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# SOME IMIDAZO[1,2-*a*] PYRIDINE DERIVATIVES AS POSSIBLE ANTIMYCOBACTERIALS

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## SUMMARY

Some new hydrazide-hydrazones and 4-thiazolidinones incorporating an imidazo[1,2-*a*]pyridine moiety were synthesized and the new and structurally related compounds which were previously reported were screened for antituberculosis activity.

## ÖZET

İmidazo[1,2-*a*]piridin artığı taşıyan bazı yeni hidrazid-hidrazon ve 4-tiyazolidinon yapısındaki bileşiklerin sentezleri yapılmış, yeni bileşiklerin ve daha önce bildirilmiş yapısal benzerlikteki bileşiklerin antitüberküloz etkileri araştırılmıştır.

**Key words**: hydrazide-hydrazones, thiosemicarbazides, 4-thiazolidinones imidazo[1,2-*a*]pyridine, antituberculosis activity.

## INTRODUCTION

The treatment of tuberculosis is still one of the major problems due to the rise of multidrug-resistant tuberculosis in clinical practise. In our previous studies (1-3) we described the synthesis of imidazo[1,2-*a*]pyridine-3-carbohydrazides and related compounds, which are structurally similar to isonicotinic acid hydrazide (INH), the principal drug for the treatment of tuberculosis. As a con-

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tinuation of our programme concerning heterocycles we synthesized some new hydrazide-hydrazones **5**, **6** and 4-thiazolidinones **8**, **9** incorporating an imidazo[1,2-*a*]pyridine moiety. The new compounds **5**, **6**, **8** and **9** and structurally related compounds **1-4**, **7**, **10** and **11**, which were previously reported were evaluated for *in vitro* antituberculosis activity against *Mycobacterium tuberculosis* $H_{37}R_v$ (4).

## RESULTS AND DISCUSSION

The synthetic pathway used in the preparation of the compounds is outlined in the Scheme. 2-Methylimidazo[1,2-*a*]pyridine-3-carbohydrazide **1** (5) and 2,7/8-dimethylimidazo[1,2-*a*]pyridine-3-carbohydrazides, **2**,**3** (5), were obtained by refluxing the corresponding esters with hydrazine.

Condensation of **1-3** with appropriate aldehydes yielded the corresponding hydrazide-hydrazones **4-6** , which on condensation with mercaptoacetic acid afforded 4-thiazolidinones **7- 9**. Acylthiosemicarbazides , **10** , were synthesized by the addition of 2-methylimidazo[1,2-*a*]pyridine-3-carbohydrazide to isothiocyanic acid (**10a**) (3) or aryl/alkyl isothiocyanates (**10b-h**) (1). **10b-f** , on treatment with ethyl bromoacetate gave the desired thiazolidinones **11b-f** (1). The IR spectra of compounds **5**, **6**, **8** and **9** showed CO bands at 1621-1663 $cm^{-1}$ (CONHN-). A new strong band at 1707-1718 $cm^{-1}$ in the spectra of **8** and **9** provided firm support for ring closure. After reaction with mercaptoacetic acid the $^1$H-NMR spectra of compounds **8** and **9** displayed two doublets at about 3.83-3.94 ppm due to the nonequivalance of the methylene protons (6). The singlet at about 8.32-8.34 ppm in the spectra of **5** and **6** was shifted upfield to 5.94-5.95 ppm by the loss of the $sp^2$ character of the involved C-atom.

Spectral data of representative derivatives are given in Experimental. Some physical and analytical data of **5**, **6**, **8** and **9** are given in Table 1. The new compounds and structurally related compounds which were previously reported were evaluated for antituberculosis activity against *M. tuberculosis* $H_{37}R_v$ (Table 2) . **10h** , **10g** , **10a** and **5d** exhibited varying degrees of inhibition in the *in vitro* primary screen conducted at 12.5 mcg/ml. Rifampin was used as the standart in the tests. Only **10h** effecting >99% inhibition in the primary screen at 12.5 mcg/ml was re-tested at lower concentration to determine the actual minimum inhibitory concentration (MIC). The MIC of **10h** was found to be 6.25 mcg/ml.

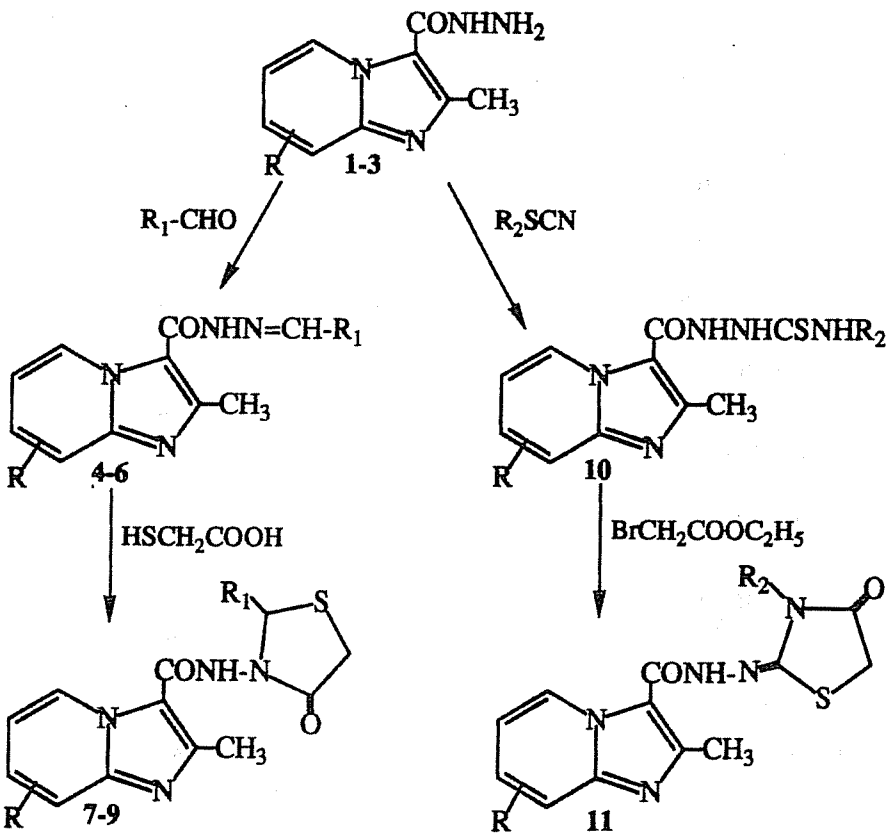
CONHNH2
CH3
N
N
R
1-3
R1-CHO
R2SCN
CONHN=CH-R1
CH3
4-6
CONHNHCSNHR2
10
HSCH2COOH
BrCH2COOC2H5
R1
S
CONH-N
O
7-9
R2
11

**Table 1:** Some physical and analytical data of **5,6,8** and **9**

| Comp. | Formula (MW) | Mp (°C) | Yield (%) | Analysis calcd./found C | H | N |
|---|---|---|---|---|---|---|
| **5a** | $C_{17}H_{16}N_4O$ (292.3) | 233-5 | 89 | 69.84<br>69.62 | 5.51<br>5.70 | 19.16<br>18.78 |
| **5b** | $C_{17}H_{15}ClN_4O$ (326.7) | 262-5 | 92 | 62.48<br>62.53 | 4.62<br>4.58 | 17.14<br>17.10 |
| **5c** | $C_{18}H_{18}N_4O \cdot H_2O$ (324.37) | 212-5 | 90 | 66.65<br>66.58 | 6.20<br>5.99 | 17.27<br>17.22 |
| **5d** | $C_{17}H_{15}N_5O_3$ (337.3) | 247-8 | 94 | 60.52<br>60.59 | 4.48<br>4.49 | 20.76<br>20.73 |
| **5e** | $C_{18}H_{18}N_4O_2$ (322.35) | 245-7 | 98 | 67.06<br>67.07 | 5.62<br>5.64 | 17.38<br>17.33 |
| **6a** | $C_{17}H_{16}N_4O$ (292.33) | 205 | 89 | 69.84<br>69.94 | 5.51<br>5.52 | 19.16<br>19.20 |
| **6b** | $C_{17}H_{15}ClN_4O \cdot 0.5\ H_2O$ (335.5) | 242-5 | 81 | 60.80<br>61.32 | 4.80<br>4.55 | 16.68<br>16.80 |
| **6c** | $C_{18}H_{18}N_4O \cdot 3H_2O$ (360.3) | 204 | 89 | 59.98<br>60.37 | 6.71<br>6.37 | 15.54<br>15.75 |
| **6d** | $C_{17}H_{15}N_5O_3$ (337.3) | 255-61 | 76 | 60.52<br>60.50 | 4.48<br>4.53 | 20.76<br>20.95 |
| **6e** | $C_{18}H_{18}N_4O_2 \cdot H_2O$ (340.43) | 208 | 84 | 63.51<br>63.52 | 5.92<br>6.28 | 16.42<br>16.45 |
| **8a** | $C_{19}H_{18}N_4O_2S \cdot C_2H_5OH \cdot H_2O$ (430.51) | 131-2 | 87 | 58.58<br>58.07 | 6.08<br>5.45 | 13.01<br>13.02 |
| **8b** | $C_{19}H_{17}ClN_4O_2S \cdot H_2O$ (418.87) | 132-5 | 42 | 54.47<br>55.16 | 4.57<br>4.62 | 13.37<br>13.28 |
| **8c** | $C_{20}H_{20}N_4O_2S \cdot H_2O$ (398.45) | 115 | 89 | 60.27<br>60.87 | 5.56<br>5.94 | 14.06<br>13.30 |
| **8e** | $C_{20}H_{20}N_4O_3S \cdot H_2O$ (414.47) | 134-7 | 81 | 57.95<br>58.14 | 5.35<br>5.56 | 13.51<br>12.79 |
| **9c** | $C_{20}H_{20}N_4O_2S \cdot H_2O$ (398.45) | 135-40 | 98 | 60.27<br>60.15 | 5.56<br>5.55 | 14.06<br>14.05 |
| **9e** | $C_{20}H_{20}N_4O_3S \cdot H_2O$ (414.47) | 134-7 | 89 | 57.95<br>57.36 | 5.35<br>5.27 | 13.51<br>13.34 |

Table 2: Primary antituberculosis screen results*

| Comp. | R | $R_1$ | $R_2$ | MIC vs $H_{37}R_v$ | Inhibition % |
|---|---|---|---|---|---|
| **10h** | H | – | $C_6H_4CH_3$(4) | <12.5 | 99 |
| **10g** | H | – | $C_6H_5$ | >12.5 | 58 |
| **10a** | H | – | H | >12.5 | 34 |
| **5d** | 7-$CH_3$ | $C_6H_4NO_2$ (2) | – | >12.5 | 32 |
| **4d** | H | $C_6H_4NO_2$ (2) | – | >12.5 | 30 |
| **6b** | 8-$CH_3$ | $C_6H_4Cl$ (4) | – | >12.5 | 26 |
| **10f** | H | – | $C_4H_9$ (n) | >12.5 | 22 |
| **10b** | H | – | $CH_3$ | >12.5 | 19 |
| **5c** | 7-$CH_3$ | $C_6H_4CH_3$ (4) | – | >12.5 | 18 |
| **5a** | 7-$CH_3$ | $C_6H_5$ | – | >12.5 | 16 |
| **10c** | H | – | $C_2H_5$ | >12.5 | 15 |
| **2** | 7-$CH_3$ | – | – | >12.5 | 10 |
| **6c** | 8-$CH_3$ | $C_6H_4CH_3$ (4) | – | >12.5 | 9 |
| **6e** | 8-$CH_3$ | $C_6H_4OCH_3$ (4) | – | >12.5 | 8 |
| **10d** | H | – | $C_3H_5$ | >12.5 | 8 |
| **4c** | H | $C_6H_4CH_3$ (4) | – | >12.5 | 4 |
| **1** | H | – | – | >12.5 | 3 |
| **9b** | 8-$CH_3$ | $C_6H_4Cl$ (4) | – | >12.5 | 3 |
| **6a** | 8-$CH_3$ | $C_6H_5$ | – | >12.5 | 1 |
| **11e** | H | – | $C_3H_7$ (n) | >12.5 | 1 |
| **3** | 8-$CH_3$ | – | – | >12.5 | 0 |
| **4a** | H | $C_6H_5$ | – | >12.5 | 0 |
| **4b** | H | $C_6H_4Cl$ (4) | – | >12.5 | 0 |
| **9d** | 7-$CH_3$ | $C_6H_4NO_2$ (2) | – | >12.5 | 0 |
| **5b** | 7-$CH_3$ | $C_6H_4Cl$ (4) | – | >12.5 | 0 |
| **5e** | 7-$CH_3$ | $C_6H_4OCH_3$ (4) | – | >12.5 | 0 |
| **6d** | 8-$CH_3$ | $C_6H_4NO_2$ (2) | – | >12.5 | 0 |
| **7a** | H | $C_6H_5$ | – | >12.5 | 0 |
| **7b** | H | $C_6H_4Cl$ (4) | – | >12.5 | 0 |
| **7c** | H | $C_6H_4CH_3$ (4) | – | >12.5 | 0 |
| **7d** | H | $C_6H_4NO_2$ (2) | – | >12.5 | 0 |
| **8a** | 7-$CH_3$ | $C_6H_5$ | – | >12.5 | 0 |
| **8b** | 7-$CH_3$ | $C_6H_4Cl$ (4) | – | >12.5 | 0 |
| **8c** | 7-$CH_3$ | $C_6H_4CH_3$ (4) | – | >12.5 | 0 |
| **8e** | 7-$CH_3$ | $C_6H_4OCH_3$ (4) | – | >12.5 | 0 |
| **9a** | 8-$CH_3$ | $C_6H_5$ | – | >12.5 | 0 |
| **9c** | 8-$CH_3$ | $C_6H_4CH_3$ (4) | – | >12.5 | 0 |
| **9e** | 8-$CH_3$ | $C_6H_4OCH_3$ (4) | – | >12.5 | 0 |
| **10e** | H | – | $C_3H_7$ (n) | >12.5 | 0 |
| **11b** | H | – | $CH_3$ | >12.5 | 0 |
| **11d** | H | – | $C_3H_5$ | >12.5 | 0 |
| **11c** | H | – | $C_2H_5$ | >12.5 | 0 |
| **11f** | H | – | $C_4H_9$ (n) | >12.5 | 0 |

* Comment: MIC of Rifampin = 0.031 mcg/ml, 97% inhibition.

## EXPERIMENTAL

### Chemical studies

Melting points were determined with a Buchi 530 melting point apparatus in open capillaries and are uncorrected. IR (KBr) and $^1$H-NMR ([$D_6$]DMSO) were recorded on Perkin-Elmer 1600 and Bruker AC 200 (200 MHz) instruments respectively. Microanalyses were performed on a Carlo Elba 1106 elemental analyzer. All starting materials were purchased from E.Merck (Darmstadt, Germany).

### 2,7/8-Dimethylimidazo[1,2-*a*]pyridine-3-carbohydrazides 2,3 (5)

0.01 Mol of ethyl 2,7/8-dimethylimidazo[1,2-*a*]pyridine-3-carboxylate was refluxed with 0.1 mol of $H_2NNH_2$ in 15 ml of $C_2H_5OH$ (96%) for 5 h and cooled. The crystals were washed with $H_2O$ and recrystallized from $C_2H_5OH$ (96%). **2**,mp 192-194 °C; **3**, mp 215-218 °C.

### 2,7/8-Dimethylimidazo[1,2-*a*]pyridine-3-carbohydrazide hydrazones 5, 6

0.01 Mol of hydrazide (**2** or **3**) was refluxed with 0.01 mol of the appropriate aldehyde in 30 ml of $C_2H_5OH$ (96%) for an hour. The solid that separated was recrystallized from $C_2H_5OH$ (96%).

**5a**: IR : 1625 (C=O) cm$^{-1}$. $^1$H-NMR : δ(ppm) = 2.39 (3H, s, 7-$CH_3$), 2.54 (3H, s, 2-$CH_3$), 6.89 (1H, d, 6-H), 7.38-7.70 (6H, m, 8-H and $C_6H_5$), 8.32 (1H, s, N=CH), 8.78 (1H, d, 5-H), 11.32 (1H, s, CONH).

**6a**: IR : 1622 (C=O) cm$^{-1}$. $^1$H-NMR : δ(ppm) = 2.52 (3H, s, 8-$CH_3$), 2.57 (3H, s, 2-$CH_3$), 6.94 (1H, t, 6-H), 7.23 (1H, d, 7-H) , 7.42-7.68 (5H, m, $C_6H_5$), 8.34 (1H, s, N=CH), 8.73 (1H, d, 5-H), 11.41 (1H, s, CONH).

### 2-Aryl-3-[(2,7/8-dimethylimidazo[1,2-*a*]pyridine-3-yl)carbonyl]amino-4-thiazolidinones 8, 9

A mixture of hydrazone (**5** or **6**) (0.01 mol) and $HSCH_2COOH$ (0.15 mol) was refluxed in dry benzene (30 ml ) using a Dean-Stark water separator for 6 h .Excess benzene was evaporated *in vacuo*.The residue was triturated with saturated $NaHCO_3$ until $CO_2$ evolution ceased and allowed to stand overnight. The solid thus obtained was washed with $H_2O$, dried and recrystallized from $C_2H_5OH$-$H_2O$ mixture.

**8a:** IR: 1642 (NHCO), 1710 (thiazolidinone C=O) $cm^{-1}$. $^1$H-NMR: δ(ppm) = 2.16 (3H, s, 7-$CH_3$), 2.36 (3H, s, 2-$CH_3$), 3.83-3.94 (1H, each, 2d, J=16 Hz, $CH_2$-S), 5.94 (1H, s, CH-S), 6.86 (1H, d, 6-H), 7.33 (1H, s, 8-H), 7.37-7.55 (5H, m, $C_6H_5$), 8.66 (1H, d, 5-H), 10.06 (1H, s, CONH).

**9a:** IR: 1653 (NHCO), 1718 (thiazolidinone C=O) $cm^{-1}$. $^1$H-NMR: δ(ppm) = 2.18 (3H, s, 8-$CH_3$), 2.45 (3H, s, 2-$CH_3$), 3.83-3.94 (1H, each, 2d, J=16 Hz, $CH_2$-S), 5.95 (1H, s, CH-S), 6.92 (1H, t, 6-H), 7.20 (1H, d, 7-H), 7.37-7.56 (5H, m, $C_6H_5$), 8.60 (1H, d, 5-H), 10.12 (1H, s, CONH).

***In vitro* evaluation of antituberculosis activity** (4)

Primary screen was conducted at 12.5 mcg/ml against *M. tuberculosis* $H_{37}R_v$ in BACTEC 12B medium using BACTEC 460 radiometric system. Compounds affecting<90% inhibition in the primary screen (MIC>12.5 mcg/ml) were not evaluated further. Compounds demonstrating at least 90% inhibition in the primary screen were re-tested at a lower concentration (MIC) in CABTEC 460. The MIC was defined as the lowest concentration inhibiting 99% inoculum.

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