UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 6-K

REPORT OF FOREIGN PRIVATE ISSUER PURSUANT TO RULE 13a-16 OR 15d-16 UNDER THE SECURITIES EXCHANGE ACT OF 1934

For the month of October, 2023.

Commission File Number: 001-40530

GH Research PLC

(Exact name of registrant as specified in its charter)

Joshua Dawson House
Dawson Street
Dublin 2
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Ireland
(Address of principal executive office)

Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F:

Form 20-F ☒ Form 40-F ____

GH Research PLC will deliver a poster presentation and host an industry interactive discussion during the 36th ECNP Congress, which is scheduled to take place in Barcelona, Spain between October 7 - 10, 2023.

A copy of the poster presentation is attached hereto as Exhibit 99.1.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

GH Research PLC

Date: October 6, 2023

By: /s/ Julie Ryan
Name: Julie Ryan
Title: Vice President, Finance

Determination of inhibition constants for three psychedelic drugs for 5-HT_{1A} and 5-HT_{2A} receptors in postmortem human brain

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Poster number P.0411

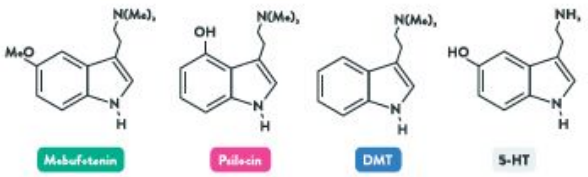
Background

- Psychedelic drugs show promise for the treatment of psychiatric disorders.
- Acute effects of psychedelic drugs are believed to be attributable to interactions with serotonin (5-hydroxytryptamine; 5-HT) receptor subtypes, primarily 5-HT_{2A}, but psychedelic drugs are also known to interact at other 5-HT receptors, including 5-HT_{1A} (Halberstadt et al. 2011).
- Activation of 5-HT_{2A} and 5-HT_{1A} receptors produces opposing actions (excitation and inhibition of pyramidal cell activity, respectively) (Pokorny et al. 2016).
- Differing affinity and functional activity at these receptors may help explain the distinct psychoactive effects induced by different psychedelic drugs.

Objectives

- The aim of this study was to compare the affinity, as measured by the inhibition constant (Ki) of the classical psychedelic drug mebufotenin (5-methoxy-N, N-dimethyltryptamine [5-MeO-DMT]) for 5-HT_{1A} and 5-HT_{2A} receptors, with two other classical psychedelic drugs, psilocin and N, N-dimethyltryptamine (DMT), in postmortem human brain tissue using radioligand binding.

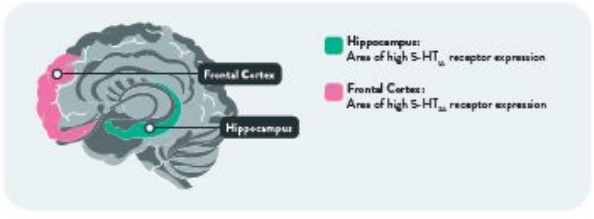
Figure 1. The molecular structures of mebufotenin, psilocin, DMT and 5-HT



Methods

- Postmortem human brain samples were obtained from from the hippocampus (area of high 5-HT_{1A} receptor expression) and the frontal cortex (area of 5-HT_{2A} receptor expression) of n=4 donors with no history of psychiatric or neurological disorders following sudden death.
- [^{3}H]8-OH-DPAT binding defined by WAY100635 was used to radiolabel 5-HT_{1A} receptors and [^{3}H]MDL-100,907 binding defined by ketanserin was used to radiolabel 5-HT_{2A} receptors.
- IC50, Hill Slope, and Ki were calculated using non-linear regression.
- Affinity for 5-HT_{1A} and 5-HT_{2A} receptors was defined as: Ki = 1–10 nM, high affinity; 10-100 nM, moderate affinity; 100-1000 nM, weak affinity; >1000 nM inactive.

Figure 2. Brain regions sampled for 5-HT_{1A} and 5-HT_{2A} receptor binding



Results

- Affinity for 5-HT_{1A}
  - Mean Ki values (n=3) for mebufotenin, psilocin, and DMT were 1.8, 48, and 38 nM respectively at 5-HT_{1A} receptors in the hippocampus (Table 1).
  - Example data from n=1 donor are shown in Figure 3.
- Affinity for 5-HT_{2A}
  - Mean Ki values (n=3) for mebufotenin, psilocin, and DMT were 122, 37, and 117 nM respectively at 5-HT_{2A} receptors in the frontal cortex (Table 1).
  - Example data from n=1 donor are shown in Figure 4.
- Hill slopes for all compounds approximated to unity suggesting a one-site binding model.
- The selectivity ratios of mebufotenin, psilocin, and DMT for 5-HT_{1A} receptors over 5-HT_{2A} receptors were 68-, 0.78-, and 3.1-fold, respectively (Table 1).

Figure 3. Example inhibition curves at 5-HT_{1A} receptor

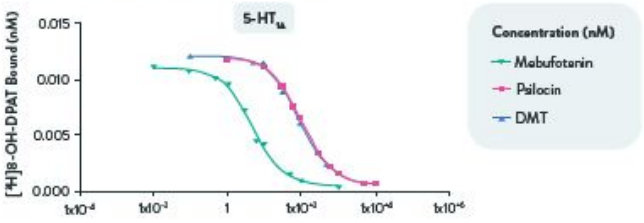


Figure 4. Example inhibition curves at 5-HT_{2A} receptor

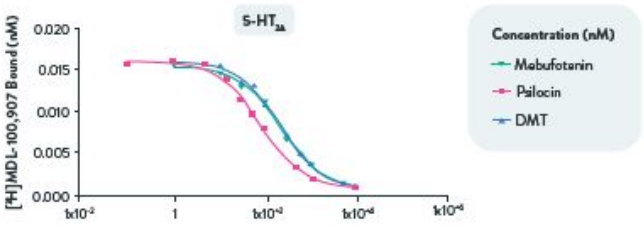


Table 1. Selectivity of three psychedelic drugs for 5-HT_{1A} vs 5-HT_{2A} receptors in postmortem human brain

	5-HT_{1A}		5-HT_{2A}		
Compound	Mean Ki (nM)	Affinity	Mean Ki (nM)	Affinity	Selectivity Ratio for 5-HT_{1A}
Mebufotenin	1.8	High	122	Weak	68
Psilocin	48	Moderate	37	Moderate	0.78
DMT	38	Moderate	117	Weak	3.1

Conclusions

- Mebufotenin has high affinity for the 5-HT_{1A} receptor in postmortem human brain samples with 68-fold selectivity for 5-HT_{1A} receptors over 5-HT_{2A} receptors.
- Psilocin is a non-selective ligand with equal and moderate affinity for 5-HT_{1A} and 5-HT_{2A} receptors.
- DMT is also a non-selective ligand with moderate and weak affinity for 5-HT_{1A} and 5-HT_{2A} receptors, respectively.
- These differences in the overall affinity of mebufotenin, psilocin, and DMT for 5-HT_{1A} and 5-HT_{2A} receptors may partly explain the distinct psychoactive effects induced by different psychedelic drugs.
- Ongoing clinical trials with a proprietary, inhaled, rapid-acting formulation of mebufotenin (GH001), including a Phase 2b trial in patients with treatment-resistant depression (NCT05800860), will further determine how the distinct binding profile of mebufotenin would translate into its clinical profile.

References:

Pokorny T, Preller KH, Kraehenmann R, Vollenweider FX. Modulatory effect of the 5-HT_{1A} agonist buspirone and the mixed non-hallucinogenic 5-$HT_{1A/2A}$ agonist ergotamine on psilocybin-induced psychedelic experience. Eur Neuropsychopharmacol. 2016;26(4):756-66.

Halberstadt AL, Koedood L, Powell SB, Geyer MA. Differential contributions of serotonin receptors to the behavioral effects of indoleamine hallucinogens in mice. J Psychopharmacol. 2011;25(11):1548-61.

Disclosures:

V McDonald and CK Olsen are employees of GH Research. GH Research sponsored this study with Sygnature Discovery. S Cheetham and M Burnett are employees of Sygnature Discovery.

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