evaluated for anti-tuberculous activity using the BACTEC method; only **IVe** showed activity (8% inhibition) at 6.25 μg mL^{-1}.

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