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4-HYDROXY-2-QUINOLONES. 56*. 4-(ADAMANT-1-YL)THIAZOLYL-2-AMIDES OF 1-R-4-HYDROXY-2-OXO-QUINOLINE-3-CARBOXYLIC ACIDS AS POTENTIAL ANTITUBERCULAR AGENTS

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The synthesis, antitubercular, anti-HIV, and antitumor activity of the 4-(adamant-1-yl)thiazolyl-2-amides of 1-R-4-hydroxy-2-oxoquinoline-3-carboxylic acids have been studied. An efficient method for purifying the 4-hydroxy-2-oxoquinoline derivatives from their metal salts is proposed.

Keywords: adamantane, 4-hydroxy-2-quinolone, thiazole, antitubercular activity.

The unique nature of the structure of adamantane has attracted the attention of chemists and biologists comparatively recently (after 1964 when the first data for the antiviral activity of 1-aminoadamantane was obtained [2]). Since then an active study of the chemical and pharmacological properties of this skeletal hydrocarbon has been initiated and this has led to the preparation of biologically active materials with a broad spectrum of activity [2-11]. Thanks to its very marked lipophilic nature the adamantane fragment is often the pharmacophore in these compounds and is responsible for their biological activity. A heterocyclic fragment (or some other) serving as a convenient function permits a broad variation of the structure and, hence, the properties of the final compounds.

On this basis, and bearing in mind the recent, sharply accentuated, worldwide problem of tuberculosis therapy we have synthesized the 4-(adamant-1-yl)thiazolyl-2-amides of 1-R-4-hydroxy-2-oxoquinoline-3-carboxylic acids (**1a-n**) as potential, antitubercular agents with the use of a previously developed method [12] (Scheme 1).

In the ^{1}H NMR spectra of the amides **1a-n** the signals for the protons of all the functional groups are quite readily interpreted with relation to their chemical shifts, intensities, and multiplicities. Moreover, the 1-substituted adamantane fragment as expected from its symmetry, shows a clear distinction of the three types of β-, γ-, and δ-protons [2] (Table 1).

The presence of the 4-OH group in the structure of the amides **1a-n** (and in related compounds) is responsible for the formation of strongly colored complexes with nickel and, particularly, with iron salts. According to our data, the threshhold of sensitivity for this reaction for a 2% solution of the amides **1** is

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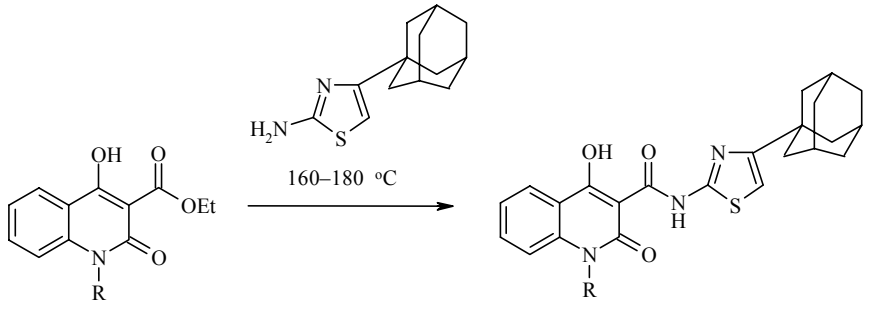
TABLE 1. ^{1}H NMR Spectra, δ, ppm for Amides **1a-n**

Compound	OH (1H, s)	NH (1H, s)	H_{arom} quinolone				5-H thiazole	$H_{adamantane}$			R
			5-H (1H, d)	7-H (1H, t)	8-H (1H, d)	6-H (1H, t)		γ (3H, s)	δ (6H, s)	β (6H, s)	
1a	15.04	13.59	8.04	7.74	7.46	7.33	6.85	2.05	1.92	1.74	12.19 (1H, s, NH)
1b	15.17	13.63	8.13	7.89	7.58	7.42	6.88	2.04	1.92	1.74	3.70 (3H, s, Me)
1c	15.06	13.34	8.13	7.85	7.59	7.36	6.78	2.05	1.93	1.75	4.35 (2H, q, NCH_2); 1.30 (3H, t, Me)
1d	15.14	13.49	8.12	7.80	7.57	7.38	6.80	2.02	1.91	1.74	6.00 (1H, m, CH=); 5.22 (2H, d, NCH_2); 4.97 (2H, d, CH_2=)
1e	15.10	13.59	8.16	7.83	7.66	7.37	6.81	2.05	1.93	1.76	4.28 (2H, t, NCH_2); 1.76 (2H, $NCH_2C\underline{H}_2$, overlapping β-$H_{adamantane}$); 1.00 (3H, t, Me)
1f	15.13	13.44	8.14	7.82	7.59	7.38	6.83	2.04	1.93	1.75	4.29 (2H, t, NCH_2); 1.75 (2H, $NCH_2C\underline{H}_2$, overlapping β-$H_{adamantane}$); 1.42 (2H, m, $C\underline{H}_2$Me); 0.95 (3H, t, Me)
1g	15.19	13.65	8.14	7.83	7.69	7.40	6.84	2.03	1.91	1.74	4.20 (2H, t, NCH_2); 2.28 (1H, m, CH); 0.94 (6H, d, 2Me)
1h	15.12	13.58	8.12	7.82	7.64	7.37	6.81	2.03	1.93	1.75	4.28 (2H, t, NCH_2); 1.75 (2H, $NCH_2C\underline{H}_2$, overlapping β-$H_{adamantane}$); 1.41 (4H, m, $(C\underline{H}_2)_2$Me); 0.90 (3H, t, Me)
1i	15.15	13.60	8.14	7.82	7.67	7.38	6.85	2.04	1.92	1.75	4.27 (2H, t, NCH_2); 1.75 (1H, CH, overlapping β-$H_{adamantane}$); 1.47 (2H, q, $CH_2C\underline{H}_2$); 0.94 (6H, d, 2Me)
1j	15.15	13.64	8.14	7.85	7.66	7.40	6.84	2.05	1.93	1.75	4.30 (2H, t, NCH_2); 1.75 (2H, $NCH_2C\underline{H}_2$, overlapping β-$H_{adamantane}$); 1.36 (6H, m, $(C\underline{H}_2)_3$Me); 0.88 (3H, t, Me)
1k	15.14	13.59	8.13	7.83	7.65	7.40	6.83	2.04	1.92	1.75	4.29 (2H, t, NCH_2); 1.75 (2H, $NCH_2C\underline{H}_2$, overlapping β-$H_{adamantane}$); 1.37 (8H, m, $(C\underline{H}_2)_4$Me); 0.87 (3H, t, Me)
1l	15.16	13.65	8.13	7.82	7.68	7.39	6.86	2.04	1.92	1.74	4.27 (2H, t, NCH_2); 1.74 (2H, $NCH_2C\underline{H}_2$, overlapping β-$H_{adamantane}$); 1.29 (10H, m, $(C\underline{H}_2)_5$Me); 0.85 (3H, t, Me)
1m	15.13	13.63	8.14	7.84	7.66	7.40	6.81	2.05	1.93	1.75	4.32 (2H, t, NCH_2); 1.75 (2H, $NCH_2C\underline{H}_2$, overlapping β-$H_{adamantane}$); 1.27 (12H, m, $(C\underline{H}_2)_6$Me); 0.85 (3H, t, Me)
1n	15.20	13.70	8.13	7.84	7.69	7.40	6.87	2.03	1.91	1.74	4.31 (2H, t, NCH_2); 1.74 (2H, $NCH_2C\underline{H}_2$, overlapping β-$H_{adamantane}$); 1.24 (14H, m, $(C\underline{H}_2)_7$Me); 0.84 (3H, t, Me)

Scheme 1



2a–n **1a–n**

1, **2 a** R = H; **b** R = Me; **c** R = Et; **d** R = $CH_2CH{=}CH_2$; **e** R = C_3H_7; **f** R = C_4H_9; **g** R = *i*-C_4H_9; **h** R = C_5H_{11}; **i** R = *i*-C_5H_{11}; **j** R = C_6H_{13}; **k** R = C_7H_{15}; **l** R = C_8H_{17}; **m** R = C_9H_{19}; **n** R = $C_{10}H_{21}$

3-5 μg/ml. At a higher iron content the solutions are predominantly yellow or dark red in color. The ability of the amides **1** to form colored complexes can be used to develop methods for their qualitative and quantitative analysis. However, this property gives rise to a particular difficulty in their purification. The nearly universal presence of metallic salts in many solvents and added reagents means that the 4-hydroxy-2-oxoquinolines are predominantly yellow in color and this is impossible to remove, even after many crystallizations. In the case of the water soluble hydrochloride salts of the dialkylaminoalkylamides of 1-R-4-hydroxy-2-oxoquinoline-3-carboxylic acids [13] this problem was readily resolved using the disodium salt of ethylenediaminetetraacetic acid (Trilon B). For the purification of the amides **1a-n** this method proves unsuitable because of the low solubility of the given complexone in organic solvents. The problem was resolved using the disubstituted salt of ethylenediaminetetraacetic acid with triethylamine. The reasonably high solubility of this salt in DMF at room temperature permits its use in the purification of both the amides **1** and of their structural analogs.

The combination in a single molecule of the quinolone, thiazole, and adamantane systems (active in relation to many microorganisms) led us to propose that the amides **1a-n** would also affect tuberculosis mycobacteria. In fact, a microbiological investigation carried out in the scope of the TAACF program (Tuberculosis Antimicrobial Acquisition and Coordinating Facility, Contract No. 01-AI-45246) showed that the majority of the amides **1a-n** at a concentration of 12.5 μg/ml caused a significant retardation in the growth of *Mycobacterium Tuberculosis* H37Rv ATCC 27294 (Table 2). The minimum inhibitory concentration for the most active of these (the allyl- (**1d**) and isobutyl- (**1g**) derivatives) are 3.13 and 0.78 μg/ml respectively and this opens up real grounds for developing antitubercular compounds based on them. It was interesting that these compounds show activity towards the *Mycobacterium avium* complex presenting as related forms of nontubercular mycobacteria giving rise in man to an illness morphologically and clinically difficult to differentiate from tuberculosis. This can usefully differentiate the amides **1d,g** from the used antitubercular preparations which, as is known [14], do not act on the agents of nontubercular mycobacterioses. At the present time, the therapy of such illnesses is even less effective than for tuberculosis.

Several of the compounds synthesized by us (the amides **1a,b,d**) were also tested as potential anti-HIV and antitumor agents. Investigation of the action of these compounds on the infective AIDS virus of cell lymphocytes was carried out by method [15] and has shown that they do not possess this kind of activity. The amides **1a,b,d** proved to be slightly active towards the main forms of malignant tumors in man: leukemia (CCRF-CEM, HL-60(TB), K-562, MOLT-4, RPMI-8226, SR), lung cancer (A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, NCI-H460, NCI-H522), large intestine (COLO 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, SW-620), CNS cancer (SF-295, SF-539, SNB-19, SNB-75, U251), melanoma

TABLE 2. Characteristics of the 4-(Adamant-1-yl)thiazolyl-2-amides of 1-R-4-Hydroxy-2-oxoquinoline-3-carboxylic Acids

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %	Inhibition of the growth of *M. Tuberculosis H37Rv ATCC 27294* at 12.5 micrograms/ml, %
		C	H	N			
1a	$C_{23}H_{24}N_3O_3S$	65.49 / 65.38	5.85 / 5.73	9.81 / 9.95	>340	95	59
1b	$C_{24}H_{26}N_3O_3S$	66.18 / 66.03	6.13 / 6.00	9.50 / 9.63	281-283	97	81
1c	$C_{25}H_{28}N_3O_3S$	66.52 / 66.64	6.20 / 6.26	9.42 / 9.33	254-256	90	28
1d	$C_{26}H_{28}N_3O_3S$	67.69 / 67.51	6.22 / 6.10	9.02 / 9.08	230-232	93	95
1e	$C_{26}H_{30}N_3O_3S$	67.07 / 67.22	6.44 / 6.51	9.10 / 9.04	239-241	94	51
1f	$C_{27}H_{32}N_3O_3S$	67.80 / 67.75	6.71 / 6.74	8.72 / 8.78	181-183	88	49
1g	$C_{27}H_{32}N_3O_3S$	67.87 / 67.75	6.83 / 6.74	8.66 / 8.78	201-203	91	99
1h	$C_{28}H_{34}N_3O_3S$	68.09 / 68.26	6.87 / 6.96	8.64 / 8.53	194-196	92	18
1i	$C_{28}H_{34}N_3O_3S$	68.11 / 68.26	7.08 / 6.96	8.58 / 8.53	213-215	87	12
1j	$C_{29}H_{36}N_3O_3S$	68.88 / 68.75	7.25 / 7.16	8.20 / 8.29	172-174	90	7
1k	$C_{30}H_{38}N_3O_3S$	69.07 / 69.20	7.48 / 7.36	8.19 / 8.07	166-168	89	0
1l	$C_{31}H_{40}N_3O_3S$	69.60 / 69.63	7.67 / 7.54	7.92 / 7.86	175-177	90	3
1m	$C_{32}H_{42}N_3O_3S$	70.22 / 70.04	7.60 / 7.71	7.73 / 7.67	131-133	87	14
1n	$C_{33}H_{44}N_3O_3S$	70.48 / 70.43	7.97 / 7.88	7.35 / 7.47	150-152	92	15

(LOX-IM VI, MALME-3M, SK-MEL-28, SK-MEL-5, UACC-257), ovarian cancer (IGR-OV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8), kidney (786-0, A498, ACHN, CAKI-1, SN12C, TK-10, UO-31), prostate (PC-3, DU-145), and mammary gland (MCF7, MCF7/ADR-RES, MDA-MB-231/ATCC, HS 578T, MDA-MB-435, MDA-N, BT-549). The investigations were carried out as *in vitro* experiments in the National Cancer Institute (USA) using method [16].

EXPERIMENTAL

^{1}H NMR spectra for the synthesized compounds were recorded on a Bruker WP-100 SY instrument (100 MHz) using DMSO-d_6 as solvent and TMS as internal standard.

4-(Adamant-1-yl)thiazolyl-2-amides of 1-R-4-Hydroxy-2-oxoquinoline-3-carboxylic Acids (1a-n) (General Method). A mixture of the corresponding ethyl 1-R-4-hydroxy-2-oxoquinoline-3-carboxylate (0.01 mol), 4-(adamant-1-yl)-2-aminothiazole (2.34 g, 0.01 mol), and DMF (1 ml) was stirred and held at 160-180°C for 10 min. The product was cooled, ethanol (30 ml) was added, then thoroughly stirred and the precipitate was filtered off. The obtained amide **1** was washed on the funnel with alcohol and dried. It was crystallized from DMF with the addition of the necessary solution of the disubstituted salt of ethylenediaminetetraacetic acid with triethylamine in DMF.

Method for Preparation of a Solution of the Disubstituted Salt of Ethylenediaminetetraacetic Acid with Triethylamine in DMF. A mixture of ethylenediaminetetraacetic acid (2.92 g, 0.01 mol), triethylamine (2.8 ml, 0.02 mol), and freshly distilled DMF (40 ml) was stirred until solution of the precipitate (to speed the reaction the mixture can be heated to 50°C). The product was left for several hours at room temperature and then filtered. The solution obtained was stored in an air tight, stoppered container.

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