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Synthesis and biological evaluation of novel 2 (4`-hydroxynaphthyl) chromen-4-one as a CK2 inhibitor

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Protein kinase CK2 is a potential drug target for many diseases including cancer, inflammatory disorders, Alzheimer's disease, Parkinson's disease and viral infections. Significant efforts have been made for the discovery of potent inhibitors of this enzyme. Herein, we report on the synthesis, characterization, and biological evaluation of novel flavonoid compounds as CK2 inhibitors. The tested compounds were 2 (4`-hydroxynaphthyl) chromen-4-one which is a naphthyl backbone flavonoid with an IC_{50} value of 0.45±0.059 µM and 2(4-hydroxyphenyl)-4H-chromen-4-one a phenyl based derivative with an IC_{50} value of 0.33±0.048 µM. Cell viability was tested using MCF-7 cells. Both compounds were able to reduce the cell viability around 50 % in concentration of 100 µM after 48 h. Molecular modeling studies were performed to understand the binding mode of both compounds.

1. Introduction

Casein kinase 2, CK2, a heterotetrameric holoenzyme, is a ubiquitously expressed serine/threonine protein kinase in mammalian cells. CK2 enhances cancer phenotype by blocking apoptosis or stimulating cell growth. Abnormal high levels of this enzyme were detected in several types of cancer including breast, lung, and colorectal, thus, inhibition of this kinase can induce the physiological process of apoptosis, leading to tumor cell death. CK2 is now considered as an important drug target for cancer therapy, and quite a number of CK2 inhibitors from different chemical classes has been developed, such as anthraquinone/xanthenone, benzofuran derivatives, indenoindoles, coumarins and flavonoids (Cozza et al. 2012; Alchab et al. 2015; Haidar et al. 2015; Cozza and Pinna 2016; Haidar et al. 2017). More than 4000 compounds belonging to the group of natural botanic flavonoids are known so far (Ren et al. 2003). These compounds have many biological effects, such as, antioxidative, anti-mutagenic, anti-inflammatory, and antiviral properties (Patel et al. 2007). Many studies have demonstrated the anticancer effect of the flavonoids both *in vitro* and *in vivo*. Some flavonoids or their derivatives were proven to be active CK2 inhibitors. Fig. 1 presents the chemical structures of some known CK2 inhibitors with flavonoid structure. Different chemical methods were applied to synthesize flavonoids, among them the Baker-Venkatraman rearrangement, oxidative cyclization of 2-hydroxy chalcones (Cabrera et al. 2007; Thejan 2011), or hydrolysis of flavylium salts (Dorofeenko et al. 1977; Yakovenko et al. 1981; Golub et al. 2013). Flavylium salts can be prepared by aldol condensation of 2`-hydroxyacetophenone and benzaldehyde derivatives in the presence of tri-ethyl orthoformate and perchloric acid (Dorofeenko et al. 1977; Yakovenko et al. 1981; Golub et al. 2013). In this work we were able to prepare 4`-hydroxyflavonoid derivatives with naphthalene backbones instead of benzene, using 4-hydroxynaphthalin-1-carbaldehyde as starting material. This was based on the assumption that the extra aromatic ring might enhance the affinity to the hydrophobic pocket in the active site of CK2 according to the fact that the aromatic and/or apolar portions of CK2 inhibitors are responsible for the major interactions with the active site of the enzyme. The phenyl based analog was resynthesized for comparison since it was never tested as CK2 inhibitor before. Here, we describe the synthesis and characterization as well

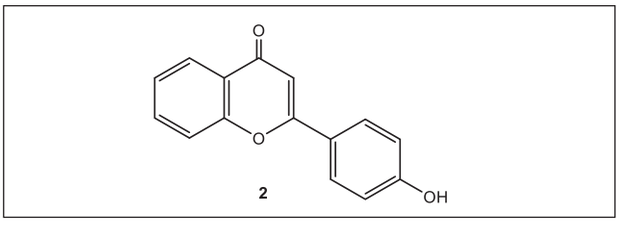


Fig. 2: Chemical structure of compound **2**

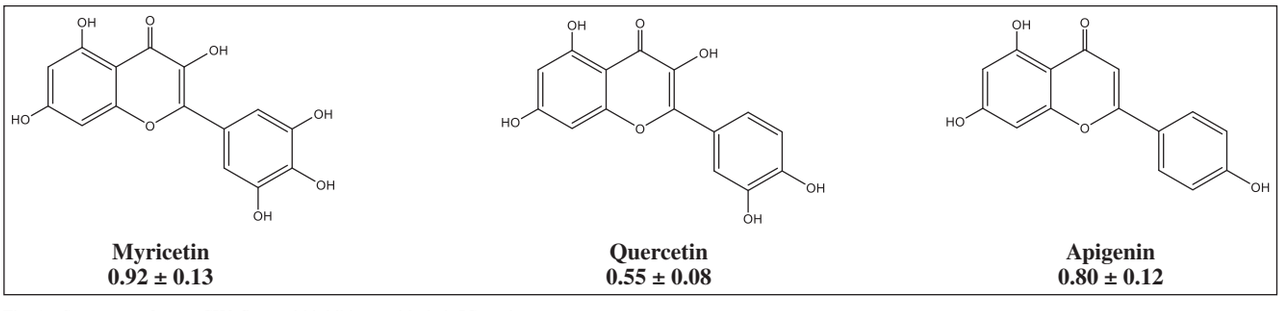
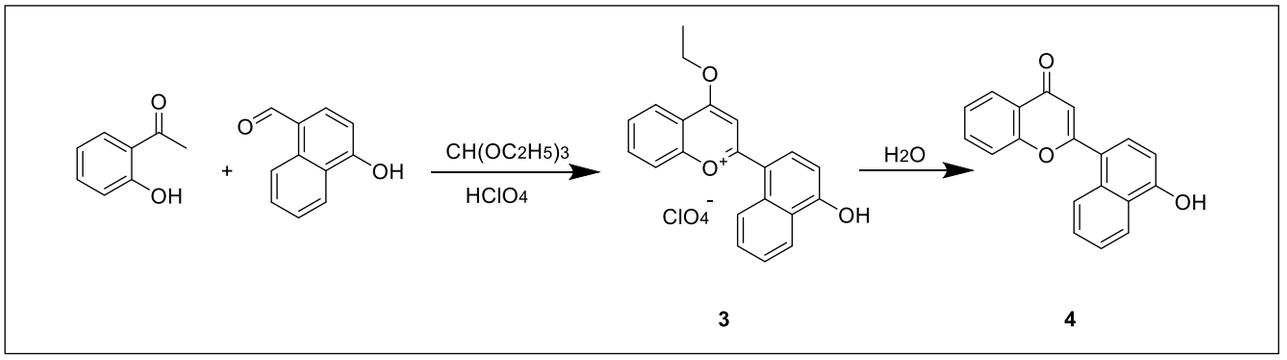


Fig. 1: Structures of some CK2 flavonoid inhibitors with their IC_{50} values



Scheme: Synthesis pathway to compound **4**: 2 (4` hydroxynaphthyl) chromen-4-one.

as the biological evaluation of novel flavonoid derivatives as CK2 inhibitors, together with molecular modeling study to illustrate their binding mode to the active site; also, our recently developed structure based pharmacophore was used to evaluate the results.

2. Investigations, results and discussion

2.1. Synthesis

A two-steps synthesis procedure was applied to synthesize compound **4**, analogues to the known compound **2** which was resynthesized to evaluate it activity against CK2. The first step was an aldol condensation in acidic media between 2`-hydroxy-acetophenone and aromatic aldehydes, in the presence of triethyl orthoformate to prepare flavylium salts. The salt undergoes hydrolysis in the second step to produce flavonoid derivatives. The aromatic aldehydes used in this study are 4`-hydroxybenzaldehyde and 4` hydroxy 1-naphthaldehyde in order to prepare compounds **2** and **4**, respectively. Figure 2 presents the chemical structures of compound **2** while the scheme presents the synthesis pathway to compounds **4**.

2.2. Inhibition of human protein kinase CK2

The new synthesized compound (4`-hydroxynaphthyl) chromen-4-one **(4)** was tested for its inhibitory activity towards the human CK2 holoenzyme and compared with the activity of compound **2** following the procedure described earlier (Olgen et al. 2007). It is important to mention that compound **2** is a commercially available compound which was to the best of our knowledge never tested as CK2 inhibitor. The synthetic peptide RRRDDDSDDD was used as substrate, which is reported to be most efficiently phosphorylated by CK2. The purity of the CK2 holoenzyme was superior to 99 %. For initial testing, inhibition was determined at inhibitor concentrations of 10 µM in DMSO as solvent. The reaction with pure solvent without inhibitor was used as positive control and set to 0% inhibition. Reactions without CK2 were used as negative control and were taken as 100% inhibition, both compounds showed more than 80% inhibition in this initial test. IC_{50} values were determined by measuring CK2 inhibition at eight different concentrations ranging from 0.001 to 100 µM in appropriate intervals and calculated from the resulting dose-response curve (Gratz et al. 2010). The IC_{50} value of compound **4** turned out to be 0.45±0.059 µM, while the IC_{50} value of compound **2** was 0.33±0.048 µM. However, the difference between the IC_{50} values of both compounds was statistically not significant ($P > 0.05$). Extending the structure of **2** with an extra aromatic ring did not affect the activity considerably. As a control the well-known inhibitor of CK2, emodin (Fig. 3) was subjected to the same test and showed an IC_{50} value of 0.58±0.05 µM. The three compounds presented in Fig. 1 namely: myricetin, quercetin, and apigenin were not tested by us, for that reason we cannot compare their activity with the activity of our compounds correctly, even though compounds **2** and **4** seems to be in the same range of activity.

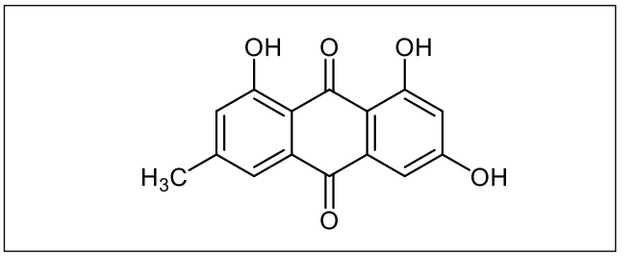


Fig. 3: Chemical structure of the known CK2 inhibitor emodin

2. 3. Effect of CK2 inhibitors 2 and 4 on cell proliferation

Cell viability was tested using the MTT, (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylte- tetrazolium bromide) assay. This assay is a colorimetric assay, which measures the conversion of MTT into violet formazan which is produced by succinate dehydrogenase of the intact mitochondria in viable cells. As it is clear from Fig. 4, compounds **2** and **4** were able to reduce the cell viability around 50 % after 48 h of incubation and with concentration of 100 µM. No effects were observed with 20 µM of inhibitors concentration (data not shown). These results indicate that the tested compounds showed a moderate effect in cell viability. Actually this finding does not contradict the *in vitro* results, as other factors are involved in such assays as cell permeability and type of cell lines.

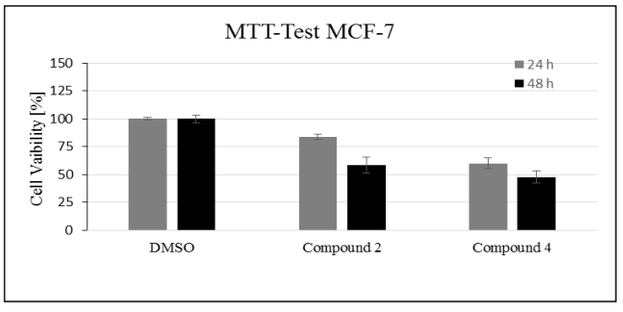


Fig. 4: Cell viability was evaluated by MTT assay using MCF-7 cells after 24 and 48 h treatment of the compounds with 100µM concentration. Values were shown as mean ± SD, n= 3

2.4. Molecular docking of compounds 2 and 4

In order to further understand the binding mode of the inhibitors, compounds **2** and **4** were docked in the crystal structure of CK2 co-crystalized with apigenin (PDB ID: 4DGM), using the parameters described in the experimental section. Figure 5 shows

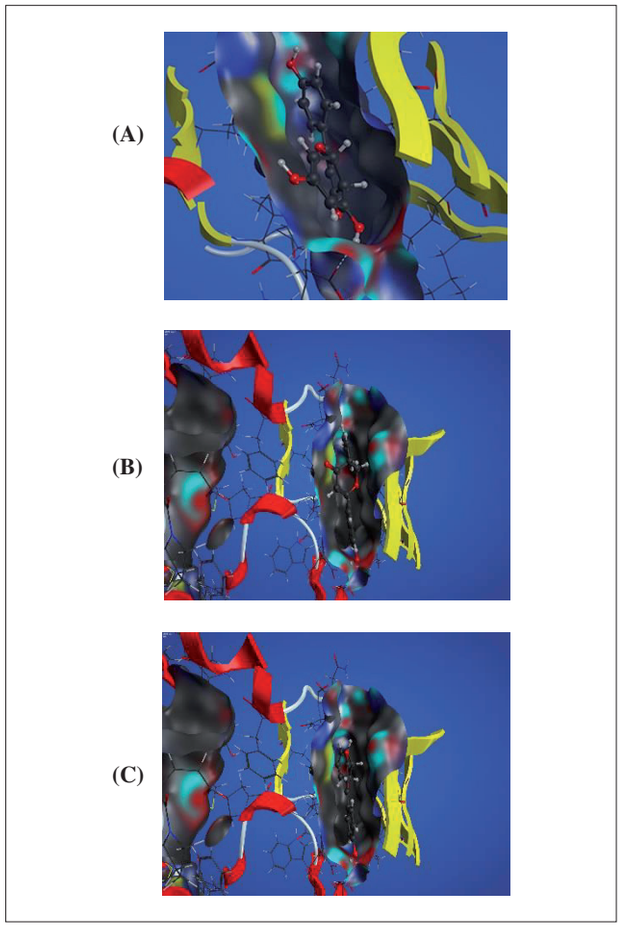


Fig. 5: Snapshots representing the docked complexes of (A) apigenin (B) compound **2** and (C) compound **4** with the ATP binding site of CK2

the best obtained conformation and orientation of compounds **2** and **4** (in 3D form) in the ATP active site of CK2, with S score equals to -9.696 and -13.3367 respectively, while apigenin has S score of –11.423 after extraction and redocking. Figure 6 shows the 2D-interactions between each compound and the amino acid residues in the ATP binding site of CK2. Compound **2** forms an interaction network with the active site of the enzyme, a direct hydrogen bond with two aspartate 75, while compound **4** had two *arene – arene* interactions with histidine 160 and methionine 163 beside two indirect bonds with 4`-hydroxyl group via water molecules. For comparison apigenin can form two bonds with aspartate 175 beside two indirect bonds via water molecules. Recently we described a structure-based pharmacophore model for a set of flavonoids as CK2 inhibitors (Jabbour et al. 2016), compounds **2** and **4** fit well with all features of the newly developed pharmacophore as described and shown in Fig. 7 which indicates that both compounds has similar features to the active flavonoids.

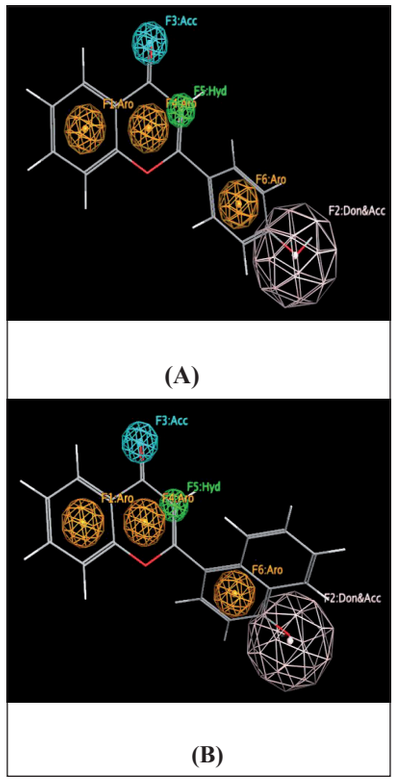


Fig. 7: Alignment of the formerly developed structure-based pharmacophore model with compounds **2** (**A**) and **4** (**B**). **Acc**: H-bond acceptor, **Aro**: Aromatic center, **Hyd**: Hydrophobic centroid, **Don&Acc**: H-bond donor and H-bond acceptor.

In this work we were able to synthesize a novel flavone derivative compound **4** with a good *in vitro* activity against CK2 in the sub-micro molar range in order to expand the boundaries of application of flavonoid synthesis beyond benzaldehyde derivatives, and also to explore the ability of naphthyl moiety to create a more stable and active inhibitors of this kinase. As a matter of fact the activity of compound **4** was in the same rang of the activity of compound **2** and even better than other known CK2 inhibitors such

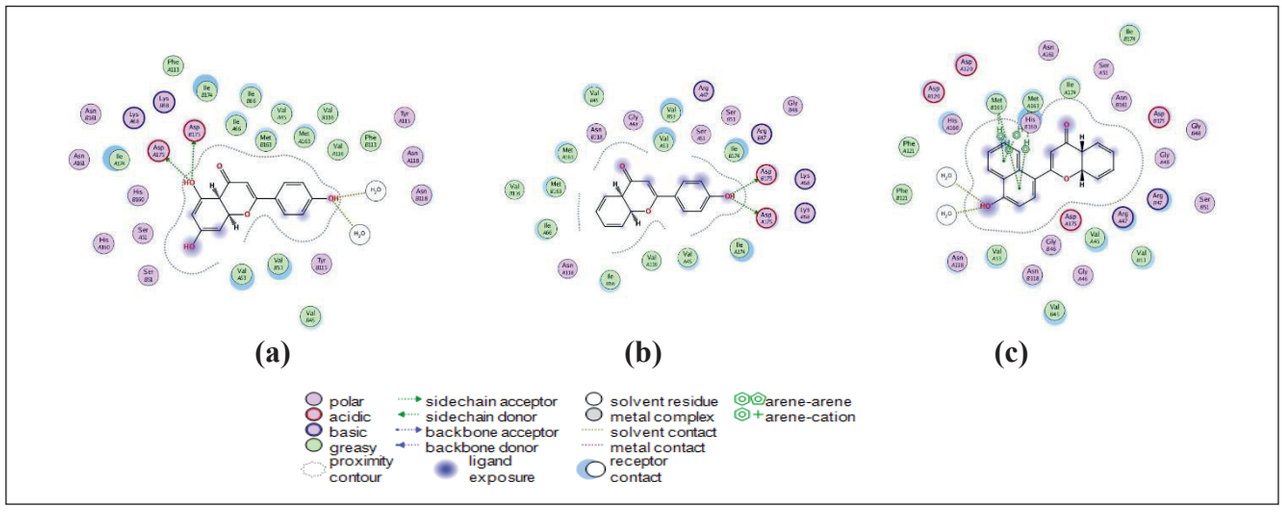


Fig. 6: Two - dimensional representation of the interactions between the ATP binding site of CK2 and apigenin (a), compounds **2** (b), and compound **4** (c)

as emodin, also the binding mode was illustrated by a molecular modeling approach.

3. Experimental

3.1. Synthesis

Starting materials, solvents, and reagents were purchased from commercial sources and were used without further purification. The reactions were monitored by TLC on silica-gel plates (Merck 60F254). Melting point was determined using electro thermal apparatus 9100, and used without calibration. IR spectra were recorded on KBr on Jasco FT/IR-4200 apparatus. UV spectra were recorded using Shimadzu UV-BC 3101. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Ultra Shield 400 instrument (400 MHz for ^{1}H, 100 MHz for ^{13}C). Elemental analyses were performed on EURO-EA instrument. CK2 activity was analyzed by a PA800 capillary electrophoresis from Beckman Coulter (Krefeld, Germany).

3.1.1. General procedure for the preparation of the flavylium salts

In 25 ml round bottom flask, a mixture of 1 mM of 2`-Hydroxyacetophenone, 2 mM mole of the aromatic aldehyde, and 1.4 ml triethyl orthoformate was prepared. Then, 0.1 ml of perchloric acid 70% was added drop wise, and the mixture was stirred at room temperature for 3 h. The precipitate was removed by filtration, washed with dry ether then recrystallized using glacial acetic acid to gain the corresponding flavylium salt.

3.1.2. General procedure for the hydrolysis of the flavylium salts

The pure flavylium salt was refluxed with 25 ml of distilled water for 5-10 min, the precipitated flavonoid was removed by filtration, recrystallized using ethanol.

3.1.3. Characterization of compound

4-Ethoxy-2-(4-hydroxyphenyl) chromenium perchlorate (1):
Orange powder. Yield 63.8 %, mp 254-256 ˚C, IR (ν cm^{-1}): 3438, 3079, 1103, 1598, 1531, 1618. ^{1}H NMR (CD_3OD, 400 MHz, 298K) δ/ppm: 10.350 (s, 1H, OH), 8.51-8.44 (m, 2H, $H_{2'}$, $H_{6'}$), 8.36-8.33 (m, 1H, Ar-H), 8.22-8.10 (m, 2H, Ar-H), 8.03 (s, 1H, H_3), 7.83 (ddd, *J* = 8.19, 6.24, 1.96 Hz, 1H, Ar-H), 7.20-6.99 (m, 2H, $H_{3'}$, $H_{5'}$), 3.59 (q, *J* = 7.06, 7.06, 7.05 Hz, 2H, CH_2), 1.16 (t, *J* = 7.04, 7.04 Hz, 3H, CH_3). ^{13}C NMR (CD_3OD, 100 MHz, 298K) δ/ppm: 134.239, 132.726, 128.695 ($C_{2'}$, $C_{6'}$), 125.459, 125, 124.354, 122.570, 120.469, 118.311, 117.13, 116.019 ($C_{3'}$, $C_{5'}$), 98.038 (C_4), 70.501 (C_3), 66.310 (CH_2), 13.416 (CH_3).
2-(4-Hydroxyphenyl)chromen-4-one (2):
Pale yellow solid. Yield: 75.84 %, mp 274-276 ˚C (Lit.: 270-273 ˚C) (Kshatriya et al. 2014), UVλ_{max} (methanol, nm): 219.5, 253, 326. IR (ν, cm^{-1}): 3434.6, 3200, 1633.41, 1600, 1565.92, 1456.9. ^{1}H NMR (DMSO-d6, 400 MHz, 298K) δ/ppm: δ 10.340 (S, 1H, OH), δ 8.031 (dd, *J* = 7.94, 1.48 Hz, 1H, H_5), δ 8.00-7.94 (m, 2H, $H_{2'}$, $H_{6'}$), δ 7.814 (ddd, *J* = 8.58, 6.99, 1.69 Hz, 1H, H_7), δ7.753 (dd, *J* = 8.52, 0.92 Hz, 1H, H_8), δ 7.482 (ddd, *J* = 8.02, 6.99, 1.20 Hz ,1H, H_6), δ 7.00-6.90 (m, 2H, $H_{5'}$, $H_{3'}$), δ 6.88 (S, 1H, H_3). ^{13}C NMR (DMSO-d6, 100 MHz, 298K) δ/ppm: 177.283 (C_4), 163.540 (C_2), 161.267 ($C_{4'}$), 155.806 (C_{10}), 134.588 (C_7), 129.127 ($C_{2'}$, $C_{6'}$), 125.793 (C_6), 125.199 (C_5), 123.787 (C_9), 122.047 ($C_{1'}$), 118.837 (C_8), 116.419 ($C_{3'}$, $C_{5'}$), 105.280 (C_3). Elemental analysis: calcd: C, 75.623%, H, 4.22%, found: C 75.99%, H 3.85%.
4-Ethoxy-2-(4-hydroxynaphthalen-1-yl) chromenium perchlorate (3):
Dark brown powder. Yield: 91.7 %, mp 233-235 ˚C, IR (ν, cm^{-1}): 3427, 1114, 1619, 1535, 1597. ^{1}H NMR (CD_3CN, 400 MHz, 298K) δ/ppm: 9.17 (s, 1H, OH), 8.55 (m, 1H, Ar-H), 8.45-8.34 (m, 2H,Ar-H), 8.27 (d, *J*= 8.33, 1H, $H_{2'}$), 8.19 (ddd, *J*= 8.71, 7.13, 1.58 Hz, 1H, Ar-H), 8.09 (m, 1H, Ar-H),7.87 (ddd, *J* = 8.17, 7.19, 1.07 Hz, 1H, Ar-H), 7.81 (ddd, *J*= 8.54, 6.88, 1.42 Hz, 1H, Ar-H), 7.77 (s, 1H, H_3), 7.71-7.66 (m, 1H, Ar-H), 7.17 (d, *J*= 8.33 Hz, 1H, $H_{3'}$), 4.83 (q, *J*= 7.03, 7.03, 7.03 Hz, 2H, CH_2), 1.67 (t, *J*= 7.02, 7.02 Hz, 3H, CH_3). ^{13}C NMR (CD_3CN, 100 MHz, 298K) δ/ppm: 206.9, 177.337, 174.422, 160.843, 156.662, 138.036, 136.176, 131.837, 130.274, 129.056, 126.768, 124.95,124.479, 124.305, 123.432, 119.161, 118.783, 108.725, 102.519, 70.612(CH_2), 13.328(CH_3). Elemental analysis: calcd: C, 60.5%, H, 4.08%, found: C, 60.1%, H, 3.65%.
2 (4`-Hydroxynaphthyl) chromen-4-one (4):
Golden brown crystals. Yield: 81.25 %, mp 240-241 ˚C, UV λ_{max} (methanol, nm): 214.5, 234, 308, 348. IR (ν, cm^{1}): 3434.6, 3123, 1617.02, 1508.06, 1476.02, 1559.17. ^{1}H NMR (DMSO-d6, 400 MHz, 298K) δ/ppm: 10.98 (s, 1H, OH), 8.28 (dd, *J* = 8.29, 0.99 Hz ,1H, H_5), 8.11 (m, 2H, $H_{5'}$, $H_{8'}$), 7.84 (ddd, *J* = 8.70, 7.15, 1.73 Hz, 1H, H_7), 7.75 (d, *J* = 7.95 Hz ,1H, $H_{2'}$), 7.69 (dd, 1H, H_8), 7.62 (ddd, *J* = 8.45, 6.81, 1.54 Hz, 1H, H_6), 7.55 (dddd, *J* = 8.98, 8.05, 7.06, 1.18 Hz, 2H, $H_{6'}$, $H_{7'}$), 7.01 (d, *J* = 7.97 Hz ,1H, $H_{3'}$), 6.59 (s, 1H, H_3). ^{13}C NMR (DMSO-d6, 100 MHz, 298K) δ/ppm: 177.403 (C_4), 166.187 (C_2), 156.855 ($C_{4'}$), 156.592 (C_{10}), 134.715 (C_7), 131.8 ($C_{9'}$), 130.448 ($C_{2'}$), 128.371 ($C_{6'}$), 125.996 ($C_{7'}$), 125.777 ($C_{6'}$), 125.369 ($C_{8'}$), 125.0 ($C_{10'}$), 124.990 ($C_{5'}$), 123.846 (C_9), 123.176 (C_5), 120.961 ($C_{1'}$), 119 (C_8), 111.830 ($C_{3'}$), 107.969 (C_3). Elemental analysis: calcd: C, 79.1%, H, 4.1%, found: C, 78.679%, H, 3.714%.

3.2. Biological evaluation

3.2.1. Inhibition of human CK2 holoenzyme

The preparation of the human recombinant CK2 holoenzyme was performed according to a protocol previously described (Gratz et al. 2010). For the expression of the α-subunit (CSNK2A1) and β-subunit (CSNK2B) of the human protein kinase CK2, the pT7-7 expression system in *Escherichia coli* BL21 (DE3) was used. Fractions exhibiting CK2 activity were combined and analyzed by SDS-PAGE and Western Blot. The capillary electrophoresis based assay was used for testing the inhibitors of the human CK2 as described earlier, 2 µL of the dissolved inhibitors (stock solution concertation: 10 µM in DMSO) were mixed with 78 µL of CK2 supplemented kinase buffer which was composed of 1 µg CK2 holoenzyme, 50 mM Tris/HCl (pH 7.5), 100 mM NaCl, 10 mM $MgCl_2$ and 1 mM DTT. The reaction was initiated by the addition of 120 µL assay buffer, which contains 25 mM Tris/HCl (pH 8.5), 150 mM NaCl, 5 mM $MgCl_2$, 1 mM DTT, 100 µM ATP and 190 µM of the substrate peptide RRRDDDSDDD. The reaction was carried out for 15 min at 37 °C and stopped by the addition of 4 µL EDTA (0.5 M). Subsequently the reaction mixture was analyzed by a PA800 capillary electrophoresis from Beckman Coulter (Krefeld, Germany). Acetic acid (2 M, adjusted with conc. HCl to a pH of 2.0) was used as the electrolyte for electrophoretic separation. The separated substrate and product peptide were detected at 214 nm using a DAD-detector. IC_{50} values were calculated from the resulting dose–response curves.

3.2.2. Cell viability assay

The effect of CK2 inhibitors on the viability of MCF-7 cells was evaluated using MTT assay (Mosmann 1983). MCF-7 breast cancer cells (kindly provided by the Department of Clinical Radiology of the University Hospital Muenster, Germany), were cultured in RPMI 1640 medium containing GlutaMax (Life Technologies) and 10% fetal calf serum. MTT assay was performed in 96-well plates. Cells were seeded at a density of 1 x 10^5 cells per well. Cells were incubated for 24 or 48 h at 37 °C in a humidified atmosphere (5% CO_2). After overnight incubation, seeding medium was removed and replaced with fresh medium containing the inhibitor at 20 or 100 µM. DMSO, at a final concentration of 1%, served as a control. Afterwards MTT reagent (Sigma Aldrich, Germany) was added at a final concentration of 0.5 mg/mL. After incubation for 2 h at 37 °C medium was discarded and 200 µL DMSO were added for solubilization the formazan. After mixing, the absorption was determined at 570 nm with a reference wavelength of 630 nm using a microplate reader. CK2 inhibitors were assayed in triplicates, and the experiments were repeated three times.

3.3. Statistical analysis

Prism 6 (GraphPad Software) was used to evaluate the IC_{50} values and their statistical significance with Student's *t* test. Values were considered statistically significant at *p* below 0.05.

3.4. Computational study

Computational work was performed on Intel (R) Core (TM) processor 3.20 GHz, using Molecular Operating Environment software package (MOE, Chemical Computing Group, Montreal, Canada) (Molecular Operating Environment (MOE)).

3.4.1. Protein preparation

Three dimensional 3D structure of the CK2 complex with apigenin was obtained from the Protein Data Bank (PDB) using PDB ID: (4DGM) having a resolution of 1.65 Å. The structure was optimized by using QuickPrep function implemented in the software. Then water molecules were removed from the structure and 3D protonation was done to change the state into ionization level. In the second step, energy minimization was performed using defaults parameters, where the force field was Amber 99.

3.4.2. Docking study

The docking of the selected compounds from the database (compounds) into the active site of CK2 enzyme (4DGM) was achieved using MOE-Dock implemented on MOE. The docking parameters were set as Rescoring 1: London dG, Placement: triangle matcher, Retain 30, Refinement Force field, and Rescoring 2: GBVI/WSA dG. Docking part of MOE can give correct conformation of the ligand to obtain minimum energy structure. The top conformation for each compound was selected based on the S score and visual inspection was carried out by Lgplot implemented in MOE. Compounds showing significant interaction with the residues of binding pocket of CK2 were picked as promising hits. Prior to dock, the initial ligand from the complex structure was extracted. For the scoring function, lower scores indicate more favorable poses. The unit for the scoring function is Kal/mol, and the S score refers to the final score, which is the score of the last stage that was not set to None. The Lig X function in MOE was used for conducting interactive ligand modification and energy minimization in the active site of the receptor.

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Conflicts of interest: None declared.

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