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ARTICLE

Synthesis of (1′*S**,2*R**,3*R**)- and (1′*S**,2*R**,3*S**)-*N*-arylsulfonyl-2-(1′-halogenethyl)-3-methylindolines and their selective toxicity against SH-SY5Y cell line

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Abstract

N-tosyl-2- and *N*-tosyl-4-halogen-substituted derivatives of 2-(1-methylbut-2-en-1-yl)aniline were synthesized and their molecular iodine-mediated cyclization was investigated. The cyclization upon interaction of *N*-tosyl-6-methyl-2-(1-methylbut-2-en-1-yl)aniline with molecular iodine in methyl *tert*-butyl ether or acetonitrile was studied, as well as the interaction of this sulfonamide with *N*-bromosucinimide in dichloromethane. Synthesized (2*R**,3*R**)- and (2*R**,3*S**)-*N*-arylsulfonyl-2-(1-halogenoethyl)-3-methylindoline derivatives showed cytotoxic activity against HEK293 cells, SH-SY5Y, Jurkat, and HepG2 cell lines. The compounds (2*R**,3*S**)-*N*-arylsulfonyl-7-bromo-2-(1-halogenoethyl)-3-methylindoline *cis*-**4a**, stereoisomeric (2*R**,3*R**)-*trans*-**4h** and (2*R**,3*S**)-*N*-tosyl-7-chloro-2-(1-halogenoethyl)-3-methylindoline *cis*-**4h** demonstrated selective toxicity against SH-SY5Y cell line ($IC_{50} \approx 3 \div 5$ μM), and did not affect HEK293, Jurkat, and HepG2 cells.

1 | INTRODUCTION

The synthesis and study of benzo-fused heterocycles along with their biological activity is a rapidly developing area of research in bioorganic chemistry.[1] Annelated heterocyclic backbone is frequently observed in compounds being widely used in agricultural chemistry, natural and biological materials, and other fields. Considering the utility of these compounds, the development of efficient methods for their synthesis is crucial for both the fundamental and industrial organic chemistry. The importance of benzo-fused nitrogen-containing derivatives[2] is apparent for researcher's attention, and numerous preparation methods with wide range of starting materials and activating reagents have been proposed. In these syntheses numerous amino-aryl-substituted alkenes,[3] as readily available starting substrates, including allylaniline derivatives[4] and cycloalkenyl homologues,[5] also take a worthy place. For cyclization of these molecules the following reactions are commonly used: metal-complex catalysis,[6] ozonolysis of *ortho*-alkenylanilines,[5] oxidation with *m*-CPBA,[7] tandem oxidation with osmium tetraoxide and sodium periodate,[8] or with hydrogen peroxide,[9] as well as intramolecular aminohydroxylation.[4,10] It is quite noteworthy that, despite the low activation of the double bond of the allyl substituent, the alkenylanilanilines have found application even in the intramolecular cycloaddition reaction.[11]

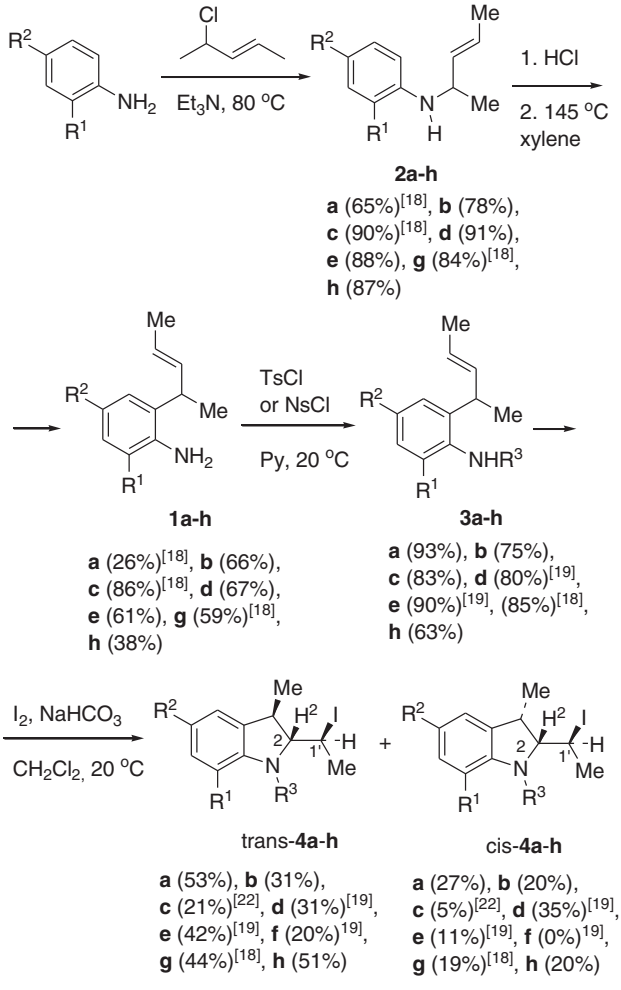
The favorable mutual arrangement of the alkenyl substituent and the amine group near the aromatic core of these amino arylalkenes promotes the formation of heterocycles mediated by both electrophiles[12] and nucleophiles.[13] The spatial proximity of these fragments within certain limits allows alteration of substituents at the nitrogen atom, reagents or reaction conditions, thereby guiding its direction and producing heterocycles with diverse structures.[14] In most well-known examples, when using electrophilic reagents, along with target problem of constructing a heterocyclic fragment, the prerequisites for their subsequent easy modification are also provided. There are numerous methods for obtaining

functionalized heterocycles from aminoaryl substituted alkenes, including the promising approaches based on the interactions of allylaniline derivatives with molecular brome[15] or iodine,[16] which in some cases ensures the directed synthesis of biologically active substances.[17]

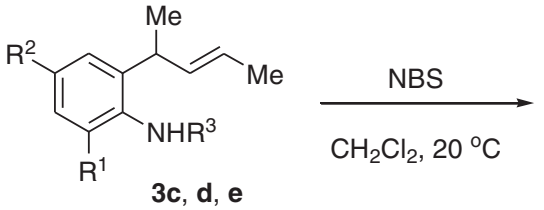
Earlier we discovered the product of tosylate 2-(1-methylbut-2-en-1-yl)aniline iodocyclization, which showed cytotoxic activity against HEK293, HepG2, and Jurkat cells.[18] The starting alkenyl anilines for producing such heterocycles can be synthesized from arylamines and the product of commercially available piperylene hydrohalogenation. For these purposes, the diene is usually converted to chloropentene in reaction with concentrated HCl solution. Further transformations of intermediate compounds are fairly simple and require the usage of widely available reagents. Therefore, it is reasonable to continue studying synthesis and comparing the biological activity of the synthesized heterocycles, including halogenation products, which, in our opinion, are beneficial for two reasons. First, halogencyclization of *N*-tosyl-substituted *ortho*-pentenylanilines proceeds as a diastereoselective reaction resulting in the formation of two isomeric heterocycles, differing only in configuration of substituents at C-3 carbon atom. It was shown on some *N*-tosylates of 2-(1-methylbut-2-en-1-yl)anilines, which possess substituents in the aromatic moiety and provide (+)–*I*–- effect.[19] At the same time, the contribution of substituents with other electronic effects at the aromatic ring on the ratio of isomers remains poorly studied.[20] Second, it is curious and informative to compare the biological activity of 2-(1-haloethyl)indoline derivatives differing only in configuration at the C-3 atom. Since the antiproliferative activity in products of the halogencyclization of tosyl-substituted *ortho*-alkenylanilines was found for the first time, their biological effectiveness is practically unexplored. Therefore, an assessment of cytotoxic activity of the resulting isomeric heterocycles carrying bromine or iodine atoms at halogenethyl fragment is essential, and the practical importance of the study is evident.

2 | RESULTS AND DISCUSSION

The amines **1** required for this study were synthesized by *N*-alkenylation of the corresponding anilines with chloropentene in triethylamine and the subsequent thermal Claisen rearrangement of hydrochloride *N*-pentenylaniline **2** in xylene. Toluenesulfonyl amides **3**, which were used for heterocyclization, were synthesized by reacting amines **1a**,[18] **1b**, and **1h** with tosyl chloride in pyridine. A mixture of *cis*-**4** and *trans*-**4** heterocycles was obtained by reacting tosylates with molecular iodine (Scheme 1) or NBS (Scheme 2). The results of experiments that establish the stereoisomers **4** ratio dependence on the nature of the substituents at the aromatic core, nitrogen atom, cyclization agent, and cytotoxicity are summarized in Tables 1 and 2. However, this dependence, unfortunately, is not preparatively critical. When molecular iodine is used as a cyclizing agent in dichloromethane, the *trans*-isomer of 2-(1′-iodoethyl)indolines **4** predominates in all cases. During the initial theoretical analysis of the molecule of toluenesulfonylamides **3** using the Hyperchem program,[22] an equal probability of the propenyl fragment of pentenyl location was found in alkenylanilines **3A** and **3B** in such a way that the double bond is most available for the generation of the iodonium complex **A** or **B**, from which the corresponding *trans*- or *cis*-isomers of indoline **4** are formed. Therefore, the

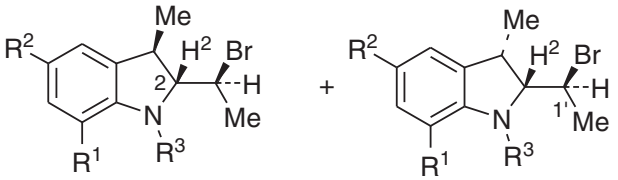


SCHEME 1 The sequence of stages for the preparation of isomeric 2-(1-iodoethyl) substituted indolines *trans*-**4a-h** and *cis*-**4a-h**



3c, **d**, **e**

R^3 = Ts, R^1 = R^2 = H (**c**), R^1 = CH_3, R^2 = H (**d**);
R^1 = H, R^2 = CH_3, R^3 = Ns (**e**)



trans-**4i**, **k**, **l** cis-**4i**, **k**, **l**

trans-**4i** + cis-**4i**, 65% overal yield;
trans-**4k**, 53%, cis-**4k**, 11%;
trans-**4l** + cis-**4l**, 27% overal yield.

R^3 = Ts, R^1 = R^2 = H (**i**), R^1 = CH_3, R^2 = H (**k**);
R^1 = H, R^2 = CH_3, R^3 = Ns (**l**).

SCHEME 2 Synthesis of isomeric 2-(1-bromoethyl) substituted indolines *trans*-**4i, k, l** and *cis*-**4i, k, l**

proposed mechanism based on these calculations, which suggests that the structure of halogenated cyclization products depends on the partial blockade of halogen access to the double bond by sufficiently bulky aromatic rings of the aniline and arylsulfonyl moieties, is not entirely correct (Figure 1).

It is possible that the reaction of tosylates **3a**-**d** with molecular iodine, besides spatial factors, can be mediated by kinetic, conformational, electronic effects depending on the nature of substituents in the aromatic ring. Experimental values, obtained by measuring the integrals of protons in the 1H NMR spectra of the mixture of amino halogenation reaction products, show the iodocylization of *ortho*-bromo-substituted *N*-tosylate **3a** leads to indolines *cis*-**4a** and *trans*-**4a** in a ratio of ≈1:2, individualized by chromatography. When 4-bromo-substituted arylsulfonylamide **3b** interacts with molecular iodine, indolines of *cis*-**4b** and *trans*-**4b** in a ratio of ≈1:3 are formed. The pure sample of *trans*-**4b** heterocycle is separated from this mixture by double crystallization out of ethanol, and the isomer *cis*-**4b** is obtained by chromatography of its enriched mother liquor.

TABLE 1 The ratio of *cis*- and *trans*-isomers of indolines **4** depending on the substituents nature on the aromatic ring of original sulfonyl amide **3**, the nature of the halogenating agent and solvent

Tosylate	R^1	R^2	R^3	X	Cyclization product	*cis*-/*trans*-isomers ratio[a]
3a	Br	H	Ts	I	*cis*-/*trans*-**4a**	1:2
3b	H	Br	Ts	I	*cis*-/*trans*-**4b**	1:4
3c	H	H	Ts	I	*cis*-/*trans*-**4**c	1:2[21]
3c	H	H	Ts	I	*cis*-/*trans*-**4**c	2:3[b]
3d	Me	H	Ts	I	*cis*-/*trans*-**4d**	1:3[19]
3d	Me	H	Ts	I	*cis*-/*trans*-**4d**	1:3[b]
3d	Me	H	Ts	I	*cis*-/*trans*-**4d**	2:1[c]
3d	Me	H	Ts	I	*cis*-/*trans*-**4d**	1:3[d]
3d	Me	H	Ts	I	*cis*-/*trans*-**4d**	1:3[e]
3e	H	Me	Ts	I	*cis*-/*trans*-**4e**	1:5[19]
3e	H	Me	Ns	I	*cis*-/*trans*-**4f**	1:6[19]
3e	H	Me	Ns	I	*cis*-/*trans*-**4f**	1:4[b]
3g	H	Cl	Ts	I	*cis*-/*trans*-**4g**	2:3[18]
3h	Cl	H	Ts	I	*cis*-/*trans*-**4h**	1:2
3c	H	H	Ts	Br	*cis*-/*trans*-**4i**	1:1
3d	Me	H	Ts	Br	*cis*-/*trans*-**4k**	1:5
3e	H	Me	Ns	Br	*cis*-/*trans*-**4l**	2:3

[a]The ratio is determined by measuring the intensity integrals of the signals in the ^{1}H NMR-spectrum of the reaction products crude mixture.
[b]The reaction is carried out in methyl *tert*-butyl ether in the presence of $NaHCO_3$.
[c]The reaction is carried out in acetonitrile in the presence of $NaHCO_3$.
[d]The reaction is carried out in CH_2Cl_2 in the presence of LiOH.
[e]The reaction is carried out in methyl *tert*-butyl ether in the presence of LiOH.

TABLE 2 In vitro activity of compounds in human cell lines (HEK293, SH-SY5Y, Jurkat, and HepG2)

	IC_{50} (μM)[a]			
ID	**HEK293**	**SH-SY5Y**	**Jurkat**	**HepG2**
cis-**4c**	10.72[18]	–[b]	14.96[18]	40.83[18]
cis-**4k**	13.92 ± 0.58	4.32 ± 0.40	60.20 ± 15.70 ($P = .0001$[c])	42.53 ± 7.09 ($P = .0008$[c])
trans-**4k**	49.61 ± 5.72 ($P = .001$[c])	6.72 ± 1.33	20.42 ± 7.56	67.62 ± 3.34 ($P = .0003$[c])
trans-**4a**	53.72 ± 6.94 ($P = .003$[c])	4.25 ± 0.77	56.58 ± 6.34 ($P = .006$[c])	–[d]
cis-**4b**	78.76 ± 14.90 ($P = .01$[c])	3.67 ± 0.32	70.22 ± 13.60 ($P = .03$[c])	–
cis-**4d**	104.10 ± 5.32 ($P = .0002$[c])	6.16 ± 2.96	–[d]	–
trans-**4d**	–[d]	27.05 ± 4.89	88.78 ± 13.07	75.74 ± 2.11
trans-**4h**	–	4.23 ± 1.11	–[d]	–[d]
cis-**4a**	–	2.88 ± 0.35	–	–
trans-**4b**	–	–[d]	–	–
trans-**4e**	–	–	–	–
trans-**4f**	–	–	–	–
cis-**4h**	–	3.39 ± 0.93	–	–
Doxorubicin	1.76 ± 0.05	0.47 ± 0.006	6.84 ± 0.47	6.39 ± 0.19

[a]IC_{50} (μM) values obtained from MTT assays. Cells were incubated with compounds for 48 hours. Values were the mean ± SD from two independent experiments, performed in triplicate.
[b]Not tested.
[c]Corresponding cell line vs SH-SY5Y cells. IC_{50} values differences for certain cell lines proved by one-way ANOVA with Dunnett's post hoc test.
[d]Non-active, $IC_{50} > 100$ μM.

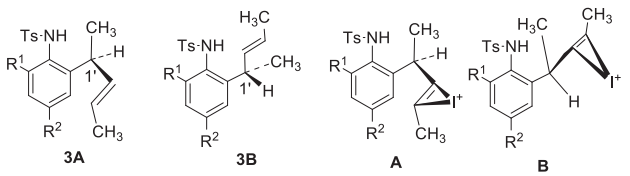


FIGURE 1 Possible modifications of the spatial arrangement of the alkenyl fragment in tosylates **3**

In these conditions the intramolecular amino halogenation of tosylate **3c** in the presence of molecular iodine previously resulted in the ≈1:2 ratio of *cis*-/*trans* indoline **4c** isomers.[21] This ratio was also reproduced in our study. Additionally, it was established that the halogencyclization of tosylamide **3c** in methyl *tert*-butyl ether is able to favor the ratio toward *cis*-isomer of indoline **4c** (≈2:3) (Table 1).

It is possible under the reaction conditions the prevalence of *trans*-isomer of indolines **4** is not guided by the alkenyl group of **3A** or **3B,** when using molecular iodine as the cyclization agent. The ratio of the isomeric indolines *cis*-/*trans*-**4d**, determined by the integrals measurement of the proton signals in the ^{1}H NMR spectrum, which are formed by the interaction of the tosylamide **3d** with molecular iodine, is also sensitive to the nature of the solvent. So, if the reaction is carried out in dichloromethane then the ratio is 1:3,[19] and it is significantly different in acetonitrile. With intramolecular amino halogenation of tosylate **3d** in the presence of acetonitrile *cis*-**4d** isomer prevails (*cis*-/*trans*-isomer ratio is ≈2:1), and methyl *tert*-butyl ether contributes to a shift of the ratio toward the *trans*-**4d** isomer (*cis*-/*trans*-**4d** ratio is ≈1:3).

A significant change of the ratio of the sulfonylamide **3d** iodocyclization reaction products toward the formation of the cis-**4d** isomer when using acetonitrile as a solvent in comparison with the same data in methylene chloride or methyl *tert*-butyl ether is probably due to different solvation effects of CH_2Cl_2, *t*-BuOMe and MeCN at dissolving molecular iodine in them. Probably, this factor contributes to a significant deceleration of the formation of the iodonium complex-precursor of the heterocycle *trans*-**4d**. Or, with the same degree of probability, we can assume an increase in this case in the reaction mixture of the formation amount of the iodonium complex, the isomer *cis*-**4d** precursor.

It was previously established that iodocyclization of tosylamide **3e** produces indolines *cis*-/*trans*-**4e** in a ratio of 1:5.[19] The greatest difference in the ratios of *cis*-**4f** and *trans*-**4f** isomers is observed during intramolecular amino halogenation, when the compound **3e** interacts with iodine. Regardless of the alkali metal bicarbonate or

carbonate ($NaHCO_3$ or K_2CO_3) used in the reaction, the ratio of *cis*-**4f**:*trans*-**4f** isomers of iodocylization in dichloromethane is 1:6.[19] In this work, it was established that when methyl *tert*-butyl ether is used as a solvent, the *cis*-**4f**:*trans*-**4f** ratio changes to ≈1:4.

Slightly different values of the ratio of isomeric indolines were obtained by iodocyclization of chlorine substituted toluenesulfonylamides **3g**[18] and **3h** in dichloromethane. In both cases, the *trans*-isomer of indoline **4g**[18] and its 5-chloro-substituted analog **4h** predominate.

When interacting tosylate **3c** with NBS, the ratio of the resulting cyclization products of *cis*-**4i** and *trans*-**4i** is ≈1:1. However, it is not possible to individualize the isomers from this mixture. From an ethanol solution the indolines *cis*-**4i** and *trans*-**4i** crystallize together, and they are isolated together by chromatography on the silica gel column (Scheme 2). In the interaction of **3d** tosylate with NBS, the ratio of the resulting cyclization products *cis*-**4k** and *trans*-**4k** is ≈1:5. The reaction of the nosyl derivative **3e** with NBS also results in an indivisible mixture of indolines *cis*-**4l** and *trans*-**4l** in a 2:3 ratio (Table 1).

Reliable assignment of iodocyclization products to *cis*-**4** and *trans*-**4** isomers was performed by means of intensive spectral studies (Figures 2 and 3), as well as by the comparison with previously obtained data, confirmed by X-ray structural analysis of heterocycles *trans*-**4c**. The structure of the *trans*-**4c** compound (X = I, $R^1 = R^2 = H$, R^3 = Ts) was previously proved using an X-ray diffraction study. It was also shown that the chemical shift of protons in the methyl group at the C-3 nodal atom of the *trans*-**4c** heterocycle is shifted to a strong field.[21] The upfield shift of this methyl group, regardless of the location of the halogen atom on the aromatic ring, is observed in indolines *trans*-(**4a**, **b**, **h**) (δ = 0.65-0.97 ppm) compared to the protons of the methyl group C^3CH_3 in isomers *cis*-(**4a**, **b**, **h**) (δ = 1.26-1.32 ppm). The protons of methyl group at the iodoethyl fragment of *trans*-(**4a**, **b**, **h**) compounds, as well as the unbrominated *trans*-**4c** analog,[21] can be traced in a weaker field (δ = 1.85-2.00 ppm) than protons of the same group in isomers *cis*-(**4a**, **b**, **h**) (δ = 1.45-1.78 ppm).

A primary theoretical analysis with structure modeling and energy minimization using the Hyperchem program[22] of the indolines **4** *cis*- and *trans*-isomers allowed us to compare some numerical values of substituents spatial orientation. The analysis showed the dihedral angle $N—C^2—C^{1\prime}\text{-}CH_3$ in *trans*-isomers of indolines **4** with a high probability can be equal to approximately 160° to 170°, that is, the nitrogen atom and the methyl group are practically *trans*-relative to each other.

This agrees with the X-ray diffraction data of *trans*-**4c** heterocycle[21] crystals. Moreover, in case of the analogue of these isomers with the *N*-mesyl substituent, the range of calculated dihedral angle values remains practically unchanged.

This example confirms the well-known data that the *trans*-location of the electronegative nitrogen atom of indoline ring with respect to the methyl group of the $C^{1\prime}—CH_3$ iodoethyl fragment helps shifting the doublet signal of its three protons into a weaker field, which is observed experimentally (see Figure 3). In the case of the *cis*-isomers of indolines **4**, judging the $N—C^2—C^{1\prime}—CH_3$ dihedral angle, there is a high probability of *cis*-conformation of the electronegative nitrogen atom and the iodoethyl fragment methyl group $C1'—CH_3$, since it will

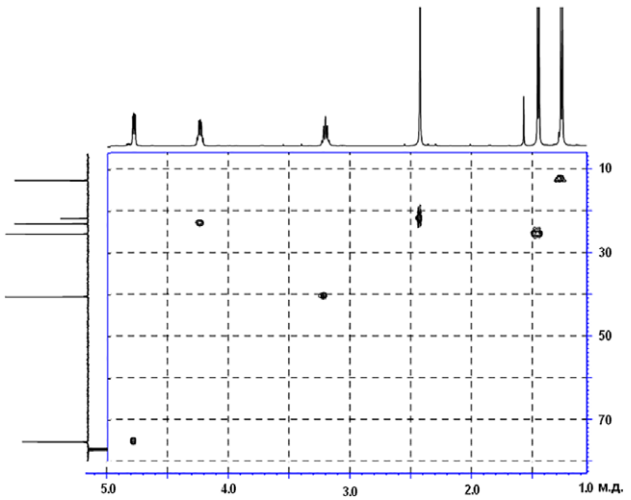


FIGURE 2 HSQC spectrum of *cis*-**4a** molecule (aliphatic fragment, $CDCl_3$)

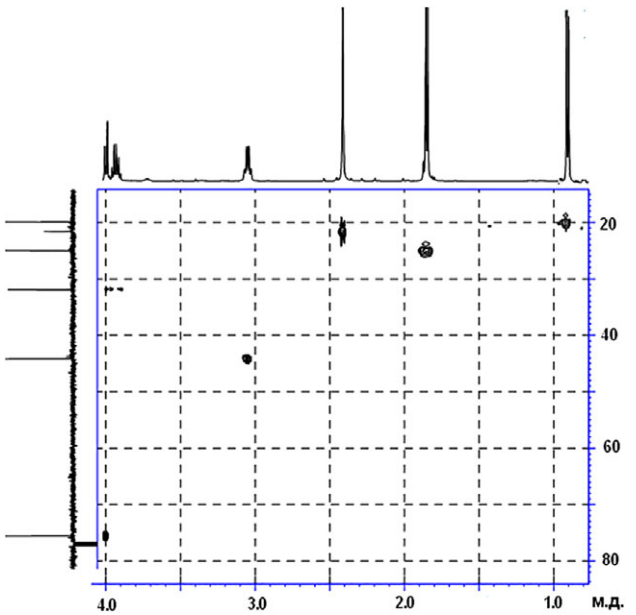


FIGURE 3 HSQC spectrum of *trans*-**4a** molecule (aliphatic fragment, $CDCl_3$)

be located in the range of 30° to 40°. Therefore, it is likely that the *cis*-effect of the substituent virtually does not contribute to the signal shift of this group into a weaker field (see Figure 2). The experimental data of the spin-spin coupling constants of the nodal protons H2, H3, and the iodoethyl link H1 satisfactorily fit into the real intervals of the Karplus-Conroy curve[23] for the calculated values of their dihedral angles.

As follows from the data presented in Table 2, most of the synthesized compounds exhibit moderate or low cytotoxic activity against the conditionally normal HEK293 cells and tumor cell lines Jurkat and HepG2. Attention is drawn to the ability of the compounds to significantly suppress the survival of SH-SY5Y neuroblastoma cells, as evidenced by the rather low IC_{50} values. The lack of effect on the viability of all investigated cell lines was observed for *trans*-**4b**, *trans*-**4e**, and *trans*-**4f** compounds, whose 3-methyl and iodoethyl groups have a mutual *trans*-orientation.

The cytotoxic effect of indolines *cis*-**4d** and *cis*-**4k**, in which an electron-donating group with the (+*I*)-effect is located at the C-7 atom of the aromatic ring, is more pronounced compared to *trans*-analogs. In contrast, the cytotoxic effect of indolines *trans*-**4a** and *trans*-**4h**, in which the carbon atom C-7 contains bromine and chlorine atoms, which have (−*I*)-and (+*M*) effects, is higher than its *cis*-analogs. Moreover, the bromo-analogue *trans*-**4a** demonstrates efficacy against three cell lines, whereas the chlorine derivative *trans*-**4h** shows only activity in the neuroblastoma cell line. Indoline *cis*-**4b**, containing a halogen atom at the C-5 atom of aromatic ring, has cytotoxic properties, comparing to its *trans*-**4b** isomer. The *trans*-isomer of indoline **4e**, which has an electron-donating methyl group at the C-5 atom of aromatic ring, and the (+*I*)-effect, was non-toxic to all studied cell lines. The previously described *cis*-**4c** heterocycle exhibits moderate cytotoxic activity with respect to HepG2 cells (IC_{50} 40.83 μM) and Jurkat (IC_{50} 14.96 μM).[18]

As noted earlier, sulfonylamides **4** are selective for SH-SY5Y cells, most significantly suppressing their viability. At the same time, the effect of isomerism on trophicity to one or another cell line was not observed for both C-7-substituted representatives **4a**, **4d**, **4k** and **4h**, and C-5-substituted analogues **4b**. Differences in the severity of cytotoxic effect were revealed, depending on isomerism in some derivatives. In particular, the iodoethyl analogue *cis*-**4d**, the bromo-ethyl derivative *cis*-**4k** with methyl substituent at C-7 aromatic carbon atom, as well as analogs *cis*-**4a**, *cis*-**4h** with chlorine and bromide atoms at the aromatic carbon atom, are effective in lower concentrations than the corresponding *trans*-isomers. There is a tendency for IC_{50} values decrease when the iodine atom is replaced by bromine, for both *cis*-isomers **4d**, **4k**, and for *trans*-analogs **4d**, **4k**. Significant difference in biological activity is observed between *cis*-**4b** and *trans*-**4b** isomers. The latter is almost non-toxic, whereas the *cis*-isomer exhibits cytotoxic activity at low concentrations. Effective concentrations of indolines *cis*-**4a**, *trans*-**4a**, *cis*-**4b**, *cis*-**4d**, *cis*-**4h**, *trans*-**4h**, *cis*-**4k** and *trans*-**4k** were comparable with the previously described heterocycles of a different structure.[24]

With respect to the Jurkat cell lines, the *trans*-**4a**, *trans*-**4d,** and *trans*-**4k** isomers are effective at lower concentrations than the *cis*-**4a**, *cis*-**4d** and *cis*-**4k** isomers. However, the *trans*-**4b** regioisomer, in which the bromine is located at the carbon atom C-5 in aromatic nucleus, exhibited the lower toxicity compared to the analogue *cis*-**4b**. In relation to HepG2 cell lines, only 2-(1-bromoethyl) substituted indolines *cis*-**4k** and *trans*-**4k**, as well as the iodoethyl analogue *trans*-**4d**, showed moderate cytotoxicity.

3 | CONCLUSIONS

Thus, the halocyclization of the homologues of *N*-tosyl-2-(1-methylbut-2-en-1-yl)aniline and 2-chloro-, 2-bromo-, and 4-bromo-derivatives is completed by the formation of *N*-tosyl-2-(1-halogeneethyl)-3-methylindolines, differing only in the configuration of substituents at the carbon atom C-3. The ratio of isomers depends on the nature of the substituents in the aromatic ring, the solvents used. It is not possible yet to change the direction of cyclization to the formation of predominantly one of these stereoisomers. The cytotoxic activity data suggest the necessity of the further studies for compounds *cis*-**4a**, *trans*-**4h**, and *cis*-**4h**, which showed specific selectivity against SH-SY5Y cell line. From a practical point of view, the tandem *cis*-**4h** and *trans*-**4h** is attractive for more detailed investigation, since they are the stereoisomeric products of iodocyclization of *N*-tosyl-2-chloro-6-(1-methylbut-2-en-1-yl)aniline. Their efficiency toward SH-SY5Y cell line is comparable, and crystallization of the reaction mixture from ethanol after halogenation will facilitate their purification to obtain a mixture of two isomers with similar biological efficiency.

4 | EXPERIMENTAL SECTION

All common reagents and solvents were obtained from commercial suppliers without further purification. Preparative chromatographic separations were performed on silica gel MN 60 (35-75 μm) and reactions followed by TLC analysis using silica gel plates Sorbfil ZAO Sorbpolimer, Krasnodar, Russia; the substances were

detected with iodine vapor. GLC was used to control the purity of the reaction products on a Chrom-5 chromatograph, carrier gas—helium (50 ml/min), flame ionization detector, 1200 × 3 mm columns, stationary phase—SE-30 (5%) on Chromaton N-AW DMCS carrier, operating temperature 50°C to 300°C. The spectral analyses were performed on the equipment of the core facility of the Ufa Institute of Chemistry, Russian Academy of Sciences. Melting points were determined on a Boetius table. The IR spectra were recorded on a spectrophotometer with Fourier transformer IRPrestige-21 Shimadzu. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III instrument at 500.13 and 125.13 MHz, respectively. The internal standard was TMS. Spectra methods of homo- and heteronuclear correlation COSY and HMBC were used for correct assignment of signals in the NMR spectra. Chemical shift in ppm is quoted relative to solvent signals calibrated as follows for $CDCl_3$: δH ($CHCl_3$) = 7.26, δC ($CDCl_3$) = 77.2. Mass spectra were obtained on a Shimadzu LCMS-2010EV instrument, with Luna 5μ C(18) 150 × 4.6 mm column and octadecylsilan sorbent, the mobile phase was 95:5 MeCN–H_2O. Elemental analysis was performed on CHNS Elemental Analyzer EURO EA-3000. The halogene content was determined by the Schoeniger flask technique, followed by potentiometric titration.

4.1 | 4-Bromo-2-[(2*E*)-1-methylbut-2-en-1-yl]aniline (1b)

Gaseous HCl was passed in the solution of amine **2b** (3 g, 12.5 mmol) in xylene (10 ml) for 20 minutes. Then the reaction mixture heated in an oil bath at boiling xylene for 6 hours, controlling the course of the rearrangement by GLC. After the initial amine **2b** disappear, the reaction mixture was cooled to room temperature, the NaOH solution (20 ml, 20%) was added and mixture was thoroughly shaken to completely neutralize HCl. The organic phase was separated, the solvent was removed in vacuo, the residue was chromatographed on a silica gel column (100 g, benzene as eluent). Yield 2.0 g (66%), R_f 0.56 (C_6H_6), viscous oil. MS (20 eV), m/z (I_r, %): 240, 242 $[M + H]^+$ (20), 281, 283 $[M + CH_3CN + H]^+$ (100), 322, 324 $[M + 2CH_3CN + H]^+$ (25). ^{1}H NMR, $CDCl_3$, δ, ppm.: 1.37 d (3H, CH_3, *J* 7.0 Hz), 1.71 d (3H, CH_3, *J* 3.6 Hz), 3.33-3.36 m (1H, $H^{1\prime}$), 3.65 br. s (2H, NH_2), 5.43-5.55 m (2H, $H^{2\prime}C{=}CH^{3\prime}$), 6.49 d (1$H_{arom.}$, *J* 8.4 Hz), 7.07 d.d (1$H_{arom.}$, *J* 2.0 Hz, *J* 8.4 Hz), 7.13 d (1$H_{arom.}$, *J* 2.0 Hz). ^{13}C NMR, $CDCl_3$, δ, ppm.: 17.87, 19.32 ($2CH_3$), 37.15 ($C^{1\prime}$), 110.84, 131.51, 143.10 (C^1, C^2, C^4), 117.41, 124.76, 129.59, 129.63, 134.37 (C^3, C^5, C^6, $C^{2\prime}$, $C^{3\prime}$). Found, %: C 54.81; H 5.77; Br 33.12; N 5.69. $C_{11}H_{14}BrN$. Calculated, %: C 55.02; H 5.88; Br 33.27; N 5.83. A significant amount of 4-bromoaniline as a decomposition product was present in the reaction mixture, which was released in the subsequent fractions.

4.2 | 2-Chloro-{6-[(2*E*)-1-methylbut-2-en-1-yl]phenyl}amine (1h)

2-Chloro-{6-[(2*E*)-1-methylbut-2-en-1-yl]phenyl}amine (**1h**) was received by two different procedures: (a) 2-chloropentene (6.9 g, 0.1 mol) was added to 2-chloroaniline (25 g, 0.2 mol) and stirred. After a few minutes, a stormy reaction begins with the formation of a precipitate. The reaction mixture was heated at 150°C for 7 hours, cooled to room temperature, a solution of NaOH (8 g, 0.2 mol) in water (50 ml) was added, thoroughly shaken until the hydrochlorides were completely neutralized, the organic phase was separated, and dried over KOH. The organic phase was decanted from the desiccant. The 2-chloroaniline (decomposition product) from unreacted amine **2h** and the reaction product **1h** was separated by distillation in vacuum. The fraction containing amine **2h** and the reaction product **1h** was collected in one flask. From this fraction the compound **1h** was isolated by chromatography on a silica gel column (250 g, C_6H_6-PE = 1:4 as eluent). Yield 7.5 g (38%). R_f 0.29 (C_6H_6). IR, ν, cm^{-1}:3460, 3382 (NH_2), 1616, 1452, 1304, 1253, 1078, 972, 770, 734, 662, 612, 572, 532. ^{1}H NMR, $CDCl_3$, δ, ppm.: 1.38 d (3H, CH_3, *J* 7.0 Hz), 1.70 d (3H, CH_3, *J* 3.7 Hz), 3.35-3.49 m (1H, $H^{1\prime}$), 4.15 br. s (2H, NH_2), 5.45-5.59 m (2H, $H^{2\prime}C{=}CH^{3\prime}$), 6.69 t (1$H_{arom.}$, *J* 7.8 Hz), 7.04 d.d (1$H_{arom.}$, *J* 0.9, *J* 7.6 Hz), 7.16 d.d (1$H_{arom.}$, *J* 1.3, *J* 8.0 Hz). ^{13}C NMR, $CDCl_3$, δ, ppm.: 17.83, 19.43 ($2CH_3$), 37.86 ($C^{1\prime}$), 120.04, 130.92, 140.89 (C^1, C^2, C^6), 118.44, 125.02, 125.24, 127.06, 134.37 (C^3, C^4, C^5, $C^{2\prime}$, $C^{3\prime}$). Found, %: C 67.40; H 7.09; Cl 17.91; N 7.03. $C_{11}H_{14}ClN$. Calculated, %: C 67.51; H 7.21; Cl 18.12; N 7.16. (b) In a solution of amine **2h** (5 g, 25.5 mmol) in xylene (15 ml), gaseous HCl was passed in for 30 minutes. Then the reaction mixture was heated in an oil bath at boiling xylene for 9 hours, controlling the course of the rearrangement by GLC. In the reaction mixture, in addition to the target product of the reaction **2h**, the formation of several by-products and a significant amount of 2-chloroaniline was observed. After the initial amine disappeared, the reaction mixture was cooled to room temperature, a 20% solution of NaOH (40 ml) was added and thoroughly shaken to complete neutralization of HCl. The organic phase was separated and the solvent was removed in a vacuum. The compound **2h** in the amount of 1.7 g (34%) with R_f 0.29 (C_6H_6) was isolated in the form of a fluid darkening in air by chromatography of the residue on a silica gel column (150 g, C_6H_6 as eluent).

4.3 | (4-Bromophenyl)[(2*E*)-1-methylbut-2-en-1-yl]amine (2b)

The 4-chloro-2-pentene (6 g, 58.1 mmol) was added to 4-bromaniline (10 g, 58.14 mmol) in Et_3N (30 ml). The reaction mixture was heated in a water bath at 80°C for 2 hours. The excess of Et_3N was evaporated under reduced pressure on a rotary evaporator; to the remaining mixture CH_2Cl_2 (60 ml) was added, then saturated $NaHCO_3$ aqueous solution (2 × 100 ml), and the mixture was gently shaken in a separatory funnel until CO_2 emission ceased. The organic layer was dried over KOH, decanted from the desiccant, the solvent was evaporated on a rotor evaporator. The reaction product was isolated by distillation in vacuo, b. p. 124-127°C (2 mm Hg). Yield 11 g (78%). MS, (20 eV), m/z (I_r, %): 213, 215 $[M\text{-}C_5H_8 + CH_3CN + H]^+$ (100), 240, 242 $[M + H]^+$ (55), 254, 256 (50), 281, 283 $[M + CH_3CN + H]^+$ (100). IR, ν, cm^{-1}:3413 (NH), 1593, 1495, 1316, 965, 812, 678, 650, 624, 596, 504, 487. ^1H NMR, $CDCl_3$, δ, ppm: 1.27 d (3H, CH_3, *J* 6.6 Hz), 1.67 d (3H, CH_3, *J* 6.2 Hz), 3.83-3.90 m (1H, $H^{1\prime}$), 3.61 br. s (1H, NH), 5.35-5.61 m (2H, $H^{2\prime}C{=}CH^{3\prime}$), 6.47 d ($2H_{arom.}$, *J* 8.6 Hz), 7.22 d ($2H_{arom.}$, *J* 8.6 Hz). ^{13}C NMR, $CDCl_3$, δ, ppm: 17.63, 21.91 ($2CH_3$), 50.50 ($C^{1\prime}$), 108.50, 146.49 (C^1, C^4), 114.91, 131.74 ($C^{2.6}$, $C^{3.5}$), 125.47, 133.85 ($C^{2\prime}$, $C^{3\prime}$). Found, %: C 54.88; H 5.74; Br 33.09; N 5.70. $C_{11}H_{14}BrN$. Calculated, %: C 55.02; H 5.88; Br 33.27; N 5.83.

4.4 | (2-Chlorophenyl)[(2*E*)-1-methylbut-2-en-1-yl]amine (2h)

(2-Chlorophenyl)[(2*E*)-1-methylbut-2-en-1-yl]amine (**2h**) was synthesized as described for compound **2b** from 30 g (235 mmol) of 2-chloroaniline and 24.6 g (235 mmol) of chloropentene. The reaction product was isolated by distillation in vacuo, b. p. 116-117°C (2 mm Hg). Yield 40 g (87%). MS, m/z (I_r, %): 169 $[M\text{-}Cl]^+$ (100), 196 $[M + H]^+$ (70), 210 (50), 237 $[M + CH_3CN + H]^+$ (65). IR, ν, cm^{-1}:3364 (NH), 1599, 109, 1325, 1032, 965, 740. ^1H NMR, $CDCl_3$), δ, ppm: 1.34 d (3H, CH_3, *J* 6.5 Hz), 1.68 d (3H, CH_3, *J* 6.5 Hz), 3.96 quintet (1H, $H^{1\prime}$, *J* 6.5 Hz), 4.26 br. s (1H, NH), 5.40-5.70 m (2H, $H^{2\prime}C{=}CH^{3\prime}$), 6.60 d.t ($1H_{arom.}$, *J* 1.2, *J* 7.8 Hz), 6.67 d ($1H_{arom.}$, *J* 8.0 Hz), 7.10 d.t ($1H_{arom.}$, *J* 1.3, *J* 8.0 Hz), 7.25 d.d ($1H_{arom.}$, *J* 1.2, *J* 7.8 Hz). ^{13}C NMR, $CDCl_3$, δ, ppm: 17.64, 22.03 ($2CH_3$), 50.30 ($C^{1\prime}$), 112.20, 116.80, 125.31, 127.58, 129.02, 133.63 (C^3, C^4, C^5, C^6, $C^{2\prime\prime}$, $C^{3\prime\prime}$), 119.50, 143.29 (C^1, C^2). Found, %: C 67.37; H 7.05; Cl 17.88; N 6.97. $C_{11}H_{14}ClN$. Calculated, %: C 67.51; H 7.21; Cl 18.12; N 7.16.

4.5 | *N*-{2-bromo-6-[(2*E*)-1-methylbut-2-en-1-yl]phenyl}-4-methylbenzenesulfonamide (3a)

Tosylchloride (0.57 g, 3 mmol) was added to a solution of compound **1a**[18] (0.65 g, 2.7 mmol) in dry pyridine (2 ml). The reaction mixture was kept for 24 hours at 20°C. Water (30 ml) was added and mixed for 30 minutes. The solvent was evaporated in vacuo; H_2O (30 ml) and CH_2Cl_2 (60 ml) were added to the remaining stock, shaken in a separatory funnel, the organic phase was separated, washed consequently with 10% HCl (10 ml) and water (10 ml), and dried over Na_2SO_4. After removal of the solvent in vacuo, the remaining stock (≈1.5 g) was purified by chromatography on a silica gel column (5 g, C_6H_6 as eluent). Yield 1.0 g (93%). Compound **3a** was slowly crystallized from ethanol. MS, m/z (I_r, %): (Scan E^+) 394, 396 $[M + H]^+$ (100); (Scan E^-) 392, 394 $[M - H]^-$ (100). NMR spectrum ^1H ($CDCl_3$), δ, ppm: 1.28 d (3H, CH_3, *J* 6.8 Hz), 1.66 d (3H, CH_3, *J* 4.2 Hz), 2.42 s (3H, CH_3), 4.27-4.30 m (1H, $H^{1\prime}$), 5.44-5.57 m (2H, $H^{2\prime}C{=}CH^{3\prime}$), 6.42 s (1H, NH), 7.11 dt ($1H_{arom.}$, *J* 2.5, *J* 7.9 Hz), 7.21-7.30 m ($4H_{arom.}$), 7.56 dd ($2H_{arom.}$, *J* 1.8, *J* 8.3 Hz). Found, %: C 54.70; H 4.96; Br 20.01; N 3.44; S 7.93. $C_{18}H_{20}BrNO_2S$. Calculated, %: C 54.83; H 5.11; Br 20.26; N 3.55; S 8.13.

4.6 | *N*-{4-bromo-2-[(2*E*)-1-methylbut-2-en-1-yl]phenyl}-4-methylbenzenesulfonamide (3b)

N-{4-bromo-2-[(2*E*)-1-methylbut-2-en-1-yl]phenyl}-4-methylbenzenesulfonamide (**3b**) was synthesized as described for compound **3a**, by the interaction of alkenylaniline **2b** (0.9 g, 3.45 mmol) and TsCl (0.86 g, 4.5 mmol) in pyridine (3 ml). Chromatographic purification on a silica gel column (eluent—C_6H_6) gave 1.11 g (75%) of sulfonylamide **3b**, viscous oil, R_f 0.43 (C_6H_6). MS (20 eV), m/z (I_r, %): 392, 394 $[M - H]^-$ (100). IR, ν, cm^{-1}:3278 (NH), 1483, 1332,1164, 1091, 814, 664, 585, 568, 546. ^1H NMR, $CDCl_3$, δ, ppm: 0.98 d (3H, CH_3, *J* 7.0 Hz), 1.64 d (3H, CH_3, *J* 5.6 Hz), 2.39 s (3H, CH_3), 3.08 quintet (1H, $H^{1\prime}$, *J* 7.0 Hz), 5.25-5.35 m (2H, $H^{2\prime}C{=}CH^{3\prime}$), 6.71 s (1H, NH), 7.22-7.24 m (3H, $H_{arom.}$), 7.28 s (2H, $H_{arom.}$), 7.60 d (2H, $H_{arom.}$, *J* 8.2 Hz). ^{13}C NMR, $CDCl_3$, δ, ppm: 17.82, 19.69, 21.48 ($3CH_3$), 36.71 ($C^{1\prime}$), 125.98, 126.09, 130.06, 130.29, 133.83 ($C^{3\prime}$, $C^{5\prime}$, $C^{6\prime}$, $C^{2\prime\prime}$, $C^{3\prime\prime}$), 127.10, 129.64 ($C^{2,6}$, $C^{3\ 5}$), 119.82, 133.28, 136.35, 140.04, 143.94 (C^1, C^4, $C^{1\prime}$, $C^{2\prime}$, $C^{4\prime}$). Found, %: C 54.66; H 4.98; Br 20.03; N 3.42; S 7.96.

$C_{18}H_{20}BrNO_2S$. Calculated, %: C 54.83; H 5.11; Br 20.26; N 3.55; S 8.13.

4.7 | *N*-{2-chloro-6-[(2*E*)-1-methylbut-2-en-1-yl]phenyl}-4-methylbenzenesulfonamide (3h)

N-{2-chloro-6-[(2*E*)-1-methylbut-2-en-1-yl]phenyl}-4-methylbenzenesulfonamide (**3h**) was synthesized as described for compound **3a**, by the interaction of alkenylaniline **2h** (0.7 g, 3.58 mmol) and TsCl (0.74 g, 3.76 mmol) in pyridine (5 ml). The resulting crude tosylate (0.96 g) was dissolved in EtOH (3 ml) by boiling. Colorless crystals of compound **3h** (0.79 g, 63%), m. p. 125-128°C (EtOH). MS (20 eV), m/z (I_r, %): 350 $[M + H]^+$ (100); 348 $[M - H]^-$ (100). ^{1}H NMR, $CDCl_3$, δ, ppm.: 1.32 d (3H, CH_3, *J* 6.8 Hz), 1.69 d (3H, CH_3, *J* 4.2 Hz), 2.44 s (3H, CH_3), 4.28-4.40 m (1H, $H^{1\prime}$), 5.47-5.57 m (2H, $H^{2\prime}C{=}CH^{3\prime}$), 6.17 s (1H, NH), 7.05-7.27 m (5$H_{arom.}$), 7.55 d (2$H_{arom.}$, *J* 8.1 Hz). ^{13}C NMR, $CDCl_3$, δ, ppm.: 18.04, 20.94, 21.61 (3CH_3), 36.87 ($C^{1\prime}$), 123.82, 126.94, 127.70, 128.45, 129.20, 135.46 (C^3, C^4, C^5, $C^{1\prime}$, $C^{4\prime}$, $C^{2\prime\prime}$, $C^{3\prime\prime}$), 130.48, 132.77, 137.16, 143.25, 148.65 (C^1, C^2, C^6, $C^{1\prime}$, $C^{4\prime}$). Found, %: C 61.67; H 5.63; Cl 9.92; N 3.87. $C_{18}H_{20}ClNO_2S$. Calculated, %: C 61.79; H 5.76; Cl 10.13; N 4.00.

4.8 | Preparation of *cis*-4 and *trans*-4 compounds (general procedure)

The I_2 (1.2 mmol) was added to the stirring suspension of tosylate **3** (1 mmol) and $NaHCO_3$ (5 mmol) in CH_2Cl_2 (10 ml). The course of the reaction was monitored by TLC. After the initial tosylate **3** disappeared, a 5% aqueous solution of $Na_2S_2O_3{\cdot}5H_2O$ (10 ml) was added and the reaction mixture was stirred for 20 minutes. The reaction products were extracted with CH_2Cl_2 (20 ml), the organic phase was separated, washed in H_2O (10 ml) and dried over Na_2SO_4. The solvent was evaporated in vacuo, the residue was chromatographed on silica gel column (eluent—C_6H_6) or crystallized from 95% EtOH.

4.9 | (2*R**,3*R**)-7-bromo-2-[(1*S**)-1-iodoethyl)-3-methyl-1-[(4-methylphenyl) sulfonyl]indoline (*trans*-4a)

(2*R**,3*R**)-7-bromo-2-[(1*S**)-1-iodoethyl)-3-methyl-1-[(4-methylphenyl)sulfonyl]indoline (*trans*-**4a**) was synthesized by reaction of sulfonyl amide **3a** (0.79 g, 2 mmol) and I_2 (0.61 g, 2.4 mmol) in presence of K_2CO_3 (0.22 g) in CH_2Cl_2 (40 ml). After appropriate treatment of the reaction mixture, 1.2 g of a crude residue was obtained, from which the compound *trans*-**4a** was isolated by chromatography on a silica gel column (15 g, C_6H_6 as eluent). Yield 0.56 g (53%), white powder, m. p. >360°C (EtOH). MS (20 eV), m/z (I_r, %): 392, 394 $[M - I]^+$ (25), 479, 481 (50), 520, 522 $[M + H]^+$ (45), 563, 565 $[M + CH_3CN + H]^+$ (20), 607, 609 $[M + 2Na + CH_3CN + H]^+$ (100). IR, ν, cm^{-1}:565, 579, 597, 670, 771, 778, 1171, 1363, 1378, 1437, 1458. ^{1}H NMR, $CDCl_3$, δ, ppm: 0.91 d (3H, CH_3, *J* 7.3 Hz), 1.85 d (3H, CH_3, *J* 6.8 Hz), 2.41 s (3H, CH_3), 3.05 d.k (1H, H^3, *J* 1.5, *J* 7.3 Hz), 3.93 d.k (1H, $H^{1\prime}$, *J* 6.8, *J* 8.6 Hz), 4.00 d.d (1H, H^2, *J* 1.5, *J* 8.6 Hz), 7.03 t (1H, $H_{arom.}$, *J* 7.5 Hz), 7.07 d.d (1H, $H_{arom.}$, *J* 1.0, *J* 7.3 Hz), 7.27 d (2H, $H_{arom.}$, *J* 8.3 Hz), 7.47 d.d (1H, $H_{arom.}$, *J* 1.0, *J* 7.3 Hz), 7.71 d (2H, $H_{arom.}$, *J* 8.3 Hz). ^{13}C NMR, $CDCl_3$, δ, ppm: 19.92 (C^3CH_3), 21.97 (CH_3), 24.99 ($C^{1\prime}CH_3$), 31.90 ($C^{1\prime}$), 41.13 (C^3), 75.50 (C^2), 114.85 (C^7Br), 123.27, 133.17 (C^4, C^6), 127.65 (C^5), 128.36 ($C^{3\prime\prime,5\prime\prime}$), 129.48 ($C^{2\prime\prime,6\prime\prime}$), 135.18 ($C^{1\prime\prime}$), 139.89, 142.26 ($C^{7a}$, C^{3a}), 144.51 ($C^{4\prime\prime}$). Found, %: C 41.41; H 3.59; Br 15.25; I 24.23; N 2.58; S 6.02. $C_{18}H_{19}BrINO_2S$. Calculated, %: C 41.56; H 3.68; Br 15.36; I 24.39; N 2.69; S 6.16.

4.10 | (2*R**,3*S**)-7-bromo-2-[(1*S**)-1-iodoethyl)-3-methyl-1-[(4-methylphenyl) sulfonyl]indoline (*cis*-4a)

Subsequent elution of the chromatographic column resulted in the heterocycle *cis*-**4a** (0.28 g, 27%) as colorless crystals, m.p. 195-196°C (EtOH). MS (20 eV), m/z (I_r, %): 520, 522 $[M + H^+]^+$ (100), 607, 609 $[M + 2Na + CH_3CN + H]^+$ (100). IR, ν, cm^{-1}:561, 575, 598, 666, 680, 785, 800, 816, 1167, 1358, 1378, 1436, 1456. ^{1}H NMR, $CDCl_3$, δ, ppm.: 1.26 d (3H, CH_3, *J* 7.2 Hz), 1.45 d (3H, CH_3, *J* 7.0 Hz), 2.42 s (3H, CH_3), 3.19 quintet (1H, H^3, *J* 7.2 Hz), 4.23 d.k (1H, $H^{1\prime}$, *J* 4.2, *J* 7.0 Hz), 4.77 d.d (1H, H^2, *J* 4.2 Hz, *J* 7.2 Hz), 6.94 d (1$H_{arom.}$, *J* 7.3 Hz), 7.06 t (1$H_{arom.}$, *J* 7.7 Hz), 7.27 d (2$H_{arom.}$, *J* 8.2 Hz), 7.46 d (1$H_{arom.}$, *J* 8.0 Hz), 7.77 d (2$H_{arom.}$, *J* 8.2 Hz). ^{13}C NMR, $CDCl_3$, δ, ppm: 12.50 (C^3CH_3), 21.64 (CH_3), 22.86 ($C^{1\prime}CH_3$), 25.37 ($C^{1\prime}$), 40.43 (C^3), 75.13 (C^2), 116.27 (C^7), 121.66, 132.71 (C^4, C^6), 128.45 (C^5), 128.49 ($C^{3\prime\prime,5\prime\prime}$), 129.51 ($C^{2\prime\prime,6\prime\prime}$), 135.22 ($C^{1\prime\prime}$), 141.58, 143.80 ($C^{7a}$, C^{3a}), 144.53 ($C^{4\prime\prime}$). Found, %: C 41.40; H 3.57; Br 15.24; I 24.25; N 2.59; S 6.06. $C_{18}H_{19}BrINO_2S$. Calculated, %: C 41.56; H 3.68; Br 15.36; I 24.39; N 2.69; S 6.16.

4.11 | (2*R**,3*R**)-5-bromo-2-[(1*S**)-1-iodoethyl)-3-methyl-1-[(4-methylphenyl) sulfonyl]indoline (*trans*-4b)

(2*R**,3*R**)-5-bromo-2-[(1*S**)-1-iodoethyl)-3-methyl-1-[(4-methylphenyl)sulfonyl]indoline (*trans*-**4b**) was prepared by interaction of compound **3b** (1.04 g, 2.64 mmol) with I_2 (0.92 g, 3.6 mmol). After appropriate treatment of the reaction mixture, 1.2 g of a crude residue was obtained, from which the compound *trans*-**4b** was isolated by crystallization from 220 ml of ethanol. *Trans*-**4b** heterocycle was obtained in the amount of 0.74 g with 10% impurity of indoline *cis*-**4b**. Recrystallization from EtOH (180 ml) gives a 0.43 g (31%) analytically pure sample of *trans*-**4b**. Colorless crystals, m. p. 198-199°C (EtOH). MS (20 eV), m/z (I_r, %): 129 (100), 520, 522 $[M + H^+]^+$ (35). IR, ν, cm^{-1}:542, 582, 595, 663, 667, 810, 961, 1003, 1036, 1089, 1120, 1163, 1181, 1355, 1379, 1464, 1469. ^1H NMR, $CDCl_3$, δ, ppm: 0.65 d (3H, CH_3, *J* 7.1 Hz), 2.00 d (3H, CH_3, *J* 7.1 Hz), 2.37 s (3H, CH_3), 3.06 d.q (1H, H^3, *J* 2.5, *J* 7.1 Hz), 3.32 d.d (1H, H^2, *J* 2.5, *J* 5.7 Hz), 4.47 d.q (1H, $H^{1\prime}$, *J* 5.7, *J* 7.1 Hz), 7.13 d (1H, $H_{arom.}$, *J* 1.8 Hz), 7.21 d (2H, $H_{arom.}$, *J* 8.1 Hz), 7.35 d.d (1H, $H_{arom.}$, *J* 1.8, *J* 7.6 Hz), 7.54 d (2H, $H_{arom.}$, *J* 8.1 Hz), 7.56 d (1H, $H_{arom.}$, *J* 7.6 Hz). ^{13}C NMR, $CDCl_3$, δ, ppm: 21.53 (C^3CH_3), 22.11 (CH_3), 24.33 ($C^{1\prime}CH_3$), 33.44 ($C^{1\prime}$), 41.84 (C^3), 74.97 (C^2), 117.63, 133.83, 138.87, 139.99, 144.59 (C^{3a}, C^5, C^{7a}, $C^{1\prime}$, $C^{4\prime}$), 118.29, 127.38, 131.05 (C^4, C^6, C^7), 127.26, 129.67 ($C^{3\prime\prime,5\prime\prime}$, $C^{2\prime\prime,6\prime\prime}$). Found, %: C 41.37; H 3.50; Br 15.18; I 24.24; N 2.54; S 5.98. $C_{18}H_{19}BrINO_2S$. Calculated, %: C 41.56; H 3.68; Br 15.36; I 24.39; N 2.69; S 6.16.

4.12 | (2*R**,3*S**)-5-bromo-2-[(1*S**)-1-iodoethyl)-3-methyl-1-[(4-methylphenyl) sulfonyl]indoline (*cis*-4b)

(2*R**,3*S**)-5-bromo-2-[(1*S**)-1-iodoethyl)-3-methyl-1-[(4-methylphenyl)sulfonyl]indoline (*cis*-**4b**) was isolated by chromatography on silica gel column (20 g) (eluent—C_6H_6) from the residue after evaporation of the first filtrate (220 ml) (see synthesis of compound *trans*-**4b**). Compound *cis*-**4b** was obtained in the amount of 0.28 g (20%) in the form of a viscous mass. When rubbed in ethanol, it crystallizes to form a white powder, m. p. 136-139°C (EtOH). MS (20 eV), m/z (I_r, %): 129 (100), 520, 522 $[M + H^+]^+$ (5). IR, ν, cm^{-1}:591, 668, 816, 974, 1004, 1093, 1166, 1176, 1215, 1280, 1349, 1358, 1378, 1440, 1454, 1465. ^1H NMR, $CDCl_3$, δ, ppm: 1.34 d (3H, CH_3, *J* 7.4 Hz), 1.78 d (3H, CH_3, *J* 7.1 Hz), 2.36 s (3H, CH_3), 2.77 quintet (1H, H^3, *J* 7.4 Hz), 4.34 d.q (1H, $H^{1\prime}$, *J* 4.6, *J* 7.1 Hz), 4.54 d.d (1H, H^2, *J* 4.6 Hz, *J* 7.4 Hz), 7.03 d (1H, H^4, *J* 1.5 Hz), 7.18 d (2$H_{arom.}$, *J* 8.0 Hz), 7.38 d.d (1$H_{arom.}$, *J* 1.5 Hz, *J* 7.4 Hz), 7.49-7.51 m (3$H_{arom.}$). ^{13}C NMR, $CDCl_3$, δ, ppm: 11.76 (C^3CH_3), 21.54 (CH_3), 23.69 ($C^{1\prime}CH_3$), 25.43 ($C^{1\prime}$), 39.32 (C^3), 72.31 (C^2), 118.34, 135.16, 140.32, 140,59, 144.26 (C^{3a}, C^5, C^{7a}, $C^{1\prime}$, $C^{4\prime}$), 120.10, 125.90, 131.03 (C^4, C^6, C^7), 126.96 ($C^{3\prime\prime,5\prime\prime}$), 129.72 ($C^{2\prime\prime,6\prime\prime}$). Found, %: C 41.39; H 3.55; Br 15.26; I 24.19; N 2.58; S 6.02. $C_{18}H_{19}BrINO_2S$. Calculated, %: C 41.56; H 3.68; Br 15.36; I 24.39; N 2.69; S 6.16.

Compounds *cis*-**4c** and *trans*-**4c** were synthesized previously.[21]

4.13 | (2*R**,3*R**)-2-[(1*S**)-1-iodoethyl)-3,7-dimethyl-1-[(4-methylphenyl)sulfonyl] indoline (*trans*-4d)

(2*R**,3*R**)-2-[(1*S**)-1-iodoethyl)-3,7-dimethyl-1-[(4-methylphenyl)sulfonyl]indoline (*trans*-**4d**) was obtained according to the previously described procedure.[19] It is synthesized in the form of foam, does not crystallize from EtOH. IR, ν, cm^{-1}:543, 548, 569, 589, 598, 665, 778, 1089, 1168, 1361, 1597. MS, m/z (I_r, %): 456 $[M + H]^+$ (100), 301 $[M - H_3CC_6H_4SO_2H + H]^+$ (30). ^1H NMR spectral data corresponded to those described in work.[19]

4.14 | (2*R**,3*S**)-2-[(1*R**)-1-iodoethyl)-3,7-dimethyl-1-[(4-methylphenyl)sulfonyl] indoline (*cis*-4d)

(2*R**,3*S**)-2-[(1*R**)-1-iodoethyl)-3,7-dimethyl-1-[(4-methylphenyl)sulfonyl]indoline (*cis*-**4d**) was obtained according to the previously described procedure.[19] Colorless needles were crystallized from EtOH, m. p. 169-171°C (EtOH). IR, ν, cm^{-1}:578, 604, 677, 786, 994, 1151, 1162, 1168, 1363, 1377, 1598. MS, m/z (I_r, %): 456 $[M + H]^+$ (100), 301 $[M - H_3CC_6H_4SO_2H + H]^+$ (20). ^1H NMR spectral data corresponded to those described in the work.[19]

4.15 | (2*R**,3*R**)-2-[(1*S**)-1-iodoethyl)-3,5-dimethyl-1-[(4-methylphenyl)sulfonyl] indoline (*trans*-4e)

(2*R**,3*R**)-2-[(1*S**)-1-iodoethyl)-3,5-dimethyl-1-[(4-methylphenyl)sulfonyl]indoline (*trans*-**4e**) was described in the work.[19]

4.16 | (2*R**,3*R**)-2-[(1*S**)-1-iodoethyl)-3,5-dimethyl-1-[(2-nitrophenyl)sulfonyl] indoline (*trans*-4f)

^1H and ^{13}C NMR data were described earlier.[19] Additional characteristics: m. p. 169-171°C (EtOH). IR, ν, cm^{-1}:1546,

1487, 1464, 1456, 1372, 1367, 1174, 1166, 1037, 774, 610, 595, 584, 535, 525. MS, m/z (I_r, %): 487 $[M + H]^+$ (100), 359 $[M - I]^+$ (25), 301 $[M - O_2NC_6H_4SO_2H + H]^+$ (25).

Compounds *cis*-**4g** and *trans*-**4g** were synthesized previously.[18]

4.17 | (2*R**,3*R**)-7-chloro-2-[(1*S**)-1-iodoethyl)-3-methyl-1-[(2-nitrophenyl) sulfonyl]indoline (*trans*-4h)

(2*R**,3*R**)-7-chloro-2-[(1*S**)-1-iodoethyl)-3-methyl-1-[(2-nitrophenyl)sulfonyl]indoline (*trans*-**4h**) was synthesized by the reaction of sulfonyl amide **3h** (0.76 g, 2.2 mmol) and I_2 (0.56 g, 2.2 mmol) in CH_2Cl_2 (10 ml). After appropriate treatment of the reaction mixture, 0.95 g of crude residue was obtained, and the *trans*-**4a** compound was isolated by chromatography on a silica gel column. Yield 0.53 g (51%). Colorless crystals, m. p. 127-130°C (EtOH). MS, m/z (I_r, %): 476 $[M + H^+]^+$ (100). IR, ν, cm^{-1}:536, 564, 580, 599, 625, 661, 671, 729, 779, 1172, 1363, 1378, 1439, 1460. ^1H NMR, $CDCl_3$, δ, ppm: 0.97 д (3H, CH_3, *J* 7.2 Hz), 1.87 d (3H, CH_3, *J* 6.9 Hz), 2.41 s (3H, CH_3), 3.07 k (1H, H^3, *J* 7.2 Hz), 3.97 quintet (1H, $H^{1\prime}$, *J* 6.9 Hz), 4.07 d (1H, H^2, *J* 8.8 Hz), 7.03 d (1H, $H_{arom.}$, *J* 7.4 Hz), 7.09 t (1H, $H_{arom.}$, *J* 7.6 Hz), 7.26-7.29 m (3H, $H_{arom.}$), 7.73 d (2H, $H_{arom.}$, *J* 8.1 Hz). ^{13}C NMR, $CDCl_3$, δ, ppm: 20.20 (C^3CH_3), 21.58 (CH_3), 25.03 ($C^{1\prime}CH_3$), 31.91 ($C^{1\prime}$), 43.17 (C^3), 75.88 (C^2), 122.68, 127.22, 130.17 (C^4, C^5, C^6), 128.18 ($C^{3\prime\prime,5\prime\prime}$), 129.43 ($C^{2\prime\prime,6\prime\prime}$), 126.17, 135.22, 138.25, 142.02 (C^7, $C^{1\prime\prime}$, C^{3a}, C^{7a}), 144.29 ($C^{4\prime\prime}$). Found, %: C 45.28; H 3.89; Cl 7.22; I 26.28; N 2.68; S 6.56. $C_{18}H_{19}ClINO_2S$. Calculated, %: C 45.44; H 4.03; Cl 7.45; I 26.67; N 2.94; S 6.74.

4.18 | (2*R**,3*S**)-7-chloro-2-[(1*S**)-1-iodoethyl)-3-methyl-1-[(2-nitrophenyl) sulfonyl]indoline (*cis*-4h)

Subsequent chromatography of the previous mixture on a silica gel column yields 0.21 g (20%) of the heterocycle *cis*-**4h** as colorless crystals, m. p. 180-181°C (EtOH). MS, m/z (I_r, %): 476 $[M + H^+]^+$ (100). IR, ν, cm^{-1}:505, 538, 549, 580, 591, 742, 787, 807, 914, 941, 980, 995, 1059, 1090, 1167, 1185, 1358, 1376, 1460. ^1H NMR, $CDCl_3$, δ, ppm: 1.28 d (3H, CH_3, *J* 7.2 Hz), 1.45 d (3H, CH_3, *J* 6.8 Hz), 2.42 s (3H, CH_3), 3.19 quintet (1H, H^3, *J* 7.2 Hz), 4.25 d.q (1H, $H^{1\prime}$, *J* 3.9, *J* 6.8 Hz), 4.82 d.d (1H, H^2, *J* 3.9 Hz, *J* 7.2 Hz), 6.91 d ($1H_{arom.}$, *J* 7.0 Hz), 7.13 t ($1H_{arom.}$, *J* 7.7 Hz), 7.26-7.30 m ($3H_{arom.}$), 7.79 d ($2H_{arom.}$, *J* 8.1 Hz). ^{13}C NMR ($CDCl_3$), δ, м.д.: 12.40 (C^3CH_3), 21.65 (CH_3), 23.00 ($C^{1\prime}CH_3$), 25.21 ($C^{1\prime}$), 40.26 (C^3), 75.26 (C^2), 121.00, 128.23, 129.59 (C^4, C^5, C^6), 128.43 ($C^{3\prime\prime,5\prime\prime}$), 129.49 ($C^{2\prime\prime,6\prime\prime}$), 127.95, 135.39, 139.81, 143.60 (C^{3a}, C^7, C^{7a}, $C^{1\prime\prime}$), 144.45 ($C^{4\prime\prime}$). Found, %: C 45.40; H 3.92; Cl 7.24; I 26.35; N 2.69; S 6.56. $C_{18}H_{19}ClINO_2S$. Calculated, %: C 45.44; H 4.03; Cl 7.45; I 26.67; N 2.94; S 6.74.

4.19 | Bromocyclization of tosylamides 3c, 3d, and 3f

A solution of the corresponding tozylamide (4 mmol) in CH_2Cl_2 (10 ml) and *N*-bromosucinimide (0.79 g, 4.4 mmol) was stirred until the starting amide disappeared, controlling the course of the reaction by TLC. A 10% solution of sodium thiosulfate (10 ml) was added, reaction mixture stirred for 5 minutes, diluted with CH_2Cl_2 (20 ml) and water (10 ml). The organic layer was separated, dried over $MgSO_4$ and solvent was evaporated in vacuum. The residue was chromatographed on a silica gel column (90 g, C_6H_6 as eluent).

4.20 | (2*R**,3*R**)- and (2*R**,3*S**)-2-[(1*S**)-1-bromoethyl)-3-methyl-1-[(4-methylphenyl)sulfonyl]indoline (*cis*-4i and *trans*-4i)

(2*R**,3*R**)- and (2*R**,3*S**)-2-[(1*S**)-1-bromoethyl)-3-methyl-1-[(4-methylphenyl)sulfonyl]indoline (*cis*-**4i** and *trans*-**4i**) were obtained from 1.26 g (4 mmol) tosylate **3c**. After treatment of the reaction mixture, 1.6 g of wet weight was obtained, crystallization of which from ethanol gives a 1.05 g (65%) mixture of crystals *cis*-**4i** and *trans*-**4i** (1:1 ratio). White amorphous powder. The compounds *cis*-**4i** and *trans*-**4i** could not be individualized.

4.21 | (2*R**,3*R**)-2-[(1*S**)-1-bromoethyl)-3,7-dimethyl-1-[(4-methylphenyl)sulfonyl] indoline (*trans*-4k)

(2*R**,3*R**)-2-[(1*S**)-1-bromoethyl)-3,7-dimethyl-1-[(4-methylphenyl)sulfonyl]indoline (*trans*-**4k**) was obtained from tosylate **3d** (1.32 g). Yield 0.88 g (53%). White amorphous powder. MS, m/z (I_r, %): (Scan E^+) 328 [M-Br] (65%), 408, 410 $[M + H]^+$ (100), 449, 451 $[M + CH_3CN + H^+]^+$ (20), 815, 817, 819 $[2\,M + H]^+$ (10); (Scan E) 442, 444, 446 $[M + Cl^-]$ (100). IR, ν, cm^{-1}:526, 540, 558, 572, 587, 608, 667, 781, 817, 952, 987, 1015, 1091, 1160, 1168, 1302, 1353, 1379, 1462, 1596. ^1H NMR,

$CDCl_3$, δ, ppm: 0.43 d (3H, CH_3, *J* 7.2 Hz), 1.85 d (3H, CH_3, *J* 6.6 Hz), 2.36 s (3H, CH_3), 2.58 s (3H, CH_3), 2.97 d. k (1H, H^3, *J* 1.7, *J* 6.6 Hz), 3.82 d.d (1H, H^2, *J* 1.7, *J* 7.9 Hz), 3.95 quintet (1H, $H^{1\prime}$, *J* 7.9 Hz), 6.87 d (1H, $H_{arom.}$, *J* 6.8 Hz), 7.05-7.11 m (2H, $H_{arom.}$), 7.17 d (2H, $H_{arom.}$, *J* 8.0 Hz), 7.37 d (2H, $H_{arom.}$, *J* 8.0 Hz). ^{13}C NMR, $CDCl_3$, δ, ppm: 20.07 (C^3CH_3), 20.66 (CH_3), 21.48 (CH_3), 22.88 ($C^{1\prime}CH_3$), 41.93 (C^3), 53.65 ($C^{1\prime}$)), 74.48 (C^2), 121.48, 126.29, 130.79 (C^4, C^5, C^6), 128.01 ($C^{3\prime\prime,5\prime\prime}$), 129.46 ($C^{2\prime\prime,6\prime\prime}$), 131.39 ($C^{1\prime\prime}$, C^5), 134.24, 139.69 (C^{7a}, C^{3a}), 144.24 ($C^{4\prime\prime}$). Found, %: C 55.72; H 5.30; Br 19.35; N 3.31; S 7.69. $C_{19}H_{22}BrNO_2S$. Calculated, %: C 55.88; H 5.43; Br 19.57; N 3.43; S 7.85.

4.22 | (2*R**,3*S**)-2-[(1*R**)-1-bromoethyl)-3,7-dimethyl-1-[(4-methylphenyl)sulfonyl] indoline (*cis*-4k)

Yield 0.18 g (11%), white powder, m. p. 156-159 °C (EtOH). MS, m/z (I_r, %): 408, 410 $[M + H]^+$ (100), 442, 444, 446 [M + Cl] (100). IR, ν, cm^{-1}:516, 538, 569, 590, 602, 634, 673, 706, 754, 790, 808, 845, 906, 923, 946, 991, 1006, 1065, 1090, 1164, 1185, 1258, 1290, 1352, 1377, 1462, 1598. ^1H NMR, $CDCl_3$, δ, ppm: 1.17 d (3H, CH_3, *J* 7.4 Hz), 1.47 d (3H, CH_3, *J* 6.8 Hz), 2.39 s (3H, CH_3), 2.58 s (3H, CH_3), 2.64 q (1H, H^3, *J* 7.4 Hz), 4.03-4.09 m (1H, $H^{1\prime}$), 4.60 d.d (1H, H^2, *J* 5.7, *J* 7.4 Hz), 6.76 d (1H, $H_{arom.}$, *J* 6.9 Hz), 7.07-7.12 m (2H, $H_{arom.}$), 7.16 d (2H, $H_{arom.}$, *J* 8.3 Hz), 7.45 d (2H, $H_{arom.}$, *J* 8.3 Hz). ^{13}C NMR, $CDCl_3$, δ, ppm: 12.76 (C^3CH_3), 19.68 (CH_3), 21.57 (CH_3), 23.39 ($C^{1\prime}CH_3$), 38.39 (C^3), 46.40 ($C^{1\prime}$), 73.36 (C^2), 120.13, 126.98, 130.51 (C^4, C^5, C^6), 127.65 ($C^{3\prime\prime,5\prime\prime}$), 129.37 ($C^{2\prime\prime,6\prime\prime}$), 132.12, 135.26, 140.71, 140.84 ($C^{1\prime\prime}$, C^7, C^{7a}, C^{3a}), 143.86 ($C^{4\prime\prime}$). Found, %: C 55.76; H 5.32; Br 19.41; N 3.27; S 7.75. $C_{19}H_{22}BrNO_2S$. Calculated, %: C 55.88; H 5.43; Br 19.57; N 3.43; S 7.85.

4.23 | (2*R**,3*R**)- and (2*R**,3*S**)-2-[(1*S**)-1-bromoethyl)-3,5-dimethyl-1-[(2-nitrophenyl)sulfonyl]indoline (*cis*-4l and *trans*-4l)

(2*R**,3*R**)- and (2*R**,3*S**)-2-[(1*S**)-1-bromoethyl)-3,5-dimethyl-1-[(2-nitrophenyl)sulfonyl]indoline (*cis*-**4l** and *trans*-**4l**) were obtained from 1.08 g (3 mmol) tosylate **3f**. Yield 1.3 g crude mixture of indolines *cis*-**4l** and *trans*-**4l** (2:3 ratio). Crystallization of this mixture from ethanol results in 0.36 g (27%) mixture of crystals *cis*-**4l** and *trans*-**4l** in 2:3 ratio. White amorphous powder. The compounds *cis*-**4l** and *trans*-**4l** could not be individualized.

4.24 | Biological tests

Compounds **4a-k** were assessed for their cytotoxic activity against human embryonic kidney 293 cells (HEK293), human neuroblastoma cell line (SH-SY5Y), hepatocellular carcinoma cell line (HepG2), and human T-cell lymphoblast-like line (Jurkat) using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.[25] HEK293, SH-SY5Y and HepG2 cells were maintained in DMEM (Biolot, Russia) supplemented with 2 mM L-glutamine (Biolot, Russia), 50 μg/ml gentamicin sulfate (Invitrogen, USA) and 10% fetal bovine serum (FBS, Invitrogen, USA). Jurkat cells were maintained in RPMI (Invitrogen, USA) supplemented with 1% L-glutamine, 50 μg/ml gentamicin sulfate and 10% FBS. All cells were cultured at 37°C and 5% CO_2. Cells were seeded on 96-well plates at a density of 2×10^4 cells/well for HEK293, 3×10^4 cells/well for SH-SY5Y, 2×10^4 cell/well for HepG2 and 1×10^5 cells/well for Jurkat cells. Studied compounds were previously dissolved in 100% DMSO (Sigma-Aldrich, UK) to 100 μM stock solutions and diluted in completed DMEM or RPMI immediately before adding them to the assay plates. After 24 hours of culturing cells were treated with compounds at final concentrations of 1, 10, 100 μM for 48 hours. A final concentration of DMSO in samples and controls on the plate was 0.1%. Cell viability was determined by conventional MTT assay according to manufacturer's instruction using «2300 EnSpire Multimode Plate Reader» (Perkin Elmer, USA) at 540 nm. The dose of the compound that inhibited 50% cell viability (IC_{50} value) was calculated using nonlinear regression analysis (GraphPad Prism v.5.02; GraphPad Software Inc., USA). The viability of control group was set at 100%, and viability of treated groups was determined through the comparison of its optical density with control. Data were expressed as mean ± SD calculated from three independent experiments, performed in triplicate. Differences between experimental groups were analyzed by one-way ANOVA followed by Dunnett's post hoc test.

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