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Hyperpolarisation of Mirfentanil by SABRE in the Presence of Heroin

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Mirfentanil
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Mirfentanil detection: Mirfentanil, a fentanyl derivative and μ-opioid partial agonist, is hyperpolarised via the hyperpolarisation technique Signal Amplification By Reversible Exchange (SABRE). In a series of simulated samples consisting of mirfentanil and heroin, the amount of mirfentanil was varied from 0.63^% w/w--3.80^% w/w. Mirfentanil was readily detected in the ^{1}H NMR spectrum (single transient) at all the concentrations studied when SABRE was employed.

Mirfentanil, a fentanyl derivative that is a μ-opioid partial agonist, is hyperpolarised via Signal Amplification By Reversible Exchange (SABRE), a *para*-hydrogen-based technique. [Ir(IMes)(COD)Cl] (IMes=1,3-*bis*(2,4,6-trimethylphenyl)imidazole-2-ylidene, COD=cyclooctadiene) was employed as the polarisation transfer catalyst. Following polarisation transfer at 6.5 mT, the pyrazine-protons were enhanced by 78-fold (polarisation, P=0.04^%). The complex $[Ir(IMes)(H)_2(mirfentanil)_2(MeOH)]^+$ is proposed to form based on the observation of two hydrides at δ <M->22.9 (*trans* to mirfentanil) and <M->24.7 (*trans* to methanol). In a mixture of mirfentanil and heroin, the former could be detected using SABRE at concentrations less than 1^% w/w. At the lowest concentration analyzed, the amount of mirfentanil present was 0.18^^mg (812^^μM) and produced a signal enhancement of <M->867-fold (P=0.42^%). following polarisation transfer at 6.5^^mT.

1. Introduction

Mirfentanil, **1**, is a fentanyl derivative that appears to be a μ-opoid partial agonist.[1] Studies have shown **1** possesses moderate selectivity for μ-opioid receptors (IC_{50}=7.99^^nM) compared to κ- or δ-receptors (IC_{50}=480^^nM and 1428^^nM respectively).[2] Despite being a promising analgesic,[3] inducer of antinociception (without suppressing splenic natural killer activity),[4] and having a limited effect on the ventilatory response to hypercarbia (25—150^^μg $Kg^{<M->1}$),[5] significant adverse effects were found at higher doses (>2000^^ng^$mL^{<M->1}$ in blood plasma) that was linked to increased heart rates (greater than 130^^bpm), epileptiform EEG potentials and a convulsion in volunteers studied.[6]

Morphine (**3^a**) and heroin (**3^b**) are both opiates and as such are analgesics. They both possess euphoric properties. **3^b** is more potent than **3^a** due to greater brain penetration and rapid enzyme-catalysed deacetylation in the blood to form 6-acetylmorphine, which is then subsequently hydrolysed to **3^a**.[7] Therefore, **3^b** is a drug of abuse. A number of reports have cited an increase in **3^b**-related overdose due to the fact that **3^b** is often “cut”

with other drugs such as **2** or one of its derivatives, known as fentalogs, due to their euphoria inducing effects.[8] Some countries, such as the USA, have seen a sharp rise in **3^b**-linked deaths.[9]

The concentration of **2** or a fentalog in a sample of **3^b** is typically low (*ca.* mg) and so commonly used methods such as GC-MS struggle to detect them against the strong background of **3^b**, although methods have been developed to combat this.[10]

Polarisation methodologies could aid in the detection of **2** or a fentalog, despite their low concentration in bulk samples. Signal Amplification By Reversible Exchange[11] (SABRE) is one such technique. SABRE utilizes *para*-hydrogen (p-H_2) as the source of polarisation. An iridium centred catalyst is typically employed to facilitate polarisation from p-H_2 derived hydrides, and the spin-1/2 nuclei of the analyte molecule being polarised, through the established J-coupling network. A number of *N*-heterocycles, inclusive of drug molecules, have been polarised by SABRE.[11--12]

In a previous report, three pyridyl fentalogs were successfully polarised *via* SABRE.[13] **2** was also appraised in this previous report but was not polarised due to lack of sufficient donor atoms to the iridium catalyst used. Even a combined SABRE-relay[14] and catalyst separated hyperpolarisation (CASH)-SABRE[15] approach did not facilitate the polarisation of **2**. Although these fentalogs have, to date, not been encountered on the recreational drug scene, proof-of-concept for the detection of fentalogs using SABRE has been established. However, **1** is a known fentalog with known toxicity that could be encountered. Therefore, development of technique to detect this fentalog at low concentration in a seized drug sample is desirable. In terms of harm reduction point-of-care services, being able to quickly analyse and detect materials at a low threshold in a seized drug sample is very important for safe-guarding vulnerable individuals. In the light of this, a route by which **1** can be detected, via SABRE, against a strong background signal of **3^b**, is described to potentially aid harm reduction point-of-care services.

2. Results and Discussion

2.1. Synthesis of 1

The synthesis of **1** is outlined in scheme^^1<schr1>. The synthetic pathway is adapted from a procedure reported by Bagley *et^^al.*[16] and utilizes 1-phenethyl-4-piperidone as the starting material. The overall yield of this four-step pathway was 62^%. Briefly, 1-phenethyl-4-piperidone was converted into the hydroxylamine, **4**, before being reduced in the presence of $LiAlH_4$ to give **5.HCl**, following an acidic work-up. A copper-mediated coupling was then utilized to form **6** in 34^% yield; this step was the lowest yielding step of the synthetic pathway. Acylation of **6** with 2-furoyl chloride formed the target compound, **1**. The ^{1}H, ^{13}C and IR data for all of these compounds is reported in the SI and is consistent with their molecular structures.

<?><?><?>Dear Author, Figure^^1<figr1/or> is not mentioned in the text<?><?><?>

2.2. SABRE-based hyperpolarisation of 1

Initial studies were focused on the hyperpolarisation of **1** solely using [Ir(IMes)(COD)Cl] (IMes=1,3-*bis*(2,4,6-trimethylphenyl)imidazole-2-ylidene, COD=cyclooctadiene), **7**, as the polarisation transfer catalyst in a ratio of 4^:^1. Following polarisation transfer in a 6.5 mT magnetic field, the sample was transferred rapidly to a measurement field of 1.4 T. Resultantly, the pyrazine protons (δ 8.62) were enhanced by 78-fold (Figure^^2<figr2/or>A). This equates to a polarisation (P) level of 0.04^%. Conducting polarisation transfer in earth's magnetic field resulted in a much lower enhancement of only 11-fold (P=0.005^%) for the pyrazine protons (Figure^^2<xfigr2>B). This contrasts with previous *para*-substituted pyridyl fentalogs[13] and endothelial nitric oxide synthase (eNOS) substrates[12a] that were polarised optimally at earth's magnetic field.

The hyperpolarised ^{1}H NMR spectrum of **1** in the presence of **7** produced two observable hydride resonances at <M->22.9 and <M->24.7^^ppm (Figure^^2<xfigr2>B and 2^^C). Based on previous studies,[17] the latter is due to a hydride *trans* to coordinated methanol whilst the former is a due to a hydride *trans* to **1**. The complex $[Ir(IMes)(H)_2(\mathbf{1})_2(MeOH)]^+$ (Figure^^3<figr3>A) is proposed to account for these observations. Thus, only a single molecule of **1** is *trans* to hydride; *trans* couplings have been shown to facilitate efficient transfer of hyperpolarisation when compared to *cis* couplings,[18] which are often negligible or zero.[19]

Hyperpolarisation studies of pyrazine solely (Figures^^S15--17), gave a number of hydrides in the region <M->21.7 to <M->24.7^^ppm. The appearance of the hydride region did not change when the ratio of pyrazine:**7** was changed from 20^:^1 to 4^:^1 (Figure^^S19). The most prominent hydrides are those at <M->22.8 and <M->24.7^^ppm, which account for ca. 50^% of the total integral area and possess a common J_{HH} coupling of <M->12.9^^Hz. Hydride resonances *trans* to pyrazine (pz) have been reported at <M->22.7, <M->21.9 and <M->23.0^^ppm in [Ir(IMes)(mtz)$_2$(pz)(H)$_2$]Cl (mtz=1-methyl-1,2,3-triazole),[20] [Ir(I_pClC$_6$H$_2$Me$_2$)(pz)$_2$(BnNH$_2$)(H)$_2$]Cl and [Ir(I_pClC$_6$H$_2$Me$_2$)(pz)(BnNH$_2$)$_2$(H)$_2$]Cl[12b] respectively (Figure^^3<xfigr3>B-3D respectively). The pyrazine protons of the 4^:^1 pyrazine:**7** sample were enhanced by <M->1313-fold (P=0.63^%), following polarisation transfer at 6.5 mT. For the analogous 20^:^1 pyrazine:**7** sample, the pyrazine protons were only enhanced by <M->414-fold (P=0.20^%) at the same transfer field. Both of these enhancements, and polarisation values, are significantly larger than the enhancement observed for **1**.

Addition of 50 μL of water to the 4^:^1 pyrazine:**7** sample resulted in the most upfield hydride signal shifting by 0.3^^ppm to <M->25^^ppm. The complex [Ir(IMes)(H)$_2$(**1**)$_2$(H$_2$O)]$^+$ is proposed to account for this change in hydride region; the change in chemical shift of the most upfield hydride signal is consistent with previous recorded observations.[17] The remainder of the hydride region is unchanged upon the addition of water (Figure^^S19). The addition of water to the sample caused the enhancement of the pyrazine protons to diminish to <M->370-fold (P=0.18^%) following polarisation transfer at 6.5^^mT.

It should be noted that the previously reported *para*-substituted pyridyl fentalogs led to the production of a single observable hydride due to the formation of [Ir(IMes)(H)$_2$(fentalog)$_3$]Cl.[13] Evidently, the substitution of the pyrazine ring *ortho* to one of the nitrogen atoms in **1** causes steric encumbrance such that only a single molecule of **1** can bind *trans* to hydride in [Ir(IMes)(H)$_2$(**1**)$_2$(MeOH)]$^+$. Evidence for the formation of [Ir(IMes)(H)$_2$(**1**)$_2$(MeOH)]$^+$ is obtained from the SABRE-enhanced ^{1}H NMR spectra (figures^^2<xfigr2>A and 2B), which possess two hydride signals, due to the lack of symmetry in the complex. The unhindered nitrogen atom of the pyrazine ring is proposed to

act as the donor atom to the iridium centre as previous studies have shown that 2-picoline and 2,6-lutidine are not polarised by **7**,[21] (unless co-ligands are used[22]) due to steric hindrance around the nitrogen. Furthermore, these observations and hydride chemical shift data rule out the possibility of the furan-oxygen from acting as a ligand to the metal centre.

2.3. SABRE of a simulated sample of 1^and 3^b

A series of simulated samples were produced whereby the amount of **1** present relative to **3^b** was varied from 0.63^% to 3.80^% w/w. This translates to 0.18^^mg to 1.15^^mg of **1** in an NMR sample, which is lower than the dose required to produce an adverse effect in an adult male (assuming a blood plasma volume of 2.5^^L, 5^^mg of **1** would be required to cause an adverse effect). From a harm-reduction point-of-care perspective, being able to detect this small amount of **1** in a seized drug sample is advantageous in terms of safe-guarding, and it avoids the need for biological sample testing.

7 was again used as the polarisation transfer catalyst and was present in a 1^:^4 ratio of **7^:^1**. A control was also prepared in which **1** was replaced for **3^b**. These samples were all subjected to SABRE utilizing polarisation transfer fields of 6.5 mT and earth's magnetic field. The control sample was found not to polarise, despite **3^a** having been reported to be polarised previously, albeit using [Ir(COD)(PCy_3)(py)][PF_6] as the polarisation transfer catalyst.[12c] Steric interactions between **3^a** and **7** may have prevented ligation; no hydride ligands were observed to suggest activation of **7** into the active form of the polarisation transfer catalyst.

Following polarisation transfer at earth's magnetic field, the sample consisting of 3.80^% w/w of **1** relative to **3^b** produced an enhancement of <M->6-fold (P=0.003^%). This enhancement was calculated via internal reference to a heroin aromatic signal. The sample consisted of 1.15^^mg of **1** relative to 29.1^^mg of **3^b**. A larger enhancement of <M->42-fold (P=0.02^%) was obtained when polarisation transfer was conducted at 6.5 mT. These results are consistent with the hyperpolarisation of **1** solely with respect to the enhancement linked magnetic field dependency. An internal reference signal was utilised here because the amount of **1** present in the 0.63^% w/w sample was only visible after acquiring 128 transients (ca. 15^^min acquisition, see Figure^^4<figr4>A).

Polarisation of the 0.63^% w/w sample also led to polarisation of **1** with the enhancement again being greater at 6.5^^mT (Figure^^4<xfigr4>). The amount of **1** in the sample equated to 0.18^^mg or 81^^μM. The enhancement obtained at 6.5^^mT was <M->867-fold (P=0.42^%). These data highlight that **1** can be readily detected against a strong background of **3^b**. Furthermore, the two hydride signals are still visible at <M->22.9 and <M->24.7^^ppm, which is indicative of the same catalytic species being present in solution.

3. Conclusions

To conclude, SABRE could be used in a forensic context to qualitatively detect low amounts of **1** (<1^^mg) against a strong background signal of **3^b** via ^{1}H NMR spectroscopy. Only a single transient is required for detection. Polarisation transfer occurred optimally at 6.5 mT, although it should be noted that only two polarisation transfer fields were utilized in the study. Employment of 100^% *p*-H_2 would improve the signal intensity further (by a factor of three), as only 50^% *p*-H_2 was utilized in this study. The selective hyperpolarisation of **1** in the presence of **3^b** highlights that SABRE could be a potentially powerful forensic tool for aiding harm-reduction point-of-care services.

Experimental Section

All reagents were of commercial quality (Sigma-Aldrich, Gillingham, UK or Fluorochem Limited, Hadfield, UK) and used without further purification. Solvents (Fisher Scientific, Loughborough, UK) were dried, where necessary, using standard procedures. Complex **7** was prepared according to the procedure reported by Sola and co-workers.[23] ^{1}H NMR and ^{13}C NMR spectra were acquired on a JEOL JMN-ECS-400 (JEOL, Tokyo, Japan) NMR spectrometer operating at a proton resonance frequency of 400^^MHz and referenced to the residual solvent peak. Infrared spectra were obtained in the range 4000--400^^cm$^{<M->1}$ using a Thermo Scientific Nicolet iS10ATR-FTIR instrument (Thermo Scientific, Rochester, USA). High-resolution mass spectrometry (HRMS) data were obtained on an Agilent 6540 LC-QToF spectrometer in positive electrospray ionization mode.

1-Phenethylpiperidin-4-one Oxime (4)

1-Phenethyl-4-piperidone (49.3^^mmol) and hydroxylamine hydrochloride (74.0^^mmol, 1.5^^eq.) were dissolved in methanol (82^^mL). Aqueous potassium hydroxide was added (54.0^^mmol KOH in 15^^mL water) and the mixture was stirred at room temperature for 24^^The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. Compound **4** was obtained without further purification as an off-white solid (8.18^^g, 76^% yield); ^{1}H NMR (400^^MHz, $CDCl_3$) δ 9.05 (s (br), 1H), 7.32--7.09 (m, 5H), 2.90--2.30 (m, 12H); $^{13}C\{^{1}H\}$ NMR (100^^MHz, $CDCl_3$) δ 157.42, 140.13, 128.73, 128.47, 126.16, 60.08, 53.68, 52.44, 33.76, 31.39, 24.41; ATR-FTIR ν_{max}/cm$^{<M->1}$: 3060.4, 2908.0, 2821.5, 1666.4, 1600.8, 1495.7; HRMS ($C_{13}H_{18}N_2O$): predicted mass=219.1497 $[M+H]^+$; experimental mass=219.1498 $[M+H]^+$.

1-Phenethylpiperidin-4-amine Hydrochloride (5.HCl)

Lithium aluminium hydride (47.2^^mmol, 1.25^^eq.) was slowly dissolved in anhydrous THF (75^^mL) at 0^°C. To this mixture was slowly added **4** (37.49^^mmol) in anhydrous THF (85^^mL) with stirring. After gas evolution had subsided, the reaction mixture was carefully heated to reflux for 1^^h. The mixture was then cooled to room temperature and placed in an ice bath. The reaction was quenched by slow addition of water (1.8^^mL), aqueous NaOH (15^% w/v, 1.8^^mL) and then water again (5.4^^mL). The resulting mixture was stirred until it turned from dark grey to a light yellow. The resulting mixture was filtered to remove the white precipitate. The filtrate was concentrated *in vacuo*. The resulting oil was dissolved in diethyl ether (10^^mL) and 3^^M HCl in cyclopentyl methyl ether (13.0^^mL) was added. The resulting salt was isolated by filtration and dried under vacuum. Compound **5.HCl** was obtained as a light yellow solid (7.5^^g, 83^% yield); ^{1}H NMR (400^^MHz, DMSO-d_6) δ 8.21 (s(br), 3H), 7.35--7.13 (m, 5H) , 3.46 (s(br), H_2O), 2.97--2.94 (m, 3H), 2.73--2.70 (m, 2H), 2.02 (t, J=11.4^^Hz, 2H), 1.89 (d, *J*=11.8^^Hz, 2H), 1.55 (q, *J*=11.5^^Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100^^MHz, DMSO-d_6) δ 140.80, 129.16, 128.78, 126.41, 59.79, 51.43, 48.25, 33.30, 30.03; ATR-FTIR ν_{max}/cm$^{<M->1}$: 3399.2, 2948.8, 2822.5, 2569.9, 2101.2, 1630.0, 1600.9, 1515.6; HRMS ($C_{13}H_{20}N_2$): predicted mass=205.1705 $[M+H]^+$; experimental mass=205.1702 $[M+H]^+$.

N-(1-Phenethylpiperidin-4-yl)pyrazin-2-amine (6)

Compound **5.HCl** (2.81^^mmol, 2.0^^eq.) was dissolved in water. The resulting solution was made basic (pH=12) by the addition of aqueous NaOH. The solution was transferred to a separation

funnel and the aqueous layer was extracted three times with dichloromethane (325^^mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo* to obtain the free-base form of compound **5** as a yellow oil.

Copper powder (1.41^^mmol, 1.0^^eq.) and 2-chloropyrazine (1.41^^mmol, 1^^eq.) were suspended along with **5**. The reaction mixture was refluxed at 180^°C under inert atmosphere for 6^^h. The reaction was then cooled to room temperature and a solid formed. The solid was broken up and suspended in aqueous HCl (10^% v/v). The solid was removed by filtration. The filtrate was washed once with diethyl ether (50^^mL). The aqueous layer was made basic (pH=12) by the addition of aqueous NaOH. The aqueous layer was then extracted twice with dichloromethane (250^^mL). The combined organic layers were washed with water (50^^mL) and brine (50^^mL). The organic layers were then dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 0--10^% v/v MeOH in DCM) to obtain compound **6** as a light yellow solid (139^^mg, 34^% yield); ^{1}H NMR (400^^MHz, $CDCl_3$) δ 7.95 (dd, *J*=2.7, 1.5^^Hz, 1H), 7.85 (d, *J*=1.3^^Hz, 1H), 7.77 (d, *J*=2.8^^Hz, 1H), 7.30--7.18 (m, 5H), 4.47 (d, *J*=7.7^^Hz, 1H), 3.84--3.72 (m, 1H), 3.00 (d, *J*=11.7^^Hz, 2H), 2.85--2.81 (m, 2H), 2.66--2.60 (m, 2H), 2.27 (t, *J*=11.0^^Hz, 2H), 2.10 (d, *J*=12.0^^Hz, 2H), 1.95--1.45 (m, 3H); ^{13}C{^{1}H} NMR (100^^MHz, $CDCl_3$) δ 154.98, 141.98, 141.10, 141.08, 134.02, 131.16, 129.15, 129.13, 129.12, 128.71, 128.70, 128.69, 126.30, 126.28, 60.40, 52.52, 51.49, 34.98, 33.61, 33.55, 32.03; ATR-FTIR ν_{max}/cm$^{<M->1}$: 3261.6, 3062.3, 3030.8, 2952.8, 2761.6, 2638.3, 2480.1, 1645.3, 1597.2, 1582.8, 1518.6, 1503.5; HRMS ($C_{17}H_{22}N_4$): predicted mass=283.1923 $[M+H]^+$; experimental mass=283.1927 $[M+H]^+$.

N-(1-phenethylpiperidin-4-yl)-N-(pyrazin-2-yl)furan-2-carboxamide (Mirfentanil, 1)

Compound **6** (1.0^^mmol) was dissolved in dichloromethane (10^^mL) and treated with diisopropylethylamine (2.0^^mmol). The mixture was cooled in an ice bath and 2-furoyl chloride (2.0^^mmol) was added dropwise. The resulting solution was stirred at room temperature for 2^^h. The mixture was diluted with water (30^^mL) and the organic layer washed sequentially with brine (30^^mL) and saturated aqueous sodium bicarbonate (30^^mL). The organic layer was dried with magnesium sulfate and concentrated in vacuo. The crude oil was purified using a Biotage Isolera One Flash Purification System (eluent: 0--10^% MeOH in DCM). Mirfentanil, **1**, was obtained as a light yellow solid (145^^mg, 54^% yield); ^{1}H NMR (400^^MHz, CDCl3) δ 8.53 (s, 2H), 8.38 (s, 1H), 7.30-

-7.07 (m, 5H), 6.56--6.52 (m, 1H), 6.27--6.25 (m, 1H), 4.78 (tt, J=11.9, 3.0^^Hz, 1H), 3.07 (d, J=11.1^^Hz, 2H), 2.78--2.74 (m, 2H), 2.60--2.56 (m, 2H), 2.22 (t, J=11.6^^Hz, 2H), 1.97 (d, J=11.9^^Hz, 2H), 1.85--1.52 (m, 2H); 13^^C{1H} NMR (100^^MHz, CDCl3) δ 158.81, 150.13, 147.56, 145.93, 144.74, 143.49, 143.43, 140.12, 128.73, 128.51, 126.19, 117.64, 111.43, 60.44, 54.39, 53.14, 33.81, 30.39; ATR-FTIR vmax/cm-1: 3134.8, 3112.9, 3036.2, 3010.0, 2948.8, 2903.6, 2851.9, 2809.8, 1651.1, 1600.1, 1575.2, 1519.0; HRMS (C22H24^^N4O2): predicted mass=377.1978 [M+H]+; experimental mass=377.1973 [M+H]+.

SABRE Measurements

^{1}H NMR spectra collected for the hyperpolarised samples were acquired on an Oxford Instruments Pulsar benchtop NMR spectrometer (Abingdon, UK) on which ^{1}H has a frequency of 60^^MHz.

Mirfentanil Sample Preparation for Polarisation by SABRE

0.473^^mmol of **3^b**, was dissolved in 3.6^^mL of d_4-methanol and sonicated for 30^^s. For the lowest concentration (812^^μM), 1.1^^mg of **1** and 0.5^^mg of the SABRE pre-catalyst, **7**, were added to this stock and sonicated for 30 seconds. 0.6^^mL of this solution was then taken up by syringe and transferred into a Young's tap NMR tube. The sample was then degassed on a high-vacuum line *via* three 'cool'-pump-thaw cycles (using a acetone/CO_2 slush bath). *Para*hydrogen, at a pressure of 3.0 atmospheres was then admitted to the NMR tube. *Para*hydrogen was produced by cooling hydrogen gas to 77^^K over charcoal (50^% *para*hydrogen produced). The sample was then shaken to form the catalytically active species in solution prior to collecting a thermal ^{1}H NMR spectrum. For the collection of SABRE measurements, the hydrogen in the head-space of the tube was replenished with *para*hydrogen prior to shaking for 10^^s in either earth's magnetic field (*ca.* 0.5 G) or in a hollow tube coil (Siga Transformers, sigatransformers.co.uk) within which a vertical magnetic field of up to 150 G could be generated (see Figure^^S14). The sample was then rapidly inserted into the NMR spectrometer and a ^{1}H NMR spectrum acquired using a $\pi/2$ pulse. The aliquot was then returned to the stock solution and additional **1** added repeatedly to give four different concentrations. For each addition of **1**, **7** was also added in order to maintain a 4^:^1 ratio of **1**: **7**. Following the addition of more **1** and **7** the stock was sonicated for 30 seconds before removal of a fresh aliquot and

acquisition repeated in this way for the total four concentrations (812, 1623, 3320 and 5091^^μM mirfentanil, (**1**)).

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Conflict of Interest

The authors declare no conflict of interest.

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Scheme^^1 Synthetic pathway for the preparation of **1**. Conditions; (i) $NH_2OH.HCl$, KOH, MeOH, RT, 24 hr; (ii) $LiAlH_4$, THF, reflux, 1 hr; (iii) NaOH (aq) (to form **5**) then Cu, 2-chloropyrazine, 180^°C, 6 hr; (iv) diisopropylamine, 2-furoyl chloride, RT, 2 hr.

Figure^^1 Chemical structures of mirfentanil (**1**), fentanyl (**2**), morphine (**3^a**) and heroin (**3^b**)

Figure^^2 ^{1}H NMR spectra of **1** and **4** in the ratio of 4^:^1 (4.7^^mg of **1**) in the presence of *p*-H_2 in d_4-methanol following polarisation transfer in a magnetic field of 6.5 mT (A) or earth's magnetic field (B) compared to the sample at thermal equilibrium (C). Multiplication factors indicate scaling of the vertical axis.

Figure^^3 Chemical structures of $[Ir(IMes)(H)_2(\mathbf{1})_2(MeOH)]^+$, $[Ir(IMes)(mtz)_2(pz)(H)_2]Cl$, $[Ir(I_pClC_6H_2Me_2)(pz)_2(BnNH_2)(H)_2]Cl$ and $[Ir(I_pClC_6H_2Me_2)(pz)(BnNH_2)_2(H)_2]Cl$ (A--D respectively). L_1=IMes, L_2=$I_pClC_6H_2Me_2$, mir=**1**, mtz=1-methyl-1,2,3-triazole and pz=pyrazine

Figure^^4 ^{1}H NMR spectra **1** and **7** in the ratio of 4^:^1 (0.183^^mg of **1**) in the presence of heroin (29.1^^mg) and *p*-H_2 in d_4-methanol at thermal equilibrium (A -- 128 transients, B -- 1 transient) or following polarisation transfer at earth's magnetic field (C) or at 6.5 mT (D). All spectra are shown to the same vertical scale, except where indicated.