Natural Resources for Human Health

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Original Research

View Article online

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Received 29 April 2026
Revised 20 May 2026
Accepted 20 July 2026
Available Online 28 August 2026

Edited by Shafi Ullah Khan

KEYWORDS:
Carduus pycnocephalus
Opioid
In vitro
Flavonoids
Molecular docking

Natr Resour Human Health 2026; 6 (4): 593–609
https://doi.org/10.53365/nrfhh/226136
eISSN: 2583-1194

Flavonoids from *Carduus pycnocephalus* as opioid and cannabinoid receptors ligands: An in silico and in vitro studies

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ABSTRACT: Promising binding affinity of *Carduus pycnocephalus* L. total methanol extract to opioid and cannabinoid receptors and bioassay-guided fractionation resulted in the isolation of four flavonoids: luteolin-7-*O*-glucoside (1), kaempferol-3-*O*-rhamnoside (2), luteolin (3), and kaempferol-3-*O*-glucoside (4). This is the first time reporting flavonoids 1 and 3 in *C. pycnocephalus*. The binding affinity of these flavonoids to opioid and cannabinoid receptor subtypes (δ, κ, μ, CB1, and CB2) was evaluated in vitro, complemented by a molecular docking study.

1. INTRODUCTION

The concept of "food-as-medicine" (FAM) is gaining momentum among healthcare professionals, insurance providers, startups, and both governmental and nongovernmental public health organizations. FAM involves incorporating specific foods into personal health strategies to help prevent or manage both acute and chronic illnesses (Defraeye et al., 2025). Moreover, bioactive compounds, which are nonnutritional components found in small amounts in foods, are currently under extensive investigation for their potential health benefits. *Carduus pycnocephalus* L., a wild edible species traditionally consumed (Marengo et al., 2017), is the focus of this study.

Genus *Carduus* (family Asteraceae) encompasses 91 species growing wild in the Mediterranean region, Asia, and East African mountains (Al-Shammari et al., 2015). In Egypt, this genus is represented by three species; *C. pycnocephalus* is an annual erect herb distributed throughout the Nile region, Sinai, and Mediterranean coastal strip (Al-Shammari et al., 2015; Boulos, 2002). Many biological activities were reported for genus *Carduus,* such as anti-inflammatory, anticancer, and antimicrobial (Esmaeili et al., 2005; Jordon-Thaden and Louda, 2003; Orhan et al., 2009). The presence of different categories of compounds mainly flavonoids has been reported in the literature (Al-Shammari et al., 2015; Amer et al., 1985; El-Lakany et al., 1997; Flamini et al., 2001). Plants of the genus *Carduus* are used in Chinese folk medicine for the treatment of various ailments such as colds, stomach aches, as well as rheumatism (Al-Shammari et al., 2015). C. *pycnocephalus* is traditionally a foraged wild green/vegetable in Mediterranean regions (notably Sardinia), eaten mainly as cooked young aerial parts and valued both as food and as a folk medicinal plant (Marengo et al., 2017).

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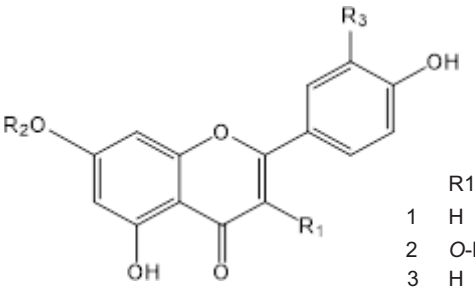
The opioid and cannabinoid receptors are G-protein-coupled receptors, which are further classified into subtypes. The opioid receptor includes three subtypes: Delta (δ), Kappa (κ), and Mu (μ) for the opioid receptors, and CB1 and CB2 subtypes for the cannabinoid receptors (Gao et al., 2011). Ligands for these receptors mainly function for pain control. Recent studies revealed that the opioid and cannabinoid receptor systems are altered during neuropathic pain. Therefore, these receptor agonists could be developed as powerful analgesics to control neuropathic pain. Plant-derived compounds activate opioid, serotonergic, and cannabinoid receptors, contributing to analgesia (Aly et al., 2025). Takeda and Sashide (Takeda and Sashide, 2025) have discussed the contribution of natural compounds as therapeutic agents for nociceptive and pathological pain. Polyphenolic compounds have been proven to have anti-inflammatory and anti-nociceptive effects in several pre-clinical in vitro and in vivo models of knee osteoarthritis (Gambari et al., 2022).

The article examines the pain-relieving properties of various extracts and active components from *C. pycnocephalus* to determine their potential as natural sources for developing new pharmaceutical agents. Here, we report the bioassay-guided fractionation and isolation of compounds from *C. pycnocephalus* based on the binding affinity to human opioid and cannabinoid receptors, adopting the radio-ligand binding assay. In addition, we conducted a detailed molecular modeling study and docking analysis to understand their binding mode and interaction mechanisms with the receptor.

2. RESULTS

2.1. Compounds identification

The air-dried aerial parts of *C. pycnocephalus* were extracted by percolation with MeOH. The total extract exhibited binding affinity for CB1, CB2, δ, and μ receptors. The methanolic extract was divided into three main fractions ($CHCl_3$, EtOAc, and H_2O), and these activities were re-evaluated. The ethyl acetate extract showed more than 40% binding affinity for opioid receptors (δ, μ). The chemical investigation of the EtOAc extract led to the isolation of four flavonoids: luteolin-7-*O*-glucoside (1), kaempferol-3-*O*-rhamnoside (2), luteolin (3), and kaempferol-3-*O*-glucoside (4). Compounds 1 and 3 are reported herein for the first time from *C. pycnocephalus*. Compounds 1–4 (Figure 1) were identified by comparing their spectroscopic data (Table 1) with those reported in the literature



	R1	R2	R3
1	H	Gluc	OH
2	*O*-Rham	H	H
3	H	H	OH
4	*O*-Gluc	H	H

Figure 1. Structures of compounds 1–4.

(Flamini et al., 2001; Fukunaga et al., 1988; Jayasinghe et al., 2004; Liu et al., 2009; Saito et al., 2012).

2.2. Radio-ligand binding for cannabinoid and opioid receptors subtypes

The most promising results are shown by kaempferol-3-*O*-rhamnoside, which exhibited good binding affinity of 65.8, 52.4, and 42.9% to μ, δ, and κ receptors, respectively (Table 2). Luteolin showed good binding affinity of 49.3, 48.6, and 60.6% for δ, κ, and μ receptors, respectively. Kaempferol-3-*O*-glucoside exhibited binding affinity of 46.7 and 53.2% for δ and μ receptors, respectively. Docking studies for Mu receptor crystal structure (PDB code: 4DKL, Manglik et al., 2012) were also investigated by Ruiu et al. (2015) and they concluded the effect of ring C substitution on the binding affinity to μ receptor. This could explain our assay results about the good binding affinity of kaempferol glycosides to that receptor.

2.3. Docking study

The validation step was conducted at the beginning of the applied molecular operating environment (MOE) program by redocking the co-crystallized ligand (BF0) within the binding pocket of the mu-opioid receptor. The validity of this process was corroborated by a low root-mean-square deviation (RMSD) value (RMSD = 1.68) and a symmetrical superimposition in orientation observed between the native (red) and redocked (green) co-crystallized poses, as illustrated in Table 3 (Ezz Eldin et al., 2022). Further, the binding modes for compounds (2–4), which emerged as the most promising candidates based on their biological assessments, as well as the standard drug and the docked BF0 antagonist, were studied in greater detail, as outlined in Tables 4, 5.

Table 1
^{13}C-NMR spectral data of compounds 1–4 (100 MHz).

Position	1	2	3	4
Solvent		DMSO-d_6		CD_3OD
C/No.		δ_C		
2	165.1	157.6	166.6	159.3
3	103.7	134.6	104.5	135.7
4	182.5	178.1	184.4	179.7
5	161.7	161.7	163.8	161.7
6	100.1	99.3	100.7	100.2
7	163.5	165.2	166.9	166.2
8	95.4	94.2	95.6	95.0
9	157.5	156.9	159.9	158.7
10	105.9	104.9	107.0	105.9
1′	121.9	120.9	124.2	123.0
2′	114.2	130.9	114.8	132.5
3′	146.4	115.8	147.6	116.3
4′	150.6	160.5	151.6	163.2
5′	116.7	115.8	117.4	116.3
6′	119.7	130.9	120.9	132.5
7′-Gluc		3-Rha		3-Gluc
1″	100.5	102.2		104.5
2″	73.7	70.8		75.9
3″	77.0	71.0		78.3
4″	70.2	71.6		71.6
5″	77.8	70.5		78.6
6″	61.2	17.9		62.88

Table 2
Percent inhibition of total extracts and isolated compounds of *C. pycnocephalus* for human cannabinoid and opioid receptors.

Extracts	Cannabinoid receptors (%)		Opioid receptors (%)		
	CB1	CB2	δ Delta	κ Kappa	μ Mu
Total	21.8	41.9	0.6	-	16.6
$CHCl_3$	-	5.5	50.8	33.7	9.3
EtOAc	-	-	48.5	21.8	42.9
Aqueous	-	-	12.2	17.9	35.9
Compounds					
1	-	-	11.8	38.9	20.1
2	23.6	-	52.4	42.9	65.8
3	17.2	10.0	49.3	48.6	60.6
4	26.6	25.3	46.7	33.9	53.2
Naloxone HCl#	-	-	44.06	56.28	70.28
AM630	48.89	30.35	-	-	-
AM251	94.09	5.92	-	-	-

AM630 (6-Iodopravadoline) is a compound that acts as a potent and selective inverse agonist for the cannabinoid receptor CB2. **AM251** is an inverse agonist at CB1 cannabinoid receptor. "-" indicates no activity.

The docked BF0 antagonist effectively occupies the deep pocket of the mu-opioid receptor, exhibiting a binding mode strikingly similar to that of the co-crystallized native ligand. It formed three H-bonds with Asp147 and Met151 amino acids at distances of 1.52 and 3.53 Å, respectively, and another H-pi bond with Val300 amino acid at 3.31 Å (Table 4). Moreover, its binding score and RMSD values were found to be −8.97 kcal/mol and 1.42, respectively.

The binding score of kaempferol-3-*O*-rhamnoside (2) was recorded as −7.31 kcal/mol with an RMSD value of 1.74. The hydroxyl group of the rhamnose unit formed one H-bond with the crucial amino acid Met151, besides two H-pi bonds being formed by the phenyl ring B with Trp293 and Tyr326 at 3.14 and 3.05 Å, respectively. Luteolin (3) has a binding interaction score of −6.52 kcal/mol with an RMSD value of 1.51. The hydroxyl group in ring B formed an H-bond with the crucial amino acid Asp147 at a distance of 2.26 Å, whereas the phenyl group of ring C formed an H-pi bond with Val 300 at a distance of 3.07 Å. Kaempferol-3-*O*-glucoside (4) binding score was −6.1 kcal/mol, and its RMSD was 1.51. Its ring B phenyl moiety formed an H-pi bond with Trp318 at a distance of 3.06 Å. In addition, the hydroxyl group of glucose at C-3 interacted with the essential amino acid Asp147 through a hydrogen bond at a distance of 2.11 Å.

3. DISCUSSION

As part of a screening program of Egyptian plants aimed at identifying new natural products with promising biological activities, the total extract of *C. pycnocephalus* demonstrated binding affinity toward CB1, CB2, and μ-opioid receptors. This affinity was improved by dividing the methanol extract into polarity-based fractions. The ethyl acetate extract showed more than 40% binding affinity for opioid receptors (δ, μ). The isolated compounds from the ethyl acetate fraction were evaluated for in vitro binding activity at human CB1, CB2, δ, κ, and μ receptors in concentrations of 22.3–34.9 μM, using a radio-ligand binding assay described previously (Leon et al., 2013; Ross et al., 1999). Many research articles have demonstrated the pharmacological activities of flavonoids, but few studies have investigated their opioid and cannabinoid receptors binding affinity assay (Ruiu et al., 2015).

Herein, it is observed that compounds (2–4) showed promising results in radio-ligand binding for μ opioid receptors and exhibited good binding interactions, and score in docking results as compared to Naloxone standard, which

Table 3
2D and 3D representation of native ligand BF0 (Red) and redocked BF0 (Green) superimposition at mu-opioid receptor with PDB: 4dkl for MOE program validation.

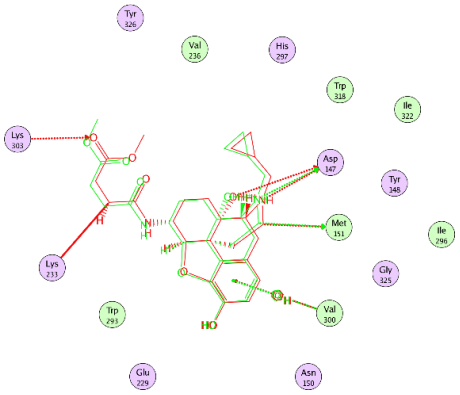
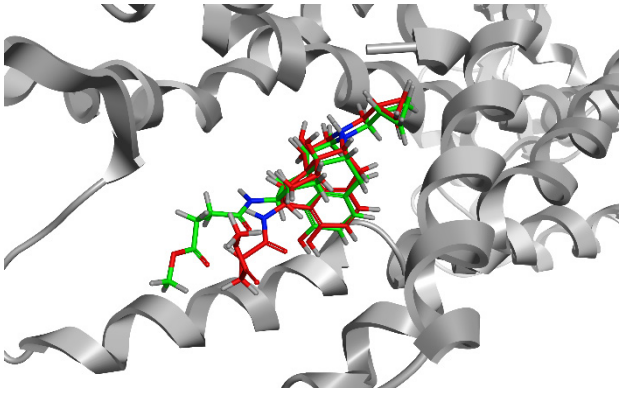
2D	3D
	

Table 4
Binding interaction scores, RMSD, amino acids, and bond types of the isolated compounds (2–4), standard, and co-crystal inside the mu-opioid receptor pocket.

Compounds	Score[a]	RMSD	Interactions	Bond type	Distance A°
BF0	−8.97	1.42	ASP147	H Donor	1.52
			MET151	H Donor	3.53
			VAL300	Pi-H	3.31
2	−7.31	1.74	MET151	H Donor	3.77
			TRP293	Pi-H	3.14
			TYR326	Pi-H	3.05
3	−6.52	1.51	ASP147	H Donor	2.26
			VAL300	Pi-H	3.07
4	−6.10	1.51	ASP147	H Donor	2.11
			TRP318	Pi-H	3.06
Naloxone	−5.91	1.53	VAL300	Pi-H	3.02

[a]S: The compound score inside the binding pocket (kcal/mol).

showed a binding score of −5.91 kcal/mol. The binding affinities observed for the tested flavonoids suggest a clear structure–activity relationship influenced by substitutions on the flavonoid scaffold. Kaempferol-3-*O*-rhamnoside exhibited the highest binding affinity across μ, δ, and κ opioid receptors. In comparison, kaempferol-3-*O*-glucoside showed moderate affinity, suggesting that the nature of the sugar moiety affects binding strength, possibly through differences in steric bulk or hydrogen-bonding capacity. According to Higgs et al.2013, flavonoid glycosides are unlikely to bind to mu-opioid receptors. In contrast, several natural aglycones were found to displace the binding of a specific mu-opioid agonist. These findings suggest that the presence of sugar moiety in flavonoid glycosides may interfere with their ability to interact with the receptor. This could demonstrate the highest binding affinity of luteolin (3) in comparison with its 7-*O*-glucoside (1) to mu-opioid receptors in our in vitro results. On the other hand, the docking results primarily provide a comparative and qualitative assessment of binding propensity rather than a quantitative predictor of pharmacological activity. Differences in solvation effects, receptor flexibility, pharmacokinetics, and metabolism can significantly influence in vivo efficacy and are not captured by docking scores. Therefore, while the results support the potential of compounds 2–4 as promising leads, they should be viewed as a preliminary indication that warrants further validation through molecular dynamics simulations and experimental in vivo studies. Our results indicate that these flavonoids hold promise as potential therapeutic analgesics, but upcoming in vivo studies are required to confirm their effectiveness.

Many animal studies have evaluated the analgesic potential of flavonoids. The in vivo antinociceptive activity of luteolin and its glycosides (Ramesh et al., 1998; Tatli et al., 2008) as well as kaempferol and its glycosides has been reported (Cárdenas et al., 1993; Parveen et al., 2007). However, further studies were required to better understand these mechanisms both in vivo and in vitro at the molecular level such as the participation of opioid receptor in their analgesic effects. It has been demonstrated that rutin, a flavonol glycoside, exhibits high binding potential to mu-opioid receptors, showing high binding affinity and interactions compared to morphinan antagonist (Tewari et al., 2021). A previous study has reported that phenolic fractions rich in flavonoids from sugarcane juice showed antinociceptive activity in the formalin test, and docking suggested that these phenolics can activate mu-opioid receptors (Gomes et al., 2023), but the individual

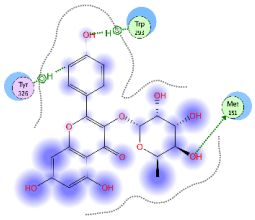
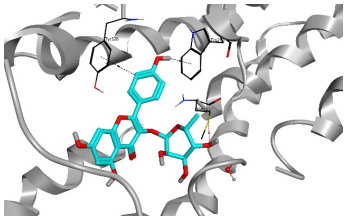
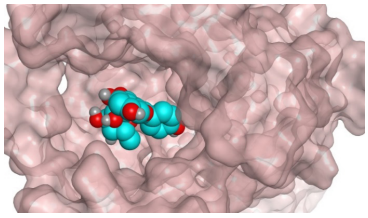
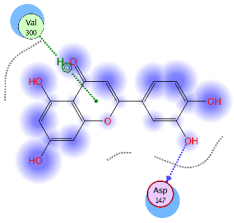
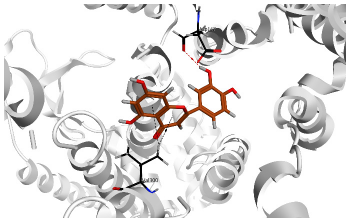
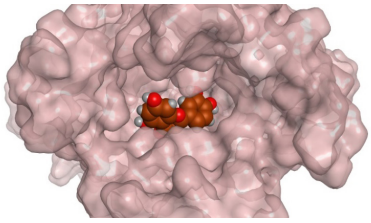
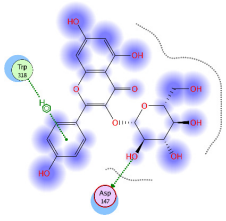
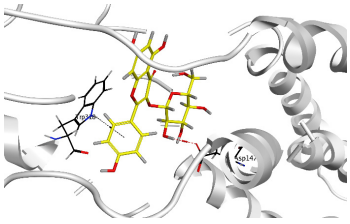
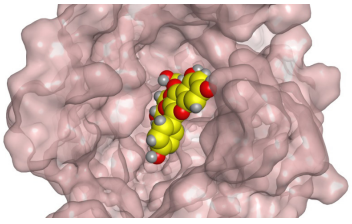
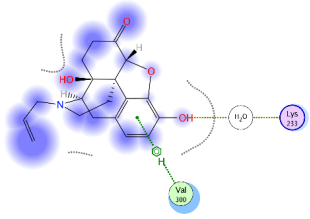
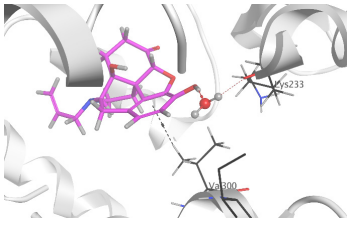
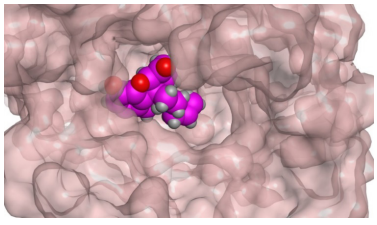
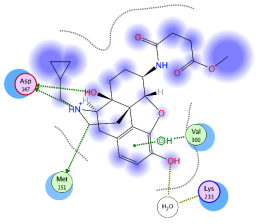
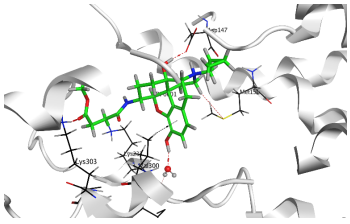
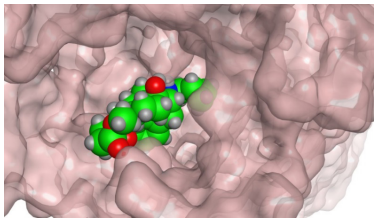
flavonoids and their glycosylation patterns were not systematically dissected. Similarly, selected flavonoids from *Maclura* (including Rutin, Morin, Kaempferol, and Quercetin) were studied primarily by computational docking and MD simulation to mu-opioid receptors, with in vivo analgesia as a functional read-out (Iqbal et al., 2025), but without direct mu-opioid receptors radioligand binding data for each flavonoid or explicit aglycone vs glycoside comparison. Our study, therefore, adds a more direct receptor-level comparison (radioligand binding) among specific aglycones and their glycosides, which have been largely missing. The anti-inflammatory and antinociceptive activities of *C. schimperi* extract and isolated compounds have been previously established (Wolde-Mariam et al., 2012), but this is the first report evaluating the analgesic potential of *C. pycnocephalus* ethyl acetate extract and its isolated compounds.

It is important to note that improving central nervous system (CNS) delivery of flavonoids is challenging because they face multiple sequential barriers: poor solubility, rapid phase-II metabolism, intestinal efflux, plasma protein binding, and blood–brain barrier (BBB) exclusion. There are many strategies to enhance BBB crossing including lipid nanoparticles that enhance solubility, protect from degradation, and increase brain levels of flavonoids (Correia et al., 2022), and intranasal delivery uses olfactory and trigeminal pathways to bypass the BBB (Wu et al., 2025).

3.1. Experimental

1. ***Plant material*:** Aerial parts of *C. pycnocephalus* were collected from a natural population growing in the north Delta coast, Gamasa City, Al-Dakahlia Province, Egypt (31°28′32.7″N 31°28′11″E) in April 2014 and authenticated by Dr. Yasser A. El-Amier, Botany Department, Ecology, Faculty of Science, Mansoura University, Mansoura 35516, Egypt. Voucher specimen (CP-DP-15) was kept in the Department of Pharmacognosy, Faculty of Pharmacy, Mansoura University. The fresh shoots were dried at room temperature, ground into a powder using a blender, and stored in plastic containers in the dark until further use.
2. ***General***: Spectroscopic experiments were recorded on a Varian Dual Broadband Probe 400 MHz spectrometer using DMSO-d6 or CD_3OD as solvents, with solvent peaks as the internal standard. Column chromatography (CC) was performed over flash silica gel (32-63μ, Dynamic Adsorbents Inc.) and reversed-phase C-18 (Polar bond, Baker, J.T.). Analytical TLC was performed on silica gel F254 aluminum sheet (20 × 20 cm, Fluka) or Silica 60 RP-18 F254S aluminum sheet (20 × 20 cm, Merck). The detection was performed at UV-254 nm. Spots were visualized by spraying with 1% Vanillin (Sigma) in conc. H_2SO_4-EtOH (10:90) followed by heating for 2 min.
3. ***Extraction*:** Powdered C. *pycnocephalus* (500 g) was macerated with MeOH (4 L × 3) at room temperature under sonication. The soluble part was evaporated to dryness under reduced pressure to afford a residue (22.5 g), suspended in distilled water and then fractionated with $CHCl_3$, EtOAc, and aqueous extract. The EtOAc fraction (800 mg) was applied to the RP_{18} column and eluted with H_2O followed by H_2O containing increasing proportions of MeOH, and finally with MeOH. Ten fractions were collected (1–10). Fraction 3 yielded compound 1 (60 mg). Fraction 4 was subjected to silica gel column elution with $CHCl_3$: MeOH: H_2O (70: 30: 3) to give compound 4 (5.9 mg). Fractions 6 and 8 were applied separately onto the top of the silica gel column and eluted with EtOAc: $CHCl_3$: MeOH: H_2O (60: 40: 40: 10) to afford compounds 2 (20.1 mg) and 3 (36.3 mg), respectively.
4. ***Radio-ligand binding for cannabinoid receptor subtypes*:** The CB1 and CB2 receptor radio-ligand binding assays of extracts and isolated compounds were performed following a previously reported method (Leon et al., 2013; Ross et al., 1999). Compounds (22–32 μM) were incubated with 0.5 nM [^{3}H]-CP 55, 940, a potent cannabinoid agonist with affinity to both subtypes, and 10 μg CB1 and CB2 membranes for 90 min in a 96-well plate. The reaction was terminated by rapid vacuum filtration through GF/C filters presoaked with 0.3% BSA using a PerkinElmer 96-well Unifilter (PerkinElmer Life Sciences Inc., Boston, MA, USA), followed by 10 washes with 50 mM Tris-EDTA buffer containing 0.2% BSA. Specific binding was defined as the difference between total and nonspecific binding.
5. ***Radio-ligand binding for opioid receptor subtypes*:** The binding affinities of extracts and isolated compounds were determined according to a previously reported method (Leon et al., 2013; Ross et al., 1999). Compounds (22–32 μM) were incubated with [^{3}H]-DAMGO (μ), [^{3}H]-U-69,593 (κ), or [^{3}H]-enkephalin (δ) for 60 min in a 96-well plate. The reaction was terminated by rapid vacuum filtration through GF/C filters presoaked with 0.3% BSA using a PerkinElmer 96-well Unifilter (PerkinElmer Life Sciences Inc., Boston, MA, USA), followed by 10 washes with 50 mM Tris-HCl buffer. Total binding is defined as binding in the presence of 1.0 % DMSO. Nonspecific binding is the binding observed in the presence of 10 μM of DAMGO (μ), nor-binaltorphimine (κ), or DPDPE (δ). Specific binding was defined as the difference between total and nonspecific binding.

Table 5
2D, 3D, and the positioning pictures of the isolated compounds (2–4), standard, and co-crystallized redocked ligand (BF0) representing the binding interactions. H-bonds were represented by red dashed lines while H-pi bonds were represented by black ones.

Compounds	2D interactions	3D interactions	3D Protein position
2			
3			
4			
Naloxone (standard drug)			
BF0 (co-crystalized ligand)			

3.2. In silico studies

3.2.1. Docking studies

The activity of isolated compounds against the mu-opioid receptor was thoroughly investigated using MOE software, version 2014.0901(Inc, 2014). Through molecular docking, we effectively elucidated the binding affinity and interactions of the isolated flavonoids with the mu-opioid receptor.

3.2.2. Preparation of the isolated flavonoids

The isolated flavonoids and the standard compound, Naloxone, were drawn using ChemDraw Ultra Software Version 12.0.2 (Cousins, 2005). Following the established protocols (Samra et al., 2021), these compounds were then prepared for docking studies. The three-dimensional structures of the studied molecules were constructed and prepared for docking through 3D protonation, assignment of

force field–based partial charges, and energy minimization. The flavonoids, along with Naloxone and the co-crystallized antagonist (BF0), were compiled into a single database (MDB file) and saved to facilitate the docking analysis with the Mu-opioid receptor.

3.2.3. Preparation of Mu-opioid receptor

The X-ray structure of the Mu-Opioid receptor was obtained from the Protein Data Bank (PDB entry: 4dkl) as documented by reference (Manglik et al., 2012). In preparation for docking studies, the target receptor underwent protonation, error correction, and energetic minimization, as reported in reference (Samra et al., 2023).

3.2.4. Validation of the MOE program

The co-crystallized ligand (BF0, bound in PDB: 4dkl) was docked into the active site to validate the MOE program. This validation process aimed to ascertain whether the MOE software could generate the binding interactions observed in the PDB, thus confirming its reliability and effectiveness in molecular modeling.

3.2.5. Docking the isolated flavonoids to the Mu-opioid receptor target

Using the same validation parameters, we confidently docked Naloxone, as well as the most promising flavonoids, into the active site of PDB ID 4dkl. Our analysis of the results focused on binding affinity and interactions. The docking procedure was executed meticulously, employing a robust docking protocol that adhered to the established methodologies (Ezz Eldin et al., 2022). Docking was performed using the Triangle Matcher algorithm for ligand placement, followed by refinement with a rigid receptor model. Binding affinities were evaluated using two scoring functions: GBVI/WSA ΔG and London ΔG. This approach enabled us to effectively investigate poses with the most accepted RMSD, scores, and interactions.

4. CONCLUSION

The present study demonstrates that *C. pycnocephalus* is a promising source of bioactive flavonoids with notable affinity toward cannabinoid and opioid receptors. Fractionation of the methanolic extract highlighted the ethyl acetate fraction as the most active, particularly against opioid receptors. Phytochemical investigation of this fraction led to the isolation and identification of four flavonoids, including luteolin-7-*O*-glucoside and luteolin, reported here for the first time from *C. pycnocephalus*. Among the isolated compounds, kaempferol-3-*O*-rhamnoside exhibited the highest binding affinity toward μ, δ, and κ opioid receptors, while luteolin and kaempferol-3-O-glucoside also showed considerable activity. The in vitro radio-ligand binding results were further supported by molecular docking studies, which revealed favorable binding interactions and scores for kaempferol glycosides and luteolin compared to the reference standard naloxone. Collectively, these findings suggest that flavonoids from *C. pycnocephalus*, particularly kaempferol derivatives, may contribute to the observed opioid receptor activity and represent promising lead compounds for the development of novel analgesic agents. Nevertheless, further in vivo pharmacological and toxicological studies are essential to validate their therapeutic potential and safety.

AUTHOR CONTRIBUTIONS

Conceptualization was done by A.A.Z.; methodology was looked into by A.A.Z., YA.E., and R.M.S.; formal analysis was the responsibility of A.A., A.A.Z., YA.E., and R.M.S; investigation was looked into by A.A., A.A.Z., YA.E., W.O., M.H.A., and R.M.S; data curation was the concern of A.A., A.A.Z., YA.E., and R.M.S.; writing—original draft preparation was done by A.A.Z., YA.E., and R.M.S.; writing—review and editing was done by A.A., A.A.Z., YA.E., and R.M.S.; funding acquisition was looked into by A.A., W.O., and M.H.A. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY

The authors declare that all the data supporting the findings of this study are contained within the paper.

FUNDING

The authors extend their appreciation to Prince Sattam bin Abdulaziz University for funding this research work through the project number: PSAU/2025/03/36371.

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SUPPLEMENTERY

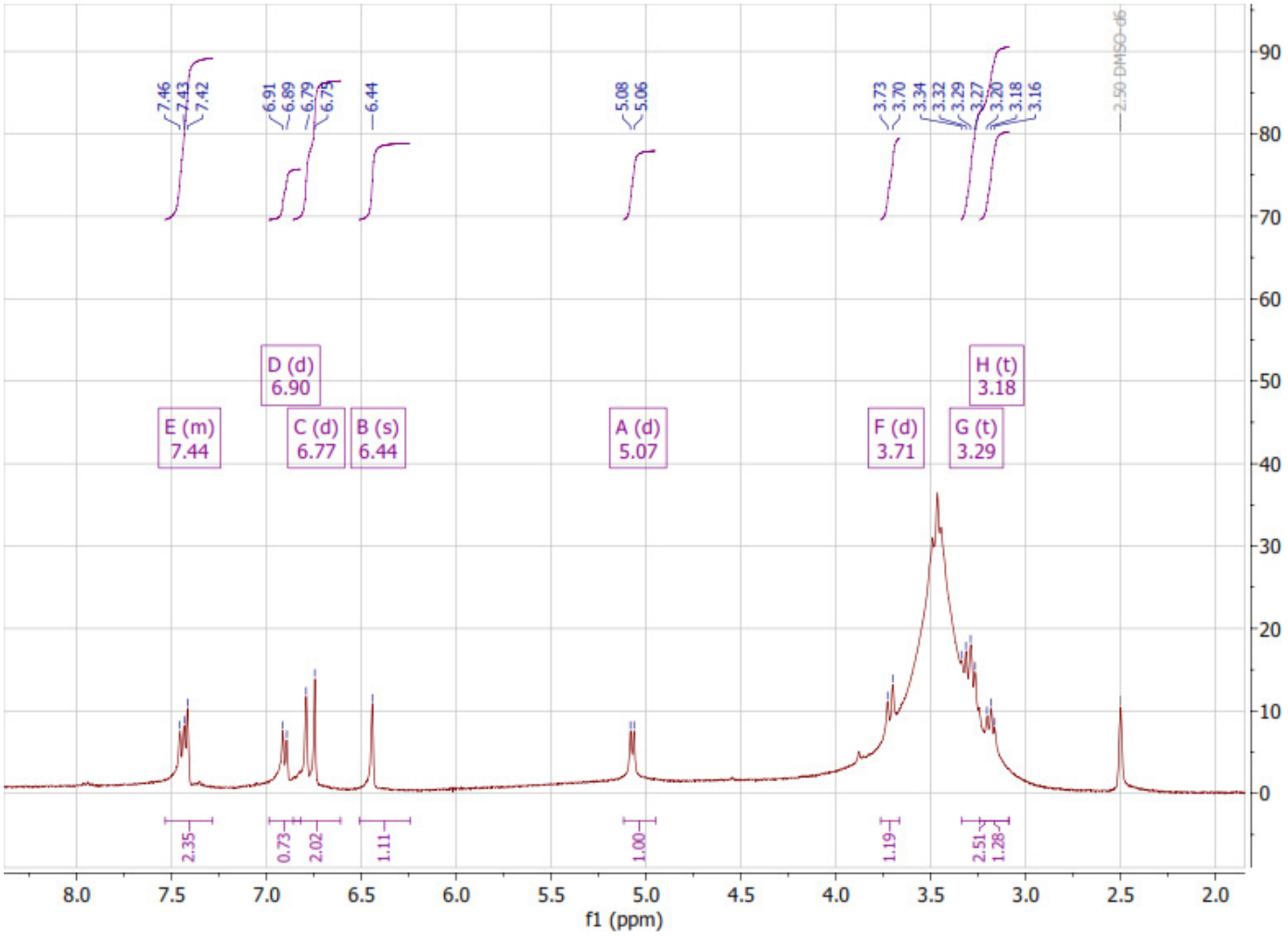

Figure S1. [1]H-NMR spectrum (DMSO-d_6, 400 MHz) of luteolin-7-*O*-glucoside (1).

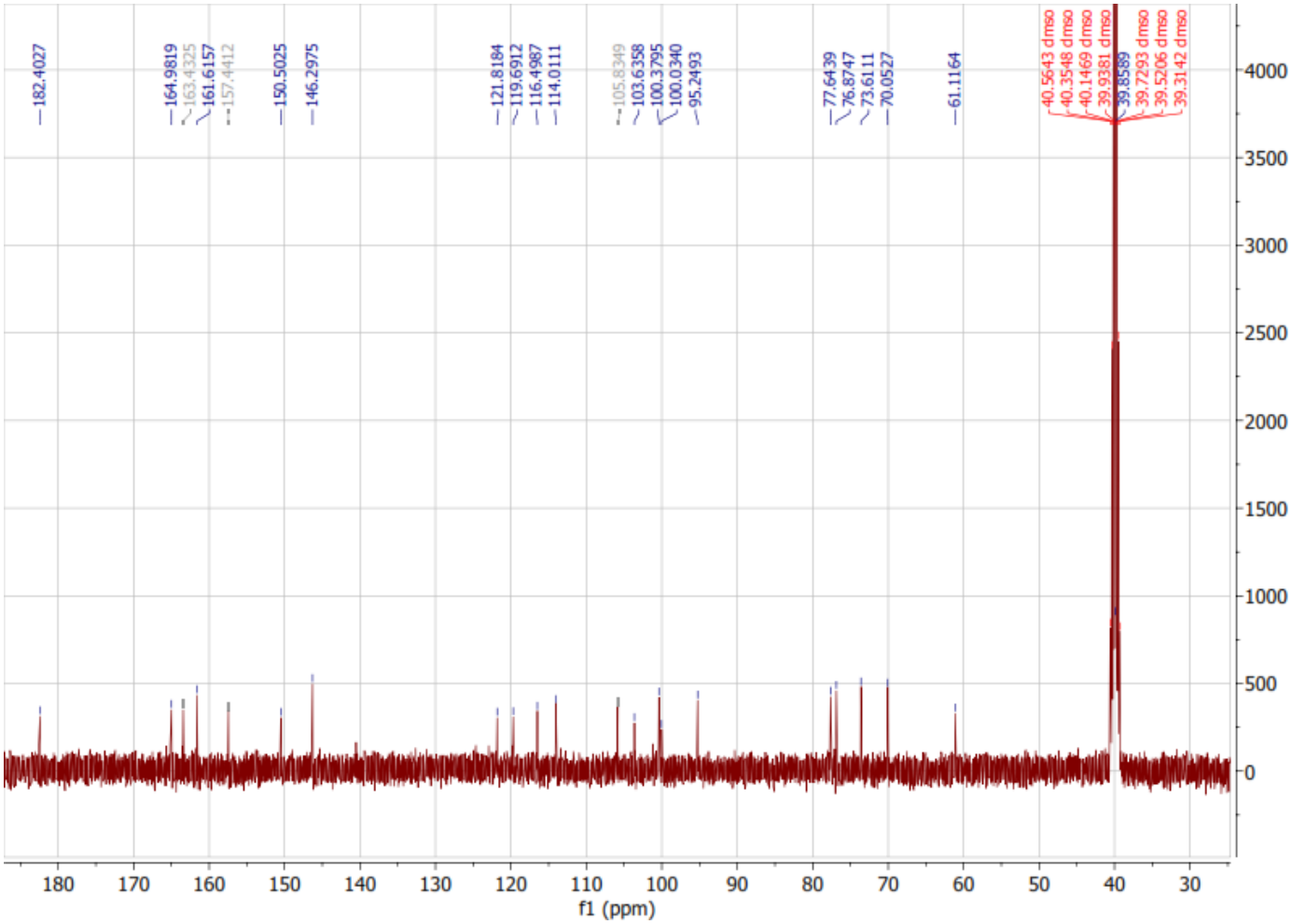

Figure S2. ^{13}C-NMR spectrum (DMSO-d_6, 100 MHz) of luteolin-7-*O*-glucoside (1).

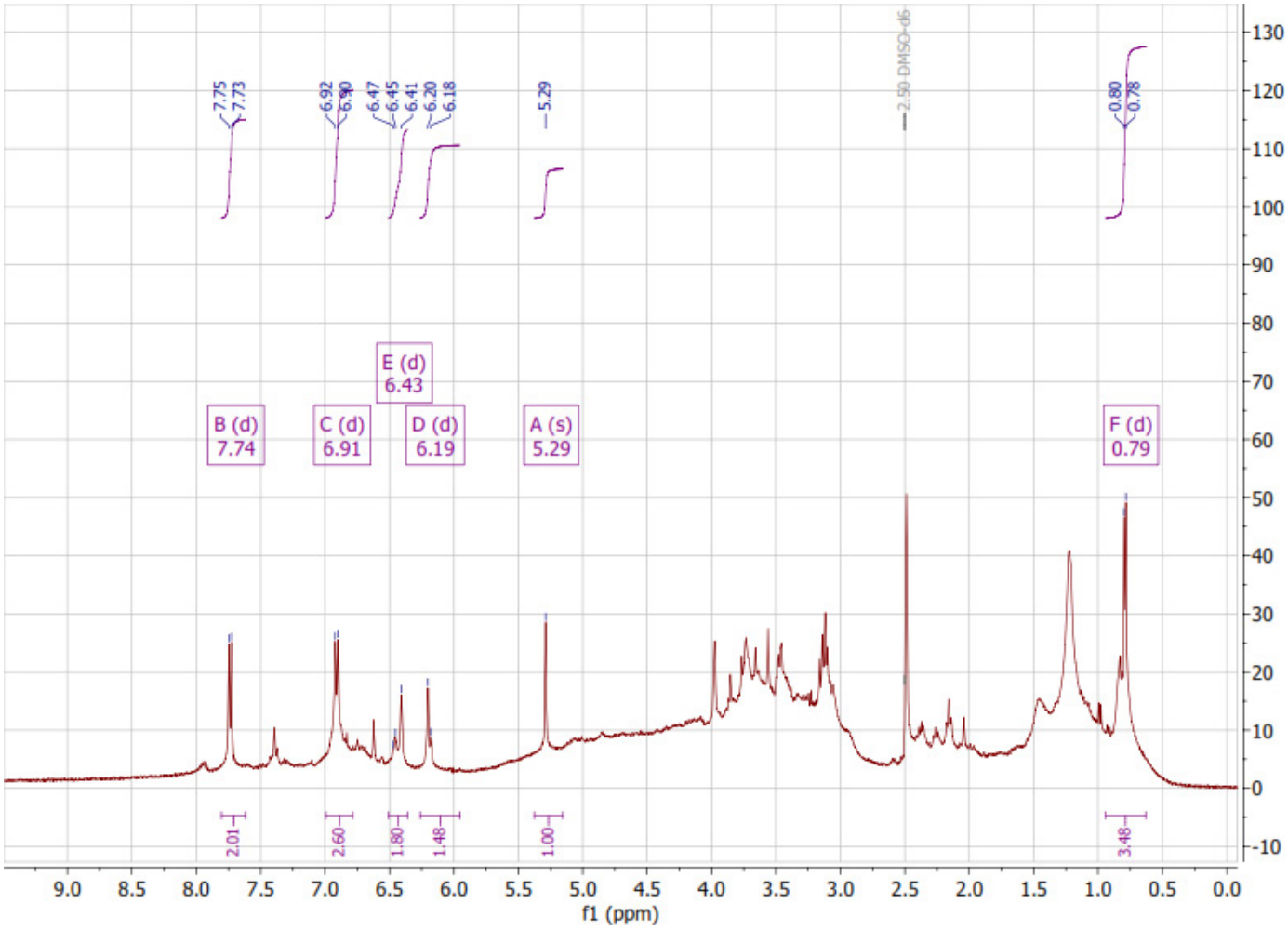

Figure S3. [1]H-NMR spectrum (DMSO-d_6, 400 MHz) of kaempferol-3-*O*-rhamnoside (2).

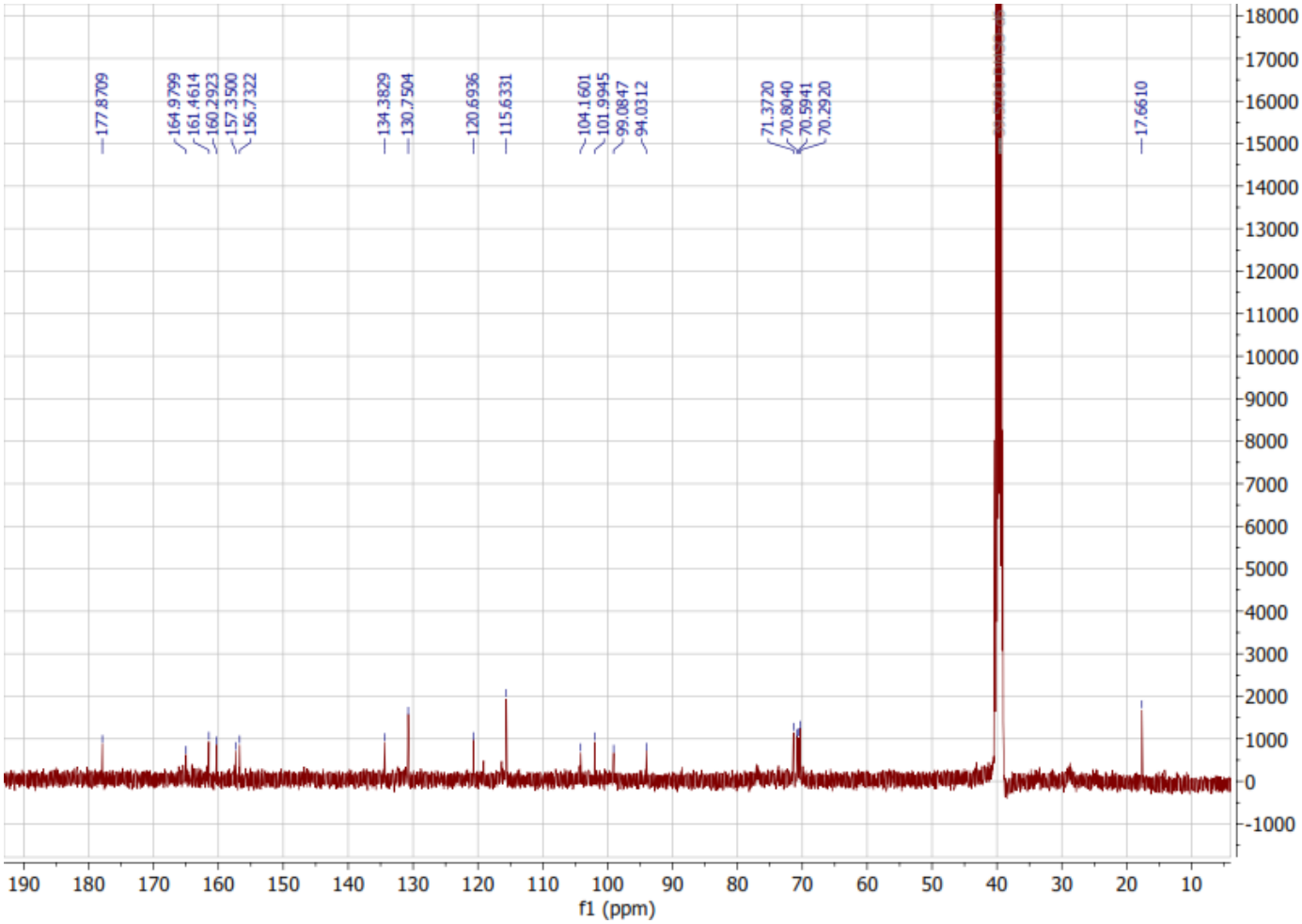

Figure S4. ^{13}C-NMR spectrum (DMSO-d_6, 100 MHz) of kaempferol-3-*O*-rhamnoside (2).

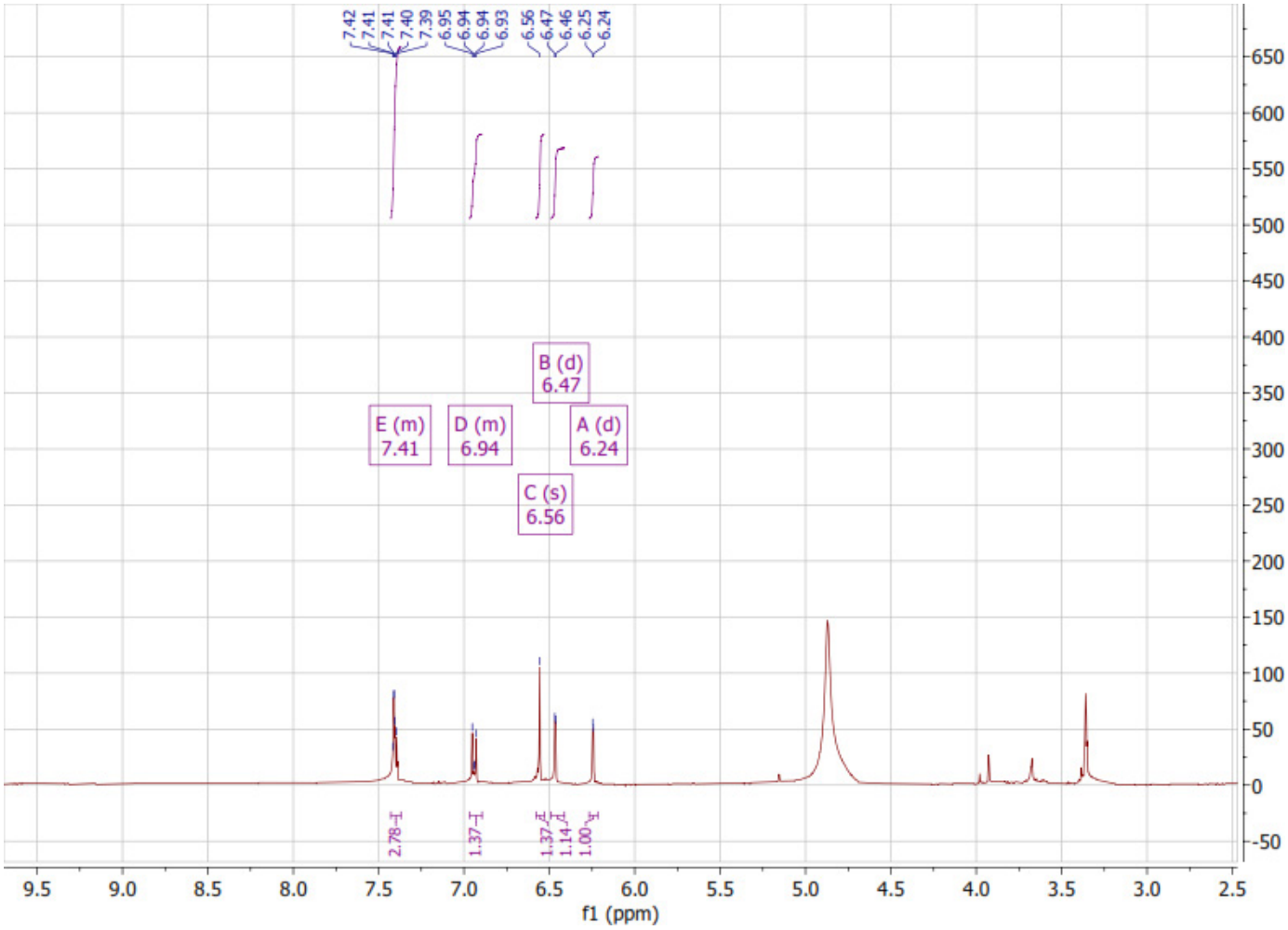

Figure S5. ^{1}H-NMR spectrum (DMSO-d_6, 400 MHz) of luteolin (3).

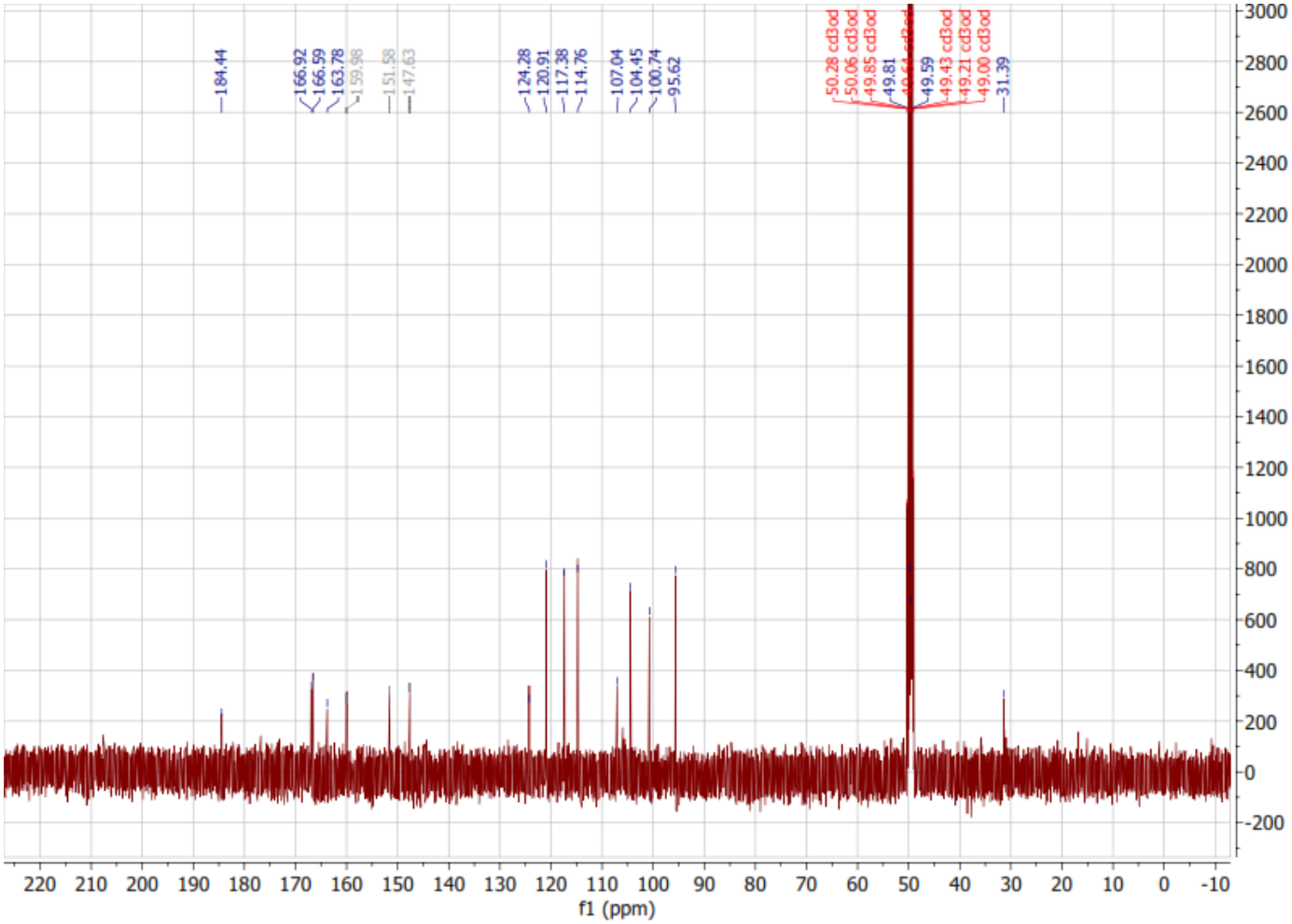

Figure S6. ^{13}C-NMR spectrum (DMSO-d_6, 100 MHz) of luteolin (3).

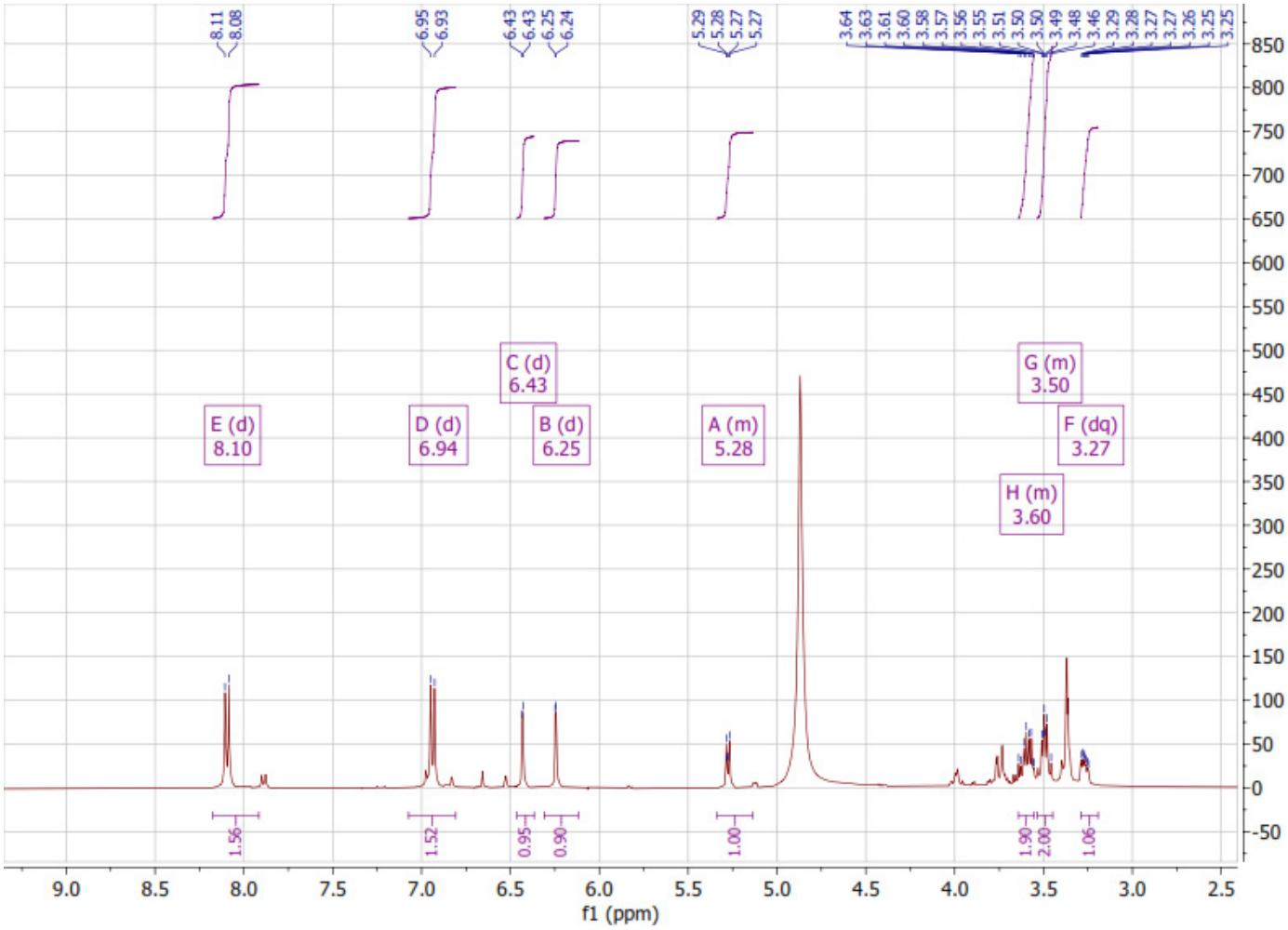

Figure S7. ^{1}H-NMR spectrum (CD_3OD, 400 MHz) of kaempferol-3-*O*-glucoside (4).

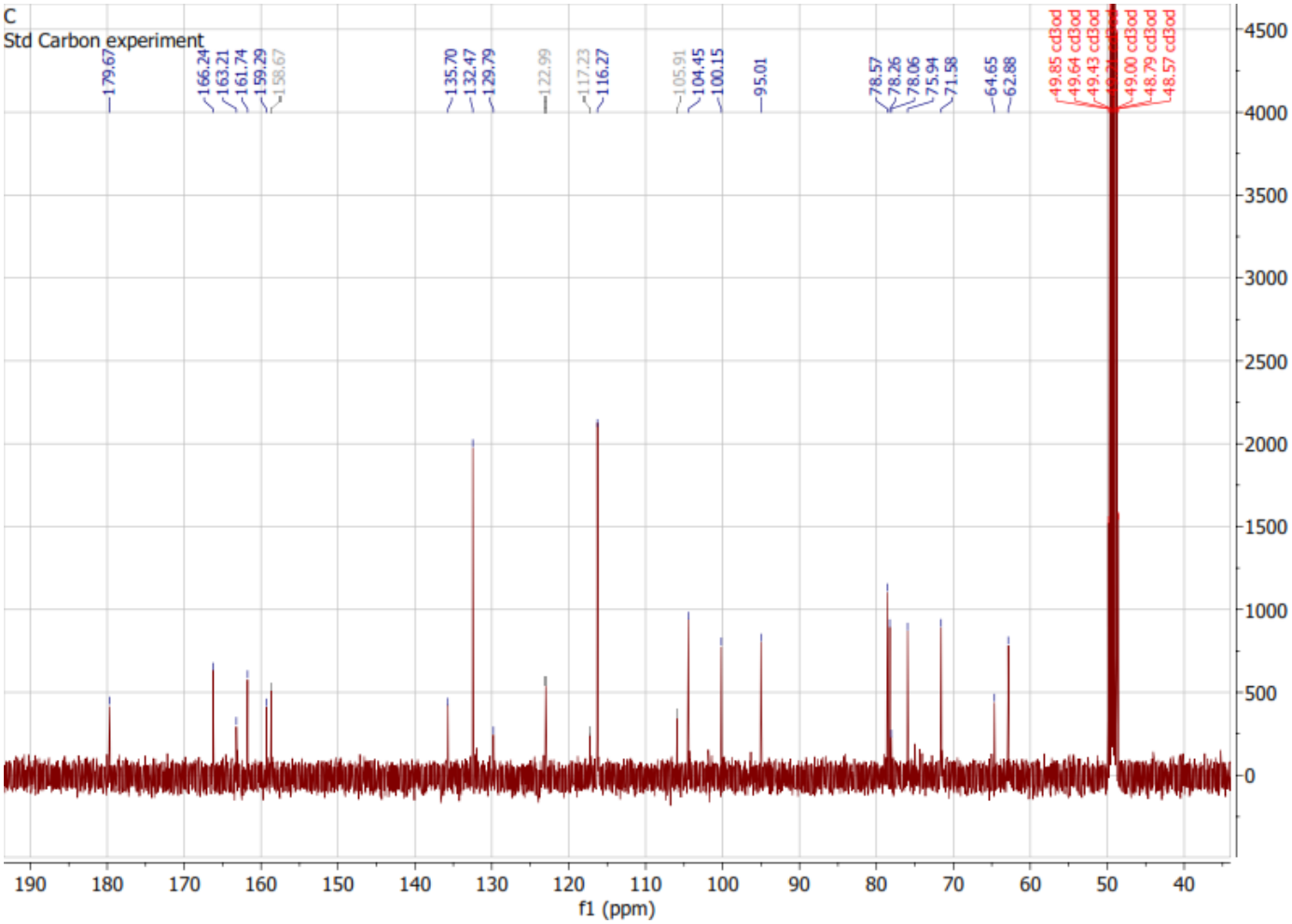

Figure S8. ^{13}C-NMR spectrum (CD_3OD, 100 MHz) of kaempferol-3-O-glucoside (4).