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3-Hetarylisocoumarins in the synthesis of 1-functionalized 3-hetarylisoquinolines

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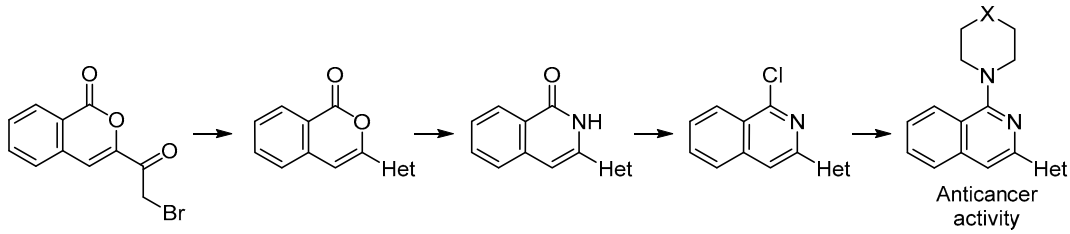


A convenient method was developed for the synthesis of novel isoquinolin-1(2*H*)-ones, 1-chloroisoquinolines, and 1-aminoisoquinolines with a heterocyclic substituent in position 3 *via* a recyclization of 3-hetarylisocoumarins with $(NH_4)_2CO_3$. 1-Aminoisoquinolines were efficiently obtained from corresponding 1-chloro-3-hetarylisoquinolines (obtained by interaction of isoquinolin-1(2*H*)-ones with $POCl_3$) and cyclic secondary amines (morpholine or 1-methylpiperazine). Literature data and preliminary results of biological assays allow to consider 1-amino-3-hetarylisoquinolines a promising family of anticancer compounds.

Keywords: isocoumarin, isoquinoline, isoquinolin-1(2*H*)-ones, nitrogen-containing heterocycles, anticancer activity, recyclization.

Nitrogen-containing heterocycles are key components of many bioactive natural products and potent drugs (Fig. 1),[1] and for this reason they are assigned as privileged motifs in drug development.[2] The diverse functions of nitrogen-containing compounds highly depend on their characteristic structures, so the elaboration of N-heterocycles and the late-stage modification of drug candidates with N-heterocycles have emerged as an important strategy in organic synthetic chemistry and drug discovery.[3] The importance of nitrogen-containing heterocycles in medicinal chemistry has motivated many research groups to develop new and efficient protocols for their synthesis.

Isoquinolones are an important family of N-heterocycles, found in naturally occurring and synthetic small molecules displaying diverse biological activities. Recently more data has emerged about isoquinolines with aromatic or heteroaromatic substituents in position 3 which have real-world applications and have been of interest to us. For instance, alkaloid of *Hypecoum erectum* corydamine **1** exhibited antimicrobial activity,[4] while compound **2** extracted from seaweed *Streptomyces* sp.[5] and compounds with general formula **3**[6] (Fig. 1) exhibits anticancer activity. The latter compounds contain an interesting combination of a heterocyclic substituent in position 3 and an amino group in position 1.

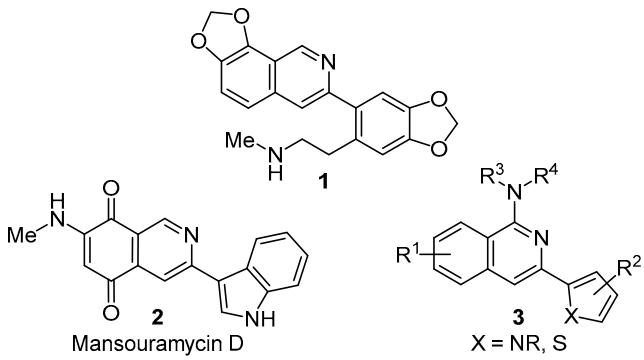


Figure 1. Compounds containing the isoquinoline motif.

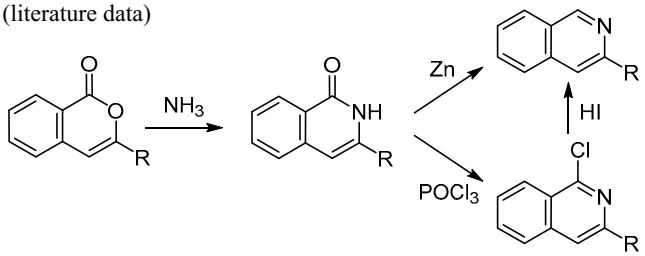
Isoquinolin-1-ones are often used as building blocks in organic synthesis, and numerous approaches to their synthesis have been developed.[7] Compounds with a substituent (methyl, benzyl) in position 1 dominate among natural and synthetic isoquinolines, and the majority of convenient approaches to construct the isoquinoline system target primarily compounds of this type (e.g., one of classical synthetic methods utilizes the Bischler–Napieralski reaction with phenylethylamine[8]).

Over the several past decades catalysis with numerous transition metals was used for the formation of isoquinolin-1-ones. Recently, isoquinolin-1(2*H*)-one derivatives have been synthesized from substituted benzamidines with aryl alkynes using Ni(II),[9] Rh(III),[10] Pd/C catalysts.[11] Also, isoquinolinones have been synthesized *via* Co-catalyzed *ortho*-C–H functionalization/annulation of arenes and alkenes with alkynylsilanes.[12] Furthermore, 1-halo- and 1-alkoxy-substituted isoquinolines were prepared *via* Ru-catalyzed cyclization of substituted *N*-methoxybenzimidoyl halides with alkynes.[13]

Most of the aforementioned methods for the synthesis of 3-substituted isoquinolines have certain drawbacks, such as the use of special or poorly accessible starting materials, expensive catalysts, multistep procedures, photoactivation, and harsh reaction conditions.

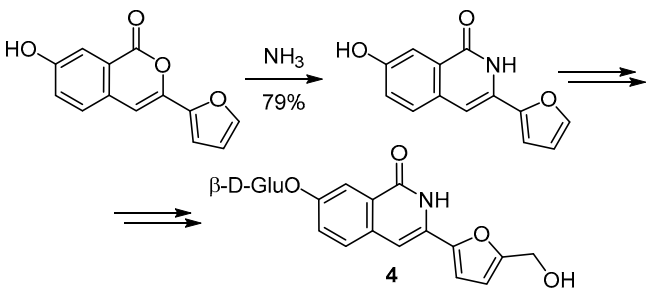
Therefore, with our goal being the creation of new 3-hetarylisoquinolines *via* convenient procedures and from easily available reagents, we focused on the methodology by Gabriel[14] – the synthesis of 3-arylisoquinolines by the recyclization of 1*H*-isochromen-1-ones (isocoumarins) (Scheme 1).

Scheme 1. Synthesis of isoquinolines from isocoumarins (literature data)



Only the first stage of this transformation – the synthesis of isoquinolin-1(2*H*)-ones – was subsequently actively studied. For example, it was recently used for the counter synthesis of the antiviral natural glucoside **4** (Scheme 2), extracted from *Isatis tinctoria* (dyer's weed).[15]

Scheme 2. Synthesis of 3-(furan-2-yl)-7-hydroxyisoquinolin-1-(2*H*)-one from 3-(furan-2-yl)-7-hydroxy-1*H*-isochromen-1-one (literature data)



Other products depicted in Scheme 1 are interesting not only for their potential practical usage, but also for further synthetic transformations. For example, the chlorine atom in position 1 of the isoquinoline ring could be easily substituted with nucleophilic reagents, such as primary and secondary amines. The previously mentioned 1-aminoisoquinolines **3** with anticancer activity (Fig. 1) were obtained *via* this approach. The necessary isoquinolin-1(2*H*)-ones, however, were synthesized by the condensation of *o*-methylbenzamides with heteroaromatic nitriles in the presence of *n*-BuLi with low yields at this step.[7] Such approach to a certain degree limits the variability of possible heterocyclic substituents.

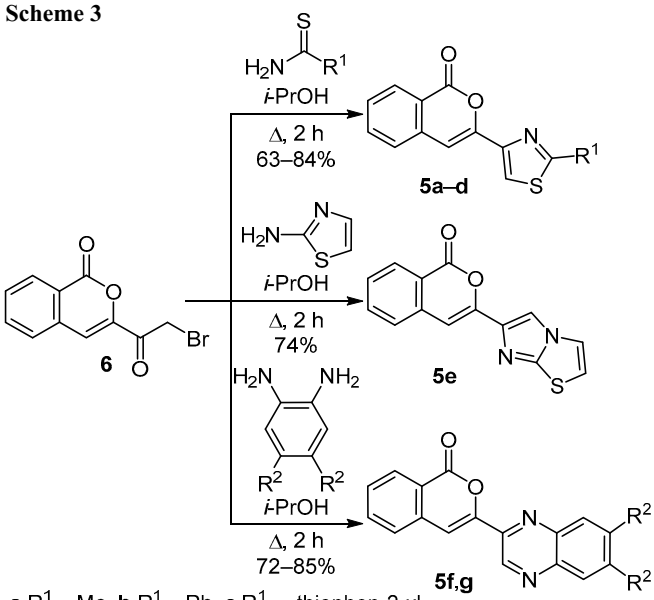
Our previous research has demonstrated that various 3-hetarylisocoumarins can be easily obtained from readily available reagents.[16–19] The goal of this work was to research the synthetic capabilities of isocoumarins as source compounds for the straightforward synthesis of 3-hetaryl-substituted isoquinolin-1(2*H*)-ones, 1-chloro- and 1-aminoisoquinolines.

Based on the literature data,[18] the most frequently used and, in our opinion, the most convenient and efficient method for the recyclization of isocoumarin into isoquinolinone is heating the source compound with NH_3 in alcohol solution. To maintain NH_3 concentration at the temperature optimal for this reaction (above 100°C) the heating must be performed in a pressure tube or an autoclave. In addition, a small number of procedures was developed for the synthesis of isoquinolines where the reaction took place in a sealed tube in THF,[20] but no increase either in yield or in the reaction rate was observed. There are several literature examples of replacing NH_3 with its derivatives – formamide[21] or $AcONH_4$[22] in this recyclization, but the major reason for this change was the ability to perform the reaction at atmospheric pressure. Several examples of successful recyclization of isocoumarin under the action of concentrated NH_3 under atmospheric pressure were applicable to the molecules of specific structure: for example, 8-nitro-substituted isocoumarins were transformed into isoquinolinones when refluxed in $MeO(CH_2)_2OH$,[23] and the condensed system of 1*H*-cyclopenta[*c*]isoquinoline-3,5-(2*H*,4*H*)-dione was formed from a corresponding isocoumarin when refluxed in formamide with a multifold excess of NH_3.[24]

The above considerations combined with the lack of success in our attempts at the recyclization of the studied 3-hetarylcoumarins under atmospheric pressure in an alcohol solution (no conversion) and the tendency of starting compounds to decompose during the prolonged heating in a strongly nucleophilic medium pushed us toward using a classic procedure of heating in a sealed tube to avoid the decomposition of the starting material. For a more precise dosage of NH_3, we decided to use its synthetic equivalent, $(NH_4)_2CO_3$.

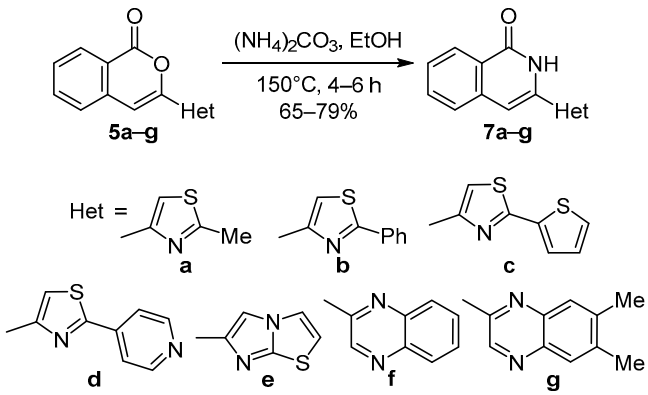
The starting compounds **5a**–**g** with thiazole, imidazothiazole, and quinoxaline substituents in position 3 of isocoumarin were synthesized from 3-(2-bromoacetyl)-isocoumarin (**6**) (Scheme 3) using methods we have developed earlier. When compounds **5a**–**g** were heated in a

Scheme 3



hydrothermal autoclave with 4 equiv of $(NH_4)_2CO_3$ at 150°C for 4 h (for compounds **5a**–**d**) or 6 h (for compounds **5e**–**g**), a series of 3-hetaryl-substituted isoquinolin-1(2*H*)-ones **7a**–**g** (Scheme 4) were obtained. Lower temperatures or shorter durations resulted in incomplete conversion.

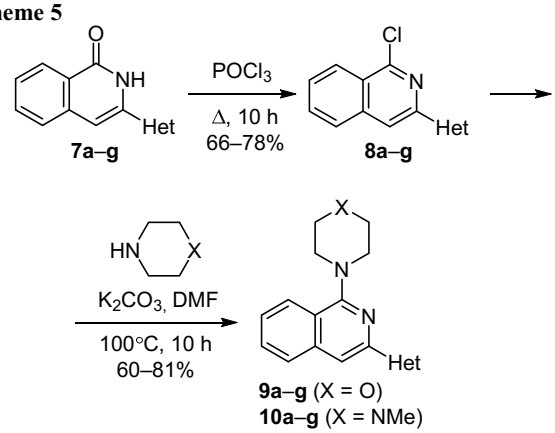
Scheme 4



The next type of compounds – 1-chloro-3-hetarylisoquinolines **8a**–**g** – was synthesized by refluxing isoquinolin-1(2*H*)-ones **7a**–**g** in $POCl_3$ (5 equiv); for most compounds, the reaction took no longer than 10 h. Nucleophilic substitution of the chlorine atom in compounds **8a**–**g** with an aliphatic amine fragment occurs when chloro derivatives are heated with 3 equiv of a cyclic secondary amine (morpholine or 1-methylpiperazine) in DMF with K_2CO_3 as a base (Scheme 5). Under these conditions, it is possible to obtain 1-aminoisoquinolines **9a**–**g** and **10a**–**g** with thiazole, imidazothiazole, and quinoxaline substituents in position 3 of the isoquinoline system with average yields of around 70%.

It should be noted that while 1-chloroisoquinolines **8a**–**g**, as well as starting isocoumarins and isoquinolinones, are poorly soluble even in solvents such as DMF or DMSO, the solubility of their amino derivatives **9a**–**g**, **10a**–**g** is

Scheme 5



much higher. Target compounds **9a**–**g**, **10a**–**g** were well soluble in EtOAc which, of course, is a favorable factor for further research of their biological activity and potential uses.

Comprehensive physicochemical research has proven the structures of synthesized compounds; data is presented in the experimental part. Classification of multiplets in ^{1}H NMR spectra of 3-substituted isocoumarins is straightforward due to characteristic signals – a singlet in position 4 of the system and a doublet of the proton in position 8; the latter is significantly shifted to the weak field because of the carbonyl group's deshielding effect.

The only significant change from isocoumarin to isoquinolin-1(2*H*)-one is a noticeable shift of the singlet of the proton in position 4 to the strong field. In order to reliably correlate signals and identify spectral properties of certain members of 1-chloro- and 1-aminoisoquinoline derivative groups, additional NMR experiments were performed: COSY, APT, and heteronuclear correlations ^{1}H–^{13}C HMBC and ^{1}H–^{13}C HMQC. The consequence of 1-chloroisoquinoline system formation is the sharp shift of isoquinoline ring signals to the weak field, especially noticeable for the signals of isoquinoline ring protons at positions 4 and 5 (Fig. 2).

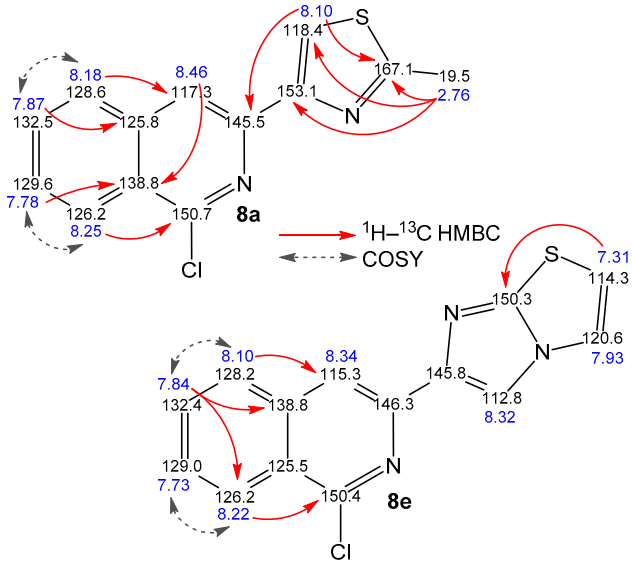


Figure 2. NMR data of 1-chloroisoquinolines **8a**,**e** (δ, ppm).

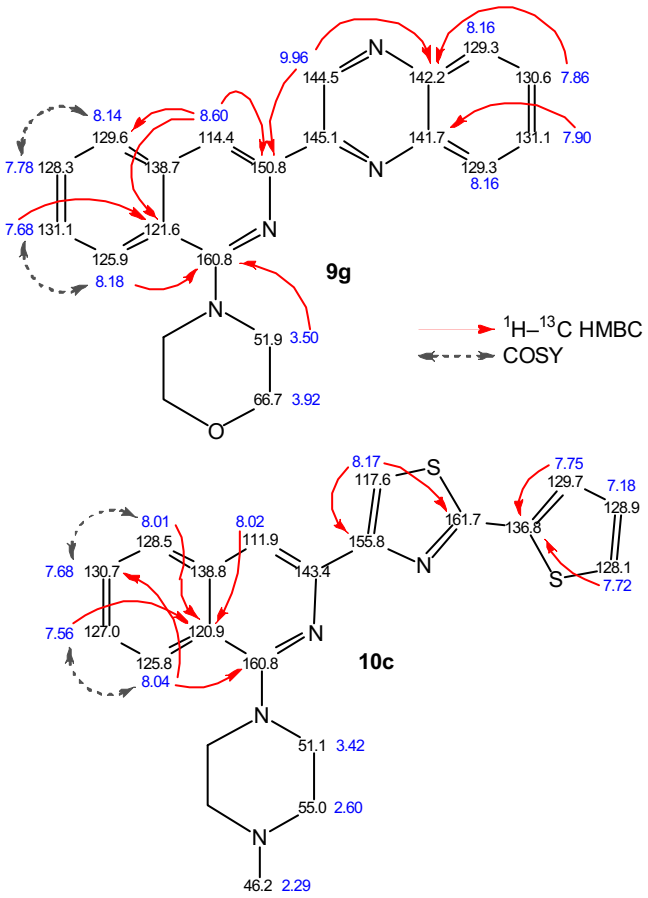


Figure 3. NMR data of 1-aminoisoquinolines **9g** and **10c** (δ, ppm).

The proton in position 4 of the isoquinoline system of 1-aminoisoquinolines **9**, **10** is deshielded, and the difference in chemical shifts of protons in positions 5 and 8 (Fig. 3) is as insignificant as it is in 1-chloro derivatives (Fig. 2), whereas it is around 0.5 ppm for corresponding isocoumarins and isoquinolinones.

Preliminary biological study of some of the synthesized compounds confirmed the starting hypothesis of anticancer activity being inherent for 1-aminoisoquinolines, with the type of amine substituent significantly influencing the activity. For example, 1-(morpholin-4-yl)-3-[2-(thiophen-2-yl)-1,3-thiazol-4-yl]isoquinoline (**9c**) is sufficiently efficient against several cancer types: melanomas MALME-3M (cancer cell growth according to one dose assay of the compound in concentration of 10^{-5} M – 0.6%) and UACC-257 (17.3%), breast MDA-MB-468 (5.8%), and colon COLO 205 (20.5%) cell lines. 1-(4-Methylpiperazin-1-yl)-3-[2-(thiophen-2-yl)-1,3-thiazol-4-yl]isoquinoline (**10c**) stops the growth of the majority of the studied cell lines; this compound is even lethal, in particular, for the COLO 205 (–51.1%), HCC-2998 (–38.2%; GI_{50} 1.72 μM, TGI 3.40 μM, LC_{50} 6.75 μM), and HT29 (–27.3%; GI_{50} 1.66 μM, TGI 3.41 μM, LC_{50} 7.00 μM) colon cancer lines. Isoquinoline **10c** was also effective against the melanoma line M14 (–44.9%; GI_{50} 1.87 μM, TGI 3.71 μM, LC_{50} 7.34 μM) and the K-562 leukemia line (–35.9%; GI_{50} 2.16 μM, TGI 4.92 μM, LC_{50} >100.0 μM). At the same time, the starting isocoumarin **5c** and 3-[2-(thiophen-2-yl)-1,3-thiazol-4-yl]isoquinolin-1(2*H*)-one (**7c**) and 1-chloro-3-[2-(thiophen-2-yl)-1,3-thiazol-4-yl]isoquinoline (**8c**) possess very low cytotoxicity and can only barely slow down the growth of certain cell lines (average values of cancer cell growth percentages were close to 100% at these compounds concentration of 10^{-5} M). A more detailed description of biological assays was published earlier.[25]

Notably, the comparison of this data with the published research[6] on the anticancer activity toward T47D cancer cell lines (human ductal breast epithelial tumor cells), DU145 (human prostate cancer cells), and HCT-15 (human colorectal adenocarcinoma cells) has demonstrated that compound **10c** causes 50% decrease of cell growth in smaller concentrations than most of thienylisoquinolines of the general formula **3** (Fig. 1), and in some cases – in lower concentrations than the reference medical compounds – etoposide and doxorubicin. These results make the active search of anticancer drugs among 1-amino-3-hetaryl-isoquinolines a promising research direction.

To conclude, we have confirmed that the recyclization of 3-hetarylisocoumarins by the reaction with ammonia is a convenient approach to the synthesis of isoquinolin-1(2*H*)-ones, 1-chloroisoquinolines, and 1-aminoisoquinolines with a heterocyclic substituent in position 3, which allowed us to significantly expand the list of presently known compounds of this type.

Experimental

^{1}H, ^{13}C NMR spectra, APT spectra, and 2D experiments (COSY, ^{1}H–^{13}C HMBC, ^{1}H–^{13}C HMQC) of obtained products were recorded on a Bruker Avance 500 spectrometer (500 and 126 MHz, respectively) in DMSO-d_6 and CF_3CO_2D solutions with TMS as internal standard. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (atmospheric pressure chemical ionization (APCI)) and HP 5890 Series II GC with HP 5972 MSD instrument (electron impact ionization (EI)). Elemental analyses were performed at the Analytical Laboratory of the Institute of Organic Chemistry of NAS of Ukraine on a vario MICRO cube instrument, their results were found to be in good agreement (±0.4%) with the calculated values. Melting points were measured on an automated melting point system OptiMelt MPA100. The reaction progress was monitored by the TLC on Merck Silica gel 60 F_{254}. In correlations of ^{1}H NMR spectra, the protons of isocoumarin and its derived isoquinoline ring are designated as H; atoms of a substituent in position 3 of the main system as H'; if the 3-heterocycle contains an additional (hetero)aromatic substituent, its protons are marked as H".

3-Hetaryl-1*H*-isochromen-1-ones 5a–g were obtained from 3-(2-bromoacetyl)-1*H*-isochromen-1-one **6** (0.01 mol) according to the method described in literature.[16]

Physical and spectral properties of compounds **5a**,**b**,**f**[16] and **5e**,**g**[17] are found in previous papers.

3-[2-(Thiophen-2-yl)-1,3-thiazol-4-yl]-1*H*-isochromen-1-one (5c). Yield 2.24 g (72%), white solid, mp 200–201°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.22 (1H, dd, *J* = 4.9, *J* = 3.8, H-4"); 7.46 (1H, s, H-4); 7.62 (1H, td, *J* = 8.0, *J* = 4.3, H-7); 7.79 (1H, dd, *J* = 3.8, *J* = 0.8, H-5"); 7.81 (1H, dd, *J* = 4.9, *J* = 0.8, H-3"); 7.86–7.88 (2H, m,

H-5,6); 8.12 (1H, s, H-5'); 8.18 (1H, d, *J* = 8.0, H-8). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 103.5; 118.6; 120.6; 127.5; 128.9; 129.0; 129.2; 129.4; 130.2; 135.8; 136.2; 137.3; 147.8; 148.8; 161.3; 162.6. Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 311 $[M]^+$ (100). Found, %: C 61.78; H 2.83; N 4.46; S 20.64. $C_{16}H_9NO_2S_2$. Calculated, %: C 61.72; H 2.91; N 4.50; S 20.59.

3-[2-(Pyridin-4-yl)-1,3-thiazol-4-yl]-1*H*-isochromen-1-one (5d). Yield 2.33 g (76%), red-yellow solid, mp 263–264°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.62–7.67 (2H, m, H-4,7); 7.83 (1H, d, *J* = 7.6, H-5); 7.90 (1H, t, *J* = 7.6, H-6); 8.21 (1H, d, *J* = 7.6, H-8); 8.30 (2H, br. d, *J* = 5.6, H-3",5"); 8.46 (1H, s, H-5'); 8.92 (2H, d, *J* = 5.6, H-2",6"). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 106.0; 119.1; 122.9; 123.5; 126.9; 129.3; 129.6; 136.7; 137.3; 141.7; 147.1; 149.6; 150.7; 161.1; 166.4. Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 306 $[M]^+$ (100). Found, %: C 66.56; H 3.21; N 9.19; S 10.32. $C_{17}H_{10}N_2O_2S$. Calculated, %: C 66.65; H 3.29; N 9.14; S 10.47.

Synthesis of 3-hetarylisoquinolin-1(2*H*)-ones 7a–g (General method). A mixture of isocoumarin **5a–g** (3.21 mmol) and $(NH_4)_2CO_3$ (1.23 g, 12.84 mmol, 4 equiv) in abs. EtOH (15 ml) was heated in a hydrothermal autoclave at 150°C and stirred for 4–6 h. When the mixture was cooled, a precipitate was formed, which was filtered off and washed with H_2O. The obtained product was purified by crystallization from EtOH–DMF, 1:1.

3-(2-Methyl-1,3-thiazol-4-yl)isoquinolin-1(2*H*)-one (7a). Yield 530 mg (69%), white solid, mp 215–217°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.73 (3H, s, CH_3); 7.31 (1H, s, H-4); 7.48 (1H, t, *J* = 7.3, H-7); 7.70 (1H, t, *J* = 7.3, H-6); 7.76 (1H, d, *J* = 7.8, H-5); 8.19 (1H, d, *J* = 7.8, H-8); 8.31 (1H, s, H-5'); 11.38 (1H, br. s, NH). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 15.1; 113.0; 120.0; 124.3; 126.8; 128.1; 130.8; 136.0; 137.2; 139.1; 176.5; one signal in the weak field overlaps with the solvent signals. Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 242 $[M]^+$ (100). Found, %: C 64.37; H 4.11; N 11.65; S 13.35. $C_{13}H_{10}N_2OS$. Calculated, %: C 64.44; H 4.16; N 11.56; S 13.23.

3-(2-Phenyl-1,3-thiazol-4-yl)isoquinolin-1(2*H*)-one (7b). Yield 742 mg (76%), white solid, mp 300–301°C. ^{1}H NMR spectrum (CF_3CO_2D), δ, ppm (*J*, Hz): 8.57 (2H, t, *J* = 7.6, H-3",5"); 8.67–8.75 (3H, m, H-4,7,4"); 8.83 (1H, d, *J* = 7.8, H-5); 8.88–8.92 (1H, t, *J* = 7.8, H-6); 8.95 (2H, d, *J* = 7.6, H-2",6"); 9.34 (1H, s, H-5'); 9.39 (1H, d, *J* = 8.1, H-8). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 114.8; 121.1; 123.0; 124.9; 125.3; 127.6; 128.4; 128.9; 131.1; 131.7; 136.8; 137.0; 138.2; 140.6; 165.7; 176.7. Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 304 $[M]^+$ (100). Found, %: C 71.11; H 3.83; N 9.12; S 10.61. $C_{18}H_{12}N_2OS$. Calculated, %: C 71.03; H 3.97; N 9.20; S 10.53.

3-[2-(Thiophen-2-yl)-1,3-thiazol-4-yl]isoquinolin-1(2*H*)-one (7c). Yield 787 mg (79%), yellow solid, mp 225–226°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.21 (1H, br. t, *J* = 4.2, H-4"); 7.34 (1H, s, H-4); 7.52 (1H, t, *J* = 7.6, H-7); 7.73 (1H, t, *J* = 7.6, H-6); 7.77 (1H, d, *J* = 3.4, H-5"); 7.75–7.84 (2H, m, H-5,3"); 8.22 (1H, d, *J* = 8.2, H-8); 8.44 (1H, s, H-5'); 11.42 (1H, br. s, NH). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 113.6; 118.3; 122.1; 124.3; 125.4; 126.8; 128.0; 130.2; 130.8; 134.8; 136.1; 137.1; 137.3; 138.8; 164.9; 168.1. Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 310 $[M]^+$ (100). Found, %: C 61.72; H 3.41; N 8.92; S 20.63. $C_{16}H_{10}N_2OS_2$. Calculated, %: C 61.91; H 3.25; N 9.03; S 20.66.

3-[2-(Pyridin-4-yl)-1,3-thiazol-4-yl]isoquinolin-1(2*H*)-one (7d). Yield 735 mg (75%), yellow solid, mp 337–338°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.44 (1H, s, H-4); 7.49–7.55 (1H, m, H-7); 7.71–7.80 (2H, m, H-5,6); 8.00–8.06 (2H, m, H-3",5"); 8.20–8.26 (1H, m, H-8); 8.63 (1H, br. s, H-5'); 8.74–8.79 (2H, m, H-2",6"); 11.38 (1H, br. s, NH). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 109.2; 118.6; 121.0; 121.9; 124.6; 125.6; 127.9; 128.4; 134.2; 137.0; 139.8; 147.5; 148.1; 159.1; 161.4. Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 305 $[M]^+$ (100). Found, %: C 66.71; H 3.71; N 13.57; S 10.48. $C_{17}H_{11}N_3OS$. Calculated, %: C 66.87; H 3.63; N 13.76; S 10.50.

3-(Imidazo[2,1-*b*][1,3]thiazol-6-yl)isoquinolin-1(2*H*)-one (7e). Yield 618 mg (72%), white solid, mp 265–266°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.16 (1H, s, H-4); 7.32 (1H, d, *J* = 4.4, H-2'); 7.40–7.47 (1H, m, H-7); 7.63–7.71 (2H, m, H-5,6); 8.04 (1H, d, *J* = 4.4, H-3'); 8.18 (1H, d, *J* = 8.0, H-8); 8.52 (1H, s, H-5'); 11.18 (1H, br. s, NH). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 113.1; 113.9; 119.7; 122.1; 122.9; 125.0; 127.7; 128.7; 131.3; 132.8; 136.9; 138.4; 150.3; 165.9. Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 267 $[M]^+$ (100). Found, %: C 62.85; H 3.27; N 15.67; S 11.86. $C_{14}H_9N_3OS$. Calculated, %: C 62.91; H 3.39; N 15.72; S 11.99.

3-(Quinoxalin-2-yl)isoquinolin-1(2*H*)-one (7f). Yield 570 mg (65%), yellow solid, mp 256–257°C. ^{1}H NMR spectrum (CF_3CO_2D), δ, ppm (*J*, Hz): 7.46 (1H, s, H-4); 7.53–7.63 (1H, m, H-7); 7.68–7.76 (2H, m, H-5',8'); 7.76–7.87 (2H, m, H-6,7); 8.07–8.17 (2H, m, H-6',7'); 8.48 (1H, d, *J* = 8.1, H-8); 9.45 (1H, d, *J* = 1.6, H-3'); 10.34 (1H, br. s, NH). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 115.6; 121.4; 128.1; 129.6; 129.7; 131.4 (2C); 132.4; 134.4; 136.7; 136.9; 138.0; 138.3; 145.8; 146.5; signals in the weak field overlap with the solvent signals. Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 273 $[M]^+$ (100). Found, %: C 74.66; H 4.12; N 15.31. $C_{17}H_{11}N_3O$. Calculated, %: C 74.71; H 4.06; N 15.38.

3-(6,7-Dimethylquinoxalin-2-yl)isoquinolin-1(2*H*)-one (7g). Yield 677 mg (70%), yellow solid, mp 301–302°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.50 (overlaps with DMSO signal, 2CH_3); 7.61 (1H, t, *J* = 7.6, H-7); 7.78–7.87 (3H, m, H-4–6); 7.91 (1H, s, H-5'(8')); 7.98 (1H, s, H-8'(5')); 8.29 (1H, d, *J* = 7.6, H-8); 9.58 (1H, s, H-3'); 10.73 (1H, br. s, NH). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 18.1; 18.5; 112.9; 117.8; 122.1; 126.0; 126.7; 127.5; 128.0; 129.6; 129.9; 130.2; 135.0; 136.6; 143.1; 143.2; 148.4; 151.1; 163.5. Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 301 $[M]^+$ (100). Found, %: C 75.56; H 5.10; N 14.19. $C_{19}H_{15}N_3O$. Calculated, %: C 75.73; H 5.02; N 13.94.

Synthesis of 1-chloro-3-hetarylisoquinolines 8a–g (General method). A mixture of compound **7a–g** (2.54 mmol) and $POCl_3$ (2.4 ml, 25.4 mmol, 10 equiv) was boiled with stirring for 10 h. The reaction mixture was cooled to room

temperature, poured onto ice (15 g), and $NaHCO_3$ was added to the neutral reaction medium. The aqueous solution was extracted with EtOAc; the organic phase was dried over Na_2SO_4, the solution was evaporated, and a spectrally pure product was obtained.

1-Chloro-3-(2-methyl-1,3-thiazol-4-yl)isoquinoline (8a). Yield 503 mg (76%), white solid, mp 139–140°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.76 (3H, s, CH_3); 7.78 (1H, t, *J* = 7.6, H-7); 7.87 (1H, t, *J* = 7.6, H-6); 8.10 (1H, br. s, H-5'); 8.18 (1H, d, *J* = 8.2, H-5); 8.25 (1H, d, *J* = 8.4, H-8); 8.46 (1H, s, H-4). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 19.5; 117.3; 118.5; 125.8; 126.2; 128.6; 129.6; 132.5; 138.8; 145.5; 150.7; 153.1; 167.1. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 261 $[M+H]^+$ (100). Found, %: C 59.62; H 3.36; Cl 13.44; N 10.53; S 12.06. $C_{13}H_9ClN_2S$. Calculated, %: C 59.88; H 3.48; Cl 13.60; N 10.74; S 12.30.

1-Chloro-3-(2-phenyl-1,3-thiazol-4-yl)isoquinoline (8b). Yield 580 mg (71%), white solid, mp 160–161°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.50–7.58 (3H, m, H-3"–5"); 7.80 (1H, t, *J* = 7.2, H-7); 7.88 (1H, t, *J* = 7.2, H-6); 8.07 (2H, d, *J* = 6.1, H-2",6"); 8.21 (1H, d, *J* = 8.0, H-5); 8.27 (1H, d, *J* = 8.0, H-8); 8.32 (1H, s, H-5'); 8.62 (1H, s, H-4). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 117.6; 119.2; 125.9; 126.2; 126.8; 128.6; 129.7; 131.1; 132.6; 133.2; 138.7; 145.2; 150.8; 154.4; 168.3. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 323 $[M+H]^+$ (100). Found, %: C 67.12; H 3.25; Cl 10.78; N 8.74; S 10.06. $C_{18}H_{11}ClN_2S$. Calculated, %: C 66.97; H 3.43; Cl 10.98; N 8.68; S 9.93.

1-Chloro-3-[2-(thiophen-2-yl)-1,3-thiazol-4-yl]isoquinoline (8c). Yield 626 mg (75%), white solid, mp 181–182°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.22 (1H, dd, *J* = 4.7, *J* = 3.9, H-4"); 7.74–7.76 (3H, m, H-7,3",5"); 7.91 (1H, t, *J* = 7.4, H-6); 8.26 (1H, d, *J* = 8.2, H-5); 8.28 (1H, s, H-5'); 8.30 (1H, d, *J* = 8.2, H-8); 8.51 (1H, s, H-4). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 117.4; 118.7; 126.0; 126.2; 128.4; 128.7; 129.0; 129.8 (2C); 132.6; 136.7; 138.7; 145.0; 150.8; 153.9; 162.3. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 329 $[M+H]^+$ (100). Found, %: C 58.34; H 2.88; Cl 10.77; N 8.37; S 19.30. $C_{16}H_9ClN_2S_2$. Calculated, %: C 58.44; H 2.76; Cl 10.78; N 8.52; S 19.50.

1-Chloro-3-[2-(pyridin-4-yl)-1,3-thiazol-4-yl]isoquinoline (8d). Yield 542 mg (66%), light-brown solid, mp 217–218°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.80 (1H, t, *J* = 7.5, H-7); 7.90 (1H, t, *J* = 7.5, H-6); 8.02 (2H, br. d, *J* = 4.2, H-3",5"); 8.21 (1H, d, *J* = 7.8, H-5); 8.28 (1H, d, *J* = 7.8, H-8); 8.49 (1H, s, H-5'); 8.65 (1H, s, H-4); 8.75 (2H, br. d, *J* = 4.2, H-2",6"). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 117.8; 120.6; 121.1; 126.1; 126.3; 128.7; 129.9; 132.7; 138.7; 139.8; 144.9; 150.9; 151.3; 155.0; 165.7. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 324 $[M+H]^+$ (100). Found, %: C 63.20; H 3.19; Cl 11.08; N 12.82; S 9.76. $C_{17}H_{10}ClN_3S$. Calculated, %: C 63.06; H 3.11; Cl 10.95; N 12.98; S 9.90.

1-Chloro-3-(imidazo[2,1-*b*][1,3]thiazol-6-yl)isoquinoline (8e). Yield 566 mg (78%), white solid, mp 227–228°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.31 (1H, d, *J* = 4.3, H-2'); 7.73 (1H, t, *J* = 7.6, H-7); 7.84 (1H, t, *J* = 7.6, H-6); 7.93 (1H, d, *J* = 4.3, H-3'); 8.10 (1H, d, *J* = 8.2, H-5); 8.22 (1H, d, *J* = 8.4, H-8); 8.32 (1H, s, H-5'); 8.34 (1H, s, H-4). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 112.8; 114.3; 115.2; 120.6; 125.5; 126.2; 128.2; 129.0; 132.4; 138.8; 145.9; 146.3; 150.3; 150.4. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 286 $[M+H]^+$ (100). Found, %: C 58.60; H 2.97; Cl 12.25; N 14.92; S 10.98. $C_{14}H_8ClN_3S$. Calculated, %: C 58.85; H 2.82; Cl 12.41; N 14.71; S 11.22.

2-(1-Chloroisoquinolin-3-yl)quinoxaline (8f). Yield 526 mg (71%), white solid, mp 203–204°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.88–7.96 (3H, m, H-7,6',7'); 7.98 (1H, t, *J* = 6.8, H-6); 8.17 (1H, d, *J* = 7.7, H-5); 8.20 (1H, d, *J* = 7.1, H-8); 8.36 (2H, d, *J* = 8.1, H-5',8'); 9.03 (1H, s, H-4); 9.84 (1H, s, H-3'). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 123.2; 125.3; 127.7; 129.4; 130.3; 130.6; 133.3; 135.6; 135.8; 136.3; 137.0; 138.0; 140.2; 140.3; 144.0; 144.3; 154.7. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 292 $[M+H]^+$ (100). Found, %: C 69.87; H 3.36; Cl 12.08; N 14.32. $C_{17}H_{10}ClN_3$. Calculated, %: C 69.99; H 3.46; Cl 12.15; N 14.40.

2-(1-Chloroisoquinolin-3-yl)-6,7-dimethylquinoxaline (8g). Yield 601 mg (74%), yellow solid, mp 204–205°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.50 (overlaps with DMSO signal, $2CH_3$); 7.88–7.93 (2H, m, H-7,5'(8')); 7.93–8.00 (2H, m, H-6,8'(5')); 8.32–8.38 (2H, m, H-5,8); 8.97 (1H, s, H-4); 9.73 (1H, s, H-3'). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 20.1; 20.7; 120.6; 124.7; 127.5; 129.3; 129.4; 130.4; 130.6; 132.9; 135.5; 135.8; 140.3; 140.6; 143.0; 144.4; 151.3; 154.4; 154.8. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 320 $[M+H]^+$ (100). Found, %: C 71.41; H 4.49; Cl 11.18; N 13.19. $C_{19}H_{14}ClN_3$. Calculated, %: C 71.36; H 4.41; Cl 11.09; N 13.14.

Synthesis of 3-hetaryl-1-(morpholin-4-yl)isoquinolines 9a–g and 3-hetaryl-1-(4-methylpiperazin-1-yl)isoquinolines 10a–g (General method). The corresponding amine (morpholine or 1-methylpiperazine, 2.85 mmol, 1.5 equiv) and K_2CO_3 (0.79 g, 5.7 mmol, 3 equiv) were added to a solution of compound **8a**–**g** (1.90 mmol) in DMF (5 ml), and the resulting mixture was heated with stirring at 100°C for 10 h. The reaction mixture was cooled to room temperature, filtered from inorganic residue, and the solvent was evaporated. EtOAc (15 ml) was added to the residue, the mixture was heated and filtered from the residue. The clear solution was kept at –10°C until yellow crystals were formed, which were filtered off, washed with cold EtOAc to give a spectrally pure product. The filtrate after crystallization still contains a significant portion of the target product, so the solvent was evaporated and the residue was recrystallized from EtOAc (10 ml).

3-(2-Methyl-1,3-thiazol-4-yl)-1-(morpholin-4-yl)isoquinoline (9a). Yield 456 mg (77%), white solid, mp 165–166°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.75 (3H, s, 2'-CH_3); 3.40 (4H, br. t, *J* = 3.8, CH_2NCH_2); 3.89 (4H, br. t, *J* = 3.8, CH_2OCH_2); 7.57 (1H, t, *J* = 7.6, H-7); 7.70 (1H, t, *J* = 7.6, H-6); 7.99 (1H, d, *J* = 8.1, H-5); 8.04 (2H, s, H-4,5'); 8.10 (1H, d, *J* = 8.4, H-8). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 19.5; 51.9; 66.7; 112.2; 117.0; 120.7; 125.8; 126.9; 128.4; 130.7; 139.0; 144.0; 155.1; 160.8; 166.4. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 312 $[M+H]^+$ (100). Found, %: C 65.66; H 5.57; N 13.39;

S 10.37. $C_{17}H_{17}N_3OS$. Calculated, %: C 65.57; H 5.50; N 13.49; S 10.30.

1-(Morpholin-4-yl)-3-(2-phenyl-1,3-thiazol-4-yl)isoquinoline (9b). Yield 497 mg (70%), light-yellow solid, mp 169–170°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.37–3.48 (4H, m, CH_2NCH_2); 3.85–3.94 (4H, m, CH_2OCH_2); 7.50–7.63 (4H, m, H-7,3"–5"); 7.72 (1H, t, *J* = 7.3, H-6); 8.03 (1H, d, *J* = 8.0, H-5); 8.08 (2H, d, *J* = 6.6, H-2",6"); 8.12 (1H, d, *J* = 8.2, H-8); 8.20 (1H, s, H-4(5')); 8.27 (1H, s, H-5'(4)). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 51.9; 66.6; 112.4; 117.7; 120.8; 125.8; 126.7; 127.0; 128.4; 129.7; 130.7; 130.8; 133.5; 138.9; 143.7; 156.5; 160.7; 167.7. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 374 $[M+H]^+$ (100). Found, %: C 70.71; H 5.21; N 11.29; S 8.66. $C_{22}H_{19}N_3OS$. Calculated, %: C 70.75; H 5.13; N 11.25; S 8.58.

1-(Morpholin-4-yl)-3-[2-(thiophen-2-yl)-1,3-thiazol-4-yl]isoquinoline (9c). Yield 548 mg (76%), light-yellow solid, mp 180–181°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.43 (4H, br. t, *J* = 4.6, CH_2NCH_2); 3.90 (4H, br. t, *J* = 4.6, CH_2OCH_2); 7.22 (1H, dd, *J* = 5.0, *J* = 3.5, H-4"); 7.60 (1H, t, *J* = 7.6, H-7); 7.72 (1H, t, *J* = 7.6, H-6); 7.76 (1H, d, *J* = 3.5, H-5"); 7.78 (1H, d, *J* = 5.0, H-3"); 8.02–8.10 (2H, m, H-4,5); 8.12 (1H, d, *J* = 8.6, H-8); 8.22 (1H, s, H-5'). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 51.9; 66.7; 112.3; 117.4; 120.9; 125.9; 127.1; 128.1; 128.6; 129.0; 129.5; 130.8; 137.0; 138.9; 143.5; 155.9; 160.8; 161.7. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 380 $[M+H]^+$ (100). Found, %: C 63.37; H 4.59; N 11.15; S 16.97. $C_{20}H_{17}N_3OS_2$. Calculated, %: C 63.30; H 4.52; N 11.07; S 16.90.

1-(Morpholin-4-yl)-3-[2-(pyridin-4-yl)-1,3-thiazol-4-yl]-isoquinoline (9d). Yield 533 mg (75%), light-brown solid, mp 193–194°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.39–3.48 (4H, m, CH_2NCH_2); 3.85–3.95 (4H, m, CH_2OCH_2); 7.60 (1H, t, *J* = 7.0, H-7); 7.72 (1H, t, *J* = 7.0, H-6); 7.96–8.06 (3H, m, H-5,3",5"); 8.12 (1H, d, *J* = 8.0, H-8); 8.20 (1H, s, H-4(5')); 8.41 (1H, s, H-5'(4)); 8.71–8.80 (2H, m, H-2",6"). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 51.9; 66.7; 112.6; 120.0; 120.6; 121.0; 125.9; 127.3; 128.6; 130.9; 139.0; 140.0; 143.4; 151.3; 157.1; 160.9; 165.3. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 375 $[M+H]^+$ (100). Found, %: C 67.51; H 4.84; N 15.05; S 8.43. $C_{21}H_{18}N_4OS$. Calculated, %: C 67.36; H 4.85; N 14.96; S 8.56.

3-(Imidazo[2,1-*b*][1,3]thiazol-6-yl)-1-(morpholin-4-yl)-isoquinoline (9e). Yield 435 mg (68%), light-yellow solid, mp 169–170°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.45–3.52 (4H, m, CH_2NCH_2); 3.83–3.90 (4H, m, CH_2OCH_2); 7.26 (1H, d, *J* = 2.6, H-2'); 7.50 (1H, t, *J* = 7.5, H-7); 7.66 (1H, t, *J* = 7.5, H-6); 7.90 (1H, s, H-4); 7.91–7.94 (2H, m, H-5,3'); 8.06 (1H, d, *J* = 8.2, H-8); 8.26 (1H, s, H-5'). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 51.9; 66.6; 110.1; 112.2; 113.6; 120.4; 120.5; 125.7; 126.3; 128.0; 130.6; 139.0; 144.6; 147.8; 159.8; 160.6. Mass spectrum, *m*/*z* (I_{rel}, %): 337 $[M+H]^+$ (100) Found, %: C 64.41; H 4.86; N 16.51; S 9.62. $C_{18}H_{16}N_4OS$. Calculated, %: C 64.27; H 4.79; N 16.65; S 9.53.

2-[1-(Morpholin-4-yl)isoquinolin-3-yl]quinoxaline (9f). Yield 449 mg (69%), light-brown solid, mp 170–171°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.49–3.55 (4H, m, CH_2NCH_2); 3.91–3.97 (4H, m, CH_2OCH_2); 7.69 (1H, t, *J* = 7.4, H-7); 7.79 (1H, t, *J* = 7.4, H-6); 7.84–7.94 (2H, m, H-6',7'); 8.12–8.22 (4H, m, H-5,8,5',8'); 8.60 (1H, s, H-4); 9.96 (1H, s, H-3'). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 52.0; 66.7; 114.5; 121.6; 126.0; 128.3; 129.2; 129.5; 129.6; 130.6; 131.1; 131.2; 138.8; 141.8; 142.3; 144.5; 150.8; 160.8. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 343 $[M+H]^+$ (100). Found, %: C 73.41; H 5.46; N 16.49. $C_{21}H_{18}N_4O$. Calculated, %: C 73.67; H 5.30; N 16.36.

6,7-Dimethyl-2-[1-(morpholin-4-yl)isoquinolin-3-yl]-quinoxaline (9g). Yield 422 mg (60%), yellow solid, mp 116–117°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.50 (overlaps with DMSO signal, $2CH_3$); 3.50 (overlaps with H_2O signal, CH_2NCH_2); 3.86–3.92 (4H, m, CH_2OCH_2); 7.65 (1H, t, *J* = 7.6, H-7); 7.75 (1H, t, *J* = 7.6, H-6); 7.88 (1H, s, H-5'(8')); 7.92 (1H, s, H-8'(5')); 8.12 (1H, d, *J* = 8.2, H-5); 8.16 (1H, d, *J* = 8.6, H-8); 8.52 (1H, s, H-4); 9.83 (1H, s, H-3'). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 20.1; 20.6; 51.9; 66.5; 118.2; 120.4; 130.6; 121.5; 128.6; 129.5; 129.6; 131.4; 132.6; 132.9; 138.1; 139.6; 143.7; 144.7; 151.1; 154.1; 158.3. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 371 $[M+H]^+$ (100). Found, %: C 74.63; H 5.67; N 15.19. $C_{23}H_{22}N_4O$. Calculated, %: C 74.57; H 5.99; N 15.12.

1-(4-Methylpiperazin-1-yl)-3-(2-methyl-1,3-thiazol-4-yl)-isoquinoline (10a). Yield 395 mg (64%), white solid, mp 159–160°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.30 (3H, s, NCH_3); 2.58–2.65 (4H, m, $C\underline{H}_2N(CH_3)C\underline{H}_2$); 2.75 (3H, s, 2'-$CH_3$); 3.38–3.46 (4H, m, CH_2NCH_2); 7.56 (1H, t, *J* = 7.4, H-7); 7.68 (1H, t, *J* = 7.4, H-6); 7.97 (1H, d, *J* = 8.0, H-5); 8.01 (1H, s, H-4(5')); 8.02 (1H, s, H-5'(4)); 8.04 (1H, d, *J* = 8.4, H-8). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 19.5; 46.4; 51.2; 55.2; 111.9; 117.0; 120.8; 125.8; 126.8; 128.4; 130.6; 139.0; 144.0; 155.3; 160.9; 166.4. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 325 $[M+H]^+$ (100). Found, %: C 66.70; H 6.27; N 17.36; S 9.98. $C_{18}H_{20}N_4S$. Calculated, %: C 66.64; H 6.21; N 17.27; S 9.88.

1-(4-Methylpiperazin-1-yl)-3-(2-phenyl-1,3-thiazol-4-yl)-isoquinoline (10b). Yield 455 mg (62%), light-yellow solid, mp 129–130°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.50 (3H, s, NCH_3); 2.79–3.00 (4H, m, $C\underline{H}_2N(CH_3)C\underline{H}_2$); 3.45–3.57 (4H, m, CH_2NCH_2); 7.49–7.60 (4H, m, H-7,3"–5"); 7.70 (1H, t, *J* = 7.5, H-6); 8.01 (1H, d, *J* = 8.1, H-5); 8.03–8.08 (3H, m, H-8,2",6"); 8.17 (1H, s, H-4); 8.25 (1H, s, H-5'). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 46.3; 51.2; 55.1; 112.0; 117.8; 120.9; 125.8; 126.7; 126.9; 128.4; 129.7; 130.7; 130.9; 133.5; 138.9; 143.7; 156.6; 160.9; 167.8. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 387 $[M+H]^+$ (100). Found, %: C 71.41; H 5.79; N 14.58; S 8.21. $C_{23}H_{22}N_4S$. Calculated, %: C 71.47; H 5.74; N 14.50; S 8.29.

1-(4-Methylpiperazin-1-yl)-3-[2-(thiophen-2-yl)-1,3-thiazol-4-yl]isoquinoline (10c). Yield 522 mg (70%), yellow solid, mp 118–119°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.29 (3H, s, NCH_3); 2.54–2.66 (4H, m, $C\underline{H}_2N(CH_3)C\underline{H}_2$); 3.38–3.46 (4H, m, CH_2NCH_2); 7.18 (1H, br. t, *J* = 4.5, H-4"); 7.56 (1H, t, *J* = 7.6, H-7); 7.68 (1H, t, *J* = 7.6, H-6); 7.72 (1H, br. s, H-5"); 7.75 (1H, d, *J* = 4.3,

H-3"); 8.00–8.06 (3H, m, H-4,5,8); 8.17 (1H, s, H-5'). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 46.2; 51.1 (2C); 55.0 (2C); 111.9; 117.6; 120.9; 125.8; 127.0; 128.1; 128.5; 128.9; 129.7; 130.7; 136.8; 138.8; 143.4; 155.8; 160.8; 161.7. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 393 $[M+H]^+$ (100). Found, %: C 64.19; H 5.19; N 14.34; S 16.39. $C_{21}H_{20}N_4S_2$. Calculated, %: C 64.26; H 5.14; N 14.27; S 16.33.

1-(4-Methylpiperazin-1-yl)-3-[2-(pyridin-4-yl)-1,3-thiazol-4-yl]isoquinoline (10d). Yield 596 mg (81%), light-brown solid, mp 179–180°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.29 (3H, s, NCH_3); 2.54–2.67 (4H, m, $C\underline{H_2}N(CH_3)C\underline{H_2}$); 3.38–3.49 (4H, m, CH_2NCH_2); 7.58 (1H, t, *J* = 7.3, H-7); 7.71 (1H, t, *J* = 7.1, H-6); 7.94–8.03 (3H, m, H-5,3",5"); 8.06 (1H, d, *J* = 8.0, H-8); 8.16 (1H, s, H-4(5')); 8.38 (1H, s, H-5'(4)); 8.75 (2H, d, *J* = 4.2, H-2",6"). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 46.3; 51.2; 55.1; 112.2; 119.8; 120.5; 120.9; 125.8; 127.1; 128.4; 130.8; 138.9; 140.0; 143.4; 151.2; 157.1; 160.9; 165.1. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 388 $[M+H]^+$ (100). Found, %: C 68.26; H 5.53; N 18.15; S 8.34. $C_{22}H_{21}N_5S$. Calculated, %: C 68.19; H 5.46; N 18.07; S 8.27.

3-(Imidazo[2,1-*b*][1,3]thiazol-6-yl)-1-(4-methylpiperazin-1-yl)isoquinoline (10e). Yield 485 mg (73%), light-yellow solid, mp 171–172°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.28 (3H, s, NCH_3); 2.56–2.64 (4H, m, $C\underline{H_2}N(CH_3)C\underline{H_2}$); 3.36–3.45 (4H, m, CH_2NCH_2); 7.23–7.27 (1H, m, H-2'); 7.50 (1H, t, *J* = 7.5, H-7); 7.64 (1H, t, *J* = 7.5, H-6); 7.86 (1H, s, H-4); 7.89 (1H, d, *J* = 8.0, H-5); 7.91–7.95 (1H, m, H-3'); 8.01 (1H, d, *J* = 8.4, H-8); 8.24 (1H, s, H-5'). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 46.4; 51.2; 55.2; 109.9; 112.2; 113.6; 120.5; 120.7; 125.8; 126.2; 128.0; 130.5; 139.0; 144.6; 147.9; 149.8; 160.8. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 350 $[M+H]^+$ (100). Found, %: C 65.37; H 5.41; N 20.11; S 9.12. $C_{19}H_{19}N_5S$. Calculated, %: C 65.30; H 5.48; N 20.04; S 9.17.

2-[1-(4-Methylpiperazin-1-yl)isoquinolin-3-yl]quinoxaline (10f). Yield 507 mg (75%), light-brown solid, mp 185–186°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.31 (3H, s, NCH_3); 2.61–2.68 (4H, m, $C\underline{H_2}N(CH_3)C\underline{H_2}$); 3.48–3.58 (4H, m, CH_2NCH_2); 7.66 (1H, t, *J* = 7.4, H-7); 7.76 (1H, t, *J* = 7.4, H-6); 7.82–7.92 (2H, m, H-6',7'); 8.09–8.14 (3H, m, H-5,5',8'); 8.16 (1H, d, *J* = 8.0, H-8); 8.53 (1H, s, H-4); 9.93 (1H, s, H-3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 46.3; 51.2; 55.1; 114.03; 121.6; 125.9; 128.1; 129.1; 129.5; 129.6; 130.5; 130.9; 131.1; 138.7; 141.7; 142.2; 144.4; 145.1; 150.8; 160.9. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 356 $[M+H]^+$ (100). Found, %: C 74.39; H 5.91; N 19.78. $C_{22}H_{21}N_5$. Calculated, %: C 74.34; H 5.96; N 19.70.

6,7-Dimethyl-2-[1-(4-methylpiperazin-1-yl)isoquinolin-3-yl]quinoxaline (10g). Yield 583 mg (80%), yellow solid, mp 188–189°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.31 (3H, s, NCH_3); 2.50 (overlaps with DMSO signal, $2CH_3$); 2.61–2.70 (4H, m, $C\underline{H_2}N(CH_3)C\underline{H_2}$); 3.48–3.56 (4H, m, CH_2NCH_2); 7.67 (1H, t, *J* = 7.4, H-7); 7.77 (1H, t, *J* = 7.4, H-6); 7.91 (1H, s, H-5'(8')); 7.94 (1H, s, H-8'(5')); 8.13 (2H, d, *J* = 8.0, H-5,8); 8.52 (1H, s, H-4); 9.85 (1H, s, H-3'). ^{13}C NMR spectrum (CF_3CO_2D), δ, ppm: 19.4; 20.0; 43.9; 48.3; 53.5; 119.7; 120.9; 128.9; 129.1; 130.4; 130.9; 131.9; 132.9; 138.1; 139.3; 142.8; 144.1; 150.6; 153.8; 157.7; signals in the weak field overlap with the solvent signals. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 384 $[M+H]^+$ (100). Found, %: C 75.11; H 6.52; N 18.32. $C_{24}H_{25}N_5$. Calculated, %: C 75.17; H 6.57; N 18.26.

***In vitro* anticancer screening of the synthesized compounds**. The synthesized compounds were screened at the National Cancer Institute (NCI), Bethesda, Maryland, U.S.A., within the Developmental Therapeutic Program.[26] The full NCI 60 cell panel engaged a total of 60 different human tumor cell lines derived from nine cancer types. The single-dose assay established the percentage of cancel cell growth inhibition at 10 μM concentrations of studied compounds. The five-dose multiple assay (0.01, 0.1, 1, 10, and 100 μM) established the GI_{50} (growth inhibitory activity, corresponds to the concentration of the compound causing 50% decrease in net cell growth) parameters, TGI value (cytostatic activity, corresponds to the concentration of the compound resulting in total growth inhibition), and LC_{50} value (cytotoxic activity – concentration of the compound causing net 50% loss of initial cells).

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