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3a-(4-Chlorophenyl)-1-methyl-3a,4-dihydroimidazo[1,5-*a*]quinazolin-5(3*H*)-one: Synthesis and In Silico Evaluation as a Ligand in the μ-Opioid Receptor

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Abstract: In the search for fused heterocycle molecules with potential biological activities, the new title compound was produced in racemic form via a four step-synthetic sequence with an overall yield of 60%. It was structurally characterised via ^{1}H-, ^{13}C-NMR and IR analyses, and the molecular composition was confirmed through a high-resolution MS experiment. After predicting its analgesic activity using PASS online software, wherein a good overlap between its enantiomers and the structure of the natural opioid morphine was observed, the compound was evaluated through docking calculations as a ligand of the μ-opioid receptor. The resulting energy values and interactions were comparable to the data obtained for morphine and its synthetic derivative fentanyl, which is used in the therapeutic treatment of severe forms of pain. Moreover, the title compound displayed favourable predicted blood–brain barrier permeation and drug-likeness.

Keywords: heterocycles; quinazolin-4(3*H*)-one; μ-opioid receptor; docking calculation; morphine; ADME prediction

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1. Introduction

Quinazolin-4(3*H*)-one's unit is present in the structure of synthetic compounds showing biological activities, such as antibacterial [1], antimalarial [2], antihypertensive [3] anti-inflammatory and analgesic activities [4]. The synthesis of 2,2-disubstituted 2,3-dihydroquinazolin-4(1*H*)-one molecules via an efficient microwave procedure and its catalysis by antimony trichloride have been reported [5]. Additionally, more complex scaffolds maintaining the same quinazoline core structure and presenting a third fused heterocycle and an aryl substituent were produced [6–9]. However, to our knowledge, no examples have been reported so far in which this third heterocycle is represented by a 4,5-dihydro-1*H*-imidazole, as in the case of our compound. Moreover, dihydroimidazoline (imidazoline) is a peculiar moiety used in several natural and pharmaceutical products [10].

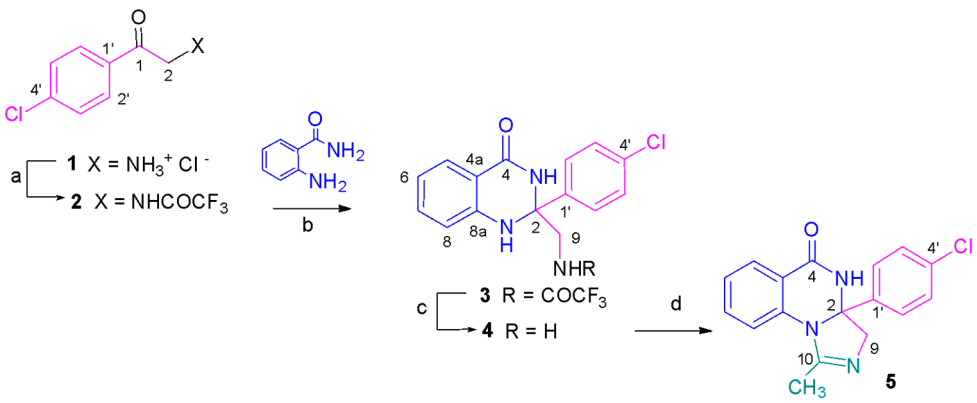
Endogenous and exogenous opioids act to mediate analgesia in painful stimuli by mechanisms involving interactions with the μ-opioid receptor (μOR) on neuronal cells [11]. Opium alkaloid morphine, the main exogenous opioid, and its synthetic derivative fentanyl, which is 100 times more potent than morphine, are often used to treat severe pain, such as cancer or post-operative pain. Another potent opioid is BU72, which shows an extremely high affinity for the μOR. In addition, methadone is a synthetic opioid with potent analgesic effects this is able to partially activate the μ-receptor and is commonly used in the treatment of opioid addiction [12]. The activation of the μOR is responsible for the efficacy of these potent analgesics [13]; for this reason, this is a target of interest for the development of new therapeutic agents that are more effective and less toxic in the management of severe forms of pain.

We report here on the synthesis and structural characterisation of 3a-(4-chlorophenyl)-1-methyl-3a,4-dihydroimidazo[1,5-*a*]quinazolin-5(3*H*)-one, the study of its interactions with the μOR with docking calculations and the prediction of pharmacokinetic parameters.

2. Results and Discussion

2.1. Chemistry

The synthetic procedure used to produce the title compound **5** is reported in Scheme 1. In detail, the commercial ammonium salt **1** was treated with trifluoroacetic anhydride in DMF at room temperature, obtaining the desired derivative **2** with 95% of yield. The condensation of **2** with anthranilamide (2-aminobenzanamide) in the presence of *p*-TsOH via refluxing in anhydrous toluene gave compound **3** with a yield of 85% [14]. By the cleavage of the trifluoroacetyl group by aqueous ammonia solution in methanol at room temperature, the free amine **4** was produced with 96% yield [15]. Refluxing **4** in ethanol with thioacetamide yielded compound **5** with a final yield of 77%, through a mechanism which involves transamidation–cyclisation of thioacetamide with the diamine unit and H_2S elimination, as reported by Levesque et al. [16]. The desired product **5** was obtained from starting **1** in four steps with a 60% global yield. No purification was required for the products obtained in the first three steps, while the final product was purified via flash chromatography on reversed stationary phase RP-18, and the purity was confirmed using an analytical HPLC technique.



Scheme 1. Synthesis of the target compound **5**. Reagents and conditions: (**a**) $(CF_3CO)_2O$, DMF, r.t., 1 h, 95%; (**b**) anthranilamide, *p*-TsOH (0.1 eq), toluene, reflux/Dean–Stark, 85%; (**c**) NH_4OH (25% aq. soln.), MeOH, r.t., 12 h, 96%; (**d**) thioacetamide, EtOH, reflux under N_2, 12 h, 77%. Numbering is for convenience, used for NMR assignments.

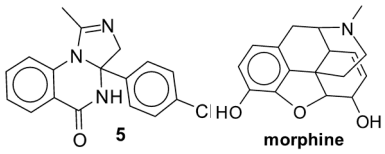
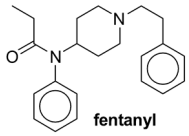
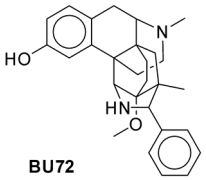
The product of each step was structurally characterised via NMR and MS analyses. The molecular composition of the final compound $C_{17}H_{14}ClN_3O$ was confirmed through the high-resolution experiment in EI-MS analysis, which also showed the relative abundance 3:1 of $^{35}Cl/^{37}Cl$ in the isotopic cluster of the molecular ion. The ESI-MS/MS analysis recorded for the $[M + H]^+$ ion at *m/z* 312 (Figure S3) provided the most intense signals derived from ethanimine fragmentation on the dihydroimidazoline ring, which was confirmed via a high-resolution experiment at *m/z* 257 in EI-MS analysis. The FT-IR spectrum displayed intense absorbance at 1668 cm^{-1} attributable to the C=O amide stretching. ^1H- and ^{13}C-NMR data with C multiplicities, as identified via an APT experiment, supported the structure of **5** (Figures S1 and S2).

2.2. In Silico Analysis

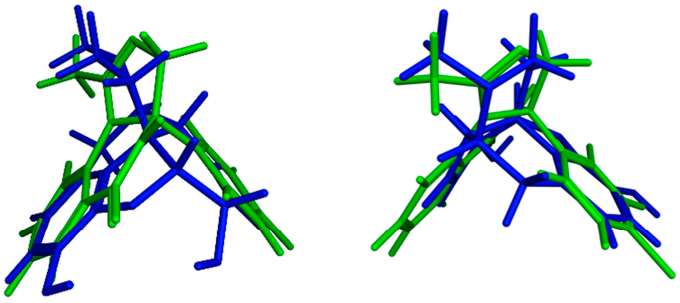
PASS online allows the prediction of a wide series of biological activities and provides indications on pharmacological targets, including interaction with metabolic enzymes and transporters [17]. By applying this prediction to our compound, it was found to be potentially active as an analgesic, with values comparable to the ones obtained for the

known opioids morphine, fentanyl and BU72 (Table 1). Additionally, a good overlap of both enantiomers (*S*)-**5** and (*R*)-**5** with morphine was observed (Figure 1).

Table 1. Potential analgesic activity evaluated via PASS online for compound **5**, in comparison with the opioids morphine, fentanyl and BU72.

Structure	 **5**	**morphine**	 **fentanyl**	 **BU72**
Pa [(a)] score	0.754	0.961	0.788	0.695
Pi [(a)] score	0.006	0.004	0.005	0.010

[(a)] Pa = probability "to be active"; Pi = probability "to be inactive".



(**a**) (**b**)

Figure 1. Overlapping of the enantiomeric forms of title compound (**a**) (*S*)-**5** (in green) and (**b**) (*R*)-**5** (in green) with morphine (in blue).

2.2.1. Docking Calculation

The available X-ray crystallographic data for the opioid BU72 as a ligand with the active μ-receptor (PDB ID: 5C1M) at a 2.07 Å resolution [13] allowed us to perform molecular docking calculations for the title compound. The energy values obtained and the detailed interactions found are reported in Table S1 and compared with morphine, fentanyl and BU72, each of which is considered in its protonated and non-protonated forms. In particular, at physiological pH 7.4, 72% of our compound should be present in the neutral and the remaining 28% in the protonated form on the imidazoline nitrogen, as calculated using MarvinSketch software (version 23.4, Chemaxon Ltd., Basel, Switzerland). Figure 2 displays the number and types of interactions in the μOR for the protonated forms of (*S*)-**5** and (*R*)-**5**. Although the original ligand BU72 used in X-ray analysis showed the best energy value (Table S1), the data obtained for compound **5**, morphine and fentanyl can be considered comparable. Moreover, protonated (*S*)-**5** displayed the same H bond with His54 and attractive charge interaction with Asp147 as BU72. Additionally, compound **5** showed a higher number of π and van der Waals interactions.

2.2.2. Pharmacokinetic Study

In order to evaluate the drug-likeness of title compound as a potential analgesic, we considered the physico-chemical parameters predicted by the software SwissADME [18], Molinspiration [19] and Molsoft L.L.C. [20]. The most significant descriptors were the topological polar surface area (TPSA), lipophilicity (LogP) and blood–brain barrier (BBB) permeation score, which are reported in Table 2 for compound **5** in comparison with the reference opioid molecules. It is noteworthy that the BBB score predicted by Molsoft for the title compound was similar to that for clinically used morphine and fentanyl, giving an indication of the high probability that compound **5** will penetrate the BBB and

that will reach the brain area for carrying out its pharmacological activity. This is also evident in the BOILED-Egg visualisation [21] (Figure S4), where, similarly to the known opioids, compound **5** lies in the yellow region, which is indicative of a high probability of brain penetration.

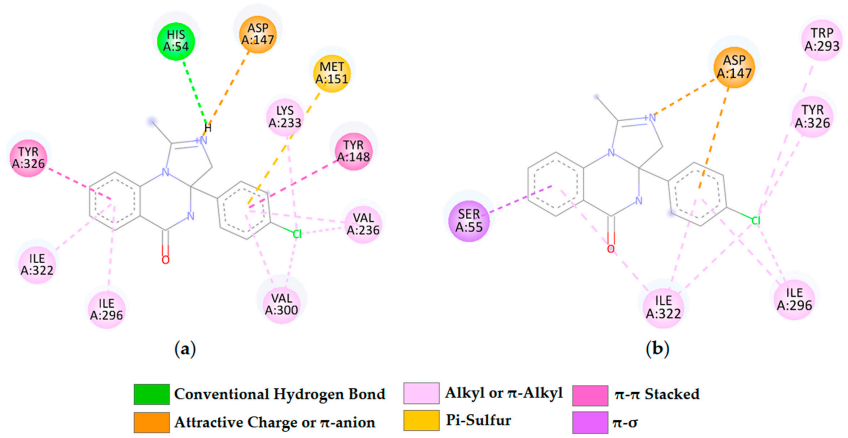


Figure 2. A 2D view of the interactions with μOR obtained via docking calculations using the Autodock Vina tool of title compound enantiomers (**a**) (*S*)-**5** and (**b**) (*R*)-**5**.

Table 2. Predicted physico-chemical properties of compound **5** in comparison with morphine, fentanyl and BU72 opioids as determined using the indicated software.

Web Tool	Properties	Compound 5	Morphine	Fentanyl	BU72
SwissADME	TPSA (Å^2)	44.70	52.93	23.55	44.73
	WLogP	1.92	0.82	3.76	3.09
	Consensus Log P	2.72	1.47	3.78	3.68
	BBB permeant	Yes	Yes	Yes	Yes
Molinspiration	TPSA (Å^2)	44.70	52.92	23.55	44.73
	miLog P	3.52	1.10	3.79	4.09
	BBB	-	-	-	-
Molsoft L.L.C.	MolPSA (Å^2)	36.49	43.21	18.21	39.69
	MolLog P	3.37	0.79	3.89	4.32
	BBB score [(a)]	5.12	4.67	5.61	4.90
	Drug-likeness model score	1.33	0.73	0.99	1.13

[(a)] BBB Score: 6—high, 0—low.

3. Materials and Methods

3.1. Chemistry

3.1.1. General

4′-Chloro-2-phenacylamine hydrochloride was purchased from Merck, while all other reagents were purchased from Sigma Aldrich (WVR, Milan, Italy) and used without further purification. The monitoring of the reactions was carried out via thin-layer chromatography (TLC) using silica gel F_{254} or reversed-phase RP-18 F_{254} (Merck, WVR, Milan, Italy), with visualisation using UV light. Flash chromatography (FC) was carried out using RP-18 Lichroprep 40–63 μm (Merck, Darmstadt, Germany). HPLC analysis of **5** using a Lichroprep RP-18, 40–63 μm (Merck, Darmstadt, Germany) in isocratic condition with MeOH/H_2O 80:20, UV detection at λ = 300 nm, t_R = 7.5 min. Melting points were determined on Reichert Thermovapor microscope, and the data are uncorrected. Infrared spectra were recorded using a FT-IR Tensor 27 Bruker spectrometer (Attenuated Transmitter Reflection, ATR configuration) at 1 cm^{-1} resolution in the absorption region 4000–600 cm^{-1}. A thin solid layer was obtained via evaporation of dichloromethane solution of the sample. The

instrument was purged with a constant dry air flux, and clean ATR crystal as a background was used. Spectra processing was carried out using Opus software package. NMR spectra were recorded on Varian-XL-300, ^{1}H-NMR at 299.94 MHz and ^{13}C-NMR at 75.43 MHz, calibrated using residual non-deuterated solvent $CDCl_3$ with values relative to TMS (δ_H 7.25 ppm and δ_C 77.0 ppm, respectively) with chemical shift values in ppm and *J* values in Hz. The following abbreviations were used to describe multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Multiplicicities for ^{13}C atoms of the final product come from the attached proton test (APT) experiment. ^{1}HNMR spectrum of **5** was recorded using a Bruker-Avance 400 spectrometer using a 5 mm BBI probe ^{1}H at 400 MHz. Electron impact (EI)–MS and high-resolution HR-EI-MS spectra (*m/z*; rel.%) were recorded using a Kratos MS80 mass spectrometer equipped with home-built computerised acquisition software. Electrospray ionisation (ESI)–MS mass spectra were recorded using a Bruker Esquire-LC spectrometer via direct infusion of a methanol solution (source temperature 300 °C, drying gas nitrogen, 4 L·min^{-1}, scan range *m/z* 100–1000).

3.1.2. Synthetic Procedure

N-[2-(4-Chlorophenyl)-2-oxoethyl]-2,2,2-trifluoroacetamide (**2**)

Trifluoroacetic anhydride (0.860 mL, 6.07 mmol) was slowly added under magnetic stirring to a suspension of 4′-chloro-2-phenacylamine hydrochloride (**1**, 500 mg, 2.43 mmol) in dry DMF (8 mL) at 5 °C. The resulting mixture was stirred for 1 h at room temperature, and then poured in water and ice and filtered with suction. The filter cake was washed with water and dried in vacuo over P_2O_5 to give **2** (612 mg, 95%), which was pure enough to be used without further purification.

Data: white powder. m.p: 116–117 °C. TLC: hexane/AcOEt 80:20 *v*/*v*, Rf: 0.42. ^{1}H-NMR ($CDCl_3$): 7.89 (d, *J* = 8.9 Hz, H2′ and H6′, 2H), 7.49 (d, *J* = 8.9 Hz, H3′ and H5′, 2H), 4.78 (bs, CH_2N, 2H). ^{13}C-NMR ($CDCl_3$): 190.9 (C1), 46.2 (C2), 157.2 ($J_{C,C,F}$ = 30 Hz, NHCO), 141.5 (C4′), 137.5 (C1′), 129.5 and 129.3 (C-2′/C6′ and C3′/C5′), 118.6 ($J_{C,F}$ = 256 Hz, CF_3). EI-MS: *m/z* (%) 265 ($M^{+\cdot}$, 1), 139(100), 111(38), 75 (18).

N-{[2-(4-Chlorophenyl)-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl]methyl}-2,2,2-trifluoroacetamide (**3**)

To a solution of 2-amino-benzamide (261 mg, 1.88 mmol) and **2** (500 mg, 1.88 mmol) in dry toluene (50 mL), a catalytic amount of *p*-toluenesulfonic acid monohydrate (36 mg, 0.188 mmol) was added. The solution was refluxed for 7 h while the H_2O formed in the reaction was continuously removed using a Dean–Stark apparatus. From evaporation of the solvent, a solid was obtained, which was resuspended using an aq. sat. solution of $NaHCO_3$. The precipitate was washed, first with dichloromethane and after with ethyl acetate, and filtered with suction. The product was pure enough to be used without further purification (612 mg, 85% yield).

Data: powder. m.p: 251 °C. TLC: hexane/AcOEt 40:60 *v*/*v*, Rf: 0.66. ^{1}H-NMR (550 µL $CDCl_3$ + 50 µL CD_3OD): 7.59 (dd, *J* = 8.1, 1.2 Hz, H5, 1H), 7.34 (d, *J* = 8.9 Hz, H3′ and H5′, 2H), 7.20 (m, 1H), 7.19 (d, *J* = 8.9 Hz, H2′ and H6′, 2H) 6.64 (m, 2H), 3.68 (s, H9, 2H).^{13}C-NMR (550 µL $CDCl_3$ + 50µL CD_3OD): 165.7 (C4), 158.5 ($J_{C,C,F}$ = 32 Hz, NHCO), 145.3 (C8a), 140.8 (C1′), 131.5 (C4′), 130.8 (C8), 129.8 and 129.1 (C2′/C6′ and C3′/C5′), 132.7 (C7), 131.5 (C5), 118.7(C6), 47.6 (C9), 118.2 ($J_{C,F}$ = 255 Hz, CF_3), 79.6 (C2), 114.8 (C4a). ESI(-)-MS: *m/z* 382 $[M - H]^-$, MS/MS (382): *m/z* 312, 269, 255.

2-(Aminomethyl)-2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (**4**)

To a solution of **3** (184 mg, 0.48 mmol) in methanol (5 mL) 25% aq. soln. ammonia (10 mL) was added and stirred at room temperature for 12 h. The mixture was evaporated in vacuo at room temperature, and the residue was resuspended using water and extracted twice with ethyl acetate. The organic phase was dried using anhydrous Na_2SO_4 and evaporated to give **4** as an oil (132 mg, 96%).

Data: TLC: $CHCl_3$/MeOH 90:10 *v*/*v*, Rf = 0.06; TLC (RP18): MeOH/H_2O 80:20 *v*/*v*, Rf = 0.12. ^{1}H-NMR ($CDCl_3$): 8.63 (br s,1H, NH), 7.68 (dd, *J* = 8.1, 1.2 Hz, H-5, 1H), 7.33 (d, *J* = 8.4 Hz, H3′ and H5′, 2H), 7.11 (d, *J* = 8.4 Hz, H2′ and H6′, 2H), 6.70 (m, 2H), 7.20 (m, 1H), 3.14 (s, H9, 2H), ^{13}C-NMR ($CDCl_3$): 166.4 (C4), 146.0 (C8a), 141.6 (C1′), 134.7 and 134.1 (C7 and C1′), 134.0 (C5), 131.5 (C4′). 129.8 and 128.6 (C2′/C6′ and C3′/C5′), 114.4 (C8), 118.9(C6), 115.4 (C4a), 79.5 (C2), 49.3 (C9). ESI (+)-MS: *m*/*z* 288 $[M + H]^+$.

3a-(4-Chlorophenyl)-1-methyl-3a,4-dihydroimidazo[1,5-*a*]quinazolin-5(3*H*)-one (**5**)

A solution of **4** (120 mg, 0.418 mmol) and thioacetamide (63 mg, 0.835 mmol) in ethanol (3 mL) was refluxed for 12 h. The solvent was evaporated, and the residue was subjected to reversed-phase FC (gradient elution water–methanol) to give pure product **5** (100 mg, 77%).

Data: white powder. m.p: 135–136 °C. TLC: $CHCl_3$/MeOH 90:10 *v*/*v*, Rf: 0.61. TLC (RP18): MeOH/H_2O 80:20 *v*/*v*; Rf: 0.32. HPLC (RP18) CH_3OH/H_2O 80: 20, t_R 7.5 min. FT-IR (cm^{-1}): 3051 (w), 2850 (w), 1769 (w), 1668 (s), 1610 (m), 1484 (m), 1238 (m), 1097 (m), 768 (m). ^{1}H-NMR ($CDCl_3$): 8.56 (br s, NH, 1H), 7.97 (dd, *J* = 7.7, 1.0 Hz, H-5, 1H), 7.49 (t, *J* = 8.4 Hz, H-7, 1H), 7.39 (d, *J* = 8.9 Hz, H3′ and H5′, 2H), 7.22 (m, 3H), 4.25 and 3.99 (two d, *J* = 15 Hz, H9, 2H), 2.17 (s, CH_3, 3H).^{13}C-NMR ($CDCl_3$): 163.40 (s, C10), 160.5 (s, C4), 141.1 (s, C8a), 137.9 (s, C-1′), 133.5 (d, C-7), 134.1 (s, C4′), 128.7 (d, C-5), 128.6 (d, C-2′ and C-6′), 127.2 (d, C3′ and C5′), 125.5 and 123.3 (two d, C6 and C8), 122.9 (s, C4a), 80.8 (s, C-2), 70.2 (t, C9), 15.4 (q, CH_3). ESI(+)-MS: *m*/*z* 312/314 $[M + H]^+$; MS/MS (312): *m*/*z* 295, 270, 256, 193, 167, 152, 120. EI-MS: *m*/*z* (%) 313 (3), 311 (9), 259 (4), 257 (12), 200 (4), 159 (4), 119 (6), 86 (20), 84 (31), 55(100). HR-MS: *m*/*z* 311.08170, calcd. for $C_{17}H_{14}{}^{35}ClN_3O$ 311.08254; *m*/*z* 257.04487, calcd. for $C_{14}H_{10}{}^{35}ClN_2O$ 257.04817.

3.2. Docking Calculation

Calculations were carried out on a PC running at 3.4 GHz on an AMD Ryzen 9 5950X 16-core (32 threads) processor with 32 GB RAM and 1 TB hard disk with Windows 10 Home 64-bit as an operating system. The ligand structure of **5**, morphine, fentanyl and BU72 were obtained via quantum chemical calculations using the Gaussian 03W revision E.01 package program set [22]. Restricted mode was used and performed in vacuo for geometry optimisation. The basis set of choice was 6-31G(d). The gradient-corrected exchange–correlation functional (B98) [23] was utilised, and the optimised structural parameters were employed in the vibrational energy calculations at the same DFT levels to characterise all stationary points as minima. For each optimised structure, no imaginary wavenumber modes were obtained, proving that a local minimum on the potential energy surface was found. All the structures were saved in pdb extension. The AutoDock Tools (ADT) package version 1.5.6rc3 [24] was used to generate the docking input files and to analyse the docking results, with Autodock Vina 1.2.0 [25,26] used for the docking calculations. The crystallographic structure of the active μ-opioid receptor (PDB ID: 5C1M) was downloaded from the Protein Data Bank (PDB; http://www.pdb.org/ accessed on 5 March 2023). The structure of μ-opioid bound to the agonist BU72 was determined via X-ray crystallography, with a resolution of 2.07 Å. The structure was modified as follows: the ligand and the crystallisation water molecules were removed, with the file saved in pdb extension. All hydrogen atoms were added using ADT, and the Gasteigere Marsili charges were calculated, with the resulting file saved in pdbqt extension. Rotatable bonds were defined for each ligand molecule. A grid box of 14 × 14 × 14 Å in the x, y and z directions with a spacing of 1.00 Å and centred at x = 2.026, y = 15.538 and z = −58.785, points in the x, y and z directions was created. Exhaustiveness was set to 100 and the number of modes = 10.

4. Conclusions

3a-(4-Chlorophenyl)-1-methyl-3a,4-dihydroimidazo[1,5-*a*]quinazolin-5(3*H*)-one was synthesised as a new compound via a four-step sequence and with a global yield of 60%. Its molecular composition was confirmed via a high-resolution MS experiment and the structure was elucidated through NMR and IR analyses. After in silico prediction

showed its potential as an analgesic and a good overlap of its 3D structure with the one of morphine was identified, it was evaluated as a ligand in the μ-opioid receptor using docking calculations, in comparison with the opioid morphine, fentanyl and BU72. Moreover, its favourable physico-chemical parameters and drug-likeness, as predicted by some online tools, makes this compound promising for further studies on the development of novel molecules to be applied in severe pain management.

Supplementary Materials: The following supporting information can be downloaded online. Figure S1: ^{1}HNMR spectrum of title compound; Figure S2: ^{13}CNMR and APT spectra of title compound; Figure S3: ESI(+)-MS spectrum of title compound and data from MS/MS fragmentation experiment; Table S1: energy values and interactions with μ-opioid receptor by docking calculations of title compound enantiomers and the known BU72, morphine and fentanyl; Figure S4: WLOGP-versus-TPSA in Brain Or IntestinaL EstimateD permeation method (BOILED)-Egg visualisation for title compound **5**, morphine, fentanyl and BU72 evaluated using Swiss-ADME software.

Author Contributions: Conceptualisation, A.D. and I.M.; investigation, A.D. and N.I.; writing—original draft preparation, A.D. and I.M.; writing—review and editing, I.M., N.I. and A.D.; supervision, I.M.; project administration, A.D.; funding acquisition, I.M. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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