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Bioorganic & Medicinal Chemistry 13 (2005) 3127–3139
Bioorganic & Medicinal Chemistry

Indolizine 1-sulfonates as potent inhibitors of 15-lipoxygenase from soybeans

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Received 29 October 2004; accepted 25 February 2005

Abstract—A number of indolizine 1-sulfonates have been prepared by cyclization of cyclopropenones with pyridines followed by trapping of the intermediate 1-indolizinol with a sulfonyl halide, and examined as inhibitors of 15-lipoxygenase (15-LO). The compounds display IC_{50} values between 15 and 42 μM; all are more active than the well-known 15-LO inhibitor quercetin (IC_{50} 51 μM). A wide variety of substituents are well tolerated. The enzyme inhibition was not affected by preincubation or the presence of a detergent and no significant particle formation was observed. Hence, inhibition from aggregates of indolizines, promiscuous inhibition, is highly unlikely.

1. Introduction

For some time we have been studying antioxidant activity for indolizine derivatives[1,2] and as part of this project, we have previously found that certain indolizine derivatives are profound inhibitors of 15-lipoxygenase (15-LO) from soybeans as well as from rabbit reticulocytes. Among the most active compounds were indolizines carrying a –OTs group in the 1-position.[2] There were no correlations between enzyme inhibition and ability to scavenge the DPPH radical or inhibit lipid peroxidation in vitro under conditions without active enzymes present. We proposed that the indolizines are so-called nonantioxidant inhibitors of 15-LO and that they mediate their activity thru a direct interaction with the enzyme. 15-LO has been implicated in oxidation of low-density lipoproteins (LDL). This process is believed to be important for the development of atherosclerosis.[3] In addition, 15-hydroperoxyeicosatetraenoic acid has been shown to decrease prostacyclin synthesis[4] and 15-LO inhibitors may thus have a pro-thrombotic effect. Even though it is not known whether these effects are clinically important in humans, inhibitors of 15-LO may have a drug potential, and we have now synthesized a number of indolizine 1-sulfonates and examined their ability to inhibit 15-LO from soybean.

2. Results and discussion

The target indolizine sulfonates were synthesized as shown in Scheme 1. 2,3-Diaryl- or 2,3-dialkylcyclopropenones **1** were reacted with pyridine **2** to generate the intermediate 1-indolizinol, which was trapped with a sulfonyl chloride, as we have previously reported for the synthesis of the tosylate **3a** and triflate **3o**[1b] (Scheme 1, Table 1). In order to elucidate the importance of $–OSO_2R$ moiety in compounds **3** for biological activity, we also synthesized the sulfone **6** as well as the compounds **7**, which are lacking a 1-substituent, via the 1-bromoindolizines **4**. We have previously described the preparation of the bromide **4a** by halogenation of the corresponding 1-indolizinol with Ph_3PBr_2.[1b] The same methodology was used to synthesize bromides **4b–d**. Minor amounts of the dibrominated products **5** were formed together with the 2,3-di(4-halophenyl)indolizines **4b** and **4c**. Metal–halogen exchange on 1-bromoindolizines followed by trapping with an electrophilic species is a convenient way to modify the indolizine 1-position.[1b] When the 1-lithioindolizine generated from **4a** was reacted with tosyl fluoride,[5] the sulfone **6** was formed although in low yield.

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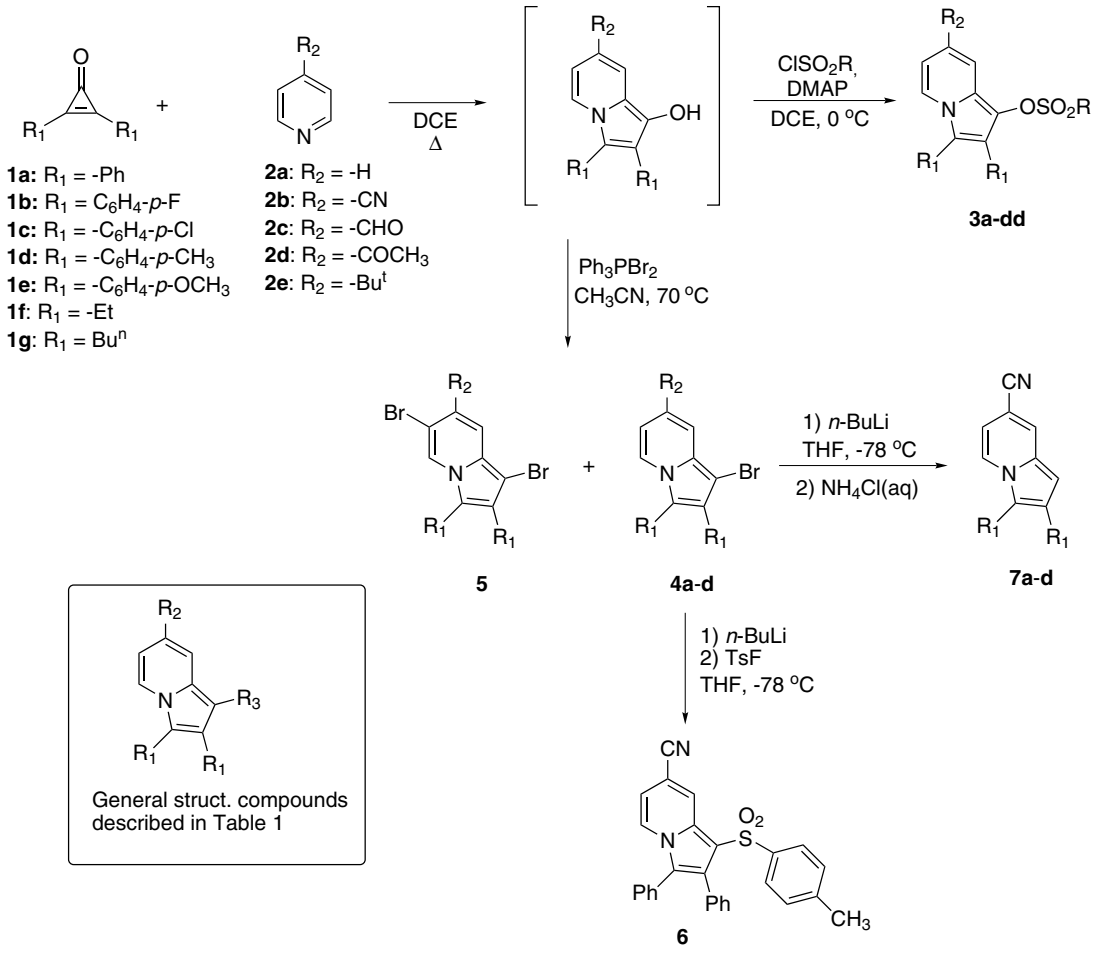
doi:10.1016/j.bmc.2005.02.056



Scheme 1.

A few azaindolizine sulfonates were also examined (Scheme 2). Cyclization of pyrimidine with cyclopropenone **1a** gives two regioisomeric azaindolizinols, which previously have been isolated as acetates.[6] We trapped the azaindolizinols with tosyl chloride to get the isomers **9** and **10**. It was crucial to perform the reaction in dioxane. When synthesis of compounds **9** and **10** in DCE was attempted, we were only able to isolate compound **12**. This product was probably formed by attack of the intermediate azaindolizinol on the cyclopropenone **1a**. The synthesis of compound **11** has been described before.[1c]

The indolizines **3**, **6** and **7** and the azaindolizines **9**–**11** were examined as inhibitors of 15-lipoxygenase from soybeans and the results are presented in Tables 1 and 2. All compounds were more active than the reference compound quercetin and a variety of substituents on the indolizine sulfonates were well tolerated. Sulfonates **3** with aryl and small alkyl groups attached to the sulfur atom (R_3, Table 1) were highly active. More bulky alkyl groups (compd **3n** and **3o**) were somewhat weaker inhibitors. If R_3 is aryl, both electron donating and withdrawing substituents may be present in active compounds and the enzyme is apparently not very sensitive to sterically demanding substituents. It seems to be a slight preference for electron donating substituents on the aryl. Also in the indolizine 2- and 3-position a variety of substituents were tolerated. Generally, aryl substituents give somewhat more active compounds than alkyl substituents (**3f** and **3g**). When 2,3-diphenylinolizine **3a** was compared with analogs bearing *para*-substituted aryls in the 2- and 3-position (compds **3b**–**e**), no significant differences could be found. Also among the different indolizine 7-substituents (R_2 in Table 1) examined (compds **3a**, **3h**–**k**), there were no significant differences in enzyme inhibition. The sulfone **6**, which is identical to the sulfonate **3a** except for the oxygen in the indolizine 1-position in **3a**, was only slightly less active, showing that the oxygen is not required for enzyme inhibition to occur. Even when the substituent in the 1-position was removed totally (compds **7a**–**d**) much of the activity was retained.

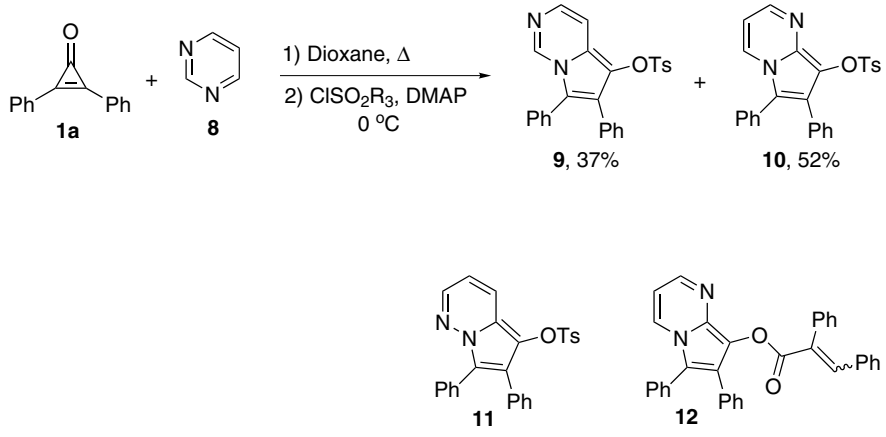
Also the azaindolizine sulfonates examined were powerful 15-lipoxygenase inhibitors (Table 2). When compared to the corresponding sulfonate derived from pyridine (compd **3h**, IC_{50} 25 μM), it appears that an extra nitrogen in the indolizine 5- or 8-position is beneficial for activity.

As discussed above, a variety of indolizine sulfonates were highly potent inhibitors of 15-lipoxygenase from soybeans. However, we were somewhat surprised that the activity was virtually independent of the substitution

Table 1. Inhibitory activity of indolizine derivatives **3**, **6** and **7** against 15-LO from soybeans

Compd no.	R_1	R_2	R_3	IC_{50} (μM)[a,b] 15-LO from soybeans
3a	–Ph	–CN	–OTs[c]	22 ± 2
3b	–C_6H_4–*p*-F	–CN	–OTs	22 ± 2
3c	–C_6H_4–*p*-Cl	–CN	–OTs	20 ± 2
3d	–C_6H_4–*p*-CH_3	–CN	–OTs	20 ± 3
3e	–C_6H_4–*p*-OCH_3	–CN	–OTs	24 ± 2
3f	–CH_2CH_3	–CN	–OTs	29 ± 2
3g	–$(CH_2)_3CH_3$	–CN	–OTs	30 ± 5
3h	–Ph	–H	–OTs	25 ± 3
3i	–Ph	–CHO	–OTs	20 ± 2
3j	–Ph	–$COCH_3$	–OTs	23 ± 1
3k	–Ph	–$C(CH_3)_3$	–OTs	22 ± 4
3l	–Ph	–CN	–OSO_2CH_3	22 ± 2
3m	–Ph	–CN	–$OSO_2(CH_2)_3CH_3$	28 ± 6
3n	–Ph	–CN	–$OSO_2CH(CH_3)_2$	42 ± 7
3o	–Ph	–CN	–OSO_2CF_3	42 ± 3
3p	–Ph	–CN	–$OSO_2N(CH_3)_2$	25 ± 2
3q	–Ph	–CN	–OSO_2Ph	24 ± 3
3r	–Ph	–CN	–OSO_2–C_6H_4–*o*-CH_3	22 ± 2
3s	–Ph	–CN	–OSO_2–C_6H_2–2,4,6-triCH_3	17 ± 2
3t	–Ph	–CN	–OSO_2–C_6H_4–*p*-$CH(CH_3)_2$	16 ± 3
3u	–Ph	–CN	–OSO_2–C_6H_4–*p*-OCH_3	25 ± 3
3v	–C_6H_4–*p*-CH_3	–CN	–OSO_2–C_6H_4–*p*-OCH_3	25 ± 3
3w	–Ph	–CN	–OSO_2–C_6H_3–2,4-diOCH_3	27 ± 5
3x	–Ph	–CN	–OSO_2–C_6H_3–3,4-diOCH_3	19 ± 2
3y	–Ph	–CN	–OSO_2–C_6H_3–2,5-diOCH_3	15 ± 2
3z	–Ph	–CN	–OSO_2–(2-thienyl)	21 ± 2
3aa	–Ph	–CN	–OSO_2–(3-thienyl)	23 ± 2
3bb	–Ph	–CN	–OSO_2–C_6H_4–*p*-Cl	22 ± 3
3cc	–Ph	–CN	–OSO_2–C_6H_4–*p*-CF_3	23 ± 6
3dd	–Ph	–CN	–OSO_2–C_6H_4–*p*-SO_2CH_3	24 ± 3
6	–Ph	–CN	–SO_2–C_6H_4–*p*-CH_3	29 ± 3
7a	–Ph	–CN	–H	30 ± 2
7b	–C_6H_4–*p*-F	–CN	–H	30 ± 6
7c	–C_6H_4–*p*-Cl	–CN	–H	33 ± 7
7d	–C_6H_4–*p*-CH_3	–CN	–H	27 ± 3

[a] Data are shown ± SD.
[b] Quercetin was used as positive control, IC_{50} 51 ± 3 μM.
[c] OTs = OSO_2–C_6H_4–*p*-CH_3.



Scheme 2.

pattern in most positions on the indolizines examined. This led us to fear that the compounds were promiscuous inhibitors that do not bind reversible to the enzyme in a classical 1:1 ratio, but form larger aggregates, which incorporate the enzyme or absorb to the enzyme surface. To be judged promiscuous, an enzyme inhibitor must inhibit in a time-dependent manner, be sensitive to detergent and to enzyme concentration, and form particles detectable by light scattering.[7] We chose to study the potential promiscuity of indolizine sulfonates **3d** and **3m** by observing the effect of preincubation and detergents on the inhibition of 15-lipoxygenase. Samples

Table 2. Inhibitory activity of azaindolizine tosylates **9**–**11** against 15-LO from soybeans

Compd no.	IC_{50} (μM)[a,b]
9	22 ± 3
10	15 ± 1
11	17 ± 2

[a] Data are shown ± SD.
[b] Quercetin was used as positive control, IC_{50} 51 ± 3 μM.

for assays of promiscuity were chosen among the substances available to ensure variation both in enzyme inhibition and solubility. It was also investigated if the compounds form particles, which could be detected by light scattering.

Inhibitory activities of the indolizines **3d** and **3m**, as well as quercetin, against 15-LO were measured with and without preincubation; the inhibitor, enzyme and buffer were mixed and the linoleic acid substrate added after 5 min or immediately. % Inhibition versus log concn inhibitor plots are shown in Figure 1. In all cases preincubation appears to have only minor effects on inhibition.

In order to see if the presence of a detergent influence the activity of the indolizines, inhibition with and without the presence of 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS) were determined for compounds **3d**, **3m** and quercetin, and the results are presented in Figure 2.

Also the presence of CHAPS had minimal effect on inhibitory activity, indicating that the compounds were not promiscuous inhibitors.

Finally, we used dynamic light scattering (DLS) in order to examine the tendency of the indolizines to form particles or aggregates. Buffered solutions (4.1 μM) of compounds **3d**, **3h** and **3m** containing 1.67% v/v DMSO, as in the enzyme inhibition experiments, were used. The results are summarized in Table 3. No particles (**3m**) or just few particles (**3d** and **3h**) were observed. In case of compound **3m**, the experiment was repeated with 15-LO present, and still no particles could be observed. Since no significant aggregation was observed and the inhibition was virtually unchanged by preincubation or detergent addition, it is highly unlikely that the indolizines are promiscuous enzyme inhibitors.

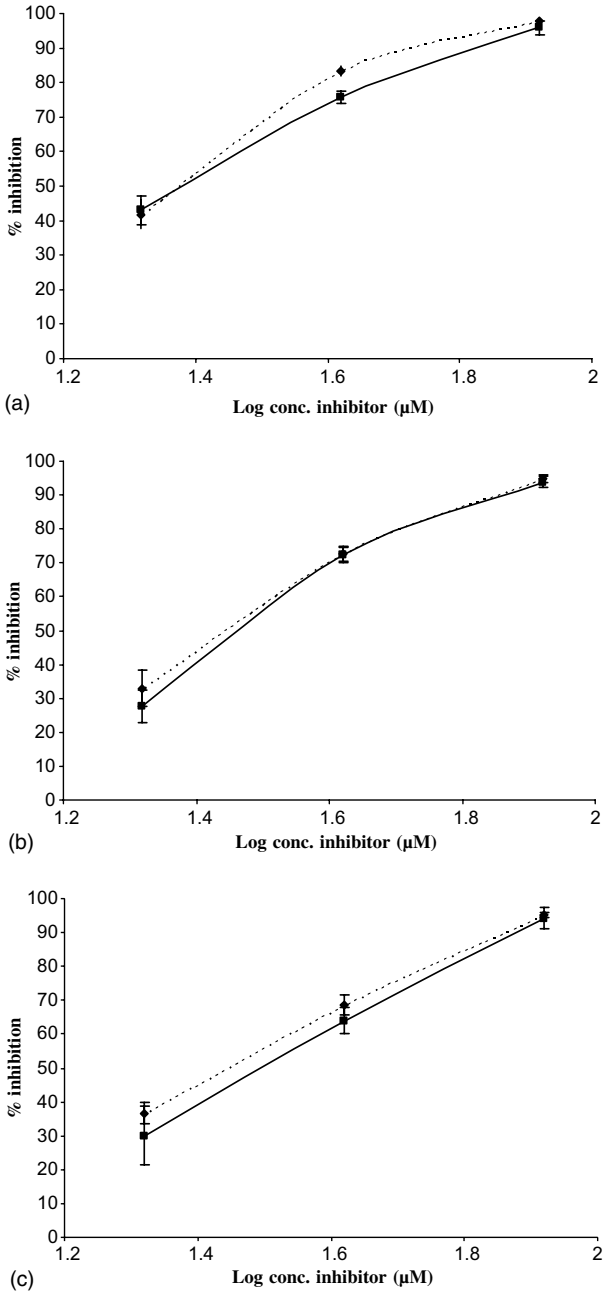


Figure 1. Effect on preincubation on inhibitory activity: activity with preincubation —■—, activity without preincubation ···♦··· for (a) compound **3d**; (b) compound **3m**; (c) quercetin.

3. Conclusions

Indolizine 1-sulfonates are profound inhibitors of 15-lipoxygenase. A wide variety of substituents are well tolerated. It is believed that the indolizines are so-called nonantioxidant inhibitors, which interact directly with the enzyme. Inhibition from aggregates of indolizines, promiscuous inhibition, is highly unlikely.

4. Experimental

15-Lipoxygenase (Type 1) was purchased from Sigma (St. Louis, MO, USA). Silica gel for flash chromatography was available from Merck (Darmstadt, Germany) (Merck No. 9385) or Fluka (Fluka No. 60752). Acetonitrile and DCE were distilled from CaH_2, and THF and 1,4-dioxane from Na/benzophenone. Other reagents were used as received. The ^1H NMR spectra were recorded at 300 MHz with a Bruker Avance DPX 300 instrument or at 200 MHz with a Bruker Avance DPX 200 instrument. The ^{13}C NMR spectra were recorded at 75 or 50 MHz, and the ^{19}F NMR spectra at 188 MHz using instruments mentioned above. The spectra are recorded at 20 °C. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. MS spectra under electron impact conditions were recorded with a

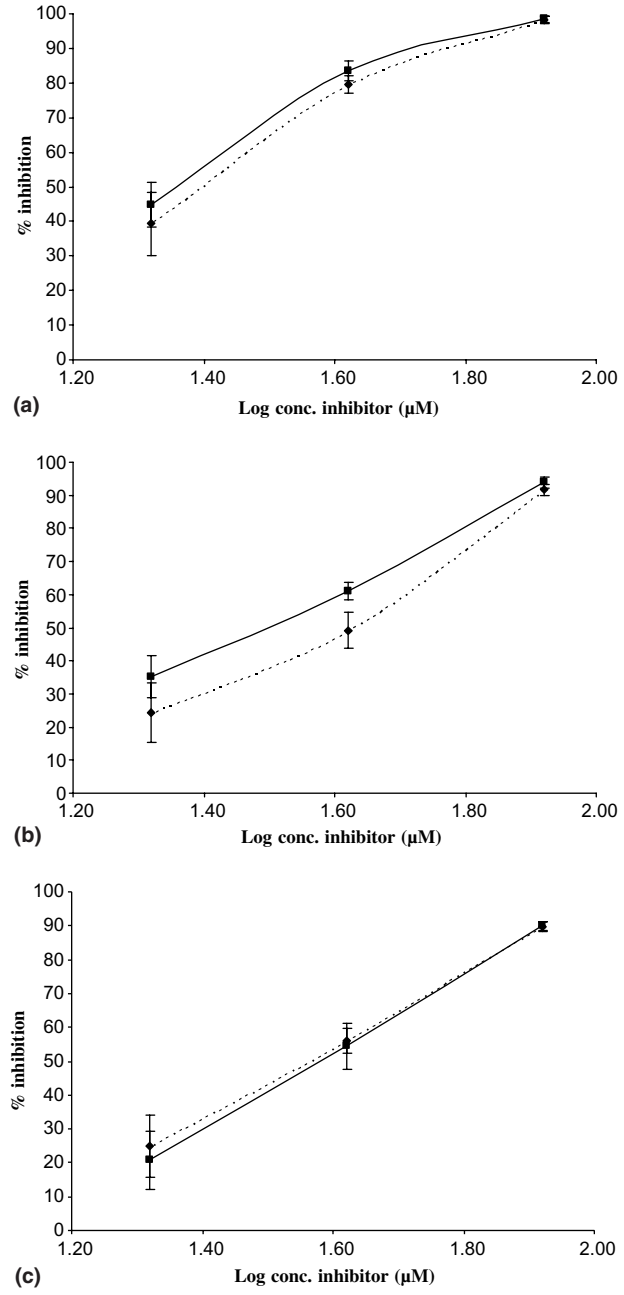


Figure 2. Effect of detergent on inhibitory activity with CHAPS —■—, without CHAPS ···♦··· for (a) compound **3d**; (b) compound **3m**; (c) quercetin.

Table 3. Particle measurements from dynamic light scattering experiments

Compd no.	KCP[a]	Particle size[b]
3d	21.2	Few particles 80 nm
3h	14.2	Few particles 63–77 nm
3m	6.1	No particles[c]

[a] Kilocounts per second.
[b] Determined after 5–10 min.
[c] Few particles observed after 1 h.

VG Prospec instrument at 70 eV ionizing voltage, and are presented as *m/z* (% rel. int.). Electrospray MS spectra were recorded with a Bruker Apex 47e FT-ICR mass spectrometer. Melting points are uncorrected. All measurements of 15-lipoxygenase activities were carried out in a Shimadzu UV-160A spectrophotometer (Shimadzu, Kyoto, Japan) at 20–22 °C. Compounds available by the literature methods: **1b**,[8] **1c**,[9] **1d**,[9] **1e**,[10] **1f**,[11] **1g**,[12] **3a**,[1b] **3o**,[1b] **5a**,[1b] **7a**,[1b] **11**.[1c]

4.1. 1-{[(4-Methylphenyl)sulfonyl]oxy}-2,3-bis(4-fluorophenyl)-7-indolizinecarbonitrile (3b)

A mixture of 2,3-bis(4-fluorophenyl)-2-cyclopropen-1-one **1b** (121 mg, 0.50 mmol) and 4-cyanopyridine **2b** (52 mg, 0.50 mmol) in dry DCE (30 mL) was refluxed under N_2 for 24 h and cooled to 0 °C, before *N*,*N*-4-dimethylaminopyridine (122 mg, 1.00 mmol) and toluene-4-sulfonyl chloride (191 mg, 1.00 mmol) were added. The resulting mixture was stirred under N_2 at 0 °C for 30 min and at ambient temperature for 24 h, washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:4); yield 138 mg (55%), yellow crystals, mp 192 °C, $R_f = 0.25$ (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.39 (s, 3H, CH_3), 6.60 (dd, 1H, $J = 7.6$ and 1.6 Hz, H-6), 6.79–6.97 (m, 4H, Ph), 7.05–7.28 (m, 6H, Ph), 7.44–7.48 (m, 2H, Ph), 7.87 (br s, 1H, H-8), 7.89 (m, 1H, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.0 (CH_3), 101.3, 111.6, 115.3, 115.7, 116.9, 117.3, 118.8, 122.4, 122.6, 123.6, 125.0, 125.2 (d, $J_{CF} = 3.55$ Hz), 126.8 (d, $J_{CF} = 2.90$ Hz), 128.8, 129.8, 131.8, 131.9, 132.1, 132.8, 133.1, 146.2, 162.9 (d, $J_{CF} = 248.98$ Hz); ^{19}F NMR (188 MHz, $CDCl_3$): δ 111.1, 114.8; MS (EI) *m/z* (rel. %): 500 (1, M^+), 345 (100), 214 (6), 131 (16), 103 (33), 91 (7); HRMS: Found 500.1006, calcd for $C_{28}H_{18}F_2N_2O_3S$ 500.1017.

4.2. 1-{[(4-Methylphenyl)sulfonyl]oxy}-2,3-bis(4-chlorophenyl)-7-indolizinecarbonitrile (3c)

The title compound was prepared from cyclopropenone **1c**, pyridine **2b** and toluene-4-sulfonyl chloride as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:4); yield 276 mg (52%), yellow crystals, mp 207–209 °C, $R_f = 0.33$ (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, CH_3), 6.55 (dd, 1H, $J = 7.65$ and 1.43 Hz, H-6), 6.79–6.81 (m, 2H, Ar), 6.97–7.12 (m, 6H, Ar), 7.35–7.38 (m, 4H, Ar), 7.85 (br s, 1H, H-8), 7.87 (br s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.1 (CH_3), 101.6, 122.1, 122.3, 123.9, 125.1, 126.9, 127.4, 128.5, 128.7, 128.8, 129.2, 129.8, 130.2, 131.6, 131.5, 131.8, 132.1, 133.8, 135.7, 146.2; MS (EI) *m/z* (rel. %): 533 (26, M^+), 381 (25), 345 (13), 157 (100), 139 (11); HRMS: Found 532.0493, calcd for $C_{28}H_{18}Cl_2N_2O_3S$ 532.0510.

4.3. 1-{[(4-Methylphenyl)sulfonyl]oxy}-2,3-bis(4-methylphenyl)-7-indolizinecarbonitrile (3d)

The title compound was prepared from cyclopropenone **1d**, pyridine **2b** and toluene-4-sulfonyl chloride as described for **3b** above. The product was purified by flash

chromatography on silica gel eluting with EtOAc–hexane (1:9) followed by (1:4); yield 190 mg (77%), yellow crystals, mp 205–208 °C, $R_f = 0.29$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 6.48 (dd, 1H, $J = 7.5$ and 1.8 Hz, H-6), 6.77–6.94 (m, 6H, Ar), 7.06–7.19 (m, 4H, Ar), 7.35–7.37 (m, 2H, Ar), 7.81 (br s, 1H, H-8), 7.87 (dd, 1H, $J = 7.5$ and 0.89 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6 (CH_3), 21.8 (CH_3), 22.0 (CH_3), 100.5, 111.0, 119.1, 122.4, 123.1, 123.3, 123.9, 124.8, 126.4, 126.9, 128.0, 128.8, 129.6, 130.2, 130.3, 130.7, 131.9, 137.0, 139.3, 145.7; MS (EI) *m/z* (rel. %): 492 (1, M^+), 337 (100), 205 (4), 131 (5), 103 (14); HRMS: Found 492.1507, calcd for $C_{30}H_{24}N_2O_3S$ 492.1491.

4.4. 1-{[(4-Methylphenyl)sulfonyl]oxy}-2,3-bis(4-methoxyphenyl)-7-indolizinecarbonitrile (3e)

The title compound was prepared from cyclopropenone **1e** (314 mg, 1.00 mmol), pyridine **2b** (104 mg, 1.00 mmol) and toluene-4-sulfonyl chloride (382 mg, 2.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:9) followed by (1:4); yield 220 mg (42%), yellow crystals, mp 204–205 °C, $R_f = 0.50$ (SiO_2, EtOAc–hexane, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.47 (dd, 1H, $J = 7.4$ and 1.6 Hz, H-6), 6.57–6.61 (m, 2H, Ar), 6.80–6.94 (m, 6H, Ar), 7.09–7.14 (m, 2H, Ar), 7.25–7.36 (m, 2H, Ar), 7.78 (dd, 1H, $J = 1.6$ and 0.90 Hz, H-8), 7.83 (dd, 1H, $J = 7.4$ and 0.90 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0 (CH_3), 55.6 (OCH_3), 55.7 (OCH_3), 100.4, 111.0, 113.8, 114.7, 115.2, 119.2, 121.5, 122.4, 122.8, 123.2, 123.4, 123.5, 124.7, 126.8, 128.6, 128.9, 129.7, 131.4, 132.2, 132.7, 145.3, 159.1, 160.3; MS (CI) *m/z* (rel. %): 525 (2, M+1), 370 (91), 282 (6), 238 (2), 152 (3), 139 (22), 135 (28), 92 (100); HRMS: Found 524.1484, calcd for $C_{30}H_{24}N_2O_5S$ 524.1506.

4.5. 1-{[(4-Methylphenyl)sulfonyl]oxy}-2,3-diethyl-7-indolizinecarbonitrile (3f)

The title compound was prepared from cyclopropenone **1f** (163 mg, 1.48 mmol), pyridine **2b** (154 mg, 1.48 mmol) and toluene-4-sulfonyl chloride (573 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:29) followed by (1:19); yield 398 mg (73%), yellow crystals, mp 110–114 °C, $R_f = 0.42$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (200 MHz, $CDCl_3$): δ 1.09 (t, 3H, $J = 7.6$ Hz, CH_3), 1.17 (t, 3H, $J = 7.6$ Hz, CH_3), 2.51 (s, 3H, CH_3), 2.53 (q, 2H, $J = 7.6$ Hz, CH_2), 2.86 (q, 2H, $J = 7.6$ Hz, CH_2), 6.49 (dd, 1H, $J = 7.4$ and 1.8 Hz, H-6), 6.94 (br s, 1H, H-8), 7.37 (d, 2H, $J = 8.2$ Hz, Ar), 7.63 (br d, 1H, $J = 7.4$ Hz, H-5), 7.77 (d, 2H, $J = 8.2$ Hz, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.4 (CH_3), 15.3 (CH_2), 16.8 (CH_3), 17.7 (CH_2), 22.1 (CH_3), 98.0, 110.1, 119.4, 121.4, 123.5, 124.3, 125.5, 127.2, 129.1, 130.4, 132.7, 146.6; MS (EI) *m/z* (rel. %): 368 (2, M^+), 213 (100), 197 (4), 183 (4), 103 (20), 91 (5); HRMS: Found 368.1194, calcd for $C_{20}H_{20}N_2O_3S$ 368.1187; Anal. Found: C, 65.07; H, 5.39. $C_{20}H_{20}N_2O_3S$ requires C, 65.20; H, 5.47.

4.6. 1-{[(4-Methylphenyl)sulfonyl]oxy}-2,3-dibutyl-7-indolizinecarbonitrile (3g)

The title compound was prepared from cyclopropenone **1g** (103 mg, 0.62 mmol), pyridine **2b** (64 mg, 0.62 mmol) and toluene-4-sulfonyl chloride (248 mg, 1.30 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel, eluting with EtOAc–hexane (1:29) followed by (1:19); yield 150 mg (57%), yellow crystals, mp 121–123 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, 3H, $J = 7.1$ Hz, CH_3), 0.93 (t, 3H, $J = 7.1$ Hz, CH_3), 1.15–1.28 (m, 4H, $2 \times CH_2$), 1.31–1.51 (m, 4H, $2 \times CH_2$), 2.32 (t, 2H, $J = 7.7$ Hz, CH_2), 2.48 (s, 3H, CH_3), 2.77 (t, 2H, $J = 7.6$ Hz, CH_2), 6.46 (dd, 1H, $J = 7.3$ and 1.7 Hz, H-6) 7.01 (br s, 1H, H-8), 7.32 (d, 2H, $J = 8.2$ Hz, Ar), 7.59 (dd, 1H, $J = 7.3$ and 0.57 Hz, H-5), 7.75 (d, 2H, $J = 8.2$ Hz, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2 ($2 \times CH_3$), 22.2 (CH_2), 23.0 (CH_2), 23.1 (CH_2), 23.4 (CH_2), 24.2 (CH_2), 29.9 (CH_2), 32.6 (CH_3), 98.0, 110.1, 121.5, 121.7, 123.2, 123.6, 124.5, 127.6, 129.1, 130.4, 132.7, 146.6; MS (EI) *m/z* (rel. %): 424 (2, M^+), 269 (100), 227 (16), 183 (7), 131 (5), 103 (15), 91 (7); Anal. Found: C, 67.76; H, 6.70; N 6.45. $C_{24}H_{28}N_2O_3S$ requires C, 67.90; H, 6.65; N, 6.60.

4.7. 2,3-Diphenyl-1-indolizinol tosylate (3h)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2a** (121 μL, 1.50 mmol) and toluene-4-sulfonyl chloride (572 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:29) followed by (1:19); yield 383 mg (58%), yellow crystals, mp 156–159 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 2.24 (s, 3H, CH_3), 6.44 (m, 1H, H-6), 6.76 (m, 1H, H-7), 6.79–6.85 (m, 4H, Ph), 6.99–7.03 (m, 3H, Ph), 7.16–7.21 (m, 2H, Ph), 7.21–7.32 (m, 5H, Ar), 7.54 (br d, 1H, $J = 9.1$ Hz, H-8), 7.91 (br d, 1H, $J = 7.2$ Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.0 (CH_3), 111.7, 117.6, 118.8, 119.6, 120.8, 121.0, 123.5, 125.4, 126.5, 128.0, 128.3, 128.8, 129.3, 129.4, 130.5, 130.8, 131.2, 131.9, 132.2, 145.0; MS (EI) *m/z* (rel. %): 440 (14, M^+), 285 (100), 256 (5), 178 (6), 157 (7), 139 (8), 106 (6), 92 (14), 78 (10); Anal. Found: C, 74.23; H, 4.92; N, 3.38. $C_{27}H_{21}NO_3S$ requires C, 73.78; H, 4.82; N, 3.19.

4.8. 1-{[(4-Methylphenyl)sulfonyl]oxy}-2,3-diphenyl-7-indolizinecarboxaldehyde (3i)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2c** (142 μL, 1.50 mmol) and toluene-4-sulfonyl chloride (572 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:29) followed by (1:19); yield 491 mg (70%), yellow crystals, mp 153–156 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, CH_3), 6.85 (br d, 1H, $J = 7.4$ Hz, H-6), 6.87–7.09 (m, 7H, Ph),

7.19–7.22 (m, 2H, Ar), 7.33–7.39 (m, 5H, Ar), 7.89 (br d, 1H, J = 7.4 Hz, H-5), 8.06 (dd, 1H, J = 1.6 and 0.83 Hz, H-8), 9.89 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0 (CH_3), 107.5, 122.4, 122.9, 124.2, 124.4, 126.8, 127.2, 127.9, 128.2, 128.6, 128.8, 129.2, 129.5, 129.6, 130.4, 130.9, 131.6, 145.6, 189.9 (CO); MS (EI) m/z (rel. %): 467 (1, M^+), 312 (100), 282 (3), 106 (25), 92 (3); Anal. Found: C, 72.30; H, 4.90; N, 3.11. $C_{28}H_{21}NO_4S$ requires C, 71.93; H, 4.53; N, 3.00.

4.9. 1-{[(4-Methylphenyl)sulfonyl]oxy}-2,3-diphenyl-7-indolizinylethanone (3j)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2d** (165 μL, 1.50 mmol) and toluene-4-sulfonyl chloride (572 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:29) followed by (1:19); yield 551 mg (76%), yellow crystals, mp 149–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 6.85 (br d, 1H, J = 7.4 Hz, H-6), 6.87–6.89 (m, 3H, Ar), 7.01–7.08 (m, 4H, Ar), 7.18–7.23 (m, 2H, Ar), 7.32–7.35 (m, 5H, Ar), 7.86 (br d, 1H, J = 7.4 Hz, H-5), 8.17 (br s, 1H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0 (CH_3), 26.0 (CH_3), 109.4, 121.4, 121.7, 122.6, 123.2, 123.8, 127.1, 127.7, 127.8, 128.2, 128.8, 129.0, 129.5, 129.6, 129.8, 130.2, 131.0, 131.3, 131.6, 145.5, 196.0 (CO); MS (EI) m/z (rel. %): 481 (1, M^+), 326 (100), 178 (5), 148 (5), 120 (23), 91 (8), 78 (4); Anal. Found: C, 72.11; H, 4.81; N, 2.92. $C_{29}H_{23}NO_4S$ requires C, 72.33; H, 4.81; N, 2.92.

4.10. 7-(1,1-Dimethylethyl)-2,3-diphenyl-1-indolizinol tosylate (3k)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2e** (121 μL, 1.50 mmol) and toluene-4-sulfonyl chloride (572 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:29) followed by (1:19); yield 386 mg (52%), yellow crystals, mp 95–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 9H, $3 \times CH_3$), 2.29 (s, 3H, CH_3), 6.52 (dd, 1H, J = 7.6 and 1.2 Hz, H-6), 6.92–7.01 (m, 6H, Ar), 7.0–7.30 (m, 8H, Ar), 7.33 (br s, 1H, H-8), 7.92 (br d, 1H, J = 7.6 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.5 ($3 \times CH_3$), 30.8 (C), 32.1 (CH_3), 111.3, 118.9, 121.0, 123.3, 125.4, 125.5, 126.8, 128.1, 128.1, 128.9, 129.3, 129.5, 130.5, 131.0, 131.2, 132.3, 132.6; MS (ESI) m/z (rel. %): 496 (100, M+1); Anal. Found: C, 74.62; H, 5.55; N, 2.87. $C_{31}H_{29}NO_3S$ requires C, 75.12; H, 5.90; N, 2.83.

4.11. 1-[(Methylsulfonyl)oxy]-2,3-diphenyl-7-indolizinecarbonitrile (3l)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2b** (156 mg, 1.50 mmol) and methanesulfonyl chloride (344 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:4); yield 411 mg (71%), yellow crystals, mp 210–212 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60 (s, 3H, CH_3), 6.51 (dd, 1H, J = 7.4 and 1.6 Hz, H-6), 7.22–7.45 (m, 7H, Ph), 7.46–7.55 (m, 3H, Ph), 7.94 (dd, 1H, J = 7.4 and 1.0 Hz, H-5), 8.02 (dd, 1H, J = 1.6 and 1.0 Hz, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.6 (CH_3), 101.4, 111.6, 118.9, 122.6, 123.6, 123.9, 124.8, 126.8, 128.3, 129.2, 129.2, 129.2, 129.5, 130.5, 130.9, 131.1; MS (EI) m/z (rel. %): 388 (5, M^+), 309 (100), 178 (5), 131 (11), 103 (27); Anal. Found: C, 67.85; H, 4.07; N, 7.03. $C_{22}H_{16}N_2O_3S$ requires C, 68.02; H, 4.15; N, 7.21.

4.12. 1-[(Butylsulfonyl)oxy]-2,3-diphenyl-7-indolizinecarbonitrile (3m)

The title compound was prepared from cyclopropenone **1a** (206 mg, 1.00 mmol), pyridine **2b** (104 mg, 1.00 mmol) and *n*-butanesulfonyl chloride (258 μL, 2.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:19) followed by (1:9); yield 263 mg (61%), yellow crystals, mp 172–174 °C, R_f = 0.46 (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.73 (t, 3H, J = 7.23 Hz, CH_3), 1.37 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 2.75 (t, 2H, J = 5.1 Hz, CH_2), 6.54 (dd, 1H, J = 7.4 and 1.7 Hz, H-6), 7.23–7.31 (m, 7H, Ph), 7.35–7.40 (m, 3H, Ph), 7.94 (dd, 1H, J = 7.4 and 0.98 Hz, H-5), 8.05 (dd, 1H, J = 1.7 and 0.98 Hz, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6 (CH_3), 23.1 (CH_2), 25.4 (CH_2), 50.8 (CH_2), 101.1, 111.5, 119.0, 122.6, 123.2, 123.6, 124.0, 125.1, 126.7, 128.2, 129.0, 129.2, 129.5, 129.7, 130.7, 130.8, 131.2; MS (EI) m/z (rel. %): 430 (2, M^+), 309 (100), 178 (5), 131 (8), 103 (19); HRMS: Found 430.1351, calcd for $C_{25}H_{22}N_2O_3S$ 430.1351.

4.13. 1-{[(2-Methyl)ethylsulfonyl]oxy}-2,3-diphenyl-7-indolizinecarbonitrile (3n)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2b** (156 mg, 1.50 mmol) and toluene-4-sulfonyl chloride (572 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:29) followed by (1:19); yield 183 mg (44%), yellow crystals, mp 195–198 °C, R_f = 0.41 (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (d, 6H, J = 6.9 Hz, $2 \times CH_3$), 3.15 (m, 1H, CH), 6.53 (dd, 1H, J = 7.4 and 1.7 Hz, H-6), 7.16 (m, 7H, Ph), 7.35–7.42 (m, 3H, Ph), 7.94 (dd, 1H, J = 7.4 and 0.95 Hz, H-5), 8.07 (dd, 1H, J = 1.7 and 0.95 Hz, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.0 ($2 \times CH_3$), 53.6 (CH), 100.9, 111.3, 119.1, 122.5, 123.4, 123.5, 124.2, 125.3, 126.2, 128.1, 128.6, 128.8, 129.3, 129.3, 129.6, 130.8, 130.9, 131.2; MS (EI) m/z (rel. %): 416 (1, M^+), 309 (100), 281 (7), 178 (8), 152 (2), 131 (10), 103 (25); HRMS: Found 416.1210, calcd for $C_{24}H_{20}N_2O_3S$ 416.1194.

4.14. 1-[(*N*,*N*-Dimethylaminosulfonyl)oxy]-2,3-diphenyl-7-indolizinecarbonitrile (3p)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2b** (156 mg, 1.50 mmol) and dimethylsulfamoyl chloride (323 μL, 3.00 mmol) as

described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:19); yield 229 mg (55%), yellow crystals, mp 212–213 °C, $R_f = 0.19$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (300 MHz, $CDCl_3$): δ 2.61 (s, 6H, $2 \times CH_3$), 6.54 (dd, 1H, $J = 7.4$ and 1.7 Hz, H-6), 7.26–7.33 (m, 7H, Ph), 7.39–7.43 (m, 3H, Ph), 7.97 (dd, 1H, $J = 7.4$ and 0.71 Hz, H-5), 8.14 (br s, 1H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.6 ($2 \times CH_3$), 100.7, 111.3, 119.2, 122.4, 123.1, 123.3, 123.9, 125.4, 128.0, 128.8, 129.3, 129.4, 129.7, 130.8, 130.9, 131.4; MS (EI) *m/z* (rel. %): 417 (1, M^+), 309 (100), 281 (7), 178 (7), 103 (23); HRMS: Found 417.1165, calcd for $C_{23}H_{19}N_3O_3S$ 417.1147.

4.15. 1-[(Phenylsulfonyl)oxy]-2,3-diphenyl-7-indolizinecarbonitrile (3q)

The title compound was prepared from cyclopropenone **1a** (206 mg, 1.00 mmol), pyridine **2b** (104 mg, 1.00 mmol) and benzenesulfonyl chloride (530 mg, 2.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:19) followed by (1:9); yield 277 mg (41%), yellow crystals, mp 208–209 °C, $R_f = 0.31$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (200 MHz, $CDCl_3$): δ 6.58 (br d, 1H, $J = 7.4$ Hz, H-6), 6.94 (br d, 2H, $J = 6.3$ Hz, Ph), 7.11–7.30 (m, 7H, Ph), 7.41–7.47 (m, 4H, Ph), 7.54 (m, 2H, Ph), 7.94 (br d, 1H, $J = 7.4$ Hz, H-5), 7.98 (br s, 1H, H-8); ^{13}C NMR (50 MHz, $CDCl_3$): δ 101.1, 111.3, 122.5, 123.4, 125.0, 127.5, 128.5, 128.8, 129.1, 129.4, 129.7, 130.4, 130.9, 134.6, 134.6; MS (EI) *m/z* (rel. %): 450 (2, M^+), 309 (100), 279 (4), 178 (6), 131 (10), 103 (24), 77 (6); HRMS: Found 450.1038, calcd for $C_{27}H_{18}N_2O_3S$ 450.1059.

4.16. 1-{[(2-Methylphenyl)sulfonyl]oxy}-2,3-diphenyl-7-indolizinecarbonitrile (3r)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2b** (156 mg, 1.50 mmol) and *o*-toluenesulfonyl chloride (572 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:19); yield 357 mg (77%), yellow crystals, mp 162–165 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 3H, CH_3), 6.56 (dd, 1H, $J = 7.4$ and 1.7 Hz, H-6), 6.90 (m, 2H, Ar), 7.08–7.17 (m, 7H, Ar), 7.30–7.42 (m, 4H, Ar), 7.43–7.64 (dd, 1H, $J = 7.9$ and 1.3 Hz, Ar), 7.89 (dd, 1H, $J = 1.7$ and 0.97 Hz, H-8), 7.96 (dd, 1H, $J = 7.4$ and 0.97 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3 (CH_3), 100.9, 111.3, 119.0, 122.5, 123.5, 123.7, 124.1, 125.0, 126.2, 127.0, 127.6, 128.5, 129.3, 129.3, 129.6, 130.3, 130.7, 130.8, 133.1, 133.9, 134.7; MS (EI) *m/z* (rel. %): 464 (1, M^+), 309 (100), 281 (2), 178 (4), 131 (8), 103 (21), 91 (4); Anal. Found: C, 72.04; H, 4.71; N, 5.80. $C_{28}H_{20}N_2O_3S$ requires C, 72.39; H, 4.34; N, 6.03.

4.17. 1-{[(2,4,6-Trimethylphenyl)sulfonyl]oxy}-2,3-diphenyl-7-indolizinecarbonitrile (3s)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2b** (156 mg, 1.50 mmol) and 2,4,6-trimethylbenzenesulfonyl chloride (752 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:19), yield 349 mg (71%), yellow crystals, mp 196–199 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_3), 2.35 (s, 6H, $2 \times CH_3$), 6.56 (dd, 1H, $J = 7.4$ and 1.7 Hz), 6.71 (br s, 2H, Ar), 6.94–7.40 (m, 10H, Ph), 7.83 (br s, 1H, H-8), 7.95 (dd, 1H, $J = 7.4$ and 0.74 Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4 (CH_3), 23.4 ($2 \times CH_3$), 100.8, 111.2, 119.1, 122.5, 123.6, 123.8, 124.1, 125.1, 127.0, 127.4, 128.2, 129.3, 129.6, 130.2, 130.6, 130.9, 132.2, 140.8, 144.4; MS (CI) *m/z* (rel. %): 493 (5, M+1), 310 (100), 281 (6), 185 (6), 178 (6), 167 (4), 151 (4), 120 (20), 105 (14), 91 (4); Anal. Found: C, 73.32; H, 5.11. $C_{30}H_{24}N_2O_3S$ requires C, 73.32; H, 5.11.

4.18. 1-{{[4-(2-Methylethyl)phenyl]sulfonyl}oxy}-2,3-diphenyl-7-indolizinecarbonitrile (3t)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2b** (156 mg, 1.50 mmol) and *p*-isopropylbenzenesulfonyl chloride (617 μL, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:19); yield 315 mg (64%), yellow crystals, mp 138–142 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 1.22 (d, 6H, $J = 6.9$ Hz, $2 \times CH_3$), 2.89 (m, 1H, CH), 6.57 (dd, 1H, $J = 7.6$ and 1.5 Hz, H-6), 6.96–7.23 (m, 9H, Ar), 7.30–7.45 (m, 5H, Ar), 7.93 (br s, 1H, H-8), 7.96 (m, 1H, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.9 ($2 \times CH_3$), 34.6 (CH), 101.0, 111.3, 122.5, 123.3, 123.5, 123.8, 125.0, 127.0, 127.2, 127.5, 128.5, 129.0, 129.4, 129.7, 130.3, 130.9, 132.1; MS (EI) *m/z* (rel. %): 492 (1, M^+), 309 (100), 279 (2), 178 (4), 131 (8), 103 (20); Anal. Found: C, 73.08; H, 5.16; N, 5.34. $C_{30}H_{24}N_2O_3S$ requires C, 73.15; H, 4.91; N, 5.69.

4.19. 1-{[(4-Methoxyphenyl)sulfonyl]oxy}-2,3-diphenyl-7-indolizinecarbonitrile (3u)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2b** (156 mg, 1.50 mmol) and *p*-methoxybenzenesulfonyl chloride (309 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:19) followed by (1:9) and finally (1:4); yield 480 mg (67%), yellow crystals, mp 212–214 °C, $R_f = 0.37$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (200 MHz, $CDCl_3$): δ 3.79 (s, 3H, OCH_3), 6.54 (dd, 1H, $J = 7.4$ and 1.7 Hz, H-6), 6.60 (m, 2H, Ar), 6.89–6.94 (m, 2H, Ph), 7.03–7.08 (m, 3H, Ph), 7.09–7.27 (m, 2H, Ph), 7.34–7.49 (m, 5H, Ar), 7.92 (dd, 1H, $J = 7.4$ and 0.96 Hz, H-5), 7.99 (dd, 1H, $J = 1.7$ and 0.96 Hz, H-8); ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.0 (OCH_3), 100.9, 111.3, 114.2, 122.5, 123.1, 123.5, 123.8, 125.1, 125.6, 126.9, 127.4, 128.4, 129.6, 130.4, 130.9, 130.9, 131.0, 164.4; MS (EI) *m/z* (rel. %): 480 (1, M^+), 309 (100), 178 (5), 131 (10), 103 (23); HRMS: Found 480.1144, calcd for $C_{28}H_{20}N_2O_4S$ 480.1157; Anal. Found: C, 69.95; H, 4.48. $C_{28}H_{20}N_2O_4S$ requires C, 69.98; H, 4.20.

4.20. 1-{[(4-Methoxyphenyl)sulfonyl]oxy}-2,3-bis(4-methylphenyl)-7-indolizinecarbonitrile (3v)

The title compound was prepared from cyclopropenone **1d** (117 mg, 0.50 mmol), pyridine **2b** (52 mg, 0.50 mmol) and *p*-methoxybenzenesulfonyl chloride (103 mg, 1.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:19) followed by (1:9) and finally (1:4); yield 132 mg (52%), yellow crystals, mp 175–176 °C, $R_f = 0.21$ (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.53 (dd, 1H, $J = 7.4$ and 1.7 Hz, H-6), 6.59 (d, 2H, $J = 9.0$ Hz, Ar), 6.82 (d, 2H, $J = 8.0$ Hz, Ar), 6.90 (d, 2H, $J = 8.0$ Hz, Ar), 7.05 (m, 2H, Ar), 7.11 (d, 2H, $J = 8.0$ Hz, Ar), 7.41 (d, 2H, $J = 9.0$ Hz, Ar), 7.91 (br d, 1H, $J = 7.4$ Hz, H-5), 7.94 (br s, 1H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6 (CH_3), 21.8 (CH_3), 55.9 (OCH_3), 100.6, 111.1, 114.1, 119.2, 122.4, 123.0, 123.4, 123.8, 124.9, 125.9, 126.4, 126.9, 128.1, 129.1, 130.2, 130.4, 130.8, 131.0, 136.9, 139.3, 164.5; MS (EI) *m/z* (rel. %): 508 (1, M^+), 337 (100), 321 (5), 309 (4), 205 (5), 191 (2), 155 (4), 131 (6), 103 (16); Anal. Found: C, 70.70; H, 4.98; N, 5.17. $C_{30}H_{24}N_2O_4S$ requires C, 70.85; H, 4.76; N, 5.51.

4.21. 1-{[(2,4-Dimethoxyphenyl)sulfonyl]oxy}-2,3-diphenyl-7-indolizinecarbonitrile (3w)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2b** (156 mg, 1.50 mmol) and 2,4-dimethoxybenzenesulfonyl chloride (710 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:4) followed by (1:2) and finally (1:1); yield 378 mg (74%), yellow crystals, mp 101–104 °C, $R_f = 0.15$ (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.72 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.09 (s, 1H, Ar), 6.28 (dd, 1H, $J = 8.9$ and 2.0 Hz, Ar), 6.52 (dd, 1H, $J = 7.4$ and 1.6 Hz, H-6), 6.96–7.61 (m, 11H, Ar), 7.91 (br d, 1H, $J = 7.4$ Hz, H-5), 7.99 (br s, 1H, H-8); ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.1 (OCH_3), 56.2 (OCH_3), 99.4, 100.6, 104.8, 111.6, 114.6, 119.1, 122.3, 123.8, 123.9, 125.3, 127.2, 128.2, 129.2, 129.4, 129.5, 130.5, 131.0, 133.9, 159.8, 166.5; MS (EI) *m/z* (rel. %): 510 (1, M^+), 309 (100), 281 (10), 279 (4), 178 (8), 138 (13), 131 (8), 103 (22), 77 (2); HRMS: Found 510.1268, calcd for $C_{29}H_{22}N_2O_5S$ 510.1249.

4.22. 1-{[(3,4-Dimethoxyphenyl)sulfonyl]oxy}-2,3-diphenyl-7-indolizinecarbonitrile (3x)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2b** (156 mg, 1.50 mmol) and 3,4-dimethoxybenzenesulfonyl chloride (710 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:4) followed by (1:2) and finally (1:1); yield 448 mg (88%), yellow crystals, mp 208–210 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.56 (d, 1H, $J = 8.6$ Hz, Ar), 6.57 (dd, 1H, $J = 7.4$ and 1.7 Hz, H-6), 6.83–6.90 (m, 3H, Ar), 7.05–7.10 (m, 4H, Ar), 7.12–7.22 (m, 2H, Ar), 7.39–7.47 (m, 3H, Ar), 7.95 (dd, 1H, $J = 7.4$ and 0.96 Hz, H-5), 8.01 (dd, 1H, $J = 1.7$ and 0.96 Hz, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.3 (OCH_3), 56.5 (OCH_3), 101.1, 110.3, 110.6, 111.4, 119.0, 122.5, 123.2, 123.5, 123.7, 127.0, 127.3, 128.1, 129.3, 129.4, 129.7, 129.8, 130.3, 131.9, 149.0, 154.2; MS (EI) *m/z* (rel. %): 510 (1, M^+), 309 (100), 281 (2), 178 (3), 131 (7), 103 (18); Anal. Found: C, 67.76; H, 4.01; N, 5.52. $C_{29}H_{22}N_2O_5S$ requires C, 68.20; H, 4.34; N, 5.49.

4.23. 1-{[(2,5-Dimethoxyphenyl)sulfonyl]oxy}-2,3-diphenyl-7-indolizinecarbonitrile (3y)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2b** (156 mg, 1.50 mmol) and 2,5-dimethoxybenzenesulfonyl chloride (710 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:4) followed by (1:2) and finally (1:1); yield 398 mg (78%), yellow crystals, mp 193–195 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 6.51 (d, 1H, $J = 7.4$ and 1.6 Hz, H-6), 6.89–7.09 (m, 10H, Ph), 7.34–7.40 (m, 3H, Ar), 7.90 (dd, 1H, $J = 7.4$ and 0.85 Hz, H-5), 7.93 (dd, 1H, $J = 1.6$ and 0.85 Hz, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.5 (OCH_3), 56.8 (OCH_3), 100.7, 111.2, 114.1, 115.8, 119.1, 122.4, 123.2, 123.3, 123.5, 123.7, 124.0, 125.1, 127.4, 128.3, 129.3, 129.6, 130.5, 130.8, 130.9, 152.5, 152.9; MS (EI) *m/z* (rel. %): 510 (1, M^+), 309 (100), 281 (2), 178 (3), 138 (2), 103 (19); Anal. Found: C, 68.03; H, 4.42; N, 5.26. $C_{29}H_{22}N_2O_5S$ requires C, 68.20; H, 4.34; N, 5.49.

4.24. 1-{[(2-Thienyl)sulfonyl]oxy}-2,3-diphenyl-7-indolizinecarbonitrile (3z)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2b** (156 mg, 1.50 mmol) and 2-thiophenesulfonyl chloride (548 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:4) followed by (1:2) and finally (1:1); yield 169 mg (37%), yellow-green crystals, mp 222–225 °C, $R_f = 0.34$ (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.57 (dd, 1H, $J = 7.6$ and 1.5 Hz, H-6), 6.79 (t, 1H, $J = 4.4$ Hz, H in thienyl), 6.93–7.02 (m, 2H, Ar), 7.11–7.16 (m, 3H, Ar), 7.23–7.29 (m, 4H, Ar), 7.41–7.57 (m, 3H, Ar), 7.94 (m, 1H, H-5), 7.96 (br s, 1H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 101.3, 111.4, 118.9, 122.6, 123.3, 123.5, 123.9, 124.8, 126.8, 127.5, 127.9, 128.6, 129.3, 129.7, 130.4, 130.7, 130.9, 134.0, 135.5, 135.9; MS (EI) *m/z* (rel. %): 456 (2, M^+), 309 (100), 279 (4), 178 (6), 131 (12), 103 (28), 84 (3); HRMS (ESI): Found 457.0670, calcd for $C_{25}H_{16}N_2O_3S_2$ 457.0675.

4.25. 1-{[(3-Thienyl)sulfonyl]oxy}-2,3-diphenyl-7-indolizinecarbonitrile (3aa)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2b** (156 mg,

1.50 mmol) and 3-thiophenesulfonyl chloride (548 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:19) followed by (1:9); yield 329 mg (72%), yellow crystals, mp 244–247 °C, $R_f = 0.23$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (300 MHz, $CDCl_3$): δ 6.57 (dd, 1H, $J = 7.3$ and 1.8 Hz, H-6), 6.93 (m, 1H, thienyl), 7.00–7.05 (m, 3H, Ar), 7.13–7.17 (m, 3H, Ar), 7.23–7.40 (m, 2H, Ar), 7.41–7.43 (m, 3H, Ar), 7.69–7.71 (m, 1H, thienyl), 7.93 (br s, 1H, H-8), 7.96 (br s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 101.2, 111.4, 122.5, 123.2, 123.4, 123.8, 124.9, 126.4, 127.6, 127.8, 128.6, 129.3, 129.4, 129.7, 130.3, 130.8, 130.9, 134.0, 134.2; MS (ESI) *m/z* (rel. %): 457 (100, M+1); HRMS (ESI): Found 457.0657, calcd for $C_{25}H_{16}N_2O_3S_2$ 457.0675.

4.26. 1-{[(4-Chlorophenyl)sulfonyl]oxy}-2,3-diphenyl-7-indolizinecarbonitrile (3bb)

The title compound was prepared from cyclopropenone **1a** (206 mg, 1.00 mmol), pyridine **2b** (104 mg, 1.00 mmol) and *p*-chlorobenzenesulfonyl chloride (422 mg, 2.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:19) followed by (1:9); yield 310 mg (64%), yellow crystals, mp 193–195 °C, $R_f = 0.38$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (200 MHz, $CDCl_3$): δ 6.50 (dd, 1H, $J = 7.4$ and 1.3 Hz, H-6), 6.74 (d, 2H, $J = 6.7$ Hz, Ar), 6.93–7.14 (m, 8H, Ar), 7.19–7.31 (m, 4H, Ar), 7.87 (br d, 1H, $J = 7.4$ Hz, H-5), 8.03 (br s, 1H, H-8); ^{13}C NMR (50 MHz, $CDCl_3$): δ 101.4, 111.5, 122.6, 122.9, 123.7, 125.0, 127.6, 128.5, 129.1, 129.2, 129.5, 129.7, 130.1, 130.3, 130.7, 130.9, 132.7, 141.4; MS (CI) *m/z* (rel. %): 310 (100), 144 (6), 112 (27), 77 (9); Anal. Found: C, 66.83; H, 3.70; N 5.51. $C_{27}H_{17}ClN_2O_3S$ requires C, 66.87; H, 3.53; N, 5.78.

4.27. 1-{[(4-Trifluoromethylphenyl)sulfonyl]oxy}-2,3-diphenyl-7-indolizinecarbonitrile (3cc)

The title compound was prepared from cyclopropenone **1a** (309 mg, 1.50 mmol), pyridine **2b** (156 mg, 1.50 mmol) and 4-(trifluromethyl)benzenesulfonyl chloride (735 mg, 3.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:19) followed by (1:9); yield 384 mg (74%), yellow crystals, mp 180–182 °C, $R_f = 0.50$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (300 MHz, $CDCl_3$): δ 6.52 (dd, 1H, $J = 7.4$ and 1.3 Hz, H-6), 6.70 (m, 2H, Ar), 6.91–7.09 (m, 5H, Ph), 7.10–7.25 (m, 5H, Ph), 7.46 (m 2H, Ar), 7.68 (br d, 1H, $J = 7.4$ Hz, H-5), 8.05 (br s, 1H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 101.6, 111.6, 118.9, 121.4, 122.6, 122.7, 123.6, 123.8, 124.9, 126.0 (q, $J_{CF} = 5.3$ Hz), 127.6, 128.7, 128.9, 129.3, 129.5, 129.7, 130.2, 130.5, 130.8, 135.8 (q, $J_{CF} = 250$ Hz, CF_3), 137.9; ^{19}F NMR (188 MHz, $CDCl_3$): δ −63.9 (CF_3); MS (EI) *m/z* (rel. %): 518 (2, M^+), 309 (100), 279 (3), 178 (4), 145 (3), 131 (9), 103 (22); HRMS: Found 518.0901, calcd for $C_{28}H_{17}F_3N_2O_3S$ 518.0912.

4.28. 1-{[(4-Methylsulfonylphenyl)sulfonyl]oxy}-2,3-diphenyl-7-indolizinecarbonitrile (3dd)

The title compound was prepared from cyclopropenone **1a** (206 mg, 1.00 mmol), pyridine **2b** (104 mg, 1.00 mmol) and 4-methylsulfonylbenzenesulfonyl chloride (580 mg, 2.00 mmol) as described for **3b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:9) followed by (1:4) and finally (1:2); yield 433 mg (82%), yellow crystals, mp 222–224 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.97 (s, 3H, CH_3), 6.58 (dd, 1H, $J = 7.4$ and 1.7 Hz, H-6), 6.78 (d, 2H, $J = 7.7$ Hz, Ar), 7.01–7.15 (m, 5H, Ar), 7.33–7.37 (m, 3H, Ar), 7.57–7.64 (m, 4H, Ar), 7.93 (dd, 1H, $J = 7.4$ and 0.74 Hz, H-5), 8.08 (br s, 1H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.6 (CH_3), 101.7, 111.7, 118.8, 122.6, 122.7, 123.6, 123.9, 124.8, 126.3, 127.9, 128.8, 128.9, 129.6, 129.8, 130.1, 130.4, 130.8, 139.7, 145.6; MS (CI) *m/z* (rel. %): 529 (1, M+1), 311 (100), 294 (5), 281 (7), 200 (24), 171 (7), 157 (49), 105 (6), 77 (10); Anal. Found: C, 63.60; H, 4.06; N, 5.05. $C_{28}H_{20}N_2O_5S_2$ requires C, 63.62; H, 3.81; N, 5.30.

4.29. 1-Bromo-2,3-bis(4-fluorophenyl)-7-indolizinecarbonitrile (4b) and 1,6-dibromo-2,3-bis(4-fluorophenyl)-7-indolizinecarbonitrile (5b)

A mixture of 2,3-bis(4-fluorophenyl)-2-cyclopropen-1-one **1b** (121 mg, 0.50 mmol) and 4-cyanopyridine **2b** (52 mg, 0.50 mmol) in dry DCE (10 mL) was refluxed under N_2 for 20 h, cooled and the solvent was removed under a stream of N_2. The residue was dissolved in dry acetonitrile (5 mL) and the mixture was stirred at ambient temperature under N_2. A mixture of triphenylphosphine dibromide in acetonitrile [generated in a separate flask from triphenylphosphine (393 mg, 1.50 mmol) and bromine (240 mg, 1.50 mmol) in acetonitrile (3 mL) at 0 °C] was added and the resulting mixture was stirred at 70 °C for 72 h, cooled and evaporated in vacuo. The products were separated by flash chromatography on silica gel eluting with EtOAc–hexane (1:29); yield 147 mg (72%) of **4b** and 24 mg (10%) of **5b**.

4.30. 1-Bromo-2,3-bis(4-fluorophenyl)-7-indolizinecarbonitrile (4b)

Yellow crystals, mp 180–182 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 6.65 (dd, 1H, $J = 7.6$ and 1.6 Hz, H-6), 6.99–7.24 (m, 8H, Ar), 7.90 (br s, 1H, H-8), 7.97 (br s, 1H, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 93.8, 101.2, 111.0, 115.6, 116.0, 116.8, 119.0, 123.1, 125.5 (d, $J_{CF} = 3.68$ Hz), 125.7, 128.5, 128.6 (d, $J_{CF} = 3.33$ Hz), 129.0, 129.3, 132.5, 132.7, 132.8, 163.0 (d, $J_{CF} = 249$ Hz); MS (EI) *m/z* (rel. %): 408/410 (100/99, M^+), 364 (25), 329 (71), 164 (17), 123 (2); HRMS: Found 408.0058, calcd for $C_{21}H_{11}BrF_2N_2$ 408.0074.

4.31. 1,6-Dibromo-2,3-bis(4-fluorophenyl)-7-indolizinecarbonitrile (5b)

Yellow crystals, mp 206–210 °C, $R_f = 0.42$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (200 MHz, $CDCl_3$): δ

7.02–7.30 (m, 8H, Ar), 7.98 (br s, 1H, H-8), 8.11 (br s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 95.0, 104.5, 105.2, 115.8, 116.1, 116.1, 117.1, 117.3, 117.4 123.3, 124.8 (d, J_{CF} = 3.08 Hz), 126.5, 128.0, 129.9 (d, J_{CF} = 3.13 Hz), 132.4, 132.5, 132.6, 132.7, 163.0 (d, J_{CF} = 250 Hz); MS (EI) *m/z* (rel. %): 486/488/490 (50/100/50, M^+), 409 (30), 408 (10), 407 (31), 328 (9), 327 (8), 326 (10), 300 (6), 204 (5), 123 (11); HRMS: Found 485.9179, calcd for $C_{21}H_{10}Br_2F_2N_2$ 485.9198.

4.32. 1-Bromo-2,3-bis(4-chlorophenyl)-7-indolizinecarbonitrile (4c) and 1,6-dibromo-2,3-bis(4-chlorophenyl)-7-indolizinecarbonitrile (5c)

The title compounds were prepared from 2,3-bis(4-chlorophenyl)-2-cyclopropen-1-one **1c** and 4-cyanopyridine **2b** as described for the synthesis of **4b** and **5b** above; yield 91 mg (41%) of **4c** and 47 mg (18%) of **5c**.

4.33. 1-Bromo-2,3-bis(4-chlorophenyl)-7-indolizinecarbonitrile (4c)

Yellow crystals, mp 210–212 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.60 (dd, 1H, J = 7.4 and 1.5 Hz, H-6), 7.15–7.41 (m, 8H, Ar), 7.90 (br s, 1H, H-8), 7.94 (br d, 1H, J = 7.4 Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 93.8, 101.5, 111.8, 118.8, 122.8, 123.1, 125.7, 126.7, 127.7, 128.8, 129.2, 130.2, 132.0, 132.1, 132.3; MS (EI) *m/z* (rel. %): 440/444 (60/45, M^+), 442 (100), 396 (8), 361 (26), 291 (11), 185 (11), 145 (14); HRMS: Found 439.9507, calcd for $C_{21}H_{11}BrCl_2N_2$ 439.9483.

4.34. 1,6-Dibromo-2,3-bis(4-chlorophenyl)-7-indolizinecarbonitrile (5c)

Yellow crystals, mp 212–215 °C, R_f = 0.48 (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09–7.41 (m, 8H, Ar), 7.92 (br s, 1H, H-8), 8.08 (br s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$), δ 95.1, 104.8, 105.4, 117.2, 123.3, 125.7, 126.5, 127.1, 128.3, 129.1, 130.4, 130.5, 131.9, 132.0, 134.6, 136.0; MS (EI) *m/z* (rel. %): 518/520/522/524 (38/100/90/33, M^+), 476 (3), 441 (27), 406 (11), 371 (5), 290 (11), 225 (16), 144 (8), 75 (2); HRMS: Found 517.8587, calcd for $C_{21}H_{10}Br_2Cl_2N_2$ 517.8562.

4.35. 1-Bromo-2,3-bis(4-methylphenyl)-7-indolizinecarbonitrile (4d)

The title compound was prepared from 2,3-bis(4-methylphenyl)-2-cyclopropen-1-one **1d** and 4-cyanopyridine **2b** as described for the synthesis of **4b** and **5b** above. Yield 411 mg (41%), yellow crystals, mp 184–186 °C, R_f = 0.47 (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 6.51 (dd, 1H, J = 7.4 and 1.8 Hz, H-6), 7.09–7.22 (m, 8H, Ar), 7.88 (br s, 1H, H-8), 7.96 (dd, 1H, J = 7.4 and 0.72 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7 (CH_3), 21.8 (CH_3), 93.4, 100.5, 111.0, 119.3, 123.2, 125.5, 126.7, 126.8, 128.9, 129.3, 129.4, 129.8, 129.9, 130.3, 130.6, 130.8, 137.6, 139.3; MS (EI) *m/z* (rel. %): 400/402 (100/100, M^+), 356 (16), 321 (50), 306 (14), 153 (13); HRMS: Found 400.0575, calcd for $C_{23}H_{17}BrN_2$ 400.0584.

4.36. 1-[(4-Methylphenyl)sulfonyl]-2,3-diphenyl-7-indolizinecarbonitrile (6)

n-Butyllithium (340 μL, 1.60 M solution in hexane, 0.49 mmol) was added dropwise to a stirred solution of 1-bromo-2,3-diphenyl-7-indolizinecarbonitrile **4a** (183 mg, 0.49 mmol) in dry THF (10 mL) at −78 °C under N_2 and the resulting mixture was stirred at −78 °C for 1 h, after which a solution of *p*-toluenesulfonyl fluoride (860 mg, 4.90 mmol) in THF (5 mL) was added. The resulting mixture was stirred for 2 h at −78 °C and for 8 h at ambient temperature. The product was isolated by flash chromatography on silica gel EtOAc–hexane (1:29) followed by (1:9) and finally (1:4); yield 26 mg (12%), yellow crystals, mp 214–217 °C, R_f = 0.33 (SiO_2, EtOAc–hexane; 1:4). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.36 (s, 3H, CH_3), 6.86 (dd, 1H, J = 7.3 and 1.7 Hz, H-6), 7.07–7.11 (m, 2H, Ar), 7.23–7.39 (m, 12H, Ar), 8.10 (br d, 1H, J = 7.3 Hz, H-5), 9.05 (br s, 1H, H-8); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9 (CH_3), 105.6, 113.1, 115.9, 118.4, 124.1, 126.5, 127.4, 127.9, 128.3, 128.4, 128.7, 129.5, 129.6, 130.8, 131.2, 131.4, 131.8, 140.4, 143.9; MS (EI) *m/z* (rel. %): 448 (100, M^+), 332 (1), 292 (7), 121 (13); HRMS: Found 448.1260, calcd for $C_{28}H_{20}N_2O_2S$ 448.1248.

4.37. 2,3-Bis(4-fluorophenyl)-7-indolizinecarbonitrile (7b)

n-Butyllithium (0.27 mL, 1.6 M solution in hexane, 0.49 mmol) was added drop wise to a stirred solution of 1-bromo-2,3-bis(4-fluorophenyl)-7-indolizinecarbonitrile **4b** (200 mg, 0.49 mmol) in dry THF (20 mL) at 78 °C under N_2 and the resulting mixture was stirred at −78 °C for an additional 2 h before saturated aqueous ammonium chloride (1 mL) was added. The reaction mixture was allowed to reach ambient temperature, the phases were separated and the organic layer was evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:49) followed by (1:29), (1:19) and finally (1:9); yield 105 mg (65%), yellow crystals, mp 198–200 °C, R_f = 0.48 (SiO_2, EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.60 (dd, 1H, J = 7.2 and 1.9 Hz, H-6), 6.97 (br s, 1H, H-1), 6.99–7.39 (m, 8H, Ar), 7.88 (br s, 1H, H-8), 7.92 (br s, 1H, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 100.2, 104.9, 110.8, 115.7, 116.1, 117.0, 117.4, 122.8, 126.6, 130.1 (d, J_{CF} = 3.48 Hz), 130.7, 130.8, 131.0 (d, J_{CF} = 3.66 Hz), 132.9, 133.1, 163.3 (d, J_{CF} = 250 Hz); MS (EI) *m/z* (rel. %): 330 (100, M^+), 227 (6), 201 (3), 164 (6), 155 (5); HRMS: Found 330.0980, calcd for $C_{21}H_{12}F_2N_2$ 330.0969.

4.38. 2,3-Bis(4-chlorophenyl)-7-indolizinecarbonitrile (7c)

The title compound was prepared from 1-bromo-2,3-bis(4-chlorophenyl)-7-indolizinecarbonitrile **4c** (111 mg, 0.250 mmol) as described for compound **7b** above; yield 70 mg (77%), yellow crystals, mp 160–162 °C. ^{1}H NMR

(200 MHz, $CDCl_3$): δ 6.61 (dd, 1H, $J = 7.4$ and 1.8 Hz, H-6), 6.97 (s, 1H, H-1), 7.19–7.29 (m, 6H, Ar), 7.44–7.50 (m, 2H, Ar), 7.90 (br d, 1H, $J = 7.4$ Hz, H-5), 7.97 (br s, 1H, H-8); ^{13}C NMR (50 MHz, $CDCl_3$): δ 100.5, 105.1, 111.0, 122.8, 124.4, 126.7, 128.8, 129.2, 130.0, 130.3, 130.4, 131.2, 132.3, 133.2, 133.6, 135.5; MS (EI) *m/z* (rel. %): 362 (100, M^+), 326 (16), 293 (13), 189 (5), 132 (3), 145 (13), 118 (2); HRMS: Found 362.0391, calcd for $C_{21}H_{12}Cl_2N_2$ 362.0396.

4.39. 2,3-Bis(4-methylphenyl)-7-indolizinecarbonitrile (7d)

The title compound was prepared from 1-bromo-2,3-bis(4-methylphenyl)-7-indolizinecarbonitrile **4c** (195 mg, 0.490 mmol) as described for compound **7b** above; yield 134 mg (83%), yellow crystals, mp 218–222 °C, $R_f = 0.27$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (200 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 6.53 (dd, 1H, $J = 7.4$ and 1.8 Hz, H-6), 6.99 (br s, 1H, H-1), 7.09–7.35 (m, 8H, Ar), 7.86 (br s, 1H, H-8), 7.93 (br d, 1H, $J = 7.4$ Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.6 (CH_3), 21.9 (CH_3), 99.4, 104.9, 110.3, 119.8, 122.9, 125.8, 126.7, 127.8, 129.0, 129.6, 130.5, 130.9, 130.9, 132.2, 137.0, 139.1; MS (EI) *m/z* (rel. %): 322 (100, M^+), 307 (4), 292 (4), 153 (6); HRMS: Found 322.1470, calcd for $C_{23}H_{18}N_2$ 322.1485.

4.40. 6,7-Diphenylpyrrolo[1,2-*c*]pyrimidin-5-ol tosylate (9) and 6,7-diphenylpyrrolo[1,2-*a*]pyrimidin-8-ol tosylate (10)

A mixture of 2,3-diphenyl-2-cyclopropen-1-one (309 mg, 1.50 mmol) and 4-cyanopyridine (156 mg, 1.50 mmol) in dry 1,4-dioxane (20 mL) was refluxed under N_2 for 24 h and cooled to 0 °C, before *N*,*N*-4-dimethylaminopyridine (366 mg, 3.00 mmol) and *p*-toluenesulfonyl chloride (572 mg, 3.00 mmol) were added. The resulting mixture was stirred under N_2 at 0 °C for 30 min and at ambient temperature for 24 h, washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated in vacuo. The products were separated by flash chromatography on silica gel eluting with EtOAc–hexane (1:19) followed by (1:9) and finally (1:4); yield 244 mg (37%) of **9** and 343 mg (52%) of **10**.

4.41. 6,7-Diphenylpyrrolo[1,2-*c*]pyrimidin-5-ol tosylate (9)

Yellow crystals, mp 178–180 °C, $R_f = 0.42$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (200 MHz, $CDCl_3$): δ 2.32 (CH_3), 6.77–6.95 (m, 4H, Ar), 7.14–7.25 (m, 3H, Ar), 7.26–7.34 (m, 7H, Ar), 7.50 (br s, 1H, pyr), 7.52 (br s, 1H, pyr), 8.82 (s, 1H, pyr); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.6 (CH_3), 111.7, 119.5, 124.0, 124.1, 127.3, 128.2, 128.8, 129.1, 129.2, 129.6, 130.4, 131.0, 131.1, 131.6, 132.9, 136.4, 145.4; MS (EI) *m/z* (rel. %): 440 (3, M^+), 285 (100), 178 (6), 107 (5), 91 (4), 79 (20); Anal. Found: C, 70.98; H, 4.60; N, 6.36. $C_{26}H_{20}N_2O_3S$ requires C, 70.89; H, 4.58; N, 6.36.

4.42. 6,7-Diphenylpyrrolo[1,2-*a*]pyrimidin-8-ol tosylate (10)

Yellow crystals, mp 197–200 °C, $R_f = 0.21$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (200 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 6.55 (m, 1H, pyr), 6.98–7.13 (m, 7H, Ar), 7.24–7.38 (m, 7H, Ar), 8.22 (br s, 1H, pyr), 8.25 (m, 1H, pyr); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0 (CH_3), 108.0, 120.4, 122.5, 123.0, 125.4, 127.0, 127.1, 128.3, 128.6, 128.8, 128.8, 129.5, 129.6, 130.6, 131.0, 131.0, 144.9, 145.0; MS (EI) *m/z* (rel. %): 440 (2, M^+), 285 (100), 255 (3), 178 (6), 107 (15), 91 (7), 79 (21); HRMS: Found 440.1195, calcd for $C_{26}H_{20}N_2O_3S$ 440.1195.

4.43. 6,7-Diphenylpyrrolo[1,2-*a*]pyrimidin-8-ol 3-diphenyl-2-propenoate (12)

A mixture of 2,3-diphenyl-2-cyclopropen-1-one **1a** (309 mg, 1.50 mmol), pyridine **8** (156 mg, 1.50 mmol) and *p*-toluenesulfonyl chloride (572 mg, 3.00 mmol) were reacted as described for the synthesis of **9** and **10** above except that in dry DCE (40 mL) was used as solvent. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:29) followed by (1:19), (1:9) and finally (1:4); yield 303 mg (41%), yellow crystals, mp 238–241 °C, $R_f = 0.33$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (300 MHz, $CDCl_3$): δ 6.49 (dd, 1H, $J = 7.2$ and 3.8 Hz, pyr), 7.08–7.26 (m, 10H, Ph), 7.28–7.40 (m, 10H, Ph), 8.08 (s, 1H, =CH), 8.13 (dd, 1H, $J = 3.8$ and 1.5 Hz, pyr), 8.24 (dd, 1H, $J = 7.2$ and 1.5 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 107.4, 116.9, 123.0, 123.5, 127.4, 128.2, 128.6, 128.6, 128.8, 129.0, 129.5, 129.6, 130.1, 130.4, 130.5, 130.6, 130.9, 131.2, 132.0, 135.0, 136.1, 142.8 (=CH), 143.6, 167.0 (CO); MS (EI) *m/z* (rel. %): 492 (22, M^+), 286 (100), 207 (42), 179 (92), 152 (4), 107 (27), 79 (36); HRMS: Found 492.1831, calcd for $C_{34}H_{24}N_2O_2$ 492.1838.

4.44. Inhibition of 15-lipoxygenase

Lipoxygenase activity was measured in borate buffer solutions (0.2 M, pH 9.00) as previously described[13,14] by the increase in absorbance at 234 nm from 30 to 90 s after addition of the enzyme, using linoleic acid (134 μM) as substrate. The final enzyme concentration was 167 U/mL. Test substances were added as DMSO solutions (final DMSO concn 1.6%); DMSO alone was added in uninhibited control experiments. Six or more parallels of controls and three or more parallels for each test substance solution were measured. To ensure constant enzyme activity throughout the experiment, the enzyme solution was kept on ice, and controls were measured at regular intervals. Calculation of enzyme activity was carried out as previously described[14] and IC50 values were determined by linear interpolation between the measuring points closest to 50% activity. Values are expressed as means ± SD. Student's *t*-test was employed for determination of statistical significance.

4.45. Inhibition of 15-lipoxygenase in preincubation experiment

The inhibitor (50 μL), the enzyme solution dissolved in DMSO (50 μL) and 0.2 M, pH 9.00 borate buffer were mixed and incubated for 5 min. The reaction was initiated with linoleic acid (final concn 134 μM) and the inhibition was measured in the same way as described above. For 15-lipoxygenase assays without incubation, the inhibitor (50 μL), linoleic acid (134 μM) and borate buffer were mixed. The reaction was initiated with 50 μL enzyme solution in DMSO and the inhibition was measured in the same way as described above.

4.46. Inhibition of 15-lipoxygenase in the presence of detergent

Borate buffer containing CHAPS to its critical micellar concentration, 0.2 mM, the inhibitor (50 μL), and linoleic acid (134 μM) were mixed. The reaction was initiated with 50 μL enzyme solution in DMSO and the inhibition was measured in the same way as described above. For 15-lipoxygenase assays without CHAPS, the inhibitor (50 μL), linoleic acid (134 μM) and borate buffer (without CHAPS) were mixed. The reaction was initiated with 50 μL enzyme solution in DMSO and the inhibition was measured in the same way as described above.

4.47. Dynamic light scattering (DLS)

Compounds were generally dissolved to 0.25 mM in DMSO and diluted with filtered 200 mM borate buffer. Compounds were analyzed with 10 mW He–Ne laser at 633 nm with a Zetasizer 1000 HSa from Malvern Instruments Limited. The measurements were done in triplicate at 25 °C, with a detector angle of 90° using the Contin algorithm for size distribution.

Acknowledgements

Quota Scholarship to S.T. is gratefully acknowledged. The authors also thank The Norwegian Research Council for the partial financing of the Bruker Avance NMR instruments used in this study.

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