Indian Journal of Chemical Technology
Vol. 30, March 2023, pp. 231-236
DOI: 10.56042/ijct.v30i2.67293

# Synthesis, DFT and antioxidant studies of 2-(alkylamino)-4-(naphth-2-yl) thiazole

J Jenisha, J Jeba Lenet & T F Abbs Fen Reji*

Department of Chemistry & Research Centre, Nesamony Memorial Christian College, (Affiliated to Manonmaniam Sundaranar University, Tirunelveli), Marthandam 629 165 Tamil Nadu, India
E-mail: jeniajin29@gmail.com

*Received 10 October 2022; accepted 19 January 2023*

2-(Alkylamino)-4-(naphth-2-yl)thiazoles have been synthesised from 2-bromoacetyl naphthalene and characterized by UV, IR, and $^1$H NMR. The geometry of the molecules is optimised using the Gaussian 09 software programme and the B3LYP/6-31G density functional theory (DFT) approach. The bond lengths, bond angles, and dihedral angles of 2-(alkyamino)-4-(naphth-2-yl)thiazoles have been studied. Vibrational bands to distinct structural groups and their relevance have been predicted using vibrational spectra analysis and shown to be reliable when compared to experimental data and with literature observations. Atomic charges have been estimated using the Mulliken population analysis. The charge transfer within the molecule is confirmed by the computed energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). The molecular docking study has been carried out.

**Keywords:** Antioxidant study, 2-(Alkylamino)- 4-(naphth-2-yl) thiazole, DFT

Medicinal chemists have always strived to design drug substances with maximal therapeutic applicability and least toxicity, despite the fact that there are a significant number of undesirable effects. In recent advances in drug synthesis, combinatorial synthesis has brought a lot of evolution. Naphthalene has been identified as a novel class of antimicrobials with broad antimicrobial activity against a variety of human diseases. They hold a prominent position among medicinally essential chemicals due to their wide range of antibacterial activities and low toxicity[1]. Naphthalenes have a pleasing structure and a wide range of biological activities, including antibacterial, antioxidant, cytotoxic, anti-inflammatory, and antiprotozoal capabilities. They are a hot topic in medicinal chemistry research as powerful lead compounds[2], the goal of this study was to design novel molecules by coupling the naphthalene ring with the thiazole ring and using vibrational spectroscopy in conjunction with standard DFT computation to derive information about their structure and bonding nature. Vibrational spectroscopic inquiry using quantum chemical computation has lately been exploited as an effective method in organic molecule structural characterization[3]. Using the Gaussian 09 programme package, structural analysis was successfully employed to calculate electronic parameters.

## Experimental Section

The spectra were documented on a Bruker Advance 400 FTNMR spectrometer (400 MHz and 300 MHz for $^1$H and $^{13}$C NMR spectra), a mass spectrometer on Agilent 6520(QTOF) positive mode ESI-MS and a Nicolet 400 FTIR spectrometer. The elemental evaluation was performed in the Central Drug Research Institute, India.

### Synthesis of 2-(alkylamino)-4-(naphth-2-yl)thiazoles

Sigma Aldrich provided the reagents and solvents utilised in this experiment. In heated ethanol, 2-bromoacetyl naphthalene was suspended. After adding N-phenylthiourea and heating it, a clear solution was formed which ultimately resulted in the formation of crystals. The crystals are filtered out and then boiled in sodium acetate water before being filtered and dried. Ethanol was used to crystallise the raw material.

### Details of the computation

Density functional theory uses electron correlation as part of its approach, making it the preferred way for calculating theoretical charge density. DFT has evolved into a useful method for determining charge density distributions over time due to its ease of adaptation to high-speed computers[4]. The Gaussian 09 software package was used to compute the theoretical properties of 2-(alkylamino)-4-(naphth-2-yl)thiazoles utilising the B3LYP level of theory augmented with the standard 6-31G basis set[4]. As a result, the predicted frequencies were unscaled, as well as the infrared intensities and bonding nature.

## Results and Discussion

### 2-(Ethylamino)-4-(naphth-2-yl)thiazole(1a)

Yellow solid; Yield 68%; m.w 254.09 ; IR: 3562 (NH), 3085(CH), 1686(C=N) cm$^{-1}$; $^1$H NMR: δ 7.39-7.55 (m, 5H, naphthalene), 7.85-7.95 (m, 2H, naphthalene), 8.23 (s, 1H, naphthalene) δ10.3 (S, 1H, NH), 8.05 (S, 1H, thiazole), 2.25 (q, 2H, $CH_2$), 1.28 (t, 3H, $CH_3$), Elemental Analysis of $C_{15}H_{14}N_2S$ Calcd. found % : C, 70.83; H, 5.55; N, 11.01; S, 12.61

### 4-(Naphth-2-yl)-2-(Propylamino)thiazole(1b)

Yellow solid; Yield 71%; m.w 268.09 ; IR: 3452 (NH), 3076 (CH), 1698 (C=N) cm$^{-1}$; $^1$H NMR: δ 7.27.5(m, 5H, naphthalene), δ 7.567.78 (m, 2H, naphthalene), δ 8.1 (s, 1H, naphthalene), δ 9.40 (S, 1H, NH), δ 8.4 (S, 1H, thiazole), 2.25 (t, 2H, $CH_2$),1.58 (m,2H,CH2), 1.18 (t, 3H, $CH_3$), Elemental Analysis of $C_{16}H_{16}N_2S$ Calcd. found % : C, 71.63; H, 6.55; N,10.01; S,11.61

### 2-(Butylamino)-4-(naphth-2-yl)thiazole(1c)

Yellow solid; Yield 70%; m.w 282.09; IR: 3624 (NH), 3055 (CH), 1636 (C=N) cm$^{-1}$; $^1$H NMR: δ 7.17.4 (m, 5H, naphthalene), 7.77.9 (m, 2H, naphthalene), 8.13 (s, 1H, naphthalene), 9.40 (S, 1H, NH), 8.4 (S,1H, thiazole), 2.25 (t, 2H, $CH_2$), 1.58 (m, 2H, $CH_2$), 1.38 (t, 2H, $CH_2$), 1.08 (t, 3H, $CH_3$), Elemental Analysis of $C_{17}H_{18}N_2S$ Calcd. found % : C 72.33, H 6.42, N9.01, S-11.31

### 4-(Naphth-2-yl)-2-(2-propylamino)thiazoles(1d)

Yellow solid; Yield 72%; m.w 268.09 ; IR: 3425 (NH), 3045 (CH), 1642 (C=N) cm$^{-1}$; $^1$H NMR: δ 7.43-7.66 (m, 5H, naphthalene), 7.837.91(m, 2H, naphthalene), 8.10 (s, 1H, naphthalene), 9.40 (S, 1H NH), 8.4 (S, 1H, thiazole), 2.28 (d, 1H, CH),1.18 (m, 6H, $2CH_3$), Elemental Analysis of $C_{16}H_{16}N_2S$ Calcd. found % : C, 71.60; H ,6.05; N,10.41; S,11.95

### Optimized geometry

Geometrical optimization attempts to locate minima on the potential energy surface, predicting molecular system equilibrium configurations (Table 1). Figure 1 depicts the optimal molecular structure as well as the numbering scheme for 2-(alkylamino)-4-(naphth-2-yl)thiazoles.

### Frontier molecular orbital analysis

The wave-like features of electrons are incorporated into Molecular Orbital Theory when

Table 1 — Optimized geometrical parameters of 2-alkylamino-4-(naphth-2-yl)thiazoles

| Position | Atoms | Bond Length | | | |
|---|---|---|---|---|---|
| | | 1a | 1b | 1c | 1d |
| Thiazole | C – S | 1.844 | 1.846 | 1.808 | 1.847 |
| Thiazole | C – N | 1.305 | 1.307 | 1.306 | 1.306 |
| Thiazole | C – C | 1.367 | 1.367 | 1.367 | 1.367 |
| Thiazole | C – H | 1.076 | 1.076 | 1.076 | 1.076 |
| Naphthalene | C – C | 1.388 | 1.388 | 1.388 | 1.388 |
| Naphthalene | C – H | 1.086 | 1.086 | 1.086 | 1.086 |
| Chain | C – N | 1.467 | 1.468 | 1.368 | 1.473 |
| Chain | N – H | 1.012 | 1.012 | 1.012 | 1.012 |
| Chain | C – H | 1.099 | 1.100 | 1.100 | 1.098 |
| Chain | C – C | 1.529 | 1.534 | 1.539 | 1.539 |

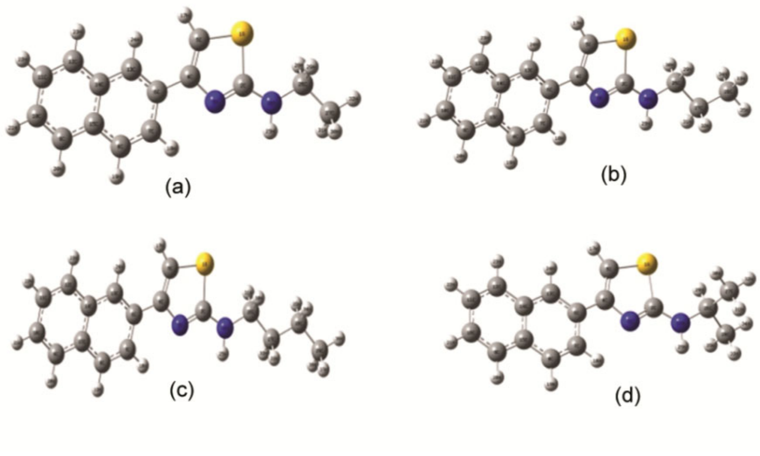

Fig. 1 — Optimized molecular structure of 2-alkylamino-4-(naphth-2-yl)thiazole

Table 2 — Electronic parameters of 2-alkylamino-4-(naphth-2-yl)thiazole

| Parametres (a.u) | A | B | C | D |
|---|---|---|---|---|
| Total Energy (a.u) | - 1087.5284 | -1126.8325 | -1166.1365 | -1126.835 |
| Dipole Moment (debye) | 2.8781 | 3.0431 | 3.1377 | 2.8017 |
| $E_{HOMO}$ | 0.22434 | -0.22410 | -0.22400 | -0.22435 |
| $E_{LUMO}$ | -0.01093 | -0.01042 | -0.01019 | -0.01079 |
| ΔE | 0.2134 | 0.2137 | 0.2139 | 0.2136 |
| Ionization Potential (I) | 0.22434 | 0.22410 | 0.22400 | 0.22435 |
| Electro affinity (A) | 0.01093 | 0.01042 | 0.01019 | 0.01079 |
| Electro Negativity (χ) | 0.1176 | 0.1172 | 0.1170 | 0.1175 |
| Hardness( η) | 0.1067 | 0.1068 | 0.1069 | 0.1086 |
| Softness(S) | 4.6860 | 4.6816 | 4.6772 | 4.6040 |

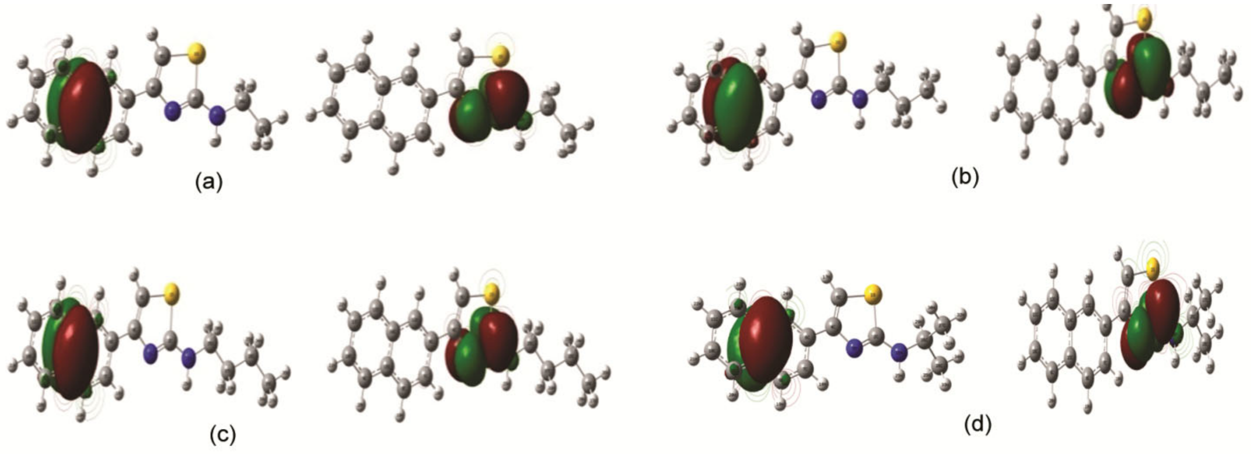

Fig. 2 — HOMO-LUMO of 2-alkylamino-4-(naphth-2-yl)thiazoles

discussing bonding behaviour. A combination of atomic orbitals describes the bonding between the atoms. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are the two most important frontier molecular orbitals (LUMO). To explain charge transfer within the molecule, a HOMO-LUMO study was performed. Figure 2 shows a graphical representation of HOMO-LUMO of 2-**(**alkylamino**)**-4-(naphth-2-yl)thiazoles based on the relative energy of the molecular orbitals. The energies of HOMO and LUMO are 0.2134, 0.2137, 0.2139, 0.2136 respectively, and the energy gap describes the charge transfer interactions that occur within the molecule, which determine the molecule's bioactivity. The HOMO-LUMO energy gap is an indicator of kinetic stability. A large HOMO-LUMO energy gap point out low chemical reactivity and high kinetic stability because it is energetically unable to add electrons to a LUMO[5].

The Koopmans theorem[6] states that the HOMO-LUMO orbital energies are given by

$-\varepsilon_{HOMO} = I$ and $-\varepsilon_{LUMO} = A$

where I = ionization potential and A= electron affinity.

The absolute electro negativity (χ), the absolute hardness (η) and softness(s) of a molecule can be determined using HOMO-LUMO energies, according to the literature review.

$\chi = (I+A)/2 \quad \eta = (I-A)/2$ and $S = 1/2\,\eta$

The electro negativity, hardness, and softness of the named compound can be determined using this equation. The results are presented in Table 2.

### Dipole moments

Dipole moments and higher multipole moments are predicted by DFT. The first derivative of energy with respect to an applied electric field is the dipole moment[7]. The self consistent field (SCF) energy of the compounds are found to be –1087.52 a.u.,-1126.83, -1166.13 and –1126.83 a.u. with dipole moments of 2.87, 3.04, 3.13, Debye and 2.80 Debye respectively. If the compounds own

Table 3 — Mulliken atomic charges of 2-alkylamino-4-(naphth-2-yl)thiazoles

| Atom | Mulliken Atomic Charge | | | |
|---|---|---|---|---|
| | 1a | 1b | 1c | 1d |
| $S_1$ | 0.148 | 0.423 | 0.415 | 0.411 |
| $C_2$ | 0.182 | 0.181 | 0.181 | 0.177 |
| $N_3$ | -0.436 | -0.433 | -0.437 | -0.437 |
| $C_4$ | 0.217 | 0.216 | 0.217 | 0.218 |
| $C_5$ | -0.509 | 0.509 | -0.509 | -0.509 |
| $C_6$ | 0.090 | 0.091 | 0.090 | 0.090 |
| $C_7$ | -0.141 | -0.141 | -0.421 | -0.422 |
| $C_8$ | -0.167 | -0.167 | -0.168 | -0.168 |
| $C_9$ | -0.155 | -0.155 | -0.156 | -0.156 |
| $C_{10}$ | -0.130 | -0.129 | -0.130 | -0.130 |
| $C_{11}$ | -0.134 | -0.134 | -0.134 | -0.134 |
| $C_{12}$ | -0.152 | -0.152 | -0.152 | -0.532 |
| $C_{13}$ | -0.189 | 0.188 | 0.188 | -0.891 |
| $C_{14}$ | 0.055 | 0.055 | 0.055 | 0.055 |
| $C_{15}$ | 0.079 | 0.079 | 0.079 | 0.079 |
| $N_{16}$ | -0.780 | -0.783 | -0.773 | -0.772 |
| $H_{17}$ | 0.172 | 0.175 | 0.171 | 0.170 |
| $H_{18}$ | 0.155 | 0.155 | 0.155 | 0.155 |
| $H_{19}$ | 0.127 | 0.128 | 0.126 | 0.126 |
| $H_{20}$ | 0.128 | 0.129 | 0.128 | 0.128 |
| $H_{21}$ | 0.124 | 0.125 | 0.124 | 0.123 |
| $H_{22}$ | 0.124 | 0.125 | 0.124 | 0.124 |
| $H_{23}$ | 0.126 | 0.127 | 0.126 | 0.126 |
| $H_{24}$ | 0.125 | 0.126 | 0.125 | 0.125 |
| $H_{25}$ | 0.344 | 0.346 | 0.343 | 0.342 |
| $C_{26}$ | 0.317 | 0.325 | 0.312 | 0.303 |
| $C_{27}$ | -0.116 | -0.110 | -0.113 | -0.116 |
| $C_{28}$ | -0.148 | -0.121 | -0.180 | -0.146 |
| $C_{29}$ | -0.114 | -0.228 | -0.125 | 0.291 |
| $H_{30}$ | 0.128 | 0.140 | 0.127 | 0.131 |
| $H_{31}$ | 0.131 | 0.163 | 0.126 | 0.135 |
| $H_{32}$ | -0.128 | 0.164 | 0.127 | 0.148 |
| $H_{33}$ | 0.133 | 0.166 | 0.156 | 0.160 |

higher dipole moments, then their intermolecular interaction will be stronger[8]. The 2-(butylamino)-4-(naphth-2-yl)thiazoles compound has a higher dipole moment than other compounds, so its dipole-dipole interaction with another molecule is stronger.

### Mulliken atomic charges

The way atoms are defined has a big impact on their atomic charges. In the use of quantum chemical calculations, it is very significant[9]. Table 3 shows the mulliken atomic charges estimated with the 6-31G basis set. The findings show that nitrogen atoms are negatively charged and serve as electron acceptors. Negatively charged carbon atoms also serve as electron acceptors. Carbons, sulphur, and hydrogens that remain have positive charges and operate as electron donors.

### Docking study

A prominent molecular docking technique can be used to examine the interaction energy between chemicals and proteins[10]. In 2-(alkylamino)-4-(naphth-2-yl)thiazoles derivatives were selected for the docking studies with 5cp6 (PDB ID) using PyRx virtual scrренning tool. binding affinity is given in Table 4. The docked image of compounds is shown in Figure 4. Among the four compounds, 2-(butylamino)-4-(naphth-2-yl)thiazole **1c** is the most active and 2-(2-propylamino)-4-(naphth-2-yl)thiazole is the less active against cancer protein 5cp6.

Table — 4 Docking score of 2-alkylamino-4-(naphth-2-yl)thiazoles

| Compd | Docking Score KJmol$^{-1}$ | H-Bond |
|---|---|---|
| 1a | -8.4 | LS5 229, GLN 131, ILE 10 |
| 1b | -8.4 | HIS 295, SER 94, THR 98, GLY 97 |
| 1c | -8.9 | GLN 131, ILE 10, LS5 299 |
| 1d | -8.3 | GLN 131, ILE 10, ASP 92 |

### Antioxidant studies

The *in vitro* antioxidant activity of 2-(Ethylamino)-4-(naphth-2-yl)thiazole (1a), 4-(naphth-2-yl)-2-

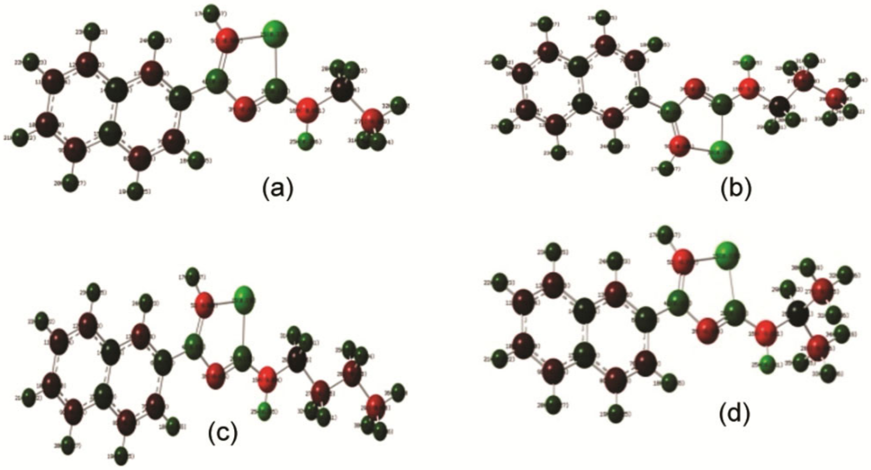

Fig. 3 — Mulliken atomic charges of 2-alkylamino-4-(naphth-2-yl)thiazoles

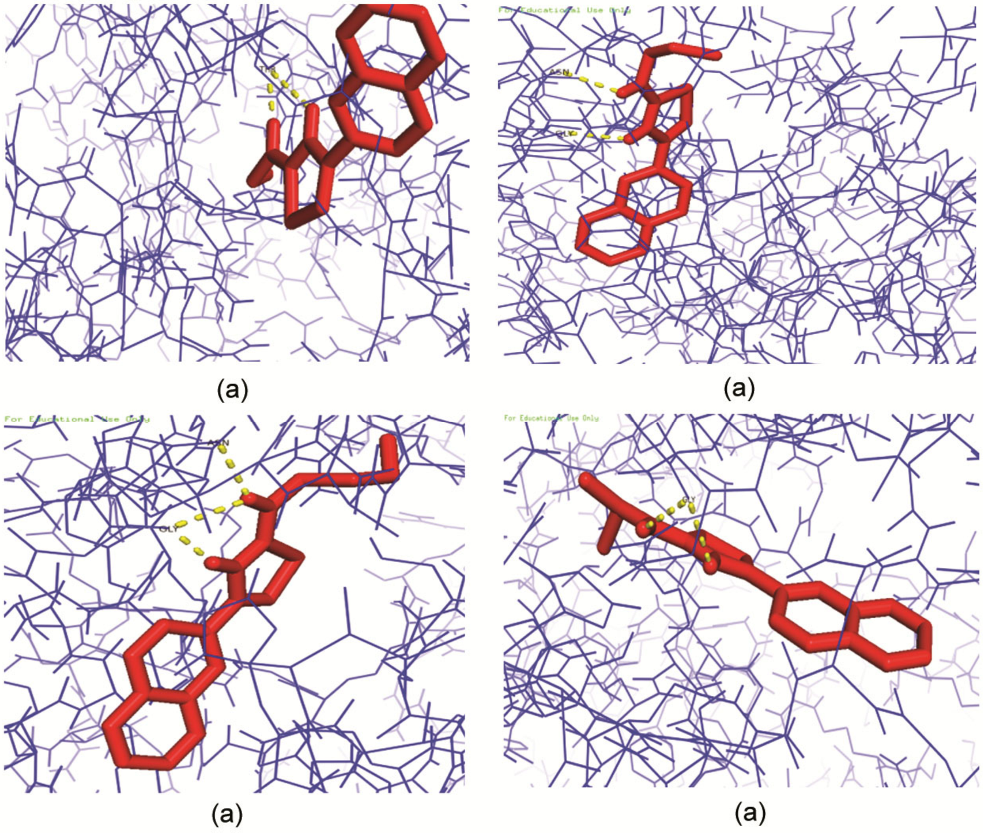

Fig. 4 — Docking images of 2-alkylamino-4-(naphth-2-yl)thiazoles

propylamino thiazole (1b), 2-(butylamino)-4-(naphth-2-yl)thiazole (1c), and 4-(naphth-2-yl)-2-(2-propylamino)thiazoles (1d) was evaluated using DPPH radical scavenging assay. DPPH is responsible for the absorbance at 517nm hence decolouration can be quantitatively measured from the changes in absorbance at 517nm. The antioxidant activity of synthesized compounds was compared with standard antioxidant (BHA). The results shows that the compounds 2-(butylamino)-4-(naphth-2-yl)thiazole(1d) exhibited significant antioxidant capacity (Table 5).

Table 5 — Antioxidant activity of 2-alkylamino-4-(naphth-2-yl)thiazoles

| Compound | $IC_{50}$ value (μM) |
|---|---|
| 1a | 248 |
| 1b | 127 |
| 1c | 141 |
| 1d | 398 |
| BHA (Std) | 156 |

## Conclusion

2-**(**Alkylamino**)**-4-(naphth-2-yl)thiazoles have been synthesized. The structures of the compounds are confirmed on the basis of FT-IR, $^1$H NMR, DFT methods are used to optimise the structure of 2-**(**alkylamino**)**-4-(naphth-2-yl)thiazoles utilising the basis sets 3-61G. Atomic charge distributions are calculated by determining the electron population of each atom. The charge transfer interactions occurring within the molecule, and thus the bioactivity of the titled compound, are predicted using HOMO-LUMO analysis. On the basis of docking result 2-**(**butylamino**)**-4-(naphth-2-yl)thiazole is the most active and 4-(naphth-2-yl)-2-(2-propylamino)thiazole is the less active against cancer protein 5cp6. In antioxidant studies 2-**(**butylamino**)**-4-(naphth-2-yl) thiazole exhibited significant antioxidant capacity.

## References

1 Rokade Y B & Sayyed R Z, *Rasayan J Chem*, 4 (2009) 972.

2 Sabrin R M, Ibrahim & Mohamed G A, *Phytochem Rev*, 15 (2016) 279.

3 Anzilne C, Israel S, Devi R N, Rajkumar P R & Blessy W H, *J Res Sci*, 2 (2014) 35.

4 Caricato M, Frisch M J, Hiscocks J & Frisch M J, *J Chem Phy*, 131 (2009)174104.

5 Brinda J, Rani S M, Chithra V S & Reji T F A F, *Indian J Chem*, 58 ( 2019) 1063.

6 Tsuneda T, Song J W, Suzuki S & Hirao K, *J Chem Phy*s, 133 (2010) 174101.

7 Chithra V S, Brindha J, Alwin T & Reji T F A F, *Innov Res Pedagog*, 31 (2017) 765.

8 Shahana M F & Yardily A, *J Mol Chem*, 61 (2020) 1443.

9 Rani S M, Viola rose S & Reji T F A Fen, J Xidian Univ, 14 (2020) 11.

10 Rani S M, Viola Rose S & Reji T F A F, *Indian J Biochem Biophy*, 57 (2020) 620 **.**