SYNTHESIS OF NEW QUINAZOLINE DERIVATIVES.

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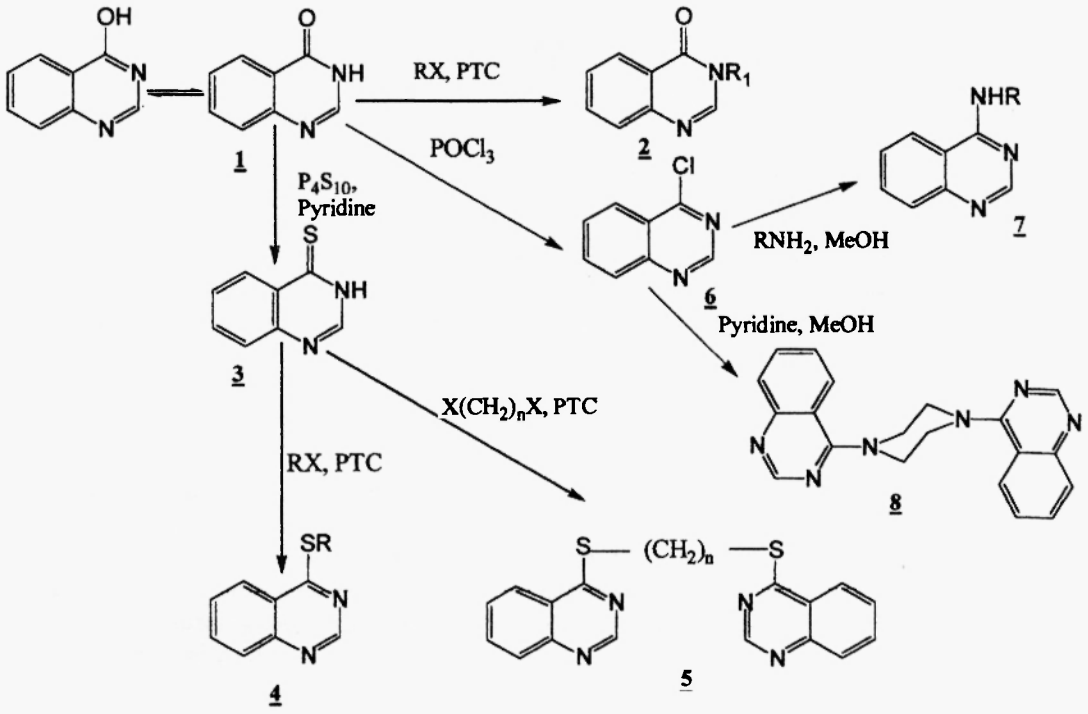
Abstract:
New quinazoline derivatives were prepared by the reaction of 4-hydroxy-quinazoline with alkyl halides under phase transfer-catalysis conditions. The hydroxy group was readily converted into a thiol function by treating with phosphorus pentasulfide in pyridine and the subsequent alkylation of the thiol group was carried out under PTC conditions. Chlorination of 4-hydroxyquinazoline was carried out with phosphorus oxychloride. Branching of alkylamino side chains to the 4-OH, 4-S, and 4-Cl quinazolines has resulted in the synthesis of several compounds identified by ^{1}H NMR.

Introduction:
Quinazoline derivatives have been reported to possess depressant, anticonvulsant and muscle relaxant properties as well as anti-inflammatory, antihypertonic, antibacterial, antifungal, analgesic and spasmolytic activities [1-6]. Attention was also drawn to this heterocyclic moiety with the aim to use it as possible pharmacophore, especially in case of tyrosine kinase inhibitors and adenosine antagonists [7].
Within the frame of our ongoing research devoted to chemosensitizers [8-11], we intended to prepare new derivatives belonging to this series.

Results and discussion:
At first, 4-hydroxy-quinazoline, **1**, was used as starting material. Alkylation was carried out under phase transfer catalysis (PTC) conditions with tetrabutylammoniumbromide (TBAB) as catalyst. In spite of the tautomeric equilibrium between N(3) and C(4), only small amounts of O-alkylated derivatives were identified but not isolated. Hence, substitution at the nitrogen atom in position 3 gave compounds **2** as the major product.
Subsequently, the OH functional group was modified.
On the one hand, the 4-thio-quinazoline **3** was prepared by treating **1** with phosphorus pentasulfide in pyridine. Alkylation of the thione only gave 4-alkylthioquinazoline derivatives **4** as already observed with thioacridines [12] or thioquinolines [13]. Dimers **5** were also prepared alkylating **3** with α,ω-alkyldihalides.

On the other hand, chlorination of 1 with phosphorus oxychloride gave the 4-chloro quinazoline 6 in good yields. Because of its strong reactivity, 6 easily reacts with amino derivatives to lead to the 4-alkylamino-quinazolines 7.
Synthetic pathways are schematised in figure 1.



Substituents and bridge length :
R = dimethylaminoethyl (a); dimethylaminopropyl (b); diethylaminoethyl (c); diisopropylaminoethyl (d); pyrrolidinoethyl (e); piperidinoethyl (f); morpholinoethyl (g).
n = 2 (h); 4 (i); 5(j); 6(k).

Figure 1. Synthetic pathways

Structure of compounds obtained was confirmed by ^{1}H NMR. Chemical data of these compounds are gathered in Table 1.

Experimental

Melting points were determined on a Büchi B540 apparatus and are given uncorrected. NMR spectra were recorded on a Brucker Avance 200 spectrometer with tetramethyl silane used as internal standard.

General procedures.

3-Alkylamino-4-oxoquinazolines, 2.

A stirred mixture of 4-hydroxy-quinazoline (5mmol), alkyl halide (5mmol), TBAB (0,1mmol) in toluene (30mL) and 50% aqueous potassium hydroxide (15 mL) was refluxed for 4 hours. The organic layer was separated, washed with water and dried over magnesium sulphate. After evaporation of solvent, the crude oily residue was purified and isolated by column chromatography on silica gel Merck with chloroform/methanol (v/v: 8/2) as mobile phase.

4-Alkylamino-quinazolines, 7.

4-Chloro-quinazoline was obtained by refluxing at 100°C for three hours a mixture of 4-hydroxy-quinazoline (5mmol) with phosphorus oxychloride (30mL). 4-Amino-substituted compounds were obtained by heating in methanol at 140°C for four hours 4-chloro-quinazoline (5mmol) with amino derivatives (5mmol) before 10% aqueous potassium hydroxide be added (50mL). The precipitated product was filtered and recrystallised in absolute ethanol.

Table 1. Chemical and physical data

Compd	Reac. time (h)	Yield (%)	Mp (°C)	^{1}H NMR(solvent)-δ(ppm), J(Hz)
1b	3	33	203*	(D_2O) - 2.05 (m, 2H); 2.75 (s, 6H); 3.09 (t,2H, J = 6); 3.9 (t,2H, J = 7.2); 7.4(m,2H); 7.6(m,1H); 7.75(d,1H, J = 8.5); 8.05(s,1H)
1d	48	30	206*	(D_2O) - 1.4(d, 12H, J = 6.1); 3.8(m, 2H); 3.7(m, 2H); 4.3(t,2H, J = 7.3); 7.5(d 2H; J = 7.7); 7.85(m,2H); 8.2(s,1H)
2c	2	75	120	($CDCl_3$) - 1.0(t, 6H, J = 4.1); 2.6(q, 4H, J = 7.5); 2.7(t, 2H, J = 5.8); 3.6(t, 2H, J = 4.7); 6.9(s, NH); 7.4(m,1H); 7.7(m, 3H); 8.6(s, 1H)
2d	2	90	90	($CDCl_3$) - 1.1(d,12H, J = 6.4); 2.8 (t, 2H, J = 5.3); 3.0(sp, 2H, J = 6.4); 3.5(t, 2H, J = 5.3); 6.9(s, NH); 7.4(td,1H, J = 1.3, 8.1); 7.7(m, 4H); 8.6(s,1H)
2e	2	82	150	($CDCl_3$) - 1.8(qn, 4H, J = 3.3); 2.7(t, 4H, J = 6); 3.2 (m, 4H); 6.8(s, NH); 7.4(td,1H, J = 1.5-7.5); 7.7(us, 2H); 7.7 (dd,1H, J = 1.3, 8.4); 8.6(s,1H)
4	4	40	258	(DMSO-d_6/TFA-d) - 4.5(s, 8H); 7.8(td, 2H, J = 1.2-7.1); 7.9(dd, 2H, J = 1.1, 8.3); 8.1(td, 2H, J = 0.7, 8.1); 8.3 (d, 2H, J = 8.2); 8.9(s, 2H)
3a	4	20	212*	(D_2O) - 2.8(m, 6H); 3.2(m, 4H); 7.1(m, 2H); 7.2(m, 2H); 8.2 (s,1H)
3b	4	32	172 *	(D_2O) -1.8(q, 2H, J = 6.9); 2.7(s, 6H); 2.8(m, 2H); 3.1(t, 2H, J = 7.5); 7.2(m, 2H); 7.5(m, 2H); 8.0(s, 1H)
3d	8	30	188*	(D_2O) - 1.3(d,12H, J = 3.8); 3.4(m, 2H); 3.7(m, 4H); 7.7(m, 2H); 8.0(m, 2H); 9.0(s, 2H)
3e	4	20	246*	(D_2O)- 2.0(us, 4H); 3.3(m, 2H); 3.7(us, 6H); 7.8(m, 2H); 8.1(m, 2H); 9.0 (s,1H)
3f	4	45	242*	(D_2O) - 1.5(us, 6H); 2.5(us, 4H); 2.7(us, 2H); 3.5(us, 2H); 7.6(m, 1H); 7.8 (m,1H); 7.9 (d, 1H, J = 8.2); 8.1(m, 1H); 8.9 (s, 1H)
3g	8	20	246*	(D_2O) - 3.7 (us,12H); 7.7(m, 2H); 7.9(m, 2H); 9.1(s, 1H)
5h	4	30	186	(DMSO-d_6/TFA-d) - 4.2(s, 2H); 4.9(s, 2H); 8.2(us, 8H); 9.2(s,2H); **
5i	4	40	126	(DMSO-d_6/TFA-d) – 1.0(s, 4H); 2.5(s, 4H); 6.7(m, 2H); 7.0 (m, 2H); 7.2(m, 4H, J = 8.1) **
5j	4	56	138	(DMSO-d_6/TFA-d) - 1.8(m, 6H); 3.5(t, 4H, J = 7); 8.1 (m, 2H); 8.3 (d, 2H, J = 8.4); 8.9(s, 2H) **
5k	4	54	365	(DMSO-d_6/TFA-d) - 1.7(s, 4H); 1.9(s, 4H); 3.5(q, 4H, J = 7.9); 8(m, 4H); 8.3(m, 2H); 9.1(m, 2H)

* as hydrochlorides

** 2 aromatic protons are hidden because of the TFA.

4-Alkylthio-quinazolines, 4:
4-Quinazoline-thiol was obtained by refluxing at 80°C for six hours a mixture of 4-hydroxy-quinazoline (5mmol) and phosphorus pentasulfide (10mmol) in pyridine (30mL). The expected product precipitated by adding cold water (200mL). Precipitate was filtered and recrystallised in ethanol.
A mixture of 4-quinazoline-thiol (5mmol), alkyl halide (1.5mmol), tetrabutylammonium bromide (0.2g) was dissolved in toluene (20mL) and 50% aqueous potassium hydroxide (15mL). Solution was refluxed for four hours and then the organic layer was separated, washed with warm water and dried over magnesium sulphate. After evaporation of solvent, the oily crude product was purified by column chromatography on silica gel Merck with petroleum ether-ethylacetate (v/v : 9/1) as mobile phase.

Bis-thioderivatives, 5.
A stirred mixture of monomer (10mmol), alkyl dibromide (5mmol) tetrabutylammonium bromide (5mmol), 50% aqueous potassium hydroxide (50mL) and butanone (150mL) was refluxed for three hours. The mixture was then filtered and solution was poured out into 500mL of boiling water. On cooling, there is a precipitation. The solid crude was washed with warm ethanol.

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