Supporting Information

Design, synthesis and melatoninergic activity of new azido- and isothiocyanato-substituted indoles

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A. Preparation of the compounds

General Methods. Melting points were determined on a Büchi 530 apparatus and are uncorrected. ^{1}H NMR spectra were taken in $CDCl_3$ and recorded either on a Bruker DRX 400 (400 MHz) spectrometer, and the spectra are reported in δ. ^{13}C NMR spectra were taken at 50 MHz on a Bruker AC 200 spectrometer. Tetramethylsilane was used as internal standard. Mass spectrometry was performed on a Finnigan AQA single-quadrupole MS instrument, equipped with an ESI source. All the experiments were carried out under an atmosphere of Argon. Elemental analyses (C, H, N) were carried out by the Microanalytical Section of the Institute of Organic and Pharmaceutical Chemistry, NHRF. DC-Alufolien plates (Kieselgel 60 F_{254}, Schichtdicke 0.2 mm, Merck) were used for analytical TLC and were visualized with ultraviolet light or developed with iodine or phosphomolybdic acid. Flash chromatography was performed using Sorbsil c60-A silica as the stationary phase.

1-(3-Bromopropyl)-1*H*-indole (3). The title compound was obtained as a pale yellow oil (70%), following the method reported by Dehaen and Hassner.[27]

1-(3-Bromopropyl)-5-methoxy-1*H*-indole (4). The title compound was obtained as a pale yellow oil (40%), following the method reported by Dehaen and Hassner for the preparation of 1-(3-bromopropyl)-1*H*-indole (**3**).[27] ^{1}H NMR ($CDCl_3$) δ 2.30 (dt, J = 6.3, 6.2 Hz, 2H, $NCH_2CH_2CH_2Br$), 3.27 (t, 2H, J = 6.2 Hz $NCH_2CH_2CH_2Br$), 3.83 (s, 3H, OCH_3), 4.27 (t, J = 6.3 Hz, 2H, $NCH_2CH_2CH_2Br$), 6.40 (t, J = 3.2 Hz, 1H, H_3), 6.86 (dd, J = 9.0, 2.2 Hz, 1H, H_6), 7.07 (d, J = 2.2 Hz, 1H, H_4), 7.09 (d, J = 3.0 Hz, 1H, H_2), 7.24 (d, J = 8.7 Hz, 1H, H_7).

1-(3-Azidopropyl)-1*H*-indole (5). A solution of sodium azide (0.42 g, 7.63 mmol) in H_2O (2 mL) was added dropwise to a stirred solution of bromide **3** (0.80 g, 3.36 mmol) in DMF (6 mL) at room temperature. The resulting mixture was then heated to 45 ^{o}C and stirred at this temperature for 3 h. Upon completion of the reaction, the mixture was poured onto crushed ice and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue

obtained was purified by flash column chromatography (cyclohexane/AcOEt 99:1) to give the desired azide **5** (60%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.07 (dt, J = 6.6, 6.5 Hz, 2H, $NCH_2CH_2CH_2N_3$), 3.24 (t, J = 6.5 Hz, 2H, $NCH_2CH_2CH_2N_3$), 4.23 (t, J = 6.7 Hz, 2H, $NCH_2CH_2CH_2N_3$), 6.57 (dd, J = 3.2, 0.8 Hz, 1H, H_3), 7.11 (d, J = 3.1 Hz 1H, H_2), 7.18 (dt, J = 7.8, 7.0, 1.0 Hz, 1H, H_5), 7.28 (dt, J = 8.1, 7.0, 1.0 Hz, 1H, H_6), 7.38 (dd, J = 8.1, 0.7 Hz, 1H, H_7), 7.70 (d, J = 7.8 Hz, 1H, H_4). ^{13}C NMR ($CDCl_3$) δ 29.4, 43.1, 48.4, 101.6, 109.3, 119.6, 121.2, 121.8, 127.9, 128.78, 135.1; MS *m/z* 200 (M^+, 40%), 172 ($M^+ - N_2$, 30%).

1-(3-Azidopropyl)-5-methoxy-1*H*-indole (6). The title compound was obtained as a pale yellow oil (55%), following the method used for the preparation of 1-(3-azidopropyl)-1*H*-indole (**5**). ^{1}H NMR ($CDCl_3$) δ 2.03 (dt, J = 6.4, 6.3 Hz, 2H, $NCH_2CH_2CH_2N_3$), 3.21 (t, J = 6.4 Hz, 2H, $NCH_2CH_2CH_2N_3$), 3.83 (s, 3H, OCH_3), 4.17 (t, J = 6.5 Hz, 2H, $NCH_2CH_2CH_2N_3$), 6.40 (d, J = 3.0 Hz, 1H, H_3), 6.87 (dd, J = 8.7, 2.4 Hz, 1H, H_6), 7.03 (d, J = 2.8 Hz, 1H, H_2), 7.07 (d, J = 2.3 Hz, 1H, H_4), 7.21 (d, J = 8.9 Hz, 1H, H_7). ^{13}C NMR ($CDCl_3$) δ 29.3, 43.2, 48.3, 55.8, 101.0, 102.6, 109.9, 112.0, 128.3, 129.4, 132.1, 154.8.

1-(3-Isothiocyanatopropyl)-1*H*-indole (7). Carbon disulfide (4.36 g, 3.4 mL, 57.4 mmol) and triphenyl phosphine (0.89 g, 3.06 mmol) were sequentially added to a solution of azide **5** (0.41 g, 2.05 mmol) in THF (15 mL). The suspension formed was stirred for 20 h at room temperature and upon completion of the reaction the solvent was removed *in vacuo*. The residue obtained was purified by flash column chromatography (cyclohexane/AcOEt 99:1) to give the desired isothiocyanate **7** (25%) as a yellowish oil. ^{1}H NMR ($CDCl_3$) δ 2.17 (dt, J = 6.3, 6.2 Hz, 2H, $NCH_2CH_2CH_2NCS$), 3.39 (t, J = 6.2 Hz, 2H, $NCH_2CH_2CH_2NCS$), 4.28 (t, J = 6.3 Hz, 2H, $NCH_2CH_2CH_2NCS$), 6.50 (dd, J = 3.1, 0.7 Hz, 1H, H_3), 7.07 (d, J = 3.2 Hz, 1H, H_2), 7.11 (dd, J = 7.9, 1.0 Hz, 1H, H_5), 7.20 (dd, J = 8.2, 1.1 Hz, 1H, H_6), 7.32 (dd, J = 8.2, 0.7 Hz, 1H, H_7), 7.62 (d, J = 7.9 Hz, 1H, H_4). ^{13}C NMR ($CDCl_3$) δ 30.2, 42.1, 42.7, 101.8, 109.0, 119.6, 121.1, 121.8, 127.7, 128.6, 131.4, 135.6.

1-(3-Isothiocyanatopropyl)-5-methoxy-1*H*-indole (8). The title compound was obtained as a pale yellow oil (88%), following the method we employed for the preparation of 1-(3-isothiocyanatopropyl)-1*H*-indole (**7**). ^{1}H NMR ($CDCl_3$) δ 2.14 (dt, J = 5.8, 5.7 Hz, 2H, $NCH_2CH_2CH_2NCS$), 3.37 (t, J = 5.4 Hz, 2H, $NCH_2CH_2CH_2NCS$), 3.82 (s, 3H, OCH_3), 4.24 (t, J = 6.2 Hz, 2H, $NCH_2CH_2CH_2NCS$), 6.41 (d, J = 2.9 Hz, 1H, H_3), 6.87 (dd, J = 8.7, 2.2 Hz, 1H, H_6), 7.04 (d, J = 2.9 Hz, 1H, H_2), 7.07 (d, J = 2.2 Hz, 1H, H_4), 7.20 (d, J = 8.7 Hz, 1H, H_7). ^{13}C NMR ($CDCl_3$) δ 30.4, 42.4, 43.1, 56.0, 101.6, 102.8, 109.9, 112.4, 128.5, 129.2, 131.2, 131.6, 154.4.

1*H*-Indole-2-carboxylic acid ethyl ester (11). Thionyl chloride (2.66 g, 1.60 ml, 22.35 mmol) was added dropwise to a suspension of 1*H*-indole-2-carboxylic acid (**9**) (2.00 g, 12.42 mmol) in absolute ethanol (12 ml) at -5 ^{o}C. The mixture was allowed to thaw and then refluxed for 2 h. The solid produced was filtered under vacuum, washed with cyclohexane and H_2O until neutral pH and dried *in vacuo*. Yield 1.96 g (85%); Mp 121-123 ^{o}C (AcOEt); the ^{1}H and ^{13}C NMR spectral data obtained for this compound are in full agreement with those reported.[28]

5-Methoxy-1*H*-indole-2-carboxylic acid ethyl ester (12). The title compound was obtained as a yellow amorphous solid in 90% yield following the method reported by Spadoni et al.[26] Mp 156-159 ^{o}C (AcOEt).

1*H*-Indole-2-methanol (13). The title compound was obtained as an an off-yellow solid (75%) following the method reported by Mahanty et al.[29] Mp 68-70 ^{o}C (AcOEt) (71 ^{o}C[29]).

5-Methoxy-1*H*-indole-2-methanol (14). Alcohol **14** was obtained as a yellow amorphous solid in 90% yield following the method reported by Spadoni et al.[26] Mp 80-83 ^{o}C (AcOEt).

1*H*-Indole-2-carboxaldehyde (15). The title compound was prepared by the method of Perez-Serrano et al.[30] Purification by trituration of the crude product with cyclohexane at 0 ^{o}C gave aldehyde **15** (85%) as an off-yellow solid. Mp 140-143 ^{o}C (AcOEt) (141-143 ^{o}C[30]).

5-Methoxy-1*H*-indole-2-carboxaldehyde (16). The title compound was obtained as an off-yellow solid in 70% yield following the method reported by Spadoni et al.[26] Mp 133-136 ^{o}C (AcOEt).

1*H*-2-Indolepropenoic acid ethyl ester (17). Ester **17** was prepared by the method reported by Bit et al.[31] The only change made to this method was the use of benzene as solvent instead of dichloromethane; the reaction temperature was set to 65 ^{o}C. Purification of the crude product by flash column chromatography (cyclohexane/AcOEt 97:3) gave the desired compound (70%) as a yellow amorphous solid. Mp 116-118 ^{o}C (AcOEt) (120-122 ^{o}C[31]); the ^{1}H NMR spectral data obtained for this compound are in full agreement with those reported.[31]

5-Methoxy-1*H*-2-indolepropenoic acid ethyl ester (18). Ester **18** was prepared by the method followed for the synthesis of its non-OMe congener **17**. Purification by recrystallization from ethanol gave the desired compound (76%) as an off-yellow solid. Mp 136-139 ^{o}C. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J = 7.0 Hz, 3H, CH_2CH_3), 3.84 (s, 3H, OCH_3), 4.27 (q, J = 7.3 Hz, 2H, CH_2CH_3), 6.20 (d, J = 16.0 Hz, 1H, CH=C*H*-$COOCH_2CH_3$), 6.74 (s, 1H, H_3), 6.92 (dd, J = 8.7, 2.3 Hz, 1H, H_6), 7.03 (d, J = 2.3 Hz, 1H, H_4), 7.63 (dd, J = 7.0, 1.4 Hz, 1H, H_7), 7.68 (d, J = 10.2 Hz, 1H, C*H*=CH-$COOCH_2CH_3$), 8.35 (bs, 1H, NH).

1*H*-Indole-2-propanol (19). The title compound was made by the method followed for the preparation of 1*H*-indole-2-methanol (**13**). The desired compound was obtained as a yellow solid (74%). Mp 53-54 ^{o}C (AcOEt) (54.5-55.5 ^{o}C[32]).

5-Methoxy-1*H*-2-indolepropanol (20). Alcohol **20** was prepared by the method used for the synthesis of 1*H*-2-indolepropanol (**19**). Purification by recrystallization from ethanol gave the desired compound (50%) as an off-yellow solid. Mp 62-65 ^{o}C. ^{1}H NMR ($CDCl_3$) δ 1.88 (dt, J = 7.1, 7.0 Hz, 2H, $CH_2CH_2CH_2OH$), 2.42 (bs, 1H, $CH_2CH_2CH_2OH$), 2.75 (t, J = 7.5 Hz, 2H, $CH_2CH_2CH_2OH$), 3.64 (t, J = 6.1 Hz, 2H, $CH_2CH_2CH_2OH$), 3.81 (s, 3H, OCH_3), 6.13 (s, 1H, H_3), 6.75 (dd, J = 8.5, 2.3 Hz, 1H, H_6),

7.00 (d, J = 2.0 Hz, 1H, H_4), 7.12 (d, J = 8.8 Hz, 1H, H_7), 8.61 (bs, 1H, NH).

2-(3-Bromopropyl)-1*H*-indole (21). A solution of phosphorous tribromide (0.26 g, 0.10 mL, 0.97 mmol) in ether (10 mL) was slowly added to a stirred solution of propanol **19** (0.40 g, 2.28 mmol) in ether (20 mL) at 0 ^{o}C. The resulting solution was then warmed to room temperature and stirred for 22 h. Upon completion of the reaction the mixture was carefully poured onto crashed ice and extracted with AcOEt. The organic phase was washed with H_2O, until neutral pH, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to give an oily residue, which was purified by flash column chromatography (cyclohexane/AcOEt 95:5). The title compound was obtained as a pale brown solid in 30% yield. ^{1}H NMR ($CDCl_3$) δ 2.22 (dt, J = 6.5, 6.4 Hz, 2H, $CH_2CH_2CH_2Br$), 2.92 (t, J = 7.3 Hz, 2H, $CH_2CH_2CH_2Br$), 3.44 (t, J = 6.5 Hz, 2H, $CH_2CH_2CH_2Br$), 6.26 (s, 1H, H_3), 7.06 (t, J = 7.3 Hz, 1H, H_5), 7.12 (t, J = 8.0 Hz, 1H, H_6), 7.28 (d, J = 8.0 Hz, 1H, H_7), 7.52 (d, J = 7.3 Hz, 1H, H_4), 7.89 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 29.8, 32.2, 33.3, 100.3, 110.6, 119.9, 120.1, 121.5, 128.9, 135.9, 137.8.

2-(3-Bromopropyl)-5-methoxy-1*H*-indole (22). The title compound was prepared by the method used for the synthesis of 2-(3-bromopropyl)-1*H*-indole (**21**). Purification by flash column chromatography (cyclohexane/AcOEt 95:5) gave the desired bromide as a pale yellow oil in 38% yield. ^{1}H NMR ($CDCl_3$) δ 2.21 (dt, J = 6.6, 6.5 Hz, 2H, $CH_2CH_2CH_2Br$), 2.90 (t, J =7 .1 Hz, 2H, $CH_2CH_2CH_2Br$), 3.43 (t, J = 6.4 Hz, 2H, $CH_2CH_2CH_2Br$), 3.81 (s, 3H, OCH_3), 6.18 (s, 1H, H_3), 6.76 (dd, J = 8.7, 2.4 Hz, 1H, H_6), 6.98 (d, J = 2.4 Hz, 1H, H_4), 7.17 (d, J = 8.7 Hz, 1H, H_7), 7.80 (bs, 1H, NH).

2-(3-Azidopropyl)-1*H*-indole (23). The title compound was prepared according to the method used for the synthesis of its congener **5**. Purification by flash column chromatography (cyclohexane/AcOEt 95:5) gave the desired compound (75%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.02 (dt, J = 6.8, 6.6 Hz, 2H, $CH_2CH_2CH_2N_3$), 2.88 (t, J = 7.3 Hz, 2H, $CH_2CH_2CH_2N_3$), 3.38 (t, J = 6.6 Hz, 2H, $CH_2CH_2CH_2N_3$), 6.28 (s,1H, H_3), 7.10 (dt, J = 7.0, 5.4 Hz, 1H, H_5), 7.13 (dt, J = 7.0, 5.5 Hz, 1H,

H_6), 7.32 (dd, J = 7.0, 1.5 Hz ,1H, H_7), 7.54 (dd, J = 6.3, 1.9 Hz, 1H, H_4), 7.91 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 25.2, 28.5, 50.6, 100.1, 110.5, 119.9, 120.0, 121.4, 128.8, 136.0, 138.0.

2-(3-Azidopropyl)-5-methoxy-1*H*-indole (24). Azide **24** was prepared by the method used for the synthesis of 2-(3-azidopropyl)-1*H*-indole (**23**). Purification by flash column chromatography (cyclohexane/AcOEt 95:5) gave the desired compound as a pale yellow oil in 66% yield. ^{1}H NMR ($CDCl_3$) δ 2.00 (dt, J = 6.9, 6.8 Hz, 2H, $CH_2CH_2CH_2N_3$), 2.86 (t, J = 7.3 Hz, 2H, $CH_2CH_2CH_2N_3$), 3.37 (t, J = 6.5 Hz, 2H, $CH_2CH_2CH_2N_3$), 3.85 (s, 3H, OCH_3), 6.20 (s, 1H, H_3), 6.80 (dd, J = 8.7, 2.5 Hz, 1H, H_6), 7.02 (d, J = 2.4 Hz, 1H, H_4), 7.21 (d, J = 8.8 Hz, 1H, H_7),7.82 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 25.4, 28.8, 50.7, 56.1, 100.3, 102.2, 111.1, 111.3, 128.4, 129.7, 136.8, 155.00.

Isothiocyanate 3-(1*H*-indol-2-yl)propyl ester (25). The title compound was prepared according to the method reported for its *N*1 counterpart **7**. Purification by flash column chromatography (cyclohexane/AcOEt 95:5) gave the desired compound (32%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.11 (dt, J = 6.3, 6.9 Hz, 2H, $CH_2CH_2CH_2NCS$), 2.92 (t, J = 7.2 Hz, 2H, $CH_2CH_2CH_2NCS$), 3.59 (t, J = 6.4 Hz, 2H, $CH_2CH_2CH_2NCS$), 6.33 (d, J = 1.3 Hz, 1H, H_3), 7.17 (dt, J = 7.0, 5.4 Hz, 1H, H_5), 7.21 (dt, J = 7.0, 5.6 Hz, 1H, H_6), 7.37 (dd, J = 7.3, 1.7 Hz, 1H, H_7), 7.61 (dd, J = 6.7, 1.9 Hz, 1H, H_4), 7.89 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 25.0, 29.4, 44.2, 100.4, 110.6, 120.0, 120.5, 121.6, 124.5, 128.7, 136.0, 137.0.

2-(3-Isothiocyanatopropyl)-5-methoxy-1*H*-indole (26). Isothiocyanate **26** was prepared by the method used for the synthesis of 2-(3-isothiocyanatopropyl)-1*H*-indole (**25**). Purification by flash column chromatography (cyclohexane/AcOEt 95:5) gave the desired compound as a pale yellow oil in 70% yield. ^{1}H NMR ($CDCl_3$) δ 2.08 (dt, J = 7.0, 6.0 Hz, 2H, $CH_2CH_2CH_2NCS$), 2.87 (t, J = 7.2 Hz, 2H, $CH_2CH_2CH_2NCS$), 3.56 (t, J = 5.9 Hz, 2H, $CH_2CH_2CH_2NCS$), 3.90 (s, 3H, OCH_3), 6.25 (s, 1H, H_3), 6.87 (dd, J = 8.7, 2.4 Hz, 1H, H_6), 7.08 (d, J = 2.0 Hz, 1H, H_4), 7.23 (d, J = 8.5 Hz, 1H, H_7), 7.90 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 25.1, 29.4, 44.2, 56.0, 100.2, 102.1, 111.3, 111.4, 128.5, 129.2, 131.1,

137.8, 154.2.

1*H*-3-Indolepropanol (28). The title compound was made by the method reported by Benghiat and Crooks[33] and used as such in the next step. Yield 85%; appearance yellow viscous oil.

4-Methylbenzenesulfonic acid 3-(1*H*-indol-3-yl)propyl ester (29). Tosylate **29** was prepared by the method reported by Beck et al.[34] Purification by trituration with cyclohexane at 0 °C gave the title compound as a beige solid in 45% yield. Mp 97-98 °C.

3-(3-Azidopropyl)-1*H*-indole (30). Azide **30** was made by the method used for the synthesis of 1-(3-azidopropyl)-1*H*-indole (**5**). Purification by flash column chromatography (cyclohexane/AcOEt 98:2) gave the desired compound as a pale yellow oil in 69% yield. ^{1}H NMR ($CDCl_3$) δ 2.05 (dt, J = 7.1, 6.8 Hz, 2H, $CH_2CH_2CH_2N_3$), 2.91 (t, J = 7.1 Hz, 2H, $CH_2CH_2CH_2N_3$), 3.36 (t, J = 6.4 Hz, 2H, $CH_2CH_2CH_2N_3$), 6.99 (s, 1H, H_2), 7.20 (dt, J = 7.8, 7.6 Hz, 1H, H_6), 7.27 (dt, J = 7.8, 7.1 Hz, 1H, H_5), 7.38 (d, J = 7.8 Hz, 1H, H_7), 7.66 (d, J = 7.8 Hz, 1H, H_4), 7.91 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 22.2, 29.2, 50.8, 111.3, 114.9, 118.8, 119.6, 121.8, 122.2, 127.4, 136.5.

Isothiocyanato 3-(1*H*-indol-3-yl)propyl ester (31). The title compound was made by the method used for the synthesis of 1-(3-isothiocyanatopropyl)-1*H*-indole (**7**). Purification by flash column chromatography (cyclohexane/AcOEt 95:5) gave the desired compound as a pale yellow oil in 81% yield. ^{1}H NMR ($CDCl_3$) δ 2.08 (dt, J = 6.7, 6.5 Hz, 2H, $CH_2CH_2CH_2NCS$), 2.93 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2NCS$), 3.49 (t, J = 6.4 Hz, 2H, $CH_2CH_2CH_2NCS$), 6.99 (s, 1H, H_2), 7.20 (t, J = 7.3, 7.0 Hz, 1H, H_6), 7.27 (t, J = 7.8, 7.0 Hz, 1H, H_5), 7.39 (d, J = 7.8 Hz, 1H, H_7), 7.63 (d, J = 7.8 Hz, 1H, H_4), 7.94 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 21.9, 30.2, 44.3, 111.6, 114.0, 118.9, 119.5, 121.7, 121.8, 122.8, 127.3, 136.4.

1,3-Dithiolano-2,2-diacetic acid diethyl ester (33). The title compound was prepared by the method reported by Berglund and Fuchs.[35] Purification by trituration with *n*-hexane at 0 °C, gave the

desired dithiolane (60%) as a white crystalline solid.

1,3-Dithiolano-2,2-diethanol (34). Diol **34** was made by the method reported by Berglund and Fuchs.[35] Purification by trituration with AcOEt/cyclohexane gave the desired compound (70%) as a white crystalline solid.

2-[(Tetrahydropyran-2-yloxy)methyl]-1,3-dithiolano-2-ethanol (35). Alcohol **35** was prepared by the method reported by Zepeda et al.[36]

2-[(Tetrahydropyran-2-yloxy)methyl]-1,3-dithiolano-2-acetaldehyde (36). The title compound was made by the method reported by Zepeda et al.[36]

3-(5-Methoxy-1*H*-indol-3-yl)propan-1-ol (37). Alcohol **37** was made by the method reported by Zepeda et al.[37]

4-Methylbenzenesulfonic acid 3-(5-methoxy-1*H*-indol-3-yl)propyl ester (38). Tosylate **38** was prepared by the method used for the synthesis of 4-methylbenzenesulfonic acid 3-(1*H*-indol-3-yl)propyl ester (**29**). Purification by flash column chromatography (cyclohexane/AcOEt 95:5) afforded the title compound as a yellowish oil in 47% yield. ^{1}H NMR ($CDCl_3$): δ 2.01 (dt, J = 6.6, 4.5 Hz, 2H, $CH_2CH_2CH_2OTs$), 2.41 (s, 3H, Ph-CH_3), 2.76 (t, J = 7.4 Hz, 2H, $CH_2CH_2CH_2OTs$), 3.83 (s, 3H, OCH_3), 4.06 (t, J = 6.2 Hz, 2H, $CH_2CH_2CH_2OTs$), 6.82 (dd, J = 8.7, 2.0 Hz, 1H, H6), 6.86 (s, 1H, H2), 6.93 (d, J = 2.4 Hz, 1H, H4), 7.21 (d, J = 8.7 Hz, 1H, H7), 7.29 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 7.8 Hz, 2H), 7.87 (bs, 1H, NH).

3-(3-Azidopropyl)-5-methoxy-1*H*-indole (39). Azide **39** was made by the method used for the synthesis of 3-(3-azidopropyl)-1*H*-indole (**30**). Purification by flash column chromatography (cyclohexane/AcOEt 95:5) gave the desired compound as a pale yellow oil in 64% yield. ^{1}H NMR ($CDCl_3$) δ 1.98 (dt, J = 6.9, 6.7 Hz, 2H, $CH_2CH_2CH_2N_3$), 2.82 (t, J = 6.9 Hz, 2H, $CH_2CH_2CH_2N_3$), 3.32

(t, J = 6.5 Hz, 2H, $CH_2CH_2CH_2N_3$), 3.86 (s, 3H, OCH_3), 6.86 (dd, J = 8.7, 2.5 Hz, 1H, H_6), 6.95 (d, J = 2.1 Hz, 1H, H_2), 7.02 (d, J = 2.1 Hz, 1H, H_4), 7.22 (d, J = 8.7 Hz, 1H, H_7), 7.86 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 22.1, 29.1, 50.9, 56.0, 100.7, 111.9, 112.2, 114.7, 122.4, 127.7, 131.5, 153.9; MS *m/z* 230 (M^+, 100%), 202 (M^+-N_2, 60%).

Isothiocyanato 3-(5-methoxy-1*H*-indol-3-yl)propyl ester (40). The title compound was prepared by the method used for the synthesis of isothiocyanato 3-(1*H*-indol-3-yl)propyl ester (**31**). Purification by flash column chromatography (cyclohexane/AcOEt 93:7) gave the desired compound as a pale yellow oil in 80% yield. ^{1}H NMR ($CDCl_3$) δ 2.02 (dt, J = 6.7, 7.0 Hz, 2H, $CH_2CH_2CH_2NCS$), 2.83 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2NCS$), 3.46 (t, J = 6.4 Hz, 2H, $CH_2CH_2CH_2NCS$), 3.82 (s, 3H, OCH_3), 6.81 (dd, J = 8.7, 2.3 Hz, 1H, H_6), 6.95 (m, 2H, H_2 + H_4), 7.20 (d, J = 8.7 Hz, 1H, H_7), 7.85 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 21.8, 30.1, 44.3, 56.0, 100.4, 106.1, 112.0, 112.3, 113.8, 122.6, 127.6, 131.6, 154.0; MS *m/z* 246 (M^+).

5-Methoxy-1*H*-3-indoleacetic acid (42). The title compound was made by the general method of conversion of indolylacetonitriles to indolylacetic acids reported by Morales-Rios et al.[38] The desired acid was obtained from commercially available 5-methoxy-1*H*-3-indoleacetonitrile (**41**) as a brownish solid in 76% yield. Mp 146-149 ^{o}C (CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 2H, CH_2COOH), 3.67 (s, 3H, OCH_3), 6.63 (dd, J = 8.8, 2.3 Hz, 1H, H_6), 6.87 (d, J = 2.3 Hz, 1H, H_2), 6.98 (s, 1H, H_4), 7.08 (d, J = 8.8 Hz, 1H, H_7), 9.33 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 31.3, 56.0, 101.0, 107.8, 111.6, 112.4, 125.0, 127.9, 131.7, 153.4, 173.7.

5-Methoxy-1*H*-3-indolethanol (43). The title alcohol was obtained as a pale yellow viscous liquid, which was used as such in the next step, following the method reported by Chou.[39]

3-(2-Chloroethyl)-5-methoxy-1H-indole (44). *p*-Toluenesulfonyl chloride (1.41 g, 7.41 mmol) was added to a solution of alcohol **43** (0.71 g, 3.71 mmol) in pyridine (4 mL) at 0 ^{o}C and the resulting

mixture was then stirred at 4 ^{o}C for 48 h. Upon completion of the reaction the suspension formed was poured onto ice water, extracted with ether (3 x 50 mL) and washed with a saturated solution of $CuSO_4$ (3 x 20 mL). The organic phase was then washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to leave an oily residue, which was purified by flash column chromatography (cyclohexane/AcOEt 93:7). The title compound was obtained in 59% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.23 (t, J = 7.6 Hz, 2H, CH_2CH$_2$Cl), 3.80 (t, J = 7.5 Hz, 2H, CH$_2$CH_2Cl), 3.90 (s, 3H, OCH_3), 6.91 (dd, J = 8.8, 2.4 Hz, 1H, H_6), 7.06 (m, 2H, H_2 + H_4), 7.27 (d, J=8.8 Hz, 1H, H_7), 8.02 (bs, 1H, NH); MS *m/z* 211 (M^+ + 2, 24%), 209 (M^+, 68%**)**, 174 (M^+ - Cl, 100%).

3-(2-Azidoethyl)-5-methoxy-1*H*-indole (45). The title compound was prepared from chloride **44** using the method employed for the synthesis of 3-(3-azidopropyl)-5-methoxy-1*H*-indole (**39**). Purification by flash column chromatography (cyclohexane/AcOEt 95:5) gave the desired compound as a pale yellow oil in 54% yield. ^{1}H NMR ($CDCl_3$) δ 3.05 (t, J = 7.1 Hz, 2H, CH_2CH$_2$N$_3$), 3.58 (t, J = 7.1 Hz, 2H, CH$_2$CH_2N$_3$), 3.90 (s, 3H, OCH_3), 6.90 (dd, J = 8.6, 2.4 Hz, 1H, H_6,), 7.05 (m, 2H, H_2, H_4), 7.27 (d, J = 8.8 Hz, 1H, H_7), 7.99 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 25.0, 51.6, 55.9, 100.4, 112.0, 112.4, 114.1, 123.0, 127.5, 131.3, 154.2; MS *m/z* 216 (M^+, 20%), 188 (M^+ - N_2, 20%), 174 (M^+ - N_3, 65%).

Isothiocyanato 3-(5-methoxy-1*H*-indol-3y)ethyl ester (46). Isothiocyanate **46** was made by the method used for the synthesis of the isothiocyanato 3-(5-methoxy-1*H*-indol-3-yl)propyl ester (**40**). Purification by flash column chromatography (cyclohexane/AcOEt 93:7) gave the desired compound as a pale yellow oil in 85% yield. ^{1}H NMR ($CDCl_3$) δ 3.15 (t, J = 6.9 Hz, 2H, CH_2CH$_2$NCS), 3.77 (t, J = 6.7 Hz, 2H, CH$_2$CH_2NCS), 3.90 (s, 3H, OCH_3), 6.90 (dd, J = 8.8, 2.3 Hz, 1H, H_6), 7.00 (d, J = 2.3 Hz, 1H, H_2), 7.09 (d, J = 2.4 Hz, 1H, H_4), 7.29 (d, J = 8.6 Hz, 1H, H_7), 8.03 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 26.5, 45.6, 55.9, 100.1, 112.1, 112.5, 114.3, 123.6, 127.6, 131.5, 154.2.

B. Elemental Analysis Data

Cmpd	Formula	Elemental Analysis
7	$C_{12}H_{12}N_2S$ (216.3)	calcd: C, 66.63; H, 5.59; N, 12.95 Found: C, 66.39; H, 5.48; N, 12.59
8	$C_{13}H_{14}N_2SO$ (246.3)	calcd: C, 63.39; H, 5.73; N, 11.37 Found: C, 63.08; H, 5.62; N, 11.09
25	$C_{12}H_{12}N_2S$ (216.3)	calcd: C, 66.63; H, 5.59; N, 12.95 Found: C, 66.30; H, 5.46; N, 12.74
26	$C_{13}H_{14}N_2SO$ (246.3)	calcd: C, 63.39; H, 5.73; N, 11.37 Found: C, 63.03; H, 5.61; N, 11.15
31	$C_{12}H_{12}N_2S$ (216.3)	calcd: C, 66.63; H, 5.59; N, 12.95 Found: C, 66.35; H, 5.40; N, 12.63
40	$C_{13}H_{14}N_2SO$ (246.3)	calcd: C, 63.39; H, 5.73; N, 11.37 Found: C, 63.06; H, 5.61; N, 11.09
46	$C_{12}H_{12}N_2SO$ (232.3)	calcd: C, 62.04; H, 5.21; N, 12.06 Found: C, 61.86; H, 5.13; N, 11.79

C. *Xenopus* melanophore model for the evaluation of agonist and antagonist activity

Melanophore cells were grown in 96-well tissue culture plates and growth medium was replaced with 0.7 x L-15 culture medium 18 h before analogs were tested.[9a, 41-44] Initial absorbance (*Ai*, 630 nm) of cells (~8,000 cells/well) was measured in each well using a Bio-Tek microtiter plate reader (model EL3115, Anachem, U.K.), then cells were treated with the varying concentrations of the analogs. The maximal concentration used was 10^{-4} M. All experiments used triplicate wells at six concentrations of analog. The final absorbance (*Af*) was measured after 60 minutes, and the fractional change in absorbance (1-*Af/Ai*) was calculated. Vehicle did not alter pigment granule distribution itself or inhibit responses to melatonin. The concentration of analog producing 50% of the maximum agonist response (EC_{50}) was determined from concentration-response curves. For evaluation of antagonist potency, cells were treated with vehicle (1% DMSO or methanol) or varying concentrations (10^{-4}-10^{-9} M) of the analogs for 60 minutes before melatonin (10^{-9} M) was added. The concentration of analog reducing melatonin-induced pigment aggregation by 50% (IC_{50}) was determined.

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