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Supporting information for article:

Synthesis, X-ray structure, antimicrobial activity, DFT and molecular docking studies of *N*-(thiophen-2-ylmethyl)thiophene-2-carboxamide

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Table S1. Net charges of title molecule.

Atoms	NPA	Atoms	NPA
C1	-0.37675	C8	-0.24790
C2	-0.25761	C9	-0.25381
C3	-0.22459	C10	-0.38212
C4	-0.29011	N1	-0.62631
C5	0.64132	O1	-0.62742
C6	-0.21015	S1	0.49530
C7	-0.21730	S2	0.42580

Table S2. Fukui function analysis results of title molecule.

Atoms	q^0_k	q_k^+	q_k^-	f_k^-	f_k^+
C1	-0.37675	-0.26461	-0.48029	0.10354	0.11214
C2	-0.25761	-0.22156	-0.27518	0.01757	0.03602
C3	-0.22459	-0.19356	-0.31355	0.08896	0.03103
C4	-0.29011	-0.21289	-0.33708	0.04697	0.07722
C5	0.64132	0.62174	0.59446	0.04686	-0.01958
C6	-0.21015	-0.23727	-0.20731	0.00284	-0.02712
C7	-0.21730	-0.11743	-0.22007	0.00277	0.09987
C8	-0.24790	-0.21315	-0.28161	0.03371	0.03475
C9	-0.25381	-0.18507	-0.27521	0.0214	0.06874
C10	-0.38212	-0.25951	-0.41733	0.03521	0.12261
N1	-0.62631	-0.60212	-0.65148	0.02517	0.02419
O1	-0.62742	-0.56166	-0.70169	0.07427	0.06576
S1	0.49530	0.36237	0.37047	0.12483	0.13293
S2	0.42580	0.48332	0.40073	0.02507	0.05752

Table S3. Second order perturbation theory analysis of Fock matrix in NBO.

Donor (*i*) (occupancy)	Type	ED_A,% ED_B,%	Acceptor (*j*) (occupancy)	Type	ED_A,% ED_B,%	$E^{(2)a}$ (kcal/mol)	E_j-E_i^b (a.u.)	$F(ij)^c$ (a.u.)
BD C1-H1 (1.98449)	σ	59 41	BD*C1-C2 (0.01862)	σ^*	50.01 49.99	3.11	1.25	0.056
BD C1-C2 (1.98200)	σ	49.99 50.01	BD*C2-H2 (0.01454)	σ^*	41.04 58.96	3.38	1.48	0.058
BD C1-C2 (1.83830)	π	52.42 47.58	BD*C3-C4 (0.37416)	π^*	55.15 44.85	16.97	0.29	0.066
BD C1-S1 (1.98194)	σ	51.89 48.11	BD*C2-H2 (0.01454)	σ^*	41.04 58.96	3.82	1.42	0.066
BD C3-H3 (1.97614)	σ	58.96 41.04	BD*C1-C2 (0.01862)	σ^*	50.01 49.99	3.19	1.23	0.056
BD C3-H3 (1.97614)	σ	58.96 41.04	BD*C1-S1 (0.01809)	σ^*	48.11 51.89	4.15	0.86	0.053
BD C2-C3 (1.97414)	σ	49.76 50.24	BD*C4-C5 (0.06094)	σ^*	48.56 51.44	4.79	1.14	0.067
BD C3-H3 (1.97723)	σ	58.56 41.44	BD*C4-S1 (0.02375)	σ^*	47.57 52.43	4.03	0.86	0.052
BD C3-C4 (1.98075)	σ	49.07 50.93	BD*C5-O1 (0.01355)	σ^*	63.51 36.49	2.01	1.31	0.046
BD C3-C4 (1.81463)	π	44.85 55.15	BD*C1-C2 (0.01862)	π^*	50.01 49.99	16.09	0.29	0.064
BD C3-C4 (1.81463)	π	44.85 55.15	BD*C5-O1 (0.01355)	π^*	63.51 36.49	20.40	0.29	0.072
BD C4-C5 (1.97850)	σ	51.44 48.56	BD*C5-O1 (0.01355)	σ^*	63.51 36.49	2.20	1.30	0.048
BD C4-C5 (1.97850)	σ	51.44 48.56	BD*C6-N1 (0.03668)	σ^*	61.67 38.33	3.78	1.02	0.058
BD C5-O1 (1.97884)	σ	28.58 71.42	BD*C3-C4 (0.37416)	σ^*	55.15 44.85	4.93	0.37	0.042
BD C6-H6a (1.97541)	σ	59.44 40.56	BD*C7-S2 (0.0253)	σ^*	47.83 52.17	5.76	0.86	0.063
BD C7-C8 (1.83527)	σ	53.69 46.31	BD*C6-N1 (0.03668)	σ^*	61.67 38.33	5.87	0.56	0.053
BD C7-C8 (1.83527)	π	53.69 46.31	BD*C9-C10 (0.35313)	π^*	54.08 45.92	16.08	0.27	0.062
BD C7-S2 (1.98269)	σ	52.17 47.83	BD*C10-H10 (0.01504)	σ^*	40.37 59.63	3.89	1.46	0.067
BD C9-C10 (1.86032)	π	45.92 54.08	BD*C7-C8 (0.40766)	π^*	46.31 53.69	11.70	0.26	0.052
BD N1-H1a (1.98652)	σ	67.58 32.42	BD*C5-O1 (0.01355)	σ^*	63.51 36.49	3.36	1.37	0.061
LP O1 (1.97911)	*n*	-	RY*C5 (0.01526)	-	-	14.82	1.85	0.148
LP O1 (1.97911)	*n*	-	BD*C4-C5 (0.06094)	σ^*	48.56 51.44	17.13	0.71	0.100
LP O1 (1.97911)	*n*	-	BD*C5-N1 (0.06825)	π^*	61.80 38.20	22.588	0.76	0.120

LP S1 (1.56023)	*n*	-	BD*C1-C2 (0.31984)	π^*	47.58 52.42	25.56	0.26	0.075
LP S1 (1.56023)	*n*	-	BD*C3-C4 (0.37416)	π^*	55.15 44.85	25.45	0.25	0.072
LP S2 (1.50458)	*n*	-	BD*C7-C8 (0.40766)	π^*	46.31 53.69	35.42	0.22	0.080
LP S2 (1.50458)	*n*	-	BD*C9-C10 (0.35313)	π^*	54.08 45.92	33.82	0.26	0.086
LP N1 (1.71119)	*n*	-	BD*C5-O1 (0.34708)	π^*	71.42 28.58	68.64	0.28	0.127
BD*C3-C4 (0.37416)	π^*	55.15 44.85	BD*C1-C2 (0.31984)	π^*	47.58 52.42	221.61	0.01	0.077
BD*C3-C4 (0.37416)	π^*	55.15 44.85	BD*C5-O1 (0.34708)	π^*	71.42 28.58	206.03	0.01	0.077
BD*C7-C8 (0.40766)	π^*	46.31 53.69	BD*C9-C10 (0.35313)	π^*	54.08 45.92	48.21	0.04	0.064

[a] $E^{(2)}$ means energy of hyperconjucative interactions (stabilization energy).
[b] Energy difference between donor (*i*) and acceptor (*j*) NBO orbitals.
[c] $F(i,j)$ is the Fock matrix element between *i* and *j* NBO orbital.
Percentage electron density over bonded atoms ($ED_{A,B}$,%).

Vibrational frequencies

In the IR spectra, the symmetric and asymmetric stretching vibrations of the amino group (–NH_2) did not show at 3500–3200 cm^{-1}. As an alternative, the –NH stretching vibration of amide group was observed as new peak. These results indicate that the reaction was successful and as expected. The N–H stretching vibrations was observed as characteristic peaks at 3273 cm^{-1} for the title compounds. The -C=O (amide I) stretching vibrations was observed as characteristic peaks at 1612 cm^{-1}, respectively. The other group wave number is the -C-N stretching vibration with -NH bending vibration (amide II) caused by the Fermi resonance effect. In the compounds, these modes was observed at 1418 cm^{-1} as shown in Figure S1. The aromatic -CH stretching vibrations was observed 3077 cm^{-1}, respectively. The methylene –CH_2 group stretching vibration was observed 2954 cm^{-1}. The -C-N and -C-S stretching vibrations were observed at 1302 and 852 cm^{-1}, respectively. These observations are agreement with similar compounds previously reported in the literature (Rubio-Pérez *et al.*, 2012; Yakan *et al.*, 2020; Iriarte *et al.*, 2008).

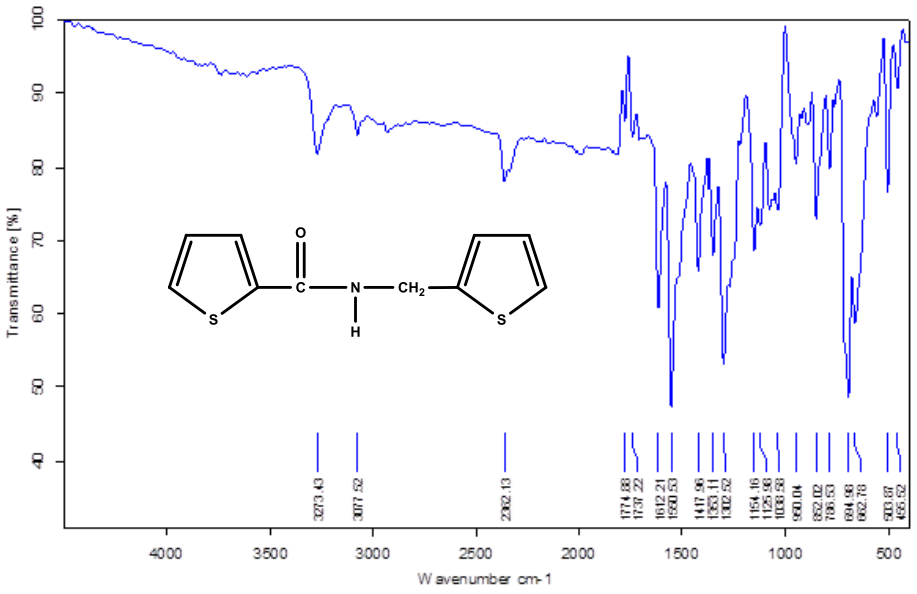

Fig. S1. IR spectrum of the compound.

NMR Spectra

^{1}H NMR spectra

The ^{1}H NMR spectrums of the compounds was recorded in $CDCl_3$ (7.28 ppm). The synthesized compound, the signal of amino proton (NH) was showed as a broad singlet at 6.74 ppm (br, 1H) which was specific for this kind of amide proton. The methylene (H7–CH_2) peak was observed at 4.76 (2H) ppm. The aromatic protons (H1-H3) of the thiophene ring were observed at 7.57-7.03 ppm as shown in Figure S2. The H1 proton coupled to the H2 proton resonated as a doublet peaks at 7.57 ppm. The H2 proton coupled to both the H3 and H1 protons resonated as a triplet peaks at 7.03 ppm. The H3 proton coupled to the H2 proton resonated as a doublet peaks at 7.48 ppm. The aromatic protons (H4-H6) of the methylene bonded thiophene ring were observed at 7.24-6.97 ppm. The H4 proton coupled to the H5 proton resonated as a doublet peaks at 7.24 ppm. The H5 proton coupled to the both the H4 and H6 protons resonated as a triplet peaks at 6.97 ppm. The H6 proton coupled to the H5 proton resonated as a doublet peaks at 7.06 ppm. These data agree with proton values of the reported similar compounds (Yakan *et al*., 2020; Choi *et al*., 2014; Kerdphon *et al*., 2015).

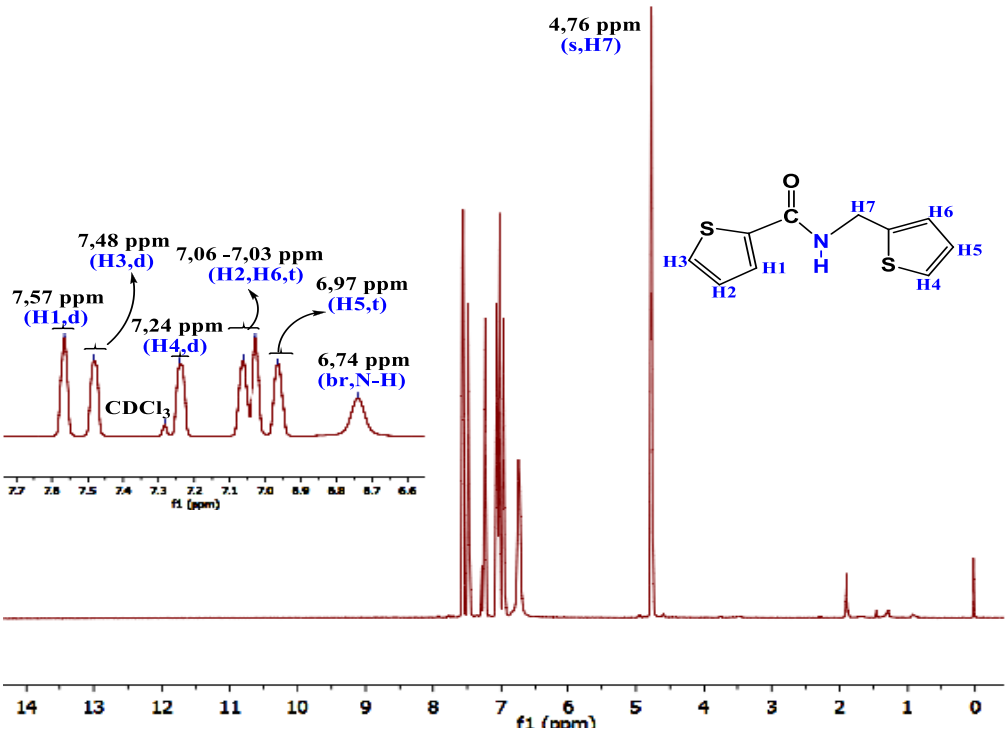

Fig. S2. ^{1}H spectrum of the title compound in $CDCl_3$.

^{13}C NMR spectra

The ^{13}C NMR spectrum of the compounds was recorded in $CDCl_3$ (77 ppm, triplet). The ^{13}C NMR spectrum of the compound was observed 10 different resonances, which are in good consistent with the purposed structures as shown in Figure S3. The title compound, the carbonyl peak (C=O) of the amide group was observed at 161.74 ppm. The C1-C4 and C6-C9 carbon atoms of thiophene rings were observed at between 140.71 and 125.36 ppm. The methylene (C5–CH_2) peak was showed at 38.67 ppm. The C1, C2, C3 C4, C6, C7, C8, and C9 carbon atoms were resonated 138.60, 130.24, 127.69, 128.41, 140.71, 126.29, 126.94, and 125.36 ppm, respectively. These data agree with proton values of the reported similar compounds (Yakan *et al.*, 2020; Choi *et al.*, 2014; Kerdphon *et al.*, 2015).

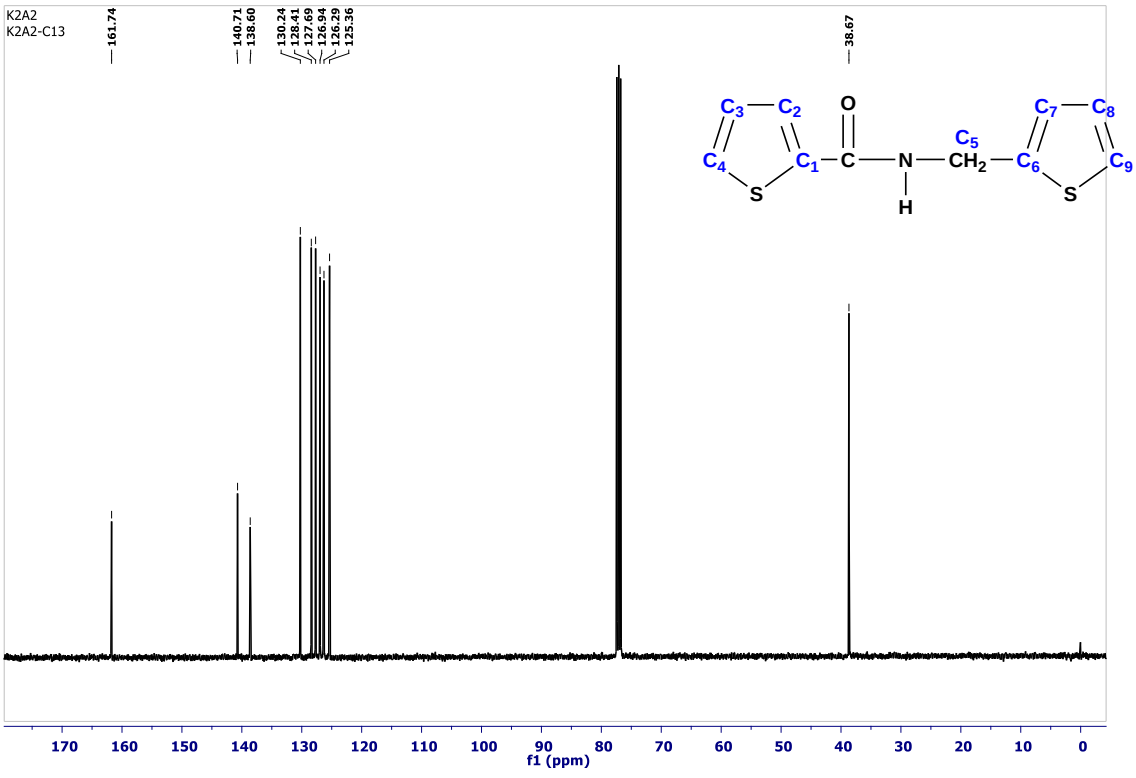

Fig. S3. ^{13}C spectrum of the title compound in $CDCl_3$.

Molecular Docking Analysis

Molecular docking studies are a powerful tool to investigate and provide a proper understanding for ligand receptor interactions in order to facilitate the design of potential drugs (Khan *et al*., 2019; Collins *et al*., 2019; Rupa *et al*., 2022). To investigate the anticancer activity of the title molecule against 1X2J lung cancer protein were performed.

Fig. S4. is illustrated the interactions between the title molecule and target protein and is illustrated hydrogen bond donor/acceptor surface. The title compound was interacted with target protein via formation of a Pi-Alkyl (with ARG415/4.52 Å), two Alkyl (with ALA366/ 4.62 Å and with VAL606/ 5.44 Å, respectively) and a hydrogen bond (with ILE416/ 3.03 Å) interactions. According to the molecular docking studies of the molecule with the 1X2J, the binding energy was found to be -6.1 kcal/mol.

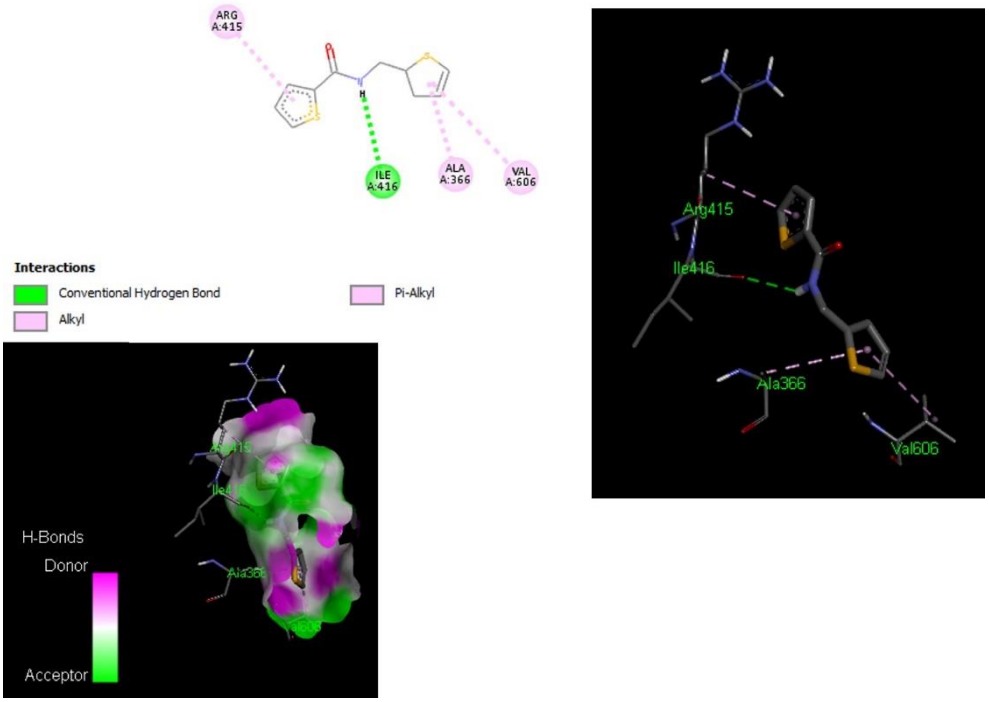

Fig. S4. Three-dimensional interactions and 2D-view of molecular docking results with title structure and 1X2J in the active site.

References

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