Synthesis and characterization of Thiophene fused arylbenzo[4,5]thieno[2,3-d]thiazole derivatives

Iram Akbar[a], Muhammad Iqbal[a,*], Muhammad Abdul Haleem[b,*], Saqib Ali[c,*]

[a]Department of Chemistry, Bacha Khan University, Charsadda 24420, KPK, Pakistan

[b]Department of Chemistry, University of Buner, Sowari, Buner, KPK, Pakistan

[c]Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan

Abstract

Heterocyclic compounds containing nitrogen and sulfur play a key role in medicinal chemistry owing to their immense pharmacological potential. Among the Sulfur and Nitrogen heterocycles 5-memebered are more important. Therefore, here an attempt has been made for synthesis of Thiophene fused arylbenzo[4,5]thieno[2,3-d]thiazole derivatives. These heterocycles have been prepared using a facile, cheap and one-pot catalytic method from 2-(2-bromophenyl)acetonitrile, substituted hetero-aromatic aldehydes, and sulfur powder. The reactions preceded in the presence 1,10- phenonthroline, K_2CO_3 and Cu(I)Cl in DMSO. Eight new thiophen-thaizole derivatives have been synthesized, purified and herein coded as **IMA-R1, IMA-R2, IMA-R3, IMA-R4, IMA-R5, IMA-R6, IMA-R7** and **IMA-R8** (Table 1)**.** These synthesized thiophen-thaizole heterocycles were characterized using different spectroscopic techniques, like ^{1}HNMR, ^{13}CNMR, FT-IR, UV-Visible and spectrofluorimetry. ^{1}HNMR spectroscopic data revealed that all the characteristic peaks that indicated the formation of the expected fused thiophene-thiazole compounds (Table 2). Similarly, the ^{13}C chemical shift values were in good agreement to the proposed molecular structures of the synthesized thiophen-thaizole heterocycles (Table 3). The λ_{max} values were found in range of 282-315 nm assignable to the conjugated system. The λ_{max} values and the spectrofourimetric emission patterns of the compounds are in accordance to the electronic properties of the substituents. FTIR spectroscopic analysis revealed the characteristic bands including a C-S stretching vibration peak which showed the formation of the desired compounds (Fig. 1).. Results of the above mentioned spectroscopic techniques have indicated the successful syntheses of the desired heterocyclic compounds.

Keywords: fused heterocyclic compounds; synthesis; spectroscopic characterization.
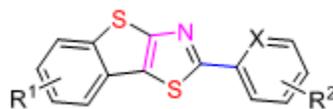
Introduction

Heterocyclic compounds containing oxygen, nitrogen and sulfur play a key role in organic chemistry and its sub-branches such as medicinal chemistry owing to their immense pharmacological potential. Of the many types, thiophene and thiazole are 5-memebered heterocyclic compounds which are ubiquitous in organic materials, natural products pharmaceuticals and bio-active molecules (W. Zhang *et al*., 2020). Their specific applications have been reviewed (P. M. Jadhav *et al*., 2021 and Archna *et al*.,2020). In early stages of COVID-19 pandemic, a thiazole containing drug *ritonavir* has been used against the novel virus (Z. Zhu *et al*., 2020). Similarly, many marketed compounds having thiophene nuclei have been listed and others patented (Archna *et al*., 2020).

Owing to their immense importance, compounds containing these nuclei are under great consideration in synthesis organic chemistry groups. Different synthetic procedures for the synthesis of these nuclei, i-e, thiophene and thiazole have been reported (S. Chen *et al*., 2018 and X. Chen *et al*., 2014). However, the fused heterocyclic systems containing both compounds have been prepared by fewer and relatively sophisticated methods. Their synthetic procedures are still being explored and developed. Heikel et al., 1973, Middleton at al., 1942 and Zhiryakov et al., developed methods to prepare benzo[4,5]-thieno[2,3-d]thiazole compounds. However, these methods needed already prepared benzothiophene skeleton and were restricted to the synthesis of amino and methyl substituted derivatives only.

Recently Deng et al., 2018 and Jiang et al., 2019 independently reported similar methods for the preparation of fused thieno[3,2-d]thiazole nucleus using aromatic aldehydes and elemental sulfur catalyzed by copper. It was a great breakthrough to use elemental sulfur as sulfur source owing to its stability, non-toxicity and being cheap. The latest procedure was developed and reported by Zhang et al., 2020 which also used elemental sulfur as sulfur source but in the end product, the positions of S-atoms are different than those of the Deng et al., 2018 and Jiang et al., 2019 (scheme 1). This is a one pot synthetic procedure using non-toxic reactants at feasible working temperature. We have synthesized new 2-Arylbenzo[4,5]thieno[2,3-d]thiazole derivatives using the latest developed procedure. To the best of our knowledge, the series of fused heterocyclic compounds arising from the substituted pyridine carboxaldehyde (scheme 2) have not been reported before.
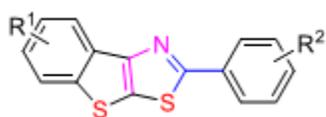
A. Deng et al., and Jiang et al.   B. Zhang et al

Scheme 1: Two forms of 2-Arylbenzo[4,5]thieno[2,3-d]thiazole skeleton, A and B differing in position of Sulfur.

Experimental

Materials

All used chemicals were dried and purified purchased from Sigma Aldrich, USA. Water used during synthesis was singly distilled. Purified solvents used were acquired from Merck, Germany,

Physical measurements

Melting points were measured in capillary tubes on a Gallenkamp melting point apparatus. Nicolet-6700 FT-IR spectrophotometer was used for measurement of spectra in range of 4000 to 400 cm^{-1}. Bruker Advance Digital 300 MHz NMR spectrometer was used for ^{1}H and ^{13}CNMR spectral analysis using chloroform as an internal reference and at room temperature, ^{1}H spectra were run at 300 MHz in CDCl$_3$.

General procedure for synthesis: An already reported method (W. Zhang *et al.,* 2020) with slight modification was followed for preparation of the compounds as depicted in scheme 2. Each of the compounds was prepared by reacting 2-(2-bromophenyl)acetonitrile (0.13 ml, 1.0 mmol) with substituted pyridinecarboxaldehyde in the presence of CuCl (0.152 g, 20 mol %), 1,10-phenonthroline (0.277 g, 20 mol %), sulfur powder S$_8$ (0.048 g, 1.5 mmol), and K$_2$CO$_3$ (0.138 g, 1.0 mmol). The substituted pyridinecarboxaldehyde derivative was 6-bromo-3-pyridinecarboxaldehyde (1 mmol, 0.186 g), 6-metoxy-3-pyridinecarboxaldehyde (1 mmol, 0.137 g), 6-methylpyridine-2-carboxaldehyde (1 mmol, 0.121 g), 5-chloro-2-formylpyridine (1 mmol, 0.142 g), 6-bromo-2-pyridinecarboxaldehyde (1 mmol, 0.186 g), 2-bromo-3-pyridinecarboxaldehyde (1 mmol, 0.186 g), 2-metoxy-6-pyridinecarboxaldehyde (1 mmol, 0.140 g) and 5-bromopyridine-2-carboxaldehyde (1 mmol, 0.186 g) corresponding to compounds IMA-R1 to IMA-R8, respectively. The reaction mixture was stirred in DMSO at 120 °C for till the disappearance of 2-(2-bromophenyl)acetonitrile in the reaction mixture as indicated by TLC.

Separation and purification: After completion of reaction, the reaction mixture was cooled to room temperature and added to 250 ml distilled water followed by mixing with 60 ml ethyl

acetate. The organic layer was obtained, dried over anhydrous sodium sulphate (Na_2SO_4) and rotary evaporated. The crude product was separated/purified by column chromatography and were characterized by FTIR, UV, ^{1}HNMR, ^{13}CNMR spectroscopic techniques.
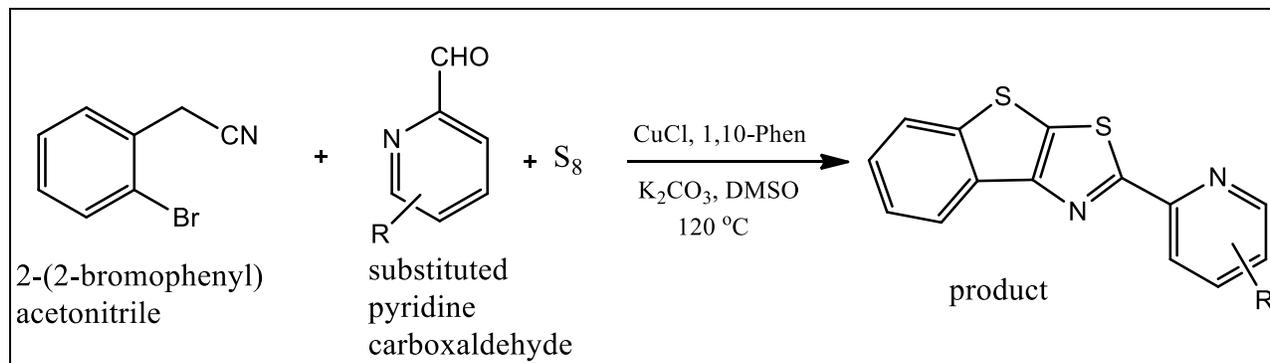
Scheme 2: Synthetic procedure for the synthesized compounds.

Table 1: Proposed structures of the synthesized compounds.

S. No	compound	Chemical Structure
1	IMA-R1	
2	IMA-R2	
3	IMA-R3	

4	IMA-R4	
5	IMA-R5	
6	IMA-R6	
7	IMA-R7	
8	IMA-R8	
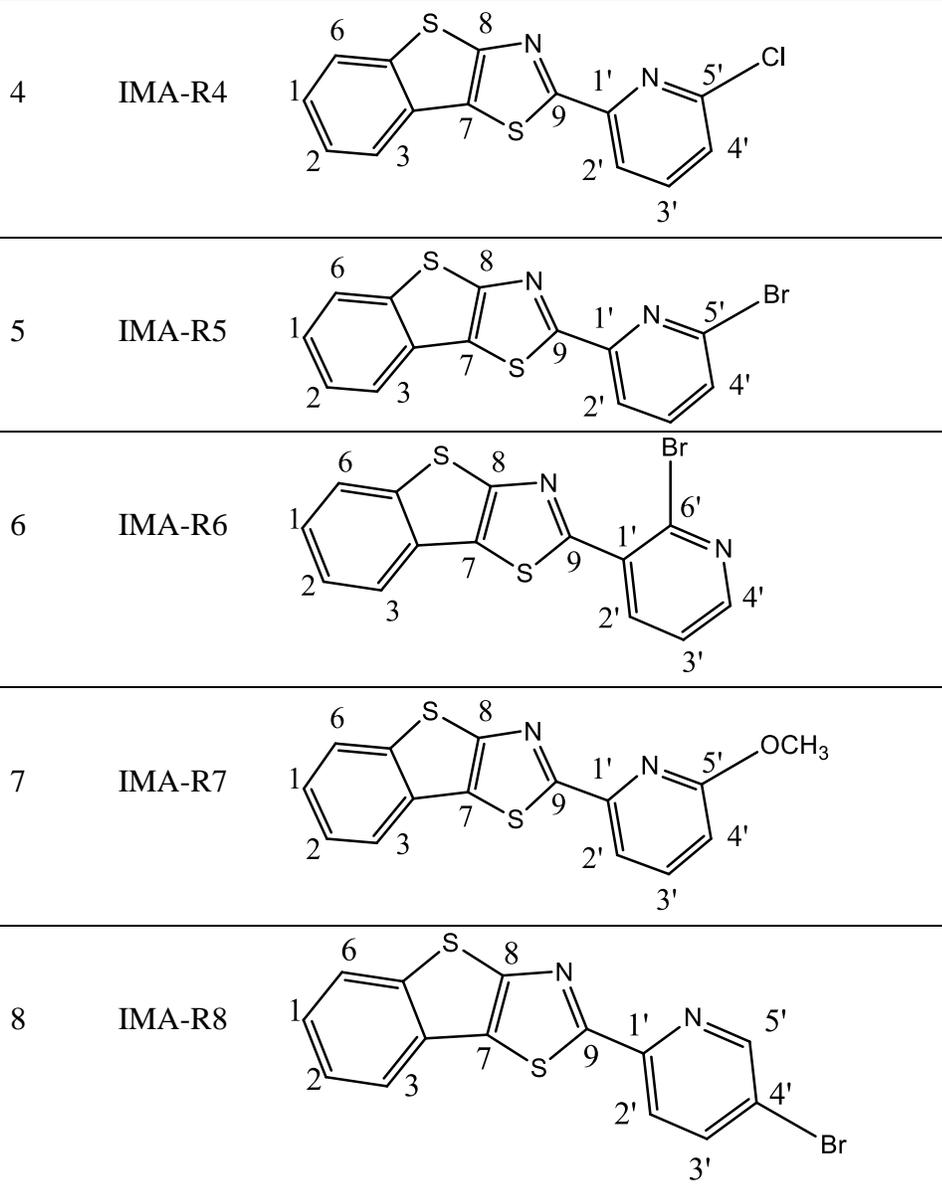
s

IMA-R1: 2-(6-bromopyridine-3-yl)benzo[4,5]thieno[2,3-d]thiazole. Yield (64%). ^{1}HNMR (300 MHz, CDCl$_3$, ppm): Ar-H, benzothienothiazole (7.744, dd, 1H), (7.562, dd, 1H). ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ: 167.7,8, 132.47, 130.90, 128.82. FTIR (cm^{-1}): 2925, 2958, 2854 (Ar-CH), 1732 (C=N), 1454 (C-N), 1378 (C-O, C-C), 800 (C-S), 663 (C-Br). UV-Vis (λ$_{max}$): 293.30 (nm).

IMA-R2: 2-(6-methoxypyridine-3-yl)benzo[4,5]thieno[2,3-d]thiazole. Yield (60%) ^{1}HNMR (300 MHz, CDCl$_3$, ppm) δ: (Ar-H) benzothienothiazole (8.05, d, 1H), (7.98, d, 1H), (7.75, m, 1H), (7.679, m, 1H), (7.596, dd, $J3$=11.9 Hz, $J4$=0.9 Hz, 1H), (7.56 ,m, 1H), (2.735, s) ^{13}C NMR (75 MHz, CDCl$_3$) δ : 138.18, 134.51, 133.87, 133.67, 132.99, 132.74, 131.66, 130.96, 130.14, 129.41, 128.41, 128.14, 127.34, 125.88, 122.73. FTIR (cm^{-1}): 3367 (OH), 2984 (Ar-CH), 1738(C=N), 1449 (C-N), 1235 (C-O), 1044 (C-C), 607 (C-S). UV-Vis (λ$_{max}$): 315.32 (nm).

IMA-R3: 2-(6-methylpyridine-2-yl)benzo[4,5]thieno[2,3-d]thiazole. Yield (65%) ^{1}HNMR (300 MHz, CDCl$_3$, ppm): (Ar-H) benzothienothiazole (8.032, d, J=8.7 Hz, 1H), (7.921, d, J=8.1 Hz, 1H), (7.789, m, 1H), (7.74-7.44, m), (2.73, s). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 133.68, 133, 132.44, 131.67, 130.92, 130.94, 129.41, 128.82, 127.34, 125.89 FTIR (cm^{-1}): 2923, 2956, 2855 (Ar-CH), 1731 (C=N), 1461, 1374, 1239 (C-N), 1045 (C-C), 743 (C-S). UV-Vis (λ$_{max}$): 285.39 (nm).

IMA-R4: 2-(6-chloroypyridine-2-yl)benzo[4,5]thieno[2,3-d]thiazole. Yield (63%). ^{1}HNMR (300MHz, CDCl$_3$, ppm): (Ar-H) benzothienothiazole (8.03, d, J=8.7 Hz, 1H), (7.92, d, J=8.1 Hz, 1H), (7.785, d, J=8.1 Hz, 2H), (7.529, m, 9H), (7.31, m). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 167.80, 139.08, 138.18, 134.51, 133.87, 133.68, 133.01, 132.74, 132.44, 131.76, 131.67, 130.96, 130.92, 130.13, 129.41, 128.82, 128.42, 128.14, 127.34, 125.88, 122.74, 122.39, 116.71. FTIR (cm^{-1}): 2961, 2926, 2856 (Ar-CH), 1744 (C=N), 1258 (C-N), 1014 (C-C), 792 (C-S), 702 (C-Cl). UV-Vis (λ$_{max}$): 284.31 (nm).

IMA-R5: 2-(6-bromoypyridine-2-yl)benzo[4,5]thieno[2,3-d]thiazole. Yield (64%). ^{1}HNMR (300MHz, CDCl$_3$, ppm): (Ar-H) benzothienothiazole (8.41, d, J=8.7 Hz, 2H), (8.16, dd, J=1.8 Hz, 2H), (7.24, m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 167.82, 153.46, 139.06, 138.16, 133.86, 133.69, 133.03, 132.76, 132.43, 132.14, 132.01, 131.69, 131.35, 130.95, 130.12, 129.42, 129.32, 128.82, 128.44,127.71, 127.35, 126.79, 126.44, 126.18, 125.86, 124.86, 123.43, 122.75, 122.47.

FTIR: (cm^{-1}): 2922, 2853 (Ar-CH), 1729 (C=N), 1243, 1461 (C-N) 1025 (C-C), 795 (C-S), 654 (C-Br). UV-Vis (λ_{max}): 281.75(nm).

IMA-R6: 2-(2-bromopyridine-3-yl)benzo[4,5]thieno[2,3-*d*]thiazole. Yield (65%). ^{1}HNMR (300MHz, CDCl$_3$, ppm): Ar-H benzothienothiazole (7.756, dd, *J*=9.6 Hz, 1H), (7.644, m, 2H), (7.51, m, 2H), (7.455, m, 2H), (7.375, m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 133.67, 132.99, 131.66, 130.98, 130.14, 129.41, 127.34, 125.88, 122.73 FTIR :(cm^{-1}): 2958, 2924, 2859 (Ar-CH), 1748 (C=N), 1236, 1459 (C-N), 1048 (C-C), 724 (C-S), 415 (C-Br). UV-Vis (λ_{max}): 286.81(nm).

IMA-R7: 2-(6-methoxypyridine-2-yl)benzo[4,5]thieno[2,3-*d*]thiazole. Yield (64%). ^{1}HNMR (300MHz, CDCl$_3$, ppm): (Ar-H) benzothienothiazole (7.790, m, 1H), (7.43-7.63, m), 7.35,dd, *J3*=7.8, *J4*=6.6 Hz), (7.732, m) (Ar-H), and (3.58, s). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 160.74, 154.29, 149.90, 134.17, 133.67, 133.00, 132.40, 132.25, 132.01, 131.67, 130.97, 130.13, 127.70, 127.34, 127.17, 126.75, 126.44, 125.87, 124.82, 122.74, 122.44, 120.24 FTIR (cm^{-1}): 3064, 2953 (Ar-CH), 1718 (C=N), 1598 (C=C), 1446 (C-N), 1273 (C-O), 752 (C-S). UV-Vis (λ_{max}): 291.48 (nm).

IMA-R8: 2-(5-bomopyridine-2-yl)benzo[4,5]thieno[2,3-*d*]thiazole. Yield (65%) ^{1}HNMR (300MHz, CDCl$_3$, ppm): Ar-H benzothienothiazole (8.03, d, *J*=7.5 Hz, 1H), (7.92, d, *J*=8.1 Hz, 1H), (7.74, m, 5H), (7.82, m), (7.50, m), (7.29, m). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 134.18, 132.40, 132.01, 127.69, 126.75, 124.84, 122.84, 120.26, 112.13 FTIR (cm^{-1}): 2925 (Ar-CH), 1725 (C=N), 1587 (C=C), 1446 (C-N), 1022 (C-C), 746 (C-S), 425 (C-Br). UV-Vis (λ_{max}): 289.32(nm).

Results and Discussion

Eight new thiophen-thaizole derivatives have been synthesized and purified. Their characterization has been done using spectroscopic techniques. Their proposed structures and the atom numbering scheme have been given in Table 1 in experimental section.

Spectroscopic studies

FT-IR studies

FTIR spectra indicated all the required peaks which helped in deduction of the structures of these synthesized compounds. The FTIR spectra have been shown in Fig.1 where the most obvious peak was that appearing around 1700 cm^{-1} in all the samples and it was assigned to the C=N

stretching vibration. The aromatic C=C stretching vibrations were assigned to the pair of peaks appeared around 1590 and 1490 cm^{-1} in all the samples. An intense peak around 700 cm^{-1} was assigned to the C-Cl stretching in IMA-R4 and C-Br stretching in IMA-R1, IMA-R5, IMA-R6 and IMA-R8. Another peak of medium intensity was observed at 1000 cm^{-1} in IMA-R2 and at 1100 cm^{-1} in IMA-R7 corresponding to the C-O stretching vibration of the samples. The aromatic C-H stretching appeared just on 3000 cm^{-1} and appears to be fused with aliphatic C-H stretch of methoxy and methyl groups. Out-of-plane bending vibrations of aromatic C-H groups appeared at 740 cm^{-1} as small broad peak in all the samples. This peak seemed merged with C-Cl/C-Br peak as well in the samples containing the C-Cl/C-Br functionality.
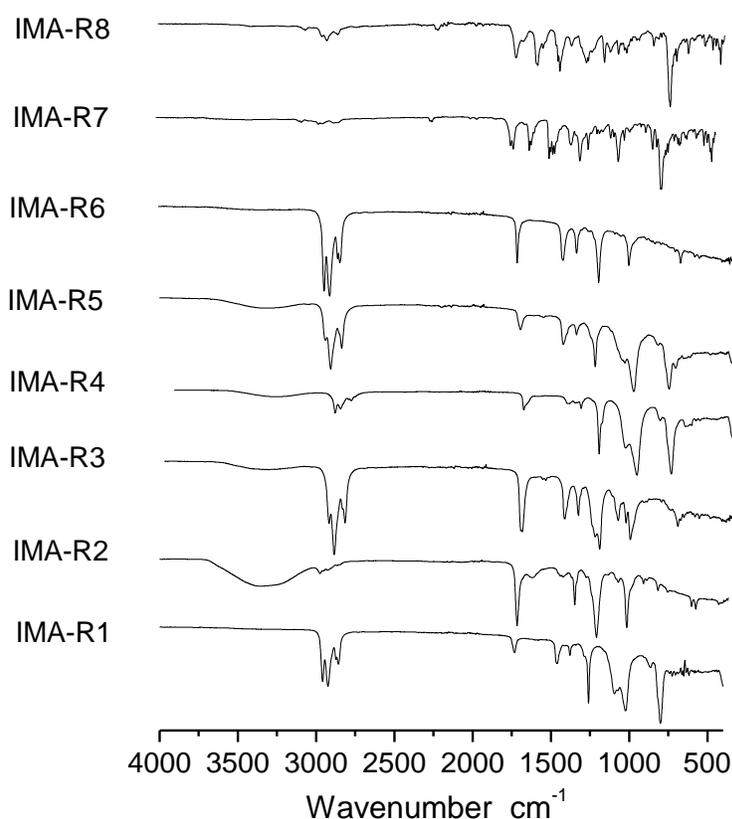

Fig.1: FTIR spectra of the synthesized compounds (IMA-R1 to IMA-R8)

^{1}HNMR spectroscopic studies

^{1}HNMR spectroscopy revealed all the characteristic peaks that indicated the formation of the expected fused thiophene-thiazole compounds. Their proposed molecular structures have been

shown in table 1. The structures show that positions 1,2,3 and 6 are common to all the compounds and their ^{1}HNMR signals are observed in the range 7.43-8.40 ppm. The range is shifted to the downfield side as compared to the signal of the unsubstituted aromatic region owing probably to the electronic effects of the sulfur atom with lone pairs and the attached 5 membered ring. Moreover, the signals of 3 and 6 are observed downfield as compared to those of 1 and 2 in all compounds probably owing to the proximity of the former with the 5 membered rings containing more electronegative N- and S-atoms.

Ideally, the signals of both protons at positions 3 and 6 should be doublet owing to the neighborhood of single proton at 2 and 1, respectively. This has been observed indeed as evident in the ^{1}HNMR spectrum of IMA-R5 as shown in Fig. 2A. Similarly, the signal of each proton at position 1 and 2 is expected to be doublet of doublet and that has been observed clearly in the ^{1}HNMR signal of IMA-R1 as shown in Fig. 2B. The signal of 3′ has been observed combined with those of 1 and 2. In this regard it can be said that the electronegative effect of N in the aromatic ring might have been offset by the electron donating effect of the attached bromine. Thus the signal occurs closer to that of the simple aromatic ring like that of oppositions 1 and 2.

Another general feature is the invariable doublet observed for position 2′ in all compounds occurring just around 8 ppm (Table 2). The rest of the positions vary according to substituents and are listed in Table 3. Similarly, the signals of position 6′ in IMA-R1 and IMA-R2 are expected to be singlets and have been observed as singlets as given in table 2. The signals of methoxy protons in IMA-R2 and IMA-R7 have been observed at 3.58 ppm as singlets. Methyl protons on aromatic ring in IMA-R3 have been observed as tall singlet at 2.73 ppm. The data of all the ^{1}HNMR spectra observed for the compounds have been summarized in table 2.

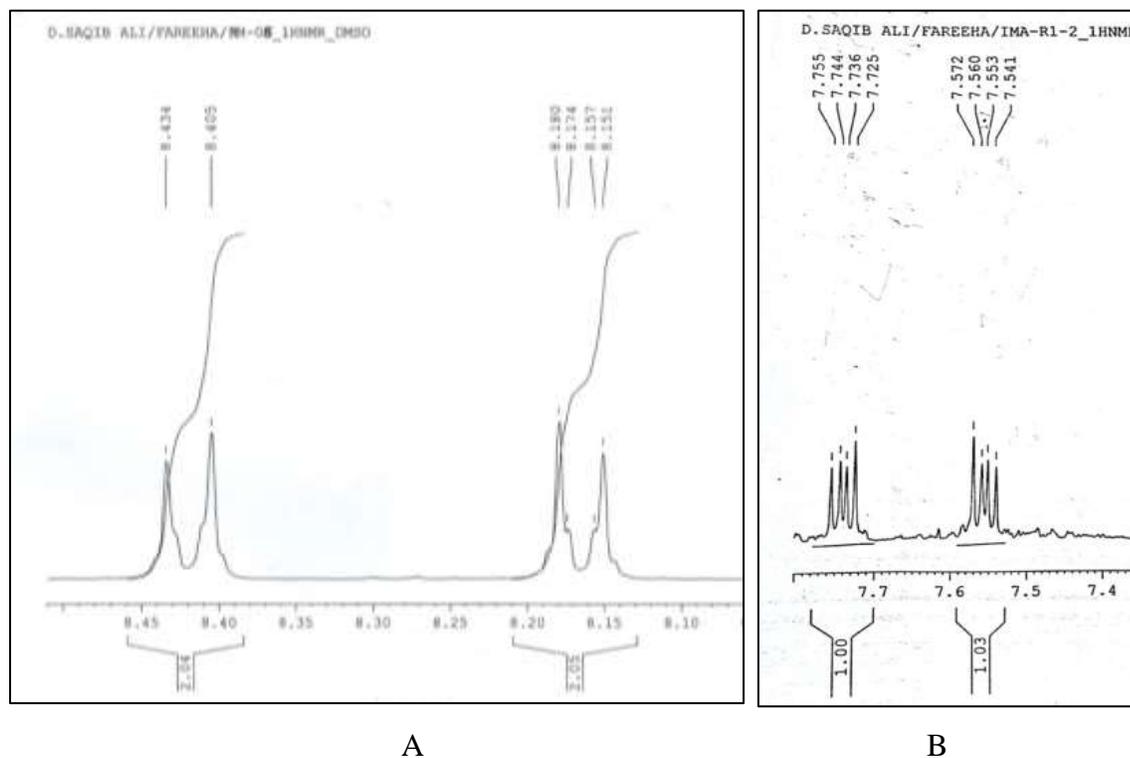A   B

Fig.2: (A) Doublets of protons at positions 3 and 6 observed in ^{1}HNMR spectrum of IMA-R5. (B) Doublet of doublet observed for protons at positions 1 and 2 in ^{1}HNMR spectrum of IMA-R1.

^{13}CNMR studies

Looking at the proposed structures of compounds in Table 1, it is apparent that the electronic environment around all the C atoms are similar except for those attached directly to N- and O- atoms. Being part of the aromatic ring, the electron withdrawing effect of O on methoxy carbon at C4′ position (in IMA-R2, entry 2 in Table 1) is almost offset and its signal appeared more downfield than the aromatic C atoms as listed in Table 3. The signal of C7′ was observed on 32 ppm while the rest of the C atoms gave signals relatively closer to one another starting at 122 ppm as shown in Fig. 3. The values of various ^{13}CNMR signals have been listed in Table 3.
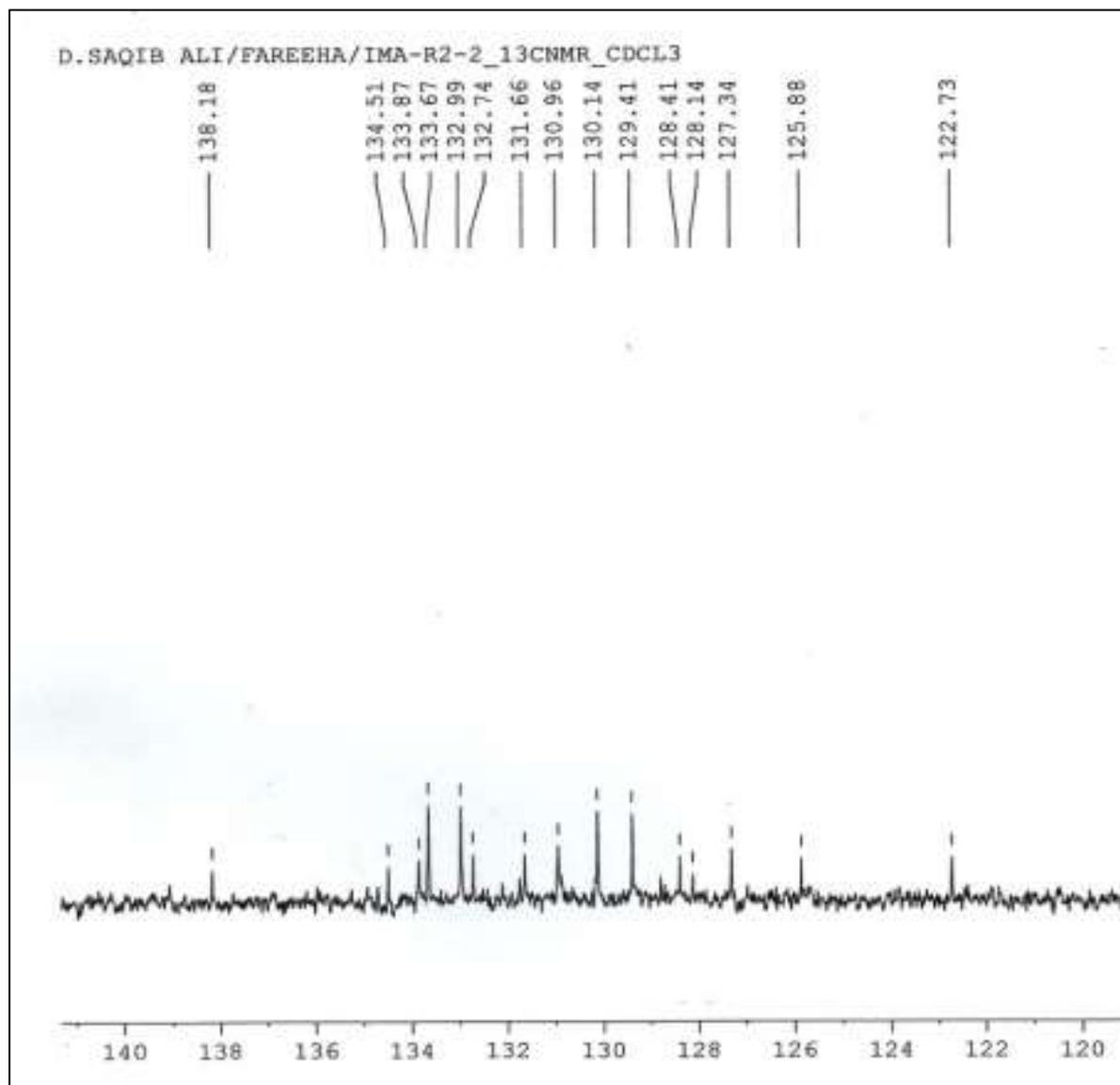
Fig. 3: ^{13}CNMR spectrum of IMA-R2 showing a signal corresponding to each C in the compound except methoxy-C which was left out because that was far off the region.

Table 2: ^{1}HNMR chemical shift (δ) assignment of synthesized compounds.

H	1	2	3	6	2′	3′	4′	5′	6′	7′
IMA-R1	7.56 (dd)	7.56 (dd)	7.74 (dd)	7.74 (dd)	7.74 (dd)	7.56 (dd)	-	N	7.74 (dd)	Br

IMA-R2	7.56 (m)	7.59 (m)	8.05 (m)	7.98 (m)	7.75 (m)	7.28 (s)	-	N	7.679 (m)	2.58 (s)
IMA-R3	7.44-7.66 (m)	7.44-7.66(m)	8.03 (d)	8.03 (d)	7.92 (d)	7.78 (m)	7.44-7.66(m)	-	N	2.73 (s)
IMA-R4	7.52 (m)	7.52(m)	7.92 (d)	7.92 (d)	8.03 (d)	7.92 (d)	7.52 (m)	-	N	Cl
IMA-R5	8.16(dd)	8.16 (dd)	8.42 (d)	8.42 (d)	7.24 (m)	8.42 (d)	8.16 (dd)	-	N	Br
IMA-R6	7.54-7.28 (m)	7.54-7.28 (m)	7.75 (d)	7.75 (d)	7.75 (d)	7.64 (d)	7.75 (d)	N	-	Br
IMA-R7	7.43-7.63(m)	7.43-7.63(m)	7.79 (dd)	7.79 (dd)	7.357 (dd)	7.73(m)	7.35 (dd)	-	N	3.58 (s)
IMA-R8	7.50 (m)	7.50 (m)	7.92 (d)	7.92 (d)	8.03 (d)	7.92 (d)	-	8.03 (d)	N	Br

Table 3: ^{13}CNMR spectroscopic values of compounds.

C No.	IMA-R1	IMA-R2	IMA-R3	IMA-R4	IMA-R5	IMA-R6	IMA-R7	IMA-R8
C1	128	125	125	125.8	124.8	125.88	124.82	124.84
C2	128	125	125	125.8	124.8	125.88	124.82	124.84
C3	128	122	125	122.7	123.4	122.73	122.74	122.84
C4	132	138.1	138	139	139.06	133.67	134.17	134.18
C5	132	138.1	138	139	139.06	133.67	134.17	134.18
C6	128	122	125	122.3	122.7	122.73	122.74	122.84
C7	128	125	125	125.8	124.8	125.88	124.82	124.84
C8	128	127	127	127	126.4	127.34	126.44	126.75
C9	167	138.1	138	167	167	133.67	160.74	134.18
C1′	132	122	138	167	167	133.67	160.74	134.18
C2′	132	134	125	122.7	123.4	133.67	112.08	126.75
C3′	130	122	138	139	139.06	122.73	134.17	134.18
C4′	132	138.1	125	122.3	125.8	133.67	112.08	112.13

C5′	N	N	138	139	139.06	N	160.74	134.18
C6′	132	138.1	N	N	N	133.76	N	N
C7′ (R₁)	Br	76.61	23.01	Cl	Br	Br	76.63	Br

UV-Visible and spectroflourimetric studies

UV-Visible spectroscopy revealed λ_{max} values in the range of 282-315 nm due to π-conjugated systems present in arylbenzo[4,5]thieno[2,3-d]thiazole compounds as shown in Fig. 4A. Methoxy-substituted derivative IMA-R2 exhibited longer λ_{max} (red shifted) at 315 nm owing to the electron donating power of methoxy group. These λ_{max} values have been found in typical ranges as observed for other compounds having similar chromophores (R. Wada *et al*., 2021).

Florescence emission intensities of the samples have been shown in Fig. 4B. Their shifting pattern is similar to those of the UV-Visible absorption spectra of the compounds. Some spectroscopic parameters have been listed in table 4.
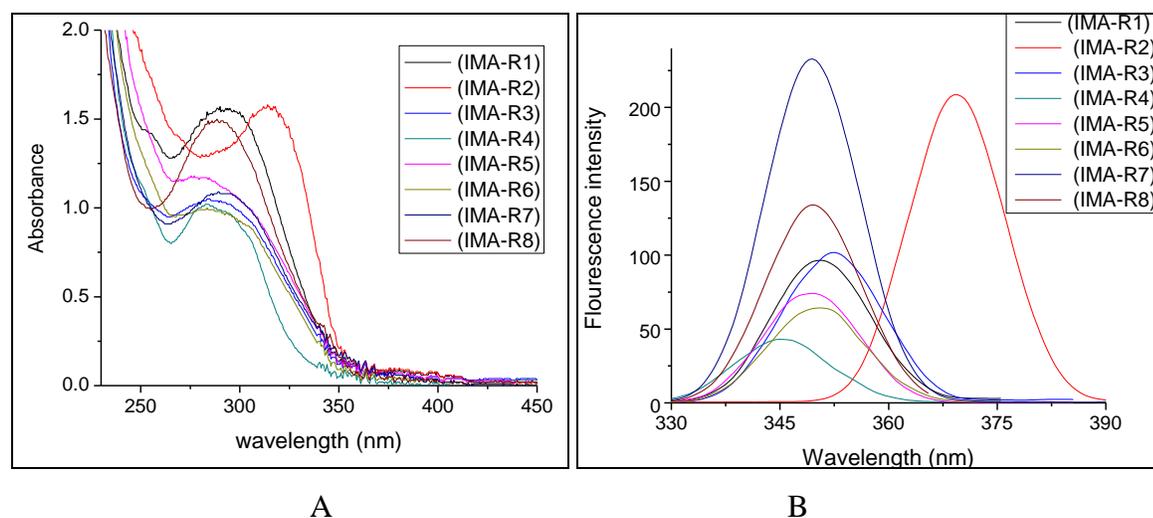

Fig. 4: UV-Visible absorption (A) and fluorescence emission (B) spectra of the compounds.

Table 4: The observed spectroscopic parameters of the compounds.

S.No	Compound	λ_{max} (nm)	Fl. Intensity	$\lambda_{exci.}$ (nm)
1	IMA-R1	293.30	208.90	369.37
2	IMA-R2	315.32	96.11	350.36
3	IMA-R3	285.39	64.37	350.12
4	IMA-R4	284.31	232.40	349.27
5	IMA-R5	281.75	133.68	349.76
6	IMA-R6	286.81	74.37	349.27
7	IMA-R7	291.48	101.38	352.53
8	IMA-R8	289.32	42.63	345.31

Conclusion

Eight derivatives of aryl benzo[4,5]thieno[2,3-*d*]thiazoles have been successfully synthesized in good yield. These were characterized using spectrofluorimetry UV-Visible, FT-IR and ^{1}HNMR and ^{13}CNMR spectroscopic techniques. The λ_{max} values were found in range of 282-315 nm assignable to the conjugated system. FTIR spectroscopy revealed the characteristic bands including a C-S stretching vibration peak which showed the formation of the desired compounds. ^{1}HNMR and ^{13}CNMR spectroscopic techniques indicated the formation of the compounds and their respective coupling constant values have been calculated. The results of these spectroscopic techniques have indicated the successful syntheses of the desired heterocyclic compounds.

Acknowledgements

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