

Supplementary information for Design and evaluation of an anthranilic acid derivative as a multitarget drug in a diet-induced metabolic syndrome model by González-Álvarez, et.al.

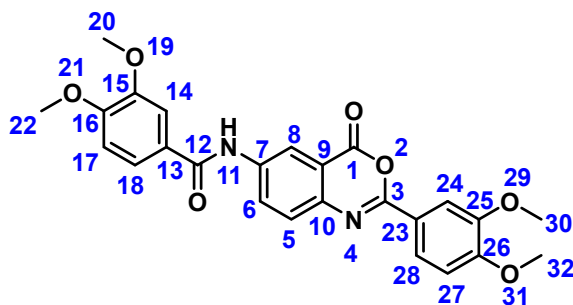
1. Complete docking results

			Dyslipidemia						Hyperglycemia					Hypertension	
Compound	Benzylamine	Benzamide	PPAR- alfa	HMG-CoA reductase	ACAT	CETP	Squalene synthase	FXR	PPAR- gamma	DPP- IV	Aldose reductase	GPR40	PTP1B	Renin	ACE
1b	4'-CF3	3',4'-diOMe	-151.6	-156.2	-121.6	-129.2	-118.7	-132.3	-165.2	-84.2	-136.0	-91.3	-107.9	-104.3	-137.2
Reference ligands			-113.8	-164.5	-110.8	-100.1	-111.6	-144.4	-116.7	-144.5	-97.1	-122.7	-150.9	-166.8	-123.0
1a	H	4'-Et	-97.6	-107.9	-90.6	-90.1	-93.7	-107.3	-108.0	-77.2	-117.9	-87.9	-94.2	-101.6	-95.7
2a	4'-Me	4'-Et	-105.8	-112.9	-91.1	-76.9	-96.3	-101.8	-104.0	-63.2	-121.5	-98.8	-79.0	-94.5	-108.3
3a	4'-OMe	4'-Et	-104.6	-110.0	-90.0	-86.9	-94.6	-100.0	-110.6	-68.6	-101.8	-94.6	-92.0	-96.3	-79.2
4a	3',4'-diOMe	4'-Et	-107.9	-108.0	-91.5	-86.7	-90.6	-100.3	-106.5	-69.3	-140.0	-111.7	-89.8	-94.4	-93.4
5a	2',4'-diOMe	4'-Et	-109.1	-106.5	-95.2	-90.1	-99.6	-97.9	-109.7	-77.4	-127.3	-100.9	-89.4	-102.8	-92.7
6a	4'-Cl	4'-Et	-102.9	-101.8	-88.5	-79.8	-86.0	-97.5	-112.2	-69.5	-119.1	-90.5	-94.5	-99.3	-89.2
7a	4'-pyr	4'-Et	-105.8	-123.3	-89.6	-89.3	-98.4	-107.8	-114.7	-67.8	-106.8	-88.5	-104.5	-103.1	-98.5
8a	4'-CF3	4'-Et	-109.7	-108.1	-96.1	-87.9	-94.4	-104.5	-112.1	-83.3	-109.5	-108.5	-93.4	-102.3	-104.3
9a	4'-COOH	4'-Et	-91.7	-91.4	-78.1	-66.3	-80.9	-88.0	-93.3	-49.3	-106.6	-84.1	-75.0	-99.6	-78.1
10a	4'-NMe2	4'-Et	-104.0	-103.3	-89.3	-83.2	-99.9	-97.3	-104.6	-80.5	-124.4	-99.9	-90.9	-89.2	-106.8
11a	H	4'-OMe	-101.4	-105.1	-90.0	-80.8	-88.2	-100.7	-103.4	-72.1	-125.4	-95.3	-95.1	-94.2	-104.5
12a	4'-Me	4'-OMe	-105.8	-107.5	-84.3	-86.0	-92.6	-94.4	-113.7	-60.6	-115.3	-85.6	-78.6	-90.2	-97.3
13a	4'-OMe	4'-OMe	-99.3	-102.6	-90.5	-88.8	-87.4	-101.4	-101.4	-69.9	-131.5	-92.2	-86.8	-100.1	-97.7
14a	3',4'-diOMe	4'-OMe	-112.8	-106.3	-89.3	-80.3	-96.7	-95.0	-110.4	-62.3	-121.9	-95.1	-88.9	-100.5	-105.4
15a	2',4'-di-OMe	4'-OMe	-115.8	-106.7	-92.7	-84.6	-100.6	-92.6	-112.8	-61.3	-126.8	-99.1	-91.9	-103.2	-97.3
16a	4'-Cl	4'-OMe	-104.8	-104.3	-91.9	-82.5	-86.8	-102.2	-105.9	-66.8	-123.1	-95.1	-99.3	-95.4	-100.0
17a	4'-CF3	4'-OMe	-101.1	-106.8	-95.5	-84.3	-89.5	-99.2	-112.5	-61.5	-122.3	-95.6	-93.4	-93.5	-104.2
17a	4'-CF3	4'-OMe	-103.9	-101.5	-94.4	-89.1	-88.2	-98.0	-114.3	-61.3	-119.9	-98.4	-94.2	-95.5	-105.2
19a	4'-COOH	4'-OMe	-106.6	-109.2	-95.9	-82.7	-87.0	-102.3	-109.6	-58.3	-123.3	-100.2	-90.6	-93.8	-80.1
20a	4'-NMe2	4'-OMe	-111.0	-108.9	-96.9	-73.7	-91.0	-89.9	-104.5	-69.6	-126.2	-99.7	-91.5	-90.6	-99.0
21a	H	4'-NO2	-99.5	-104.7	-79.2	-84.8	-84.7	-103.4	-110.4	-64.0	-125.2	-86.4	-100.6	-102.8	-102.0
22a	4'-Me	4'-NO2	-105.7	-97.1	-93.8	-75.2	-81.7	-95.1	-116.2	-64.2	-127.0	-89.2	-104.6	-99.2	-105.2
23a	4'-OMe	4'-NO2	-103.0	-105.7	-90.4	-83.1	-82.2	-98.3	-108.3	-59.2	-121.8	-94.9	-87.7	-88.3	-94.1
24a	3',4'-diOMe	4'-NO2	-111.4	-113.9	-91.5	-91.1	-90.0	-100.3	-112.8	-77.2	-121.2	-109.3	-93.4	-91.6	-90.8

25a	2',4'-di-OMe	4'-NO2	-111.7	-103.3	-88.2	-86.8	-85.5	-92.0	-108.4	-67.6	-117.4	-99.3	-94.9	-96.9	-45.6
26a	4'-Cl	4'-NO2	-106.1	-106.4	-91.6	-86.6	-83.3	-103.7	-105.8	-75.0	-112.6	-89.4	-102.1	-99.4	-93.9
27a	4'-pyr	4'-NO2	-101.8	-103.1	-92.4	-87.2	-88.8	-94.0	-106.0	-73.6	-123.0	-87.9	-98.0	-99.6	-99.1
28a	4'-CF3	4'-NO2	-113.8	-99.0	-90.9	-84.2	-87.2	-99.9	-116.7	-64.3	-121.1	-109.5	-106.1	-98.7	-119.7
29a	4'-COOH	4'-NO2	-107.1	-98.6	-94.6	-79.6	-91.1	-100.1	-111.9	-70.3	-126.8	-97.0	-92.8	-98.0	-89.5
30a	4'-NMe2	4'-NO2	-107.3	-116.5	-100.8	-81.4	-92.3	-99.9	-107.6	-58.5	-116.7	-104.2	-93.8	-92.4	-104.1
31a	H	3',5'-diNO2	-109.6	-109.7	-93.6	-93.0	-95.4	-88.7	-123.5	-79.8	-117.1	-99.3	-105.0	-97.0	-92.9
32a	4'-Me	3',5'-diNO2	-108.3	-102.0	-101.2	-86.8	-93.3	-97.2	-115.9	-78.1	-120.8	-95.7	-76.8	-102.3	-93.3
33a	4'-OMe	3',5'-diNO2	-112.8	-105.2	-94.8	-91.9	-91.3	-99.2	-122.6	-80.3	-122.3	-99.6	-78.2	-99.5	-95.3
34a	3',4'-diOMe	3',5'-diNO2	-111.4	-121.0	-94.8	-91.5	-93.3	-91.9	-110.1	-82.2	-127.2	-113.0	-94.4	-98.3	-106.2
35a	2',4'-diOMe	3',5'-diNO2	-114.9	-114.3	-96.2	-88.5	-92.0	-98.8	-118.4	-84.2	-115.4	-101.6	-100.8	-110.0	-90.9
36a	4'-Cl	3',5'-NO2	-108.4	-105.0	-86.7	-87.4	-88.7	-100.5	-116.9	-79.9	-120.7	-96.1	-83.4	-102.3	-96.4
37a	4'-pyr	3',5'-diNO2	-108.0	-109.1	-91.1	-94.4	-93.4	-89.4	-114.5	-84.2	-119.4	-92.7	-102.6	-102.0	-91.1
38a	4'-CF3	3',5'-diNO2	-113.6	-98.4	-102.0	-90.5	-98.5	-87.2	-122.7	-88.1	-142.0	-107.1	-86.1	-99.3	-99.3
39a	4'-COOH	3',5'-diNO2	-112.8	-105.9	-109.9	-94.4	-94.6	-91.6	-125.2	-64.9	-136.9	-99.3	-94.3	-105.7	-87.0
40a	4'-NMe2	3',5'-diNO2	-107.1	-106.8	-110.8	-84.7	-88.9	-97.3	-114.6	-62.0	-127.4	-99.5	-100.3	-108.6	-83.7
41a	H	3',4'-diOMe	-104.8	-103.0	-102.8	-87.3	-90.2	-94.3	-108.9	-72.8	-130.9	-92.8	-92.7	-104.9	-98.1
42a	4'-Me	3',4'-diOMe	-110.6	-109.4	-100.4	-82.0	-82.0	-101.3	-121.4	-65.6	-120.5	-93.9	-80.7	-94.7	-95.9
43a	4'-OMe	3',4'-diOMe	-118.5	-100.6	-99.9	-85.4	-92.0	-92.3	-113.9	-71.7	-118.3	-89.0	-97.0	-101.9	-111.7
44a	3',4'-diOMe	3',4'-diOMe	-125.0	-112.5	-100.6	-95.6	-99.2	-103.4	-119.5	-72.9	-132.2	-95.6	-104.8	-101.5	-90.9
45a	2',4'-di-OMe	3',4'-diOMe	-119.0	-113.3	-88.5	-85.3	-99.0	-96.6	-124.2	-63.4	-114.0	-101.2	-102.3	-96.9	-97.3
46a	4'-Cl	3',4'-diOMe	-105.2	-106.7	-96.8	-91.6	-94.4	-106.0	-115.7	-68.2	-123.4	-90.4	-98.3	-101.3	-108.3
47a	4'-pyr	3',4'-diOMe	-107.3	-102.6	-93.3	-81.7	-94.4	-96.2	-119.2	-80.9	-117.3	-91.8	-94.5	-99.4	-95.8
48a	4'-CF3	3',4'-diOMe	-118.7	-111.8	-91.8	-88.4	-100.3	-118.9	-127.9	-72.8	-140.6	-90.2	-105.8	-100.8	-98.1
49a	4'-COOH	3',4'-diOMe	-120.1	-106.6	-91.0	-87.0	-90.8	-103.3	-116.8	-75.9	-116.4	-91.0	-96.9	-105.8	-100.5
50a	4'-NMe2	3',4'-diOMe	-113.9	-104.7	-96.3	-76.3	-85.5	-101.9	-114.7	-93.7	-111.7	-95.0	-83.9	-93.0	-111.3
51a	H	4'-Cl	-98.7	-107.9	-87.3	-75.7	-88.9	-91.9	-101.6	-74.4	-117.4	-88.8	-95.2	-96.0	-100.4
52a	4'-Me	4'-Cl	-94.6	-101.4	-83.9	-79.3	-83.2	-90.2	-108.0	-56.4	-119.4	-88.2	-81.7	-95.0	-93.1
53a	4'-OMe	4'-Cl	-99.3	-108.3	-83.8	-79.2	-86.2	-100.2	-108.0	-70.6	-111.0	-97.0	-90.3	-93.9	-86.9
54a	3',4'-diOMe	4'-Cl	-105.7	-101.7	-89.4	-88.3	-82.6	-98.4	-113.0	-54.2	-101.4	-102.6	-89.6	-96.9	-86.8
55a	2',4'-diOMe	4'-Cl	-108.2	-113.6	-97.0	-86.7	-95.3	-100.0	-110.8	-76.9	-122.1	-101.2	-92.5	-106.6	-86.9
56a	4'-Cl	4'-Cl	-101.9	-105.0	-91.1	-75.9	-80.7	-94.6	-108.0	-76.2	-113.5	-90.1	-84.8	-92.1	-99.4
57a	4'-pyr	4'-Cl	-98.4	-100.8	-86.4	-77.0	-82.0	-92.0	-108.6	-66.6	-118.9	-89.1	-101.7	-91.7	-98.2

58a	4'-CF3	4'-Cl	-104.9	-107.9	-91.4	-83.8	-87.2	-96.6	-106.8	-75.3	-114.7	-103.1	-90.2	-89.6	-77.6
59a	4'-COOH	4'-Cl	-101.7	-96.0	-89.3	-78.1	-83.2	-97.4	-103.5	-64.7	-110.8	-93.7	-90.6	-97.4	-100.1
60a	4'-NMe2	4'-Cl	-103.6	-108.3	-88.5	-68.1	-85.3	-95.4	-97.2	-67.2	-121.5	-98.9	-88.7	-94.5	-103.0
61a	H	4'-NMe2	-98.4	-101.8	-81.0	-82.9	-86.0	-89.5	-115.0	-60.5	-108.8	-78.1	-92.9	-97.8	-68.6
62a	4'-Me	4'-NMe2	-102.6	-106.4	-91.5	-82.2	-85.5	-86.5	-115.6	-64.2	-110.7	-82.6	-88.6	-101.6	-111.1
63a	4'-OMe	4'-NMe2	-106.9	-105.1	-85.9	-87.0	-87.2	-99.8	-114.1	-66.3	-115.2	-89.0	-85.7	-97.9	-99.1
64a	3',4'-diOMe	4'-NMe2	-111.6	-117.2	-84.3	-88.9	-84.8	-98.9	-124.3	-76.3	-124.2	-98.5	-87.0	-104.5	-92.6
65a	2',4'-diOMe	4'-NMe2	-108.3	-101.7	-91.4	-91.1	-88.1	-94.2	-114.4	-56.7	-114.2	-101.4	-88.8	-92.2	-91.0
66a	4'-Cl	4'-NMe2	-99.0	-100.7	-88.9	-75.1	-93.9	-98.4	-120.3	-68.1	-114.3	-80.0	-92.2	-99.8	-102.9
67a	4'-pyr	4'-NMe2	-105.6	-102.5	-86.9	-81.0	-96.8	-95.7	-108.0	-78.9	-110.8	-72.8	-105.3	-98.4	-101.0
68a	4'-CF3	4'-NMe2	-110.8	-107.9	-92.7	-84.8	-90.9	-106.5	-128.7	-74.8	-105.5	-80.5	-94.5	-91.7	-89.8
69a	4'-COOH	4'-NMe2	-105.8	-100.8	-91.2	-77.1	-93.1	-104.0	-118.5	-66.2	-115.1	-86.3	-84.7	-97.4	-85.4
70a	4'-NMe2	4'-NMe2	-107.3	-103.7	-94.8	-81.2	-88.7	-94.1	-114.6	-91.1	-114.1	-98.0	-84.4	-96.0	-105.1
71a	H	4'-CF3	-104.8	-103.3	-90.0	-91.4	-82.0	-101.4	-112.4	-74.6	-122.6	-90.3	-100.0	-98.5	-65.8
72a	4'-Me	4'-CF3	-106.5	-103.9	-88.4	-83.6	-90.8	-106.8	-108.0	-73.4	-121.4	-88.4	-103.2	-94.4	-93.2
73a	4'-OMe	4'-CF3	-105.6	-108.7	-88.6	-87.1	-90.2	-99.0	-104.3	-61.9	-103.0	-98.5	-85.8	-94.1	-104.8
74a	3',4'-diOMe	4'-CF3	-118.6	-110.7	-85.8	-83.7	-95.5	-110.2	-118.4	-66.7	-132.1	-104.8	-94.7	-102.3	-94.7
75a	2',4'-diOMe	4'-CF3	-106.9	-106.4	-92.1	-95.3	-100.3	-96.8	-117.5	-70.5	-105.9	-106.9	-104.1	-103.8	-95.0
76a	4'-Cl	4'-CF3	-107.9	-110.4	-94.6	-81.0	-93.1	-109.1	-114.9	-70.9	-123.6	-92.7	-99.4	-99.4	-102.2
77a	4'-pyr	4'-CF3	-100.1	-108.0	-92.0	-86.0	-86.8	-96.6	-115.0	-66.2	-116.9	-89.2	-106.5	-101.1	-107.3
78a	4'-CF3	4'-CF3	-112.8	-109.5	-88.0	-82.4	-86.7	-99.7	-116.8	-85.0	-118.4	-97.8	-93.5	-106.9	-110.8
79a	4'-COOH	4'-CF3	-112.0	-106.3	-83.3	-83.8	-89.7	-105.5	-116.5	-85.5	-117.1	-103.7	-90.2	-93.9	-89.2
80a	4'-NMe2	4'-CF3	-110.1	-102.7	-90.3	-78.1	-84.2	-103.6	-109.5	-78.9	-109.6	-104.0	-85.7	-99.2	-99.8
81a	H	4'-SO2NH2	-108.3	-112.1	-90.2	-90.7	-92.3	-107.8	-111.2	-72.7	-112.2	-87.3	-110.4	-99.1	-103.9
82a	4'-Me	4'-SO2NH2	-107.9	-102.1	-90.0	-84.7	-83.0	-101.1	-115.6	-69.1	-113.1	-95.7	-114.4	-92.7	-117.8
83a	4'-OMe	4'-SO2NH2	-108.8	-101.3	-95.5	-88.7	-91.0	-102.8	-115.8	-72.6	-115.7	-98.2	-88.6	-84.3	-89.1
84a	3',4'-diOMe	4'-SO2NH2	-116.5	-105.5	-100.9	-93.8	-100.5	-100.6	-119.7	-85.2	-111.2	-108.7	-103.9	-104.7	-93.1
85a	2',4'-di-Ome	4'-SO2NH2	-114.3	-113.3	-102.3	-90.2	-98.2	-111.9	-123.2	-68.9	-118.8	-104.1	-114.7	-97.0	-87.6
86a	4'-Cl	4'-SO2NH2	-111.4	-114.9	-87.9	-82.0	-90.9	-102.8	-111.5	-71.1	-113.3	-89.2	-111.3	-101.8	-99.7
87a	4'-pyr	4'-SO2NH2	-106.7	-101.4	-92.7	-87.8	-85.4	-97.1	-112.5	-73.8	-113.8	-87.9	-112.7	-101.4	-103.1
88a	4'-CF3	4'-SO2NH2	-112.9	-103.0	-102.7	-90.0	-88.8	-99.6	-119.0	-80.6	-109.8	-88.3	-118.9	-102.9	-111.3
89a	4'-COOH	4'-SO2NH2	-111.4	-101.5	-95.9	-82.7	-92.0	-104.0	-115.1	-66.2	-119.4	-85.3	-120.2	-95.6	-86.0
90a	4'-NMe2	4'-SO2NH2	-108.9	-108.5	-91.3	-77.2	-84.7	-98.6	-122.6	-72.5	-111.1	-106.4	-93.8	-96.6	-102.9

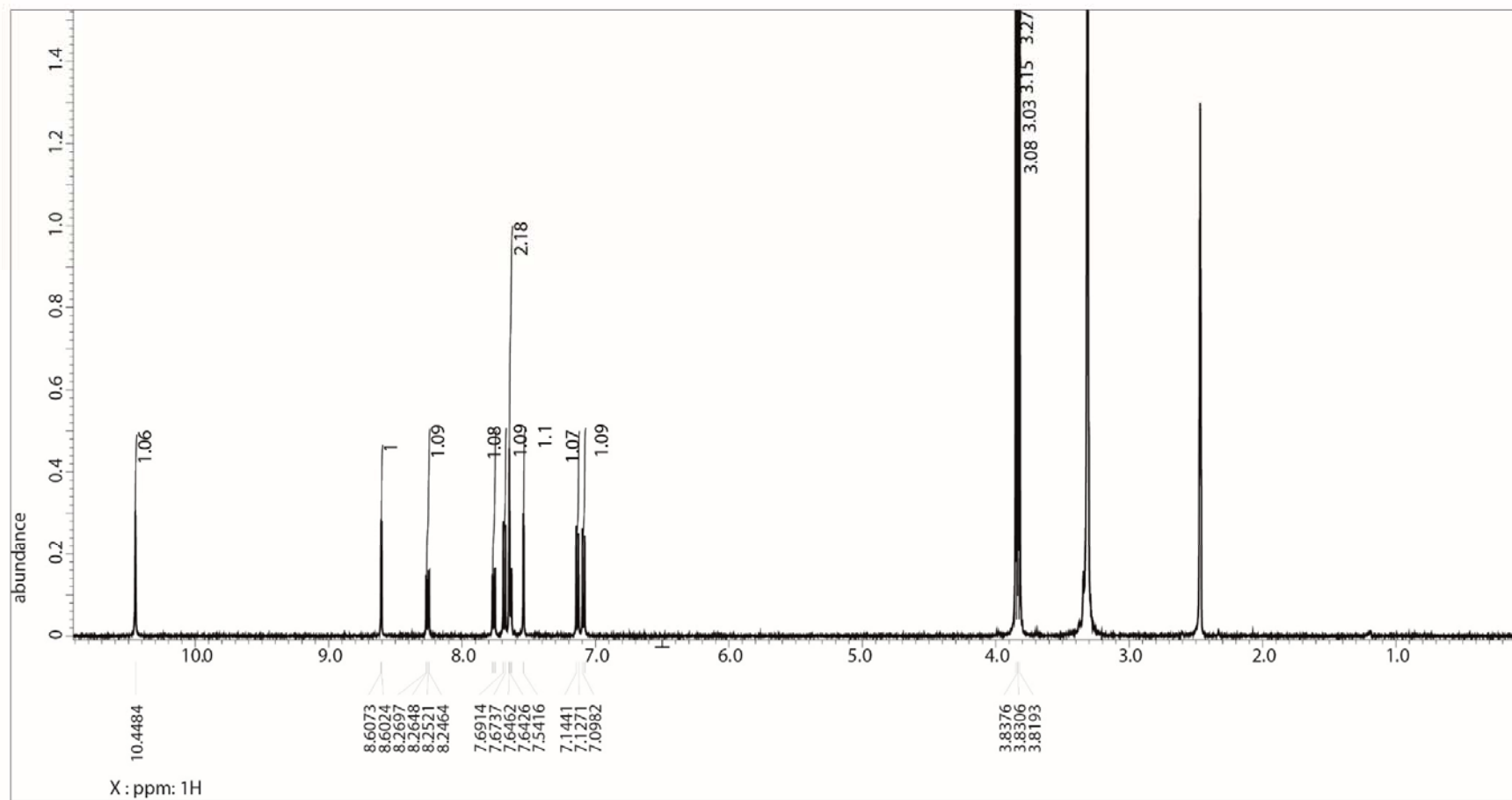
2. NMR spectra

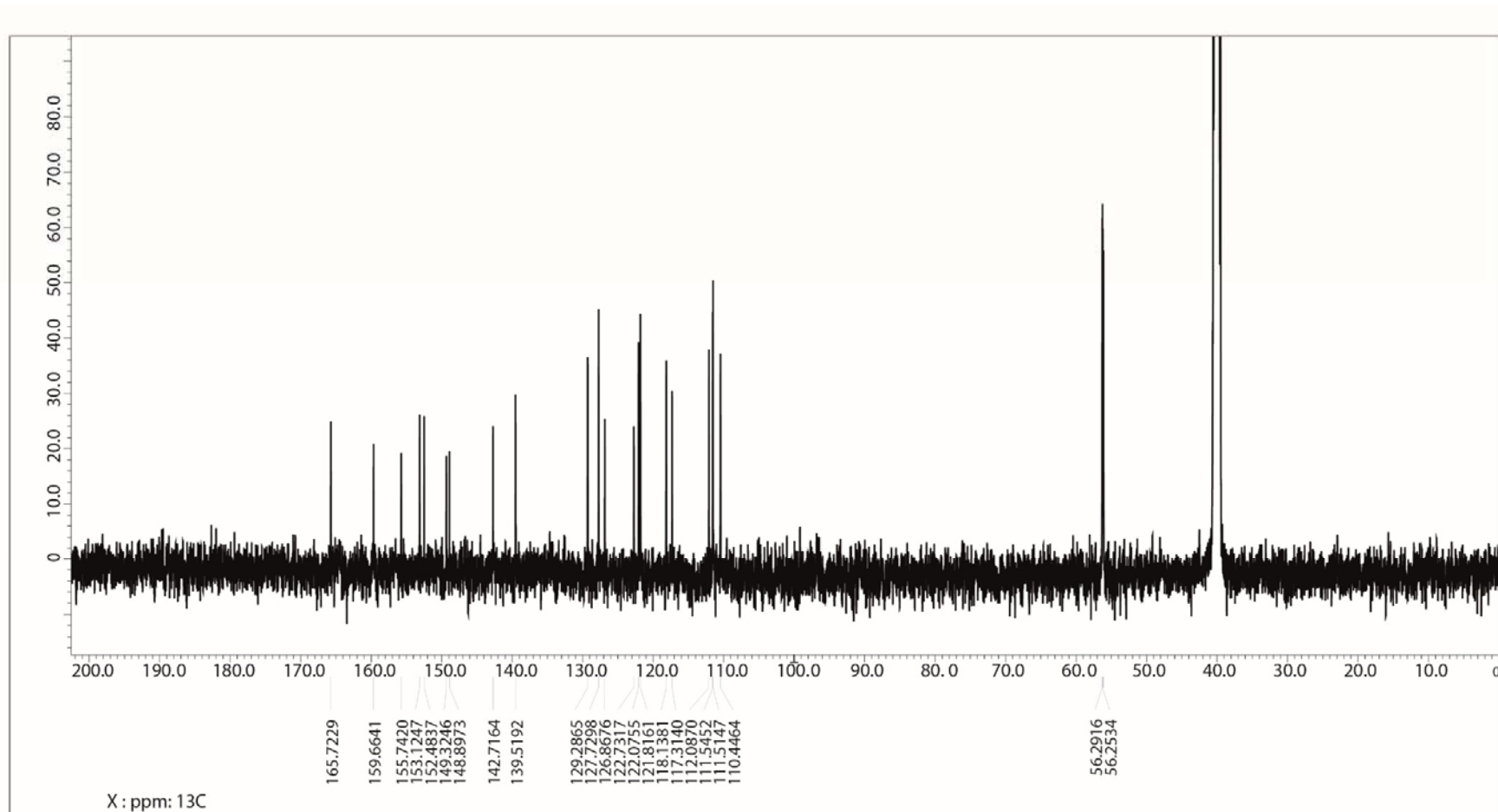


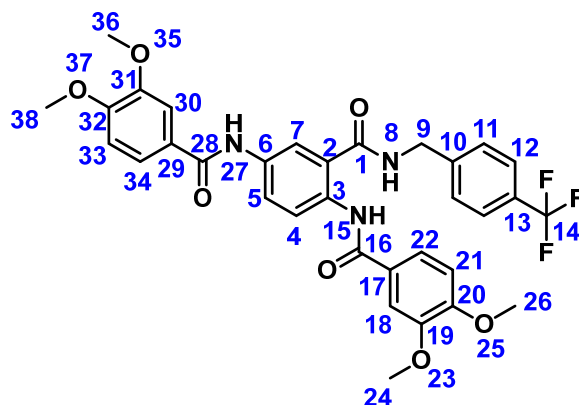
^1H NMR (DMSO- d_6 , 500 MHz) δ = 10.44 (1H, s, H11), 8.60 (1H, d, J = 2.7 Hz, H8), 8.24 (1H, dd, J = 2.7, 9.1 Hz, H6), 7.75 (1H, dd, J = 1.8, 8.7 Hz, H28), 7.68 (1H, d, J = 8.8 Hz, H5), 7.64 (1H, d, J = 1.8 Hz, H24), 7.62 (1H, dd, J = 2.1, 8.4 Hz, H18), 7.53 (1H, d, J = 2.1 Hz, H14), 7.12 (1H, d, J = 8.7 Hz, H27), 7.08 (1H, d, J = 8.4 Hz, H17), 3.85 (1H, s, H30), 3.84 (1H, s, H32), 3.83 (1H, s, H20), 3.81 (1H, s, H22).

^{13}C { ^1H } NMR (DMSO- d_6 , 125 MHz) δ = 165.72 (C12), 159.66 (C1), 155.74 (C3), 153.12 (C26), 152.48 (C16), 149.33 (C25), 148.89 (C15), 142.71 (C10), 139.51 (C7), 129.28 (C6), 127.72 (C5), 126.86 (C13), 122.73 (C23), 122.07 (C28), 121.81 (C18), 118.13 (C8), 117.31 (C9), 111.54 (C14), 111.51 (C17), 110.44 (C24), 56.29 (C30), 56.25 (C32), 56.18 (C20), 56.12 (C22).

^{15}N { ^1H } NMR (DMSO- d_6 , 50.69 MHz) δ = -211.6591 (N11).



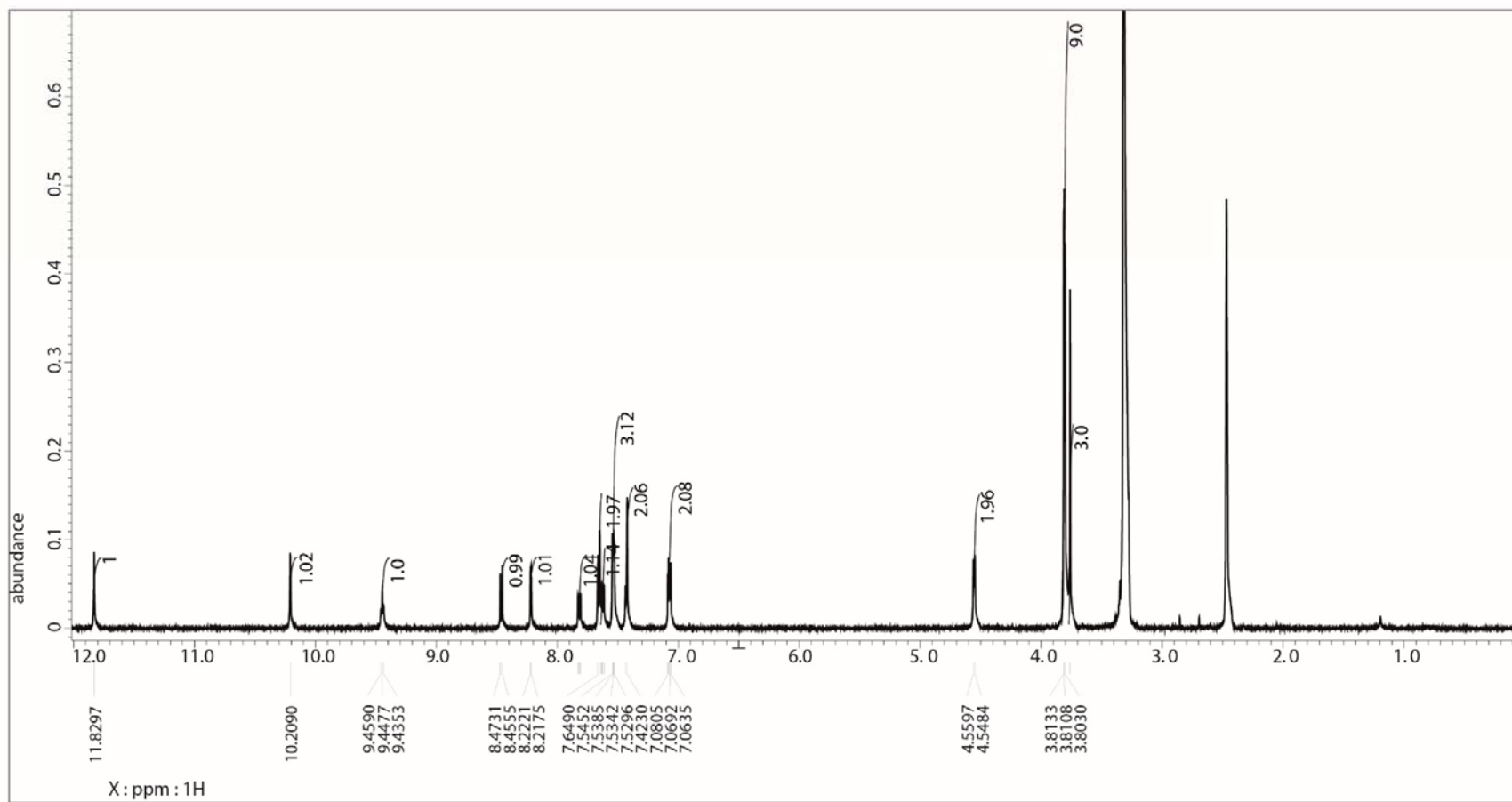


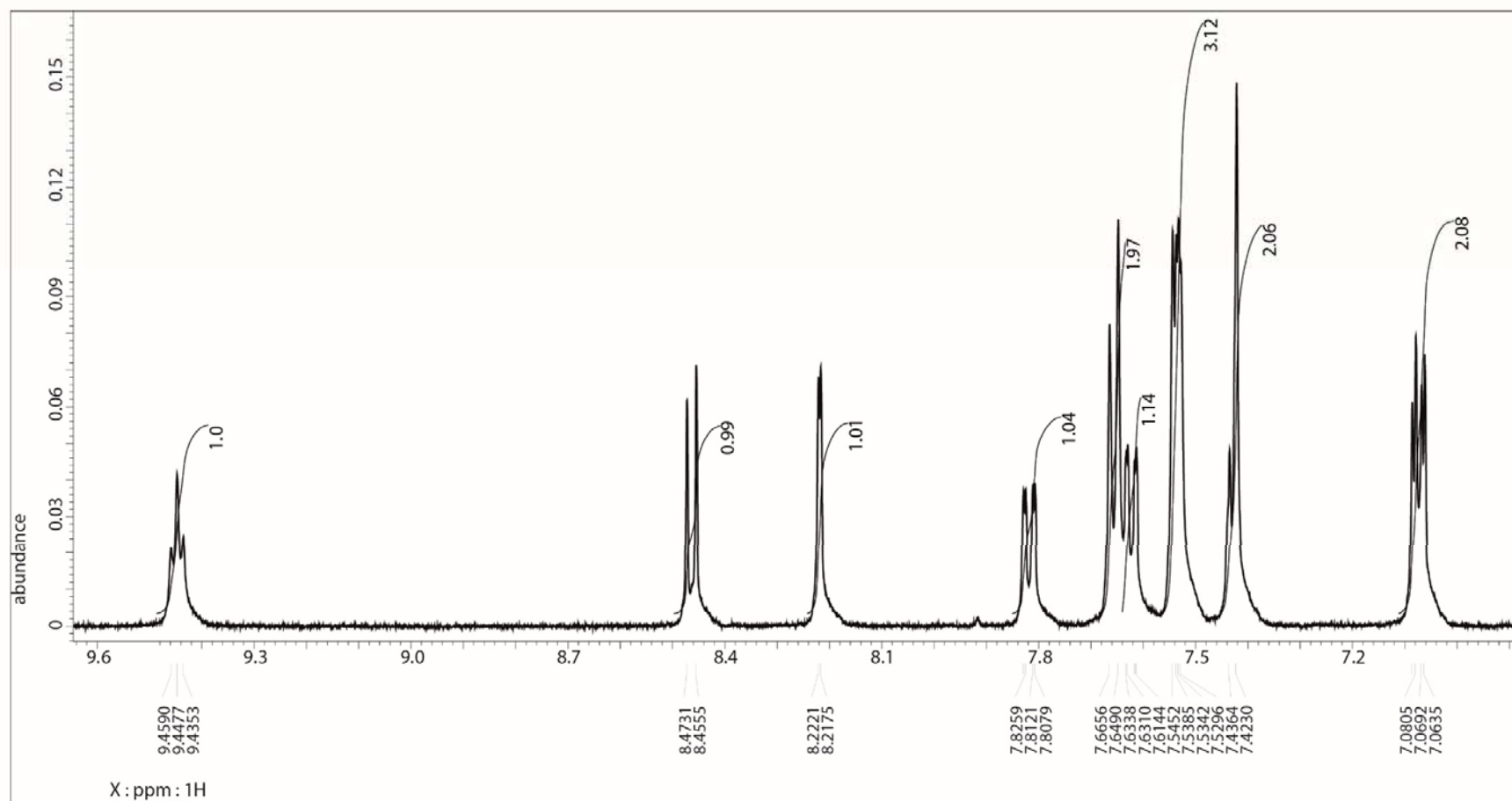


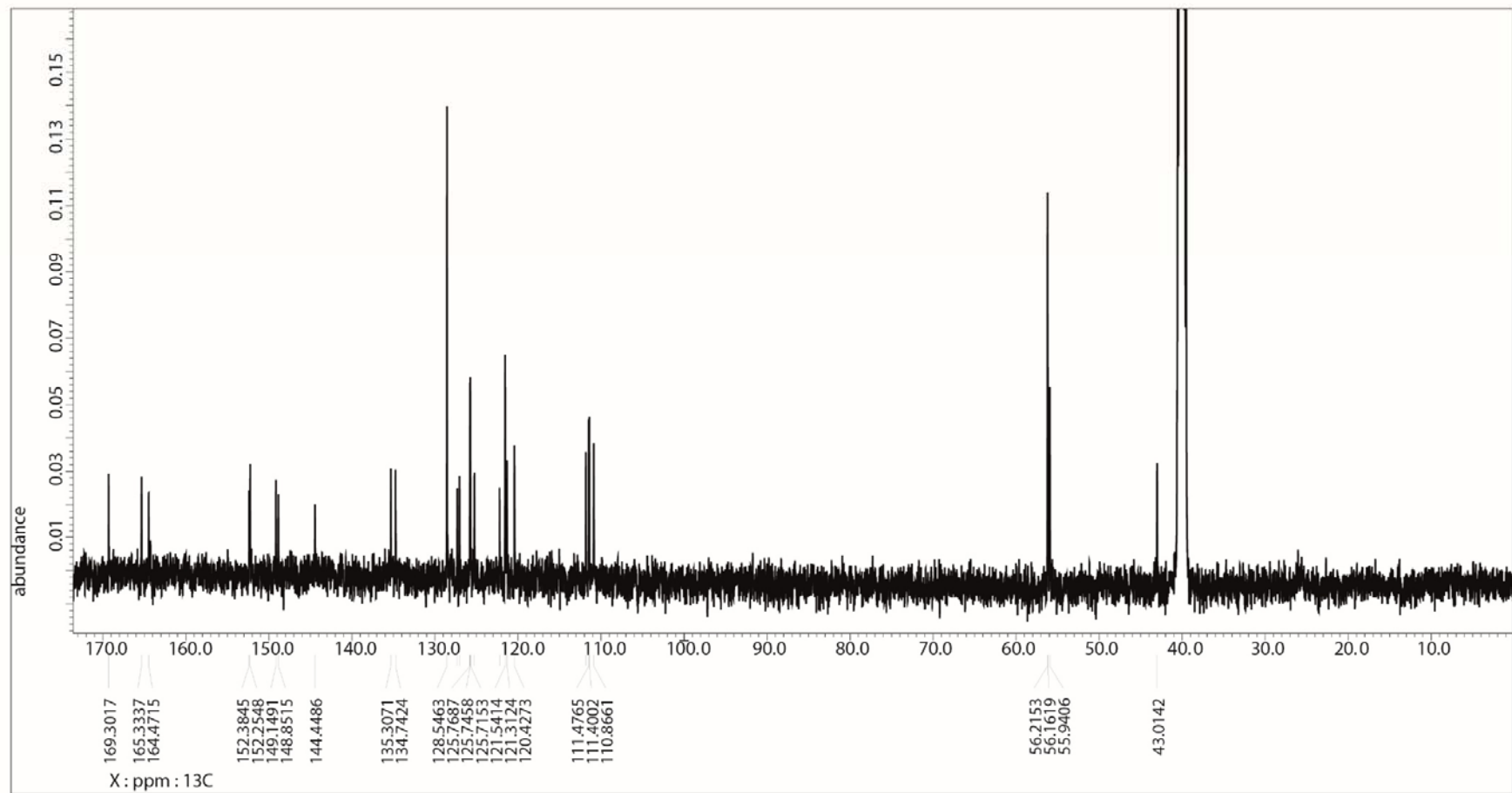
^1H NMR (DMSO- d_6 , 500 MHz) δ = 11.82 (1H, s, H15), 10.20 (1H, s, H27), 9.43 (1H, t, J = 5.9 Hz, H8), 8.45 (1H, d, J = 8.9 Hz, H4), 8.21 (1H, d, J = 2.2 Hz, H7), 7.80 (1H, dd, J = 2.2, 8.9 Hz, H5), 7.64 (2H, d, J = 8.3 Hz, H12), 7.61 (1H, d, J = 1.2, 8.3 Hz, H34), 7.53 (3H, m, H11, H30), 7.42 (2H, m, H18, H22), 7.069 (1H, d, J = 9.0 Hz, H21), 7.063 (1H, d, J = 8.3 Hz, H33), 4.54 (1H, d, J = 5.9 Hz, H9), 3.813 (3H, s, H38), 3.810 (3H, s, H36), 3.80 (3H, s, H26), 3.76 (3H, s, H24).

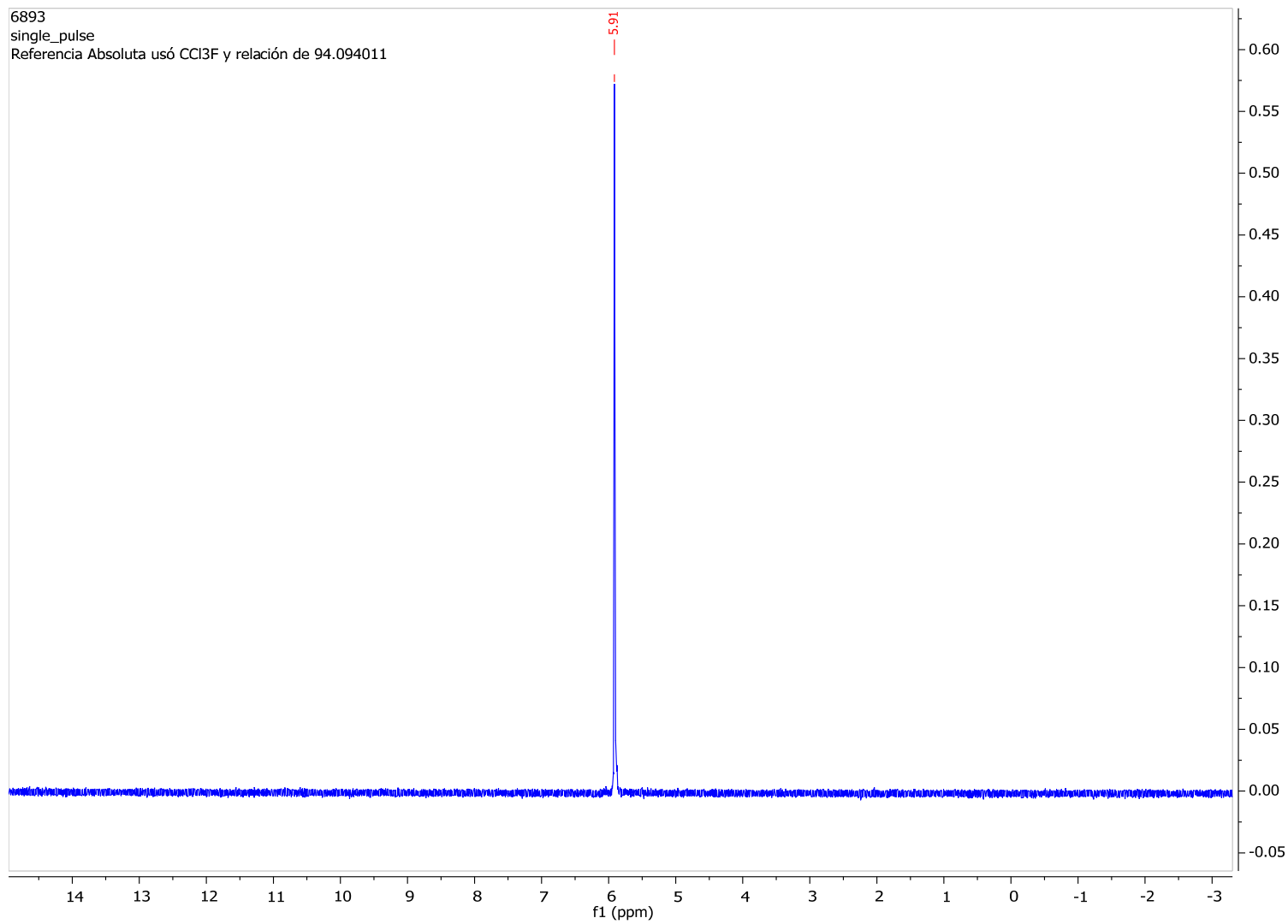
^{13}C $\{^1\text{H}\}$ NMR (DMSO- d_6 , 125 MHz) δ = 169.30 (C1), 165.33 (C16), 164.47 (C28), 152.38 (C20), 152.25 (C32), 149.14 (C19), 148.85 (C31), 144.44 (C10), 135.30 (C3), 134.74 (C6), 128.54 (11), 127.31 (C17), 127.23 (^{13}C $^2J_{\text{C,F}}$ = 31.0 Hz), 127.03 (C29), 125.45 (C12, $^3J_{\text{C,F}}$ = 2.9 Hz), 125.24 (C5), 125.23 (C14, $^1J_{\text{C,F}}$ = 252.3 Hz), 122.20 (C2), 121.54 (C4, C34), 121.31 (C7), 120.42 (C17), 111.82 (C33), 111.47 (C21), 111.40 (C30), 110.86 (C22), 56.21 (C38, C36), 56.16 (C26), 55.94 (C24), 43.01 (C9).

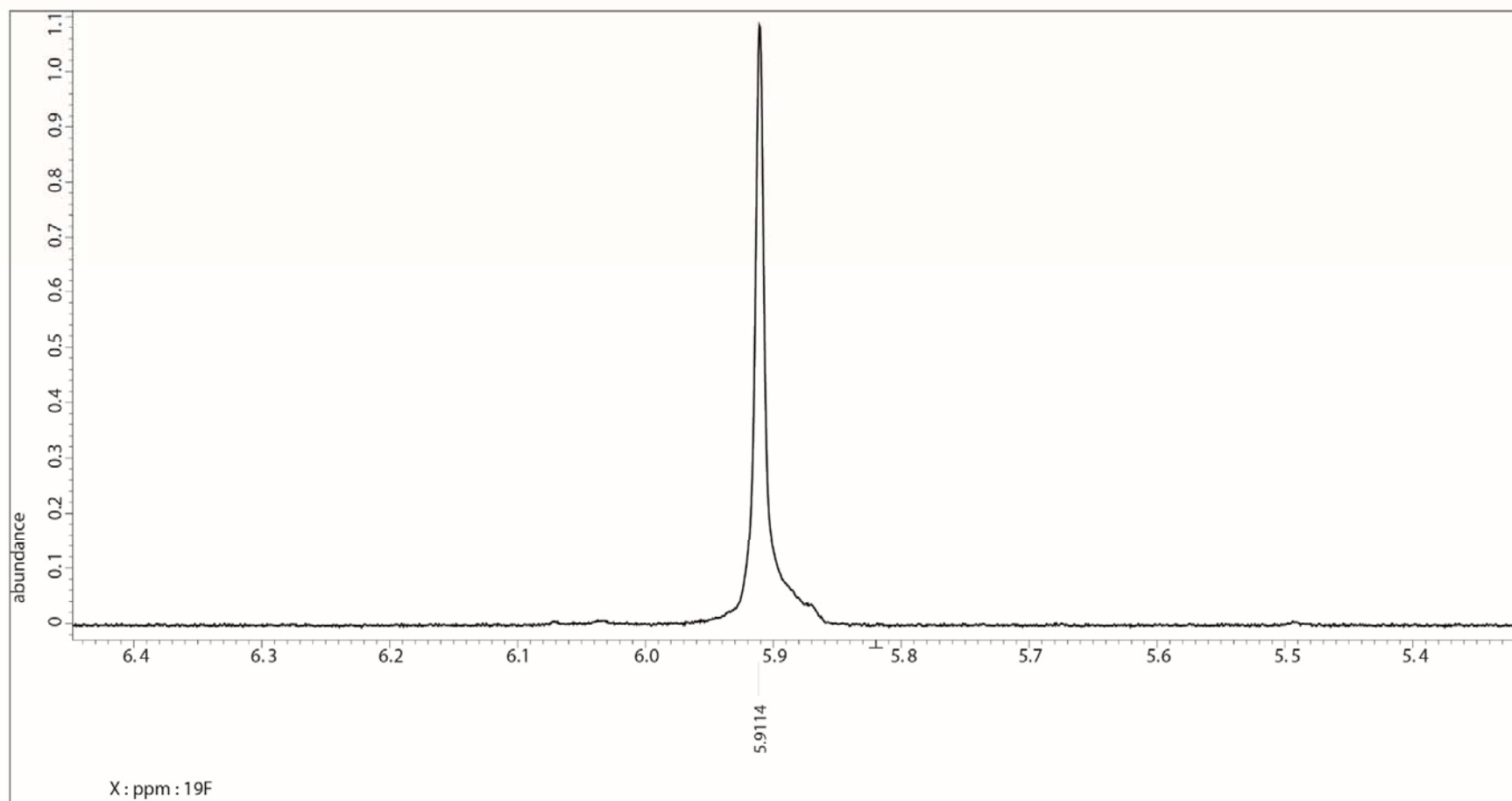
^{19}F $\{^1\text{H}\}$ NMR (DMSO- d_6 , 470.62 MHz) δ = 5.91.











Group	METABOLIC SYNDROME PARAMETERS (After 14 weeks)				
	Weight Change (mean±SD)	Blood Pressure (mean±SD)	Cholesterol (mean±SD)	Glucose (mean±SD)	Triacylglycerides (mean±SD)
CM (n=10)	161.0 ± 8.525	147.8 ± 9.176	2.1 ± 0.233	6.4 ± 0.686	2.1 ± 0.313
CM/D (n=10)	137.9 ± 6.454	120.0 ± 9.747 ^φ	2.0 ± 0.202	6.7 ± 0.649	2.1 ± 0.524
HFHF (n=10)	195.2 ± 15.700	197.0 ± 10.002 *	2.417 ± 0.369 *	8.0 ± 0.912 *	3.6 ± 0.715 *
HFHF/D (n=10)	178.5 ± 7.959	164.3 ± 9.759 *,\$	1.953 ± 0.140 \$	7.0 ± 0.588 \$	2.6 ± 0.676

Table S2. Effect after 14 days of compound **1b** on metabolic parameters associated to MetS (A) Blood Pressure (B) Cholesterol, (C) Glucose, (D) Triacylglycerides. After 14 days of treatment with compound **1b**, HFHF-M/D group have a statistically significant reduction of blood pressure, total cholesterol and glucose compared to the HFHF-M group. Also, HFHF-M/D group observed a non-statistically reduction of the triacylglycerides compared to the HFHF-M group but also non-statistical significant difference was observed to CM and CM/D groups. Data are presented as means ± Standard Deviation (SD). *Represents statistically significant differences between groups compared to their own control group (CM vs HFHF-M) (CM/D vs HFHF-M/D) (P < 0.05). ^φRepresents statistically significant differences between CM vs CM/D (P < 0.05). \$ Represents statistically significant differences between HFHF-M vs HFHF-M/D (P < 0.05).