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# Synthesis and receptor binding studies of halogenated *N*,*N*-dialkylel-(2-phenyl-1*H*-indol-3-yl)glyoxylamides to visualize peripheral benzodiazepine receptors with SPECT or PET

Idriss Bennacef,[a] Colin N. Haile,[a] Anne Schmidt,[d] Andrei O. Koren,[c] John P. Seibyl,[a,c] Julie K. Staley,[a] Frederic Bois,[a] Ronald M. Baldwin[b] and Gilles Tamagnan[a,c,*]

[a]*Yale School of Medicine, VA Connecticut HCS (116A2), West Haven, CT 06516, USA*
[b]*Vanderbilt University Medical Center, Department of Radiology and Radiological Sciences/PET Chemistry, Nashville, TN 37232-2675, USA*
[c]*Institute for Neurodegenerative Disorders, New Haven, CT 06510, USA*
[d]*Pfizer Global Research & Development, Groton/New London Labs, CNS Discovery Biology, Groton, CT 06340, USA*

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**Abstract**—A library of halogenated 2-arylindolyl-3-oxocarboxamides was prepared to develop radioligands to visualize cerebral PBR by SPECT and PET imaging. In vitro evaluation showed that most of the synthesized compounds were selective,high-affinity PBR ligands with adequate lipophilicity ($\log D_{7.4}$ in the range of 1.6–2.4). The iodinated derivative **11** ($K_i$ = 2.6 nM) and the fluorinated analog **26** ($K_i$ = 6.2 nM) displayed higher affinity than reference compounds.


## 1. Introduction

The peripheral benzodiazepine receptor (PBR) is an 18 kDa, five transmembrane protein primarily located in the outer membrane of mitochondria. PBR forms a trimeric complex that interacts in the mitochondrial permeability transition pore (MPTP) with adenosine nucleotide translocase (ANT) and voltage-dependent anion channels (VDAC). The role of PBRs remains unknown but their involvement in lipid metabolism and/or transport, steroid regulation and cell proliferation is well established.[1] PBRs are distributed throughout the body. High concentrations are observed in tissues such as adrenal glands and gonads, while brain expresses low level of PBR's primarily associated with the choroids plexus, ependymal lining, and microglia.[2] The fact that PBR knock-out mice die at an early stage of development suggests that this receptor plays a critical role in physiological processes.[3] A great deal of research is being carried out to determine PBRs involvement in normal and pathophysiological condition.[4] PBR has been implicated in cancer, auto-immune, infective, and neurodegenerative disorders. More specifically, PBR reflects neuronal injury and inflammatory lesions by increasing expression on proliferating and activated microglia. These characteristics make PBR a promising target of efforts aimed toward the diagnosis and treatment of pathologies such Alzheimer's disease,[6] Huntington's disease, Wernicke's encephalopathy, multiple sclerosis,[5] and stroke.

Imaging studies using positron emission tomography (PET) or single photon emission computed tomography (SPECT) have provided valuable information regarding the role of PBR. PET and SPECT are powerful imaging techniques allowing the visualization of brain receptors by recording the interaction of the targeted receptor and a radioligand bearing a positron emitter for PET (carbon-11, $t_{1/2}$ = 20.4 min; fluorine-18, $t_{1/2}$ = 109.7 min) or a gamma emitter for SPECT (iodine-123, $t_{1/2}$ = 13.2 h). To date, several PET radioligands for PBR have been synthesized (PK11195 and DAA1106 families) but only one SPECT probe ([$^{123}$I]iodo-(*R*)-PK11195) has been reported (Fig. 1).[6]

Recently, Primofiore et al.[7] described a series of *N*,*N*-dialkyl-(2-phenyl-1*H*-lindol-3-yl)glyoxylamides **I** (Fig. 2) as

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* Corresponding author: E-mail: gtamagnan@indd.org

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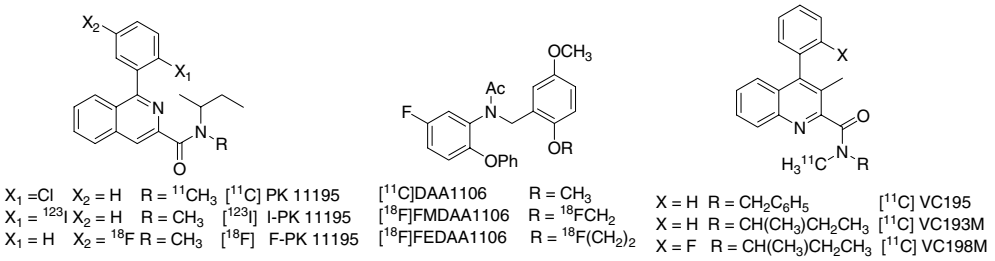



**Figure 1.**

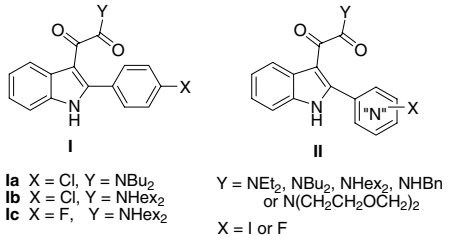



**Figure 2.**

potent and selective PBR ligands. Most compounds of this series displayed nanomolar affinity for PBR. Structure–activity relationship (SAR) studies showed that the introduction of a halogen atom in the *para*-position of the phenyl ring was beneficial and that modification of the dialkylamide substituents could be performed without significant loss of affinity. These results prompted us to design new radioligands of general structure **II** where a radionuclide (iodine-123 for SPECT or fluorine-18 for PET) would reside in the phenyl ring while the dialkylamide would help 'fine-tune' in vivo properties of the molecule. We also investigated replacing the 2-phenyl moiety with a pyridyl ring.

Herein, we describe the synthesis and in vitro evaluation of the novel *N*,*N*-dialkyl-(2-(het)aryl-1*H*-indol-3-yl)glyoxyamide derivatives.

## 2. Results and discussion

### 2.1. Chemistry

2-(4′-Iodophenyl)indole (**1**) and 2-(2′-iodophenyl)indole (**4**) were obtained from phenylhydrazine and 4′- or 2′-iodoacetophenone using the Fisher indole synthesis (method A) or the modified procedure described by Guy and Grette (method B);[8] while 2-(3′-iodophenyl) indole (**3**) was prepared from 2-(3′-bromophenyl)indole (**2**) by the powerful bromine-to-iodine exchange described by Klarpas and Buchwald.[9] Finally, the halophenylindoles **1**–**4** were acylated with oxalyl chloride and the resulting (2-arylindol-3-yl)glyoxyl chlorides were reacted with proper amines (diethylamine, dibutylamine, dihexylamine, benzylamine, and bis(2-methoxyethyl)amine) to obtain desired products **5**–**9** and **11**–**19**. Compound **15** was obtained from its bromo-analog **10** by palladium-catalyzed stannylation followed by iododestannylation (Scheme 1).

Bromopyridyl indole scaffold **20** was synthesized from 1-*tert*-butyloxycarbonylindole-2-boronic acid[10] by a Suzuki cross coupling with 2,6-dibromopyridine. Bromine-to-iodine exchange was performed using the Klarpas and Buchwald conditions. At this stage, a partial removal of the *tert*-butyloxycarbonyl moiety was observed, hence the crude material adsorbed onto silica was heated in a conventional microwave oven[11] and iodopyridinyl indole **21** was obtained in good yield. Compound **22** was finally obtained by the two-step/one-pot acylation and amidation procedure (Scheme 2).

Fluoropyridyl indole **24** was synthesized from 2-iodoindole[12] **23** by Suzuki cross coupling with 2-fluoro-5-(pinacol-borolan-2-yl)-pyridine. Acylation and amidation were carried out to obtain compounds **25**–**27** (Scheme 3).

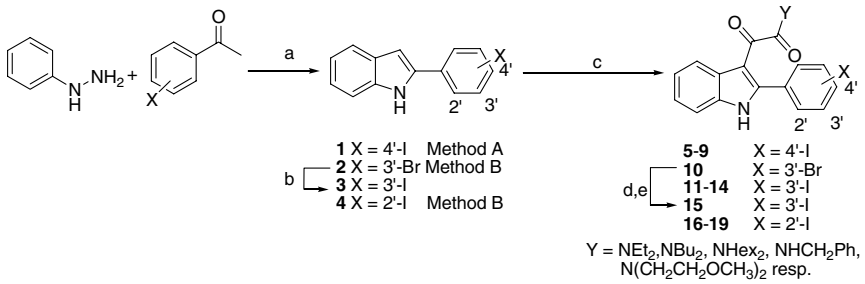
### 2.2. Structure–activity relationships

Physicochemical characterization of the new ligands consisted of measuring their in vitro benzodiazepine receptor binding affinity and lipophilicity. Competition receptor binding assays were performed with rat kidney membranes against [$^3$H]PK11195 for PBR and with guinea pig cortical membranes against [$^3$H]flunitrazepam for the central benzodiazepine receptor (CBR). The lipophilicity of compounds **6**, **11**, **12**, and **15** was determined experimentally at pH 7.4.

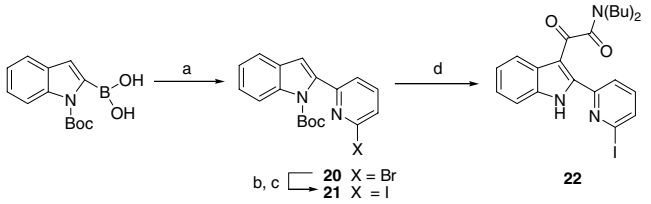
In an initial examination, substitution of the chlorine atom of molecule I (Table 1) by a bulkier iodine atom resulted in the 2- and 3-fold decrease in PBR binding affinity for Y = $N(Bu)_2$ and Y = $N(Hex)_2$, respectively (compare **Ia** and **6**, **Ib** and **7**).

To extend the SAR in this series, a further library of halogenated derivatives of general structure **II** was synthesized and characterized. All new compounds appeared to be selective PBR ligands.

In the first series, compounds bearing iodine in position 2′, 3′ or 4′ of the 2-phenyl ring were chosen as targets. We anticipated that the bulkier iodophenyl moieties would affect docking of the molecule to the receptor binding site but this might be compensated by modifying the amide part of the molecule. Hence, ethyl-, butyl-, hexyl-, and benzyl-amines were chosen to map out the effect of the alkyl substituents (Table 1).




**Scheme 1.** Reagents and conditions: (a) Method A: PPA, Δ, 4 h, or method B: 1—AcOH, cat. EtOH, Δ; 2—PPA–xylenes, 85 °C, 20 min; (b) NaI, CuI, TMEDA, 1,4-dioxane, 110 °C, 24 h; (c) 1—$(COCl)_2$, THF, 0 °C to rt, 1 h; 2—amine, THF, 0 °C to rt, overnight; (d) $Pd(PPh_3)_4$, $Me_3SnSnMe_3$, 1,4-dioxane, Δ, 72 h; (e) $I_2$, $CH_2Cl_2$, rt, overnight.




**Scheme 2.** Reagents and conditions: (a) 2,6-dibromopyridine, $K_2CO_3$, THF/$H_2O$, Δ, 6 h; (b) NaI, CuI,TMEDA, 1,4-dioxane,110 °C, 24 h; (c) MW, 1100 W, 2 min; (d) 1—$(COCl)_2$, THF, 0 °C to rt; 2—$HNBu_2$, THF, 0 °C to rt.

Compounds bearing the iodine atom in position 4′ (**5**–**8**) or 3′ (**11**–**14**) displayed the same behavior with regard to the amide nature. Here, the following order of affinities was observed: $NEt_2 > NBu_2 > NHBn \gg NHex_2$. When examining the location of the iodo substituent (compare **5**–**8** and **11**–**14**, respectively), it appeared that the *meta*-position was the better placement. Compared to the reference compounds, PBR affinity was increased by introducing iodine in the *meta*-position and by shortening the length of the amide (compare **I** and **11**).

When the iodine was in position 2′ (**16**–**19**), the pattern changed, and the affinities ranked in the following order: $NBu_2 = NEt_2 > NHex_2 > NHBn$.

Taken together, these data seem to indicate that the 3′-position was best location for the iodo substituent, and that the length of the amide alkyls should not exceed four carbons.

The $\log D_{7.4}$ values of compounds **6**, **11**, and **12** were 2.33, 2.18, and 2.25, respectively. These values are in the accepted range for good blood–brain barrier permeability (i.e., 0–3).

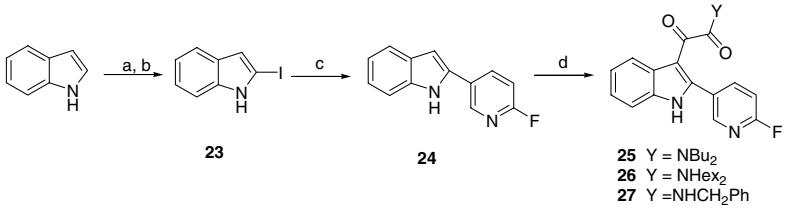
With the aim of finding a radioiodinated SPECT tracer with lower lipophilicity, iodinated ligands with an oxygenated alkyl substituent ($Y = N(CH_2CH_2OCH_3)_2$) were synthesized. The *para*-derivative **9** displayed modest binding affinity ($K_i = 72$ nM) similar to that of the non-oxygenated alkyl derivative **7** ($Y = NHex_2$, $K_i = 90$ nM). However, the *meta*-isomer **15** appeared to be more potent ($K_i = 16$ nM) than its hexyl analog **13** ($K_i = 51$ nM) and as potent as **12** ($Y = NBu_2$, $K_i = 10$ nM) while displaying lower $\log D_{7.4}$ (1.7 vs 2.2).

Replacement of the 3′-iodophenyl fragment by a 6-iodo-2-pyridinyl moiety essentially did not change the binding affinity (compare **22** and **12**).

For the design of a PET tracer, similar modifications of the structure of a reported fluorinated ligand **Ic** ($K_i = 7.2$ nM)[7] were envisaged. To achieve efficient $^{18}F$ labeling, the phenyl ring was replaced with a 3′-pyridyl one. Thus, ligands **25**–**27** ($Y = N(Bu)_2$, $N(Hex)_2$, and NHBn, respectively) were synthesized and evaluated. As in the previous series, replacement of the *meta*-CH with a nitrogen atom essentially did not change the affinity (compare **26** and **Ic**). However, in the fluoropyridyl series, the following order of affinities was observed: $N(Hex)_2 > N(Bu)_2 > NHBn$. These results suggest that the effect of the length of the amide alkyls on affinity depends on the nature of the aromatic moiety attached to position 2 of the indole scaffold.

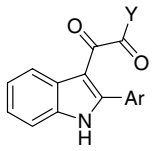
## 3. Conclusion

With the aim to develop radioligands to visualize cerebral PBR by SPECT and PET imaging, a library of halogenated 2-arylindolyl-3-oxocarboxamides was prepared. In vitro evaluation showed that most of the

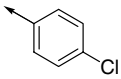
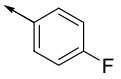
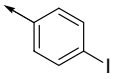
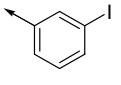
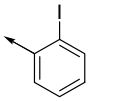
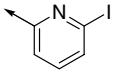
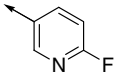



**Scheme 3.** Reagents and conditions: (a) 1—*n*-BuLi, THF, −78 °C, 30 min; 2—$CO_{2(g)}$, 10 min; (b) 1—*t*-BuLi, THF, −78 °C, 1 h; 2—1,2-diiodoethane, THF, −78 °C, 1 h; (c) 5-B(pin)–2-F–pyridine, $K_2CO_3$, THF/$H_2O$, Δ, 72 h; (d) 1—$(COCl)_2$, THF, 0 °C to rt; 2—amine, THF, 0 °C to rt.

**Table 1.** Physical properties and binding affinity of compounds **I**, **5**–**9**, **11**–**19**, **22** and **25**–**27** of General formula **II**




**II**

| Compound | Ar | Y | Formula | Mp (°C) | Appearance | Anal. | $K_i$, PBR[a] (nM) | $K_i$, CBR[a] (nM) | log $D_{7.4}$ |
|---|---|---|---|---|---|---|---|---|---|
| PK11195 | — | — | — | — | — | — | 6.9 | >65 | — |
| Ro-15-1788 | — | — | — | — | — | — | >76.5 | 1.3 | — |
| **Ia** |  | $NBu_2$ | $C_{24}H_{27}ClN_2O_2$ | — | White solid | C, H, N | 7[b] | >2070 | |
| **Ib** | | $NHex_2$ | $C_{28}H_{35}ClN_2O_2$ | — | Orange oil | C, H, N | 31[b] | >2070 | |
| **Ic** |  | $NHex_2$ | $C_{28}H_{35}FN_2O_2$ | — | Orange oil | C, H, N | 7.2 | >2070 | |
| **5** |  | $NEt_2$ | $C_{20}H_{19}IN_2O_2$ | 107 | White solid | C, H, N | 9.8 | >2070 | |
| **6** | | $NBu_2$ | $C_{24}H_{27}IN_2O_2$ | 148 | White solid | C, H, N | 15 | >2070 | 2.33 |
| **7** | | $NHex_2$ | $C_{28}H_{35}IN_2O_2$ | 130 | White solid | C, H, N | 90 | >2070 | |
| **8** | | $NHCH_2Ph$ | $C_{23}H_{17}IN_2O_2$ | 210 | Yellow solid | C, H, N | 46 | >2070 | |
| **9** | | $N(CH_2CH_2OCH_3)_2$ | $C_{22}H_{23}IN_2O_4$ | 128 | White solid | C, H, N | 72 | >2070 | |
| **11** |  | $NEt_2$ | $C_{20}H_{19}IN_2O_2$ | 192 | White solid | C, H, N | 2.6 | 255 | 2.18 |
| **12** | | $NBu_2$ | $C_{24}H_{27}IN_2O_2$ | 62 | White foam | C, H, N | 10 | >2070 | 2.25 |
| **13** | | $NHex_2$ | $C_{28}H_{35}IN_2O_2$ | — | Yellow oil | H, N, C[c] | 51 | >2070 | |
| **14** | | $NHCH_2Ph$ | $C_{23}H_{17}IN_2O_2$ | 232 | White solid | C, H, N | 21 | >2070 | |
| **15** | | $N(CH_2CH_2OCH_3)_2$ | $C_{22}H_{23}IN_2O_4$ | <65 | White solid | C, H, N | 16 | >2070 | 1.69 |
| **16** |  | $NEt_2$ | $C_{20}H_{19}IN_2O_2$ | 225 | Yellow foam | C, H, N | 14 | >2070 | |
| **17** | | $NBu_2$ | $C_{24}H_{27}IN_2O_2$ | 77 | Yellow foam | C, H, N | 9.5 | >2070 | |
| **18** | | $NHex_2$ | $C_{28}H_{35}IN_2O_2$ | 52 | Tanned foam | C, H, N | 27 | >2070 | |
| **19** | | $NHCH_2Ph$ | $C_{23}H_{17}IN_2O_2$ | 204 | Yellow foam | C, H, N | 22 | >2070 | |
| **22** |  | $NBu_2$ | $C_{23}H_{26}IN_3O_2$ | 148 | White solid | C, H, N | 7 | >2070 | |
| **25** |  | $NBu_2$ | $C_{23}H_{26}FN_3O_2$ | — | Yellow oil | C, H, N | 16 | >2070 | |
| **26** | | $NHex_2$ | $C_{27}H_{34}FN_3O_2$ | — | Oil | C, H, N | 6.2 | >2070 | |
| **27** | | $NHCH_2Ph$ | $C_{22}H_{16}FN_3O_2$ | 184 | Yellow solid | C, H, N | 45 | >2070 | |

[a] Average of 3–5 independent determinations.
[b] In house data.
[c] C: calcd, 60.22; found, 59.45.

synthesized compounds were selective, high-affinity PBR ligands with adequate lipophilicity (log $D_{7.4}$ in the range of 1.6–2.4). The iodinated derivative **11** and the fluorinated analogs **26** and **27** displayed higher affinity than reference compounds and could be used as a lead for further modification of the *N*,*N*-dialkyl-(2-(het)-aryl-1*H*-indol-3-yl)glyoxyamide motif. The optimal combination of properties (affinity, selectivity, and lipophilicity) suggests that the novel PBR ligands are promising candidates for further investigation.

## 4. Experimental

### 4.1. Chemistry

**4.1.1. General considerations.** All reactions were performed in oven dried glassware fitted with rubber septa under a positive pressure of argon. Air- and moisture-sensitive liquids were transferred by syringe or stainless steel cannula. Thin layer chromatography plates were visualized by exposure to ultraviolet light (UV), and then were stained by submersion in ethanol–formaldehyde (35%) hydrochloric acid (25%) mixture (2:1:1 v/v/v), followed by brief heating with a heat gun. Flash chromatography was performed as described by Still et al.[13] employing silica gel (60 Å pore size, 230–400 mesh, 40–63 μm). Proton nuclear magnetic resonance ($^1$H NMR) spectra and carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on a Bruker AMX-400 MHz or a Bruker Advance 500 MHz spectrometer at 23 °C. Proton chemical shifts are expressed in parts per million (ppm; $\delta$ scale) downfield from tetramethylsilane in the NMR solvent ($CHCl_3$: $\delta$ 7.26, $(CH_3)_2SO$: $\delta$ 2.50). Carbon chemical shifts are expressed in parts per million (ppm; $\delta$ scale) downfield from tetramethylsilane and are referenced to the carbon resonance

of the NMR solvent ($CDCl_3$: $\delta$ 77.16, $(CD_3)_2SO$: $\delta$ 39.52). Data are represented as follows: Chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad), integration and coupling constant ($J$) in hertz (Hz).[14] Commercial reagents and solvents were used as received except for ethyl ether and tetrahydrofuran, which were distilled from sodium/benzophenone immediately before use.

### 4.1.2. Cyclization

**4.1.2.1. 2-(4-Iodophenyl)indole (1).** 4-Iodoacetophenone (4.0 g,) and phenylhydrazine (2.64 g) were mixed with polyphosphoric acid (34 g), and the mixture was heated with stirring. The temperature of the reaction mixture was kept at 105 °C for 4 h. The mixture was poured into crushed ice, stirred for 10 min, extracted with $CH_2Cl_2$ (3×), dried over $MgSO_4$, filtered, and concentrated. The crude, diluted in acetone, was triturated with $H_2O$. After suction filtration, desired product was obtained as a brown solid (3.80 g, 12 mmol, 74%). $^1$H NMR (DMSO-$d_6$) $\delta$ 11.59 (s, 1H), 7.83–7.81 (m, 2H), 7.68–7.66 (m, 2H), 7.54 (d, $J$ = 7.9 Hz, 1H), 7.41 (d, $J$ = 8.1 Hz, 1H), 7.12 (dt, $J$ = 8.0 Hz, $J$ = 1.0 Hz, 1H), 7.01 (dt, $J$ = 7.2 Hz, $J$ = 1.0 Hz, 1H), 6.94 (d, $J$ = 1.1 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 138.0, 137.6, 136.9, 132.1, 128.9, 127.3, 122.3, 120.6, 119.9, 111.7, 99.7, 93.5.

**4.1.2.2. 2-(3-Bromophenyl)-1*H*-indole (2).** 3′-Bromoacetophenone (2.0 g, 10.0 mmol, 1 equiv) and phenylhydrazine (1.30 g, 12.0 mmol, 1.2 equiv) were stirred in ethanol (15 mL). Acetic acid (eight drops) was added and the mixture was refluxed. After 5 h, solvent was removed and the crude was taken in EtOAc (50 mL), washed with oxalic acid (5%), water, brine, and dried over $MgSO_4$. Filtration and evaporation yielded 1-[1-(3-bromophenyl)ethyliden]-2-phenylhydrazine (2.6 g, 9.0 mmol, 90%) as a light yellow solid. Crude (2.0 g, 6.9 mmol) in xylene (30 mL) and polyphosphoric acid (15 g) was stirred at 85 °C during 20 min. Water (150 mL) was added to the warm crude, the mixture was stirred for 10 min and poured into water (300 mL) and stirred for 20 min. EtOAc was added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (3× 100 mL), and the combined organic layers were washed with $H_2O$ and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (hexane/EtOAc 98:2) yielded **2** as white powder (1.56 g, 5.75 mmol, 83%), mp = 150 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 11.68 (s, 1H), 8.14 (t, $J$ = 1.7 Hz, 1H), 7.93 (dt, $J$ = 7.7 Hz, $J$ = 1.0 Hz, 1H), 7.59 (d, $J$ = 7.9 Hz, 1H), 7.56–7.57 (m, 1H), 7.48–7.44 (m, 2H), 7.17 (dt, $J$ = 8.2 Hz, $J$ = 1.0 Hz, 1H), 7.08–7.04 (m, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 137.6, 136.2, 134.9, 131.4, 130.3, 128.8, 127.6, 124.3, 122.8, 122.5, 120.7, 119.9, 111.8, 100.3, Anal. ($C_{14}H_{10}BrN$) C, H, N.

**4.1.2.3. 2-(3-Iodophenyl)-1*H*-indole (3).** *N*,*N*′-Dimethylethylenediamine (14.4 μL, 0.13 μmol) and then dry dioxane (2 mL) were successively introduced in a sealed tube with stirring bar (dried at 100 °C) charged with 2-(3-bromophenyl)-1*H*-indole (544 mg, 2 mmol, 1 equiv), CuI (33.1 mg, 0.17 mmol, 0.09 equiv), and NaI (636 mg, 4.23 mmol). After heating at 110 °C during 20 h, the suspension was cooled and ammonium hydroxide (28–30%) was added. The mixture was extracted with $CH_2Cl_2$ (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (hexane/EtOAc 100:1–98:2) yielded **3** as a white solid (516 mg, 1.6 mmol, 81%). $^1$H NMR (DMSO-$d_6$) $\delta$ 11.65 (s, 1H), 8.30–8.29 (m, 1H), 7.94 (ddd, $J$ = 7.9 Hz, $J$ = 0.8, $J$ = 0.7 Hz, 1H), 7.71 (ddd, $J$ = 7.8 Hz, $J$ = 0.8 Hz, $J$ = 0.6 Hz, 1H), 7.58 (d, $J$ = 7.8 Hz, 1H), 7.45 (d, $J$ = 8.1 Hz, 1H), 7.30 (t, $J$ = 7.9 Hz, 1H), 7.17 (dt, $J$ = 8.0 Hz, $J$ = 1.0 Hz, 1H), 7.06 (dd, $J$ = 8.6 Hz, $J$ = 0.8 Hz, 1H), 7.04–7.02 (m, 1H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 137.4, 136.8, 136.5, 134.9, 134.3, 131.0, 129.5, 124.8, 123.2, 121.3, 120.9, 111.5, 101.2, 95.4.

**4.1.2.4. 2-(Iodophenyl)-1*H*-indole (4).** 2-Iodoacetophenone (2.46 g, 10.0 mmol, 1 equiv) and phenyl hydrazine (1.30 g, 12.0 mmol, 1.2 equiv) were stirred in ethanol (15 mL). Acetic acid (eight drops) was added and the mixture was refluxed. After 5 h, solvent was removed and the crude was taken up in EtOAc (50 mL), washed with oxalic acid (5%), water, brine, and dried over $MgSO_4$. Filtration and evaporation yielded 1-[1-(2-iodophenyl)ethyliden]-2-phenylhydrazine (3.36 g, 10.0 mmol, 100%) as a viscous brown oil. Crude (3.36 g, 10 mmol) in xylene (45 mL) and polyphosphoric acid (17 g) were vigorously stirred at 85 °C during 20 min. Water (150 mL) was added to the warm crude, the mixture was stirred for 10 min and poured into water (300 mL) and stirred 20 min. EtOAc was added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (3× 100 mL), and the combined organic layers were washed with $H_2O$ and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (hexane/EtOAc 98:2) yielded **4** (2.35 g, 7.37 mmol, 77%) as a brown oil. $^1$H NMR (DMSO-$d_6$) $\delta$ 11.4 (s, 1H), 8.05 (dd, $J$ = 7.8 Hz, $J$ = 0.8 Hz, 1H), 7.61 (d, $J$ = 7.9 Hz, 1H), 7.57–7.49 (m, 2H), 7.44 (dd, $J$ = 8.1 Hz, $J$ = 0.7 Hz, 1H), 7.18–7.14 (m, 2H), 7.05 (dt, 7.9 Hz, $J$ = 0.9 Hz, 1H), 6.72 (dd, $J$ = 2 Hz, $J$ = 0.6 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 140.3, 139.4, 138.3, 136.6, 131.3, 130.1, 128.6, 128.1, 121.9, 120.6, 119.6, 111.8, 102.4, 98.8; Anal. ($C_{14}H_{10}IN$) C, H, N.

**4.1.2.5. *tert*-Butyl 2-(6-bromopyridin-2-yl)-1*H*-indole-1-carboxylate (20).** 1-*tert*-Butoxycarbonylindole-2-boronic acid (3 g, 11.5 mmol), 2,6-dibromopyridine (3.28 g, 13.8 mmol), and $Pd(PPh_3)_4$ (417 mg, 0.36 mmol) in THF/2 M $K_2CO_3$ (20 mL/20 mL) were refluxed overnight. Purification by flash chromatography on silica gel (hexane/EtOAc 98:2) yielded **20** (2.92 mg, 7.82 mmol, 68%) as a white solid, mp = 166 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 8.12 (d, $J$ = 8.3 Hz, 1H), 7.94 (t, $J$ = 7.8 Hz, 1H), 7.84 (d, $J$ = 7.5 Hz, 1H), 7.76–7.72 (m, 2H), 7.47 (dt, $J$ = 8.3 Hz, $J$ = 1.1 Hz, 1H), 7.36 (t, $J$ = 7.7 Hz, 1H), 7.12 (s, 1H), 1.39 (s, 9H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 153.4, 149.6, 140.8, 140.5, 137.6, 137.5,

128.4, 127.1, 125.9, 123.6, 122.4, 121.9, 114.4, 112.0, 84.0, 27.4.

**4.1.2.6. 2-(6-Iodopyridin-2-yl)-1*H*-indole (21).** *N*,*N*′-Dimethylethylenediamine (53.7 μL, 44.0 mg, 0.50 mmol), and then dry dioxane (5 mL) were successively introduced in a sealed tube with stirring bar (dried at 100 °C) charged with *tert*-butyl 2-(6-bromopyridin-2-yl)-1*H*-indole-1-carboxylate (1.87 g, 5 mmol), CuI (47.8, 0.25 mmol), and NaI (1.5 g, 62.5 mmol). After heating at 110 °C during 24 h, the suspension was cooled and ammonium hydroxide (28–30%) was added. The mixture was extracted with $CH_2Cl_2$ (3×). The combined organic layers were dried ($MgSO_4$), filtered and adsorbed on $SiO_2$ (20 g). The dry powder was heated in a conventional microwave oven (1100 watts) during 2 min. Extraction with acetone, suction filtration (3×), and concentration yielded **21** (1.34 g, 4.19 mmol, 84%) as an off-white solid, mp = 158 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 11.60 (s, 1H), 8.03 (d, $J$ = 7.8 Hz, 1H), 7.76 (d, $J$ = 7.7 Hz, 1H), 7.77–7.53 (m, 3H), 7.21–1.17 (m, 2H), 7.06 (t, $J$ = 7.7 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 152.4, 139.3, 137.8, 135.9, 133.1, 128.5, 123.2, 121.2, 120.1, 119.6, 119.0, 112.6, 102.2.

**4.1.2.7. 2-(6-Fluoropyridin-3-yl)-1*H*-indole (24).** 2-Iodoindole (1.22 g, 5.02 mmol), 2-fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-pyridine (1.232 g, 5.52 mmol), and $Pd(PPh_3)_4$ (0.6 g, 0.52 mmol) in THF/2 M $K_2CO_3$ (18 mL/12 mL) were refluxed for 72 h. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3×). Combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (hexane/EtOAc 85:15–80:20) yielded **24** as a yellow solid (769 mg, 3.63 mmol, 72%), mp = 256 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 11.48 (s, 1H), 8.76–8.75 (m, 1H), 8.43 (dt, $J$ = 8.3 Hz, $J$ = 2.6 Hz, 1H), 7.57 (d, $J$ = 7.8 Hz, 1H), 7.43 (d, $J$ = 8.1 Hz, 1H), 7.32 (dd, $J$ = 8.6 Hz, $J$ = 2.9 Hz, 1H), 7.15 (t, $J$ = 7.1 Hz, 1H), 7.05–7.00 (m, 2H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 162.0 (d, $J$ = 236.3 Hz), 144.1 (d, $J$ = 15.3 Hz), 138.8 (d, $J$ = 8.3 Hz), 137.6, 133.8, 128.7, 127.3, 122.5, 120.7, 120.0, 111.8, 110.3 (d, $J$ = 37.7 Hz), 100.3.

**4.1.3. General procedure for the synthesis of *N*,*N*-dialkyl-[5-substituted-2-(4-substitutedphenyl)indol-3-yl]glyoxylamide derivatives 5–14 and 16–19.** At 0 °C, oxalyl chloride (10 equiv) was added dropwise to the appropriate indole (1 equiv) in THF (0.15 M). The mixture was stirred for 1 h at room temperature and evaporated to dryness. At 0 °C, appropriate amine (10 equiv) in THF (0.3 M) was added dropwise to the crude in THF (0.15 M). After one night at rt, $Et_2O$ was added and the mixture was washed with 2 N HCl (3×), $NaHCO_3$ 5%, $H_2O$ and brine, dried over $MgSO_4$, filtered, and concentrated.

**4.1.3.1. *N*,*N*-Diethyl-2-(2-(4-iodophenyl)-1*H*-indol-3-yl)-2-oxoacetamide (5).** Compound **5** was obtained from 2-(4-iodophenyl)-1*H*-indole (500 mg, 1.6 mmol) in THF (10 mL), oxalyl chloride (300 mg, 2.36 mmol), and diethylamine (490 mg, 10.0 mmol) in THF (5 mL). Purification by flash chromatography on silica gel (hexane/EtOAc 80:20) yielded **5** (635 mg, 1.42 mmol, 89%) as a white solid, mp = 107 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 12.59 (s, 1H), 8.14 (d, $J$ = 7.3 Hz, 1H), 7.96 (d, $J$ = 8.3 Hz, 2H), 7.57 (d, $J$ = 7.3 Hz, 1H), 7.45 (d, $J$ = 8.3 Hz, 2H), 7.40–7.34 (m, 2H), 3.23 (q, $J$ = 7.0 Hz, 2H), 3.17 (q, $J$ = 7.2 Hz, 2H), 1.10 (t, $J$ = 7.0 Hz, 3H), 0.91 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 187.5, 167.3, 146.6, 137.1, 136.1, 132.3, 130.6, 127.0, 123.9, 122.9, 121.2, 112.5, 110.1, 97.1, 42.1, 38.2, 14.0, 12.5. EI-MS $m/z$ : 448 (21), 447 (100), 346 (5), 200 (4), 101 (33), Anal. ($C_{20}H_{19}IN_2O_2$) C, H, N.

**4.1.3.2. *N*,*N*-Dibutyl-2-(2-(4-iodophenyl)-1*H*-indol-3-yl)-2-oxoacetamide (6).** Compound **6** was obtained from 2-(4-iodophenyl)-1*H*-indole (400 mg, 1.25 mmol) in THF (10 mL), oxalyl chloride (1.6 g, 12.5 mmol), and dibutylamine (1.5 g, 11.6 mmol) in THF (5 mL). Purification by flash chromatography on silica gel (hexane/EtOAc 80:20) yielded **6** (473 mg, 0.94 mmol, 76%) as a white solid, mp = 148 °C. $^1$H NMR ($CDCl_3$) $\delta$ 10.12 (s, 1H), 8.08 (d, $J$ = 7.9 Hz, 1H), 7.31 (d, $J$ = 8.4 Hz, 2H), 7.25–7.21 (m, 1H), 7.16–7.14 (m, 2H), 6.85 (d, $J$ = 8.3 Hz, 2H), 3.06–3.02 (m, 4H), 1.47–1.43 (m, 2H), 1.21–1.07 (m, 4H), 0.88 (t, $J$ = 7.0 Hz, 3H), 0.73 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 187.2, 168.3, 146.0, 137.7, 135.9, 131.5, 130.5, 127.5, 124.4, 123.7, 122.2, 112.1, 96.7, 48.5, 44.9, 30.8, 29.5, 20.8, 20.3, 14.5, 14.1. EI-MS $m/z$ 504 (15), 503 (100). Anal. ($C_{24}H_{27}IN_2O_2$) C, H, N.

**4.1.3.3. *N*,*N*-Dihexyl-2-(2-(4-iodophenyl)-1*H*-indol-3-yl)-2-oxoacetamide (7).** Compound **7** was obtained from 2-(4-iodophenyl)-1*H*-indole (400 mg, 1.25 mmol) in THF (10 mL), oxalyl chloride (1.26 g, 9.84 mmol), and dihexylamine (1.6 g, 8.7 mmol) in THF (5 mL). Purification by flash chromatography on silica gel (eluent: hexane/EtOAc 85:15) yielded **7** (565 mg, 1.0 mmol, 81%), as a white solid, mp = 130 °C. $^1$H NMR ($CDCl_3$) $\delta$ 11.34 (s, 1H), 7.99 (d, $J$ = 7.1 Hz, 1H, H7), 7.20–7.17 (m, 1H), 7.09–7.06 (m, 1H), 7.03–7.00 (m, 3H), 6.58 (d, $J$ = 7.7 Hz, 2H), 3.07–2.98 (m, 4H), 1.30–0.85 (m, 16H), 0.84 (t, $J$ = 8.0 Hz, 3H), 0.71 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 186.6, 168.7, 146.8, 137.5, 136.3, 131.2, 130.4, 127.5, 124.1, 123.6, 121.6, 112.9, 110.4, 96.4, 49.0, 45.5, 32.1, 31.7, 28.7, 27.4, 27.3, 26.7, 23.1, 22.8, 14.6, 14.3. EI-MS $m/z$ 559 ($MH^+$, 100), 560 (33). Anal. ($C_{28}H_{35}IN_2O_2$) C, H, N.

**4.1.3.4. *N*-Benzyl-2-(2-(4-iodophenyl)-1*H*-indol-3-yl)-2-oxoacetamide (8).** Compound **8** was obtained from 2-(4-iodophenyl)-1*H*-indole (400 mg, 1.25 mmol) in THF (10 mL), oxalyl chloride (1 g, 7.7 mmol), and benzylamine (1.5 g, 14.0 mmol) in THF (5 mL). Purification by flash chromatography on silica gel (hexane/EtOAc 60:40) yielded **8** (380 mg, 0.79 mmol, 63%) as a white solid, mp = 210 °C. $^1$H NMR ($CDCl_3$) $\delta$ 12.45 (s, 1H), 9.08 (t, $J$ = 9.2 Hz, 1H), 8.01 (d, $J$ = 8.0 Hz, 1H), 7.80 (d, $J$ = 8.2 Hz, 2H), 7.50 (d, $J$ = 8.0 Hz, 1H), 7.38 (d, $J$ = 8.3 Hz, 2H), 7.34 (d, $J$ = 7.6 Hz, 2H), 7.31–7.27 (m, 2H), 7.23–7.21 (m, 3H), 4.09 (d, $J$ = 6.0 Hz, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 187.5, 166.7, 146.4, 138.7, 137.2, 136.2, 131.7, 128.7, 127.9, 127.6, 127.3, 123.8, 122.7, 121.2,

112.4, 109.6, 96.7, 42.1. EI-MS *m/z* 482 (8), 481 (25), 413 (15), 218 (100), 196 (29), Anal. ($C_{23}H_{17}IN_2O_2$) C, H, N.

**4.1.3.5. 2-(2-(4-Iodophenyl)-1*H*-indol-3-yl)-*N*,*N*-bis(2-methoxyethyl)-2-oxoacetamide (9).** Compound **9** was obtained from 2-(4-iodophenyl)-1*H*-indole (479 mg, 1.5 mmol) in THF (7 mL), oxalyl chloride (1.91 g, 15 mmol) and bis(2-methoxyethyl)amine (2.5 g, 19 mmol) in THF (7 mL). Purification by flash chromatography on silica gel (hexane/EtOAc 70:30) yielded **9** (538 mg, 1.06 mmol 71%) as a white solid, mp = 120 °C. $^1$H NMR ($CDCl_3$) $\delta$ 9.18 (s, 1H), 8.09 (d, $J$ = 7.9, 1H), 7.39 (d, $J$ = 8.1 Hz, 2H), 7.25–7.21 (m, 1H), 7.17–7.13 (m, 2H), 6.95 (d, $J$ = 8.1 Hz, 2H), 3.47–3.44 (m, 4H), 3.42 (t, $J$ = 5.6 Hz, 2H), 3.29 (s, 3H), 3.27 (t, $J$ = 5.7 Hz, 2H), 3.15 (s, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 186.6, 168.9, 146.2, 137.8, 135.9, 131.4, 130.7, 127.5, 124.5, 123.7, 122.0, 112.1, 111.0, 96.7, 71.5, 70.4, 59.4, 59.1, 48.9, 46.2, Anal. ($C_{22}H_{23}IN_2O_4$) C, H, N.

**4.1.3.6. *N*,*N*-Diethyl-2-(2-(3-iodophenyl)-1*H*-indol-3-yl)-2-oxoacetamide (11).** Compound **11** was obtained from 2-(3-iodophenyl)-1*H*-indole (100 mg, 0.31 mmol) in THF (5 mL), oxalyl chloride (632 mg, 5.0 mmol), and diethylamine (400 mg, 5.5 mmol) in THF (2.5 mL). Trituration into EtOAc yielded **11** (87 mg, 0.194 mmol, 64%) as a white solid, mp = 192 °C. $^1$H NMR ($CDCl_3$) $\delta$ 10.08 (s, 1H), 8.11 (d, $J$ = 7.9 Hz, 1H), 7.65–7.64 (m, 1H), 7.55 (d, $J$ = 8.0 Hz, 1H), 7.20–7.13 (m, 3H), 6.96 (d, $J$ = 7.7 Hz, 1H), 6.56 (t, $J$ = 7.8 Hz, 1H), 3.24 (q, $J$ = 7.0 Hz, 2H), 3.13 (q, $J$ = 7.2 Hz, 2H), 1.11 (t, $J$ = 7.0 Hz, 3H), 0.90 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 187.2, 168.0, 145.6, 138.7, 138.4, 136.0, 133.3, 130.3, 129.2, 127.4, 124.5, 123.6, 122.1, 112.3, 111.2, 93.8, 43.4, 39.9, 14.4, 13.0. EI-MS *m/z* 447 (12), 446 (38), 346 (20), 220 (17), 219 (10), 127 (8), 77 (9), 62 (100), 61 (27), Anal. ($C_{20}H_{19}IN_2O_2$) C, H, N.

**4.1.3.7. *N*,*N*-Dibutyl-2-(2-(3-iodophenyl)-1*H*-indol-3-yl)-2-oxoacetamide (12).** Compound **12** was obtained from 2-(3-iodophenyl)-1*H*-indole (100 mg, 0.31 mmol) in THF (5 mL), oxalyl chloride (649 mg, 5.1 mmol), and dibutylamine (667 mg, 5.2 mmol) in THF (2.5 mL). Purification by flash chromatography on silica gel (hexane/EtOAc 70:30) yielded **12** (133 mg, 0.27 mmol, 86%) as a white solid, mp = 62 °C. $^1$H NMR ($CCl_3$) $\delta$ 9.20 (s, 1H), 8.17 (d, $J$ = 6.8 Hz, 1H), 7.75–7.74 (m, 1H), 7.65 (d, $J$ = 8,0 Hz, 1H), 7.29 (d, $J$ = 7.7 Hz, 1H), 7.27–7.18 (m, 3H), 6.88 (t, $J$ = 7.8 Hz, 1H), 3.10 (t, $J$ = 7.8 Hz, 2H), 3.04 (t, $J$ = 7.2 Hz, 2H), 1.50–1.45 (m, 2H), 1.22–1.08 (m, 6H), 0.83 (t, $J$ = 7.0 Hz, 3H), 0.76 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 186.9, 168.5, 145.9, 138.5, 138.4, 136.2, 133.2, 130.2, 129.0, 127.4, 124.2, 123.5, 121.8, 112.8, 110.8, 93.8, 49.0, 45.7, 31.0, 29.7, 20.8, 20.4, 14.3, 14.1, Anal. ($C_{24}H_{27}IN_2O_2$) C, H, N.

**4.1.3.8. *N*,*N*-Dibutyl-2-(2-(3-iodophenyl)-1*H*-indol-3-yl)-2-oxoacetamide (13).** Compound **13** was obtained from 2-(3-iodophenyl)-1*H*-indole (100 mg, 0.31 mmol) in THF (5 mL), oxalyl chloride (600 mg, 4.72 mmol), and dihexylamine (943 mg, 5.1 mmol) in THF (2.5 mL). Purification by flash chromatography on silica gel (hexane/EtOAc 80:20) yielded **13** (157 mg, 0.28 mmol, 91%) as a yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ 10.95 (br s, 1H), 8.04 (d, $J$ = 7.8 Hz, 1H), 7.58 (s, 1H), 7.42 (d, $J$ = 7.8 Hz, 1H), 7.15–7.11 (m, 1H), 7.06–7.05 (m, 2H), 7.70 (d, $J$ = 6.1 Hz, 1H), 6.24–6.22 (m, 1H), 3.12 (t, $J$ = 7.7 Hz, 2H), 3.03 (t, $J$ = 7.3 Hz, 2H), 1.49–1.47 (m, 2H), 1.23–1.07 (m, 14H), 0.81 (t, $J$ = 7.1 Hz, 3H), 0.73 (t, $J$ = 7.0 Hz, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 186.9, 168.5, 145.9, 138.5, 138.4, 136.3, 133.3, 130.3, 129.0, 127.5, 124.2, 123.4, 121.9, 112.8, 110.8, 93.7, 49.3, 46.0, 32.0, 31.7, 28.9, 27.6, 27.3, 26.8, 23.0, 22.9, 14.5, 14.4, Anal. ($C_{28}H_{35}IN_2O_2$) H, N, C, calcd 60.22, found 59.45.

**4.1.3.9. *N*,*N*-Diethyl-2-(2-(3-iodophenyl)-1*H*-indol-3-yl)-2-oxoacetamide (14).** Compound **14** was obtained from 2-(3-iodophenyl)-1*H*-indole (100 mg, 0.31 mmol) in THF (5 mL), oxalyl chloride (519 mg, 4.09 mmol), and benzylamine (513 mg, 5.37 mmol) in THF (2.5 mL). Trituration into EtOAc yielded **14** (104 mg, 0.217 mmol, 70%) as a white solid, mp = 232 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 12.54 (s, 1H), 9.16 (t, $J$ = 6.0 Hz, 1H), 8.07 (d, $J$ = 7.9 Hz, 1H), 8.02 (s, 1H), 7.92 (d, $J$ = 8.2, 1H), 7.65 (d, $J$ = 7.7 Hz, 1H), 7.54 (d, $J$ = 7.9 Hz, 1H), 7.39–7.22 (m, 8H), 4.12 (d, $J$ = 5.9 Hz, 2H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 187.6, 166.8, 145.7, 138.7, 138.3, 137.9, 136.2, 133.8, 130.4, 129.5, 128.7, 127.9, 127.5, 127.3, 123.9, 122.8, 121.3, 112.5, 109.7, 94.8, 42.2, Anal. ($C_{23}H_{17}IN_2O_2$) C, H, N.

**4.1.3.10. 2-(2-(3-Bromophenyl)-1*H*-indol-3-yl)-*N*,*N*-bis(2-methoxyethyl)-2-oxoacetamide (10).** Compound **10** was obtained from 2-(3-iodophenyl)-1*H*-indole (816 mg, 3 mmol) in THF (15 mL), oxalyl chloride (3.81 g, 30 mmol), and bis(2-methoxyethyl)amine (4 g, 30 mmol) in THF (7 mL). Purification by flash chromatography on silica gel (hexane/EtOAc 60:40–1:1) yielded **10** (1.17 g, 2.55 mmol, 85%) as a white solid, mp = 120 °C. $^1$H NMR ($CDCl_3$) $\delta$ 10.78 (s, 1H), 8.01 (d, $J$ = 7.9 Hz, 1H), 7.50 (t, $J$ = 1.7 Hz, 1H), 7.23 (m, 1H), 7.13–7.11 (m, 1H), 7.04–7.03 (m, 2H), 6.69 (d, $J$ = 7.6 Hz, m, 1H), 6.46 (t, 7.9 Hz, 1H), 3.51 (t, 5.6 Hz, 2H), 3.44–3.39 (m, 4H), 3.31 (t, $J$ = 5.4 Hz, 2H), 3.21 (s, 3H), 3.11 (s, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 186.3, 169.2, 146.0, 136.1, 133.2, 132.6, 130.1, 128.2, 127.4, 124.3, 123.5, 122.0, 121.7, 112.6, 110.6, 71.3, 70.2, 59.2, 59.0, 49.2, 46.5, Anal. ($C_{22}H_{23}BrN_2O_4$) C, H, N.

**4.1.3.11. *N*,*N*-Bis(2-methoxyethyl)-2-(2-(3-(trimethylstannyl)phenyl)-1*H*-indol-3-yl)-2-oxoacetamide.** 2-(2-(3-Bromophenyl)-1*H*-indol-3-yl)-*N*,*N*-bis(2-methoxyethyl)-2-oxoacetamide (**10**) (1 g, 2.18 mmol), $Pd(PPh_3)_4$ and $(Me_3Sn)_2$ in 1,4-dioxane were refluxed for 72 h and evaporated. Purification by flash chromatography on silica gel (hexane/EtOAc/$Et_3N$ 98:2:0.1%–60:40:0.1%) yielded desired compound (250 mg, 0.49 mmol, 99%)as a white solid, mp <65 °C. $^1$H NMR ($CDCl_3$) $\delta$ 8.43 (s, 1H), 8.07–8.05 (m, 1H), 7.48 (br s, 1H), 7.41–7.39 (m, 1H), 7.35–7.33 (m, 1H), 7.22–7.18 (m, 2H), 7.13–7.08 (m, 2H), 3.26 (t, $J$ = 5.5 Hz, 2H), 3.19 (t, $J$ = 6.1 Hz, 2H), 3.13 (t, $J$ = 5.6 Hz, 2H), 3.09 (s, 3H), 3.05 (t,

$J$ = 6.0 Hz, 2H), 3.01 (s, 3H), 0.19–0.08 (m, 9H). $^{13}$C NMR ($CDCl_3$) $\delta$ 181.5, 168.7, 147.6, 143.2, 137.8, 137.0, 135.6, 130.8, 130.2, 128.1, 127.6, 124.5, 123.6, 122.5, 111.5, 111.4, 71.6, 70.5, 59.1, 48.9, 45.9, −8.98. Anal. ($C_{25}H_{32}N_2O_4Sn$) C, H, N.

**4.1.3.12. 2-(2-(3-Iodophenyl)-1*H*-indol-3-yl)-*N*,*N*-bis(2-methoxyethyl)-2-oxoacetamide (15).** *N*,*N*-Bis(2-methoxyethyl)-2-(2-(3-(trimethylstannyl)phenyl)-1*H*-indol-3-yl)-2-oxoacetamide (272 mg, 0.50 mmol), iodine (153 mg, 0.60 mmol) in $CH_2Cl_2$ were stirred overnight at rt. Aqueous sodium thiosulfate was added, after discoloration, $MgSO_4$ was added, mixture was filtered and concentrated. Purification by flash chromatography on silica gel (hexane/EtOAc/$Et_3N$ 70:30:0.1%) yielded **15** (252 mg, 0.50 mmol, 99%) as a white solid, mp <65 °C. $^1$H NMR ($CDCl_3$) $\delta$ 10.76 (s, 1H), 8.01 (d, $J$ = 7.9 Hz, 1H), 7.68 (t, $J$ = 1.6 Hz, 1H), 7.43–7.41 (m, 1H), 7.13–7.09 (m, 1H), 7.05–7.04 (m, 2H), 7.74 (d, $J$ = 7.6 Hz, 1H), 6.33 (t, $J$ = 7.8 Hz, 1H), 3.50 (t, $J$ = 5.2 Hz, 2H), 3.43 (t, $J$ = 5.1 Hz, 2H), 3.41 (t, $J$ = 5.6 Hz, 2H), 3.31 (t, $J$ = 5.5 Hz, 2H), 3.21 (s, 3H), 3.11 (s, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 186.4, 169.2, 145.9, 138.6, 138.2, 136.1, 133.3, 130.2, 128.9, 127.4, 124.3, 123.5, 121.8, 112.6, 110.6, 93.7, 71.4, 70.3, 59.2, 59.1, 49.2, 46.7, Anal. ($C_{22}H_{23}IN_2O_4$) C, H, N.

**4.1.3.13. *N*,*N*-Diethyl-2-(2-(2-iodophenyl)-1H-indol-3-yl)-2-oxoacetamide (16).** Compound **16** was obtained from 2-(2-iodophenyl)-1*H*-indole (309 mg, 0.969 mmol) in THF (10 mL), oxalyl chloride (1.48 g, 11.6 mmol), and diethylamine (1.26 g, 17.2 mmol) in THF (5 mL). Trituration into EtOAc yielded **16** (272 mg, 0.61 mmol, 63%), white solid, mp = 225 °C. $^1$H NMR ($CDCl_3$) $\delta$ 8.94 (s, 1H), 8.32–8.30 (m, 1H), 7.79 (dd, $J$ = 8.0 Hz,$J$ = 0.8 Hz, 1H), 7.36–7.33 (m, 2H), 7.28–7.24 (m, 3H), 7.04 (dt, $J$ = 7.8 Hz, $J$ = 1.7 Hz, 1H), 3.17–3.14 (br m, 2H), 3.0–2.95 (br m, 2H), 1.05 (t, $J$ = 7.0 Hz, 3H), 0.69 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 187.7, 167.4, 147.4, 139.1, 136.5, 135.5, 133.2, 131.6, 127.9, 126.9, 124.7, 123.7, 122.9, 112.2, 111.8, 99.3, 43.5, 38.8, 14.4, 12.8, Anal. ($C_{20}H_{19}IN_2O_2$) C, H, N.

**4.1.3.14. *N*,*N*-Dibutyl-2-(2-(4-iodophenyl)-1*H*-indol-3-yl)-2-oxoacetamide (17).** Compound **17** was obtained from 2-(2-iodophenyl)-1*H*-indole (330 mg, 1.03 mmol) in THF (10 mL), oxalyl chloride (1.54 g, 12.1 mmol), and dibutylamine (1.21 g, 9.38 mmol) in THF (5 mL). Purification by flash chromatography on silica gel (hexanes/EtOAc 90:10–80:20) yielded **17** (322 mg, 0.64 mmol, 62%). White solid, mp = 77 °C. $^1$H NMR ($CDCl_3$) $\delta$ 9.44 (s, 1H), 8.22 (d, $J$ = 7.4 Hz, 1H); 7.73 (dd, $J$ = 7.9 Hz, $J$ = 0.9 Hz, 1H), 7.30 (dd, $J$ = 7.0 Hz, $J$ = 1.6 Hz, 1H), 7.24–7.18 (m, 3H), 7.11 (dt, $J$ = 7.5 Hz, $J$ = 1.1 Hz, 1H), 6.97 (dt, $J$ = 7.8 Hz, $J$ = 1.7 Hz, 1H), 3.11–2.94 (br m, 2H), 2.93–7.79 (br m, 2H), 1.46–1.39 (m, 2H), 1.15–0.95 (m, 6H), 0.81–0.72 (m, 6H). $^{13}$C NMR ($CDCl_3$) $\delta$ 187.4, 167.8, 147.4, 139.0, 136.6, 135.6, 132.9, 131.5, 127.8, 126.8, 124.5, 123.5, 122.7, 112.1, 112.0, 99.4, 49.2, 44.7, 31.0, 29.6, 20.7, 20.4, 14.3, 14.1. EI-MS *m*/*z* 502 (6), 347 (16), 346 (100), 329 (25), 220 (76), 219 (96), 190 (27), 164 (15), 160 (58), 156 (11), Anal. ($C_{24}H_{27}IN_2O_2$) C, H, N.

**4.1.3.15. *N*,*N*-Dibutyl-2-(2-(2-iodophenyl)-1*H*-indol-3-yl)-2-oxoacetamide (18).** Compound **18** was obtained from 2-(2-iodophenyl)-1*H*-indole (348 mg, 1.09 mmol) in THF (10 mL), oxalyl chloride (.26 g, 9.92 mmol), and dihexylamine (1.28 g, 6.92 mmol) in THF (5 mL). Purification by flash chromatography on silica gel (hexane/EtOAc 90:10–80:20) yielded **18** (480 mg, 0.86 mmol, 79%) as a tanned solid, mp = 52 °C. $^1$H NMR ($CDCl_3$) $\delta$ 9.90 (s, 1H), 8.17 (d, $J$ = 7.6 Hz, 1H), 7.66 (d, $J$ = 7.8 Hz, 1H), 7.27 (d, $J$ = 7.8 Hz, 1H), 7.22–7.13 (m, 2H), 7.07 (dd, $J$ = 7.5 Hz, $J$ = 0.9 Hz, 1H), 6.99 (t, $J$ = 7.4 Hz, 1H), 6.89 (dt, $J$ = 7.8 Hz, $J$ = 1.4 Hz, 1H), 3.13–2.92 (br m, 2H), 2.91–2.74 (br m, 2H), 1.44–1.39 (m, 2H), 1.24–0.93 (m, 14H), 0.82 (t, $J$ = 6.9 Hz, 3H), 0.72 (t, $J$ = 6.7 Hz, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 187.2, 167.9, 147.7, 138.9, 136.6, 135.8, 132.8, 131.3, 127.7, 126.8, 124.4, 123.4, 122.6, 112.3, 111.8, 99.4, 49.5, 45.0, 32.0, 31.7, 28.9, 27.4, 27.2, 26.8, 23.0, 22.9, 14.5, 14.4. EI-MS *m*/*z* 558 (4), 347 (17), 346 (100), 273 (11), 271 (11), 220 (46), 219 (60), 191 (17), 190 (23), 85 (33), 57 (37), Anal. ($C_{28}H_{35}IN_2O_2$) C, H, N.

**4.1.3.16. *N*,*N*-Dibutyl-2-(2-(4-iodophenyl)-1*H*-indol-3-yl)-2-oxoacetamide (19).** Compound **19** was obtained from 2-(2-iodophenyl)-1*H*-indole (316 mg, 0.99 mmol) in THF (10 mL), oxalyl chloride (1.52 g, 12.0 mmol), and benzylamine (1.20 g, 11.2 mmol) in THF (5 mL). Trituration into EtOAc yielded **19** (321 mg, 0.669 mmol, 68%) as a yellow solid, mp = 204 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 12.48 (s, 1H), 8.97 (t, $J$ = 6.1 Hz, 1H), 8.15 (d, $J$ = 7.5 Hz, 1H), 8.00 (d, $J$ = 7.7 Hz, 1H), 7.53–7.50 (m, 3H), 7.36–7.27 (m, 5H), 7.24–7.22 (m, 2H), 4.09–4.02 (m, 1H), 3.91–3.87 (m, 1H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 187.0, 166.7, 148.8, 138.9, 138.6, 137.3, 135.8, 131.9, 131.1, 128.6, 127.8, 127.5, 127.2, 126.7, 123.8, 122.7, 121.6, 112.4, 110.5, 100.6, 41.9. EI-MS *m*/*z* 480 (9), 447 (24), 347 (11), 346 (61), 221 (13), 220 (76), 219 (100), 191 (15), 190 (28), 165 (10), 91 (28), 77 (12), Anal. ($C_{23}H_{17}IN_2O_2$) C, H, N.

**4.1.3.17. *N*,*N*-Dibutyl-2-(2-(6-iodopyridin-2-yl)-1*H*-indol-3-yl)-2-oxoacetamide (22).** Oxalyl chloride (635 mg, 5 mmol) was added dropwise, over 1 h, to 2-(6-iodopyridin-2-yl)-1*H*-indole (160 mg, 0.5 mmol) in THF (2 mL) at 0 °C. Four drops of DMF were added and the crude was stirred for 1 more hour. Crude was evaporated to give a brown solid that was reuptake in THF (2 mL). Dibutylamine (645 mg, 5 mmol) in THF (1 mL) was then added dropwise. The mixture was stirred for one night at rt. Purification by column chromatography (hexanes/EtOAc 75:25–70:30) yielded **22** (114 mg, 0.23 mmol, 44%) as a white solid, mp = 148 °C. $^1$H NMR ($CDCl_3$) $\delta$ 10.36 (br s, 1H), 8.61 (d, $J$ = 7.8 Hz, 1H), 7.77 (d, $J$ = 8.1 Hz, 1H), 7.60 (t, $J$ = 7.9 Hz, 1H), 7.38 (d, $J$ = 8.1 Hz, 1H), 7.25–7.24 (m, 2H), 7.18–7.15 (m, 1H), 3.44 (t, $J$ = 7.8 Hz, 2H), 3.17 (t, $J$ = 7.8 Hz, 2H), 1.35–1.60 (m, 2H), 1.50–1.43 (m, 2H), 1.39–1.31 (m, 2H), 0.92 (t, $J$ = 7.4 Hz, 3H), 0.68 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 187.5, 169.1, 150.8, 149.1, 141.4, 140.3. 135.6, 128.0, 125.3, 125.2, 124.2, 123.5, 121.4, 112.5, 111.6, 48.5, 45.1, 30.9, 29.8, 20.8, 20.3, 14.3, 13.9.

**4.1.3.18. *N*,*N*-Dibutyl-2-(2-(6-fluoropyridin-3-yl)- 1*H*-indol-3-yl)-2-oxoacetamide (25).** Oxalyl chloride (95.3 mg, 0.75 mmol) was added dropwise, over 1.5 h, to 2-(6-fluoropyridin-3-yl)-1*H*-indole (106 mg, 0.5 mmol) in THF (2 mL) at 0 °C. Dibutylamine (300 mg, 2.33 mmol) in THF (2 mL) was then added dropwise. After 2 h, EtOAc was added and the mixture was washed with 2 N HCl (1×), 3% NaOH (1×) and brine, organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (hexane/EtOAc 80:20) yielded **25** (95 mg, 0.24 mmol, 48%) as a yellow oil. $^1$H NMR (DMSO-$d_6$) $\delta$ 8.53 (d, $J$ = 2.2 Hz, 1H), 8.28 (dt, $J$ = 8.1 Hz,$J$ = 2.4 Hz, 1H), 8.10 (d, $J$ = 6.7 Hz, 1H), 7.58 (d, $J$ = 7.8 Hz, 1H), 7.43 (dd, $J$ = 8.4 Hz, $J$ = 2.5 Hz, 1H), 7.39–7.31 (m, 2H), 3.14–3.06 (m, 4H), 1.52–1.13 (m, 8H), 0.92 (t, $J$ = 7.1 Hz, 3H), 0.79 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 187.1, 167.6, 163.7 (d, $J$ = 237 Hz), 148.8 (d, $J$ = 15.9 Hz), 144.2 (d, $J$ = 8.5 Hz), 143.1, 136.5, 126.9, 126.0, 124.1, 123.0, 121.2, 112.7, 110.9, 109.2 (d, $J$ = 37.5 Hz), 47.5, 43.8, 30.4, 29.2, 20.1, 19.6, 14.0, 13.8, Anal. ($C_{23}H_{26}FN_3O_2$) C, H, N.

**4.1.3.19. *N*,*N*-Hexyl-2-(2-(6-fluoropyridin-3-yl)-1*H*-indol-3-yl)-2-oxoacetamide (26).** Oxalyl chloride (95.3 mg, 0.75 mmol) was added dropwise, over 1.5 h, to 2-(6-fluoropyridin-3-yl)-1*H*-indole (100 mg, 0.47 mmol) in THF (2 mL) at 0 °C. Dihexylamine (742 mg, 4.0 mmol) in THF (2 mL) was then added dropwise. After 2 h, the mixture was evaporated. Purification by flash chromatography on silica gel (hexane/EtOAc 80:20) yielded **26** (188 mg, 0.42 mmol, 88%) as a yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ 11.3 (br s, 1H), 8.06 (d, $J$ = 2.3 Hz, 1H), 7.82 (d, $J$ = 6.85 Hz, 1H), 7.15–7.05 (m, 4H), 6.24 (d, $J$ = 8.2 Hz, 1H), 3.13 (t, $J$ = 7.6 Hz, 2H), 3.08 (t, $J$ = 7.8 Hz, 2H), 1.46–1.42 (m, 2H), 1.26–1.20 (m, 2H), 1.24–1.98 (m, 6H), 0.83 (t, $J$ = 7.0 Hz, 3H), 0.70 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 186.0, 169.0, 164.8 (d, $J$ = 243.1 Hz), 148.2 (d, $J$ = 15.1 Hz), 142.8 (d, $J$ = 8.4 Hz), 136.3, 126.9, 125.2 (d, $J$ = 4.7 Hz), 124.4, 123.6, 121.2, 112.8, 110.8, 109.2 (d, $J$ = 37.5 Hz), 48.8, 45.5, 31.5, 31.4, 28.6, 27.5, 27.1, 26.7, 23.0, 22.7, 14.4, 14.2. Anal. ($C_{27}H_{34}FN_3O_2$) C, H, N.

**4.1.3.20. *N*-Benzyl-2-(2-(6-fluoropyridin-3-yl)-1*H*-indol-3-yl)-2-oxoacetamide (27).** Oxalyl chloride (95.3 mg, 0.75 mmol) was added dropwise, over 1.5 h, to 2-(6-fluoropyridin-3-yl)-1*H*-indole (106 mg, 0.5 mmol) in THF (2 mL) at 0 °C. Benzylamine (428 mg, 4.0 mmol) in THF (2 mL) was then added dropwise. After 2 h, the mixture was evaporated. Purification by flash chromatography on silica gel (hexane/EtOAc 60:40) yielded **27** (107 mg, 0.29 mmol, 58%) as a yellow solid, mp = 184 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 12.57 (br s, 1H), 9.13 (t, $J$ = 6.1 Hz, 1H), 8.46 (d, $J$ = 2.3 Hz, 1H), 8.19 (dt, $J$ = 8.3 Hz, $J$ = 2.5 Hz, 1H), 8.01 (d, $J$ = 7.9 Hz, 1H), 7.52 (d, $J$ = 8.0 Hz, 1H), 7.40–7.20 (m, 8H), 4.08 (d, $J$ = 6.0 Hz, 2H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 187.2, 166.8, 163.5 (d, $J$ = 138.7 Hz), 148.3 (d, $J$ = 15.6 Hz), 143.6 (d, $J$ = 8.6 Hz), 142.9, 138.6, 136.3, 128.9, 128.7, 127.9, 127.4, 127.2, 126.4, (d, $J$ = 4.1 Hz), 124.1, 122.9, 121.3, 112.5, 110.5, 109.3 (d, $J$ = 37.7 Hz), 42.1, Anal. ($C_{22}H_{16}FN_3O_2$) C, H, N.

### 4.2. Radioligand binding assays

Peripheral and central benzodiazepine receptor binding assays on membranes from rat kidney (PBR) and guinea pig cortex (CBR) were performed according to standard receptor binding procedures. Briefly, frozen rat kidney (Pel-Freez) and guinea pig cortex were homogenized in tissue (for PBR: 50 mM Tris–HCl buffer (pH 7.4 at 4 °C) containing 2.0 mM $MgCl_2$; for CBR: 50 mM Tris acetate pH 7.4 at 4 °C) using a Polytron and spun in a centrifuge at 40,000*g* for 10 min. Membranes were recovered after multiple rounds of separation by centrifugation and resuspension in fresh ice-cold tissue buffer. The final pellets were resuspended in assay buffer (for PBR assays: 50 mM Tris–HCl buffer (pH 7.4 at 22 °C) containing 2 mM $MgCl_2$; for CBR assays: 50 mM Tris Acetate (pH 7.4 at 4 °C)). Incubations were initiated by the addition of tissue to 96-well plates containing test drugs and radioligand (for CBR assays: 1.0 nM [$^3$H]PK-11195 (Perkin Elmer); for CBR assays: 1.0 nM [$^3$H]Flunitrazepam (Amersham); final volume of 250 μl). Non-specific binding was determined by radioligand binding in the presence of a saturating concentration of PK-11195 (10 μM) for PBR assays or Ro-15-1788 (10 μM) for CBR assays. After an appropriate incubation period (for PBR assays: 2 h at room temperature; CBR assays: 90 min at 4 °C), assay samples were rapidly filtered through Whatman GF/B filters (pre-soaked in 0.5% polyethylenimine and dried) and rinsed with ice-cold 50 mM Tris buffer (pH 7.7 at 4 °C). Membrane-bound [$^3$H]PK-11195 and [$^3$H]Flunitrazepam levels were determined by liquid scintillation counting of the filters in BetaScint using a Beta-plate counter. The $IC_{50}$ value (concentration at which 50% inhibition of specific binding occurs) was calculated by linear regression of the concentration-response data. $K_i$ values were calculated according to the Cheng–Prusoff equation, $K_i = IC_{50}/(1 + (L/K_d))$, where $L$ is the concentration of the radioligand used in the experiment and the $K_d$ value is the dissociation constant for the radioligand (determined previously by saturation analysis).

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2006.07.001.

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