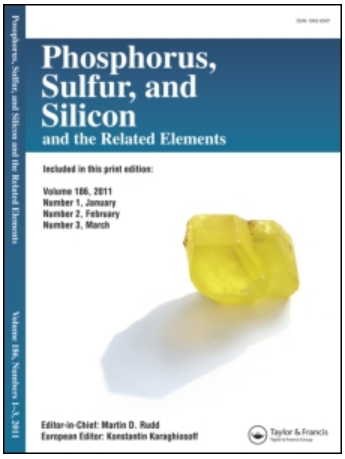

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SOME NEW SELENIUM CONTAINING ANALOGUES OF PYRIDOCARBAZOLES AND INDOLOCARBAZOLES

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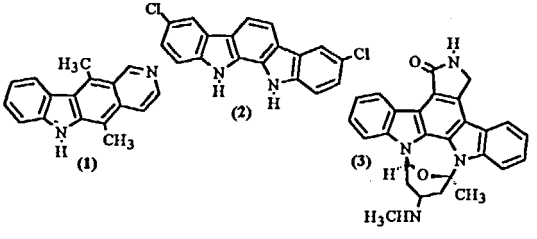
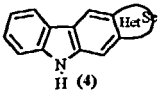
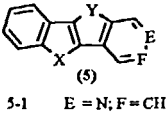
Pyridocarbazole moiety is found for example in alkaloids from the ellipticine **1** series and indolocarbazole in tjipanozole **2** and staurosporine **3**.



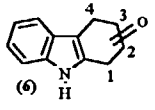
All these compounds show antitumor activities or work as protein kinase inhibitors. The goal of the research presented here was the introduction of a selenium containing ring system in replacement of a pyridine or a pyrrole ring to prepare compounds of general structure **4** and **5**. These are ring D or ring B and/or C analogues of the natural compounds.





5-1 E = N; F = CH
5-2 E = CH; F = N

For the ring D analogues **4**, the starting compounds are the tetrahydrocarbazolones **6**.

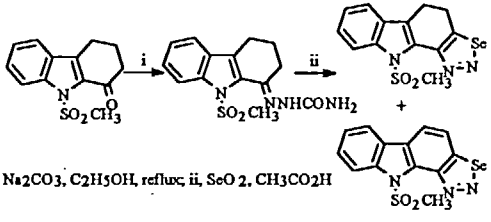


6-1: 1-one 6-2: 2-one 6-3: 3-one 6-4: 4-one

Ketone 6-1 was prepared from tetrahydrocarbazole by a Riley oxidation or through a combination of JAPP-KLINGEMANN and FISCHER indole synthesis from cyclohexanone [1]

The other carbazolones were obtained from 1,3 or 1,4 cyclohexanedione (and the corresponding monoacetals) by FISCHER indole synthesis [2].

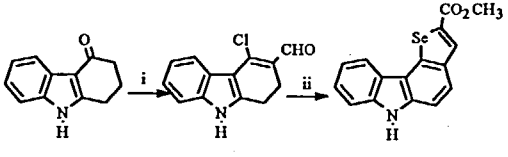
Selenediazole was obtained by reacting semicarbazone of ketone 6-1 with selenium dioxide (scheme 1) in acetic acid [1, 2].



i, $NH_2CONHNH_3Cl$, Na_2CO_3, C_2H_5OH, reflux; ii, SeO 2, CH_3CO_2H

SCHEME 1

The same reaction was made with ketone 6-4. The cyclisation always gave a mixture of the dihydro and the fully aromatic compound. Introduction of a selenophene as a D-ring was achieved using the classical method [3] starting from the chloro aldehyde derivative (scheme 2).

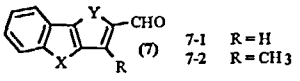


i, $POCl_3$, DMF; ii, Na_2Se, DMF, $ClCH_2CO_2CH_3$, CH_3ONa, CH_3OH

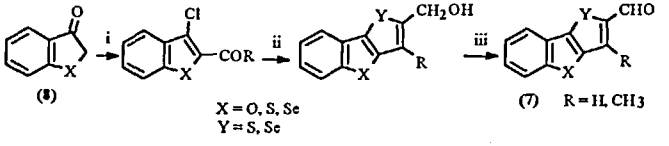
SCHEME 2

The reaction only succeeded from ketone 6-4. Ketone 6-1 could not be transformed into the chloroaldehyde.

The ring B and/or C analogues 5 were obtained from the tricyclic compounds 7.



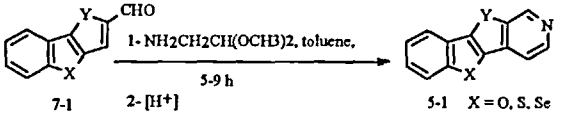
These compounds **7** were synthesized starting from the different ketones **8** earlier described [4] using a Vilsmeier Haack Arnold reaction and by building the C ring by condensation with sodium chalcogenide and chloroacetate (scheme 3) [5]



i, POCl3, DMF; CH3MgI, reflux; CrO3-H2SO4 conc, rt, 24h; ii, Na 2Y, DMF, ClCH2CO2CH3, CH3ONa, CH3OH; LiAlH4, reflux, 3h; iii, PCC, CH2Cl2, 2-3h, rt

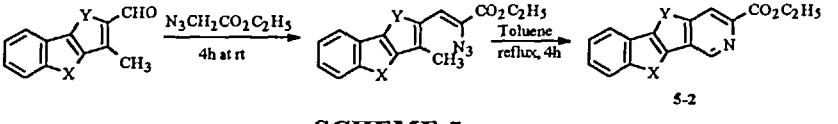
SCHEME 3

Introduction of the pyridine ring from the tricyclic system was made by using classical methods for construction of the six membered ring: Pomeranz-Fritsch and Bischler-Napieralski cyclisations, Staudinger reaction followed by aza-Wittig/electrocyclisation and decomposition of azidoacrylates [6] The Pomeranz-Fritsch method is described in scheme 4.



SCHEME 4

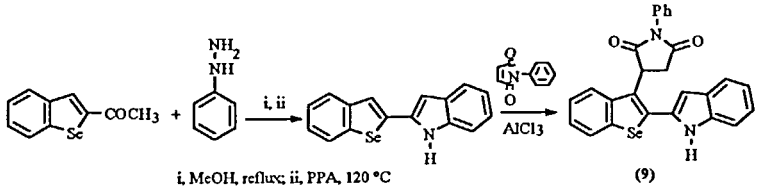
Bischler-Napieralski and Staudinger-aza-Wittig/electrocyclisation did not afford the desired compounds. The thermal decomposition of azidoacrylates obtained from compounds **7** (R = CH_3) gave the desired tetracyclic compounds (scheme 5).



SCHEME 5

Selenium analogues of indolocarbazole systems **9** have been approached by two ways. The first attempt was made by synthesizing

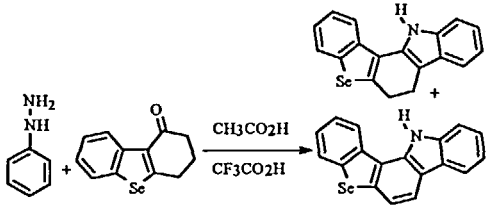
2'-indolo-2-benzo[*b*]selenophene using a FISCHER indole synthesis followed by an electrocyclisation (scheme 6).



SCHEME 6

The electrocyclisation tried stopped at the stage of an electrophilic substitution leading to an open-analogue of the ring system contained in staurosporine.

An another way to access the pentacyclic ring system was to use the FISCHER indole synthesis applied onto ketones prepared in a classical way [7]. The five membered ring system was obtained as a mixture of the dihydro and the fully aromatic derivative (scheme 7). Separation of the compounds being difficult, the mixture has been treated with DDQ leading only to the fully aromatic compound.



SCHEME 7

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