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Green Synthesis, Characterization and their Biological Activities of Schiff's Bases of Certain Benzothiazole Derivatives

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ABSTRACT

Heterocyclic compounds play very important role in industries with wide applications. There are number of heterocyclic compounds used as medicine in different therapeutic targets. Substituted-1, 3-benzothiazoles are one of the important classes of bicyclic hetero-compounds. These moieties are serving as unique and versatile scaffolds for experimental drug design. 1,3-Benzothiazole derivatives have attracted considerable attention in synthetic as well as pharmaceutical chemistry, because of its potent and significant pharmacological activities, some substituted amino benzothiazoles have been synthesized from 2,4-dimethylaniline by utilization of industrial waste (Mixture of NaCl and NaBr) for ring cyclization. The synthesized compounds are characterized by spectral analysis and their biological activities were evaluated.

Keywords: Green Chemistry, Benzothiazole, IR,NMR, MS, Schiff's bases & Microbial activity.

INTRODUCTION:

The most of common heterocyclic compounds like thiazole is an important pharmacophore in drug discovery and development process in industries. Most of heterocyclic compound like thiazole and their derivatives covers wide range of therapeutics targets including anti-inflammatory[1, 2], antifungal[3], antiviral[4],

analgesic[5], antioxidant [6,7], antipsychotic [8], anticonvulsant [9], antidiabetic [10, 11], anti-tubercular [12, 13] and anti-cancer [14] etc.

Thiazole is naturally found in vitamin-B (Thiamin). This vitamin is water soluble, which helps the body to release energy from carbohydrates at the time of metabolism and its enzyme play a vital role in decarboxylation of α-keto acid and as an electron sink. It is helpful for normal functioning of the nervous system due to its role in the synthesis of the acetylcholine a neurotransmitter. Cancer is most common dreadful disease affecting abnormal growth of cells. It changes the genetic activity of cell [15, 16]. Globally, cancer is major leading causes of death. The WHO report (2018) shows around 10 million people died by cancer, every year. About 0.3 million new cancer cases are diagnosed in children aged between one to ninteen years [17,18]. There is no age factor for cancer disease. Cancer chemotherapy causes several adverse effects, which include multiple drug resistance, adverse events, unwanted side effects, and selectivity. Benzothiazole with Schiff's base [19] will increase the biological activities [20, 21], we also considered the acetophenone moiety with functional group like -NO_2, -Br, -OCH_3, [22, 23, 24] and -Cl enhanced the biological activities of synthesized drugs.

Along with conventional approaches, effective and eco-friendly alternative reactions are being developed with commercially available reagents and the principles of green chemistry [25].This method avoid the use of toxic solvents. Reactions are performed by using industrial waste as a reagent and water as the solvent, making the process relatively low cost with generation of recyclable salt. Multistep reactions of the C-2-substituted benzothiazole played a special role in the designing of biologically active compounds [26, 27].The advantages of these reactions are effectiveness, simple experimental implementation and high yields.

EXPERIMENTAL:

Materials and reagents:

All the chemicals, which have been used for synthesis of Schiff's base were supplied by Sigma Aldrich, Loba chemie and Merck. All the reactions were monitored and purity of the products was checked by thin-layer chromatography (TLC) and mixed melting point. TLC was performed on Merck 60 F-254 silica gel plates with visualization by short UV light and further with iodine chamber, as well as by gas chromatography (GC). The GC was performed on Shimadzu 2014 with capillary column (RTX5, 30 meter). Melting points were determined in capillary tubes in silicon oil bath using a Veego melting point apparatus. 1H NMR and 13C NMR spectra were recorded on BRUKER AVANCE Neo 500 MHz NMR spectrometer. The sample was dissolved in $CHCl_3$. Chemical shifts are reported from internal tetramethylsilane standard and chemical shifts are given in δ units. Infrared spectra were taken on BRUKER AVANCE IVDR FTIR. The GC-MS spectra were recorded on a Shimadzu GC-MS.

Antimicrobial activity:

The antimicrobial activities of all the synthesized compounds were evaluated by the Kirby-Bauer disk diffusion method [28,29]. The strains were procured from Institute of Microbial Technology, Chandigarh. All cultures were maintained at 4ºC. Cover nutrient agar slants throughout the experiment. The cultures were incubated overnight at 37ºC in nutrient broth before using for antimicrobial activity. Five hundred micro liters of overnight old bacterial/fungal suspension were spread over the nutrient agar plates using a sterile cotton swab in order to get a uniform microbial growth. DMSO was used to dissolve synthesized compounds. Under aseptic conditions, empty sterilized discs (Whatman No. 5, 6 mm diameter) were impregnated with different concentrations (25, 50, 75, and 100 µg/disc) of respective synthesized compounds and placed on the agar surface. Paper disc moistened with aqueous DMSO was placed on seeded Petri-plates as a vehicle control. The plates were left for 30 min. at room temperature to allow the diffusion of synthesized compounds and then incubated at 37 ºC for 24 h. The antimicrobial activity was evaluated by measuring the zone of inhibition against the test of microorganism. All experiments were carried out in triplicates.

Synthesis of 2-hydrazinyl-4, 6-dimethyl-1, 3-benzothiazole (4) : A mixture of 2, 4-dimethylaniline **(1)** (1.0 mmol) and ammonium thiocyanate (1.1 mmol) in 30% hydrochloric acid (1.1 mmol) was stirred at 80°C for 6-8 hours, monitored by GC. The solid filtered gave **(2)**. Mixture of **(2)** (1.0 mmol) was mixed industrial waste salt (Sodium chloride/bromide) (2.0 mmol) followed by addition of sulphuric acid. It was stirred at 80°C for 1-2 hour, monitored by GC. The solid filtered gave **(3)**. Mixture of **(3)** (1.0 mmol) in water followed by addition of hydrazine hydrate (1.5 mmol) was stirred at 100-110°C for 1-2 hours. The progress was monitored by GC. The solid filtered gave 2-hydrazinyl-4,6-dimethyl-1,3-benzothiazole **(4)**.

General method for the synthesis 4, 6-dimethyl-2-[(2*E*)-2-(1-phenylethylidene) hydrazinyl]-1, 3-benzothiazole derivatives (**6 a-i)**: A mixture of 2-hydrazinyl-4, 6-dimethyl-1, 3-benzothiazole **(4)** (1.0 mol.), and substituted aromatic ketones moiety (**5a-i)** (1.05 mol) was mixed in a 50 mL round bottom flask with water as solvent and refluxed for 4 h. The progress of the reaction was monitored by TLC and GC. The rate of reaction was controlled by applying occasional stirring. A crystalline solid was obtained. The product was filtered, washed with water and recrystallized from ethanol: water, which gave corresponding benzothiazole derivatives (6 a-i) as products. ^{1}H NMR (500 MHz, $CDCl_3$-d6, ppm), ^{13}C NMR (500 MHz, $CDCl_3$) analysis and M+ ion peak in mass analysis of synthesised compounds (6 a-i) as follows:

4, 6-dimethyl-2-{(2*Z*)-2-[1-(3-nitrophenyl) ethylidene] hydrazinyl}-1, 3-benzothiazole (**6a**): ^{1}H NMR (500 MHz, $CDCl_3$-d6, ppm): δ 2.29 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.9-9.4 (m, 6H, Ar-H; ^{13}C NMR (500 MHz, $CDCl_3$): δ 13.3, 17.7, 21.0, 71.7, 124.2 - 147, 168.1, MS, m/z: 339 $(M+H)^+$.

2-{(2*Z*)-2-[1-(2,4-dichlorophenyl) ethylidene] hydrazinyl}-4, 6-dimethyl-1, 3-benzothiazole (6b):

^{1}H NMR (500 MHz, $CDCl_3$-d6, ppm): δ 2.28 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 6.89-7.36 (m, 5H, Ar-H; ^{13}C NMR (500 MHz, $CDCl_3$): δ 17.31, 18.0, 21.93, 118 - 146, 167.1; MS, m/z: 363.0 (M+H) +, m/z: 365.0 $(M+H+2)^+$.

2-{(2*Z*)-2-[1-(4-bromophenyl)ethylidene] hydrazinyl}-4,6-dimethyl-1,3-benzothiazole (6c) : ^{1}H NMR (500 MHz, $CDCl_3$-d6, ppm): δ 2.19 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.97-7.68 (m, 6H, Ar-H; ^{13}C NMR (500 MHz, $CDCl_3$): δ 13.24, 18.08, 21.28, 118.97 – 146.76, 168.0; MS, m/z: 373.0 (M+H) +, m/z: 375.0 $(M+H+2)^+$.

2-{(2*Z*)-2-[1-(2-methoxyphenyl)ethylidene]hydrazinyl}-4,6-dimethyl-1,3-benzothiazole (6d) : ^{1}H NMR (500 MHz, $CDCl_3$-d6, ppm): δ 2.20 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 6.94-7.80 (m, 6H, Ar-H; ^{13}C NMR (500 MHz, $CDCl_3$): δ 13.39, 18.71, 21.25, 113.82 – 160.91, 167.77; MS, m/z: 324.0 (M+H) +, m/z: 325.0 $(M+H+2)^+$.

4, 6-dimethyl-2-[(2*Z*)-2-(1-phenylethylidene) hydrazinyl]-1, 3-benzothiazole (6e): ^{1}H NMR (500 MHz, $CDCl_3$-d6, ppm): δ 2.24 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 7.01-7.88 (m, 7H, Ar-H; ^{13}C NMR (500 MHz, $CDCl_3$): δ 13.53, 18.14, 21.29, 118.0 – 146.0, 167.98; MS, m/z: 293.0 (M+H) +, m/z: 294.0 $(M+H+2)^+$.

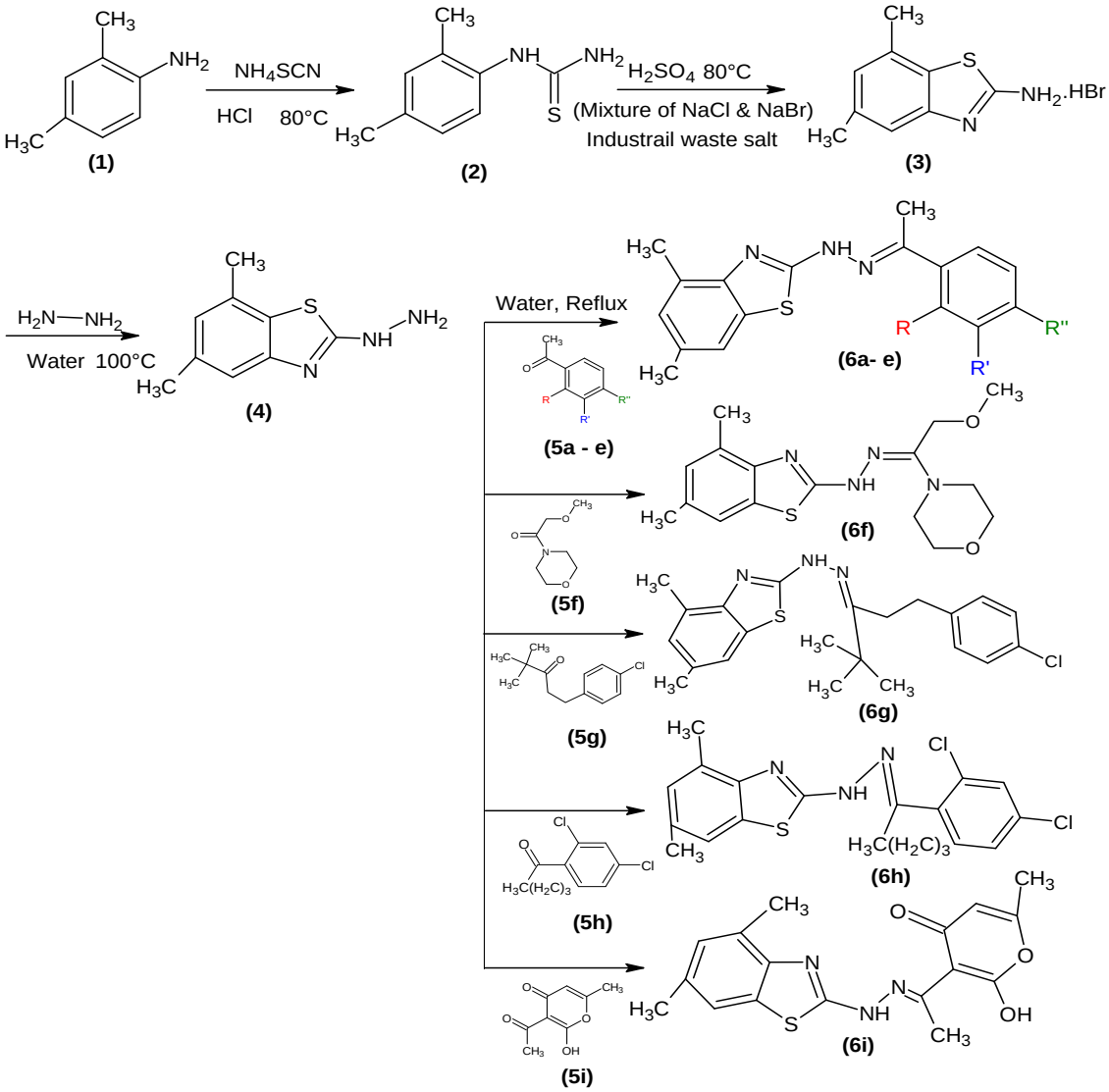
2-{(2*Z*)-2-[2-methoxy-1-(morpholin-4-yl) ethylidene] hydrazinyl}-4, 6-dimethyl-1, 3-benzothiazole (6f) : ^{1}H NMR (500 MHz, $CDCl_3$-d6, ppm): δ 2.36 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 3.70 (s, 2H, CH_2), 4.52 (t, 8H, CH_2),6.94-7.28 (m, 2H, Ar-H; ^{13}C NMR (500 MHz, $CDCl_3$): δ 10.21, 21.10, 118.87 – 148.83, 172.32; MS, m/z: 334.0 (M+H) +, m/z: 338.0 $(M+H+3)^+$.

2-{2-[1-(4-chlorophenyl)-4, 4-dimethylpentan-3-ylidene] hydrazinyl}-4, 6-dimethyl-1, 3-benzothiazole (6g) : ^{1}H NMR (500 MHz, $CDCl_3$-d6, ppm): δ 1.29 (s, 9H, CH_3), 2.20 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 1.33 (t, 2H, CH_2), 1.70 (t, 2H, CH_2), 6.89-7.45 (m, 7H, Ar-H; ^{13}C NMR (500 MHz, $CDCl_3$): δ 17.70, 21.30, 27.0, 29.2, 30.2, 37.2, 71.7, 124.0 – 139.50, 158.9; MS, m/z: 397.0 $(M+H)^+$.

2-{2-[1-(2,4-dichlorophenyl) pentylidene] hydrazinyl}-4,6-dimethyl-1,3-benzothiazol (6h) : ^{1}H NMR (500 MHz, $CDCl_3$-d6, ppm): δ 0.89 (s, 9H, CH_3), 2.30 (s, 3H, CH_3), 2.65 (t, 3H, CH_3), 1.38 (t, 2H, CH_2), 1.73 (t, 2H, CH_2), 2.90 (t, 2H, CH_2), 6.98-8.65 (m, 5H, Ar-H; ^{13}C NMR (500 MHz, $CDCl_3$): δ 13.86, 18.13, 21.46, 22.68, 26.52, 30.89, 114.52 – 151.49, 158.98; MS, m/z: 406.0 (M+H) +, m/z: 408.0 $(M+H+3)^+$.

3-{(1*E*)-1-[2-(4, 6-dimethyl-1, 3-benzothiazol-2-yl) hydrazinylidene] ethyl}-2-hydroxy-6-methyltetrahydro-4*H*-pyran-4-one (6i) : ^{1}H NMR (500 MHz, $CDCl_3$-d6, ppm): δ 1.35 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.14 (t, 3H, CH_3), 2.21 (t, 3H, CH_3), 3.25 (t, 1H, CH), 3.52 (t, 2H, CH_2), 4.32 (t, 1H, CH), 4.80 (t, 1H, CH), 7.14-7.87 (m,

2H, Ar-H; ^{13}C NMR (500 MHz, $CDCl_3$): δ 11.73, 16.83, 20.81, 28.61, 39.78, 98.35 – 170.05, 180.37, 204.58; MS, m/z: 347.4.0 (M+H) +.



Scheme 1: Synthetic route of compounds (6a-i)

RESULTS AND DISCUSSION

A series of 4, 6-dimethyl-2-[(2*E*)-2-(1-phenylethylidene) hydrazinyl]-1, 3-benzothiazole derivatives, (**6a-i)** was synthesized according to Scheme I. The physical data and yield of synthesized compounds (**6a-i)** are reported in Table 1**.**

The structure of the title compounds (**6a-i)** was confirmed by FT-IR, NMR and MS. As a representative analysis of compound (**6a)** Figure-1, the direct IR spectrum showed C=C/C=N absorption bands at 1629-1475 cm^{-1}. The ^1H NMR spectrum of

compound (**6a)** Figure-2 displayed three singlets at aliphatic region δ 2.29 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), and a multiplet at aromatic region at 6.9-9.4 (m, 6H, Ar-H; ^{13}C NMR spectrum of compound (**6a)** Figure-3 revealed the three signal of methyl carbon δ 13.3, 17.7, 21.0, and a signal at 71.7, connecting to Schiff's Bases. Aromatic carbons showed at 124.2 - 147, carbon between two hetro atoms (S and N) 168.1. Structure of compound (**6a)** Figure-4 was further confirmed by molecular ion peak at *m*/*z* 339 $(M+H)^+$. Structures of all the derivatives were ascertained similarly.

Table. 1. Physical data and yield of synthesized compounds (6a-i)

Comp.	R	R'	R"	Yield %	MP
4	-	-	-	95.4	178--180°C
6a	H	NO_2	H	89.7	246-249°C
6b	Cl	H	Cl	91.55	144-146°C
6c	H	H	Br	85.66	185-188°C
6d	OCH_3	H	H	86.8	153-155°C
6e	H	H	H	92.11	152-155°C
6f	-	-	-	79.62	179-183°C
6g	-	-	-	82.32	176-179°C
6h	-	-	-	87.23	168-171° C
6i	-	-	-	75.68	205-208°C

Antimicrobial Activity The synthesized compounds **(6a-i)** were screened for their antibacterial activity against the standard Gram-negative bacteria, *E. coli* (MTCC 443), *P. aeruginosa* (MTCC 1688) and Gram-positive *S. aureus* (MTCC 96), S. *pyogenus* (MTCC 442), Gentamycin, Ampicillin and Chloramphenicol, Ciprofloxacin were used as reference.

Antifungal activity against *C. albicans* (MTCC 227), *A. niger* (MTCC 282), *A. clavatus* (MTCC 1323). Nystatin and Greseofulvin were used as reference, which is a fast-growing non-pathogenic strain to assess the activity of the compounds in primary screening. The results of antimicrobial activity are reported in Tables 2 and 3.

Table. 2. Antibacterial screening of compounds (6a-i) (zone of inhibition in mm)

ANTIBACTERIAL ACTIVITY				
Sample	***E.coli***	***P. aeruginosa***	***S. aureus***	***S. pyogenus***
6a	250	250	100	62.5
6b	250	50	200	125
6c	500	100	250	500
6d	500	250	500	100
6e	500	250	62.5	500
6f	250	500	250	250
6g	250	250	250	125
6h	125	125	100	125
6i	500	250	500	500
Gentamycin	0.05	1	0.25	0.5
Ampicillin	100	-	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50

Table.3. Antifungal screening of compounds (6a-i) (zone of inhibition in mm)

ANTIFUNGAL ACTIVITY			
Sample Code	***C. albicans***	***A. niger***	***A. clavatus***
6a	250	250	250
6b	250	500	500
6c	500	500	1000
6d	500	>1000	>1000
6e	500	>1000	>1000
6f	500	500	>1000
6g	250	200	200
6h	500	250	>1000
6i	>1000	>1000	>1000
Nystatin	100	100	100
Greseofulvin	500	100	100

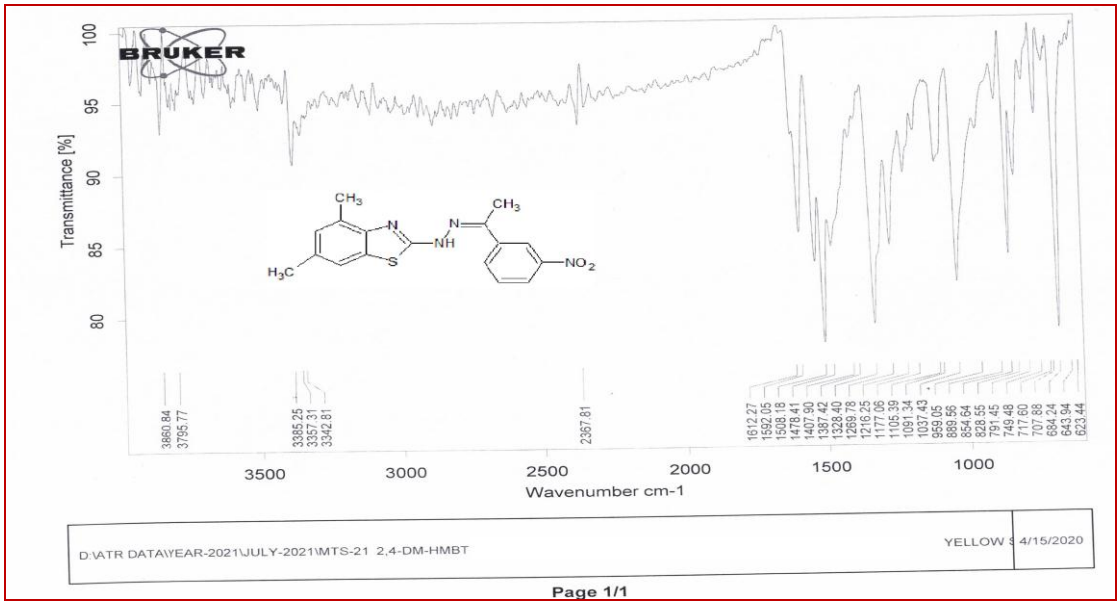


Figure. 1. FT-IR Spectrum of compound (6a)

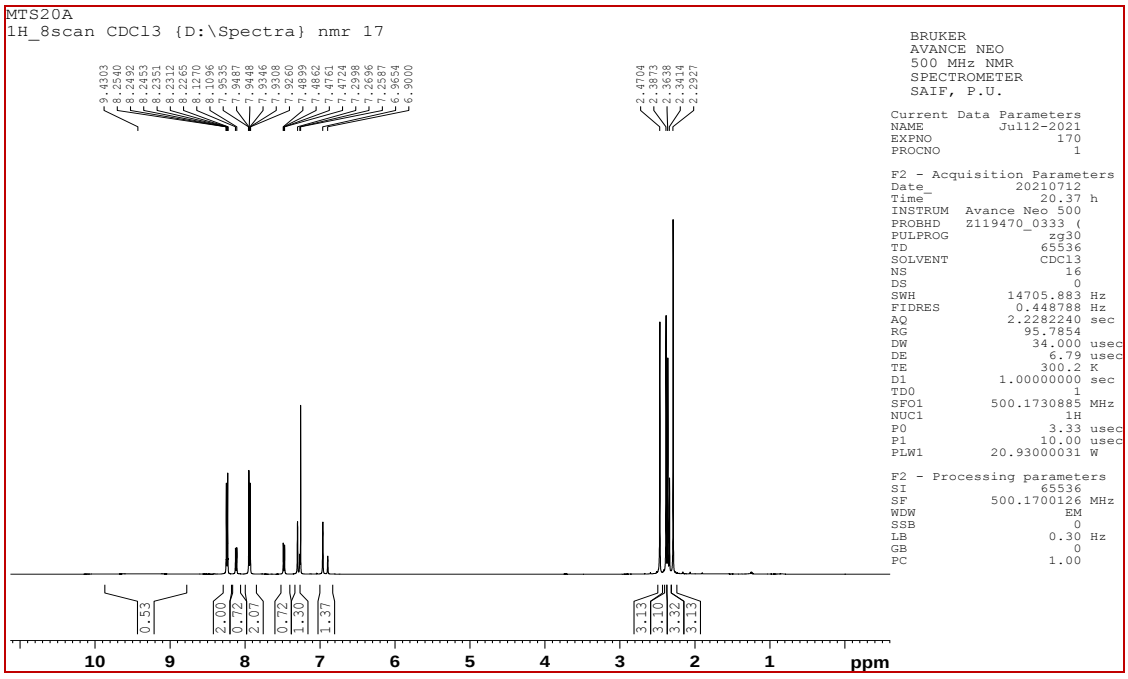


Figure 2: ^{1}H NMR Spectrum of compound (6a)

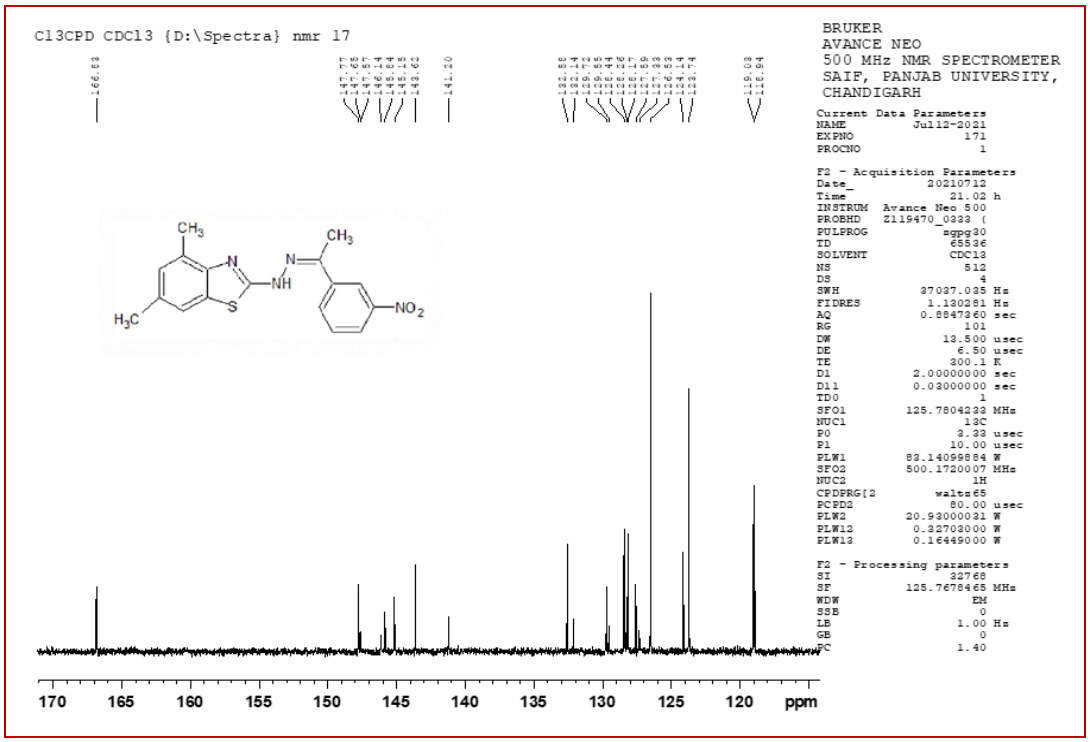


Figure. 3. ^{13}C NMR Spectrum of compound (6a)

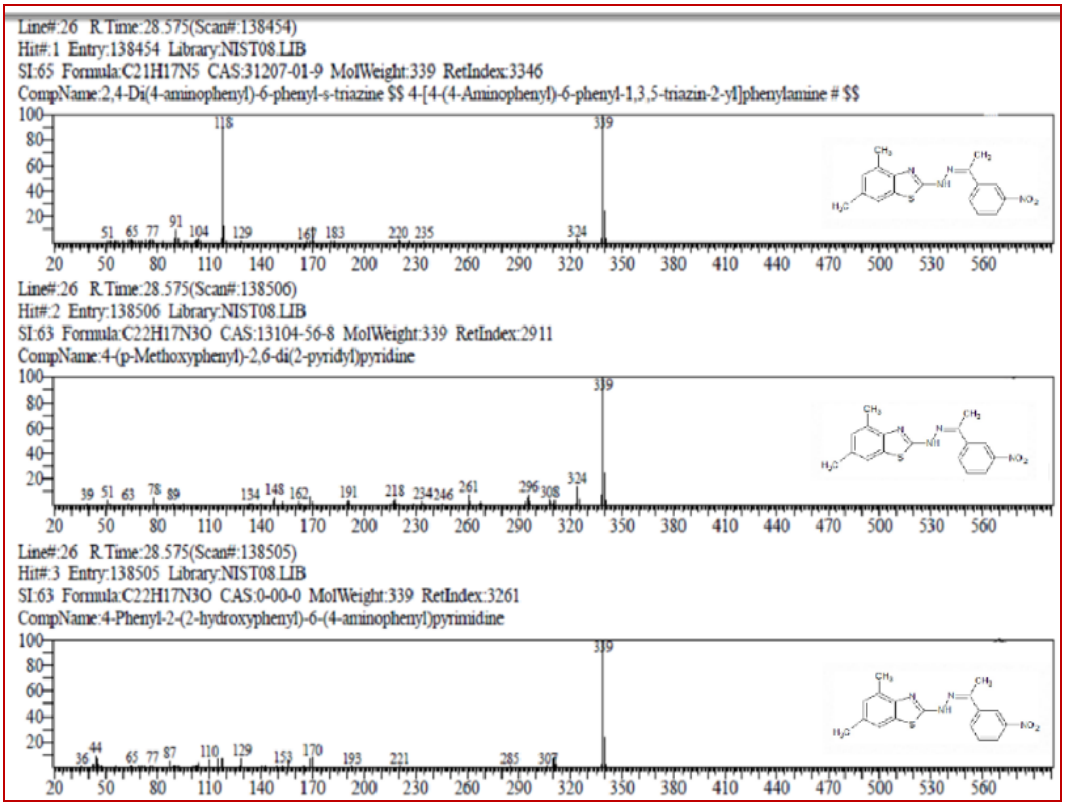


Figure. 4. Mass Spectrum of compound (6a)

CONCLUSION:

In the present work, the synthesis and biological screening of benzothiazole derivatives has been reported. Out of all the synthesised (6a-i) compounds, 3-{(1*E*)-1-[2-(4, 6-dimethyl-1, 3-benzothiazol-2-yl) hydrazinylidene] ethyl}-2-hydroxy-6-methyltetrahydro-4*H*-pyran-4-one (6i) was found highly active against all the tested bacteria and fungus as compared to reference drugs. So this process is commercially highly effective as it saves man power, time, utility, health and safety of man. It is environment friendly, because industrial waste has been used, which is critical to dispose.

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