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Highly potent and selective zwitterionic agonists of the δ-opioid receptor. Part 1

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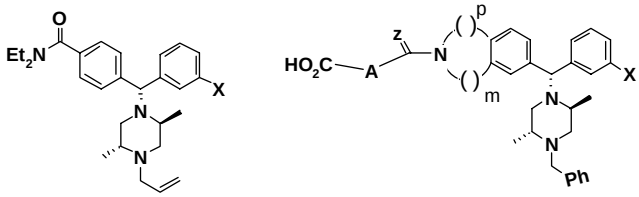
Abstract—A series of zwitterionic δ-opioid agonists, with targeted physicochemistry, as a strategy to limit potential for CNS exposure, were prepared. These agents were found to possess exquisite potency and selectivity over mu and κ-opiate activity. Furthermore, analogue **3a** was found to display restricted CNS exposure, as evidenced by its inactivity in a rodent hyperlocomotion assay of central opiate activity. Dog pharmacokinetic studies on **3a** indicated encouraging oral bioavailability.

Irritable bowel syndrome (IBS) is a highly common functional bowel disorder, which significantly impacts on the quality of life for those who suffer its effects. While several mechanistic approaches to the treatment of IBS have been identified, their efficacy is often limited and new therapies are still required to treat this debilitating condition.[1]

In this first communication, we wish to report our preliminary findings targeting selective agonism of *peripheral* delta (δ)-opioid receptors, as a strategy to both treat IBS and, by excluding these agents from the CNS, minimise the potential for centrally mediated adverse events associated with compounds possessing opiate activity. These studies, to the best of our knowledge, have resulted in the identification of the most potent and selective δ-opioid agonists[2] yet reported. Furthermore, the physicochemical design strategy outlined below has also successfully delivered agents which are CNS excluded, yet retain the potential to be orally bioavailable, as assessed by dog pharmacokinetic studies.

Small, non-peptidic agonists of the δ-opioid receptor **1a**[3a] and **1b**,[3b] Figure 1, have been known since the early 1990s. The optimisation of these intriguing non-peptidic compounds into drugs, however, remains a significant and enduring challenge.[3]



(**1a**) X = -OMe. SNC-80
δ (pIC_{50}) =8.7, μ (pIC_{50}) = <5
(**1b**) X = -OH. BW373U86
δ (pIC_{50}) = 9.2

(**2**) X = -OMe, -OH, -F
p = 1, m = 1. Z = 2H or O
(**3**) X = -OMe, -OH, -F
p = 2, m = 1. Z = 2H or O
A = alkyl or phenyl

Figure 1.

Central to our own strategy was a plan to exploit the attractive primary pharmacology observed in agonists such as **1a** and **1b** and to design compounds which possessed physicochemical properties consistent with the potential for good oral absorption, but which were likely to possess more limited potential for CNS penetration. While there have been many reports in the literature defining properties which afford good oral absorption,[4] properties, which define good passive

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diffusion across the blood–brain barrier (BBB), appear less clearly characterised, though they are generally regarded to be more stringent.[5] We recognised at the outset, however, that our target permeability profile of good oral exposure and CNS exclusion was extremely challenging and that any physicochemical window to achieve this was likely to be narrow at best.

Our target was to identify an orally bioavailable, potent δ-opioid receptor agonist (pIC_{50} ~9) with high selectivity over mu (μ) and kappa (κ) sub-types (≥500-fold) which showed minimal CNS exposure, as measured in a mouse hyperlocomotion model of central opiate activity.

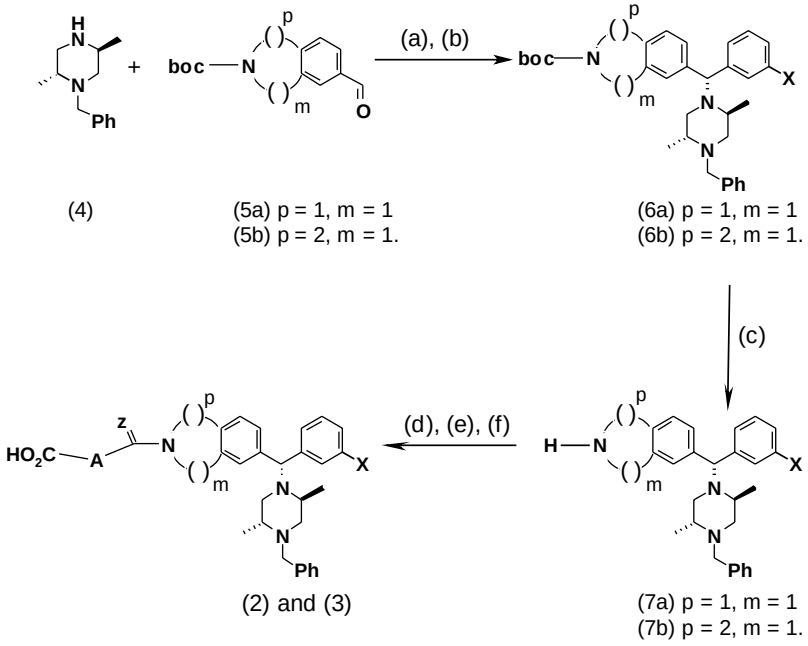
Our design strategy (**2** and **3**), Figure 1, focused on zwitterionic compounds, which were precedented to exhibit limited CNS penetration.[6] Within this class, we then targeted compounds with a moderately positive log D (~2) and relatively high MWt (500–550), which we felt occupied the most likely physicochemical window for achieving reasonable oral (GI) absorption with minimal BBB penetration potential.[5] As an in vitro measure of likely permeability, we sought compounds with moderate flux in a Caco-2 screen[7] (apical-basolateral (A-B) rate ~5%/h), indicative in our assay of permeability likely to be consistent with GI absorption, though not considered high enough to indicate significant CNS penetration.

Execution of this strategy has led to the discovery of exquisitely potent and selective zwitterionic δ-opioid agonists which were found in a rodent hyperlocomotion model of CNS activity, to be highly peripherally selective. Furthermore, initial dog pharmacokinetic studies on **3a** have shown this series to possess encouraging oral bio availability (~20%).

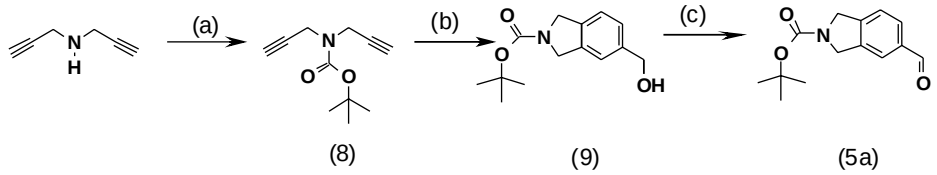
All compounds **2** and **3** were prepared by the general method shown in Scheme 1. Reaction of (−)-(2*R*,5*S*)-1-benzyl-2,5-dimethylpiperazine **4**[8] and the appropriate aldehyde **5a** or **5b** in the presence of benzotriazole in toluene, under Dean–Stark conditions, produced the intermediate imine. These underwent diastereoselective aryl Grignard addition using the method of Katritsky,[9] to give intermediates **6a** or **6b** as the major isomeric products isolated. Conversion to the target compounds was then accomplished using the general methods previously described.[9] BOC-deprotection using HCl(g) in CH_2Cl_2, (to give **7a** and **7b**), followed by acylation or alkylation of the secondary resulting amine, with the appropriate ester-containing reagent and subsequent ester hydrolysis using 2 N NaOH in dioxan/H_2O, gave the respective acids. Phenolic compounds **2b**, **2d**, **2g**, **2h**, **2i**, **2j**, **3b**, **3d**, **3g** and **3i** were then accessed, from their anisole precursors, using BBr_3 in CH_2C1_2 at −78 °C.

Aldehyde **5a** was prepared as shown in Scheme 2. BOC-protection of dipropargylamine gave **8**, which was treated with propargyl alcohol and Wilkinson's catalyst in EtOH at 0 °C, to give alcohol **9** in 62% yield over 2 steps. Oxidation of the alcohol to the aldehyde **5a** was then achieved in 51% yield using palladium acetate in DMF.

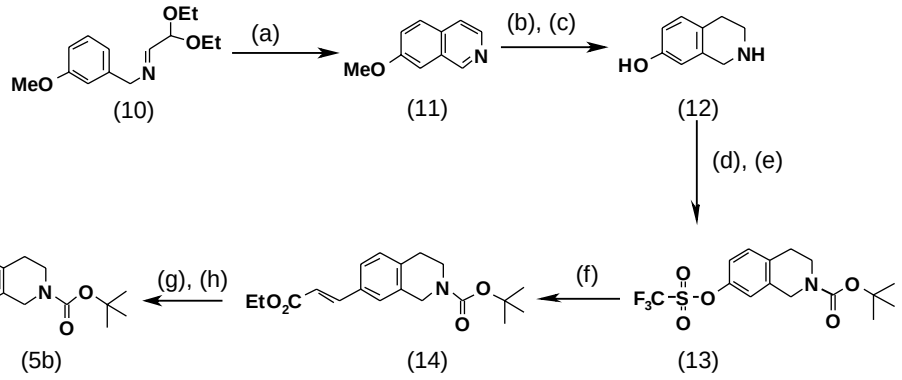
Aldehyde **5b** was prepared as shown in Scheme 3. Cyclisation of imino-acetal **10** using $BF_3{\cdot}OEt_2$ gave isoquinoline **11** in good yield (72%). Demethylation using 48% HBr at reflux, followed by selective reduction of the



Scheme 1. Synthesis of 5-[(*R*)-[(2*S*,5*R*)-4-benzyl-2,5-dimethylpiperazinyl](aryl)methyl]isoindoline (**2**) and 7-(*R*)-[(2*S*,5*R*)-4-benzyl-2,5-dimethylpiperazinyl](aryl)methyl]-1,2,3,4-tetrahydroisoquinolines **3**. Reagents and conditions: (a) benzotriazole, toluene, Dean–Stark conditions, 3 h; (b) add to aryl magnesium bromide, THF, −20 °C–rt, 1 h; (c) HCl(g), CH_2Cl_2, 0 °C; (d) acylation or alkylation; (e) ester hydrolysis; (f) BBr_3, CH_2Cl_2, −78 °C (for **2b**, **2d**, **2g**, **2h**, **2i**, **2j**, **3b**, **3d**, **3g** and **3i**).



Scheme 2. Synthesis of *tert*-butyl 5-formyl-1,3-dihydro-2*H*-isoindole-2-carboxylate **5a**. Reagents and conditions: (a) Di-*tert*-butyl-dicarbonate, NEt_3, CH_2Cl_2, 0 °C–rt; (b) propargyl alcohol, Wilkinson's catalyst, EtOH, 0 °C–rt; (62% over two steps); (c) $Pd(OAc)_2$, 4-iodo-toluene, tetraethyl ammonium chloride, $NaHCO_3$, DMF, 100 °C, 2 h (51%).



Scheme 3. Synthesis of *tert*-butyl 7-formyl-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (**5b**). Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, $(CF_3CO)_2O$, 0 °C–rt (72%); (b) 48% HBr, reflux (64%); (c) glacial acetic acid, PtO_2, H_2, 40 p.s.i., 16 h; (d) di-*tert* butyl carbonate, H_2O/THF (2:5), NEt_3, rt, 16 h (91%); (e) *N*-phenylbis(trifluoromethanesulfonimide), CH_2Cl_2, rt, 48 h (76%); (f) ethyl acrylate, $Pd(OAc)_2$, (*o*-Tol)$_3$P, NEt_3, CH_3CN, reflux, 16 h (44%); (g) OsO_4, *N*-methyl morpholine *N*-oxide, acetone/H_2O (5:1), 16 h, rt (53%); (h) sodium periodate, Et_2O/H_2O (4:3), rt (98%).

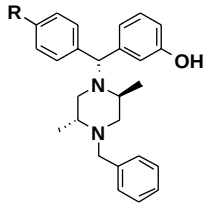
isoquinoline heteroaromatic ring using H_2 and PtO_2 as catalyst, furnished **12**. N-BOC-protection and conversion of the phenolic hydroxyl to the triflate then gave **13**, which was readily converted to the α,β-unsaturated ester **14** using ethyl acrylate and $Pd(OAc)_2$. **14** was then converted to the target aldehyde **5b** in two steps using OsO_4 and periodate cleavage of the resulting diol.

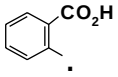
Functional δ-opioid activity was initially demonstrated using a mouse isolated electrically stimulated vas deferens assay.[10] Functional selectivity at μ and κ-opioid receptors was determined using the electrically stimulated guinea pig isolated myenteric plexus preparation.[11] Activity at the human δ-opioid receptor expressed in CHO cells was determined either by radioligand binding or functionally using cytosensor technology developed at Pfizer. The mouse hyperlocomotion assay was performed by the method reported previously.[12]

Initial evaluation of a range of zwitterionic compounds[8] in the mouse hyperlocomotion model, Table 1, in an attempt to define the property space which could confer limited CNS exposure, yielded some intriguing SAR. Lipophilic amine, SNC-80 (**1a**), demonstrated pronounced CNS effects (ED_{200} 400 μg/kg), indicative of its ability to rapidly penetrate the BBB and consistent with its moderate MWt (449), low H-bond donor count and relatively high log D (3.3). Simple propionic acid analogue **15** also showed effects at low dose, with threshold effects seen at 100 μg/kg, consistent with its also very high Caco-2 flux permeability (A-B, 23%/h), comparable to SNC-80, despite being less lipophilic (log D 2.1). Encouragingly, acetic acid analogue **16**, which possessed a still lower log D (1.1) than **15**, showed reduced permeability, Caco-2 (6%/h), and this was also reflected in a 10-fold increase in the dose required for observation of threshold effects in the CNS hyperlocomotion model. That differentiated profiles could be observed in the hyperlocomotion model in this low MWt series was highly encouraging. From an analogue design perspective, however, working within such a narrow MWt window, unfortunately, proved impractical. Interestingly, we noted that biphenyl analogue **17** possessed a similar moderate Caco-2 profile (A-B, 3%/h) to **16**, (A-B, 6%/h), despite possessing similar log D to a highly fluxed propionic acid analogue **15**, (A-B, 23%/h). This suggested to us that targeting higher MWt compounds (500–550) with moderate log D (~2) might allow us to access compounds with the permeability profile we sought, but in a series with greater synthetic scope for analogue design, to assist optimisation of the overall profile.

Our initial work in this area[13] had indicated that while encouraging, variable, permeability could be observed in such zwitterionic compounds, no clear SAR could be discerned. The design of compounds of types **2** and **3** was, therefore, also driven by a pragmatic desire to work in a readily synthetically accessible template, allowing easy and sequential modification of the acid moiety as a mechanism to tune MWt and log D to quickly allow systematic SAR development. The secondary amine in both the isoindoline or tetrahydroisoquinoline moieties provided an ideal location to effect

Table 1. Functional agonist activity against δ (mouse vas deferens) and mouse hyperlocomotion data for zwitterionic δ-opioid agonists SNC-80, **15**, **16** and **17**



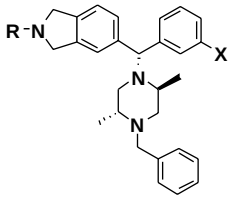
Compound[a]	R	δ-pIC$_{50}$[b]	MWt	Log D	Caco-2 (%/h)	Mouse locomotion (iv)[c]
SNC-80	—	8.7	449	3.3	23 ER = 1	400 μg/kg
15	–(CH$_2$)$_2$–CO$_2$H	9.9	459	2.1	23 ER = 1	100 μg/kg
16	–CH$_2$–CO$_2$H	9.8	445	1.1	6 ER = 2	1000 μg/kg
17		10.7	507	2.3	3 ER > 5	NT

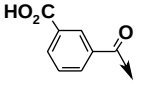
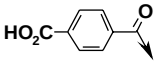
NT, not tested. ER, efflux ratio (ratio of apical-basolateral (A-B):basolateral-apical (B-A)).
[a] All compounds are full agonists and single homochiral diastereomers.
[b] Mouse vas deferens.
[c] Threshold dose at which effects were observed.

these changes. Initial analogues prepared are shown in Table 2.

Isoindolines **2a** and **2c** were found to possess moderate activity against the δ-opioid receptor (pIC$_{50}$ 7.6 and 6.2, respectively). Conversion of each of these anisoles to their respective phenols, **2b** (δ, pIC$_{50}$ 9.3) and **2d** (δ, pIC$_{50}$ 9.0) however, significantly increased potency in each case. Attempts to replace the phenolic hydroxy group in **2d**, with either a *meta*-fluoro **2e** or hydrogen

Table 2. Functional agonist activity against δ (mouse vas deferens) and μ and κ (guinea pig myenteric plexus) receptors for 5-[(*R*)-[(2*S*,5*R*)-4-benzyl-2,5-dimethylpiperazinyl](aryl)methyl] isoindoline **2a**–**j**



Compound[a]	R	X	δ-Agonist activity (pIC$_{50}$)[b]	μ-Agonist activity (pIC$_{50}$)[c]	κ-Agonist activity (pIC$_{50}$)[c]
2a	–CH$_2$–CO$_2$H	–OMe	7.6	NT	NT
2b	–CH$_2$–CO$_2$H	–OH	9.3	6.9	5.9
2c	–(CH$_2$)$_2$–CO$_2$H	–OMe	6.2	<5	<5
2d	–(CH$_2$)$_2$–CO$_2$H	–OH	9.0	6.2	5.1
2e	–(CH$_2$)$_2$–CO$_2$H	–F	7.6	NT	NT
2f	–(CH$_2$)$_2$–CO$_2$H	–H	7.2	NT	NT
2g		–OH	9.5	7.3	5.4
2h		–OH	8.5	NT	NT
2i		–OH	8.8	7.0	5.9
2j		–OH	8.1	5.5	6.4

[a] All compounds are full agonists and single homochiral diastereomers.
[b] Mouse vas deferens.
[c] Guinea pig myenteric plexus.

2f, resulted in a significant drop in potency. A series of acid-containing benzamide analogues **2g**, **2i** and **2j** were also prepared to explore the role of the acid orientation in conferring potency in this series, with the *ortho*-acid analogue **2g** found to be highly potent against the δ-opioid receptor (pIC_{50} 9.5) and >100-fold selective over μ and κ sub-types.

The *ortho*-acid benzyl analogue **2h** was found be approximately 10-fold less potent than its amide analogue **2g**.

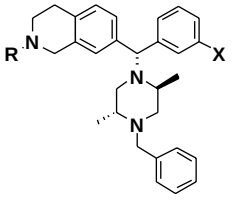
Work undertaken in the homologous tetrahydroisoquinoline series **3** showed that even greater potency and selectivity could be achieved, Table 3. For example, acetic acid analogue **3a** (pIC_{50} 8.7) was found to be approximately 10-fold more potent than the equivalent isoindoline **2a** (pIC_{50} 7.6), with excellent human translational pharmacology (human δ binding pIC_{50} 8.3). As in the isoindoline series, conversion of the anisole in **3a** to the phenol was found to result in a significant increase in potency (δ, pIC_{50} 10.4), with excellent selectivity over μ (pIC_{50} 6.5) and κ (pIC_{50} 6.0) receptors. Propionic acid analogue **3d** (δ, pIC_{50} 11.3) was found to be approximately 10-fold more potent than its lower homologue **3b**, again demonstrating excellent selectivity over μ and κ. Attempts to replace the phenolic hydroxy moiety found in **3d** with a *meta*-fluoro group, **3e**, resulted in a precipitous drop in activity (pIC_{50} 7.0). Interestingly and to our surprise, amides **3g** (δ, pIC_{50} 12.0) and **3i** (pIC_{50} 11.8) demonstrated exceptional levels of potency and selectivity.

While tetrahydroisoquinoline series **3** afforded excellent pharmacological profiles, our goal of combining this pharmacology with moderate Caco-2 permeability in a CNS-excluded agent was found to be extremely challenging. For example, we discovered that all phenolic analogues screened in this series **3b**, **3d**, **3g** and **3i**, while extremely potent and possessing our target moderate, positive, lipophilicity, showed very poor permeability characteristics (Caco-2 (A-B) <1%/h), effectively eliminating them from consideration for further progression. Indeed, within this series, we discovered that permeability hinged on the presence or absence of this single, phenolic, H-bond donor (e.g., **3d** (OH, <1%/h) vs **3c** (OMe, 11%/h)). Attempts to temper the deleterious effects of the phenolic OH, by replacing it with a fluoro group, **3e** unfortunately gave compounds with too rapid permeability (Caco-2 >30%/h).

In the case of exquisitely potent phenol **3g** (δ, pIC_{50} ~12, Caco-2 A-B <1%/h), we hoped that replacing the phenolic –OH with –OMe **3f** or –F **3h**, while predicted to result in a drop in potency, would still yield potent compounds and with reasonable flux. Disappointingly, and somewhat to our surprise, **3h** and **3f** both showed a massive loss in potency relative to **3g**, which precluded their progression. A more equitable balance between target potency and permeability was, however, found in the anisole analogues **3a** and **3c**.

Overall, **3a** was selected for further evaluation, as it possessed a profile closest to our target pharmacology (δ, pIC_{50} 8.7, >500-fold selective over μ and κ) and moder-

Table 3. Functional agonist activity against δ (mouse vas deferens), μ and κ (guinea pig myenteric plexus) receptors and Caco-2 permeability data for 7-(*R*)-[(2*S*,5*R*)-4-benzyl-2,5-dimethylpiperazinyl](aryl)methyl]-l,2,3,4-tetrahydroisoquinolines **3a**–**3i**



Compound[a]	R	X	δ-Agonist activity (pIC_{50})[b]	μ-Agonist activity (pIC_{50})[c]	κ-Agonist activity (pIC_{50})[c]	MWt	Log D (pH 7.4)	Caco-2 (A-B) (%/h)	Mouse hyperlocomotion (iv, μg/kg)
SNC-80 **1a**	—	—	8.7	<5	5.9	449	3.3[e]	23 ER = 1	400 (ED_{200})
3a	$–CH_2–CO_2H$	–OMe	8.7[d]	5.3	5.9	514	2.5	5 ER = 4	No effect at 10,000
3b	$–CH_2–CO_2H$	–OH	10.4	6.5	6.0	500	2.1	<1	NT
3c	$–(CH_2)_2–CO_2H$	–OMe	7.9	<5	6	528	2.3	11 ER = 1.6	NT
3d	$–(CH_2)_2–CO_2H$	–OH	11.3	6	5.3	514	2.1	<1	NT
3e	$–(CH_2)_2–CO_2H$	–F	7.0	NT	NT	516	2.1[e]	>30 ER = 1	NT
3f	$–CO–CH_2–CO_2H$	–OMe	7.8	NT	NT	542	1.3	NT	NT
3g	$–CO–CH_2–CO_2H$	–OH	~12	6.7	6.4	528	0.4	<1	NT
3h	$–CO–CH_2–CO_2H$	–F	7.7	NT	NT	530	1.0[e]	14 ER = 0.7	NT
3i	$–CO–CO_2H$	–OH	11.8	6.7	6.4	514	1.6	<1	NT

NT, not tested. ER, efflux ratio (ratio of apical-basolateral (A-B):basolateral-apical (B-A)).

[a] All compounds are full agonists and single homochiral diastereomers.

[b] Mouse vas deferens.

[c] Guinea pig myenteric plexus.

[d] (human) δ-opioid binding (pIC_{50} = 8.3).

[e] Calculated log D (pH 7.4).

ate Caco-2 flux (A-B, 5%/h). Evaluation of this analogue in the mouse hyperlocomotion model of CNS exposure showed the compound to be very poorly centrally penetrant with no effects seen at 10,000 μg/kg, relative to (**1a**, ED_{200} 400 μg/kg) and no convulsant or seizure behaviour observed.

Based on this overall profile, compound **3a** was progressed to dog pharmacokinetic studies to assess whether the physicochemical design parameters, which had successfully prevented CNS exposure, were compatible with achieving oral bioavailability. Encouragingly, **3a** demonstrated moderate clearance (17 ml/min/kg) and Vd (5.4 L/kg), with 20% oral bioavailability, indicative of significant, though incomplete, oral absorption (ca. 30–50%) in this study.

In summary, a series of zwitterionic δ-opioid agonists were designed with relatively high MWt (500–550) and moderately positive log D (~2) as strategy to minimise potential for CNS penetration, yet retain potential for oral (GI) absorption. These compounds were found to possess excellent and full functional agonist potency against the δ-opioid receptor and very high selectivity over μ and κ-opioid sub-types. In addition, analogue **3a** was found to possess moderate permeability in the Caco-2 assay and poor CNS penetration properties, as evidenced by its inactivity in a mouse hyperlocomotion model of opiate activity up to 10 mg/kg. Dog pharmacokinetic studies on **3a** showed it to be orally bioavailable (20%), indicating that despite being non-BBB penetrant, it was still significantly orally absorbed in the GI tract (30–50%).

Further work, describing the successful optimisation of this approach as a strategy for designing orally bioavailable, CNS excluded, compounds, will be the subject of a future communication from these laboratories.

Acknowledgments

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