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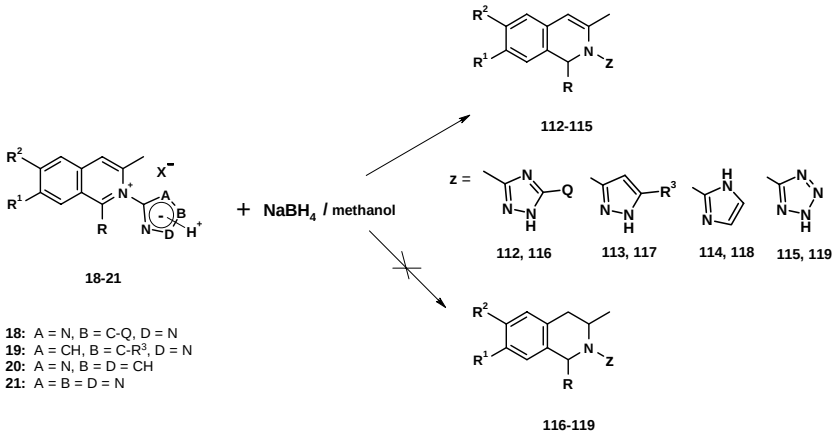


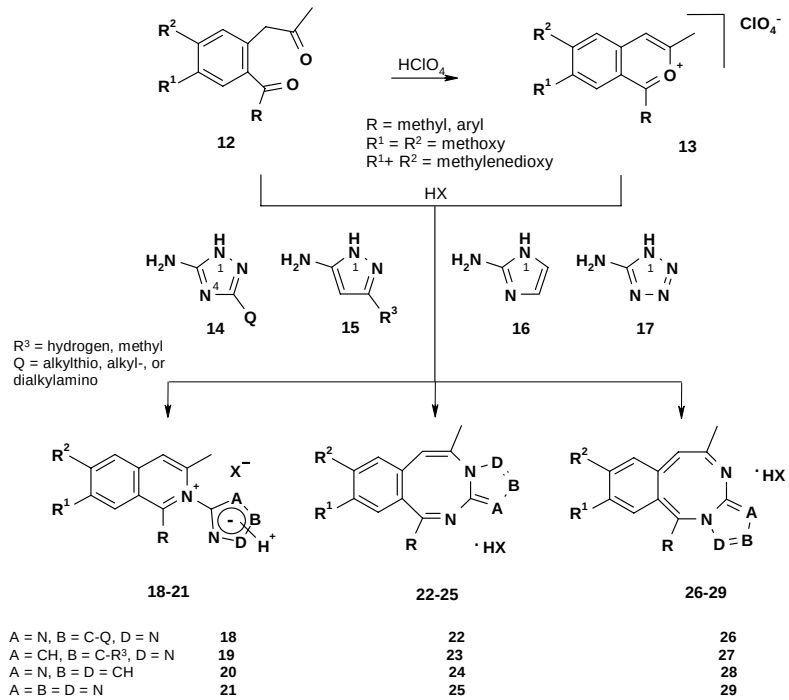
18: A = N, B = C-Q, D = N
19: A = CH, B = C-R^3, D = N
20: A = N, B = D = CH
21: A = B = D = N

Different *N*-azinyl-, *N*-aryl- and *N*-methylisoquinolinium salts, prepared for this purpose, were also reduced using the above reaction conditions so that we can explain the formation of the 1,2-dihydroisoquinolines (**112-115**). It was stated that the unexpected outcome of the above reductions was caused by the electron withdrawing effect of the heteroring in position 2 of the isoquinolinium moiety.

I. Introduction

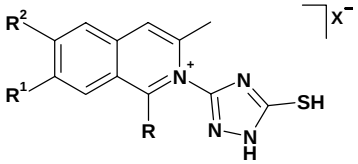
The CNS activity of the 2,3-benzodiazepines is well known from the literature. US authors patented the synthesis and antiarrytmic activity of some 2,4-benzodiazocine derivatives.

In course of 5-HT_7 CNS research program of EGIS Pharmaceuticals Ltd. we decided to react the 2'-acylphenylacetones (**12**) or the benzo[*c*]pyrilium salts (**13**) formed from them with strong acids with α-aminoazoles (**14-17**) to yield either the *N*-azolylisoquinolinium salts (**18-21**) or the 2,4-benzodiazocine derivatives (**22-25**, and **26-29**, respectively).



A = N, B = C-Q, D = N	**18**	**22**	**26**
A = CH, B = C-R^3, D = N	**19**	**23**	**27**
A = N, B = D = CH	**20**	**24**	**28**
A = B = D = N	**21**	**25**	**29**

In the above reactions, *N*-azolylisoquinolinium salts were obtained. The synthesised *N*-(5'-alkylthio-1,2,4-triazol-3'-yl)isoquinolinium salts (**18**) posessed favourable 5-HT_7 receptor binding activity. So that we can extend the above studies, we have planned the synthesis of *N*-(5'-thiolo-1'*H*-1,2,4-triazol-3'-yl)isoquinolininum salts (**30**). These salts can be *S*-alkylated to yield *N*-(5'-alkylthio-1,2,4-triazol-3'-yl)isoquinolinium salts (**18**) or alkylated with α,ω-dihaloalkanes to give isoquinolinium salts (**31** or **32**), respectively.



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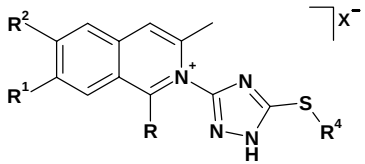
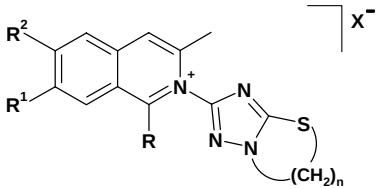


18, Q = S-R^4
R^4 = alkyl



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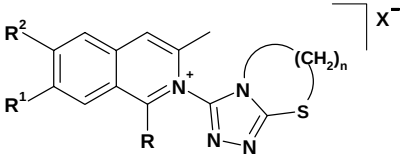
n = 2- 4



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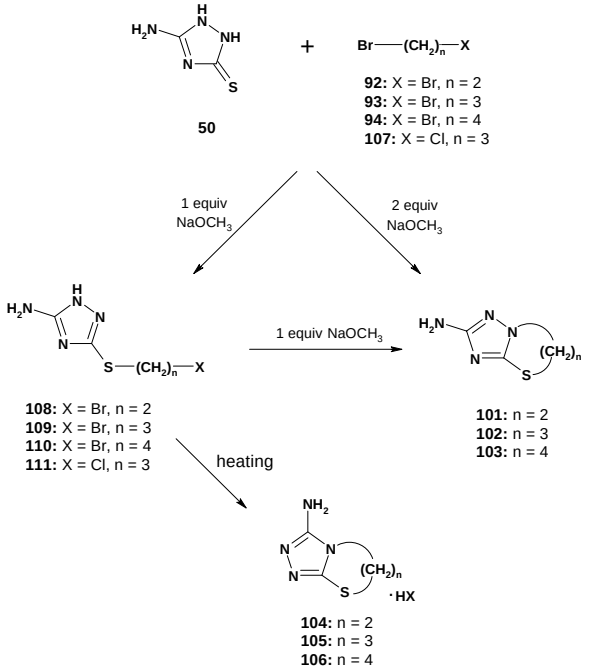
To help the penetration of above derivatives through blood-brain barrier, their reduction with sodium borohydride was decided to yield either 1,2-dihydroisoquinoline (**33-36**) or 1,2,3,4-tetrahydroisoquinoline (**37-40**) derivatives, respectively.

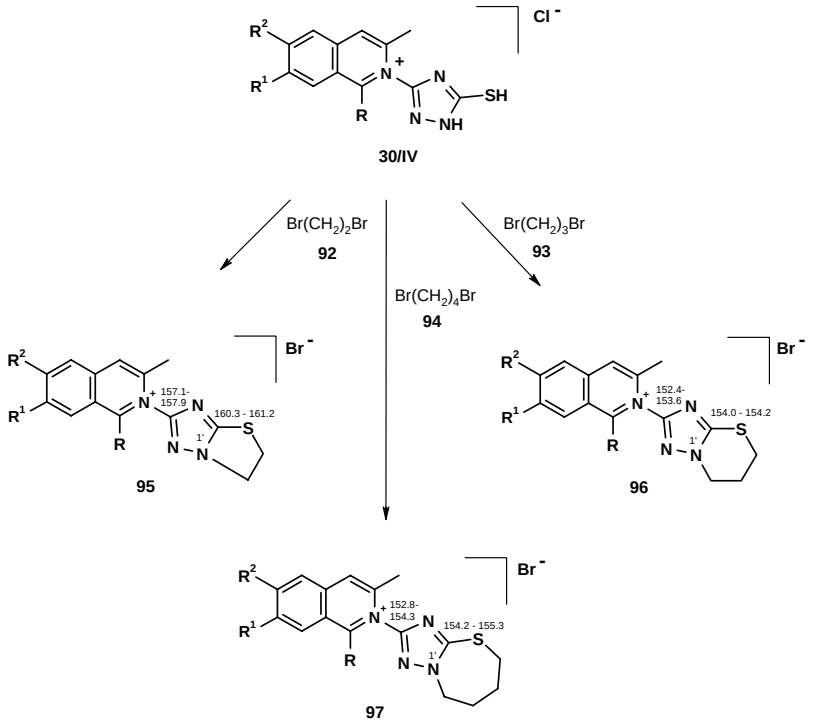
Thus the 2'-acylphenylacetone (**12c**) was condensed with the corresponding triazole derivatives **101-103** to yield derivatives **95, 96** and **97**, respectively.

5. A general method was elaborated for the synthesis of isomeric amino-thiazolo[1,2,4]triazole, amino-[1,2,4]triazolo[1,3]thiazine and amino-[1,2,4]triazolo[1,3]thiazepine derivatives, respectively.

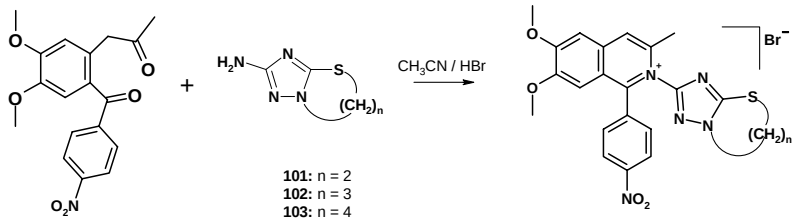


2-Amino-5,6,7,8-tetrahydro-[1,2,4]triazolo[5,1-*b*][1,3]thiazepine (**103**) and 3-amino-5,6,7,8-tetrahydro-[1,2,4]triazolo[3,4-*b*][1,3]thiazepine (**106**) represent new ring systems, as well. The structure of the above isomers was proved by UV-, ^{1}H- and ^{13}C-NMR spectroscopy.

6. The reduction of *N*-azolylisoquinolinium salts (**18-21**) with sodium borohydride in methanol did not lead to 1,2,3,4-tetrahydro isoquinolines (**116-119**), expected on the basis of previous literature data, but to 1,2-dihydroisoquinolines (**112-115**).

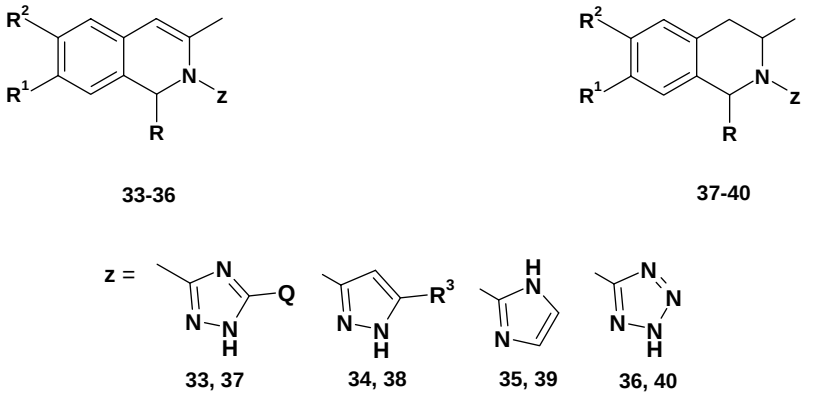


The *N*-triazolilisoquinolinium salts condensed with the thiazole, thiazine and thiazepine rings (**95-97**, respectively) represent new ring systems. Their structure was proved by ^{13}C-NMR spectroscopy as well as by synthetic way.



12c

10

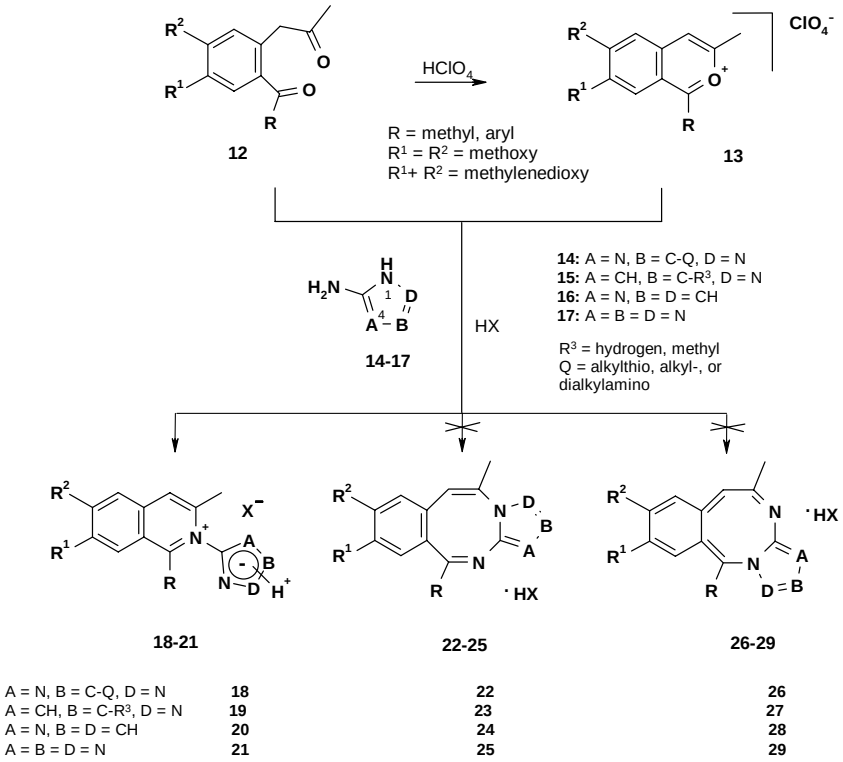


II. Methods of studies

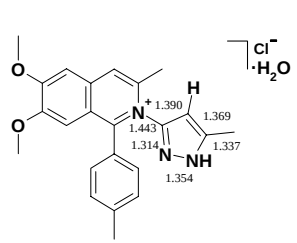
Common methods of synthetic organic chemistry were used. The reactions, separations of products as well as their purification was followed by TLC. Some reactions performed in semi-micro scale were followed by HPLC-MS. The structure of products obtained was proved on the basis of their ^{1}H-, ^{13}C-NMR, IR, UV and MS spectra. In some cases, the structure of the compounds was determined by single crystal X-ray crystallography. Biological studies were performed at the Pharmacological and Biochemical Departments of EGIS Pharmaceuticals Ltd.

III. Results

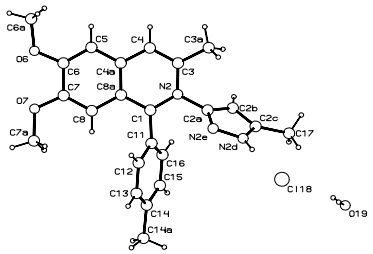
1. In the planned reactions of 2'-acylphenylacetones (**12**) or the benzo[*c*]pyrilium salts (**13**) and α-aminoazoles (**14-17**), *N*-azolylisoquinolinium salts (**18-21**) were formed. The possible formation of anthracene or phenanthrene type 2,4-benzodiazocines (**22-25** and. **26-29**, respectively) was excluded by ^{1}H- and ^{13}C-NMR spectra of the products obtained as well as by NOE studies.



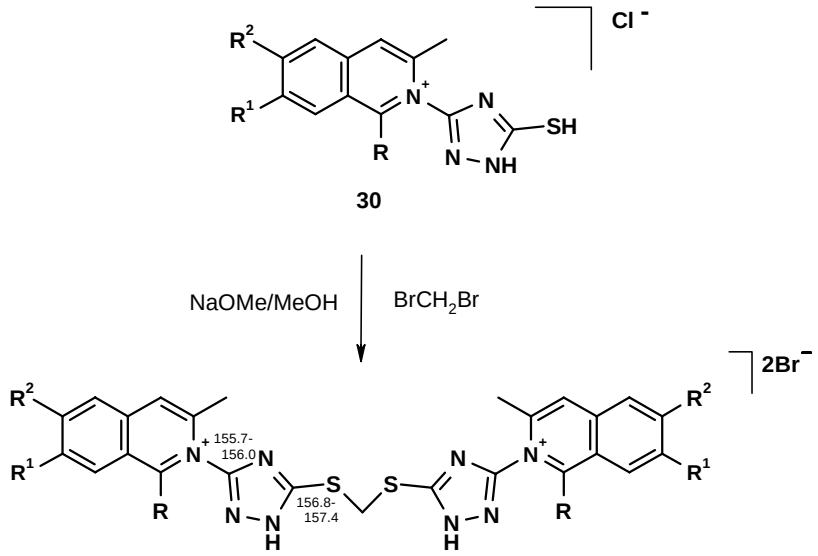
The final proof of the structure of products was obtained by the X-ray structure determination of derivatives **19a**, **18b** and **21a**, respectively.



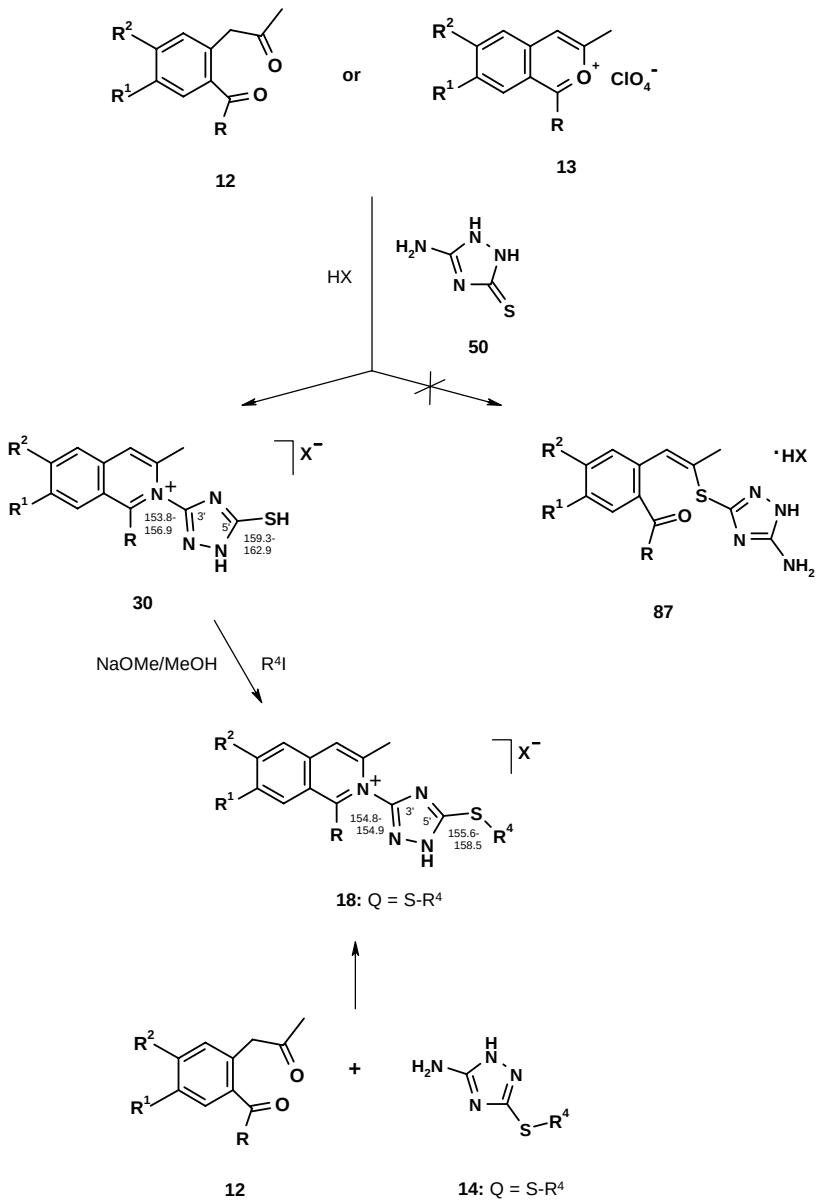
19a

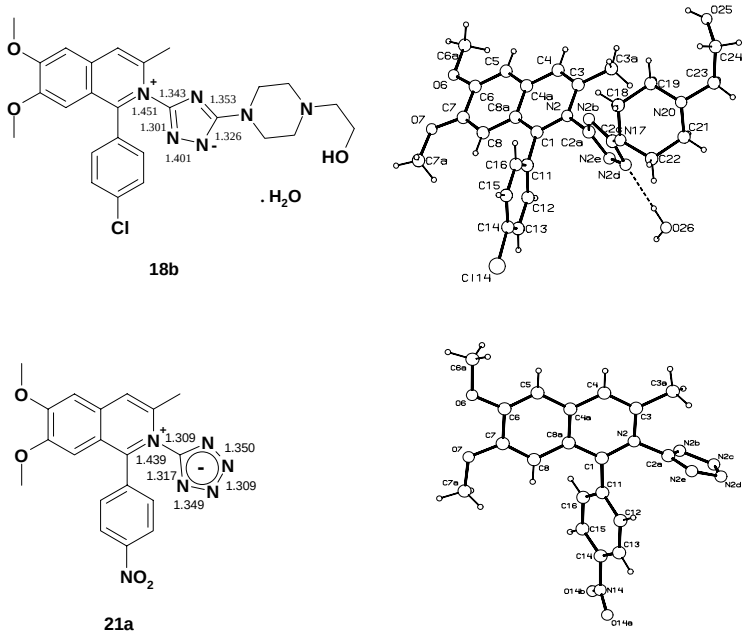


4. The reaction of *N*-(5'-thiolo-1'*H*-1,2,4-triazol-3-yl)isoquinolinium salts (**30**) with dibromomethane led to type **91** products



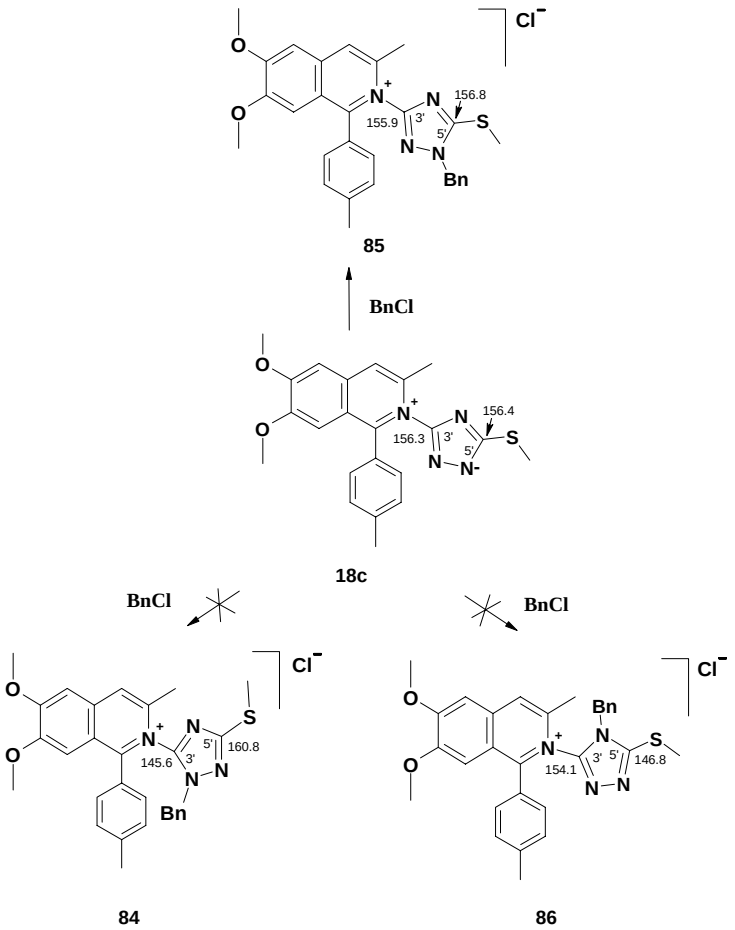
After performing the above reaction with 1,2-dibromoethane (**92**), 1,3-dibromopropane (**93**) and 1,4-dibromobutane (**94**), [*N*-(5',6'-dihydro-thiazolo[3,2-*b*][1,2,4]triazol-2-yl)isoquinolinium]-bromides (**95**), [*N*-(6',7'-dihydro-5*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-2-yl)isoquinolinium]-bromides (**96**) and [*N*-(5',6',7',8'-tetrahydro-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-2-yl)isoquinolinium]-bromides (**97**) were obtained, respectively.





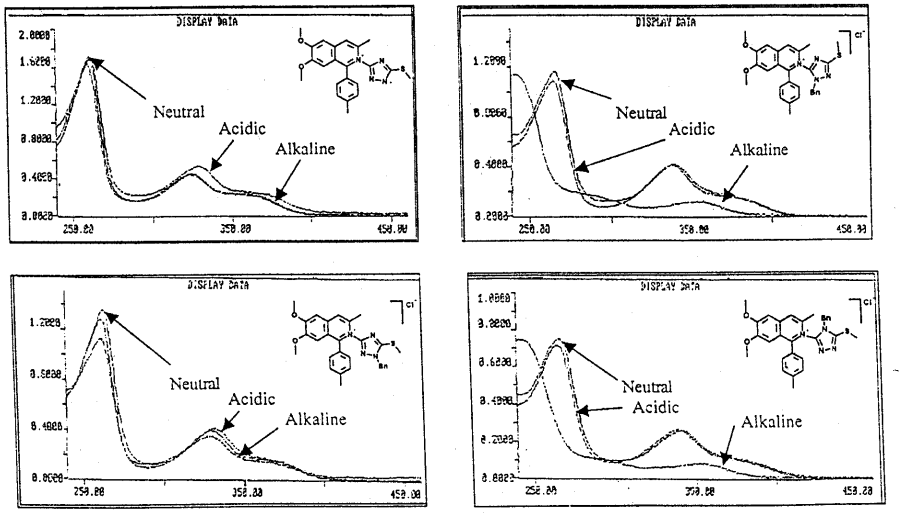
2. The tautomeric structure of the *N*-azolylisoquinolinium salts obtained in solid state was studied by X-ray crystallography. It was stated that the negative charge is fully delocalised on nitrogen atoms of the tetrazole ring of **21a**, while it is localised on the nitrogen atom 1' of the triazole ring in derivative **18b**. The **19a** *N*-pyrazolilisoquinolinium salt exists in 1*H* tautomeric form.

The tautomeric structure of the *N*-triazolylisoquinolinium salts (**18**) in solution was studied with ^{13}C-NMR and UV spectroscopy. Comparing the ^{13}C NMR chemical shifts of atoms C-3' and C-5' of **18c** taken in DMSO-d_6 solution with those of derivatives **84, 85** and **86** made it possible to prove the 1H tautomeric form of **18c**.



The above tautomeric structure is in agreement with the results of the direct alkylation of 18c with benzyl chloride to yield **85**.

The UV spectra of **18c** and those of **84**, **85** and **86** taken in ethanol under neutral, acidic and alkaline conditions pointed out the 1H tautomeric form of **18c** again.



As the ^{13}C-NMR and UV spectra of all *N*-triazolylisoquinolinium salts prepared previously showed good agreement with the corresponding spectra of **18c**, it can be stated that all derivatives of type **18** exist in the 1*H* tautomeric form. in DMSO-d_6 and ethanolic solution.

3. The reactions of 2'-acylphenylacetones (**12**) or the corresponding benzo[*c*]pyrilium salts (**13**) with 5-amino-1,2-dihydro-1,2,4-triazol-3-thione (**50**) also led to type **18** *N*-(5'-thiolo-1'*H*-1,2,4-triazol-3'-yl)isoquinolinium salts (**30**), the structure of which was proved by means of their UV-, ^{1}H- and ^{13}C-NMR spectra, as well as by their direct *S*-alkylation resulting in derivatives **18**.

SYNTHESIS OF *N*-AZOLYLISOQUINOLINIUM SALTS

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Under the direction of: József Reiter, DSc

EGIS Pharmaceuticals Ltd., Chemical Research Division

Budapest, 2004