Preparation and Properties of Antitubercular 1-Piperidino-3-Arylthioureas [1]

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1-Piperidino-3-arylthioureas, of interest in the investigation of novel heterocyclic structures for their antitubercular activity, may be conveniently prepared in good yield and purity by the reaction of 1-aminopiperidine with aryl isothiocyanates in ethanol. The reaction takes place readily without the complication of thiourethane contaminants, and the products may be suitably identified by significant characteristics in the infrared spectra and the hydrogen and carbon magnetic resonance spectra.

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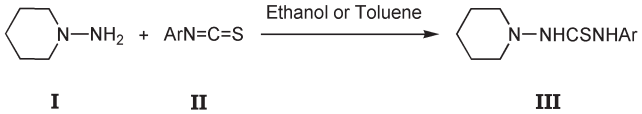
In spite of the fact that certain heterocyclic compounds have been among the most effective antitubercular medications prescribed for patients for some fifty years [2-4], much remains unknown about the scope of heterocyclic structures that will possess this important anti-infective activity [5]. Since the designation of tuberculosis as a global public health crisis by the World Health Organization in the last decade [6], new strains have appeared of *Mycobacterium tuberculosis* characterized by increased virulence or strong resistance to drugs commonly used in the past in treatment [7-10]. With a third of the world's population now infected with the bacillus and as many as three million deaths per year attributed to the disease [11,12], the medical and research communities have been faced with a declining number of antimycobacterials appropriate for an effective therapeutic regimen against this ancient killer [13-15]. There is an urgent need for advances in the design of antitubercular agents that will lead to newer and more powerful drugs [16]. The chemistry of heterocyclic compounds is likely to serve as a wellspring for the discovery of such drugs [17-21].

Recent disclosures from our laboratory [22] and others [23-25] have noted the role of the thiourea moiety in novel structures bearing antitubercular characteristics, but not much work has been done to date to extend this observation to heterocyclic systems. As part of our ongoing exploration of this issue, we now report on the preparation and properties of a series of 1-piperidino-3-arylthioureas (**III**).

Scheme



I **II** **III**

We have found that the compounds are readily formed from 1-aminopiperidine (**I**) and isothiocyanates (**II**) in good yield and purity as stable highly-crystalline solids. The reactions take place cleanly without formation of by-products (see Scheme). The resulting thioureas may be characterized in straightforward ways by standard spectrometric techniques and show activity against both laboratory strains and drug-resistant clinical isolates of *M. tuberculosis*.

In a typical example, compound **I** was treated with *m*-tolyl isothiocyanate (**IIe**, Ar = 3-CH_3Ph, 1.09 equivalents) in refluxing absolute ethanol for two hours. At the end of this time, hot filtration of the reaction mixture induced immediate crystallization of the product within the filtrate. The white needles were isolated and rinsed with absolute ethanol to give **IIIe** (Ar = 3-CH_3Ph, 84%) in analytically pure form. In each case examined, the reaction could be tested for completion through the distinguishing spectrometric features of the 1-piperidino-3-arylthioureas. Among the more noteworthy of these were 1) N-H bands consistent with the thiourea moiety near 3280 and 3160 wavenumbers in the infrared spectrum, 2) N-H peaks near δ 9.5 and 9.2 ppm in the hydrogen nmr spectrum, each integrating for one hydrogen, and 3) a signal near δ 177 ppm for the thiocarbonyl unit in the carbon nmr spectrum (see Experimental). Conspicuously absent in the isolated products were the exceptionally intense infrared bands belonging to the parent mustard oils **II** in the 2000 cm^{-1} region. Our results on the preparation of these materials are summarized in the Table.

We would like to comment briefly on the choice of solvent. In general, the selection of a solvent for the reaction of a nitrogenous base with an isothiocyanate should be made carefully. Alcohols have sometimes been used for this purpose [26,27], but we have observed that some

Table
Thioureas III

Entry	Compound	Ar	% Yield	mp °C	ν^{max} N-H, cm^{-1}	^{1}H-NMR	^{13}C-NMR
1.	**IIIa**	Ph	74	158-9	3289, 3177	δ9.60, 9.28	δ 177
2.	**IIIb**	4-CH_3OPh	76	140-1	3292, 3143	9.44, 9.10	178
3.	**IIIc**	4-$(CH_3)_2N$Ph	72	164-5	3284, 3160	9.32, 9.00	178
4.	**IIId**	2-CH_3Ph	78	183-4	3276, 3136	9.47, 9.23	177
5.	**IIIe**	3-CH_3Ph	84	173	3246, 3135	9.53, 9.22	177
6.	**IIIf**	4-CH_3Ph	76	158	3314, 3146	9.51, 9.13	177
7.	**IIIg**	4-$(CH_3)_2$CHPh	62	148-50	3267, 3135	9.49, 9.18	177
8.	**IIIh**	4-PhCH_2OPh	81	141-3	3292, 3148	9.42, 9.16	177
9.	**IIIi**	4-CH_3CH_2OCOPh	80	169-70	3276, 3174	9.87, 9.53	177
10.	**IIIj**	2,4-Cl_2Ph	55	161	3243, 3130	9.95, 9.71	177
11.	**IIIk**	4-FPh	60	158-9	3260, 3172	9.59, 9.30	177
12.	**IIIl**	2,4,6-F_3Ph	68	177	3283, 3144	9.49, 9.17	180

amino compounds are not sufficiently nucleophilic to react with isothiocyanates rapidly. In such cases, reaction of the mustard oil with an alcohol solvent (ROH) may lead to substantial contamination of the product with the related thiourethane (ArNHCSOR) [28]. The thiourethane is frequently removed from the desired thiourea only with some difficulty. Heteroaromatic amines and other aromatic amines typically fall into this less nucleophilic category, especially when they are substituted, and are more opportunely reacted in non-hydroxylic solvents, including toluene and tetrahydrofuran. Although we explored the use of both toluene and ethanol in the preparations described in this paper (see Experimental), 1-aminopiperidine was sufficiently reactive in all cases examined to permit the use of ethanol, frequently resulting in analytically pure thioureas.

In terms of biological assessment of the 1-piperidino-3-arylthioureas, the evaluation of compound **IIIa** (Ar = Ph) is representative. The substance was assayed *in vitro* in several strains of *M. tuberculosis*. The compound appears to have similar levels of activity against both susceptible and drug-resistant organisms. Thus in strain Erdman, a fully drug-susceptible strain, the minimum inhibitory concentration (MIC) was 32 μg/mL. In a panel of strains isolated from the clinic showing resistance to the current frontline medication isoniazid, the following MIC data were obtained: strain 1889, 32 μg/mL; strain 303, 8 μg/mL; strain 35829, 16 μg/mL. Concerning overall effectiveness, these MIC data are of the same order of magnitude as those for antitubercular thioureas that have recently been reported, but not so potent as some individual examples from the thiourea class [22,23]. A full account of the biological evaluation of these materials will appear in due course.

In summary, we have found that 1-piperidino-3-arylthioureas, prepared in the exploration of novel heterocyclic structures for antitubercular activity, may be conveniently formed in good yield and purity by the reaction of 1-aminopiperidine with aryl isothiocyanates in ethanol. The reaction takes place readily without the formation of thiourethane contaminants, and the products may be reliably identified by their salient spectrometric characteristics.

EXPERIMENTAL

General methods were as previously described in detail [9,22], including safety notes and information on instrumentation, commercial suppliers of analytical services, solvents and reagents. Although compounds **IIIa** and **IIIb** had been alluded to in the literature some time ago [29], they have now been fully characterized by up-to-date methods as shown below.

1-Piperidino-3-phenylthiourea (**IIIa**).

The reaction of 1.41 g (10.4 mmoles) of phenyl isothiocyanate (**IIa**) to 1.02 g (10.2 mmoles) of *N*-aminopiperidine **I** in absolute ethanol was completed during 30 minutes of reflux. The mixture was cooled slowly to room temperature and the resulting solid filtered. On concentration of the mother liquor using a Dean Stark trap, a second crop was obtained. The total crude yield was 1.79 g (74 %). Three ether washes of the combined crops gave analytically pure material with a recovery of 83%, mp 158-9º, lit mp 159-160º [29]; ir: 3289 (w), 3177 (m), 3045 (w), 2950 (w), 2930 (m), 2855 (w), 2822 (w), 1600 (w), 1589 (w), 1536 (s), 1493 (s), 1443 (s), 1378 (w), 1316 (w), 1289 (m), 1272 (s), 1255 (m), 1201 (s), 1152 (m), 1088 (m), 1036 (m), 991 (m), 933 (m), 909 (w), 866 (m), 803 (m), 762 (m), 735 (s), 680 (s); ^{1}H nmr (DMSO-d_6): δ 9.60 (1H, s), 9.28 (1H, s), 7.60 (2H, d, J = 9 cps), 7.30 (2H, m), 7.10 (1H, m), 2.91 (2H, m), 2.51 (2H, m), 1.66 (5H, m), 1.10 (1H, m); ^{13}C (DMSO-d_6): δ 177.4, 139.3, 128.2, 124.8, 56.3, 25.5, 23.1; HR-MS (fast atom bombardment, MH^+) calculated for $C_{12}H_{18}N_3S$ 236.1221, found 236.1222.

Anal. Calcd. for $C_{12}H_{17}N_3S$: C, 61.24; H, 7.28. Found: C, 60.95; H, 7.41.

1-Piperidino-3-(4-methoxyphenyl)thiourea (**IIIb**). Solvent Studies.

Method A, Ethanol. In a manner similar to that noted above, 1.0 g (10 mmoles) of *N*-aminopiperidine **(I)** and 1.7 g (10.3 mmoles) of *p*-methoxyphenyl isothiocyanate (**IIb**) gave a first crop of silky white needles 1.76 g (66%). Concentration of the mother liquor gave additional product, overall yield (78%) mp 140° (corr.); ir as below, Method C.

Method B, Toluene, Two Crops. With the same quantities as

above in Method A, save for the substitution of toluene for ethanol, a first crop of 48% was obtained. Concentration of the mother liquor using a Dean Stark trap gave a second crop, total yield 76%. Three ether washes followed by recrystallization from ethanol gave analytically pure material, melting point 140-1º (corr.); ir as below, Method C.

Anal. Calcd. for $C_{13}H_{19}N_3OS$: C, 58.84; H, 7.22. Found: C, 59.11; H, 7.34.

Method C, Toluene, One Crop. With the same quantities as above in Method A, save for the substitution of toluene for ethanol, the yield of analytically pure white, flaky crystals was 1.76 g (48%), mp 140-1° (corr), lit mp 140-1° [29]; ir: 3292 (w), 3143 (w), 2935 (w), 2826 (w), 1538 (s), 1509 (s), 1493 (s), 1466 (w), 1439 (w), 1293 (w), 1273 (w), 1232 (s), 1212 (s), 1177 (m), 1163 (m), 1147 (m), 1091 (m), 1033 (s), 991 (w), 928 (w), 865 (m), 838 (m), 808 (m), 740 (m), 698 (w); ^{1}H nmr (DMSO-d_6): δ 9.44 (1H, s), 9.10 (1H, s), 7.40 (2H, d, J = 9), 6.86 (2H, d, J = 9), 3.74 (3H, s), 2.93 (2H, m), 2.52 (2H, m), 1.65 (5H, m), 1.08 (1H, s (broad)); ^{13}C (DMSO-d_6): δ 177.9, 156.8, 132.2, 126.8, 113.4, 55.5, 25.5, 23.1; HR-MS (fast atom bombardment, MH^+) calculated for $C_{13}H_{20}N_3OS$ 266.1327, found 266.1333.

Anal. Calcd. for $C_{13}H_{19}N_3$ OS: C, 58.84; H, 7.22. Found: C, 58.88; H, 7.38.

1-Piperidino-3-(4-dimethylaminophenyl)thiourea (**IIIc**).

Since the 4-dimethylaminophenyl isothiocyanate (**IIc**) as received from the commercial source is typically non-granular, 2.34 g (13.1 mmoles) was first dissolved in 25 mL of absolute ethanol with warming. The warm solution was added by pipet to a stirred solution at room temperature of 1.00 g (10 mmoles) of *N*-aminopiperidine (**I**) in 5 mL of absolute ethanol over a period of about 5 minutes. The homogeneous mixture was refluxed for 80 minutes and filtered hot. White needles appeared almost immediately. After standing, the product (**IIIc**) was collected by filtration; 1.99 g (72%), mp 164-5°; ir: 3284 (w), 3160 (w), 2932 (w), 2823 (w), 1612 (w) 1520 (s), 1494 (s), 1439 (m), 1382 (w), 1344 (m), 1274 (m), 1243 (m), 1205 (s), 1186 (s), 1160 (m), 1149 (m), 1126 (m), 1087 (m), 1060 (w), 1034 (m), 990 (m), 946 (w), 908 (w), 866 (w), 816 (s), 801 (s), 767 (s), 732 (m), 688 (w); ^{1}H nmr (DMSO-d_6): δ 9.32 (1H,s), 9.00 (1H,s), 7.30 (2H, d, J = 9 cps), 6.69 (2H, d, J = 9 cps), 2.88 (8H, m), 2.52 (2H, broad m), 1.62 (5H, m), 1.08 (1H, m); ^{13}C nmr (DMSO-d_6): δ 177.7, 147.9, 128.4, 126.2, 111.8, 55.1, 25.3, 22.5; HR-MS (fast atom bombardment, MH^+) calculated for $C_{14}H_{23}N_4S$ 278.1565, found 278.1566.

Anal. Calcd. for $C_{14}H_{22}N_4S$: C, 60.39; H, 7.96. Found: C, 60.60; H, 8.09.

1-Piperidino-3-(*o*-tolyl)thiourea (**IIId**).

The addition of 1.63 g (10.9 mmoles) of *o*-tolyl isothiocyanate (**IId**) in 5 mL of absolute ethanol by pipet in small portions to a stirred solution of 1.00 g (10 mmoles) of *N*-aminopiperidine (**I**) in 10 mL of absolute ethanol was followed by refluxing for two hours and hot filtration. White crystals appeared immediately in the filtrate. After cooling, filtration and drying, the yield was 1.95 g (78%), mp 183-4°; ir: 3276 (w), 3136 (w), 2943 (w), 2853 (w), 2808 (w), 1583 (w), 1533 (s), 1499 (s), 1479 (s), 1457 (s), 1252 (m), 1221 (s), 1146 (w), 1088 (w), 1062 (w), 1032 (m), 992 (m), 925 (w), 857 (m), 810 (m), 792 (m), 770 (w), 733(s); ^{1}H nmr (DMSO-d_6): δ 9.47 (1H, s), 9.23 (1H, s), 7.59 (1H d, J = 9), 7.18 (3H, m), 2.94 (2H, d , J = 9), 2.53 (2H, m), 2.24 (3H, s), 1.65 (5H, m), 1.08 (1H; m broad); ^{13}C nmr (DMSO-d_6): δ 177.1, 136.4, 128.7, 124.4. 56.0, 25.1, 22.8, 20.48; HR-MS (fast atom bombardment, MH^+) calculated for $C_{13}H_{20}N_3S$ 250.1378, found 250.1380.

Anal. Calcd. for $C_{13}H_{19}N_3S$: C, 62.61; H, 7.68. Found: C, 62.97; H, 7.92.

1-Piperidino-3-(*m*-tolyl)thiourea (**IIIe**).

In a manner similar to that for **IIId**, 1.00 g (10.0 mmoles) of *N*-aminopiperidine (**I**) and 1.63 g (10.9 mmoles) of *m*-tolyl isothiocyanate (**IIe**) gave analytically pure white needles, 2.09 g (84%) mp 173°; ir: 3246 (w), 3135 (m), 3038 (w), 2988 (w), 2940 (m), 2858 (w), 2828 (w), 1609 (w), 1590 (m), 1536 (s), 1505 (s), 1478 (m), 1440 (m), 1380 (w), 1346 (w), 1308 (w). 1291 (m), 1272 (m), 1257 (m), 1228 (w), 1213 (s), 1152 (w), 1148 (m), 1089 (m), 1034 (m), 994 (m), 968 (w), 909 (w), 901 (w), 877 (m), 869 (w), 855 (w), 838 (w), 791 (s), 782 (s), 719 (s), 688 (s); ^{1}H nmr (DMSO-d_6): δ 9.53 (1H, s), 9.22 (1H, s), 7.48 (1H, d, J = 9 cps), 7.42 (1H, s), 7.15 (1H, m), 6.93 (1H, d, J = 9 cps), 2.92 (2H, m), 2.52 (2H, m), 2.31 (3H, s), 1.69 (5H, s), 1.08 (1H, s); ^{13}C nmr (DMSO-d_6): δ 177.0, 138.8, 137.2, 127.7, 125.1, 124.6, 121.3, 55.2, 25.1, 22.7, 20.9; HR-MS (fast atom bombardment) calculated for $C_{13}H_{19}N_3S$ 250.1378, found 250.1377.

Anal. Calcd. for $C_{13}H_{19}N_3S$: C, 62.61; H, 7.68. Found: C, 62.48; H, 7.92.

1-Piperidino-3-(*p*-tolyl)thiourea (**IIIf**).

By a method analogous to that for **IIIc**, *p*-tolyl isothiocyanate (**IIf**, 1.63 g, 10.9 mmoles) was reacted with 1.00 g (10.0 mmoles) of *N*-aminopiperidine (**I**) for two hours to give 1.90 g of analytically pure product (76%), mp 158°; ir: 3314 (w), 3146 (w), 2935 (m), 1539 (s), 1512 (s), 1491 (s), 1381 (w), 1306 (w), 1290 (m), 1275 (s), 1205 (m), 1170 (m), 1144 (m), 1086 (m), 988 (m), 929 (w), 864 (m), 843 (w), 825 (s), 806 (m), 785 (s), 733 (s), 695 (w); ^{1}H nmr (DMSO-d_6): δ 9.51 (1H, s), 9.13 (1H, s), 7.47 (2H, d, J = 9), 7.08 (2H, d, J = 9), 2.92 (2H, m), 2.51 (2H, m), 2.25 (3H, m), 1.62 (5H, m), 1.08 (1H, m); ^{13}C nmr (DMSO-d_6): δ 177.1, 136.4, 133.5, 128.3, 124.4, 55.6, 25.1, 22.8, 20.4; HR-MS (fast atom bombardment) calculated for $C_{13}H_{19}N_3S$ 250.1378, found 250.1380.

Anal. Calcd. for $C_{13}H_{19}N_3S$: C, 62.61; H, 7.68. Found: C, 62.78; H, 7.72.

1-Piperidino-3-(4-i-propylphenyl)thiourea (**IIIg**).

In a manner similar to that for **IIId**, 0.78 g (4.4 mmoles) of 4-*i*-propylphenyl isothiocyanate (**IIg**) and 4.1 g (4.1 mmoles) of *N*-aminopiperidine (**I**) gave 0.73 g of glistening white crystals (62%), mp 148-150°; ir: 3267 (w), 3135 (m), 3033 (w), 2954 (m), 2935 (m), 2859 (w), 2830 (w), 1584 (w), 1537 (s), 1514 (s), 1493 (s), 1466 (m), 1442 (m), 1417 (m), 1381 (w), 1361 (w), 1338 (w), 1302 (w), 1270 (s), 1255 (s), 1205 (s), 1149 (m), 1103 (w), 1087 (w), 1060 (w), 1049 (m), 1037 (m), 1018 (w), 996 (w), 928 (m), 909 (w), 871 (m), 861 (w), 835 (s), 809 (w), 799 (m), 768 (m), 743 (w), 702 (m); ^{1}H nmr (DMSO-d_6): δ 9.49 (1H, s), 9.18 (1H, s), 7.50 (2H, d, J = 9), 7.20 (2H, d, J = 9), 2.92 (3H, m), 2.54 (2H, m), 1.64 (5H, m), 1.19 (6H, d, J = 6), 1.08 (1H, m); ^{13}C nmr (DMSO-d_6): δ 177.1, 144.6, 136.7, 125.6, 125.1, 124.4, 55.2, 32.9, 25.1, 23.9, 22.7; HR-MS (fast atom bombardment) calculated for $C_{15}H_{23}N_3S$ 278.1691, found 278.1688.

Anal. Calcd. for $C_{15}H_{23}N_3S$: C, 64.94; H, 8.36. Found: C, 65.05; H, 8.47.

1-Piperidino-3-(4-benzyloxyphenyl)thiourea (**IIIh**).

In a manner similar to that for **IIId**, 2.68 g (11.1 mmoles) of 4-benzyloxyphenyl isothiocyanate **(IIh)** and 1.00 g (10.0 mmoles) of *N*-aminopiperidine (**I**) gave the title compound in 81% yield, mp 141-3°; ir: 3292 (w), 3148 (m), 3031 (w), 2935 (m), 2916 (w), 2828 (w), 1542 (s), 1507 (s), 1492 (s), 1467 (m), 1452 (m), 1413 (w), 1377 (m), 1294 (m), 1275 (m), 1234 (s), 1208 (s), 1163 (s), 1146 (m), 1104 (m), 1091 (m), 1061 (w), 1035 (m), 1000 (s), 946 (w), 935 (w), 913 (m), 864 (m), 857 (m), 828 (s), 805 (m), 752 (s), 737 (s), 695 (s); ^{1}H nmr (DMSO-d_6): δ 9.42 (1H, s), 9.16 (1H, s), 7.41 (7H, m), 7.00 (2H, m), 5.09 (2H, s), 2.92 (2H, m), 2.49 (2H, m), 1.69 (5H, s), 1.09 (1H, m); ^{13}C nmr (DMSO-d_6): δ 177.4, 155.4, 137.1, 132.1, 128.3, 127.7, 127.6, 126.4, 114.0, 69.2, 55.2, 25.14, 22.8; HR-MS (fast atom bombardment) calculated for $C_{19}H_{23}N_3OS$ 342.1640, found 342.1641.

Anal. Calcd. for $C_{19}H_{23}N_3OS$, C, 66.83; H, 6.79. Found: C, 66.67; H, 6.83.

1-Piperidino-3-(4-ethoxycarbonylphenyl)thiourea (**IIIi**).

By a method analogous to that for **IIIc**, 4-ethoxycarbonylphenyl isothiocyanate **(IIi**, 2.28 g, 11.3 mmoles) reacted with 1.00 g (10 mmoles) of *N*-aminopiperidine (**I**) to produce analytically pure material, 2.46 g (80%), mp 169-170°; ir: 3276 (w), 3174 (w), 2956 (w), 2932 (w), 2827 (w), 1715 (s), 1605 (m), 1583 (w), 1534 (s), 1482 (s), 1464 (m), 1442 (m), 1406 (s), 1365 (w), 1295 (w), 1265 (s), 1201 (s), 1173 (s), 1150 (m), 1099 (s), 1037 (m), 1023 (m to s), 1013 (m to s), 993 (m), 929 (w), 911 (w), 873 (m), 857 (m), 803 (s), 775 (m), 748 (s), 710 (s), 660 (m); ^{1}H nmr (DMSO-d_6): δ 9.87 (1H, s), 9.53 (1H, s), 7.91 (4H, s), 4.30 (2H, m), 2.92 (2H, m), 2.56 (2H, m), 1.69 (5H, s), 1.31 (3H, m); ^{13}C nmr (DMSO-d_6): δ 176.6, 165.3, 143.4, 129.1, 125.1, 122.9, 60.4, 55.2, 25.0, 22.7, 14.1; HR-MS (fast atom bombardment) calculated for $C_{15}H_{21}N_3O_2S$ 308.1433, found 308.1434.

Anal. Calcd. for $C_{15}H_{21}N_3O_2S$: C, 58.61; H, 6.89. Found: C, 58.61; H, 7.00.

1-Piperidino-3-(2,4-dichlorophenyl)thiourea (**IIIj**).

N-Aminopiperidine (**I**, 1.00 g, 10.0 mmoles) in toluene reacted with 2,4-dichlorophenyl isothiocyanate (**IIj**, 2.04 g, 10.0 mmoles) to deposit a voluminous white solid, which was collected by filtration and dried to give **IIIj**, 1.68 g (55%), mp 161°; ir: 3243 (w), 3130 (m), 2982 (w), 2947 (m), 2852 (w), 2815 (w), 1570 (m), 1536 (s), 1497 (s), 1448 (m), 1439 (m), 1376 (m), 1300 (m), 1272 (m), 1248 (s), 1205 (m), 1137 (m), 1092 (s), 1062 (w), 1053 (m), 1030 (m), 993 (m), 939 (w), 865 (m), 854 (s), 825 (m), 811 (s), 787 (m), 745 (m), 684 (m), 668 (m); ^{1}H nmr (DMSO-d_6): δ 9.95 (1H, s), 9.71 (1H, s), 8.35 (1H, d, J = 9 cps), 7.69 (1H, d, J = 1 cps), 7.42 (1H, dd, J = 9, 1 cps), 2.95 (2H, m), 2.60 (2H, m), 1.65 (5H, m), 1.12 (1H, m); ^{13}C nmr (DMSO-d_6): δ 177.4, 135.5, 129.5, 128.7, 128.2, 128.0, 127.4, 55.4, 25.7, 23.0; HR-MS (fast atom bombardment, MH^+) calculated for $C_{12}H_{16}N_3SCl_2$ 304.0442, found 304.0443.

Anal. Calcd. for $C_{12}H_{15}N_3SCl_2$: C, 47.37; H, 4.97. Found: C, 47.50; H, 4.97.

1-Piperidino-3-(4-fluorophenyl)thiourea (**IIIk**).

A solution of 0.70 g (4.6 mmoles) of *p*-fluorophenyl isothiocyanate (**IIk**) in absolute ethanol reacted with 0.41 g (4.1 mmoles) of *N*-aminopiperidine (**I**) to give the title compound (60%), mp 158-9°; ir: 3260 (w), 3172 (w), 2947 (w), 1540 (s), 1498 (s), 1413 (w), 1256 (m), 1212 (s), 1151 (m), 1100 (m), 1038 (m), 999 (m), 937 (w), 871 (m), 840 (s), 818 (s), 733 (s); ^{1}H nmr (DMSO-d6): δ 9.59 (1H, s), 9.30 (1H, s), 7.60 (2H, m), 7.18 (2H, m), 2.92 (2H, m), 2.50 (2H, s), 1.64 (5H, s); 1.09 (1H, m); ^{13}C nmr (DMSO-d_6): δ 177.4, 160.7, 157.5, 135.3, 126.8, 114.5, 114.3, 55.2, 25.0, 22.7; HR-MS (fast atom bombardment) calculated for $C_{12}H_{16}N_3SF$ 254.1127, found 254.1128.

Anal. Calcd. for $C_{12}H_{16}N_3SF$: C, 56.89; H, 6.36. Found: C, 56.91; H, 6.45.

1-Piperidino-3-(2,4,6-trifluorophenyl)thiourea (**IIIl**).

In a manner similar to that for **IIId**, 2,4,6-trifluorophenyl isothiocyanate (**IIl**) (1.56 g, 6.11 mmoles) was reacted with 0.751 g (7.51 mmoles) of *N*-aminopiperidine (**I**) to give **IIIl** (68%), mp 177°; ir: 3283 (w), 3144 (w), 2953 (w), 1604 (w), 1536 (s), 1513 (s), 1476 (s), 1450 (s), 1366 (w), 1255 (m), 1214 (m), 1172 (w), 1149 (w), 1121 (s), 1063 (w), 1041 (s), 994 (s), 923 (w), 851 (s), 834 (m), 801 (w), 764 (w); ^{1}H nmr (DMSO-d_6): δ 9.49 (1H, s), 9.17 (1H, s), 7.21 (2H, m), 2.92 (2H, m), 2.47 (2H, m), 1.58 (5 H, s), 1.10 (1H, m); ^{13}C nmr (DMSO-d_6): δ 179.7, 161.9, 160.6, 158.6, 157.5, 114.2, 100.3, 55.1, 25.0, 22.8; HR-MS (fast atom bombardment) calculated for $C_{12}H_{14}N_3SF_3$ 290.0939, found 290.0940.

Anal. Calcd. for $C_{12}H_{14}N_3SF_3$: C, 49.82; H, 4.88. Found: C, 49.87; H, 4.90.

Biological Assessments *in vitro*.

Detailed accounts have appeared of the methods used for these evaluations [9,30]. In brief, the minimum inhibitory concentrations of the antimicrobial agents were determined by a broth dilution method. *M. tuberculosis* strain Erdman (ATCC 35801) was obtained from the American Type Culture Collection, Manassas, Virginia. Other strains were clinical isolates. The minimum inhibitory concentrations of all antimicrobial agents were determined in modified 7H10 broth (7H10 agar formulation with agar and malachite green omitted; pH 6.6) supplemented with 10% Middlebrook oleic acid-albumin-dextrose-catalase (OADC) enrichment (Difco Laboratories, Detroit, Michigan) and 0.05% Tween 80.

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