Anticancer activity studies of isoquinoline derivatives – products of 3-(2-(thien-2-yl)thiazol-4-yl)isocoumarin recyclization

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Abstract – A synthetic methodology for obtaining 1-functionalized isoquinolines starting with 3-hetarylisocoumarin has been developed. Studies of anticancer activity of 3-(2-(thien-2-yl)thiazol-4-yl)isocoumarin and the obtained derivatives have been performed on 60 lines of cancer cells in Cancer National Institute of the USA. The obtained compounds demonstrated a clear and strong correlation between anticancer activity and the character of substituents in the base structure, possessed a very low cytotoxicity, and performed well against several cancer types.

Keywords – isocoumarin, 3-hetarylisocoumarin, isoquinolin-1(2*H*)-one, 1-chloroisoquinoline, 1-amino-isoquinoline, recyclisation, anticancer activity.

Introduction

Compounds with the isoquinoline ring are a long- and well-known group of drugs. Their usage in medicine started with natural alkaloids of isoquinoline family.

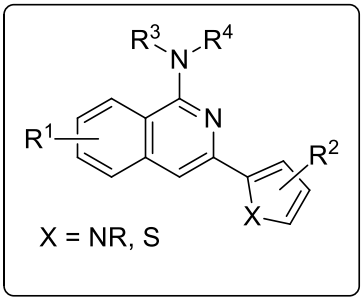


Figure I

Analyzing literature data on 1-amino-3-hetarylisoquinolines as potential anticancer agents, we realized that the number of known compounds of this type is quite limited, with the majority of them being derivatives presented in figure I [1]. Using molecular docking, the mentioned paper demonstrated that the anticancer activity of these compounds is based on the interaction with DNA (intercalation), and also on the inhibition of topomerase I and II *via* strong hydrogen bond formation. Yet, the question of importance of the aminogroup and whether similar molecules with a different polar group in position 1 would be biologicaly active remained open. Therefore, the goal of this paper is the synthesis of new 1-functionalized 3-hetarylchromones and studying the effect of substituents on their anticancer activity.

Materials and Methods

All chemicals used in the study were of the analytical grade and commercially available. All reagents and solvents were used without futher purification and drying.

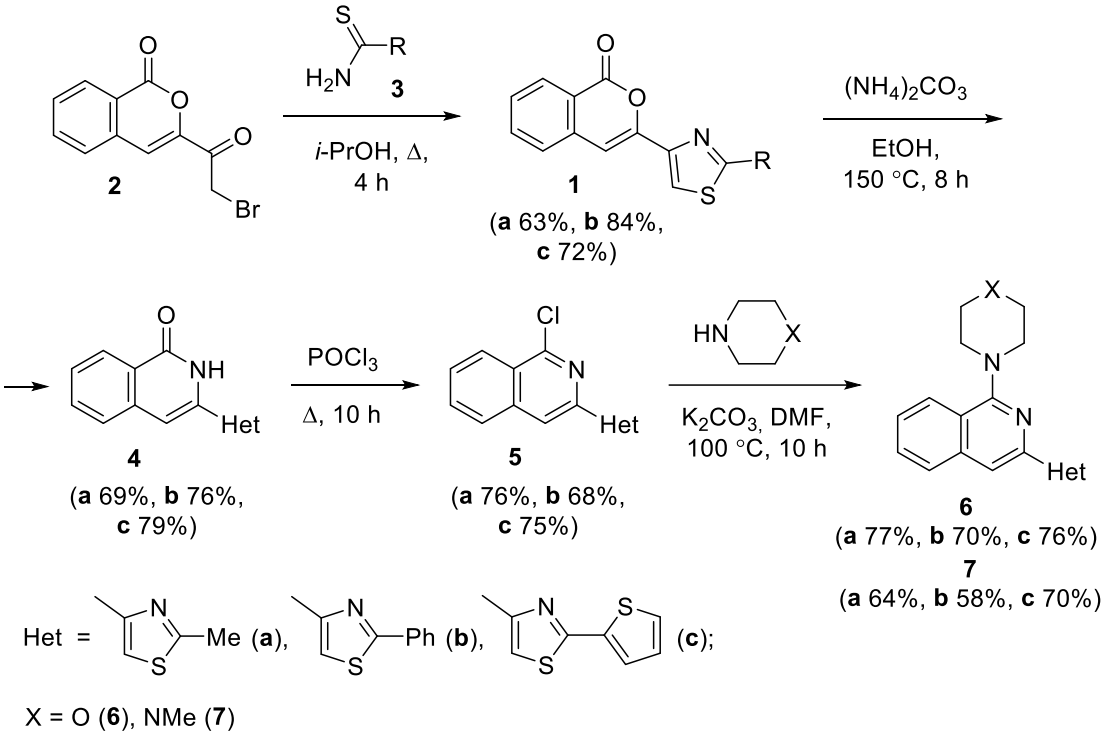
The structure of synthetized compounds was established with the help of ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.

Results and Discussion

3-(2-R-Thiazol-4-yl)isocoumarin 1 was obtained *via* heterocylization of 3-(*α*-bromacetyl)-isocoumarin 2 [2] with thioamide 3c (Scheme 1).

The subsequent transformation of isocoumarins 1 into 3-(2-R-thiazol-4-yl)isoquinolin-1(2*H*)-ones 4 was performed by heating them with ammonium carbonate at 150°C in a hydrothermal autoclave (3 atm). Synthesis of 1-chloro-3-(2-R-thiazol-4-yl)isoquinoline 5 was

performed by prolonged boiling of oxoderivatives 4 with phosphorus chloroxide. The replacement of chlorine atom of compounds 5 with morpholine and *N*-methylpiperazine moieties occurred by heating the compounds in DMF in the presence of K_2CO_3. It should be noted that switching from chloroderivative 5 to 1-aminoisoquinolines 6, 7 significantly increases solubility which is beneficial for subsequent biological studies.



Scheme 1

All products were obtained in good yields (Scheme 1) which did not depend on the substituent in the position 2 of thiazole, making this methodology suitable for obtaining other 3-(thiazol-4-yl)isocoumarin and 3-(thiazol-4-yl)isoquinoline derivatives. The conversion progress was easy to control using NMR spectra. For example, the 4-H signal of the isocoumarin cycle is a singlet at 7.2–7.5 ppm, and the corresponding isoquinolone signal is in a slightly stronger field (7.0–7.4 ppm). The formation of chloroisoquinoline is evidenced by a sharp shift of this singlet to weak field (8.5 ppm), but replacing chlorine with an amino residue made the chemical shift of 4-H to be at 8.0 ppm again.

The study of anticancer activity of compounds 1c, 4c-7c were carried out in the scope of international program DTP of National institute of health of the USA at the National Cancer Institute (NCI, Bethesda, Maryland, USA) [3] with 60 lines of cancer cells [4]. Table 1 lists sample data re the effect of studied compounds at concentration of 10^{-5} M on cancer cell growth, measured in % compared to the initial value: average value for all 60 lines, the value range, and top values for inhibiting certain cancel cell lines.

According to the data, the effect of isocoumarin 1c on cancer cells confirms the importance of its heterocyclic derivatives as compounds with low toxicity. Most of values were not much different from 100% and the only data of interest are the ones re certain lung cancer lines. Isoquinoline-1(2*H*)-one 4c was shown to be even less cytotoxic than the original isocoumarin, and a noticeable deviation from the average value was observed only with respect to one CNS

cancer line (Table 1). Compound 5c unexpectedly displayed low activity as well, despite the presence of a mobile chlorine atom.

Unlike its predecessors, amines 6c, 7c demonstrated a much higher biological activity, especially the compound 7c with *N*-methylpiperazine moiety which exhibited lethality (values of growth inhibition less than 0%) towards six cancer lines (Table 1). In addition, the morpholine derivative 6c was found to selectively inhibit the growth of one of seven studied colon cancer lines, one of six breast cancer lines, and also all melanoma lines.

Table 1

Compound / NCI code	Cancer cell grwoth, %		
	Average value	Value range	Smallest values (cell line / cancer type)
1c / NSC 814057	96.42	97.93	41.03 (T-47D / breast cancer) 47.68 (MDA-MB-468 / breast cancer) 54.41 (MCF7 / breast cancer)
4c / NSC 814058	101.66	78.57	51.94 (SF-268 / CNS cancer)
5c / NSC 814059	92.36	96.96	41.33 (T-47D / breast cancer)
6c / NSC 814061	86.18	123.47	0.58 (MALME-3M / melanoma) 5.77 (MDA-MB-468 / breast cancer) 17.32 (UACC-257 / melanoma) 20.45 (COLO 205 / colon cancer)
7c / NSC 814060	39.75	145.66	-51.14 (COLO 205 / colon cancer) -44.88 (M14 / melanoma) -38.24 (HCC-2998 / colon cancer) -35.92 (K-562 / leukemia) -27.28 (HT29 / colon cancer) -25.60 (NCI-H460 / non-small cell lung cancer)

Conclusion

The developed approaches to the synthesis of 1-functionalized isoquinolines starting with 3-hetarylisocoumarin are based on the use of simple methods and available reagents and provide a wide variety of target products, making them a good base for further biological studies. The study of anticancer activity of 3-(2-thien-2-yl)thiazol-4-yl)isocoumarin and its isoquinoline derivatives that was carried out on 60 cancer cell lines in the USA National Cancer Institute has demonstrated that 4-(1-(4-morpholin-1-yl)isoquinolin-3-yl)-2-(thien-2-yl)thiasole is sufficiently efficient against several cancer types: melanomas MALME-3M и UACC-257, breast cancer MDA-MB-468 and colon cancer COLO 205. 4-(1-(4-Methylpiperazin-1-yl)isoquinolin-3-yl)-2-(thien-2-yl)thiazole stops the growth of the majority of the studied cell lines; this compound is even lethal, in particular, for the COLO 205, HCC-2998, and HT29 colon cancer lines, as well as for the M14 melanoma line and the K-562 leukemia line. At the same time, the starting isocoumarin and 3-(2-(thien-2-yl)thiazol-4-yl)isoquinolin-1(2*H*)-on and 1-chloro-3-(2-(thien-2-

yl)thiazol-4-yl)isoquinoline possess very low cytotoxicity and can only barely slow down the growth of certain cell lines.

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