Chemistry of Heterocyclic Compounds, Vol. 44, No. 8, 2008

4-HYDROXY-2-QUINOLONES 148*. SYNTHESIS AND ANTI-TUBERCULAR ACTIVITY OF 1-HYDROXY-3-OXO-6,7-DIHYDRO-3H,5H-PYRIDO[3,2,1-*ij*]QUINOLINE-2-CARBOXYLIC ACID N-R-AMIDES

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An improved method for the preparation of ethyl 1-hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-ij]quinoline-2-carboxylate has been proposed and a series of hetarylamides has been synthesized from it. A comparative analysis has been carried out of the antitubercular activities of the synthesized compounds with the active structural analogs 4-hydroxy-2-oxo-1,2-dihydroquinoline-3 and 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-ij]quinoline-2-carboxamides studied before.

Keywords: hetarylamides, 4-hydroxy-2-oxoquinoline-3-carboxylic acids, amidation, antitubercular activity, X-ray structural analysis.

The main problem in the treatment of tuberculosis is the rapid development of resistant pathogens of this dangerous infection to antimicrobial preparations [2, 3]. According to WHO service multiple medicine resistant tuberculosis is diagnosed today in an average of 7% of patients which can rapidly seriously destabilize to a world wide epidemiological situation and develop into a global human threat [4]. Besides improving prophylactic and diagnostic measures there is now an increase in developing three avenues of research, if not for a removal agenda of the problem of polyresistant strains then at least to lowering their severity. The first of these includes the development of strict control schemes *via* a short course of intensive chemotherapy using a combination of already existing pharmaceutical agents which significantly inhibits the development of stability towards it [4, 5]. The second route combines genetic investigation of decoding nucleotides in the *Mycobacterium tuberculosis* genome in order to discover the genes responsible for the course of cell mutation and hence suited to the development of antibiotic resistance [6, 7]. In the future such a route will certainly permit conceptually novel agents and methods of attack of tuberculosis to develop. However, the value of the third direction based on an empirical selection of a leading structure from a number of synthesized and then pharmacologically studied compounds has not been exhausted at the present level of development of science.

* For Communication 147 see [1].

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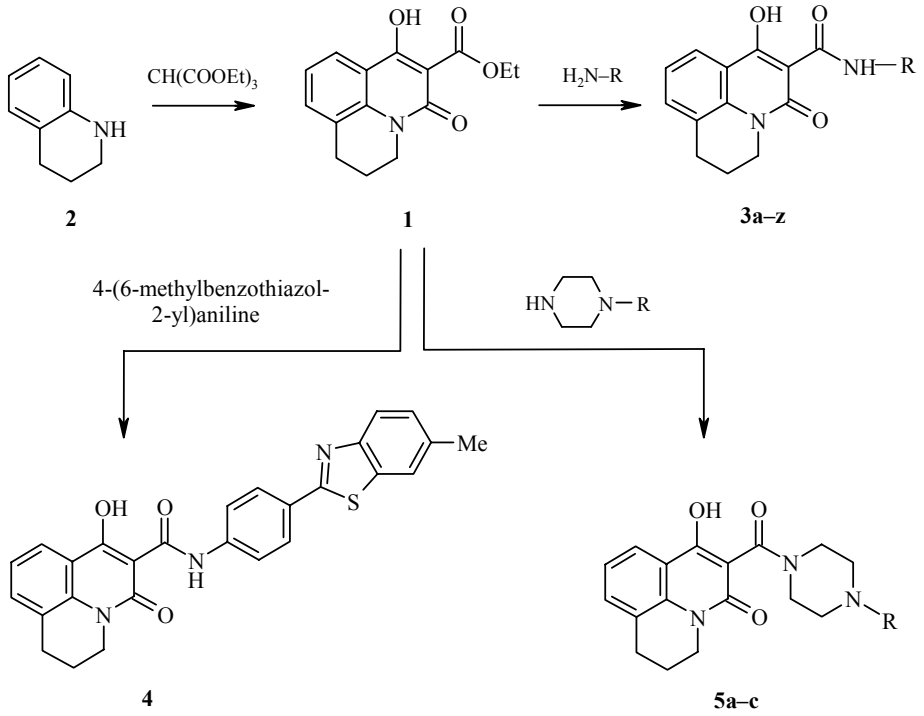
As a particular result of this it is almost impossible to forecast *a priori* the important parameters for many future medicines and one substance rather than another can only stand out as the result of a detailed study of a broad combination of actual properties. This report is a part of such an investigation.

Compounds with high antimicobacterial activity have previously been found by us amongst 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid heterylamides [8]. On this basis it was of interest to exchange the trihydropyrrole nucleus annelated to the quinoline ring for a tetrahydropyridine. In contrast to the completely planar pyrroloquinolone system [9] the pyridoquinolone atom skeleton is unlikely to have a single planar disposition. Hence such a modification can give extremely useful information as to how the part of the molecule undergoing structural change interacts with the biological target.



2 **1** **3a–z**

4 **5a–c**

3a R = pyridin-4-yl, **b** R = pyridin-3-yl, **c** R = pyridin-2-yl, **d** R = 3-hydroxypyridin-2-yl, **e** R = 3-methylpyridin-2-yl, **f** R = 4-methylpyridin-2-yl, **g** R = 5-methylpyridin-2-yl, **h** R = 6-methylpyridin-2-yl, **i** R = pyridimin-2-yl, **j** R = thiazol-2-yl, **k** R = 4-methylthiazol-2-yl, **l** R = 5-methylthiazol-2-yl, **m** R = 4-ethoxycarbonylmethylthiazol-2-yl, **n** R = 4-(1-adamantyl)thiazol-2-yl, **o** R = 4-phenylthiazol-2-yl, **p** R = 4-(4-chlorophenyl)thiazol-2-yl, **q** R = 4-(4-bromophenyl)thiazol-2-yl, **r** R = 5-methyl-1,3,4-thiadiazol-2-yl, **s** R = 5-ethyl-1,3,4-thiadiazol-2-yl, **t** R = 5-propyl-1,3,4-thiadiazol-2-yl, **u** R = 5-isopropyl-1,3,4-thiadiazol-2-yl, **v** R = benzothiazol-2-yl, **w** R = 6-fluorobenzothiazol-2-yl, **x** R = 4-chlorobenzothiazol-2-yl, **y** R = 6-bromobenzothiazol-2-yl, **z** R = 6-methylbenzothiazol-2-yl; **5a** R = Me·HCl, **b** R = CH_2Ph·HCl, **c** R = $CHPh_2$·HCl.

The synthesis and purification of the starting ethyl 1-hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido-[3,2,1-*ij*]quinoline-2-carboxylate (**1**) was carried out by treatment of 1,2,3,4-tetrahydroquinoline (**2**) with an equimolar ratio of triethoxycarbonylmethane using a known method [10]. Thanks to the additional methylene unit, the conformational mobility of the reaction centers in the tetrahydroquinoline is undoubtedly greater than in the indoline. Hence the steric hindrance to acylation, and particularly to subsequent intramolecular cyclization, must be less. In fact, the pyridoquinoline ester **1** is formed very readily and in high yields while any anomalies observed in the reaction of triethoxycarbonylmethane with indoline [11] are not seen in this case.

TABLE 1. Characteristics of the 1-Hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid N-R-Amides **3-5**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a	$C_{18}H_{15}N_3O_3$	67.37 / 67.28	4.79 / 4.71	13.00 / 13.08	183-185	93
3b	$C_{18}H_{15}N_3O_3$	67.34 / 67.28	4.76 / 4.71	13.12 / 13.08	169-171	94
3c	$C_{18}H_{15}N_3O_3$	67.25 / 67.28	4.66 / 4.71	13.02 / 13.08	196-198	89
3d	$C_{18}H_{15}N_3O_4$	64.01 / 64.09	4.39 / 4.48	12.53 / 12.46	191-193	80
3e	$C_{19}H_{17}N_3O_3$	68.15 / 68.05	5.17 / 5.11	12.61 / 12.53	164-166	81
3f	$C_{19}H_{17}N_3O_3$	68.13 / 68.05	5.18 / 5.11	12.64 / 12.53	215-217	92
3g	$C_{19}H_{17}N_3O_3$	68.04 / 68.05	5.05 / 5.11	12.46 / 12.53	226-228	95
3h	$C_{19}H_{17}N_3O_3$	68.10 / 68.05	5.15 / 5.11	12.44 / 12.53	267-269	95
3i	$C_{17}H_{14}N_4O_3$	63.26 / 63.35	4.30 / 4.38	17.29 / 17.38	217-219	82
3j	$C_{16}H_{13}N_3O_3S$	58.77 / 58.70	4.09 / 4.00	12.95 / 12.84	203-205	90
3k	$C_{17}H_{15}N_3O_3S$	59.74 / 59.81	4.48 / 4.43	12.22 / 12.31	225-227	88
3l	$C_{17}H_{15}N_3O_3S$	59.73 / 59.81	4.39 / 4.43	12.36 / 12.31	230-232	89
3m	$C_{20}H_{19}N_3O_5S$	58.15 / 58.10	4.70 / 4.63	10.07 / 10.16	184-186	85
3n	$C_{26}H_{27}N_3O_3S$	67.58 / 67.66	5.81 / 5.90	9.03 / 9.10	288-290	91
3o	$C_{22}H_{17}N_3O_3S$	65.55 / 65.49	4.20 / 4.25	10.48 / 10.41	241-243	94
3p	$C_{22}H_{16}ClN_3O_3S$	60.40 / 60.34	3.77 / 3.68	9.52 / 9.60	267-269	90
3q	$C_{22}H_{16}BrN_3O_3S$	54.71 / 54.78	3.26 / 3.34	8.65 / 8.71	286-288	95
3r	$C_{16}H_{14}N_4O_3S$	56.16 / 56.13	4.04 / 4.12	16.30 / 16.36	210-212	84
3s	$C_{17}H_{16}N_4O_3S$	57.35 / 57.29	4.60 / 4.53	15.79 / 15.72	177-179	82
3t	$C_{18}H_{18}N_4O_3S$	58.30 / 58.36	4.97 / 4.90	15.03 / 15.12	173-175	86
3u	$C_{18}H_{18}N_4O_3S$	58.45 / 58.36	4.88 / 4.90	15.17 / 15.12	195-197	88
3v	$C_{20}H_{15}N_3O_3S$	63.60 / 63.65	4.11 / 4.01	11.09 / 11.13	294-296	95
3w	$C_{20}H_{14}FN_3O_3S$	60.82 / 60.75	3.65 / 3.57	10.71 / 10.63	329-331	90
3x	$C_{20}H_{14}ClN_3O_3S$	58.38 / 58.32	3.36 / 3.43	10.27 / 10.20	345-347	89
3y	$C_{20}H_{14}BrN_3O_3S$	52.55 / 52.64	3.03 / 3.09	9.26 / 9.21	303-305	96
3z	$C_{21}H_{17}N_3O_3S$	64.40 / 64.44	4.29 / 4.38	10.65 / 10.73	296-298	92
4	$C_{27}H_{21}N_3O_3S$	69.42 / 69.36	4.60 / 4.53	9.05 / 8.99	277-279	90
5a	$C_{18}H_{21}N_3O_3 \cdot HCl$	59.34 / 59.42	6.00 / 6.09	11.64 / 11.55	261-263	80
5b	$C_{24}H_{25}N_3O_3 \cdot HCl$	65.56 / 65.52	5.90 / 5.96	9.47 / 9.55	236-238	77
5c	$C_{30}H_{29}N_3O_3 \cdot HCl$	69.76 / 69.83	5.77 / 5.86	8.03 / 8.14	217-219	83

In the presence of a small amount of DMF (ensuring better mixing of the reagents and preventing local superheating of the reaction mixture) ester **1** is amidated by primary and secondary amines at 160ºC in the course of several minutes to give the 1-hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*if*]quinoline-2-carboxylic acid N-R-amides **3-5** in good yields (Table 1).

All of the N-R-amides **3-5** are colorless, crystalline materials with sharp melting points and, with the exception of the hydrochlorides **5a-c**, are virtually insoluble in water. The overall ^{1}H NMR spectra of the N-R-amides **3-5** are extremely similar to the spectra of the corresponding 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acids [8]. The only significant difference is the two proton quintet at high field (~ 2.0 ppm) due to the protons of the 6-methylene group in the pyridoquinolone ring (Table 2).

In the case of the 4-(1-adamantyl)thiazolyl-2-amide **3n** an X-ray structural analytical study (see Fig. 1 and Tables 3 and 4) has confirmed the proposal above that the change from pyrroloquinolones to pyridoquinolone has to cause a conformational restructuring of the molecule.

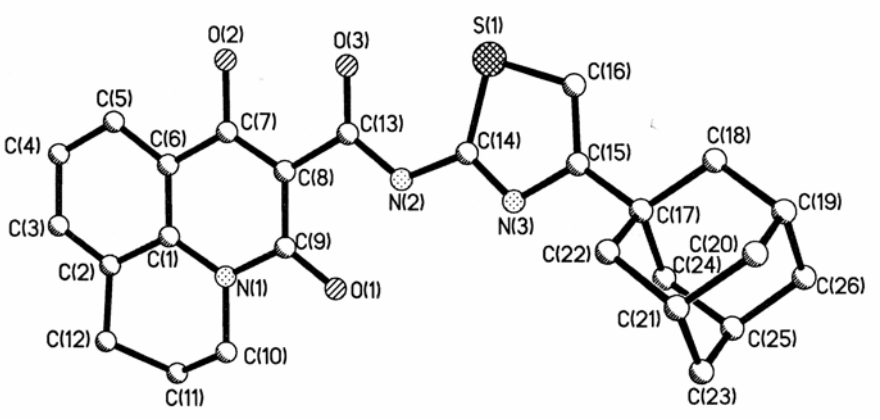


Fig. 1. The structure of the amide **3n** molecule with atom numeration.

It was found that two molecules (**A** and **B**) exist in the independent part of the unit cell differing in some geometric parameters. As in the case of the 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid amides [9], the quinolone fragment and atoms $O_{(1\}}$, $C_{(10\}}$, $C_{(12\}}$, $O_{(2\}}$, $C_{(13\}}$, $O_{(3\}}$, $N_{(2\}}$, and $C_{(14\}}$ lie in a single plane in both conformers to within 0.03 Å. This is likely due to the presence of the two intramolecular hydrogen bonds: $O_{(2)}$–$H_{(2O)}$···$O_{(3)}$ (H···O 1.72 in **A** and 1.53 Å in **B**, O–H···O 160º in **A** and 150º in **B**) and $N_{(2)}$–$H_{(2N)}$···$O_{(1)}$ (H···O 1.89 in **A** and 1.91 Å in **B**, N–H···O 140º in **A** and **B**). The formation of the intramolecular hydrogen bonds also leads to lengthening of the bonds $O_{(1)}$–$C_{(9)}$ to 1.245(4) in **A** and 1.254(5) in **B** and $O_{(3)}$–$C_{(13)}$ to 1.238(5) in **A** and 1.259(5) in **B** when compared to their mean value of 1.210 Å [12]. A shortened intramolecular contact $H_{(5a)}$···$O_{(2)}$ of 2.42 Å is found in the **A** molecule (sum of van der Waal radii 2.46 Å [13]). At the same time the "additional" $C_{(11)}$ atom deviates as expected from the mean square place passing through the remaining ring atoms by 0.51 in molecule **A** and by -0.56 Å in **B**.

As a result of annelation with the quinolone ring the tetrahydropyridine ring takes on a *chair* type conformation (folding parameters [14]: S = 0.58, θ = 39.6º, ψ = 7.3º for **A** and S = 0.68, θ = 36.1º, ψ = 1.9º for **B**). A shortened intramolecular contact $H_{(10b)}$···$O_{(1)}$ of 2.35 in **A** and 2.36 Å in **B** (2.46 Å) arises. The five membered thiazole heterocycle is somewhat noncoplanar with the planar fragment (torsional angle $C_{(130}$–$N_{(20}$–$C_{(14)}$–$S_{(1)}$ -11.0(6) in **A** and 11.0(6)º in **B** and this is likely due to a repulsion between the carbonyl group oxygen atom and the sulfur atom [shortened intramolecular contact $S_{(1)}$···$O_{(3)}$ 2.77 Å in **A** and **B** (3.13 Å)]. The adamantane substituent is placed in such a way that the $C_{(18)}$–$C_{(17)}$ bond is virtually coplanar with the plane of the thiazole ring (torsional angle $C_{(18)}$–$C_{(17)}$–$C_{(15)}$–$C_{(16)}$ -11.1(6) in **A** and 10.0(6)º in **B)**.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Compound	Chemical shifts, δ, ppm (*J*, Hz)								
	1-OH (1H, s)	NH (1H, s)	Pyridoquinoline ring						R
			H-10 (1H, d)	H-8 (1H, d)	H-9 (1H, t)	5-CH_2 (2H, t)	7-CH_2 (2H, t)	6-CH_2 (2H, q)	
1	2	3	4	5	6	7	8	9	10
3a	15.91	12.93	7.99 (*J* = 8.0)	7.50 (*J* = 7.4)	7.21 (*J* = 7.9)	4.15 (*J* = 5.8)	3.01 (*J* = 6.0)	2.13 (*J* = 6.0)	8.45 (2H, d, *J* = 6.1, H-2',6'); 7.60 (2H, d, *J* = 6.1, H-3',4')
3b	16.12	12.76	7.99 (*J* = 8.3)	7.42 (*J* = 7.3)	7.17 (*J* = 7.6)	4.15 (*J* = 5.6)	3.00 (*J* = 6.2)	2.14 (*J* = 5.9)	8.71 (1H, d, *J* = 2.2, H-2'); 8.29 (1H, d, *J* = 3.4, H-6'); 8.20 (1H, d, *J* = 7.9, H-4'); 7.27 (1H, t, *J* = 6.5, H-5')
3c	16.15	12.88	7.97 (*J* = 8.0)	7.45 (*J* = 7.1)	7.18 (*J* = 7.9)	4.17 (*J* = 5.7)	2.99 (*J* = 6.2)	2.13 (*J* = 5.8)	8.34 (1H, d, *J* = 4.4, H-6'); 8.22 (1H, d, *J* = 8.4, H-3'); 7.75 (1H, t, *J* = 7.7, H-4'); 7.09 (1H, t, *J* = 5.8, H-5')
3d	15.89	12.87	7.98 (*J* = 8.1)	7.46 (*J* = 7.4)	7.19 (*J* = 7.5)	4.18 (*J* = 5.9)	3.01 (*J* = 6.2)	2.14 (*J* = 5.9)	9.85 (1H, s, OH); 7.90 (1H, dd, *J* = 4.4 и *J* = 1.8, H-6'); 7.27 (1H, d, *J* = 8.1, H-4'); 7.06 (1H, t, *J* = 6.6, H-5')
3e	16.42	12.44	7.97 (*J* = 7.9)	7.52 (*J* = 7.0)	7.23 (*J* = 7.5)	4.16 (*J* = 5.7)	3.02 (*J* = 6.3)	2.11 (*J* = 6.0)	8.28 (1H, d, *J* = 4.5, H-6'); 7.67 (1H, d, *J* = 7.5, H-4'); 7.20 (1H, t, *J* = 6.0, H-5'); 2.34 (3H, s, CH_3)
3f	16.20	12.81	7.97 (*J* = 8.0)	7.43 (*J* = 7.1)	7.16 (*J* = 7.8)	4.16 (*J* = 5.9)	3.00 (*J* = 6.3)	2.13 (*J* = 5.9)	8.17 (1H, d, *J* = 6.0, H-6'); 8.05 (1H, s, H-3'); 6.90 (1H, d, *J* = 4.8, H-5'); 2.42 (3H, s, CH_3)
3g	16.27	12.78	7.99 (*J* = 8.3)	7.42 (*J* = 7.4)	7.16 (*J* = 7.9)	4.18 (*J* = 6.0)	3.01 (*J* = 6.1)	2.14 (*J* = 6.0)	8.15 (1H, s, H-6'); 8.12 (1H, d, *J* = 8.5, H-3'); 7.53 (1H, dd, *J* = 8.5 and *J* = 1.8, H-4'); 2.33 (3H, s, CH_3)
3h	16.12	12.88	See R	7.58 (*J* = 7.4)	7.27 (*J* = 7.5)	4.14 (*J* = 5.7)	2.99 (*J* = 6.0)	2.08 (*J* = 5.8)	7.97 (2H, d, *J* = 8.2, H-3' + H-10); 7.74 (1H, t, *J* = 8.0, H-4'); 7.06 (1H, d, *J* = 7.6, H-5'); 2.45 (3H, s, CH_3)
3i	16.37	13.13	7.99 (*J* = 8.0)	7.47 (*J* = 7.3)	7.19 (*J* = 7.7)	4.17 (*J* = 5.8)	3.01 (*J* = 6.2)	2.14 (*J* = 5.9)	8.68 (2H, d, *J* = 4.5, H-4',6'); 7.16 (1H, t, *J* = 4.9, H-5')
3j	15.18	13.65	8.00 (*J* = 8.3)	See R	7.20 (*J* = 7.5)	4.18 (*J* = 5.7)	3.01 (*J* = 6.2)	2.14 (*J* = 5.8)	7.47 (2H, m, H-5' + H-8); 7.11 (1H, d, *J* = 3.7, H-4')
3k	15.24	13.52	7.99 (*J* = 8.2)	7.45 (*J* = 7.4)	7.18 (*J* = 7.6)	4.18 (*J* = 5.6)	3.01 (*J* = 6.2)	2.14 (*J* = 5.7)	6.62 (1H, s, H-5'); 2.35 (3H, s, CH_3)
3l	15.28	13.47	7.99 (*J* = 8.2)	7.47 (*J* = 7.4)	7.19 (*J* = 7.8)	4.18 (*J* = 5.6)	3.00 (*J* = 6.0)	2.14 (*J* = 5.6)	7.10 (1H, s, H-4'); 2.45 (3H, s, CH_3)
3m	15.12	13.56	7.97 (*J* = 8.0)	7.45 (*J* = 7.1)	7.18 (*J* = 8.0)	See R	2.99 (*J* = 6.0)	2.13 (*J* = 5.7)	6.95 (1H, s, H-5'); 4.15 (4H, m, OCH_2 + 5-CH_2); 3.67 (2H, s, CH_2); 1.30 (3H, t, *J* = 7.1, CH_3)
3n	15.30	13.53	8.01 (*J* = 8.2)	7.48 (*J* = 7.5)	7.20 (*J* = 7.8)	4.19 (*J* = 5.9)	3.02 (*J* = 6.3)	2.15 (*J* = 5.9)	6.57 (1H, s, H-5'); 2.08 (3H, s, γ-H-nodal adamantane); 1.95 (6H, m, δ-H adamantane); 1.78 (6H, s, β-H adamantane)

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10
3o	15.19	13.73	8.01 (J = 8.0)	7.48 (J = 7.3)	7.21 (J = 7.6)	4.20 (J = 5.7)	3.02 (J = 6.2)	2.16 (J = 5.7)	7.90 (2H, d, J = 8.0, H-2,6 Ph); 7.41 (1H, s, H-5 thiazole); 7.36 (2H, t, J = 7.3, H-3,5 Ph); 7.26 (1H, t, J = 7.2, H-4 Ph)
3p	14.94	13.86	7.96 (J = 8.1)	7.58 (J = 7.2)	7.28 (J = 7.7)	4.15 (J = 5.8)	2.98 (J = 6.0)	2.09 (J = 5.5)	7.92 (2H, d, J = 8.8, H-3,5 Ph); 7.78 (1H, s, H-5 thiazole); 7.43 (2H, d, J = 8.8, H-2,6 Ph)
3q	14.92	13.90	8.00 (J = 8.0)	See R	7.33 (J = 7.5)	4.18 (J = 5.7)	3.01 (J = 6.1)	2.10 (J = 5.4)	7.89 (2H, d, J = 8.0, H-3,5 Ph); 7.80 (1H, s, H-5 thiazole) 7.62 (2H, m, H-2,6 Ph + H-8)
3r	14.89	13.92	8.02 (J = 8.3)	7.51 (J = 7.1)	7.22 (J = 7.5)	4.21 (J = 5.8)	3.03 (J = 6.2)	2.16 (J = 5.9)	2.71 (3H, s, CH_3)
3s	14.84	13.87	7.97 (J = 8.0)	7.48 (J = 7.1)	7.20 (J = 7.5)	4.18 (J = 5.9)	2.98 (J = 6.3)	2.15 (J = 5.8)	3.06 (2H, q, J = 7.8, CH_2); 1.43 (3H, t, J = 7.6, CH_3)
3t	14.87	13.92	8.01 (J = 8.1)	7.51 (J = 7.2)	7.22 (J = 7.5)	4.21 (J = 5.9)	See R	2.16 (J = 5.8)	3.00 (4H, m, $C\underline{H}_2CH_2Me$ + CH_2-7); 1.84 (2H, m, $C\underline{H}_2Me$); 1.07 (3H, t, J = 7.0, CH_3)
3u	14.91	13.91	8.00 (J = 8.1)	7.52 br. (J = 7.0)	7.23 (J = 7.5)	4.22 (J = 5.9)	3.03 (J = 6.2)	2.16 (J = 5.6)	3.39 (1H, m, CH); 1.45 (6H, d, J = 7.2, $2CH_3$)
3v	14.87	14.02	See R	7.62 (J = 6.8)	See R	4.19 (J = 5.6)	3.02 (J = 6.1)	2.11 (J = 5.4)	8.01 (2H, m, H-7' + H-10); 7.83 (1H, d, J = 7.9, H-4'); 7.49 (1H, t, J = 7.7, H-6'); 7.35 (2H, m, H-5' + H-9)
3w	14.92	14.00	8.04 (J = 8.2)	7.61 (J = 7.0)	See R	4.21 (J = 5.8)	3.00 (J = 6.3)	2.14 (J = 5.5)	7.80 (2H, m, H-7',5'); 7.27 (2H, m, H-4' + H-9)
3x	14.83	13.95	See R	7.57 (J = 7.1)	See R	4.18 (J = 5.8)	3.03 (J = 6.2)	2.12 (J = 5.6)	8.03 (2H, m, H-7' + H-10); 7.66 (1H, d, J = 7.8, H-5'); 7.33 (2H, m, H-6'+H -9)
3y	14.98	14.09	8.03 (J = 8.0)	See R	7.33 (J = 7.5)	4.18 (J = 5.8)	3.02 (J = 6.3)	2.11 (J = 6.0)	8.26 (1H, s, H-7',); 7.76 (1H, d, J = 8.7, H-4'); 7.62 (2H, m, H-5' + H-8)
3z	15.11	13.86	8.02 (J = 8.1)	7.63 (J = 7.0)	7.34 (J = 7.7)	4.22 (J = 5.9)	3.01 (J = 6.2)	2.10 (J = 5.8)	7.80 (1H, s, H-7'); 7.72 (1H, d, J = 8.3, H-4'); 7.29 (1H, d, J = 8.2, H-5'); 2.42 (3H, s, CH_3)
4	16.05	12.89	8.01 (J = 7.9)	7.60 (J = 7.4)	7.31 (J = 7.6)	4.19 (J = 5.8)	3.02 (J = 6.2)	2.11 (J = 6.0)	8.10 (2H, d, J = 8.2, H-2,6 Ph); 7.91 (1H, d, J = 7.9, H-4''); 7.87 (3H, m, H-3,5 Ph + H-7''); 7.35 (1H, d, J = 8.2, H-5''); 2.44 (3H, s, CH_3)
5a	See R	–	7.86 (J = 8.2)	7.31 (J = 7.0)	7.08 (J = 7.5)	4.04 (J = 5.7)	2.97 (J = 6.0)	2.08 (J = 5.3)	11.10 (2H, br. s, OH + HN^+); 3.23 (8H, br. s, $4CH_2$ piperazine); 2.82 (3H, s, CH_3)
5b	See R	–	7.85 (J = 8.0)	7.32 (J = 7.2)	7.07 (J = 7.7)	4.05 (J = 5.9)	2.97 (J = 6.1)	2.07 (J = 6.0)	11.56 (2H, br. s, OH + HN^+); 7.74 (2H, d, J = 7.0, H-2,6 Ph); 7.40 (3H, m, H-3,4,5 Ph); 4.33 (2H, s, $C\underline{H}_2Ph$); 3.28 (8H, br. s, $4CH_2$ piperazine)
5c	12.50	11.14 (HN^+)	See R	See R	7.15 (J = 7.6)	4.00 (J = 5.8)	2.93 (J = 6.2)	1.98 (J = 5.9)	7.94-7.28 (12H, m, H-10,8 + 2Ph); 5.61 (1H, s, $C\underline{H}Ph_2$); 3.24 (8H, br. s, $4CH_2$ piperazine)

TABLE 3. Bond Lengths (*l*) in the Amide Structure **3n**

Bond	*l*, Å	Bond	*l*, *Å*
$S_{(1A)}$–$C_{(14A)}$	1.706(5)	$S_{(1A)}$–$C_{(16A)}$	1.727(5)
$N_{(1A)}$–$C_{(1A)}$	1.370(4)	$N_{(1A)}$–$C_{(9A)}$	1.391(4)
$N_{(1A)}$–$C_{(10A)}$	1.462(5)	$N_{(2A)}$–$C_{(13A)}$	1.367(5)
$N_{(2A)}$–$C_{(14A)}$	1.392(5)	$N_{(3A)}$–$C_{(14A)}$	1.285(5)
$N_{(3A)}$–$C_{(15A)}$	1.386(5)	$O_{(1A)}$–$C_{(9A)}$	1.246(4)
$O_{(2A)}$–$C_{(7A)}$	1.327(5)	$O_{(3A)}$–$C_{(13A)}$	1.238(5)
$C_{(1A)}$–$C_{(6A)}$	1.393(5)	$C_{(1A)}$–$C_{(2A)}$	1.396(5)
$C_{(2A)}$–$C_{(3A)}$	1.372(6)	$C_{(2A)}$–$C_{(12A)}$	1.492(6)
$C_{(3A)}$–$C_{(4A)}$	1.402(7)	$C_{(4A)}$–$C_{(5A)}$	1.346(6)
$C_{(5A)}$–$C_{(6A)}$	1.410(5)	$C_{(6A)}$–$C_{(7A)}$	1.437(5)
$C_{(7A)}$–$C_{(8A)}$	1.403(5)	$C_{(8A)}$–$C_{(9A)}$	1.458(5)
$C_{(8A)}$–$C_{(13A)}$	1.487(6)	$C_{(10A)}$–$C_{(11A)}$	1.482(7)
$C_{(11A)}$–$C_{(12A)}$	1.514(7)	$C_{(15A)}$–$C_{(16A)}$	1.381(6)
$C_{(15A)}$–$C_{(17A)}$	1.512(5)	$C_{(17A)}$–$C_{(18A)}$	1.510(6)
$C_{(17A)}$–$C_{(24A)}$	1.536(6)	$C_{(17A)}$–$C_{(22A)}$	1.556(5)
$C_{(18A)}$–$C_{(19A)}$	1.517(6)	$C_{(19A)}$–$C_{(20A)}$	1.520(7)
$C_{(19A)}$–$C_{(26A)}$	1.543(7)	$C_{(20A)}$–$C_{(21A)}$	1.525(6)
$C_{(21A)}$–$C_{(23A)}$	1.513(6)	$C_{(21A)}$–$C_{(22A)}$	1.535(6)
$C_{(23A)}$–$C_{(25A)}$	1.527(6)	$C_{(24A)}$–$C_{(25A)}$	1.532(6)
$C_{(25A)}$–$C_{(26A)}$	1.521(7)	$S_{(1B)}$–$C_{(16B)}$	1.710(4)
$S_{(1B)}$–$C_{(14B)}$	1.726(4)	$N_{(1B)}$–$C_{(9B)}$	1.369(6)
$N_{(1B)}$–$C_{(1B)}$	1.423(5)	$N_{(1B)}$–$C_{(10B)}$	1.491(5)
$N_{(2B)}$–$C_{(13B)}$	1.319(5)	$N_{(2B)}$–$C_{(14B)}$	1.389(5)
$N_{(3B)}$–$C_{(14B)}$	1.298(5)	$N_{(3B)}$–$C_{(15B)}$	1.397(5)
$O_{(1B)}$–$C_{(9B)}$	1.254(5)	$O_{(2B)}$–$C_{(7B)}$	1.323(5)
$O_{(3B)}$–$C_{(13B)}$	1.260(5)	$C_{(1B)}$–$C_{(6B)}$	1.400(6)
$C_{(1B)}$–$C_{(2B)}$	1.428(6)	$C_{(2B)}$–$C_{(3B)}$	1.398(6)
$C_{(2B)}$–$C_{(12B)}$	1.476(6)	$C_{(3B)}$–$C_{(4B)}$	1.364(6)
$C_{(4B)}$–$C_{(5B)}$	1.370(6)	$C_{(5B)}$–$C_{(6B)}$	1.408(6)
$C_{(6B)}$–$C_{(7B)}$	1.416(6)	$C_{(7B)}$–$C_{(8B)}$	1.376(5)
$C_{(8B)}$–$C_{(9B)}$	1.435(6)	$C_{(8B)}$–$C_{(13B)}$	1.465(6)
$C_{(10B)}$–$C_{(11B)}$	1.466(7)	$C_{(11B)}$–$C_{(12B)}$	1.455(7)
$C_{(15B)}$–$C_{(16B)}$	1.347(6)	$C_{(15B)}$–$C_{(17B)}$	1.492(6)
$C_{(17B)}$–$C_{(22B)}$	1.525(5)	$C_{(17B)}$–$C_{(24B)}$	1.542(6)
$C_{(17B)}$–$C_{(18B)}$	1.558(5)	$C_{(18B)}$–$C_{(19B)}$	1.525(6)
$C_{(19B)}$–$C_{(20B)}$	1.517(6)	$C_{(19B)}$–$C_{(26B)}$	1.522(7)
$C_{(20B)}$–$C_{(21B)}$	1.519(6)	$C_{(21B)}$–$C_{(23B)}$	1.540(6)
$C_{(21B)}$–$C_{(22B)}$	1.543(5)	$C_{(23B)}$–$C_{(25B)}$	1.496(6)
$C_{(24B)}$–$C_{(25B)}$	1.568(6)	$C_{(25B)}$–$C_{(26B)}$	1.515(8)

All of the synthesized amides **3-5** underwent microbiological screening towards *Mycobacterium tuberculosis* H37Rv ATCC 27294 using a radiometric method [15, 16]. It was found that some of the substances tested at a concentration of 6.25 μg/ml *in vitro* showed high antitubercular activity and inhibited the tuberculosis micobacterium growth by 99-100% (Table 5).

A comparative analysis of the antimicobacterial properties of amides **3-5** and their structural analogs (the corresponding 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2- and 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid hetarylamides with the smallest N_1 alkyl substituents in the quinolone ring showed the same dependence of observed antimicrobial activity on the heterocycle chemical structure in the amide fragment of the molecule. Hence the pyridyl-4-amides are always more active than their 3-analogs and these, in turn, markedly exceed in strength the antitubercular effect of the 2-isomers. Amongst the 3-hydroxy series and some monomethyl-substituted pyridyl-2-amides the transition to the pyridoquinoline-

TABLE 4. Valence Angles (ω) in the Amide Structure **3n**

Angle	ω, deg	Angle	ω,deg.
1	2	3	4
$C_{(14A)}–S_{(1A)}–C_{(16A)}$	89.3(2)	$C_{(1A)}–N_{(1A)}–C_{(9A)}$	123.4(3)
$C_{(1A)}–N_{(1A)}–C_{(10A)}$	120.2(3)	$C_{(9A)}–N_{(1A)}–C_{(10A)}$	116.4(3)
$C_{(13A)}–N_{(2A)}–C_{(14A)}$	122.8(4)	$C_{(14A)}–N_{(3A)}–C_{(15A)}$	110.5(3)
$N_{(1A)}–C_{(1A)}–C_{(6A)}$	120.7(3)	$N_{(1A)}–C_{(1A)}–C_{(2A)}$	122.9(3)
$C_{(6A)}–C_{(1A)}–C_{(2A)}$	116.4(3)	$C_{(3A)}–C_{(2A)}–C_{(1A)}$	120.2(4)
$C_{(3A)}–C_{(2A)}–C_{(12A)}$	119.3(4)	$C_{(1A)}–C_{(2A)}–C_{(12A)}$	120.5(4)
$C_{(2A)}–C_{(3A)}–C_{(4A)}$	122.1(4)	$C_{(5A)}–C_{(4A)}–C_{(3A)}$	119.1(4)
$C_{(4A)}–C_{(5A)}–C_{(6A)}$	118.9(4)	$C_{(1A)}–C_{(6A)}–C_{(5A)}$	123.1(4)
$C_{(1A)}–C_{(6A)}–C_{(7A)}$	118.6(3)	$C_{(5A)}–C_{(6A)}–C_{(7A)}$	118.3(4)
$O_{(2A)}–C_{(7A)}–C_{(8A)}$	120.8(4)	$O_{(2A)}–C_{(7A)}–C_{(6A)}$	118.4(4)
$C_{(8A)}–C_{(7A)}–C_{(6A)}$	120.8(4)	$C_{(7A)}–C_{(8A)}–C_{(9A)}$	119.1(4)
$C_{(7A)}–C_{(8A)}–C_{(13A)}$	119.1(4)	$C_{(9A)}–C_{(8A)}–C_{(13A)}$	121.8(4)
$O_{(1A)}–C_{(9A)}–N_{(1A)}$	118.4(3)	$O_{(1A)}–C_{(9A)}–C_{(8A)}$	124.2(3)
$N_{(1A)}–C_{(9A)}–C_{(8A)}$	117.4(3)	$N_{(1A)}–C_{(10A)}–C_{(11A)}$	115.0(4)
$C_{(10A)}–C_{(11A)}–C_{(12A)}$	114.7(4)	$C_{(2A)}–C_{(12A)}–C_{(11A)}$	111.2(4)
$O_{(3A)}–C_{(13A)}–N_{(2A)}$	123.6(4)	$O_{(3A)}–C_{(13A)}–C_{(8A)}$	121.1(4)
$N_{(2A)}–C_{(13A)}–C_{(8A)}$	115.3(4)	$N_{(3A)}–C_{(14A)}–N_{(2A)}$	119.0(4)
$N_{(3A)}–C_{(14A)}–S_{(1A)}$	116.4(3)	$N_{(2A)}–C_{(14A)}–S_{(1A)}$	124.6(3)
$C_{(16A)}–C_{(15A)}–N_{(3A)}$	114.7(4)	$C_{(16A)}–C_{(15A)}–C_{(17A)}$	126.8(4)
$N_{(3A)}–C_{(15A)}–C_{(17A)}$	118.2(4)	$C_{(15A)}–C_{(16A)}–S_{(1A)}$	109.1(4)
$C_{(18A)}–C_{(17A)}–C_{(15A)}$	112.1(4)	$C_{(18A)}–C_{(17A)}–C_{(24A)}$	108.5(4)
$C_{(15A)}–C_{(17A)}–C_{(24A)}$	111.4(3)	$C_{(18A)}–C_{(17A)}–C_{(22A)}$	106.9(4)
$C_{(15A)}–C_{(17A)}–C_{(22A)}$	108.5(3)	$C_{(24A)}–C_{(17A)}–C_{(22A)}$	109.3(3)
$C_{(17A)}–C_{(18A)}–C_{(19A)}$	112.4(4)	$C_{(18A)}–C_{(19A)}–C_{(20A)}$	110.6(4)
$C_{(18A)}–C_{(19A)}–C_{(26A)}$	106.7(4)	$C_{(20A)}–C_{(19A)}–C_{(26A)}$	110.3(5)
$C_{(19A)}–C_{(20A)}–C_{(21A)}$	108.8(4)	$C_{(23A)}–C_{(21A)}–C_{(20A)}$	108.2(4)
$C_{(23A)}–C_{(21A)}–C_{(22A)}$	110.4(4)	$C_{(20A)}–C_{(21A)}–C_{(22A)}$	109.7(4)
$C_{(21A)}–C_{(22A)}–C_{(17A)}$	110.3(3)	$C_{(21A)}–C_{(23A)}–C_{(25A)}$	110.9(4)
$C_{(25A)}–C_{(24A)}–C_{(17A)}$	109.9(3)	$C_{(26A)}–C_{(25A)}–C_{(23A)}$	108.1(4)
$C_{(26A)}–C_{(25A)}–C_{(24A)}$	108.1(4)	$C_{(23A)}–C_{(25A)}–C_{(24A)}$	111.2(4)
$C_{(25A)}–C_{(26A)}–C_{(19A)}$	109.9(4)	$C_{(16B)}–S_{(1B)}–C_{(14B)}$	87.3(2)
$C_{(9B)}–N_{(1B)}–C_{(1B)}$	122.1(4)	$C_{(9B)}–N_{(1B)}–C_{(10B)}$	115.6(4)
$C_{(1B)}–N_{(1B)}–C_{(10B)}$	122.1(4)	$C_{(13B)}–N_{(2B)}–C_{(14B)}$	128.1(4)
$C_{(14B)}–N_{(3B)}–C_{(15B)}$	111.0(4)	$C_{(6B)}–C_{(1B)}–N_{(1B)}$	118.5(4)
$C_{(6B)}–C_{(1B)}–C_{(2B)}$	123.9(4)	$N_{(1B)}–C_{(1B)}–C_{(2B)}$	117.6(4)
$C_{(3B)}–C_{(2B)}–C_{(1B)}$	115.9(4)	$C_{(3B)}–C_{(2B)}–C_{(12B)}$	123.1(4)
$C_{(1B)}–C_{(2B)}–C_{(12B)}$	121.0(4)	$C_{(4B)}–C_{(3B)}–C_{(2B)}$	122.0(4)
$C_{(3B)}–C_{(4B)}–C_{(5B)}$	120.4(4)	$C_{(4B)}–C_{(5B)}–C_{(6B)}$	122.6(4)
$C_{(1B)}–C_{(6B)}–C_{(5B)}$	115.2(4)	$C_{(1B)}–C_{(6B)}–C_{(7B)}$	119.6(4)
$C_{(5B)}–C_{(6B)}–C_{(7B)}$	125.1(4)	$O_{(2B)}–C_{(7B)}–C_{(8B)}$	124.9(4)
$O_{(2B)}–C_{(7B)}–C_{(6B)}$	114.5(4)	$C_{(8B)}–C_{(7B)}–C_{(6B)}$	120.6(4)
$C_{(7B)}–C_{(8B)}–C_{(9B)}$	120.3(4)	$C_{(7B)}–C_{(8B)}–C_{(13B)}$	116.7(4)
$C_{(9B)}–C_{(8B)}–C_{(13B)}$	123.0(4)	$O_{(1B)}–C_{(9B)}–N_{(1B)}$	120.2(4)
$O_{(1B)}–C_{(9B)}–C_{(8B)}$	121.2(4)	$N_{(1B)}–C_{(9B)}–C_{(8B)}$	118.6(4)
$C_{(11B)}–C_{(10B)}–N_{(1B)}$	111.0(4)	$C_{(12B)}–C_{(11B)}–C_{(10B)}$	114.7(5)
$C_{(11B)}–C_{(12B)}–C_{(2B)}$	112.5(4)	$O_{(3B)}–C_{(13B)}–N_{(2B)}$	118.6(4)
$O_{(3B)}–C_{(13B)}–C_{(8B)}$	122.6(4)	$N_{(2B)}–C_{(13B)}–C_{(8B)}$	118.8(4)
$N_{(3B)}–C_{(14B)}–N_{(2B)}$	120.9(4)	$N_{(3B)}–C_{(14B)}–S_{(1B)}$	115.8(3)
$N_{(2B)}–C_{(14B)}–S_{(1B)}$	123.3(3)	$C_{(16B)}–C_{(15B)}–N_{(3B)}$	112.1(4)
$C_{(16B)}–C_{(15B)}–C_{(17B)}$	128.0(4)	$N_{(3B)}–C_{(15B)}–C_{(17B)}$	119.9(3)
$C_{(15B)}–C_{(16B)}–S_{(1B)}$	113.5(3)	$C_{(15B)}–C_{(17B)}–C_{(22B)}$	108.6(3)
$C_{(15B)}–C_{(17B)}–C_{(24B)}$	110.0(3)	$C_{(22B)}–C_{(17B)}–C_{(24B)}$	107.9(3)
$C_{(15B)}–C_{(17B)}–C_{(18B)}$	112.1(3)	$C_{(22B)}–C_{(17B)}–C_{(18B)}$	109.4(3)

TABLE 4 (continued)

1	2	3	4
$C_{(24B)}$–$C_{(17B)}$–$C_{(18B)}$	108.7(4)	$C_{(19B)}$–$C_{(18B)}$–$C_{(17B)}$	108.8(4)
$C_{(20B)}$–$C_{(19B)}$–$C_{(26B)}$	108.4(4)	$C_{(20B)}$–$C_{(19B)}$–$C_{(18B)}$	108.5(4)
$C_{(26B)}$–$C_{(19B)}$–$C_{(18B)}$	112.9(4)	$C_{(19B)}$–$C_{(20B)}$–$C_{(21B)}$	110.5(4)
$C_{(20B)}$–$C_{(21B)}$–$C_{(23B)}$	110.7(4)	$C_{(20B)}$–$C_{(21B)}$–$C_{(22B)}$	108.3(4)
$C_{(23B)}$–$C_{(21B)}$–$C_{(22B)}$	107.8(4)	$C_{(17B)}$–$C_{(22B)}$–$C_{(21B)}$	110.9(3)
$C_{(25B)}$–$C_{(23B)}$–$C_{(21B)}$	109.3(4)	$C_{(17B)}$–$C_{(24B)}$–$C_{(25B)}$	109.5(3)
$C_{(23B)}$–$C_{(25B)}$–$C_{(26B)}$	110.5(4)	$C_{(23B)}$–$C_{(25B)}$–$C_{(24B)}$	109.2(4)
$C_{(26B)}$–$C_{(25B)}$–$C_{(24B)}$	109.9(5)	$C_{(25B)}$–$C_{(26B)}$–$C_{(19B)}$	109.1(4)

2-carboxylic acid derivative **3d-g** unexpectedly led to a slight overall increase in activity. The effect of a methyl group in position 6 of the pyridyl-2-amide residue was to fully deactivate the molecule in all cases independently of the structure of the quinolone part. Amidation of the hydroxyquinoline carboxylic acids by 2-aminopyrimidine was also unhelpful since the specific activity of the compounds obtained in this way never exceeded 20-25%. On the other hand, the thiazol-2-yl amides showed much higher and stable results. It was found that substituents in position 4 or 5 of the thiazole generally increased the activity but they should not be sterically bulky. Introduction of a second nitrogen atom into the five-membered ring (the 1,3,4-thiadiazolyl-2-amides) proved even more favourable to antitubercular activity and almost always retained the ability to block the growth of the tubercular micobacteria by 90-100% at low minimum inhibitory concentration (MIC). On the other hand the structure of the quinolone fragment proved to have a more marked influence on the activity of the benzothiazole derivatives. If the complete absence of antimicobacterial properties of a 4-(6-methyl-benzothiazol-2-yl)anilide (**4**) was quite predictable the comparatively low activity of the benzothiazol-2-yl amide **3v** and also its halo (**3w-y**) and methyl (**3z**) analogs proved somewhat unexpected.

TABLE 5. Antitubercular Activity of Compounds **3-5**

Com-pound	Inhibition of the growth of *M. tuberculosis*, %	MIC*, μg/ml	Com pound	Inhibition of the growth of *M. tuberculosis*, %	MIC*, μg/ml
3a	100	6.25	**3p**	73	—
3b	57	—	**3q**	63	—
3c	14	—	**3r**	100	3.13
3d	17	—	**3s**	100	0.78
3e	58	—	**3t**	100	1.56
3f	13	—	**3u**	100	3.13
3g	15	—	**3v**	9	—
3h	0	—	**3w**	39	—
3i	20	—	**3x**	25	—
3j	99	6.25	**3y**	100	6.25
3k	100	3.13	**3z**	20	—
3l	100	3.13	**4**	0	—
3m	100	6.25	**5a**	0	—
3n	18	—	**5b**	0	—
3o	32	—	**5c**	0	—

* According to the criteria adopted in the TAACF (Tuberculosis Antimicrobial Acquisition and Coordinating Facility), the actual MIC only being determined for compounds showing activity not less than 90% in the first stage.

In summarising our investigation it should be noted that annelation of the quinolone ring with the tetrahydropyridine ring generally did not cardinally affect the antitubercular properties. In this case we can conclude that the $N_{(1)}$-alkyl substituents in the 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid hetarylamides (in common with the trihydropyrrole or tetrahydropyridine fragments in the corresponding 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2- and 1-hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline 2-carboxylic acid derivatives) did not play a direct role in the binding to the biological target. Most likely, in some degree, it affects the ability to interact with receptors *via* one of the key functional groups (the carbonyl at position 2 of the quinolone ring). The second such center is evidently the NH grouping in the amide fragment. Confirmation of this comes from the repeated observation of full loss of activity in the secondary amides of type **5**.

EXPERIMENTAL

Commercial 1,2,3,4-tetrahydroquinoline and triethoxycarbonylmethane were obtained from the Fluka company. ^{1}H NMR spectra for the synthesized compounds were recorded on a Bruker WM-360 instrument (360 MHz) using DMSO-d_6 and with TMS as internal standard.

Ethyl 1-hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylate (1). 1,2,3,4-Tetrahydroquinoline (**2**) (12.5 ml, 0.1 mol) was added dropwise with stirring to triethoxycarbonylmethane (21.1 ml, 0.1 mol) heated to 215ºC such that the reaction mixture temperature did not change outside the range ±5ºC from the initial value. The ethanol evolved in the process could be liberated via a fractionating column without increasing the starting reagents. After the addition of all of the 1,2,3,4-tetrahydroquinoline the reaction mixture was held for 10-15 min at the same temperature and then cooled to about 100ºC. Aqueous Na_2CO_3 solution (10%, 300 ml) was added and heated to 70-80ºC. The obtained solution of the 1-O-sodium salt of ester **1** was purified with carbon and filtered. After cooling, the filtrate was acidified with dilute (1:1) HCl to pH 4.5-5. The precipitated ester **1** was filtered off, washed with water, and dried. Yield 26.23 g (96%). Colorless needles with mp 102-104ºC (hexane). According to data in [17] yellow needles with mp 101ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.10 (1H, s, OH); 7.88 (1H, d, *J* = 8.0, H-10); 7.49 (1H, d, *J* = 7.3, H-8); 7.18 (1H, d, *J* = 7.5, H-9); 4.33 (2H, q, *J* = 7.0, OCH_2); 3.99 (2H, t, *J* = 5.6, NCH_2); 2.94 (2H, t, *J* = 6.1, 7-CH_2); 2.00 (2H, quin, *J* = 6.0, 6-CH_2); 1.32 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$).

1-Hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid N-R-amides 3a-z, 4 (General Method). A mixture of ester **1** (2.73 g, 0.01 mol), the corresponding primary amine (0.01 mol), and DMF (1 ml) was stirred and held at 160ºC for 3-5 min. The starting reagents initially dissolved and then began to crystallize out to the final amide after vigorous evolution of ethanol. Ethanol (10-15 ml) was added to the uncooled reaction mixture (beware of sudden effervescence) and the product was thoroughly triturated. The precipitated hetarylamide **3** or anilide **4** was filtered off, washed with alcohol, dried, and crystallized from DMF.

1-Hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid 4-R-piperazin-1-ylamide Hydrochlorides 5a-c. The 4-R-piperazin-1-ylamide bases (0.01 mol) obtained by in the preceding experiment were suspended in ethanol (10 ml) and a solution of gaseous HCl in ethanol was added to pH 3 (the precipitate dissolved) after which it was left for several hours in an ice chest. The separated 4-R-piperazin-1-ylamide hydrochloride crystals **5a-c** were filtered off, washed with ether, and dried.

X-ray Crystallographic Study. Crystals of amide **3n** are triclinic (DMF), at 20ºC: *a* = 7.293(1), *b* = 11.298(1), *c* = 26.995(3) Å, α = 91.20(1)º, β = 91.74(1)º, γ = 90.06(1)º, *V* = 2222.8(4) Å^3, M_r = 462.57, *Z* = 4, space group $P\bar{1}$, d_{calc} = 1.382 g/cm^3, μ(MoKα) = 0.181 mm^{-1}, *F*(000) = 980. The unit cell parameters and intensities of 18142 reflections (7800 independent, R_{int} = 0.057) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning to $2\theta_{max}$ = 50º).

The structure was solved by a direct method using the SHELXTL program package [18]. The positions of the hydrogen atoms were revealed from electron density difference synthesis and refined using the "riding" model with $U_{iso} = nU_{eq}$ for a non-hydrogen atom bound to the given hydrogen (n = 1.5 for the hydroxyl group and n = 1.2 for all remaining hydrogen atoms). The structure was refined in F^2 full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms to wR_2 = 0.215 for 7609 reflections (R_1 = 0.082 for 3121 reflections with $F > 4\sigma$ (F), S = 1.080). The full crystallographic information has been placed in the Cambridge structural data base (reference No. CCDC631476). The interatomic distances and valence angles are given in Tables 3 and 4.

The authors thank the National Institute for Allergic Infectious Diseases (USA) for carrying out the study within the TAACF program of the antitubercular properties of the compounds synthesized by us (contract No. 01-A1-45246).

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