LGD-2226 - A Rare Glimpse Into a New SARM

Visit Umbrella Labs here: https://umbrellalabs.is

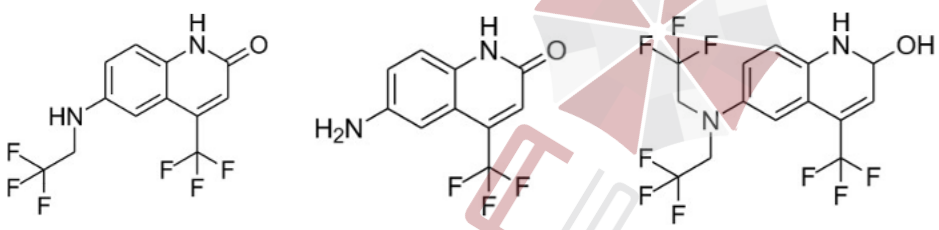
History & Context

LGD-2226 was first reported in 2006 together with by 10 similar compounds by a group of researchers from Ligand Pharmaceuticals Inc. from San Diego, California, in a paper including its synthesis.[1] LGD-2226 is a selective androgen receptor modulator (SARM). This class has been proposed to be promising both for medical application but also for performance enhancement in athletes. Unlike classical steroids, SARMs have fewer side effects, but still retain anabolic activity. In addition, androgens are problematic to administer orally, because they suffer from a massive first-pass effect and damage the liver at the same time. SARMs have two main advantages: They usually do not have any hepatotoxic effects, but they also have fewer side effects connected their direct activation of androgen receptors (e.g. acne, prostate growth or hair loss/ growth in unwanted areas), because SARMs only activate specific subsets of the androgen receptor (like androgen receptors in skeletal muscle to promote growth).

Effect of LGD-2226

In the original publication outlining the synthesis of LGD-2226, the authors also investigated in vitro and in vivo effects in rats of the compound. LGD-2226 showed a greater efficacy in activating the human androgen receptor compared to all other compounds synthesized in the same study, and it seems to also be more effective than the strongest endogenous human androgen dihydrotestosterone (DHT). LGD-2226 was specific for the androgen receptor, showing no significant binding affinities for progesterone, corticoid or oestrogen receptors. The authors also showed that LGD-2226 uses the same receptor binding site as the endogenous androgens.[1]

Castrated rats receiving LGD-2226 treated with 3 mg/kg of LGD-2226 per day showed a strong anabolic effect on muscle growth compared to testosterone, but a much weaker effect on prostate growth. Regular testosterone, which also increased muscle mass, did significantly increase the prostate volume at the same time. This shows that LGD-2226 does selectively address muscle tissue in contrast to prostate tissue, which makes it interesting to treat cachexia, especially in older males or to increase muscle growth in younger patients with fewer side effects compared to testosterone & other anabolic steroids.

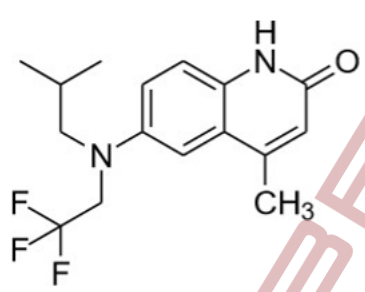


Metabolites of LGD-2226 in equine liver microsomes

A further study from 2007 on LGD-2226 showed that the compound also shows the strong activating effect on the androgen receptor compared to similar compounds, but could also decreases the activity of the receptor in certain bone cells, just like other synthetic and natural androgens. Further animal studies on rats showed that LGD-2226 can reduce bone breakdown in androgen deficient rats, which mostly seemed to affect cancellous bone (the sponge-like interior of large bones) during shorter LGD-2226 administration intervals, but a longer study group showed effects on all parts of bone, suggesting that LGD-2226 is effective in treatment of osteoporosis. It also increased sexual function in castrated rats.[2]

A study on the metabolites of LGD-2226 in horse liver microsomes showed the primary metabolites of LGD- 2226 arise from N-dealkylation and reduction of the ketone (structure shown below) these metabolites may have residual activity against the androgen receptor as well. [3]

Through the discovery of LGD-2226, which represents first compound in SARM class called "2-quinolinones" researcher have started to look for other members of a similar structure to identify other promising compounds and found alternative synthetic strategies. However, the comparison between all compounds showed that LGD-2226 remained one of the most active compounds. There are however many other similar structures with promising characteristics as well.[4]



Another 2-quinolinone with promising characteristics identified in follow-up studies (not named)

In particular, the following compound was tested as possible competitor to LGD-2226 since it also showed a great affinity to the androgen receptor, low prostate growth stimulation but a stronger positive effect on bone metabolism.

Soon after its discovery, LGD-2226 reportedly was examined in preclinical trails (data not public) which was then abandoned, on suspicion that toxicity could be too high to pursue the clinical development of the drug.[5]

A lot of scientific literature has been published in recent years concerning the development of methods to screen for LGD-2226 and other 2- quinolinone SARMs in urine & blood samples during doping control.[6]

Other techniques focus on detecting SARMs in bovine muscle tissue to monitor issue in meat production to comply with food safety regulations.[7]

Conclusion

LGD-2226 garnered attention for its potent binding capabilities and selective effects on the androgen receptor, showcasing promise in early evaluations. While the development company ultimately decided to halt its progression due to concerns over toxicity—a decision made with limited publicly available data—this reflects a cautious approach in pharmaceutical development. Notably, this decision was taken during a period (between 2007 and 2008) when the SARM market was less developed than it is today, which could have influenced the assessment of LGD-2226's risk-to-benefit ratio. In recent times, the SARM landscape has evolved, with a variety of compounds offering diverse profiles. Interestingly, despite the discontinued status of LGD-2226, there has been a surge in research aimed at detecting its presence in doping tests. This suggests that the compound may still be in use within certain circles, driven by its perceived performance-enhancing qualities.

References

[1] A. van Oeveren, M. Motamedi, N. S. Mani, K. B. Marschke, F. J. López, W. T. Schrader, A. Negro-Vilar, L. Zhi, *Journal of medicinal chemistry* **2006**, 49, 6143.

[2] J. N. Miner, W. Chang, M. S. Chapman, P. D. Finn, M. H. Hong, F. J. López, K. B. Marschke, J. Rosen, W. Schrader, R. Turner et al., *Endocrinology* **2007**, 148, 363.

[3] C. Cutler, M. Viljanto, P. Taylor, P. Hincks, S. Biddle, P. van Eenoo, *Drug testing and analysis* **2022**, 14, 349.

[4] a) A. van Oeveren, B. A. Pio, C. M. Tegley, R. I. Higuchi, M. Wu, T. K. Jones, K. B. Marschke, A. Negro- Vilar, L. Zhi, *Bioorganic & medicinal chemistry letters* **2007**, 17, 1523; b) A. van Oeveren, M. Motamedi, E. Martinborough, S. Zhao, Y. Shen, S. West, W. Chang, A. Kallel, K. B. Marschke, F. J. López et al., *Bioorganic & medicinal chemistry letters* **2007**, 17, 1527.

[5] X. Zhang, J. C. Lanter, Z. Sui, *Expert opinion on therapeutic patents* **2009**, 19, 1239.

[6] a) M. Thevis, M. Kohler, A. Thomas, J. Maurer, N. Schlörer, M. Kamber, W. Schänzer, *Analytical and bioanalytical chemistry* **2008**, 391, 251; b) E. R. Cooper, G. Hughes, A. Kauff, E. Sutherland, Z. Ashley, A. K. Heather, *Drug testing and analysis* **2021**, 13, 903; c) L. Luosujärvi, M. Haapala, M. Thevis, V. Saarela, S. Franssila, R. A. Ketola, R. Kostiainen, T. Kotiaho, *Journal of the American Society for Mass Spectrometry* **2010**, 21, 310; d) A. Hansson, H. Knych, S. Stanley, M. Thevis, U. Bondesson, M. Hedeland, *Drug testing and analysis* **2015**, 7, 673; e) E. Ventura, A. Gadaj, G. Monteith, A. Ripoche, J. Healy, F. Botrè, S. S. Sterk, T. Buckley, M. H. Mooney, *Journal of chromatography. A* **2019**, 1600, 183; f) M. Thevis, W. Schänzer, *Journal of mass spectrometry : JMS* **2008**, 43, 865; g) M. Thevis, M. Kohler, J. Maurer, N. Schlörer, M. Kamber, W. Schänzer, *Rapid communications in mass spectrometry : RCM* **2007**, 21, 3477; h) M. Thevis, M. Kohler, N. Schlörer, G. Fusshöller, W. Schänzer, *European journal of mass spectrometry* (Chichester, England) **2008**, 14, 153.

[7]A. Gadaj, E. Ventura, A. Ripoche, M. H. Mooney, *Food chemistry: X* **2019**, 4, 100056.

To learn more information about **LGD-2226**, visit:
https://umbrellalabs.is/shop/sarms/sarm-capsule/lgd-2226-sarm-powder-capsule/