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Synthesis and antiproliferative activity characterization of new imidazothiazolotriazine oxindolylidene derivatives containing various substituents in the oxindole ring

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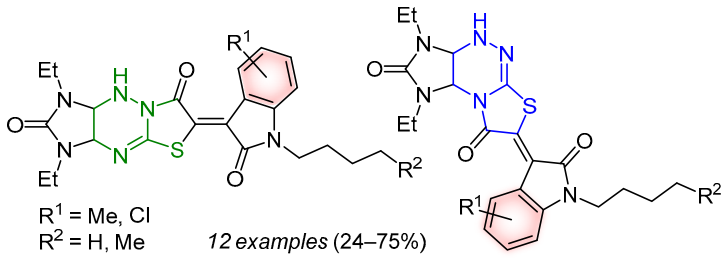


Condensation of 1,3-diethyltetrahydroimidazo[4,5-*e*]thiazolo[3,2-*b*][1,2,4]triazine-2,7-dione with isatins followed by framework rearrangement in the thiazolotriazine moiety was used to synthesize two new series of oxindolylidenetetrahydroimidazo[4,5-*e*]thiazolo-[3,2-*b*][1,2,4]triazine-2,7-diones and oxindolylidenetetrahydroimidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazine-2,8-diones containing various substituents in the oxindole moiety. The obtained compounds were tested for antiproliferative activity. The greatest activity was observed in the case of 1-alkyl-7-methyloxindolylidene derivatives of imidazo[4,5-*e*]thiazolo[2,3-*c*]triazine, which not only inhibited the growth of more than half of the studied cell lines, but also caused cell death in the SF-539 cell line (central nervous system cancer, mean growth percent –7.82%) and MDA-MB-435 (melanoma, –30.97 and –13.64%).

Keywords: imidazothiazolotriazines, isatins, antiproliferative activity, condensation, rearrangement.

Polyheteroatomic heterocyclic compounds are widely represented in medicinal chemistry and materials science.[1] Some 1,2,4-triazine derivatives containing fused rings of other heterocycles are used as antibiotics (toxoflavin, fervenulin, and reumycin),[2] effective antiviral drugs (triazavirin[3] and remdesivir[4]), and have been identified as bacterial pigments (nostocine, pseudoiodinin, and fluviols) that also show antitumor activity against certain cell lines.[5]

We have previously developed methods for the synthesis of oxindolylidene derivatives of imidazothiazolotriazines,[6] studied the influence of substituents in the imidazothiazolotriazine system and at the oxindole nitrogen atom on the biological activity and found compounds with pronounced antiproliferative effects in submicromolar and micromolar concentrations against a panel of 60 tumor cell lines (Fig. 1).[7]

Specific structure–activity relationships were established on the basis of our research: 1) 1,3-diethyl-substituted derivatives were more active than 1,3-dimethyl- or 1-alkyl-3-phenyl-substituted compounds; 2) imidazothiazolo[2,3-*c*]-triazine derivatives having an angular molecular structure had higher activity than the isomeric linear imidazothiazolo-[3,2-*b*]triazines; 3) the antiproliferative activity increased and then decreased with growing length of the alkyl chain at the oxindole ring nitrogen atom, with the highest activity observed in the case of *N*-butyl- and *N*-amyloxindolylidene derivatives. However, practically all of the studied compounds lacked other substituents in the oxindole part of the molecule.

The aim of the current work was to synthesize and study the antiproliferative activity of oxindolylidene derivatives of imidazothiazolotriazines bearing substituents in the benzene ring of the oxindole moiety (Fig. 1).

The starting isatins **1a–c** were synthesized according to the Sandmeyer method[8] from the corresponding anilines (Scheme 1). The *N*-butyl- and *N*-amylisatins **1d–i** containing substituents in the benzene ring were obtained by alkylation of isatins **1a–c** with butyl and amyl bromides according to a previously published procedure.[7c]

Isatins **1d–i** containing various substituents in the oxindole ring were combined with imidazothiazolotriazine **2** under the reaction conditions that we previously used for

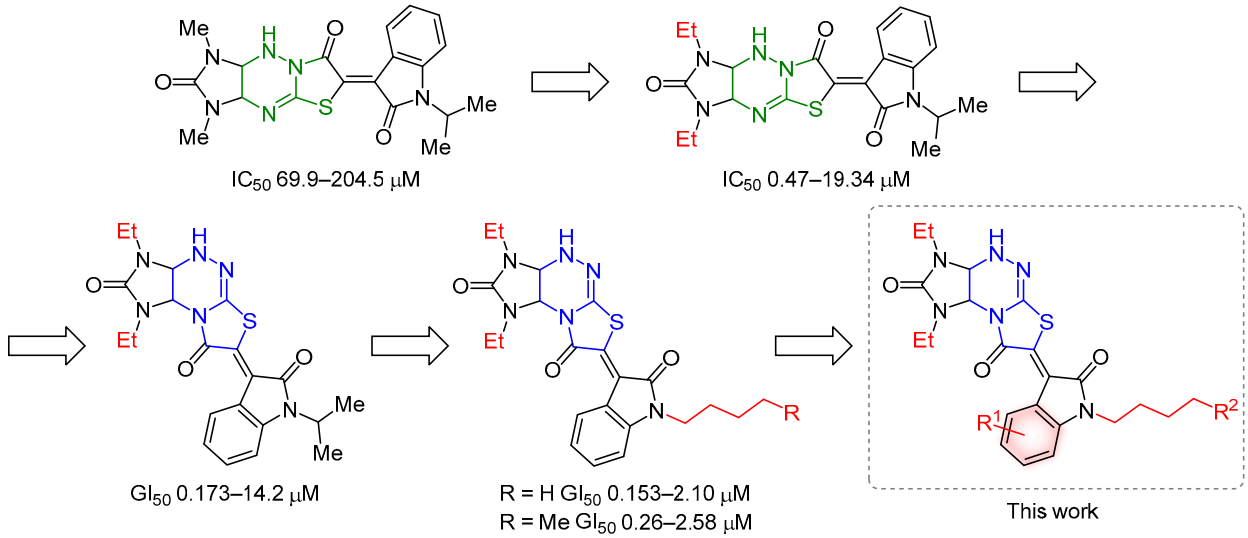
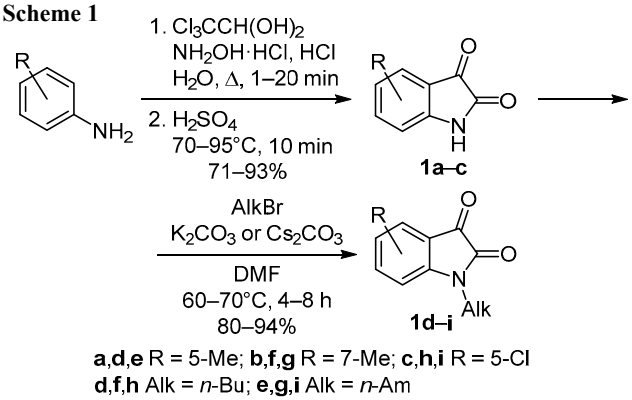


Figure 1. Structural optimization of imidazothiazolotriazine oxindolylidene derivatives showing antiproliferative activity (IC_{50}, GI_{50} – half-maximal inhibitory concentrations).

Scheme 1



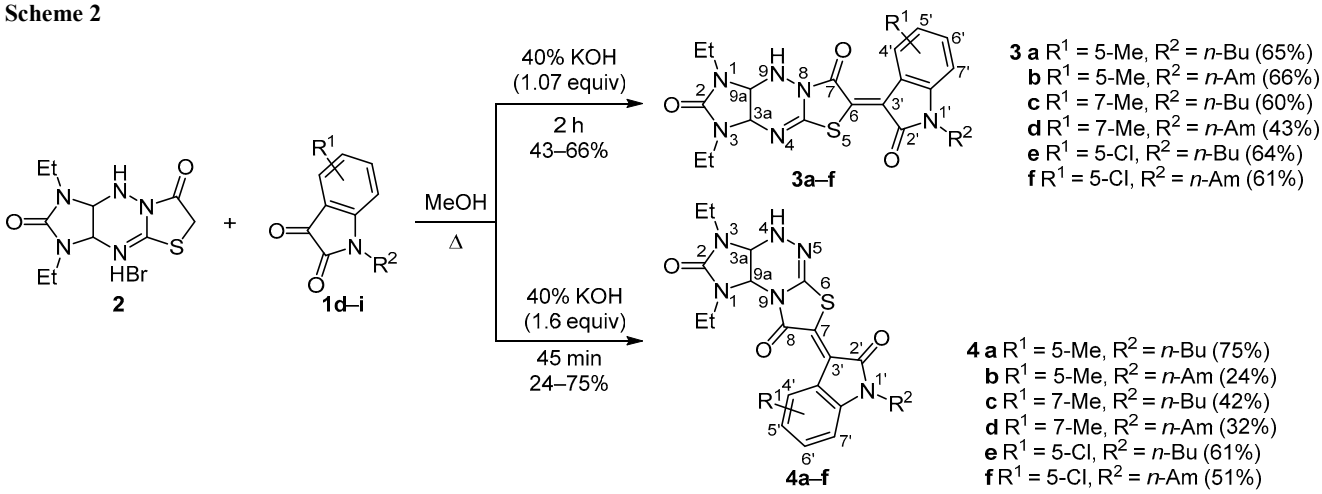
the preparation of isomeric imidazothiazolotriazine oxindolylidene derivatives **3a**–**f** and **4a**–**f** in the presence of various amounts of 40% aqueous KOH solution.[6b] The condensation of compound **2** with isatins **1d**–**i** in the presence of KOH (1.07 equiv) led to imidazo[4,5-*e*]-thiazolo[3,2-*b*][1,2,4]triazin-7-one oxindolylidene derivatives **3a**–**f** in 43–66% yields. Increasing the amount of alkali to 1.6 equiv resulted not only in condensation with isatins, but also rearrangement of the thiazolotriazine ring system, giving rise to the isomeric structures **4a**–**f** in 24–75% yields (Scheme 2).

The structures of isomers **3a**–**f** and **4a**–**f** were confirmed by IR, ^{1}H and ^{13}C NMR, and high-resolution mass spectral data. According to ^{1}H NMR data, the condensation proceeded diastereoselectively, producing exclusively *Z*-isomers **3a**–**f** and **4a**–**f**. The downfield shift of 4'-H proton signal to the range of 8.62–8.87 ppm relative to the other protons of indole moiety was explained by the deshielding effect of 7-C=O or 8-C=O carbonyl groups in the thiazolidinone system.[6,9]

The spectra of compounds **4a**–**f**, compared to the spectra of linear structures **3a**–**f**, showed characteristic downfield shifts of NH proton signal from 6.93–7.00 to 7.84–8.11 ppm and one of the bridging group CH protons from 4.98–5.01 to 5.74–5.76 ppm.

All synthesized compounds **3a**–**f** and **4a**–**f** were tested *in vitro* at 10 μM concentration against a panel of 60 cancer cell lines representing nine types of oncological diseases (leukemia, melanoma, cancers of the lungs, colon, central nervous system (CNS), ovaries, kidneys, prostate, and breast), obtained from the National Cancer Institute of the USA. Testing was performed using Sulforhodamine B,

Scheme 2



with results presented in Table 1. The growth range covers the lowest and highest growth percent detected among all tested cell lines.

Among compounds **3a**–**f**, only 1-butyl-7-methyl derivative **3c** exhibited moderate antiproliferative activity against two cell lines: K562 (leukemia, growth percent 46.11%) and MDA-MB-435 (melanoma, 35.37%). As expected, isomers **4a**–**f** were generally more potent inhibitors of tumor cell growth. While 1-alkyl-5-methyl derivatives **4a**,**b** were practically inactive against all 60 cell lines, 1-alkyl-5-chloro derivatives **4e**,**f** suppressed the growth of K562 (leukemia, 25.29 and 38.33%, respectively), SR (leukemia, 14.08 and 28.65%, respectively), and MDA-MB-435 cell lines (melanoma, 6.07 and 29.95%, respectively). The highest activity was observed in the case of 1-alkyl-7-methyl derivatives **4c**,**d** (Fig. 2) that not only inhibited the growth of more than half of the studied cell lines, but also partially destroyed the cells of SF-539 (CNS cancer, growth percent –7.82%, compound **4c**) and MDA-MB-435 cell lines (melanoma, –30.97 and –13.64%, compounds **4c**,**d**, respectively). However, compared to analogs **4g**,**h** lacking substituents in the benzene ring of the oxindole moiety,[7c]

Table 1. The antiproliferative activity of compounds **3a**–**f** and **4a**–**f** at 10 μM concentration

Compound	Mean growth, %	Growth range, %	The most sensitive cell line	Positive antiproliferative effect*
3a	88.98	50.96–110.72	HOP-92 (lung cancer)	0/60
3b	99.82	77.20–141.99	UACC-62 (melanoma)	0/60
3c	85.35	35.37–119.30	MDA-MB-435 (melanoma)	2/60
3d	95.92	71.51–115.35	UACC-62 (melanoma)	0/60
3e	102.97	73.40–145.27	UO-31 (renal cancer)	0/60
3f	99.75	71.33–122.12	SR (leukemia)	0/60
4a	90.88	58.14–117.38	CAKI-1 (renal cancer)	0/60
4b	94.79	60.94–129.77	LOX IMVI (melanoma)	0/60
4c	39.05	–30.97–117.38	MDA-MB-435 (melanoma)	42/60
4d	47.46	–13.64–97.09	MDA-MB-435 (melanoma)	34/60
4e	71.14	6.07–131.81	MDA-MB-435 (melanoma)	7/60
4f	85.87	28.65–132.69	SR (leukemia)	3/60

* The ratio between the number of cell lines with growth percent from 0 to 50 and the total number of cell lines.

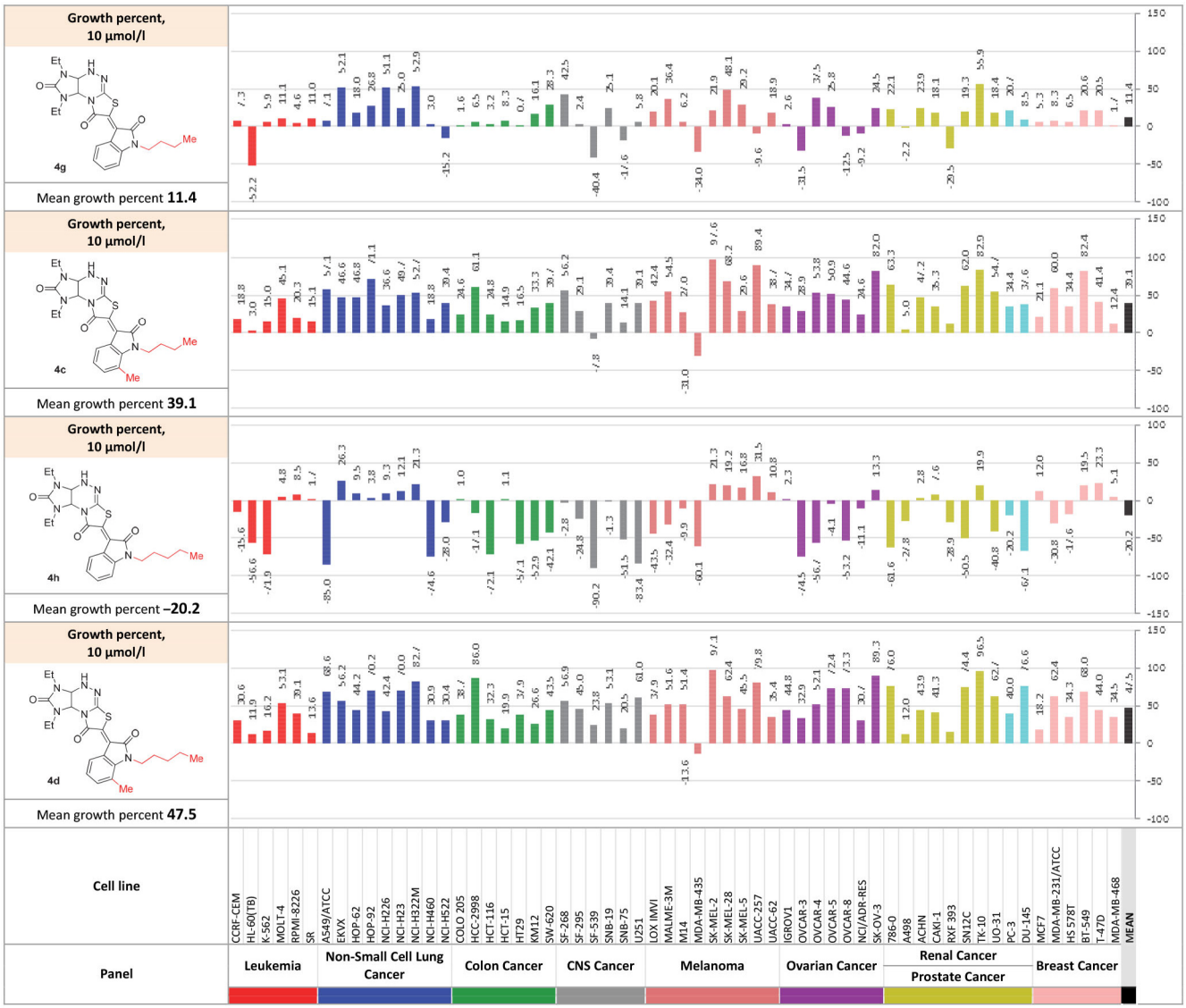


Figure 2. The percent growth diagrams for cells treated with compounds **4c**,**d**,**g**,**h**

all synthesized compounds **3a**–**f** and **4a**–**f** were found to be significantly less active (Fig. 2).

Thus, condensation reactions of 1,3-diethyltetrahydroimidazo[4,5-*e*]thiazolo[3,2-*b*][1,2,4]triazine-2,7-dione with isatins, followed by molecular framework rearrangement in the thiazolotriazine moiety allowed to obtain two new series of isomeric imidazothiazolotriazine oxindolylidene derivatives containing various substituents in the oxindole ring system. Two compounds exhibited antiproliferative activity against more than half of the tested cell lines and produced cytotoxic effects against SF-539 (CNS cancer) and MDA-MB-435 (melanoma) cell lines. However, the introduction of substituents at positions 5 or 7 of the oxindole moiety in oxindolylidenetetrahydroimidazo[4,5-*e*]-thiazolo[3,2-*b*][1,2,4]triazine-2,7-diones and oxindolylidene-tetrahydroimidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazine-2,8-diones resulted in reduced antiproliferative activity, up to its complete disappearance.

Experimental

IR spectra were recorded on a Bruker ALPHA spectrometer for samples in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired using Bruker AM 300 (300 and 75 MHz, respectively) and Bruker DRX-500 (500 and 125 MHz, respectively) spectrometers for samples in DMSO-d_6 solutions. The residual solvent signals (2.50 ppm for ^{1}H nuclei, 39.5 ppm for ^{13}C nuclei) were used as internal standards. High-resolution mass spectra were recorded on a Bruker micrOTOF II instrument, electrospray ionization in positive ion mode (capillary voltage 4500 V), mass scanning range 50–3000 Da, external or internal calibration (Electrospray Calibrant Solution, Fluka). The solutions in MeCN or MeOH were introduced by a syringe, flow rate 3 μl·min^{-1}, atomizing gas – nitrogen (4 l·min^{-1}), interface temperature 180°C. The melting points of compounds were determined on a Boetius micro hot stage.

Synthesis of isatins 1a–c (General method). Synthesis of isonitrosoacetanilides. Anhydrous Na_2SO_4 (114.66 g, 807 mmol) was added to a solution of chloral hydrate (17.86 g, 108 mmol) in H_2O (240 ml), and the mixture was stirred for 10 min. A solution of the appropriately substituted aniline (100 mmol) in a mixture of concd HCl (8.6 ml) and H_2O (60 ml) was added, followed by hydroxylamine hydrochloride (21.96 g, 316 mmol) solution in H_2O (100 ml). The obtained suspension was heated for 40 min to the boiling temperature, maintained at reflux for 1–2 min in the case of *o*- and *p*-toluidines or 20 min in the case of *p*-chloroaniline, then cooled. The obtained suspensions were filtered at 35–40°C, the products were washed on filter with H_2O and dried at 50°C.

2-(Hydroxyimino)-*N*-(*p*-tolyl)acetamide. Yield 15.75 g (88%), mp 154–156°C (mp 162°C[8a]).

2-(Hydroxyimino)-*N*-(*o*-tolyl)acetamide. Yield 15.25 g (86%), mp 116–119°C (mp 121°C[8a]).

***N*-(4-Chlorophenyl)-2-(hydroxyimino)acetamide**. Yield 19.44 g (98%), mp 171–174°C (mp 160°C[10]).

Cyclization of isonitrosoacetanilides. Dry isonitroso-aceto-*p*-toluidide or isonitrosoaceto-*o*-toluidide was gradually added to concd H_2SO_4 (60 ml) that was preheated to 50°C, while ensuring that the temperature did not exceed 70°C (90°C in the case of *N*-(4-chlorophenyl)-2-(hydroxyimino)-acetamide). The reaction mixture was heated to 80°C (95°C in the case of 4-chloroisonitrosoacetanilide) and maintained for 10 min. The reaction mixture was allowed to cool and then poured onto crushed ice (300 g), stirred, and left for 30 min. The precipitate of isatin was filtered off, washed with cold H_2O, and dried at 50°C.

5-Methyl-1*H*-indole-2,3-dione (1a). Yield 10.06 g (71%), dark-red solid, mp 152–156°C (mp 185–187°C[11]). IR spectrum, ν, cm^{-1}: 3287 (NH), 2922 (Alk C–H), 1746, 1718 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 2.25 (3H, s, CH_3); 6.80 (1H, d, *J* = 8.0, H-7); 7.31 (1H, s, H-4); 7.39 (1H, d, *J* = 8.0, H-6); 10.92 (1H, s, NH). ^{13}C NMR spectrum (75 MHz), δ, ppm: 20.0 (CH_3); 112.0 (C-7); 117.7 (C-3a); 124.7 (C-4); 132.0 (C-5); 138.7 (C-6); 148.5 (C-7a); 159.4 (2-C=O); 184.5 (3-C=O). Found, *m*/*z*: 162.0553 [M+H]$^+$. $C_9H_8NO_2$. Calculated, *m*/*z*: 162.0550.

7-Methyl-1*H*-indole-2,3-dione (1b). Yield 11.48 g (75%), brownish-orange solid, mp 169–174°C (mp 267–269°C[11]). IR spectrum, ν, cm^{-1}: 3295 (NH), 1736 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 2.18 (3H, s, CH_3); 6.98 (1H, t, *J* = 7.6, H-5); 7.33 (1H, d, *J* = 7.4, H-4); 7.42 (1H, d, *J* = 7.5, H-6); 11.07 (1H, s, NH). ^{13}C NMR spectrum (75 MHz), δ, ppm: 15.4 (CH_3); 117.5 (C-3a); 121.5 (C-7); 122.0, 122.5 (C-4,5); 139.4 (C-6); 149.2 (C-7a); 159.9 (2-C=O); 184.7 (3-C=O). Found, *m*/*z*: 162.0552 [M+H]$^+$. $C_9H_8NO_2$. Calculated, *m*/*z*: 162.0550.

5-Chloro-1*H*-indole-2,3-dione (1c). Yield 16.54 g (93%), orange solid, mp 171–175°C (mp 250°C[10]). IR spectrum, ν, cm^{-1}: 3436 (NH), 3095, 3069 (Ar C–H), 1746, 1705 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 6.92 (1H, d, *J* = 8.3, H-7); 7.54 (1H, d, *J* = 2.2, H-4); 7.61 (1H, dd, *J* = 8.3, *J* = 2.3, H-6); 11.14 (1H, s, NH). ^{13}C NMR spectrum (75 MHz), δ, ppm: 114.3 (C-7); 119.5 (C-3a); 124.6 (C-4); 127.3 (C-5); 137.8 (C-6); 149.8 (C-7a); 159.5 (2-C=O); 183.8 (3-C=O). Found, *m*/*z*: 181.9996 [M+H]$^+$. $C_8H_5ClNO_2$. Calculated, *m*/*z*: 182.0003.

Synthesis of alkylated isatins 1d–i (General method). Alkylation of isatins **1a–c** was performed in a flask equipped with a calcium chloride tube. A hot (40°C) solution of isatin **1a**,**c** (10 mmol) in DMF (5 ml) was treated with thoroughly ground anhydrous K_2CO_3 (2.07 g, 15 mmol) or Cs_2CO_3 (4.89 g, 15 mmol) in the case of isatin **1b**. The obtained suspension was stirred at 40°C for 1 h, then heated to 60°C (for isatins **1a**,**c**) or 70°C (for isatin **1b**). The appropriate alkyl bromide (15 mmol) was added, and stirring was continued at the same temperature for 4 h (for isatins **1d**,**e**) or 8 h (for isatins **1f**–**i**). The suspension was cooled to the room temperature and poured onto crushed ice (100 g), stirred and allowed to crystallize for 20 min. In the case if the oily material did not crystallize, the obtained mixture was frozen and thawed 1-2 times. The precipitates of isatins **1d**–**i** were filtered off at slurry temperature not higher than 5–10°C, washed with cold H_2O, and air-dried at room temperature or in dessicator until constant mass was achieved.

1-Butyl-5-methyl-1*H*-indole-2,3-dione (1d). Yield 1.97 g (91%), orange solid, mp 80–83°C (mp 174.2–176.4°C,[12] red liquid[13]). IR spectrum, ν, cm^{-1}: 3032 (Ar C–H), 2961, 2931, 2868 (Alk C–H), 1724 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.90 (3H, t, *J* = 7.2, CH_3); 1.26–1.39 (2H, m, CH_2); 1.53–1.62 (2H, m, CH_2); 2.28 (3H, s,

5-CH_3); 3.63 (2H, t, *J* = 7.0, NCH_2); 7.08 (1H, d, *J* = 8.0, H-7); 7.36 (1H, s, H-4); 7.47 (1H, d, *J* = 8.0, H-6). ^{13}C NMR spectrum (75 MHz), δ, ppm: 13.6 (CH_3); 19.5, 20.0 (CH_2, 5-CH_3); 28.9 (CH_2); 39.2 (NCH_2); 110.6 (C-7); 117.4 (C-3a); 124.7 (C-4); 132.5 (C-5); 138.5 (C-6); 148.6 (C-7a); 158.1 (2-C=O); 183.8 (3-C=O). Found, *m*/*z*: 218.1173 $[M+H]^+$. $C_{13}H_{16}NO_2$. Calculated, *m*/*z*: 218.1176.

5-Methyl-1-pentyl-1*H*-indole-2,3-dione (1e). Yield 1.91 g (83%), dark-orange solid, mp 70–72°C (red liquid[13]). IR spectrum, ν, cm^{-1}: 2951, 2926, 2863 (Alk C–H), 1727 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.85 (3H, t, *J* = 6.5, CH_3); 1.29–1.31 (4H, m, $2CH_2$); 1.56–1.61 (2H, m, CH_2); 2.28 (3H, s, 5-CH_3); 3.62 (2H, t, *J* = 7.1, NCH_2); 7.07 (1H, d, *J* = 8.0, H-7); 7.36 (1H, s, H-4); 7.47 (1H, d, *J* = 8.1, H-6). ^{13}C NMR spectrum (75 MHz), δ, ppm: 13.8 (CH_3), 20.0, 21.7, 26.4, 28.3 ($3CH_2$, 5-CH_3); 39.4 (NCH_2); 110.5 (C-7); 117.3 (C-3a); 124.6 (C-4); 132.4 (C-5); 138.5 (C-6); 148.6 (C-7a); 158.0 (2-C=O); 183.7 (3-C=O). Found, *m*/*z*: 232.1335 $[M+H]^+$. $C_{14}H_{18}NO_2$. Calculated, *m*/*z*: 232.1332.

1-Butyl-7-methyl-1*H*-indole-2,3-dione (1f). Yield 2.01 g (93%), dark-orange solid, mp 57–60°C (mp 63.8–64.3°C[14]). IR spectrum, ν, cm^{-1}: 2957, 2871 (Alk C–H), 1732 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.92 (3H, t, *J* = 7.3, CH_3); 1.31–1.39 (2H, m, CH_2); 1.54–1.62 (2H, m, CH_2); 2.48 (3H, s, 7-CH_3); 3.82 (2H, t, *J* = 7.5, NCH_2); 7.04 (1H, t, *J* = 7.5, H-5); 7.40 (1H, d, *J* = 7.3, H-4); 7.45 (1H, d, *J* = 7.7, H-6). ^{13}C NMR spectrum (75 MHz), δ, ppm: 13.5 (CH_3); 18.1, 19.4 (CH_2, 7-CH_3); 31.0 (CH_2); 41.0 (NCH_2); 118.6, 121.5 (C-3a,7); 122.6, 123.3 (C-4,5); 142.1 (C-6); 148.2 (C-7a); 159.0 (2-C=O); 183.8 (3-C=O). Found, *m*/*z*: 218.1180 $[M+H]^+$. $C_{13}H_{16}NO_2$. Calculated, *m*/*z*: 218.1176.

7-Methyl-1-pentyl-1*H*-indole-2,3-dione (1g). Yield 2.12 g (92%), dark-red solid, mp 60–62°C (mp 63–64°C[15]). IR spectrum, ν, cm^{-1}: 3073, 3027 (Ar C–H), 2954, 2930, 2865 (Alk C–H), 1732 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.87 (3H, t, *J* = 6.6, CH_3); 1.29–1.34 (4H, m, $2CH_2$); 1.58–1.63 (2H, m, CH_2); 2.47 (3H, s, 7-CH_3); 3.81 (2H, t, *J* = 7.6, NCH_2); 7.04 (1H, t, *J* = 7.5, H-5); 7.40 (1H, d, *J* = 7.2, H-4); 7.46 (1H, d, *J* = 7.6, H-6). ^{13}C NMR spectrum (75 MHz), δ, ppm: 13.8 (CH_3); 18.1, 21.7, 28.3, 28.6 (3-CH_2, 7-CH_3); 41.2 (NCH_2); 118.6, 121.4 (C-3a,7); 122.6, 123.3 (C-4,5); 142.1 (C-6); 148.2 (C-7a); 159.0 (2-C=O); 183.8 (3-C=O). Found, *m*/*z*: 232.1326 $[M+H]^+$. $C_{14}H_{18}NO_2$. Calculated, *m*/*z*: 232.1332.

1-Butyl-5-chloro-1*H*-indole-2,3-dione (1h). Yield 1.90 g (80%), dark-orange solid, mp 73–76°C. IR spectrum, ν, cm^{-1}: 3087, 3047 (Ar C–H), 2959, 2933, 2873 (Alk C–H), 1734 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.90 (3H, t, *J* = 7.3, CH_3); 1.28–1.40 (2H, m, CH_2); 1.52–1.62 (2H, m, CH_2); 3.65 (2H, t, *J* = 7.1, NCH_2); 7.22 (1H, d, *J* = 8.4, H-7); 7.58 (1H, d, *J* = 2.1, H-4); 7.69 (1H, dd, *J* = 8.5, *J* = 2.2, H-6). ^{13}C NMR spectrum (75 MHz), δ, ppm: 13.5 (CH_3); 19.4, 28.8 ($2CH_2$); 39.3 (NCH_2); 112.4 (C-7); 118.8 (C-3a); 123.9 (C-4); 127.3 (C-5); 136.9 (C-6); 149.2 (C-7a); 157.8 (2-C=O); 182.4 (3-C=O). Found, *m*/*z*: 238.0632 $[M+H]^+$. $C_{12}H_{13}ClNO_2$. Calculated, *m*/*z*: 238.0629.

5-Chloro-1-pentyl-1*H*-indole-2,3-dione (1i). Yield 2.36 g (94%), dark-red solid, mp 69–73°C. IR spectrum, ν, cm^{-1}: 3090, 3054 (Ar C–H), 2955, 2929, 2859 (Alk C–H), 1748, 1727 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.85 (3H, t, *J* = 6.4, CH_3); 1.29–1.32 (4H, m, $2CH_2$); 1.56–1.60 (2H, m, CH_2); 3.64 (2H, t, *J* = 6.9, NCH_2); 7.21 (1H, d, *J* = 8.4, H-7); 7.58 (1H, d, *J* = 2.1, H-4); 7.69 (1H, dd, *J* = 8.4, *J* = 2.2, H-6). ^{13}C NMR spectrum (75 MHz), δ, ppm: 14.3 (CH_3); 22.3, 26.8; 28.8 ($3CH_2$); 40.1 (NCH_2); 112.9 (C-7); 119.3 (C-3a); 124.4 (C-4); 127.8 (C-5); 137.5 (C-6); 149.7 (C-7a); 158.3 (2-C=O); 182.9 (3-C=O). Found, *m*/*z*: 252.0791 $[M+H]^+$. $C_{13}H_{15}ClNO_2$. Calculated, *m*/*z*: 252.0786.

Synthesis of imidazo[4,5-*e*]thiazolo[3,2-*b*][1,2,4]triazine oxoindolinylidene derivatives 3a–f (General method) was performed according to a published procedure.[6b] A suspension of imidazothiazolotriazine hydrobromide **2** (0.350 g, 1 mmol) and the appropriate isatin **1d–i** (1 mmol) in MeOH (7.5 ml) was treated by dropwise addition of 40% aqueous KOH solution (0.107 ml, 1.07 mmol). The reaction mixture was stirred and heated at reflux for 2 h, then cooled and filtered. The collected precipitates were washed on filter with MeOH and dried at 50°C.

(*Z*)-6-(1-Butyl-5-methyl-2-oxoindolin-3-ylidene)-1,3-diethyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*]thiazolo[3,2-*b*]-[1,2,4]triazine-2,7(1*H*,6*H*)-dione (3a). Yield 304 mg (65%), orange solid, mp 230–233°C. IR spectrum, ν, cm^{-1}: 3434, 3211 (NH), 2966, 2936, 2871 (Alk C–H), 1689, 1640 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.89 (3H, t, *J* = 7.3, CH_3); 0.98 (3H, t, *J* = 7.0, CH_3); 1.16 (3H, t, *J* = 7.2, CH_3); 1.25–1.32 (2H, m, CH_2); 1.54–1.63 (2H, m, CH_2); 2.33 (3H, s, 5'-CH_3); 3.10–3.19 (3H, m, NCH_2); 3.30–3.40 (1H, m, NCH_2); 3.75 (2H, t, *J* = 6.9, 1'-NCH_2); 4.94 (1H, d, *J* = 7.5, 9a-CH); 4.98 (1H, d, *J* = 6.0, 3a-CH); 6.96 (1H, s, NH); 7.06 (1H, d, *J* = 8.0, H-7'); 7.27 (1H, d, *J* = 7.9, H-6'); 8.69 (1H, s, H-4'). ^{13}C NMR spectrum (75 MHz), δ, ppm: 12.7, 13.4, 13.5 ($3CH_3$); 19.4, 20.8 (5'-CH_3, CH_2); 29.0 (CH_2); 34.4, 35.0 ($2NCH_2$); 39.4 (1'-NCH_2); 63.1, 64.2 (C-3a,9a); 108.9 (C-7'); 119.4 (C-3a'); 124.9 (C-3'); 128.0 (C-4'); 129.3 (C-6); 131.1, 132.0 (C-5',6'); 141.3 (C-7a'); 150.0 (4a-C=N); 157.6 (2-C=O); 160.3 (7-C=O); 166.8 (2'-C=O). Found, *m*/*z*: 469.2008 $[M+H]^+$. $C_{23}H_{29}N_6O_3S$. Calculated, *m*/*z*: 469.2016.

(*Z*)-1,3-Diethyl-6-(5-methyl-2-oxo-1-pentylindolin-3-ylidene)-3,3a,9,9a-tetrahydroimidazo[4,5-*e*]thiazolo[3,2-*b*]-[1,2,4]triazine-2,7(1*H*,6*H*)-dione (3b). Yield 318 mg (66%), orange solid, mp 230–232°C. IR spectrum, ν, cm^{-1}: 3432, 3219 (NH), 2972, 2934, 2873 (Alk C–H), 1691, 1640 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.83 (3H, t, *J* = 6.8, CH_3); 0.97 (3H, t, *J* = 7.0, CH_3); 1.16 (3H, t, *J* = 7.2, CH_3); 1.26–1.33 (4H, m, $2CH_2$); 1.57–1.62 (2H, m, CH_2); 2.33 (3H, s, 5'-CH_3); 3.09–3.21 (3H, m, NCH_2); 3.34–3.40 (1H, m, NCH_2); 3.74 (2H, t, *J* = 7.0, 1'-NCH_2); 4.94 (1H, d, *J* = 6.0, 9a-CH); 4.98 (1H, d, *J* = 5.9, 3a-CH); 6.96 (1H, s, NH); 7.06 (1H, d, *J* = 8.1, H-7'); 7.27 (1H, d, *J* = 8.0, H-6'); 8.69 (1H, s, H-4'). ^{13}C NMR spectrum (75 MHz), δ, ppm: 12.6, 13.4, 13.7 ($3CH_3$); 20.8, 21.6 (5'-CH_3, CH_2); 26.6, 28.3 ($2CH_2$); 34.4, 35.0 ($2NCH_2$); 39.5 (1'-NCH_2); 63.2, 64.2 (C-3a,9a); 108.8 (C-7'); 119.4 (C-3a'); 124.7 (C-3'); 128.0 (C-4'); 129.3 (C-6); 131.1, 132.0 (C-5',6'); 141.2 (C-7a'); 149.9 (4a-C=N); 157.6 (2-C=O); 160.3 (7-C=O); 166.8 (2'-C=O). Found, *m*/*z*: 483.2162 $[M+H]^+$. $C_{24}H_{31}N_6O_3S$. Calculated, *m*/*z*: 483.2173.

(*Z*)-6-(1-Butyl-7-methyl-2-oxoindolin-3-ylidene)-1,3-diethyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*]thiazolo[3,2-*b*]-[1,2,4]triazine-2,7(1*H*,6*H*)-dione (3c). Yield 280 mg (60%), bright-orange solid, mp 219–222°C. IR spectrum, ν, cm^{-1}: 3229 (NH), 2964, 2931, 2870 (Alk C–H), 1692, 1640 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.90 (3H, t, *J* = 7.3, CH_3); 0.97 (3H, t, *J* = 7.0, CH_3); 1.16 (3H, t, *J* = 7.2, CH_3); 1.25–1.37 (2H, m, CH_2); 1.51–1.61 (2H, m, CH_2); 2.50 (3H, s, 7'-CH_3); 3.10–3.21 (3H, m, NCH_2); 3.33–3.40 (1H, m, NCH_2); 3.94 (2H, t, *J* = 7.3, 1'-NCH_2); 4.94 (1H, d, *J* = 6.0, 9a-CH); 4.98 (1H, d, *J* = 5.9, 3a-CH); 6.93 (1H, s, NH); 7.01 (1H, t, *J* = 7.8, H-5'); 7.21 (1H, d, *J* = 7.6, H-6'); 8.82 (1H, d, *J* = 7.8, H-4'). ^{13}C NMR spectrum (75 MHz), δ, ppm: 12.7, 13.4, 13.5 ($3CH_3$); 18.4, 19.4 (7'-CH_3, CH_2); 31.3 (CH_2); 34.4, 35.1 ($2NCH_2$); 41.4 (1'-NCH_2); 63.1, 64.3 (C-3a,9a); 119.5 (C-7'); 120.3 (C-3a'); 122.2 (C-5'); 124.3 (C-3'); 125.6 (C-4'); 129.6 (C-6); 135.7 (C-6'); 140.9 (C-7a'); 150.0 (4a-C=N); 157.7 (2-C=O); 160.2 (7-C=O); 167.8 (2'-C=O). Found, *m*/*z*: 469.2010 $[M+H]^+$. $C_{23}H_{29}N_6O_3S$. Calculated, *m*/*z*: 469.2016.

(*Z*)-1,3-Diethyl-6-(7-methyl-2-oxo-1-pentylindolin-3-ylidene)-3,3a,9,9a-tetrahydroimidazo[4,5-*e*]thiazolo[3,2-*b*]-[1,2,4]triazine-2,7(1*H*,6*H*)-dione (3d). Yield 207 mg (43%), orange solid, mp 206–208°C. IR spectrum, ν, cm^{-1}: 3398, 3234 (NH), 2974, 2933, 2873 (Alk C–H), 1698, 1678, 1641 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.85 (3H, t, *J* = 6.6, CH_3); 0.96 (3H, t, *J* = 7.1, CH_3); 1.15 (3H, t, *J* = 7.1, CH_3); 1.26–1.31 (4H, m, $2CH_2$); 1.54–1.60 (2H, m, CH_2); 2.50 (3H, s, 7'-CH_3); 3.06–3.18 (3H, m, NCH_2); 3.33–3.40 (1H, m, NCH_2); 3.93 (2H, t, *J* = 7.3, 1'-NCH_2); 4.92–4.99 (2H, m, 3a,9a-CH); 6.97–7.04 (2H, m, NH, H-5'); 7.21 (1H, d, *J* = 7.6, H-6'); 8.81 (1H, d, *J* = 7.8, H-4'). ^{13}C NMR spectrum (75 MHz), δ, ppm: 12.7, 13.4, 13.8 ($3CH_3$); 18.4 (7'-CH_3); 21.7, 28.3, 28.9 ($3CH_2$); 34.4, 35.1 ($2NCH_2$); 41.6 (1'-NCH_2); 63.0, 64.3 (C-3a,9a); 119.6 (C-7'); 120.3 (C-3a'); 122.3 (C-5'); 124.3 (C-3'); 125.7 (C-4'); 129.7 (C-6); 135.7 (C-6'); 141.0 (C-7a'); 150.1 (4a-C=N); 157.7 (2-C=O); 160.3 (7-C=O); 167.8 (2'-C=O). Found, *m*/*z*: 483.2170 $[M+H]^+$. $C_{24}H_{31}N_6O_3S$. Calculated, *m*/*z*: 483.2173.

(*Z*)-6-(1-Butyl-5-chloro-2-oxoindolin-3-ylidene)-1,3-diethyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*]thiazolo[3,2-*b*]-[1,2,4]triazine-2,7(1*H*,6*H*)-dione (3e). Yield 312 mg (64%), light-orange solid, mp 236–237°C. IR spectrum, ν, cm^{-1}: 3435, 3224 (NH), 2964, 2933, 2895, 2874 (Alk C–H), 1703, 1644 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.88 (3H, t, *J* = 7.3, CH_3); 0.97 (3H, t, *J* = 7.0, CH_3); 1.15 (3H, t, *J* = 7.1, CH_3); 1.21–1.31 (2H, m, CH_2); 1.53–1.60 (2H, m, CH_2); 3.09–3.18 (3H, m, NCH_2); 3.27–3.37 (1H, m, NCH_2); 3.77 (2H, t, *J* = 7.0, 1'-NCH_2); 4.93 (1H, d, *J* = 6.1, 9a-CH); 4.99 (1H, d, *J* = 5.7, 3a-CH); 6.99 (1H, s, NH); 7.22 (1H, d, *J* = 8.5, H-7'); 7.51 (1H, d, *J* = 8.6, H-6'); 8.87 (1H, s, H-4'). ^{13}C NMR spectrum (75 MHz), δ, ppm: 13.2, 13.9, 14.0 ($3CH_3$); 19.2, 29.5 ($2CH_3$); 35.0, 35.6 ($2NCH_2$); 40.2 (1'-NCH_2); 63.7, 64.6 (C-3a,9a); 111.3 (C-7'); 121.2 (C-3a'); 123.9 (C-3'); 126.8, 127.4, 131.4, 132.5 (C-4',5',6,6'); 142.6 (C-7a'); 149.8 (4a-C=N); 158.2 (2-C=O); 161.2 (7-C=O); 167.2 (2'-C=O). Found, *m*/*z*: 489.1479 $[M+H]^+$. $C_{22}H_{26}ClN_6O_3S$. Calculated, *m*/*z*: 489.1470.

(*Z*)-6-(5-Chloro-2-oxo-1-pentylindolin-3-ylidene)-1,3-diethyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*]thiazolo[3,2-*b*]-[1,2,4]triazine-2,7(1*H*,6*H*)-dione (3f). Yield 306 mg (61%), light-orange solid, mp 233–236°C. IR spectrum, ν, cm^{-1}: 3435, 3223 (NH), 2975, 2934, 2873 (Alk C–H), 1697, 1642 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.84 (3H, t, *J* = 7.0, CH_3); 0.98 (3H, t, *J* = 7.1, CH_3); 1.16 (3H, t, *J* = 7.2, CH_3); 1.26–1.33 (4H, m, $2CH_2$); 1.55–1.64 (2H, m, CH_2); 3.10–3.19 (3H, m, NCH_2); 3.31–3.41 (1H, m, NCH_2); 3.77 (2H, t, *J* = 7.0, 1'-NCH_2); 4.95 (1H, d, *J* = 6.0, 9a-CH); 5.01 (1H, d, *J* = 5.9, 3a-CH); 7.00 (1H, s, NH); 7.21 (1H, d, *J* = 8.6, H-7'); 7.50 (1H, d, *J* = 8.5, H-6'); 8.87 (1H, s, H-4'). ^{13}C NMR spectrum (75 MHz), δ, ppm: 12.7, 13.5, 13.8 ($3CH_3$); 21.8, 26.6, 28.4 ($3CH_2$); 34.5, 35.1 ($2NCH_2$); 39.9 (1'-NCH_2); 63.3, 64.2 (C-3a,9a); 110.7 (C-7'); 120.7 (C-3a'); 123.7 (C-3'); 126.4, 126.9; 131.0, 132.0 (C-4',5',6,6'); 142.1 (C-7a'); 149.8 (4a-C=N); 157.8 (2-C=O); 160.4 (7-C=O); 166.70 (2'-C=O). Found, *m*/*z*: 503.1620 $[M+H]^+$. $C_{23}H_{28}ClN_6O_3S$. Calculated, *m*/*z*: 503.1627.

Synthesis of imidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazine oxoindolinylidene derivatives 4a–f (General method) was performed according to a published procedure.[6b] A suspension of imidazothiazolotriazine hydrobromide **2** (0.350 g, 1 mmol) and the appropriate isatin **1d–i** (1 mmol) in MeOH (7.5 ml) was heated at reflux and treated by dropwise addition of 40% aqueous KOH solution (0.160 ml, 1.6 mmol). The reaction mixture was further stirred and heated at reflux for 45 min, then cooled and filtered. The precipitate was washed on filter with MeOH and dried at 50°C.

(*Z*)-7-(1-Butyl-5-methyl-2-oxoindolin-3-ylidene)-1,3-diethyl-1,3a,4,9a-tetrahydroimidazo[4,5-*e*]thiazolo[2,3-*c*]-[1,2,4]triazine-2,8(3*H*,7*H*)-dione (4a). Yield 351 mg (75%), orange solid, mp 251–254°C. IR spectrum, ν, cm^{-1}: 3299, 3257 (NH), 2967, 2934, 2871 (Alk C–H), 1719, 1682 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.88 (3H, t, *J* = 7.3, CH_3); 1.04 (3H, t, *J* = 7.1, CH_3); 1.12 (3H, t, *J* = 7.0, CH_3); 1.24–1.31 (2H, m, CH_2); 1.53–1.61 (2H, m, CH_2); 2.33 (3H, s, 5'-CH_3); 3.04–3.11 (1H, m, NCH_2); 3.24–3.32 (2H, m, NCH_2); 3.46–3.53 (1H, m, NCH_2); 3.76 (2H, t, *J* = 6.9, 1'-NCH_2); 4.90 (1H, d, *J* = 5.6, 3a-CH); 5.75 (1H, d, *J* = 5.7, 9a-CH); 7.05 (1H, d, *J* = 8.0, H-7'); 7.23 (1H, d, *J* = 8.0, H-6'); 8.01 (1H, s, NH); 8.62 (1H, s, H-4'). ^{13}C NMR spectrum (125 MHz), δ, ppm: 12.8, 13.2, 13.6 ($3CH_3$); 19.6, 21.1 (5'-CH_3, CH_2); 29.2 (CH_2); 35.0, 38.1 ($2NCH_2$); 39.4 (1'-NCH_2); 61.8, 63.7 (C-3a,9a); 108.8 (C-7'); 119.7 (C-3a'); 122.4 (C-3'); 127.7 (C-4'); 130.9, 131.3, 132.5 (C-5',6',7); 136.7 (5a-C=N); 140.7 (C-7a'); 158.1 (2-C=O); 164.0 (8-C=O); 167.0 (2'-C=O). Found, *m*/*z*: 469.2005 $[M+H]^+$. $C_{23}H_{29}N_6O_3S$. Calculated, *m*/*z*: 469.2016.

(*Z*)-1,3-Diethyl-7-(5-methyl-2-oxo-1-pentylindolin-3-ylidene)-1,3a,4,9a-tetrahydroimidazo[4,5-*e*]thiazolo[2,3-*c*]-[1,2,4]triazine-2,8(3*H*,7*H*)-dione (4b). Yield 115 mg (24%), orange solid, mp 238–241°C. IR spectrum, ν, cm^{-1}: 3283 (NH), 2961, 2930, 2868 (Alk C–H), 1719, 1683 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.83 (3H, t, *J* = 6.8, CH_3); 1.04 (3H, t, *J* = 7.1, CH_3); 1.12 (3H, t, *J* = 7.0, CH_3); 1.23–1.31 (4H, m, $2CH_2$); 1.58–1.62 (2H, m, CH_2); 2.33 (3H, s, 5'-CH_3); 3.06–3.11 (1H, m, NCH_2); 3.24–3.29 (2H, m, NCH_2); 3.46–3.51 (1H, m, NCH_2); 3.76 (2H, t, *J* = 7.0, 1'-NCH_2); 4.90 (1H, d, *J* = 6.0, 3a-CH); 5.75 (1H, d, *J* = 5.8, 9a-CH); 7.05 (1H, d, *J* = 8.0, H-7');

7.23 (1H, d, *J* = 8.0, H-6'); 8.01 (1H, s, NH); 8.62 (1H, s, H-4'). ^{13}C NMR spectrum (75 MHz), δ, ppm: 12.7, 13.1, 13.8 ($3CH_3$); 21.0, 21.7 (5'-CH_3, CH_2); 26.7, 28.3 ($2CH_2$); 34.9, 38.0 ($2NCH_2$); 39.5 (1'-NCH_2); 61.7, 63.6 (C-3a,9a); 108.7 (C-7'); 119.6 (C-3a'); 122.3 (C-3'); 127.6 (C-4'); 130.8, 131.2, 132.5 (C-5',6',7); 136.6 (5a-C=N); 140.6 (C-7a'); 158.0 (2-C=O); 163.9 (8-C=O); 166.9 (2'-C=O). Found, *m*/*z*: 483.2171 $[M+H]^+$. $C_{24}H_{31}N_6O_3S$. Calculated, *m*/*z*: 483.2173.

(*Z*)-7-(1-Butyl-7-methyl-2-oxoindolin-3-ylidene)-1,3-diethyl-1,3a,4,9a-tetrahydroimidazo[4,5-*e*]thiazolo[2,3-*c*]-[1,2,4]triazine-2,8(3*H*,7*H*)-dione (4c). Yield 197 mg (42%), orange solid, mp 233–237°C. IR spectrum, ν, cm^{-1}: 3427, 3293 (NH), 2968, 2933, 2872 (Alk C–H), 1719, 1679 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.92 (3H, t, *J* = 7.1, CH_3); 1.07 (3H, t, *J* = 7.0, CH_3); 1.14 (3H, t, *J* = 6.7, CH_3); 1.31–1.38 (2H, m, CH_2); 1.59–1.63 (2H, m, CH_2); 2.52 (3H, s, 7'-CH_3); 3.13–3.15 (1H, m, NCH_2); 3.25–3.36 (2H, m, NCH_2); 3.49–3.56 (1H, m, NCH_2); 3.99 (2H, t, *J* = 6.9, 1'-NCH_2); 4.92 (1H, d, *J* = 5.0, 3a-CH); 5.74 (1H, d, *J* = 5.6, 9a-CH); 7.01 (1H, t, *J* = 7.6, H-5'); 7.17 (1H, d, *J* = 7.4, H-6'); 7.84 (1H, s, NH); 8.77 (1H, d, *J* = 7.6, H-4'). ^{13}C NMR spectrum (75 MHz), δ, ppm: 12.7, 13.0, 13.5 ($3CH_3$); 18.5, 19.4 (7'-CH_3, CH_2); 31.4 (CH_2); 34.9, 38.0 ($2NCH_2$); 41.4 (1'-NCH_2); 61.7, 63.5 (C-3a,9a); 119.4 (C-7'); 120.6, 121.9 (C-3',3a'); 122.1 (C-5'); 125.2 (C-4'); 132.8 (C-7); 134.8 (C-6'); 136.6 (5a-C=N); 140.45 (C-7a'); 158.0 (2-C=O); 163.9 (8-C=O); 167.9 (2'-C=O). Found, *m*/*z*: 469.2004 $[M+H]^+$. $C_{23}H_{29}N_6O_3S$. Calculated, *m*/*z*: 469.2016.

(*Z*)-1,3-Diethyl-7-(7-methyl-2-oxo-1-pentylindolin-3-ylidene)-1,3a,4,9a-tetrahydroimidazo[4,5-*e*]thiazolo[2,3-*c*]-[1,2,4]triazine-2,8(3*H*,7*H*)-dione (4d). Yield 154 mg (32%), orange solid, mp 234–236°C. IR spectrum, ν, cm^{-1}: 3266 (NH), 2962, 2931, 2870 (Alk C–H), 1718, 1680 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.86 (3H, t, *J* = 6.7, CH_3); 1.04 (3H, t, *J* = 7.2, CH_3); 1.12 (3H, t, *J* = 6.9, CH_3); 1.30–1.31 (4H, m, $2CH_2$); 1.57–1.61 (2H, m, CH_2); 2.52 (3H, s, 7'-CH_3); 3.04–3.13 (1H, m, NCH_2); 3.24–3.28 (2H, m, NCH_2); 3.46–3.53 (1H, m, NCH_2); 3.97 (2H, t, *J* = 7.5, 1'-NCH_2); 4.89 (1H, d, *J* = 4.9, 3a-CH); 5.74 (1H, d, *J* = 5.8, 9a-CH); 7.03 (1H, t, *J* = 7.8, H-5'); 7.19 (1H, d, *J* = 7.5, H-6'); 8.01 (1H, s, NH); 8.78 (1H, d, *J* = 7.8, H-4'). ^{13}C NMR spectrum (125 MHz), δ, ppm: 13.3, 13.6, 14.3 ($3CH_3$); 19.0, 22.2 (7'-CH_3, CH_2); 28.8, 29.5 ($2CH_2$); 35.4, 38.5 ($2NCH_2$); 42.1 (1'-NCH_2); 62.2, 64.0 (C-3a,9a); 119.9 (C-7'); 121.1, 122.4, 122.6 (C-3',3a',5'); 125.8 (C-4'); 133.3 (C-7); 135.3 (C-6'); 137.1 (5a-C=N); 140.8 (C-7a'); 158.5 (2-C=O); 164.4 (8-C=O); 168.3 (2'-C=O). Found, *m*/*z*: 483.2180 $[M+H]^+$. $C_{24}H_{31}N_6O_3S$. Calculated, *m*/*z*: 483.2173.

(*Z*)-7-(1-Butyl-5-chloro-2-oxoindolin-3-ylidene)-1,3-diethyl-1,3a,4,9a-tetrahydroimidazo[4,5-*e*]thiazolo[2,3-*c*]-[1,2,4]triazine-2,8(3*H*,7*H*)-dione (4e). Yield 297 mg (61%), orange solid, mp 235–239°C. IR spectrum, ν, cm^{-1}: 3434, 3305, 3261 (NH), 2966, 2934, 2873 (Alk C–H), 1717, 1686 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.88 (3H, t, *J* = 7.3, CH_3); 1.04 (3H, t, *J* = 7.2, CH_3); 1.13 (3H, t, *J* = 7.0, CH_3); 1.21–1.33 (2H, m, CH_2); 1.55–1.62 (2H, m, CH_2); 3.01–3.13 (1H, m, NCH_2); 3.24–3.30 (2H, m, NCH_2); 3.37–3.54 (1H, m, NCH_2); 3.79 (2H, t, *J* = 7.1, 1'-NCH_2); 4.91 (1H, d, *J* = 5.8, 3a-CH); 5.76 (1H, d, *J* = 5.9, 9a-CH); 7.21 (1H, d, *J* = 8.5, H-7'); 7.46 (1H, d, *J* = 8.6, H-6'); 8.10 (1H, s, NH); 8.80 (1H, s, H-4'). ^{13}C NMR spectrum (75 MHz), δ, ppm: 13.2, 13.5, 14.0 ($3CH_3$); 19.9, 29.6 ($2CH_2$); 35.5, 38.5 ($2NCH_2$); 40.2 (1'-NCH_2); 62.1, 64.1 (C-3a,9a); 111.0 (C-7'); 121.1, 121.3, 122.6, 126.9, 130.5, 135.6 (C-3',3a',4',5',6',7); 136.7 (5a-C=N); 141.8 (C-7a'); 158.5 (2-C=O); 164.4 (8-C=O); 167.2 (2'-C=O). Found, *m*/*z*: 489.1454 $[M+H]^+$. $C_{22}H_{26}ClN_6O_3S$. Calculated, *m*/*z*: 489.1470.

(*Z*)-7-(5-Chloro-2-oxo-1-pentylindolin-3-ylidene)-1,3-diethyl-1,3a,4,9a-tetrahydroimidazo[4,5-*e*]thiazolo[2,3-*c*]-[1,2,4]triazine-2,8(3*H*,7*H*)-dione (4f). Yield 256 mg (51%), orange solid, mp 228–232°C. IR spectrum, ν, cm^{-1}: 3435, 3273 (NH), 2957, 2932 (Alk C–H), 1718, 1686 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 0.83 (3H, t, *J* = 6.9, CH_3); 1.03 (3H, t, *J* = 7.1, CH_3); 1.13 (3H, t, *J* = 7.0, CH_3); 1.22–1.30 (4H, m, $2CH_2$); 1.57–1.64 (2H, m, CH_2); 3.01–3.13 (1H, m, NCH_2); 3.21–3.32 (2H, m, NCH_2); 3.47–3.54 (1H, m, NCH_2); 3.77 (2H, t, *J* = 7.0, 1'-NCH_2); 4.91 (1H, d, *J* = 5.8, 3a-CH); 5.76 (1H, d, *J* = 5.8, 9a-CH); 7.19 (1H, d, *J* = 8.5, H-7'); 7.45 (1H, d, *J* = 8.5, H-6'); 8.11 (1H, s, NH); 8.79 (1H, s, H-4'). ^{13}C NMR spectrum (75 MHz), δ, ppm: 12.7, 13.1, 13.8 ($3CH_3$); 21.7, 26.7, 28.3 ($3CH_2$); 34.9, 38.1 ($2NCH_2$); 39.8 (1'-NCH_2); 61.7, 63.7 (C-3a,9a); 110.4 (C-7'); 120.6, 120.8, 126.1, 126.4, 130.0, 135.1 (C-3',3a',4',5',6',7), 136.2 (5a-C=N); 141.3 (C-7a'); 158.0 (2-C=O); 163.9 (7-C=O); 166.7 (2'-C=O). Found, *m*/*z*: 503.1624 $[M+H]^+$. $C_{23}H_{28}ClN_6O_3S$. Calculated, *m*/*z*: 503.1627.

Supplementary information file containing the description of *in vitro* testing procedures for the synthesized compounds against the panel of 60 cancer cell lines, charts of growth percentages of the cells treated with compounds **3a**–**f**, **4a**–**f**, taxol, doxorubicin, daunorubicin, camptothecin, as well as ^{1}H and ^{13}C NMR spectra of compounds **1a**–**i**, **3a**–**f**, and **4a**–**f** is available at the journal website http://link.springer.com/journal/10593.

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References

1. (a) Chugunova, E. A.; Gazizov, A. S.; Burilov, A. R.; Yusupova, L. M.; Pudovik, M. A.; Sinyashin, O. G. *Russ. Chem. Bull.* **2019**, *68*, 887. (b) Makhova, N. N.; Belen'kii, L. I.; Gazieva, G. A.; Dalinger, I. L.; Konstantinova, L. S.; Kuznetsov, V. V.; Kravchenko, A. N.; Krayushkin, M. M.; Rakitin, O. A.; Starosotnikov, A. M.; Fershtat, L. L.; Shevelev, S. A.; Shirinian, V. Z.; Yarovenko, V. N. *Russ. Chem. Rev.* **2020**, *89*, 55. (c) Fershtat, L. L.; Makhova, N. N. *ChemPlusChem* **2020**, *85*, 13. (d) Chauhan, D. S.; Quraishi, M. A.; Wan Nik, W. B.; Srivastava, V. *J. Mol. Liq.* **2021**, *321*, 114747. (e) Aggarwal, R.; Hooda, M.; Kumar, P.; Sumran, G. *Top. Curr. Chem.* **2022**, *380*, 10. (f) Rakitin, O. A. In *Comprehensive Heterocyclic Chemistry IV*; Elsevier Ltd., 2022, p. 371. (g) Belen'kii, L. I.; Gazieva, G. A.; Evdokimenkova, Y. B.; Soboleva, N. O. *Adv. Heterocycl. Chem.* **2022**, *136*, 225. (h) Makhova, N. N.; Fershtat, L. L. In *Comprehensive Heterocyclic Chemistry IV*; Elsevier Ltd., 2022, p. 190.

2. Su, C.; Yan, Y.; Guo, X.; Luo, J.; Liu, C.; Zhang, Z.; Xiang, W.-S.; Huang, S.-X. *Org. Biomol. Chem*. **2019**, *17*, 477.
3. Rusinov, V. L.; Ulomskii, E. N.; Chupakhin, O. N.; Charushin, V. N. *Russ. Chem. Bull.* **2008**, *57*, 985.
4. Roy, S.; Yadaw, A.; Roy, S.; Sirasani, G.; Gangu, A.; Brown, J. D.; Armstrong, J. D.; Stringham, R. W.; Gupton, B. F.; Senanayake, C. H.; Snead, D. R. *Org. Process Res. Dev*. **2022**, *26*, 82.
5. Sahoo, C. R.; Paidesetty, S. K.; Padhy, R. N. *Drug Dev. Res*. **2019**, *80*, 878.
6. (a) Gazieva, G. A.; Shishkova, E. A.; Kulikova, L. B.; Kolotyrkina, N. G.; Sigay, N. V.; Kravchenko, A. N. *J. Heterocycl. Chem*. **2014**, *51*, 921. (b) Gazieva, G. A.; Izmest'ev, A. N.; Nelyubina, Y. V.; Kolotyrkina, N. G.; Zanin, I. E.; Kravchenko, A. N. *RSC Adv*. **2015**, *5*, 43990. (c) Izmest'ev, A. N.; Kravchenko, A. N.; Gazieva, G. A. *Mendeleev Commun*. **2022**, *32*, 678.
7. (a) Izmest'ev, A. N.; Gazieva, G. A.; Kulikov, A. S.; Anikina, L. V.; Kolotyrkina, N. G.; Kravchenko, A. N. *Russ. J. Org. Chem*. **2017**, *53*, 753. (b) Gazieva, G. A.; Izmest'ev, A. N.; Anikina, L. V.; Pukhov, S. A.; Meshchaneva, M. E.; Khakimov, D. V.; Kolotyrkina, N. G.; Kravchenko, A. N. *Mol. Diversity* **2018**, *22*, 585. (c) Izmest'ev, A. N.; Anikina, L. V.; Zanin, I. E.; Kolotyrkina, N. G.; Izmalkova, E. S.; Kravchenko, A. N.; Gazieva, G. A. *New J. Chem*. **2022**, *46*, 11632.
8. (a) Sandmeyer, T. *Helv. Chim. Acta* **1919**, *2*, 234. (b) Read, R. R. *Org. Synth. Coll.* **1941**, *1*, 321.
9. (a) Evdokimov, N. M.; Magedov, I. V.; McBrayer, D.; Kornienko, A. *Bioorg. Med. Chem. Lett*. **2016**, *26*, 1558. (b) George, G.; Auti, P. S.; Paul, A. T. *New J. Chem*. **2021**, *45*, 1381.
10. Ristovska, N.; Anastasova, F.; Stefova, M. *Molbank* **2013**, *2013*, M798.
11. Gassman, P. G.; Cue, B. W., Jr.; Luh, T.-Y. *J. Org. Chem*. **1977**, *42*, 1344.
12. Gui, Q.; Dai, F.; Liu, J.; Chen, P.; Yang, Z.; Chen, X.; Tan, Z. *Org. Biomol. Chem*. **2014**, *12*, 3349.
13. Liu, T.; Yang, H.; Jiang, Y.; Fu, H. *Adv. Synth. Catal.* **2013**, *355*, 1169.
14. Gao, W.; Lan, S.; Bairenqing, Z.; Li, Y. *Chin. J. Org. Chem*. **2014**, *34*, 2106.
15. Zhang, H. *J. Chem. Res*. **2014**, *38*, 705.