# Iodine-Catalyzed Aza-Prins Cyclization: Metal-Free Synthesis and Antiproliferative Activity of Hexahydrobenzo[*f*]isoquinolines

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**Abstract:** A series of hexahydrobenzo[*f*]isoquinolines were synthesized by an iodine-catalyzed aza-Prins cyclization under metal-free conditions. An aliphatic or an aromatic aldehyde can be used as the carbonyl component in this reaction, which can also be performed efficiently under solvent-free conditions. During this study, we discovered new compounds with moderate antitumor activities.

**Key words:** cyclizations, iodine, catalysis, heterocycles, amines, aldehydes, antitumor agents

Aza-Prins cyclization can be defined as the reaction of a homoallylic amine with a carbonyl compound in the presence of an acid (Lewis or Brønsted). This reaction provides a powerful method for the synthesis of N-heterocycles.[1,2] Thus, preparations of piperidines and tetrahydropyridines by a wide range of protocols have been reported.[3–18] However, aza-Prins reactions have been used less frequently in the construction of other ring systems.[19–23] In this context, we describe the synthesis under mild and metal-free conditions of a series of hexahydrobenzo[*f*]isoquinolines through an iodine-catalyzed aza-Prins cyclization. On the basis of the potential biological activity of the target compounds[24–26] and our continuing efforts to discover new antitumor entities,[27,28] we also examined the antiproliferative activities of the hexahydrobenzo[*f*]isoquinolines that we prepared.

*N*-[2-(3,4-Dihydronaphthalen-1-yl)propyl]-4-methylbenzenesulfonamide (**1**) was prepared from 1-tetralone in four steps: Reformatsky/dehydration reaction, reduction, Mitsunobu reaction, and hydrolysis of a *tert*-butoxycarbonyl group.[29–31] A series of commercially available aldehydes were used as the carbonyl components. On the basis of our previous works on Prins cyclization,[32,33] we performed the cyclizations by using 10 mol% of iodine as the catalyst in dichloromethane (Table 1). When an unhindered aliphatic aldehyde such as formaldehyde, acetaldehyde, or butanal was used as the carbonyl component, the reaction was complete within 1.5–3 hours (entries 1–3). For more-hindered aliphatic aldehydes, such as **2d**–**e**, the reaction time increased to one to two days, and yields were lower, although still within the practical range (entries 4 and 5). We also performed the reaction with aromatic aldehydes, including aldehydes substituted with electron-withdrawing and or electron-donating groups, and the reaction times in these cases were as much as three days (entries 6–8). The nitro-substituted aldehyde **2h** gave a low yield of the corresponding product (entry 8). We also investigated the behavior of cinnamaldehyde (**2i**) in the aza-Prins reaction with **1**, and we found that it gave the desired product **3i** in very good yield (entry 9).

The reaction time for some of the reactions shown in Table 1 was relatively long (>24 hours). With solvent-free conditions and higher temperatures, it was possible to isolate the desired N-heterocyclic compounds in shorter reaction times and in comparable or higher yields (compare Table 2 with entries 7 and 8 in Table 1).

The relative configurations of compounds **3b**–**i** were assigned by NMR analysis, including NOESY experiments. The preferential formation of the *trans*-diastereomer of the hexahydrobenzo[*f*]isoquinolines **3** can be explained in terms of the mechanism of the reaction (Scheme 1).[32] The reaction of the homoallylic amine **1** with aldehyde **2** catalyzed by the Lewis acid iodine gives the iminium ion **4**. This intermediate can lead to the final product *trans*-**3** through (*E*)-**4** or to *cis*-**3** through (*Z*)-**4**. Steric interactions should favor the pathway through (*E*)-**4**. This mechanism also explains the lower reactivities and longer reaction times of bulky aldehydes **2**. During the reaction, hydrogen iodide and hypoiodous acid (HOI) are formed. These species react to form iodine and water, thereby explaining the catalytic action of iodine.[32] The diastereoselectivity of the iodine-catalyzed aza-Prins cyclization of **1** contrasts with that of the Prins cyclizations of the corresponding alcohols with the same aldehydes, which give the *cis*-diastereomers preferentially.[32]

On the basis of the expected biological activity of hexahydrobenzo[*f*]isoquinolines **3**, we evaluated their antiproliferative activity toward human tumor cell lines and one nontumor human cell line *in vitro*. The compounds were tested at concentrations of 0.25–250 μg $mL^{-1}$ with doxorubicin (0.025–25 μg $mL^{-1}$) as the positive control. The concentration eliciting a 50% inhibition in growth ($GI_{50}$) was determined after 48 hours of cell treatment, and the

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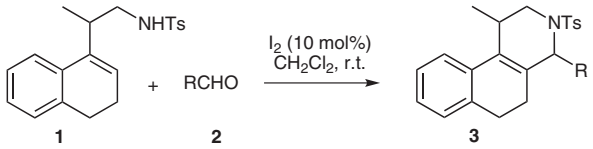
relevant results are listed in Table 3. To analyze the $GI_{50}$ parameter, we calculated the value of log $GI_{50}$ from the $GI_{50}$ value for each test compound against each tumor cell line tested (apart from the normal cell line HaCat), and then we took the average of these values. According to National Cancer Institute (NCI/EUA), if the value of the mean log $GI_{50}$ is less than 1.50, the tested compound can be considered to be active and can be classified as showing weak (1.1 < mean log $GI_{50}$ < 1.5), moderate (0 < mean log $GI_{50}$ < 1.1) or potent (mean log $GI_{50}$ < 0) activity.[34] On the basis of this criterion, compounds **3h**, *cis*-**3g** and *trans*-**3g** were considered to be inactive (mean log $GI_{50}$ > 1.5) (Table 3), whereas compound **3f** showed a weak antiproliferative effect (mean log $GI_{50}$ = 1.4), and compounds **3c** (mean log $GI_{50}$ = 1.0) and **3d** (mean log $GI_{50}$ < 1.0) showed moderate activity. These results suggest that a lateral carbon chain is important to the antiproliferative effect. Alkyl groups, such as propyl (**3c**) or isopropyl (**3d**) are better substituents than aryl groups. When the aryl group was substituted by an electron-withdrawing group (**3h**) or electron-donating group (**3g**), the compounds were inactive. The compounds **3c** and **3d** showed similar moderate activities; however, **3c** was more active toward K562 and NCI-ADR/RES, whereas **3d** was more active toward PC-3, OVCAR-3, and MCF-7. Compound *trans*-**3g** selectively inhibited the growth of NCI-ADR/RES, OVCAR-3, PC-3, and K562, whereas *cis*-**3g** was active against PC-3 and NCI-ADR/RES.

**Table 1** Iodine-Catalyzed Aza-Prins Cyclization in Dichloromethane



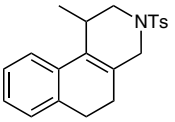
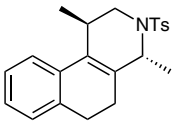
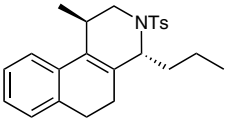
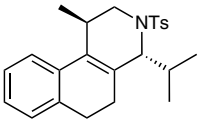
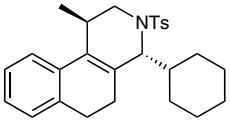
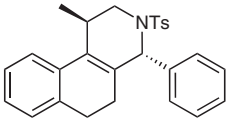
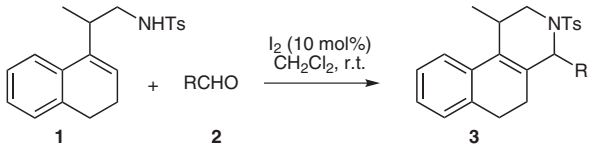
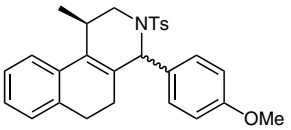
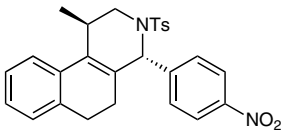
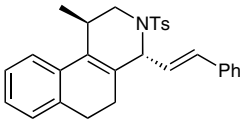

| Entry | Aldehyde | Time (h) | Product | Yield[a] (%) |
|---|---|---|---|---|
| 1 | HCHO (**2a**) | 1.5 |  **3a** | 63% |
| 2 | MeCHO (**2b**) | 3 |  **3b** | 75% (*cis*/*trans* 1:5) |
| 3 | PrCHO (**2c**) | 3 |  **3c** | 76% (*cis*/*trans* 1:6) |
| 4 | *i*-PrCHO (**2d**) | 24 |  **3d** | 50% (*cis*/*trans* 1:11) |
| 5 | CyCHO (**2e**) | 48 |  **3e** | 54% (*cis*/*trans* 1:6) |
| 6 | PhCHO (**2f**) | 5 |  **3f** | 64% (*cis*/*trans* 1:1.15) |

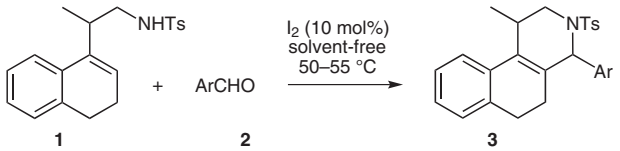
**Table 1** Iodine-Catalyzed Aza-Prins Cyclization in Dichloromethane (continued)

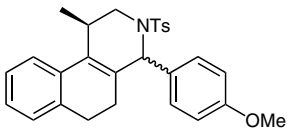
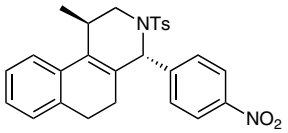



| Entry | Aldehyde | Time (h) | Product | Yield[a] (%) |
|---|---|---|---|---|
| 7 | 4-$MeOC_6H_4CHO$ (**2g**) | 72 |  **3g** | 56% (*cis*/*trans* 1:1) |
| 8 | 4-$O_2NC_6H_4CHO$ (**2h**) | 72 |  **3h** | 28% (*cis*/*trans* 1:2) |
| 9 | (*E*)-PhCH=CHCHO (**2i**) | 24 |  **3i** | 75% (*cis*/*trans* 1:2.4) |

[a] Isolated yield.

**Table 2** Iodine-Catalyzed Aza-Prins Cyclization under Solvent-Free Conditions




| Entry | Aldehyde | Time (h) | Product | Yield[a] (%) |
|---|---|---|---|---|
| 1 | 4-$MeOC_6H_4CHO$ (**2g**) | 6 |  **3g** | 55% (*cis*/*trans* 1:1) |
| 2 | 4-$O_2NC_6H_4CHO$ (**2h**) | 4 |  **3h** | 41% (*cis*/*trans* 1:2) |

[a] Isolated yield.

In conclusion, we accomplished a metal-free synthesis of a series of hexahydrobenzo[*f*]isoquinolines **3** by means of an iodine-catalyzed aza-Prins cyclization of a homoallylic amine **1** with an aliphatic or aromatic aldehyde **2**. The reaction can also be performed under solvent-free conditions. This protocol can be used to obtain other nitrogen heterocycles in an efficient manner. During this study, we also discovered new compounds that showed moderate antitumor activity and good selectivity toward various tumor cell lines

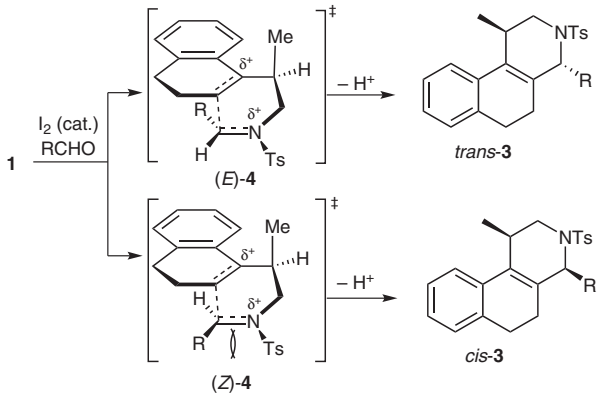


**Table 3** Antiproliferative Activities ($GI_{50}$; $\mu g \cdot mL^{-1}$) of Hexahydrobenzo[*f*]isoquinolines **3**

| Cell line[a] | Control[b] | **3c** (*cis*/*trans* 1:6) | **3d** (*cis*/*trans* 1:10) | **3f** (*cis*/*trans* 1:1.7) | **3h** (*cis*/*trans* 1:2) | *cis*-**3g** | *trans*-**3g** (*cis*/*trans* 1:6.2) |
|---|---|---|---|---|---|---|---|
| U251 | 0.025 | 121.1 | 148.6 | 45.3 | >250 | >250 | >250 |
| MCF-7 | <0.25 | 11.5 | 5.8 | 38.7 | >250 | 29.9 | 83.2 |
| NCI-ADR/RES | 0.19 | 6.7 | 10.1 | 6.0 | 19.6 | 10.6 | 2.7 |
| OVCAR-3 | 0.031 | 4.1 | 0.58 | 15.8 | >250 | 61.3 | 9.4 |
| 786-0 | 0.025 | 93.1 | 45.3 | >250 | >250 | >250 | 56.3 |
| NCI-H460 | <0.25 | 53.4 | 63.3 | 100.8 | >250 | >250 | >250 |
| PC-3 | <0.25 | 0.25 | <0.25 | <0.25 | <0.25 | 1.8 | 9.4 |
| K562 | 0.37 | 0.80 | 9.2 | 20.1 | 0.38 | 231.2 | 15.7 |
| HT-29 | 0.12 | 95.6 | 86.4 | 114.4 | >250 | 38.2 | >250 |
| HaCat | 0.068 | 50.2 | 63.4 | 133.0 | >250 | >250 | >250 |
| *Mean log* $GI_{50}$[c] | <–0.9 (P) | 1.0 (M) | <1.0 (M) | 1.4 (W) | >1.6 (I) | >1.7 (I) | >1.6 (I) |

[a] U251: glioma; MCF-7: breast; NCI-ADR/RES: ovarian resistant to multiple drugs; OVCAR-3: ovarian; 786-0: kidney; NCI-H460: lung, non-small cells; PC-3: prostate; K562: leukemia; HT-29: colon; HaCat: human keratinocyte, immortalized normal cell.
[b] Doxorubicin.
[c] NCI criteria: mean log $GI_{50} > 1.50$ = inactive (I); $1.1 <$ mean log $GI_{50} < 1.5$ = weak activity (W); $0 <$ mean log $GI_{50} < 1.1$ = moderate activity (M); mean log $GI_{50} < 0$ = potent activity (P).[34]




**Scheme 1** Mechanism for the iodine-catalyzed aza-Prins cyclization

All commercially available reagents were used without further purification unless otherwise noted. All solvents used in reactions and in chromatography were dried and purified by standard methods. THF and benzene were freshly distilled over sodium/benzophenone. $CH_2Cl_2$ was freshly distilled over $CaH_2$. TLC analyses were performed by using plates coated with silica gel 60F 254. Spots were detected by UV absorption (254 nm) or by spraying with 4- anisaldehyde and phosphomolybdic acid solutions and then charring at ~150 °C. Flash column chromatography was performed on 200–400 mesh silica gel. All NMR analyses were recorded on Bruker or Varian spectrometers with $CDCl_3$ as solvent and TMS as the internal standard. Chemical shifts are reported relative to TMS with the solvent as the internal standard. IR spectra were recorded on a Perkin-Elmer 1750-FT spectrophotometer. Low-resolution mass spectra were recorded on a Shimadzu 14B/QP5050A spectrometer, and high-resolution mass spectra were recorded on a Bruker Daltonics MicroTOF Electrospray spectrometer operating in the ESI mode.

***N*-[2-(3,4-Dihydronaphthalen-1-yl)propyl]-4-methylbenzenesulfonamide (1)**

$PPh_3$ (1.11 g, 4.23 mmol) and 2-(3,4-dihydronaphthalen-1-yl)propan-1-ol[29] (0.795 g, 4.23 mmol) were added to a stirred soln of TsNHBoc[30,31] (1.18 g, 4.23 mmol) in anhyd THF (9.4 mL). The mixture was cooled to 0 °C and DIAD (0.84 g, 4.2 mmol) was added. After 5 min, the mixture was warmed to r.t. for 1 h. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography (30% EtOAc–hexanes) to give the intermediate *tert*-butoxycarbonyl derivative; yield: 1.36 g (3.06 mmol, 72%).

A stirred soln of this product (1.31 g, 2.96 mmol) in MeOH (30 mL) was treated with $K_2CO_3$ (2.04, 14.8 mmol), and the mixture was heated to 60 °C for 19 h. The mixture was then cooled to r.t. and $H_2O$ (8 mL) was added. The aqueous phase was extracted with EtOAc (2 × 10 mL). The organic phases were combined, washed with brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (20% EtOAc–hexanes) to give **1** as a highly viscous oil; yield: 0.722 g (2.11 mmol, 50%).

IR (film): 3286, 1325, 1160, 551 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.6 Hz, 3 H), 2.21–2.15 (m, 2 H), 2.36 (s, 3 H), 2.63 (t, *J* = 8.1 Hz, 2 H), 2.91–3.00 (m, 2 H), 3.07–3.13 (m, 1 H), 4.94–4.97 (m, 1 H), 5.78 (t, *J* = 4.5 Hz), 7.10–7.11 (m, 4 H), 7.18–7.21 (m, 2 H), 7.67–7.69 (m, 2 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 17.7, 21.4, 22.8, 28.1, 33.5, 47.5, 121.9, 124.2, 126.3, 126.7, 126.8, 127.7, 129.5, 133.8, 136.7, 136.8, 137.6, 143.1.

LRMS: *m/z* (%) = 341 (2) [$M^{+\bullet}$], 186 (86), 91 (100).

HRMS (ESI): *m/z* calcd for $[C_{20}H_{23}NO_2S + Na]^+$: 364.1347; found: 364.1340.

**1-Methyl-3-tosyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinoline (3a); Typical Procedure**

$I_2$ (0.076 g, 0.030 mmol) was added to a stirred soln of **1** (0.10 g, 0.30 mmol) and **2a** (0.011 mL, 0.36 mmol) in $CH_2Cl_2$ (1.1 mL), and

the mixture was stirred for 1.5 h at r.t. $Na_2SO_3$ (0.038 g, 0.30 mmol) and $H_2O$ (10 mL) were then added, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The organic phases were combined, washed with brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20% EtOAc–hexanes) to give a colorless viscous oil; yield: 0.068 g (0.19 mmol, 63%).

IR (film): 3057, 3014, 2930, 2887, 1597, 1490, 1457, 1449, 1336, 1161, 940, 811, 764, 671, 571, 549 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.6 Hz, 3 H), 2.03–2.13 (m, 2 H), 2.42 (s, 3 H), 2.63–2.77 (m, 2 H), 2.82 (dd, *J* = 11.2, 3.6 Hz, 1 H), 2.91 (br s, 1 H), 3.30 (d, *J* = 16.8 Hz, 1 H), 3.52 (dd, *J* = 11.1, 3.0 Hz, 1 H), 3.95 (d, *J* = 16.5 Hz, 1 H), 7.07–7.11 (m, 2 H), 7.17–7.19 (m, 2 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 18.5, 21.5, 26.1, 27.8, 29.1, 48.5, 49.9, 122.1, 126.4, 126.5, 127.7, 127.8, 127.9, 129.6, 130.9, 133.1, 133.2, 135.5, 143.5.

LRMS: *m/z* (%) = 353 (9) [$M^{+\bullet}$], 198 (33), 196 (39), 182 (17), 171 (65), 155 (27), 153 (17), 143 (20), 141 (33), 129 (73), 128 (42), 127 (16), 115 (33), 91 (100).

HRMS (ESI): *m/z* calcd for $[C_{21}H_{23}NO_2S + Na]^+$: 376.1347; found: 376.1348.

**1,4-Dimethyl-3-tosyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinoline (3b)**

The reaction was performed by following the typical procedure, but using **1** (0.14 g, 0.40 mmol), **2b** (0.018 g, 0.40 mmol), $CH_2Cl_2$ (1.2 mL), and $I_2$ (0.010 g, 0.040 mmol) to give a colorless viscous oil; yield: 0.11 g (0.30 mmol, 75%; *cis*/*trans* = 1:5).

IR (film): 3062, 2972, 2928, 1337, 1160, 674, 576 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ (*trans*-**3b**) = 1.04 (d, *J* = 7.0 Hz, 3 H), 1.07 (d, *J* = 6.5 Hz, 3 H), 1.99 (ddd, *J* = 15.5, 6.0, 4.0 Hz, 1 H), 2.26–2.33 (m, 1 H), 2.41 (s, 3 H), 2.69 (ddd, *J* = 15.0, 6.0, 4.0 Hz, 1 H), 2.78 (dd, *J* = 15.0, 6.5 Hz, 1 H), 2.82–2.85 (m, 1 H), 3.29 (dd, *J* = 13.0, 3.5 Hz, 1 H), 3.70 (d, *J* = 13.0 Hz, 1 H), 4.52 (q, *J* = 6.5 Hz, 1 H), 7.11–7.14 (m, 2 H), 7.18–7.20 (m, 2 H), 7.27 (s, 1 H), 7.29 (s, 1 H), 7.75 (t, *J* = 2.0 Hz, 1 H), 7.77 (t, *J* = 2.0 Hz, 1 H); δ (*cis*-**3b**) = 0.98 (d, *J* = 6.5 Hz, 3 H), 1.46 (d, *J* = 6.5 Hz, 3 H), 2.13 (ddd, *J* = 16.5, 6.0, 3.5 Hz, 1 H), 2.26 (s, 3 H), 2.54–2.63 (m, 1 H), 3.10 (dd, *J* = 14.0, 9.5 Hz, 1 H), 3.86 (dd, *J* = 14.0, 6.7, 1.5 Hz, 1 H), 4.24 (q, *J* = 6.5 Hz, 1 H), 6.81 (t, *J* = 7.5 Hz, 1 H), 7.07–7.09 (m, 3 H), 7.63–7.70 (m, 3 H), 7.82 (d, *J* = 8.0 Hz, 1 H); other signals overlapped with the major diastereomer.

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ (*trans*-**3b**) = 15.6, 18.5, 21.5, 27.0, 28.1, 28.9, 44.6, 53.4, 122.1, 126.4, 126.6, 127.1, 127.6, 129.5, 130.5, 133.3, 133.4, 136.1, 138.6, 142.9; δ (*cis*-**3b**) = 19.7, 20.9, 21.3, 26.7, 27.1, 29.7, 46.2, 53.0, 122.9, 125.8, 126.1, 126.9, 127.3, 129.3, 129.6, 131.3, 135.6, 135.9, 137.2, 143.1.

LRMS: *m/z* (%) = 367 (0.46) [$M^{+\bullet}$], 352 (4.5), 196 (14.1), 128 (14.5), 115 (12.5), 91 (100).

HRMS (ESI): *m/z* calcd for $[C_{24}H_{29}NO_2S + H]^+$: 368.1684; found: 368.1672.

**1-Methyl-4-propyl-3-tosyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinoline (3c)**

The reaction was performed by following the typical procedure, but using **1** (0.11 g, 0.30 mmol), **2c** (0.021 g, 0.30 mmol), $CH_2Cl_2$ (1.1 mL), and $I_2$ (0.076 g, 0.030 mmol) to give a white solid: yield: 0.098 g (0.23 mmol, 76%; *cis*/*trans* = 1:6); mp 129.7–132.6 °C

IR (film): 3063, 2959, 2872, 1337, 1155, 674 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ (*trans*-**3c**) = 0.71 (t, *J* = 7.0 Hz, 3 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 1.08–1.17 (m, 1 H), 1.18–1.28 (m, 1 H), 1.46–1.54 (m, 1 H), 1.59–1.71 (m, 2 H), 2.04 (ddd, *J* = 15.4, 6.0, 3.0 Hz, 1 H), 2.26–2.33 (m, 1 H), 2.39 (s, 3 H), 2.69 (ddd, *J* = 15.1, 6.0, 3.5 Hz, 1 H), 2.77 (dd, *J* = 15.2, 6.5 Hz, 1 H), 3.41 (dd, *J* = 13.5, 4.0 Hz, 1 H), 3.81 (d, *J* = 13.5 Hz, 1 H), 4.48 (t, *J* = 5.0 Hz, 1 H), 7.11–7.13 (m, 2 H), 7.17–7.19 (m, 2 H), 7.26 (s, 1 H), 7.27 (s, 1 H), 7.75 (s, 1 H), 7.77 (s, 1 H); δ (*cis*-**3c**) = 0.86 (d, *J* = 7.0 Hz, 3 H), 1.00 (t, *J* = 7.0 Hz, 3 H), 1.81–1.82 (m, 1 H), 1.85–1.93 (m, 2 H), 2.09–2.11 (m, 2 H), 2.14 (s, 3 H), 2.53 (dd, *J* = 16.2, 6.0 Hz, 1 H), 2.60 (ddd, *J* = 15.0, 6.0, 2.0 Hz, 1 H), 2.82–2.84 (m, 1 H), 3.02 (dd, *J* = 15.0, 10.5 Hz, 1 H), 4.03 (ddd, *J* = 16.5, 7.5, 1.5 Hz, 1 H), 4.08–4.10 (m, 1 H), 6.54–6.55 (m, 1 H), 7.00 (d, *J* = 8.5 Hz, 1 H), 7.04 (d, *J* = 3.0 Hz, 2 H), 7.59 (d, *J* = 8.0 Hz, 2 H); other signals overlapped with the major diastereomer.

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ (*trans*-**3c**) = 14.3, 18.9, 19.3, 21.4, 27.4, 28.2, 28.4, 34.5, 46.2, 57.4, 122.2, 126.4, 126.5, 127.1, 127.5, 129.4, 131.0, 132.3, 133.5, 136.2, 139.2, 142.8; δ (*cis*-**3c**) = 13.7, 18.7, 19.9, 21.2, 25.3, 27.0, 28.1, 35.0, 45.8, 57.3, 122.7, 125.5, 125.9, 126.8, 129.0, 131.2, 133.2, 135.0, 136.0, 137.7, 143.0; other signals overlapped with the major diastereomer.

HRMS (ESI): *m/z* calcd for $[C_{24}H_{29}NO_2S + H]^+$: 396.1997; found: 396.1995.

**4-Isopropyl-1-methyl-3-tosyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinoline (3d)**

The reaction was performed by following the typical procedure, but using **1** (0.12 g, 0.37 mmol), **2d** (0.026 mL, 0.37 mmol), $CH_2Cl_2$ (1.4 mL), and $I_2$ (0.0093 g, 0.037 mmol) to give a colorless viscous oil: yield: 0.071 g (0.18 mmol, 50%; *cis*/*trans* = 1:11).

IR (film): 3063, 3025, 2965, 2930, 2875, 2832, 1598, 1489, 1469, 1453, 1378, 1335, 1151, 1090, 1027, 909, 814, 767, 677, 669, 594, 584 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ (*trans*-**3d**) = 0.73 (d, *J* = 7.0 Hz, 3 H), 0.90 (d, *J* = 7.0 Hz, 3 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 2.00–2.08 (m, 1 H), 2.11 (t, *J* = 4.0 Hz, 3 H), 2.32 (ddd, *J* = 15.1, 6.5, 2.0 Hz, 1 H), 2.37 (s, 1 H), 2.64–2.81 (m, 3 H), 3.62 (dd, *J* = 14.5, 5.0 Hz, 1 H), 3.84 (d, *J* = 14 Hz, 1 H), 4.40 (d, *J* = 4.0 Hz, 1 H), 7.09–7.19 (m, 4 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 2 H); δ (*cis*-**3d**) = 0.87 (d, *J* = 6.5 Hz, 3 H), 1.12 (d, *J* = 7.0 Hz, 3 H), 1.16 (d, *J* = 6.5 Hz, 3 H), 2.37 (s, 3 H), 2.56 (dd, *J* = 8.5, 3.5 Hz, 2 H), 3.10 (dd, *J* = 15.5, 10.5 Hz, 1 H), 4.14 (ddd, *J* = 13.5, 8.2, 2.0 Hz, 1 H), 6.98 (d, *J* = 8.0 Hz, 2 H), 7.04 (d, *J* = 3.0 Hz, 2 H), 7.57 (d, *J* = 8.5 Hz, 2 H); other signals overlapped with the major diastereomer.

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ (*trans*-**3d**) = 19.6, 20.3, 20.6, 21.4, 27.9, 28.4, 29.3, 32.6, 46.8, 62.5, 122.6, 126.34, 126.36, 127.2, 127.3, 129.3, 131.5, 131.9, 133.7136.6, 139.4, 142.7; δ (*cis*-**3d**) = 19.3, 20.5, 20.7, 21.1, 25.0, 27.7, 28.3, 32.4, 46.8, 62.5, 122.5, 125.5, 126.0, 126.8, 127.0, 129.0, 132.2, 133.0, 133.9, 136.4, 137.6, 142.9.

HRMS (ESI): *m/z* calcd for $[C_{24}H_{29}NO_2S + Na]^+$: 418.1817; found: 418.1815.

**4-Cyclohexyl-1-methyl-3-tosyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinoline (3e)**

The reaction was performed by following the typical procedure, but using **1** (0.11 g, 0.32 mmol), **2e** (0.036 mL, 0.32 mmol), $CH_2Cl_2$ (1.3 mL), and $I_2$ (0.0082 g, 0.032 mmol) to give a colorless viscous oil; yield: 0.071 g (0.17 mmol, 54%; *cis*/*trans* = 1:6).

IR (film): 3062, 2928, 2852, 1336, 1151, 672 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ (*trans*-**3e**) = 0.69 (d, *J* = 6.9 Hz, 3 H), 0.94–1.13 (m, 6 H), 1.66–1.69 (m, 4 H), 2.04 2.14 (m, 1 H), 2.28–2.41 (m, 2 H), 2.37 (s, 3 H), 2.66–2.79 (m, 3 H), 3.61 (dd, *J* = 14.2, 4.8 Hz, 1 H), 3.82 (d, *J* = 14.1 Hz, 1 H), 4.37 (d, *J* = 3.6 Hz, 1 H), 7.04–7.18 (m, 4 H), 7.22 (s, 1 H), 7.25 (s, 1 H), 7.71 (t, *J* = 2.4 Hz, 1 H), 7.75 (t, *J* = 2.1 Hz, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ (*trans*-**3e**) = 19.7, 21.4, 26.2, 26.8, 27.2, 27.9, 28.4, 29.6, 30.6, 31.5, 42.9, 47.0, 62.4, 122.6, 126.4, 127.2, 127.3, 129.3, 131.4, 131.7, 133.8, 136.6, 139.4, 142.7.

HRMS (ESI): *m/z* calcd for $[C_{27}H_{33}NO_2S + Na]^+$: 458.2130; found: 458.2139.

**1-Methyl-4-phenyl-3-tosyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinoline (3f)**

The reaction was performed by following the typical procedure, but using **1** (0.118 g, 0.34 mmol), **2f** (0.037 mL, 0.34 mmol), $CH_2Cl_2$ (1.4 mL), and $I_2$ (0.0088 g, 0.034 mmol) to give a colorless viscous oil:[32] yield: 0.095 g (0.22 mmol, 64%; *cis*/*trans* = 1:1.15).

**4-(4-Methoxyphenyl)-1-methyl-3-tosyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinoline (*cis*- and *trans*-3g)**

The reaction was performed by following the typical procedure, but using **1** (0.10 g, 0.30 mmol), **2g** (0.041 mL, 0.30 mmol), $CH_2Cl_2$ (1.4 mL), and $I_2$ (0.0076 g, 0.030 mmol) to give a yellow oil; yield: 0.078 g (0.17 mmol, 56%; *cis*/*trans* = 1:1). This was subjected to further purification by flash column chromatography (5% EtOAc–hexanes) to give pure samples of *cis*- and *trans*-**3g**.

***cis*-3g**

IR (film): 3060, 2954, 2920, 2858, 1509, 1337, 1157, 637 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.6 Hz, 3 H), 1.90–2.03 (m, 2 H), 2.19 (s, 3 H), 2.52–2.72 (m, 3 H), 2.83 (dd, *J* = 14.5, 10.5 Hz, 1 H), 3.79–3.82 (m, 1 H), 3.84 (s, 3 H), 5.32 (s, 1 H), 6.69–6.73 (m, 1 H), 6.86 (m, 2 H), 7.03 (s, 1 H), 7.06 (s, 1 H), 7.07–7.10 (m, 3 H), 7.36–7.41 (m, 2 H), 7.60 (t, *J* = 1.8 Hz, 1 H), 7.63 (t, *J* = 1.8 Hz, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ =18.4, 21.2, 26.1, 27.2, 27.8, 45.8, 55.3, 60.2, 113.8, 122.9, 125.7, 126.3, 126.9, 127.2, 129.2, 130.2, 130.9, 132.0, 133.2, 133.7, 136.1, 137.6, 143.1, 159.4.

HRMS (ESI): *m/z* calcd for $[C_{28}H_{29}NO_3S + Na]^+$: 482.1766; found: 482.1747.

***trans*-3g**

IR (film): 3060, 2962, 2927, 2872, 1510, 1335, 1154, 636 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.6 Hz, 3 H), 1.87–1.93 (m, 2 H), 2.30 (s, 3 H), 2.58–2.79 (m, 2 H), 2.98–3.05 (m, 1 H), 3.37 (dd, *J* = 12.9, 3.6 Hz, 1 H), 3.68 (dd, *J* = 12.6, 0.9 Hz, 1 H), 3.75 (s, 3 H), 5.45 (s, 1 H), 6.64–6.67 (m, 2 H), 6.98 (s, 1 H), 7.01 (s, 1 H), 7.08–7.17 (m, 4 H), 7.23–7.27 (m, 3 H), 7.32–7.36 (m, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 19.0, 21.6, 27.2, 28.4, 29.1, 45.9, 55.5, 60.4, 113.8, 122.6, 126.7, 127.10, 127.14, 127.9, 129.1, 130.3, 130.5, 130.6, 130.9, 132.1, 133.5, 136.5, 142.4, 159.7.

HRMS (ESI): *m/z* calcd for $[C_{28}H_{29}NO_3S + Na]^+$: 482.1766; found: 482.1764.

**4-(4-Methoxyphenyl)-1-methyl-3-tosyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinoline (3g); Solvent-Free Method.**

The reaction was performed by following the typical procedure, but using **1** (0.083 g, 0.25 mmol), **2g** (0.030 mL, 0.25 mmol), and $I_2$ (0.0063 g, 0.025 mmol) and omitting the $CH_2Cl_2$, to give a yellow oil; yield: 0.062 g (0.14 mmol, 55%, *cis*/*trans* = 1:1).

**1-Methyl-4-(4-nitrophenyl)-3-tosyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinoline (3h)**

The reaction was performed by following the typical procedure, but using **1** (0.080 g, 0.23 mmol), **2h** (0.035 mL, 0.23 mmol), $CH_2Cl_2$ (1.1 mL), and $I_2$ (0.0060 g, 0.023 mmol) to give a yellow oil; yield: 0.031 g (0.065 mmol, 28%; *cis*/*trans* = 1:2).

IR (film): 3059, 2966, 2927, 2852, 1521, 1347, 1156, 581 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ (*trans*-**3h**) = 1.23 (d, *J* = 7.0 Hz, 3 H), 1.79–1.94 (m, 2 H), 2.29 (s, 3 H), 2.59–2.70 (m, 1 H), 2.75–2.81 (m, 1 H), 3.08–3.10 (m, 1 H), 3.42 (d, *J* = 12.5, 3.5 Hz, 1 H), 3.79 (d, *J* = 13.0 Hz, 1 H), 5.56 (s, 1 H), 7.01 (s, 1 H), 7.02 (s, 1 H), 7.08–7.18 (m, 4 H), 7.30 (t, *J* = 2.0 Hz, 1 H), 7.31 (t, *J* = 2.0 Hz, 1 H), 7.40 (t, *J* = 2.0 Hz, 1 H), 7.42 (t, *J* = 2.0 Hz, 1 H), 7.97 (t, *J* = 2.0 Hz, 1 H), 7.99 (t, *J* = 2.0 Hz, 1 H); δ (*cis*-**3h**) = 1.00 (d, *J* = 7.0 Hz, 3 H), 2.01–2.09 (m, 2 H), 2.22 (s, 3 H), 3.08–3.10 (m, 1 H), 3.84 (dd, *J* = 14.5, 6.5 Hz, 1 H), 5.37 (s, 1 H), 7.34 (s, 1 H), 7.35 (s, 1 H), 7.61 (s, 1 H), 7.63 (s, 1 H), 7.66 (s, 1 H), 7.67 (s, 1 H), 8.21 (s, 1 H), 8.23 (s, 1 H); other signals overlapped with the major diastereomer.

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ (*trans*-**3h**) = 18.7, 21.3, 26.7, 28.0, 28.8, 45.9, 59.7, 122.5, 123.3, 126.7, 126.9, 127.4, 127.8, 129.1, 129.4, 129.8, 132.7, 133.3, 136.0, 137.4, 143.1, 145.1, 147.5; δ (*cis*-**3h**) = 18.5, 21.3, 26.2, 27.2, 27.6, 46.5, 60.2, 123.0, 123.7, 126.0, 126.7, 127.4, 128.4, 129.2, 129.9, 130.2, 132.6, 134.9, 135.8, 136.8, 143.7, 146.5, 147.7.

HRMS (ESI): *m/z* calcd for $[C_{27}H_{27}N_2O_4S + H]^+$: 475.1692; found: 475.1687.

**1-Methyl-4-(4-nitrophenyl)-3-tosyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinoline (3h); Solvent-Free Method**

The reaction was performed by following the typical procedure, but using **1** (0.072 g, 0.21 mmol), **3h** (0.032 g, 0.21 mmol), and $I_2$ (0.0055 g, 0.021 mmol), and omitting the $CH_2Cl_2$, to give a yellow oil; yield: 0.042 g (0.088 mmol, 41%; *cis*/*trans* = 1:2).

**1-Methyl-4-styryl-3-tosyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinoline (3i)**

The reaction was performed by following the typical procedure, but using **1** (0.10 g, 0.29 mmol), **2i** (0.039 mL, 0.29 mmol), $CH_2Cl_2$ (1.2 mL), and $I_2$ (0.0075 g, 0.029 mmol) to give a yellow oil; yield: 0.10 g (0.22 mmol, 75%, *cis*/*trans* = 1:2.4).

IR (film): 3060, 3026, 2928, 2872, 1598, 1339, 1155, 753, 674, 584 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ (*trans*-**3i**) = 1.27 (d, *J* = 7.0 Hz, 3 H), 2.02–2.09 (m, 1 H), 2.11–2.21 (m, 1 H), 2.24 (s, 3 H), 2.62–2.71 (m, 2 H), 2.80 (dd, *J* = 15.0, 6.5 Hz, 1 H), 2.93–2.95 (m, 1 H), 3.23 (dd, *J* = 12.5, 3.5 Hz, 1 H), 3.80 (d, *J* = 12.0 Hz, 1 H), 4.96 (d, *J* = 8.5 Hz, 1 H), 5.59 (dd, *J* = 15.5, 8.5 Hz, 1 H), 6.47 (d, *J* = 15.5 Hz, 1 H), 7.03–7.16 (m, 6 H), 7.18–7.32 (m, 5 H), 7.63 (t, *J* = 1.5 Hz, 1 H), 7.65 (s, 1 H); δ (*cis*-**3i**) = 1.00 (d, *J* = 6.5 Hz, 3 H), 2.23 (s, 3 H), 3.03 (dd, *J* = 14.0, 10.0 Hz, 1 H), 3.93 (dd, *J* = 13.5. 6.5, 1.5 Hz, 1 H), 4.83 (d, *J* = 7.0 Hz, 1 H), 6.12 (dd, *J* = 15.5, 6.5 Hz, 1 H), 6.56 (d, *J* = 16.0 Hz, 1 H), 6.88 (dd, *J* = 7.5 Hz, 1 H), 7.66 (t, *J* = 2.0 Hz, 1 H); other signals overlapped with the major diastereomer.

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ (*trans*-**3i**) = 18.6, 21.3, 26.7, 28.2, 29.1, 45.9, 59.8, 122.3, 123.3, 126.4, 126.9, 127.2, 127.5, 127.7, 127.8, 128.3, 129.2, 129.7, 132.1, 133.3, 134.0, 136.1, 136.2, 137.8, 142.7; δ (*cis*-**3i**) = 18.4, 26.6, 27.5, 27.9, 46.5, 59.1, 123.1, 125.9, 126.1, 126.6, 127.3, 127.7, 128.0, 128.5, 129.3, 131.8, 133.4, 133.8, 137.4, 143.1; other signals overlapped with the major diastereomer.

HRMS (ESI): *m/z* calcd for $[C_{29}H_{30}NO_2S + H]^+$: 456.1997; found: 456.1998.

**Antiproliferative Assay**

Human tumor cell lines [U251 (glioma), MCF-7 (breast), NCI-ADR/RES (ovarian expressing the multiple-drugs-resistance phenotype), 786–0 (renal), NCI-H460 (lung, non-small cells), PC-3 (prostate), OVCAR-03 (ovarian), HT-29 (colon) and K562 (leukemia)] were kindly provided by the Frederick Cancer Research & Development Center (National Cancer Institute, Frederick, MA, USA). The HaCat cell line (immortalized human keratinocytes) was kindly donated by Dr Ricardo Della Coletta, FOP/Unicamp, SP, Brazil. Stock cultures were grown in RPMI 1640 medium (5 mL) (Gibco BRL/Life Technologies) supplemented with 5% of fetal bovine serum. Penicillin and streptomycin (1000 $\mu g \cdot mL^{-1}$:1000 $UI \cdot mL^{-1}$; 1 $mL \cdot L^{-1}$) were added to the experimental cultures. Cells plated in 96-well plates (100 μL cells/well) were exposed to various concentrations of compounds **3a**–**h** diluted in DMSO (0.25, 2.5, 25, or 250 $\mu g \cdot mL^{-1}$) at 37 °C under an atmosphere of 5% $CO_2$ for 48 h. The final concentration of DMSO did not affect the viability of the cells. Afterwards, the cells were fixed with 50% trichloroacetic acid and cell proliferation was determined by spectrophotometric quantification (540 nm) of cellular protein content be means of the sul-

forhodamine B assay.[35] Doxorubicin (0.025–25 μg·mL$^{-1}$) was used as a positive control. Three measurements were obtained at the beginning of incubation (time zero, $T_0$) and at 48 h post-incubation for compound-free (C) and tested (T) cells. Cell proliferation was determined according to the equation $100 \times [(T - T_0)/C - T_0]$ for $T_0 < T \leq C$ or $100 \times [(T - T_0)/T_0]$ for $T \leq T_0$. A concentration–response curve was plotted for each cell line and from these curves, the value of $GI_{50}$ (the concentration producing a 50% inhibition in growth) was determined by means of nonlinear regression analysis using Origin 8.0 (OriginLab Corp.).[35,36] The average activity (mean of log $GI_{50}$) of each compound tested was also determined by using an Excel spreadsheet (Microsoft Corp.). Compounds were classified as inactive (mean > 1.5), weakly active (1.1 < mean < 1.5), moderately active (0 < mean < 1.1) or potently active (mean < 0) on the basis of the NCI criteria for the mean of log $GI_{50}$.[34]

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**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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