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

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of report (date of earliest event reported): May 23, 2023

TONIX PHARMACEUTICALS HOLDING CORP.

(Exact name of registrant as specified in its charter)

Nevada	**001-36019**	**26-1434750**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

26 Main Street, Chatham, New Jersey 07928
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: (862) 904-8182

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock	TNXP	The NASDAQ Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On May 23, 2023, Tonix Pharmaceuticals Holding Corp. (the "Company") announced the discovery by Company scientists of the isolation and functional characterization of the two mirror image isomers of racemic tianeptine, which is marketed ex-U.S. as a treatment for major depressive disorder ("MDD"). A copy of the press release which discusses this matter is furnished hereto as Exhibit 99.01, and incorporated herein by reference.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibit 99.01 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the United States Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the United States Securities Act of 1933 or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

Item 8.01. Other Events.

On May 23, 2023, the Company announced the discovery by its scientists of the isolation and functional characterization of the two mirror image isomers of racemic tianeptine. Company scientists discovered that the *(S)*-isomer of tianeptine activates PPAR-β/δ, restores neuroplasticity in neuronal tissue culture and is free of μ-opioid receptor activity. In contrast, *(R)*-tianeptine activates the μ-opioid receptor and lacks PPAR-β/δ activity. Based on these discoveries, the Company has begun pre-clinical development of its *(S)*-isomer, TNX-4300 (estianeptine) product candidate as a treatment for MDD, bipolar disorder, Alzheimer's Disease and Parkinson's Disease. Based on this discovery, the Company believes that the *(S)*-isomer is responsible for tianeptine's activity on PPAR-β/δ and restoring neuroplasticity, and the *(R)*-isomer for its off-target activity on the μ-opioid receptor. The scientists isolated and characterized the *(S)*-isomer, now known as TNX-4300 and under development for psychiatric and neurological diseases.

The Company expects that its ongoing work on racemic tianeptine in depression may inform and potentially accelerate the development of TNX-4300. Although the dose of tianeptine for treating depression is well-established from racemic studies, the dose range for treating neurological diseases is not yet determined. Because TNX-4300 lacks the μ-opioid receptor activity, such effects will not limit the dosing of *(S)*-tianeptine for these other indications. *(S)*-tianeptine mimics naturally occurring polyunsaturated fatty acid ligands in binding PPAR-β/δ and PPAR-γ. *(S)*-tianeptine's activation of nuclear PPAR-β/δ and PPAR-γ receptors appears to be a more direct mechanism to achieve the goal of restoring neuronal connectivity than current therapies. The PPAR-β/δ target is validated by prior work on agonists treating animal models of neurodegenerative and autoimmune diseases of the central nervous system and the concept that Alzheimer's can be considered a form of diabetes that affects the central nervous system, or type-III

diabetes. Key experiments were performed by scientists at the Company's Research and Development Center in Frederick, Maryland. The Company plans to submit data supporting tianeptine's mechanism of action for presentation at upcoming scientific conferences and for publication in peer reviewed journals.

Forward- Looking Statements

This Current Report on Form 8-K contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 and Private Securities Litigation Reform Act, as amended, including those relating to the Company's product development, clinical trials, clinical and regulatory timelines, market opportunity, competitive position, possible or assumed future results of operations, business strategies, potential growth opportunities and other statement that are predictive in nature. These forward-looking statements are based on current expectations, estimates, forecasts and projections about the industry and markets in which we operate and management's current beliefs and assumptions.

These statements may be identified by the use of forward-looking expressions, including, but not limited to, "expect," "anticipate," "intend," "plan," "believe," "estimate," "potential," "predict," "project," "should," "would" and similar expressions and the negatives of those terms. These statements relate to future events or our financial performance and involve known and unknown risks, uncertainties, and other factors which may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Such factors include those set forth in the Company's filings with the SEC. Prospective investors are cautioned not to place undue reliance on such forward-looking statements, which speak only as of the date of this press release. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

Item 9.01 Financial Statements and Exhibits.

(d)

Exhibit No.	Description.
99.01	Press Release of the Company, dated May 23, 2023
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirement 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.

TONIX PHARMACEUTICALS HOLDING CORP.

Date: May 23, 2023

By: /s/ Bradley Saenger
Bradley Saenger
Chief Financial Officer

Exhibit 99.01

Tonix Pharmaceuticals Announces the Isolation and Characterization of the *(S)*-Isomer of Tianeptine, TNX-4300 (Estianeptine), Now Under Development for Psychiatric and Neurodegenerative Diseases

TNX-4300 is a Dual PPAR-β/δ and PPAR-γ Agonist, Free from μ-Opioid Receptor Activity

TNX-4300's Mechanism of Restoring Neuroplasticity Supports Development as a First-in-Class Oral Therapy for Depression, Bipolar Disorder, Alzheimer's Disease and Parkinson's Disease

Restoring Atrophied Neuronal Connections in Psychiatric and Neurological Diseases Seen as Paramount to Achieving Better and More Durable Outcomes

CHATHAM, N.J., May 23, 2023 – Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a clinical-stage biopharmaceutical company, today announced the isolation and functional characterization of the two mirror image isomers of racemic tianeptine, which is marketed outside the U.S. as a treatment for major depressive disorder (MDD). Tonix scientists discovered that the *(S)*-isomer of tianeptine activates PPAR-β/δ, restores neuroplasticity in neuronal tissue culture and is free of μ-opioid receptor activity. In contrast, *(R)*-tianeptine activates the μ-opioid receptor and lacks PPAR-β/δ activity. Based on these discoveries, Tonix has begun preclinical development of the *(S)*-isomer, TNX-4300 (estianeptine)*, as a treatment for MDD, bipolar disorder, Alzheimer's disease, and Parkinson's disease. Tonix is planning to submit data supporting tianeptine's mechanism of action for presentation at upcoming scientific conferences and for publication in peer reviewed journals.

Tonix recently announced that tianeptine, a drug marketed outside the U.S. for more than 30 years, is a plastogen [1] that acts on nuclear PPAR-β/δ and PPAR-γ in neurons and glia to restore neuronal connectivity in depression and has direct applicability in a number of neurodegenerative diseases in which neuronal connections are atrophying.[2] The newly reported mechanism also provided clarity on why tianeptine does not cause sexual dysfunction, weight gain or several other treatment-limiting toxicities frequently associated with antidepressants.

"The tianeptine marketed outside the U.S. for treating depression is a 1:1 racemic mixture of two mirror image isomers," said Seth Lederman, M.D., Chief Executive Officer of Tonix Pharmaceuticals. "The discovery reported today is that the *(S)*-isomer is responsible for tianeptine's activity on PPAR-β/δ and restoring neuroplasticity, and the *(R)*-isomer for its off-target activity on the μ-opioid receptor. Our team of scientists isolated and characterized the *(S)*-isomer, that is now TNX-4300 and under development for psychiatric and neurological diseases."

Dr. Lederman continued, "Our ongoing work on racemic tianeptine in depression is expected to inform and potentially accelerate the development of TNX-4300. Although the dose of tianeptine for treating depression is well-established from racemic studies, the dose range for treating neurological diseases is not yet determined. Because TNX-4300 lacks the μ-opioid receptor activity, we believe such effects will not limit the dosing of the *(S)*-tianeptine for these other indications."

Gregory Sullivan, M.D., Chief Medical Officer of Tonix Pharmaceuticals, said, " *(S)*-tianeptine mimics naturally occurring polyunsaturated fatty acid ligands in binding PPAR-β/δ and PPAR-γ. *(S)*-tianeptine's activation of nuclear PPAR-β/δ and PPAR-γ receptors appears to be a more direct mechanism to achieve the goal of restoring neuronal connectivity than current therapies. Its proposed mechanism as a plastogen is consistent with its clinical effects in promoting cognition in Alzheimer's disease and bipolar disorder[2,3] in addition to posttraumatic stress disorder (PTSD) and corticosteroid-induced cognitive dysfunction. The PPAR-β/δ target is validated by prior work on agonists treating animal models of neurodegenerative and autoimmune diseases of the central nervous system[4] and the concept that Alzheimer's can be considered a form of diabetes that affects the CNS, or type-III diabetes." [5]

Key experiments were performed by scientists at Tonix's Research and Development Center (RDC) in Frederick, Maryland.

* TNX-4300 is an investigational new drug and is not approved for any indication

[1] Tonix press release, May 17, 2023 https://ir.tonixpharma.com/news-events/press-releases/detail/1389/tonix-pharmaceuticals-announces-pharmacology-and-medicinal

[2] García-Alberca JM, et al. *J Alzheimer's Dis* 2022, *88* (2), 707-720.

[3] Kauer-Sant'Anna M, et al. *J Psychopharmacol* 2019, *33* (4), 502-510.

[4] Kahremany S et al. *Br J Pharmacol* 2015, 172(3):754-70

[5] Nguyen et al., *Int J Mol Sci.* 2010, 21(9):3165

About Tianeptine

Racemic tianeptine sodium (amorphous) immediate release (dosed 3 times daily) was first marketed for depression in France in 1989 and has been available for decades in Europe, Russia, Asia, and Latin America for the treatment of depression. Tianeptine sodium has an established safety profile from decades of use in these jurisdictions. Currently no tianeptine-containing product is approved in the U.S. and no extended-release tianeptine product is approved in any jurisdiction. In animal models, tianeptine restores dendritic arborization of pyramidal neurons in the CA3 region of hippocampus and in the dentate gyrus region promotes new neuron formation and integration into hippocampal networks.[1] Tianeptine's enhancement of neuroplasticity in animal models of stress is believed to be mediated by activation of PPAR isoforms PPAR-β/δ and PPAR-γ, which makes its properties distinct from traditional monoaminergic antidepressants in the U.S. and contributes to its potential for clinical indications beyond MDD and stress disorders. Tianeptine and its MC5 metabolite are also weak mu-opioid receptor (MOR) agonists that present a potential abuse liability if illicitly misused in large quantities (typically abused at 8-80 times the therapeutic dose on a daily basis).[2] In patients who were prescribed tianeptine for depression, the French Transparency Committee found an incidence of misuse of approximately 1 case per 1,000 patients treated[3] suggesting low abuse liability when used at the antidepressant dose in patients prescribed tianeptine for depression. Clinical trials have shown that cessation of a therapeutic course of tianeptine does not appear to result in dependence or withdrawal symptoms following 6-weeks[4-8], 3-months[9], or 12-months [10] of treatment. Tianeptine's reported pro-cognitive and anxiolytic effects as well as its ability to attenuate the neuropathological effects of excessive stress responses suggest that it may also be used to treat posttraumatic stress disorder (PTSD), and neurocognitive dysfunction associated with corticosteroid use.

[1] McEwen, B. S., et al. *Mol. Psychiatry* 2010, *15* (3), 237–249.
[2] Lauhan, R., et al. *Psychosomatics* 2018, *59* (6), 547–53.
[3] Haute Authorite de Sante; Transparency Committee Opinion. Stablon 12.5 Mg, Coated Tablet, Re-Assessment of Actual Benefit at the Request of the Transparency Committee. December 5, 2012.
[4] Emsley, R., et al. *J. Clin. Psychiatry* 2018, *79* (4)
[5] Bonierbale M, et al. *Curr Med Res Opin* 2003, *19*(2):114-124.
[6] Guelfi, J. D., et al. *Neuropsychobiology* 1989, *22* (1), 41–48.
[7] Invernizzi, G. et al., *Neuropsychobiology* 1994, *30* (2–3), 85–93.
[8] Lepine, J. P., et al. *Hum. Psychopharmacol.* 2001, *16* (3), 219–227.
[9] Guelfi, J. D. et al., *Neuropsychobiology* 1992, *25* (3), 140–148.
[10] Lôo, H. et al., *Br. J. Psychiatry. Suppl.* 1992, *15*, 61–65.

Tonix Pharmaceuticals Holding Corp.*

Tonix is a clinical-stage biopharmaceutical company focused on discovering, licensing, acquiring and developing therapeutics to treat and prevent human disease and alleviate suffering. Tonix's portfolio is composed of central nervous system (CNS), rare disease, immunology and infectious disease product candidates. Tonix's CNS portfolio includes both small molecules and biologics to treat pain, neurologic, psychiatric and addiction conditions. Tonix's lead CNS candidate, TNX-102 SL (cyclobenzaprine HCl sublingual tablet), is in mid-Phase 3 development for the management of fibromyalgia with topline data expected in the fourth quarter of 2023. TNX-102 SL is also being developed to treat Long COVID, a chronic post-acute COVID-19 condition. Enrollment in a Phase 2 study has been completed, and topline results are expected in the third quarter of 2023. TNX-1900 (intranasal potentiated oxytocin), in development for chronic migraine, is currently enrolling with topline data expected in the fourth quarter of 2023. TNX-601 ER (tianeptine hemioxalate extended-release tablets), a once-daily formulation being developed as a treatment for major depressive disorder (MDD), is also currently enrolling with interim data expected in the fourth quarter of 2023. TNX-1300 (cocaine esterase) is a biologic designed to treat cocaine intoxication and has been granted Breakthrough Therapy designation by the FDA. A Phase 2 study of TNX-1300 is expected to be initiated in the third quarter of 2023. Tonix's rare disease portfolio includes TNX-2900 (intranasal potentiated oxytocin) for the treatment of Prader-Willi syndrome. TNX-2900 has been granted Orphan Drug designation by the FDA. Tonix's immunology portfolio includes biologics to address organ transplant rejection, autoimmunity and cancer, including TNX-1500, which is a humanized monoclonal antibody targeting CD40-ligand (CD40L or CD154) being developed for the prevention of allograft rejection and for the treatment of autoimmune diseases. A Phase 1 study of TNX-1500 is expected to be initiated in the third quarter of 2023. Tonix's infectious disease pipeline includes TNX-801, a vaccine in development to prevent smallpox and mpox, for which a Phase 1 study is expected to be initiated in the second half of 2023. TNX-801 also serves as the live virus vaccine platform or recombinant pox vaccine platform for other infectious diseases. The infectious disease portfolio also includes TNX-3900 and TNX-4000, classes of broad-spectrum small molecule oral antivirals.

**All of Tonix's product candidates are investigational new drugs or biologics and have not been approved for any indication.*

This press release and further information about Tonix can be found at www.tonixpharma.com.

Forward Looking Statements

Certain statements in this press release are forward-looking within the meaning of the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as "anticipate," "believe," "forecast," "estimate," "expect," and "intend," among others. These forward-looking statements are based on Tonix's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, risks related to the failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; delays and uncertainties caused by the global COVID-19 pandemic; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. Tonix does not undertake an obligation to update or revise any forward-looking statement. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2022, as filed with the Securities and Exchange Commission (the "SEC") on March 13, 2023, and periodic reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements. The information set forth herein speaks only as of the date thereof.

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