Indian Journal of Chemistry
Vol. 60B, April 2021, pp. 605-610

Synthesis, computational studies and antioxidant activity of some 3-(2-alkylamino-4-aminothiazole-5-oyl)pyridines

S Mahil Rani[a,b], J Brindha[a] & T F Abbs Fen Reji*[a]

[a] Department of Chemistry, Nesamony Memorial Christian College, Marthandam 629 165 Kanyakumari District, India

[b] Manonmaniam Sundaranar University, Tirunelveli 627 012, India

E-mail: abbsfen@gmail.com

Received 16 February 2020; accepted (revised) 3 March 2021

A series of thiazoloylpyridine derivatives has been synthesized and analyzed to confirm the structure of the product using IR, ^{1}H and ^{13}C NMR, mass spectra and analytical data. Optimized structural and electronic parameters of all the compounds have been calculated by using B3LYP/ 6-31G basis set. The Mulliken charges of all atoms have been evaluated. The calculated IR spectrum has been analyzed by comparing the experimental IR. All the synthesized compounds have been examined for antioxidant activities. The antioxidant activity of 3-(2-alkylamino-4-aminothiazol -5-oyl)pyridines have been analyzed using DPPH radical scavenging assay. The compounds **6a** and **6b** possess higher radical scavenging activity.

Keywords: Thiazole, antioxidant, optimized structure, B3LYP

All the heterocyclic compounds play an important role in drug discovery and design because of their diverse biological properties[1]. The pyridine derivatives occupy a unique place in the field of medical chemistry. Many of them are important class of antitumor compounds[2-5]. Pyridine is a fundamental building block in industrial organic chemistry, with its emphasis on solvent and regeneration in organic matter. Pyridine derivatives are significant role in many biological systems as components of many vitamins, enzymes, proteins and nucleic acid. Most of the 2-amiopyridine derivatives possess antibacterial, antifungal, cardiotonic, antimicrobial, analgesic, anti-inflammatory, antioxidant and anticancer activities[6]. Abdullah Jawad Kadhim reveals the 1,4-dihydro-pyridine drugs such as nimodipine and nefidine are favourable cardiovascular agents for the therapy of angina pectoris and hypertension[7]. Furthermore Adel M *et al*., reported that some of the pyridine derivative, like neonicotinoid insecticides was commonly used in insect control since their great protecting efficiency and low toxicity[8]. Thiazole derivatives are important source of many bio-acctive molecules such as Ritonavir, Sulfathiazol, Tiazofurin. Substituted diaminothiazole derivatives possess antitumor activity against 60 human tumor cell lines by the National Cancer Institute (NCI) and exhibit potential anticancer activity[9-11]. The 2-aminothiazole derivatives with various targets guide to the new anticancer agent[12-15]. Superoxide, and nitric oxide, hydroxyl are the oxygen centered free radicals, it is known as reactive oxygen species. They originate in the human body and can cause damage to lipids, proteins and DNA leading to a variety of diseases, including oncology, drug related toxicity and inflammation. In addition, radical reactions are key role in the development of a life time of cancer, aging, diabetes and other diseases[16]. The antioxidant treatment of diseases connected with oxidative stress has been demonstrated safe and effective. Consuming antioxidants reduces the risk of cancer, furthermore neurological and cardiovascular disease[17]. Antioxidant activity (AOA) of thiazole derivatives was recently acknowledged[18]. Some novel 4-(4-chlorophenyl)-2-aryl substituted metheniminothiazoles as potent antioxidant activities, reported by Kavitha *et al*.[19] In the present study, we report on the coherent synthesis of 3-(2-alkylamino-4-aminothiazol-5-oyl) pyridines have aminothiazole, pyridine ring systems. The study was concentrated on the synthesis and biological assessment of the synthesized compounds.

Experimental Section

All chemicals used were of analytical reagent quality. All these chemicals were obtained from M/S E. Merck and used without purification. The IR spectra were recorded on a Perkin-Elmer 883 and

Shimadzu infrared spectrophotometer in the 400–4000 cm^{-1} range as a KBr disc. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400MHz instrument utilising TMS as the internal reference. And also the elemental analysis was done. All the characterization studies were done by the CSIR-Central Drug Research Institute, Lucknow, India. Melting points were measured with an electrothermal melting point apparatus. The melting points were calculated using the Digital Program Rate melting point tool and are uncorrected.

Synthesis of 3-(2-alkylamino-4-aminothiazole-5-oyl)pyridines, 6a-e

The reaction of 3-bromoacetylpyridine with 1-alkyl-3-(N-nitroamidino)thiourea in the presence of triethylamine, afforded an orange yellow solid. Crystallisation from methanol-water (2:1) gave an orange yellow crystalline compound. As a representative example, the reaction of 3-(2-bromoacetyl)pyridine with 1-(N-nitroamidino)-3-phenylthiourea is described below in detail. The reaction yielded an orange yellow crystalline compound.

Antioxidant activity

The DPPH rating was based on the reported method. In Brief, 1 mM solution of 1,1-diphenyl-2-picryl hydrazyl radical (DPPH) in ethanol was prepared with five different concentration (0.05, 0.1, 0.25, 0.5 and 0.75 µM). Above sample mixture was shaken and permitted to 20 min under room temperature. In the presence of antioxidants, the deep violet colour of DPPH solution convert into yellow. The absorbance was then measured on spectrometer at 517 nm. The low absorption of the reaction mixture indicates high free radical scavenger activity. The ability to repel DPPH intensity was calculated using the following equation:

$$\text{DPPH scavenging effect (\%)} = A_0 - A_1 / A_0 \times 100$$

Where, A_0 - absorbance of the control reaction and

A_1 - absorbance of the sample

3-(2-Ethylamino-4-aminothiazole-5-oyl)pyridine, 6a: Yellow solid. Yield 70%. m.p.122°C. Mol. Wt. 248.07. IR (KBr): 3444 (N-H), 3063(C-H), 1644 (C=O), 1599 cm^{-1} (C=N); ^{1}H NMR: (DMSO-d_6): δ 1.606 (t, J = 2.9Hz, 3H, $-CH_3$), 2.512-2.494 (q, J = 1.6Hz, 2H, $-CH_2$), 7.458 (s, 2H, $-NH_2$), 7.279-8.118 (m, 3H, H-4, H-5, H-6 of pyridine), 7.688 (s, 1H, H-2 of pyridine), 8.525 (s, 1H, -NH); MS: *m/z* 248.07 (100.0%). Anal. $C_{11}H_{12}N_4OS$: Calcd (Found %) C, 53.21 (53); H, 4.87 (4.85); N, 22.56 (22.55); O, 6.44 (6.42); S, 12.91 (12.9).

3-(2-Propylamino-4-aminothiazole-5-oyl) pyridine, 6b: Yellow solid. Yield 68%. m.p.135°C. Mol. Wt. 262.09. IR (KBr): 3397(N-H), 3045(C-H), 1622 cm^{-1} (C=O); ^{1}H NMR: (DMSO-d_6): δ 0.915(t, J = 10.1 Hz, 3H, $-CH_3$), 1.588-1.530 (m, 2H, $-CH_2$), 2.503 (t, J = 2.4 Hz, 2H, $-CH_2$), 7.52 (s, 2H, $-NH_2$), 7.560 (d, J = 6.4Hz, 1H, H-6 of pyridine), 7.610 (s, 1H, H-2 of pyridine), 7.642 (t, J = 4.8Hz, 1H, H-5 of pyridine), 7.651(d, J = 14.8Hz,1H, H-4 of pyridine), 9.074 (s, 1H, -NH); MS: *m/z* 262.09 (100.0%). Anal. $C_{12}H_{14}N_4OS$: Calcd (Found %) C,54.94 (54.92); H, 5.38 (5.40); N, 21.36 (21.32); O, 6.10 (6.11); S, 12.22 (12.20).

3-(2-Isopropylamino-4-aminothiazole-5-oyl) pyridine, 6c: Yellow solid. Yield 62.5%. m.p.137°C. Mol. Wt. 262.09. IR (KBr): 3072(C-H), 1696(C=O), 1553 cm^{-1} (C=N); ^{1}H NMR: (DMSO-d_6): δ 1.046(d, J = 9.6Hz, 6 H, $-CH_3$), 1.488-1.512(m, 1H, -CH), 7.102 (s, 2H, $-NH_2$), 7.589(s, 1H, H-2 of pyridine), 7.979-8.018 (m, 3H, H-4, H-5, H-6 of pyridine), 8.519(s, 1H, -NH); MS: *m/z* 262.09 (100.0%). Anal. $C_{12}H_{14}N_4OS$: Calcd (Found %) C, 54.94 (54.93); H, 5.38 (5.36); N, 21.36 (21.33); O, 6.10 (6.9); S, 12.22 (12.18).

3-(2-Butylamino-4-aminothiazole-5-oyl)pyridine, 6d: Yellow solid. Yield 68%. m.p.140°C. Mol. Wt. 276.10. IR (KBr): 3271(C-H), 1682 cm^{-1} (C=O); ^{1}H NMR: (DMSO-d_6): δ 0.891 (t, J = 4.2Hz, 3H, $-CH_3$), 1.106-1.034 (m, 2H, $-CH_2$), 1.474-1.424 (m, 2H, $-CH_2$), 2.5 (t, J = 4.8Hz, 2H, $-CH_2$), 7.544 (s, 2H, $-NH_2$), 7.573 (s, 1H, H-2 of pyridine), 7.913 (d, J = 2.3Hz, 1H, H-4 of pyridine), 8.006 (m, 2H, H-5 and H-6 of pyridine), 8.717(s, 1H, -NH); MS: *m/z* 276.10 (100.0%). Anal. $C_{13}H_{16}N_4OS$: Calcd (Found %) C, 56.90 (54.88); H, 5.84 (5.86); N, 21.27 (21.24); O, 5.79 (5.77); S, 11.60 (11. 58).

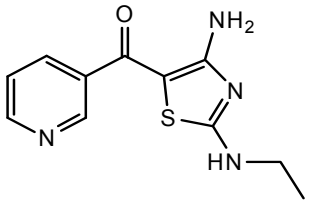
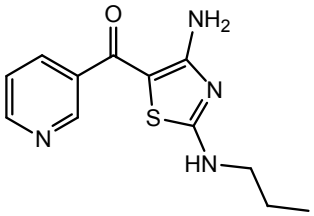
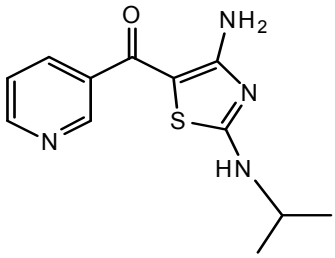
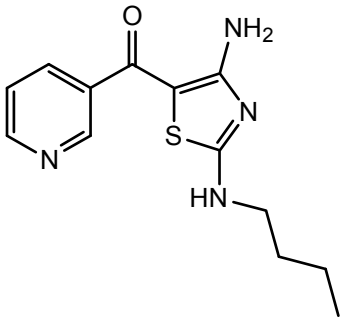
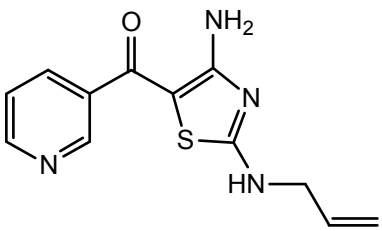
3-(2-Allylamino-4-aminothiazole-5-oyl)pyridine, 6e: Yellow solid. Yield 70%. m.p.135°C. Mol. Wt. 260.07. IR (KBr): 3395(N-H), 3248(C-H), 1624 cm^{-1} (C=O); ^{1}H NMR: (DMSO-d_6): δ 2.206 (d, J = 1.8Hz, 2H, $-CH_2$, 5.963-5.725 (m, 1H, -CH), 5.92 (d, J = 2.5Hz, 2H,$-CH_2$), 7.461 (t, J = 7.1Hz, 1H, H-5 of pyridine), 7.528 (s, 2H, $-NH_2$), 7.568 (d, J = 1.2Hz,

1H, H-4 of pyridine), 7.639 (s, 1H, H-2 of pyridine), 8.716 (d, J = 3.8Hz, 1H, H-6 of pyridine), 8.528 (s, 1H, -NH); MS: *m/z* 260.07 (100.0%). Anal. $C_{12}H_{12}N_4OS$: Calcd (Found %) C, 55.37 (55.34); H, 4.65 (4.64); N, 21.52 (21. 5); O, 6.15 (6.10); S, 12.32 (12. 31).

Results and Discussion

According to our interest to plan with some new pyridine compounds, we have prepared a series of 3-acetyl pyridine derivatives (Table I) as expressed in Scheme I. In Scheme I, the reaction of 3-acetyl pyridine with various bases and thiourea is a modern method for synthesis of 3-(2-ethylamino-4-aminothiazole-5-oyl)pyridine derivatives. Electrophilic substitutions in pyridine do not proceed or only partially; however, heteroaromatic characterization can be activated by electron-donating group. Pyridine does not exhibit alkylations and acylations reactions because they lead only to the addition at the nitrogen atom. In the 3rd position substitution reaction is

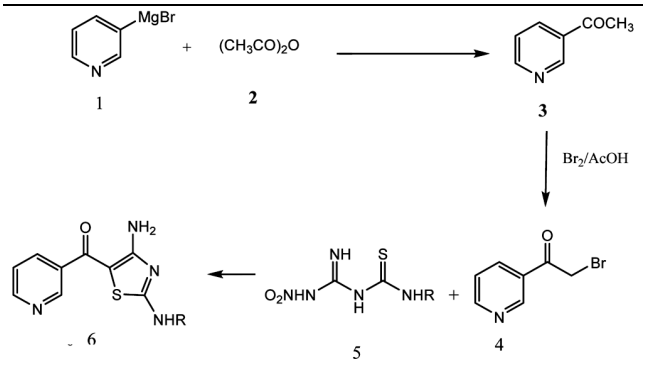
Table I — Structure of 3-(2-alkylamino-4-aminothiazole-5-oyl)pyridines

Compd	Mol. formula	Structure	Yield (%)
6a	$C_{17}H_{16}N_4OS$		75
6b	$C_{12}H_{14}N_4OS$		68
6c	$C_{12}H_{14}N_4OS$		62
6d	$C_{14}H_{20}N_4OS$		72
6e	$C_{14}H_{20}N_4OS$		70

energetically favourable. The development of adequate synthetic methods to synthesis of target compounds using 3-acetyl pyridine. 3-acetylpyridine undergoes bromination using hydrobromic acid to form bromo compound. Thereafter, addition of alkylthiourea in the presence of suitable base gave the targeted compounds. The yellow product obtained was crystallized from ethanol-water (2:1).

DPPH Radical Scavenging Assay

The fastest, simplest and inexpensive method for measuring the antioxidant capacity of a substance include the use of free radical, 2,2-diphenyl-1-picrylhydrazyl (DPPH). The main advantage of DPPH is to test the power of compounds to perform as hydrogen donors or free radical scavengers. The antioxidants tested in DPPH were also very effective in cell systems. It also provides information on the ability of compounds to donate electrons during the oxidation process. The mechanism of radical scavenging assay is based on the shifting of acid H atom from the mixture to the DPPH radical to form DPPH-H. Antioxidant activity of synthesized compounds, IC_{50} was also determined by measuring the values in Table II. All the synthesized compounds showed good and moderate activity. Compounds **6a** and **6b** showed good radical scavenging extent while compounds **6c** exhibited moderate radical scavenging activity with the comparison of standard butylated hydroxyanisole. Hence the variation exhibited in the DPPH scavenging capacity can be attributed to the effect of different substitution present in the amino group.



R- Ethyl, propyl, isopropyl, butyl, allyl

Scheme I

Table II — DPPH radical scavenging activity of 3-(2-alkylamino-4-aminothiazole-5-oyl)pyridines **6a-e**

Compd	IC_{50}
6a	79
6b	92
6c	146
6d	204
6e	474

Computational studies

The first task of the computational work is to determine the optimal geometry of the pyridinyl thiazole molecule. DFT method is used to evalute HOMO-LUMO studies utilize B3LYP method with the basis set 6-31G Gaussian 09 software[20]. DFT calculation has been recognized by the chemistry clique as a reputable and efficacious for the computation of optimized structure, vibration frequencies and Mulliken population analysis of chemical reactions[21]. In quantum mechanical chemistry, the HOMO-LUMO energies play a key role in chemical interactions. Frontier Molecular Orbital provides an insight into the reactivity of molecules and the active site can be revealed by the distribution of frontier orbital (Figure 1). The HOMO-LUMO molecular orbitals composition for synthesized compounds was calculated by DFT/6-31G energy level shown in Figure 2 and Figure 3. To

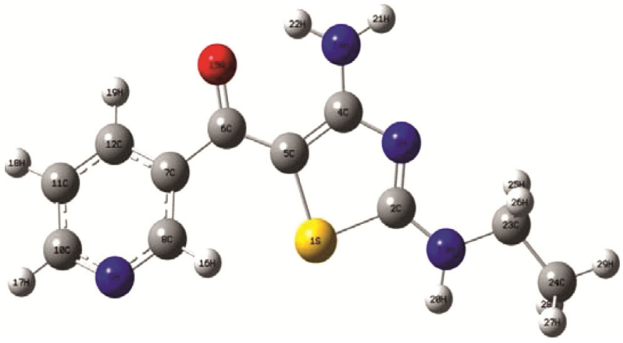


Figure 1 — Optimized structure of 3-(2-ethylamino-4-aminothiazole-5-oyl)pyridine **6a**

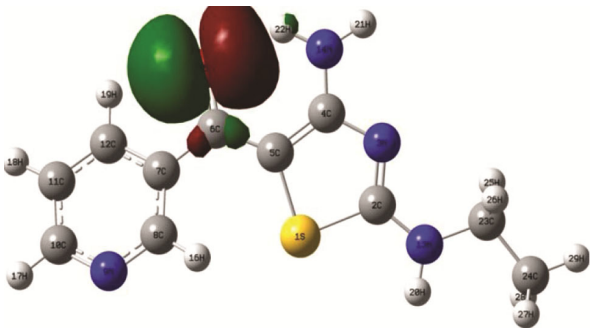


Figure 2 — HOMO of 3-(2-ethylamino-4-aminothiazole-5-oyl)pyridine **6a**

Table III — Electronic parameters of 3-(2-alkylamino-4-aminothiazol-5-oyl)pyridines

Parametres (a.u)	B3LYP/6-31G				
	6a	**6b**	**6c**	**6d**	**6e**
HOMO	−0.24985	−0.24938	−0.24985	−0.24912	−0.25089
LUMO	−0.03520	−0.03464	−0.03622	−0.03439	−0.0 3775
HOMO-LUMO	0.21465	0.21474	0.21363	0.21473	0.21314
I	0.24985	0.24938	0.24985	0.24912	0.25089
A	0.03520	0.03464	0.03622	0.03439	0.0 3775
X	0.14252	0.14201	0.14303	0.14175	0.14432
H	0.10732	0.10737	0.10685	0.10736	0.10825
S	4.65874	4.65679	4.67945	4.65701	4.61893

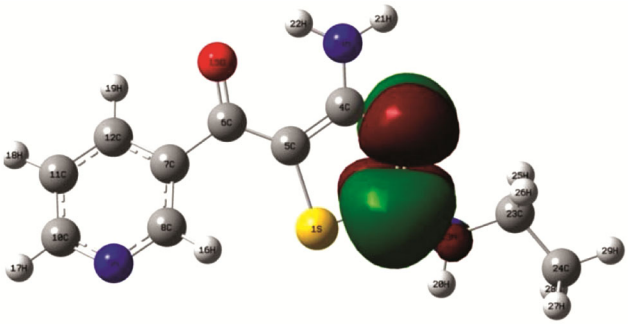


Figure 3 — LUMO of 3-(2-ethylamino-4-aminothiazole-5-oyl) pyridine **6a**

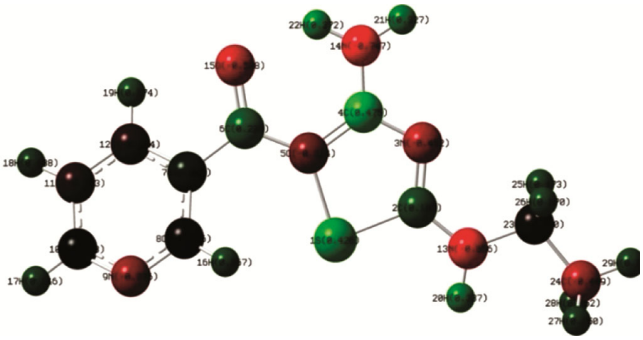


Figure 4 — Mulliken charge of 3-(2-ethylamino-4-aminothiazole-5-oyl)pyridine **6a**

analyze the energy level of the synthesized compounds, the values of HOMO and LUMO were calculated (Table III). In these evidences HOMO and LUMO are located in keto group and thiazole respectively. DFT studies also favorable for providing theoretical informations like electronegativity (χ), hardness (η), softness (S), electrophilicity index (ω). The compound **6e** shows good biological activity because the softness and energy gap value is low compared with all other compounds. Mulliken population analysis on the molecule exhibits main influence of vibrational spectra (Figure 4). All the oxygen and nitrogen carries negative charge, all hydrogen atoms possess positive charge and the carbon atoms carries either positive or negative depends on the neighbouring atom.

Conclusion

In summary, a series of 3-(2-alkylamino-4-aminothiazol-5-oyl)pyridines were synthesized from 3-acetyl pyridine with different thioureas. And all the compounds characterized for their structural investigations. The optimized structural parameters were calculated by B3LYP/ 6-31G basis set. Compounds **6a** and **6b** exhibit good antioxidant activity, and the IC50 values 79 and 92 respectively, all other compounds should be moderately active. The Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) are known as frontier molecular orbitals, which ensure the charge transfer within the molecule. The HOMO-LUMO energy gap is less; hence the compounds are more bioactive. The Mulliken population charge was analyzed.

References

1 Asif M, *Asian J Chem Pharm Sci*, 1(1) (2016) 29.
2 Al-Said M S, Bashandy M S, Al-Qasoumi S I & Ghorab M M, *Eur J Med Chem*, 46 (2011) 137.
3 Banik B K & Becker F F, *Eur J Med Chem*, 45 (2010) 4687.
4 Zhao H, Shi L, Cao J Q, Li W, Wen X & Zhao Y Q, *Chin Chem Lett*, 21 (2010) 1216.
5 Bondock S, Khalifa W & Fadda A A, *Eur J Med Chem*, 42 (2007) 948.
6 Islam F, Hossain M A M, Shah N M, Talukder Barua H, Kabir M A, Khan M J & Mullick R, *J Org Chem* (2015), https://doi.org/10.1155/2015/525239.
7 Kadhim A J,*Iraq Natl J Chem*, 47 (2012) 378.
8 El-Dean A M K, Abd-Ella A A, Hassanien R, El-Sayed M E A & Abdel-Raheem S A A, *ACS Omega*, 4(5) 8406.
9 Thomas N E, Thamkachy R, Sivakumar K C, Sreedevi K J, Louis X L, Thomas S A, Kumar R, Rajasekharan K N, Cassimeris L & Sengupta S, *Mol Cancer Ther*, 13 (2014) 10.1158/1535-7163.MCT-13-0479.
10 Kant V, *Science International*, 1(7) (2013) 253.
11 Ayati A, Bakhshaiesh T O, Moghimi S, Esmaeili R, Majidzadeh A K, Maliheh Safavi M, Firoozpour L & Foroumadi S E A, *Eur J Med Chem*,155 (2018) 483.

12 Romagnoli R, Baraldi P G, Brancale A, Ricci A, Hamel E, Bortolozzi R, Basso G & Viola G, *J Med Chem*, 54 (2011) 5144.
13 Romagnoli R, Baraldi P G, Salvador M K, Camacho M E, Preti D, Aghazadeh Tabrizi M, Bassetto M, Brancale A, Hamel E, Bortolozzi R, Basso G & Viola G, *Bioorg Med Chem*, 20 (2012) 7083.
14 Shao L, Zhou X, Hu Y, Jin Z, Liu J & Fang J, *Synth React Inorg Metal-Org Nano-Metal Chem*, 36 (2006) 325.
15 Lee Y S, Chuang S H, Huang L Y L, Lai C L, Lin Y H, Yang J Y, Liu C W, Yang S-C, Lin H S, Chang C C, Lai J Y, Jian P S, Lam K, Chang J M, Lau J Y N & Huang J J, *J Med Chem*, 57 (2014) 4098.
16 Mohana K N & Pradeep Kumar C B, *ISRN Org Chem*, 2013, Article ID 620718, 1-8.
17 Djukic M, Fesatidou M, Xenikakis I, Geronikaki A, Angelova V T, Savic V & Saso L, *Chemico-Biological Interactions*, 286 (2018) 119.
18 Kasote D M, Hegde M V & Bae H, *Int J Biol Sci*, 11 (2015) 982.
19 Kavitha P N, Mohan S & Saravanan J, *J Med Chem*, 1 (2011) 1.
20 Saranya S, Ayyappan S, Nithya R, Sangeetha R K & Gokila A, *Digest Journal of Nanomaterials and Biostructures*, 13 (2018) 97.
21 Spirtovic-Halilovic S, Salihovic M, Dzudzevicancar H, Trifunovic S, Roca S, Softic D & Zavrsnik D, *J Serb Chem Soc*, 79(4) (2014) 435.