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Diazo chemistry in the access to novel fatty acids linked to spiro-fused oxetane-pyrazolone scaffold

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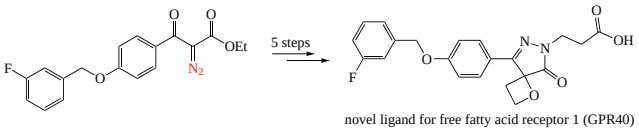
A novel free fatty acid mimetic based on the spirocyclic oxetane pyrazolone 1-oxa-6,7-diazaspiro[3.4]oct-7-en-5-one scaffold has been obtained in seven steps. The key stages are based upon the toolbox of diazo chemistry, including the SAFE diazo transfer and Rh^{II}-catalyzed O–H insertion followed by base-triggered oxetane closing.

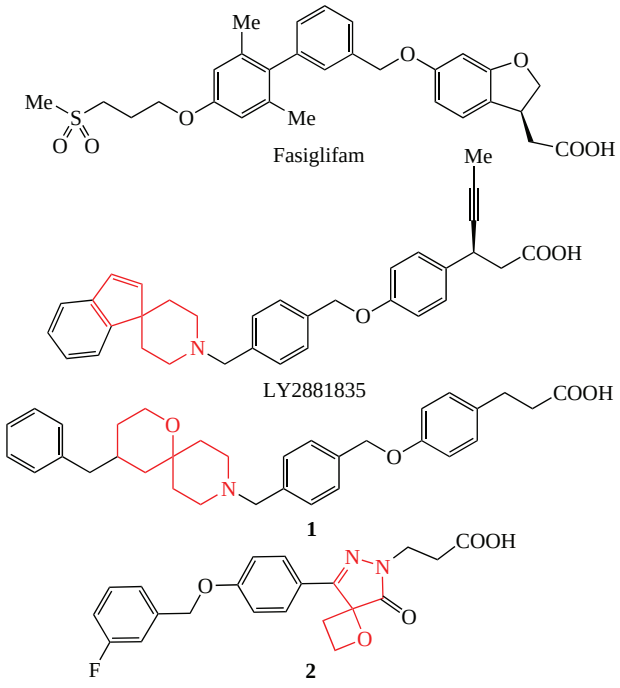


Keywords: fatty acid mimetics, free fatty acid receptor 1, GPR40, spiro compounds, pyrazolone, oxetanes, rhodium(II)-catalyzed O–H insertion, intramolecular S_N2 reaction.

Activation of free fatty acid receptor 1 (FFAR1 or GPR40) by endogenous fatty acids leads to the regulation of the insulin secretion in pancreatic β-cells and maintaining glucose homeostasis.[1] This G-protein coupled receptor has been targeted by various small molecule agonists to achieve its activation and the resulting lowering of glucose levels as an approach to treating type 2 diabetes.[2] The most advanced FFAR1 agonist is fasiglifam which demonstrated promising efficacy in patients. Unfortunately, it was disconnected in phase III clinical trial due to idiosyncratic liver toxicity.[3] This intensified the search for novel FFAR1 agonists with the aim of lowering compound's lipophilicity and decreasing the associated toxicity risks.[4]

Spirocyclic compounds have a special significance in drug design due to their pronounced three-dimensional character (enabling selective interaction with a protein target of interest[5]), high degree of saturation (expressed as fraction of sp^3-hybridized atoms[6] or F_{sp^3}), favourable physicochemical characteristics[7] and direct relevance to the natural product chemical space.[8] Among FFAR1 agonists (most of which comprise a 3-phenylpropionic acid moiety as a fatty acid mimetic), the employment of spirocycles is notable in the Eli Lilly's advanced candidate LY2881835[9] and our optimized agonist **1** containing a spirocyclic piperidine.[10] However, effect of moving a spirocyclic fragment from the periphery to the scaffold of a free fatty acid mimetic has not been explored. Our synthetic methodology research in the area of diazo chemistry[11] and the facile entry into oxetanes from diazo compounds recently reported by Davis[12] prompted us to design spiro-fused pyrazolone-oxetane[13] scaffold decorated with lipophilic 4-benzyloxyphenyl periphery to ensure affinity to FFAR1. The practical realization of this drug design idea is exemplified by the synthesis of pilot compound **2** which we describe in this Communication.

The synthesis of novel spirocyclic FFAR1 agonist **2** commenced with readily available[14] β-keto ester **3**. This C–H acidic compound was subjected to the recently developed modification of the Regitz diazo transfer reaction dubbed 'sulfonyl-azide-free' (SAFE) diazo transfer in water.[15] This reaction allows for *in situ* generation of the diazo transfer reagent in water and avoiding the handling of potentially hazardous material. Without purification, diazo compound **4** was coupled with 2-bromoethanol in the presence of a catalytic amount of rhodium(II) espionate, bis[rhodium(α,α,α′,α′-tetramethyl-benzene-1,3-dipropionic acid)], $Rh_2(esp)_2$.[16] The initial product of rhodium carbene O–H insertion reaction, compound **5**, was treated with sodium hydride in DMF. This triggered deprotonation of the β-keto ester moiety and a subsequent intramolecular S_N2 reaction[12] to give oxetane **6** in good yield over 3 steps. β-Keto esters can be coupled with various nitrogen bis-nucleophiles to produce heterocyclic compounds. In this case, we envisioned treatment with hydrazine hydrate to produce a pyrazolone[17] suitable for the installation of a carboxylic acid side chain *via* *N*-alkylation. Unfortunately, exposing compound **6** to 5-fold excess hydrazine hydrate in refluxing ethanol did not cause any appreciable conversion. Using more forcing reaction conditions



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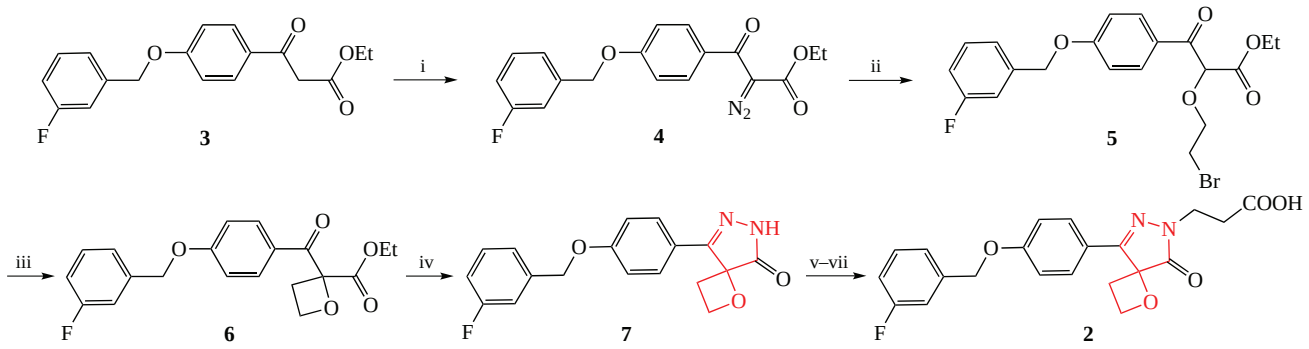

Scheme 1 *Reagents and conditions*: i, NaN_3 (2.0 equiv.), *m*-$HO_2CC_6H_4SO_2Cl$ (1.3 equiv.), K_2CO_3 (2.6 equiv.), H_2O, room temperature, 1 h; ii, $Br(CH_2)_2OH$, $Rh_2(esp)_2$ (0.3 mol%), CH_2Cl_2, room temperature, 1 h; iii, NaH (1.2 equiv.), DMF, 0 °C, 2 h (25% over 3 steps); iv, $N_2H_4{\cdot}H_2O$, 1-butanol, 140 °C, sealed tube, 18 h (73%); v, CH_2=$CHCO_2Me$ (1.2 equiv.), Bu^tOK (0.2 equiv.), DMF, 0 °C; vi, HPLC purification; vii, LiOH (2 equiv.), MeOH, room temperature, 18 h (32% over 3 steps).

(1-butanol, 115 °C, sealed tube, 6 h) did drive the reaction forward but did not provide full conversion. Finally, raising the temperature to 140 °C and prolonging the reaction time to 18 h enabled complete conversion and produced novel spirocyclic pyrazolone **7** in 73% yield after chromatography. This compound was only lacking the propionic acid side chain to become the designer ligand for FFAR1. The installation of the side chain was envisioned *via* the Michael addition to methyl acrylate[18] followed by ester hydrolysis. To our surprise, using a catalytic amount of potassium hydroxide in DMF either at room temperature or at 40 °C did not result in any conversion over 2 days. Fortunately, with a stronger base such as Bu^tOK in the same solvent at 0 °C the reaction went to completion within 30 min. Chromatographic purification on silica gel gave an impure product which had to be re-purified by high-performance liquid chromatography. Ester **8** thus obtained was hydrolyzed with lithium hydroxide in methanol. The resulting carboxylic acid **2** was obtained in 32% yield over two steps, including one HPLC purification (Scheme 1).

Molecular characteristics defining drug likeness (*i.e.* the metrics stipulated by the Lipinski's rule of five[19] as well as polar surface area and number of rotatable bonds) are important determinants of compound's uptake *in vivo* as well as desired performance as a therapeutic agent. Having enabled the new spiro-fused oxetane-pyrazolone scaffold for fatty acid mimetics, we were curious to compare this compound to other FFAR1 agonists for which efficacy has already been established (Table 1). It is obvious that compound **2** carries such advantages compared to other compounds as lower molecular weight and lipophilicity (allowing ample room for medicinal chemistry optimization[20]) as well as more rigid molecular structure, favorable from the intestinal and cellular absorption standpoint.[21]

In summary, we have developed the synthesis of a novel free fatty acid mimetic based on the hitherto undescribed spiro-fused oxetane-pyrazolone scaffold. The compound is a prototype for the library of fatty acid mimetics intended for interrogation of free fatty acid receptors such as FFAR1, a diabetes drug target. The synthesis draws from the toolbox of diazo chemistry, including the SAFE diazo transfer reaction and Rh^{II}-catalyzed O–H insertion reaction followed by base-triggered oxetane formation. The final compound is distinctly druglike and compares favorably to the know FFAR1 agonists in terms of molecular weight, lipophilicity and molecular flexibility. The results of the extended library synthesis and biological profiling will be reported in due course.

Table 1 Molecular characteristics of compounds **1**, **2**, fasiglifam and LY2881835 (calculated using www.molinspirations.com).

Compound	HBA[a]	HBD[a]	MW[b]	cLogP[c]	TPSA[d]/Å	nRotB[e]
1	5	1	513.7	6.48	59.0	10
2	7	1	358.4	2.51	88.4	7
Fasiglifam	7	1	510.6	3.13	99.1	10
LY2881835	4	1	481.6	4.96	49.8	8

[a]HBA/HBD is number of hydrogen bond acceptors/donors, respectively. [b]MW is molecular weight. [c]cLogP is calculated lipophilicity. [d]TPSA is total polar surface area. [e]nRotB is number of rotary bonds.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.01.006.

References

1 C. P. Briscoe, M. Tadayyon, J. L. Andrews, W. G. Benson, J. K. Chambers, M. M. Eilert, C. Ellis, N. A. Elshourbagy, A. S. Goetz, D. T. Minnick, P. R. Murdock, H. R. Sauls, Jr., U. Shabon, L. D. Spinage, J. C. Strum, P. G. Szekeres, K. B. Tan, J. M. Way, D. M. Ignar, S. Wilson and A. I. Muir, *J. Biol. Chem.*, 2003, **278**, 11303.
2 Z. Li, Z. Zhou and L. Zhang, *Exp. Opin. Ther. Pat.*, 2020, **30**, 27.
3 M. A Otieno, J. Snoeys, W. Lam, A. Ghosh, M. R. Player, A. Pocai, R. Salter, D. Simic, H. Skaggs, B. Singh and H.-K. Lim, *Toxicol. Sci.*, 2018, **163**, 374.
4 K. Bazydlo-Guzenda, P. Buda, M. Mach, J. Pieczykolan, I. Kozlowska, M. Janiszewski, E. Drzazga, J. Dominowski, H. Ziolkowski, M. Wieczorek and S. C. Gad, *PLoS One*, 2021, **16**, e0257477.
5 K. E. Prosser, R. W. Stokes and S. M. Cohen, *ACS Med. Chem. Lett.*, 2020, **11**, 1292.
6 W. Wei, S. Cherukupalli, L. Jing, X. Liu and P. Zhan, *Drug Discov. Today*, 2020, **25**, 1839.
7 K. Hiesinger, D. Dar'in, E. Proschak and M. Krasavin, *J. Med. Chem.*, 2021, **64**, 150.
8 E. Chupakhin, O. Babich, A. Prosekov, L. Asyakina and M. Krasavin, *Molecules*, 2019, **24**, 4165.
9 Y. Chen, M. Song, J. P. Riley, C. C. Hu, X. Peng, D. Scheuner, K. Bokvist, P. Maiti, S. D. Kahl, C. Montrose-Rafizadeh, C. Hamdouchi and A. R. Miller, *Pharmacol. Res. Perspect.*, 2016, **4**, e00278.
10 M. Krasavin, A. Lukin, D. Bagnyukova, N. Zhurilo, A. Golovanov, S. Zozulya, I. Zahanich, D. Moore and I. G. Tikhonova, *Eur. J. Med. Chem.*, 2017, **127**, 357.
11 E. Chupakhin, G. Kantin, D. Dar'in and M. Krasavin, *Mendeleev Commun.*, 2022, **32**, 382.
12 (*a*) O. A. Davis and J. A. Bull, *Angew. Chem., Int. Ed.*, 2014, **53**, 14230; (*b*) O. A. Davis, R. A. Croft and J. A. Bull, *Chem. Commun.*, 2015, **51**, 15446.
13 G. Wuitschik, M. Rogers-Evans, A. Buckl, M. Bernasconi, M. Märki, T. Godel, H. Fischer, B. Wagner, I. Parrilla, F. Schuler, J. Schneider, A. Alker, W. B. Schweizer, K. Müller and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2008, **47**, 4512.

14 J. Zeng, Y. J. Tan, J. Ma, M. L. Leow, D. Tirtorahardjo and X.-W. Liu, *Chem. – Eur. J.*, 2014, **20**, 405.
15 (*a*) D. Dar'in, G. Kantin and M. Krasavin, *Synthesis*, 2019, **51**, 4284; (*b*) D. Dar'in, G. Kantin and M. Krasavin, *Chem. Commun.*, 2019, **55**, 5239.
16 C. G. Espino, K. W. Fiori, M. Kim and J. Du Bois, *J. Am. Chem. Soc.*, 2004, **126**, 15378.
17 I. J. Bakanas and G. Moura-Letts, *Eur. J. Org. Chem*., 2016, 5345.
18 F. A. Khalifa, F. M. Abdel-Galil, B. Y. Riad and M. H. Elnagdi, *Indian J. Chem., Sect. B*, 1983, **22**, 1158.
19 C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Delivery Rev.*, 2001, **46**, 3.
20 B. Raymer and S. K. Bhattacharya, *J. Med. Chem*., 2018, **23**, 10375.
21 D. F. Veber, S. R. Johnson, H.-Y. Cheng, B. R. Smith, K. W. Ward and K. D. Kopple, *J. Med. Chem*., 2002, **45**, 2615.

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