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Green and Sustainable Strategies to Achieve a New Series of Xanthene Derivative via Free Solvent One-pot Multicomponent Reactions

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ABSTRACT: One-pot multicomponent reactions were used widely as eco-friendly pathway techniques to achieve wide range of active heterocyclic compounds specially in medical and pharmaceutical field. Herein, in this work this pathway was used to prepare a supreme type of xanthene derivatives via two stages. In the first one seven unite building involving p-hydroxy moiety (A1-7) have been prepared via four component reactions accelerated by grinding and MWI. Whereas, in the second stage the xanthene derivatives (B1-7) were prepared also via multicomponent reactions among the seven unite building and both of substituted benzaldehyde and dimedone in acidic media (boric acid). Additionally, the molecular docking of compounds (B1-3) against the HOXD13 protein which is implicated in skin cancer was theoretically investigated with acceptable results. All synthesized compounds were characterized using ¹³C-NMR, ¹H-NMR, and FT-IR spectroscopy.

INTRODUCTION

Multicomponent reactions are considered to be a supreme type of organic reactions which involve the interaction of three or more reactants to yield a single, highly selective product that incorporates all the participating molecules (Cirmarelli, 2019; Insuasty et al., 2020). These reactions accelerated via green chemistry techniques such as grinding (Achar and Mal, 2017), Ultrasonication (US) (Alizadeh et al., 2020), and microwave irradiation (MWI) (Patel et al., 2023) as well as traditional methods like reflux for a specific duration (Shao et al., 2021) or stirring at a controlled temperature. This type of reaction was discovered by the German scientist Adolph Strecker; specifically, the synthesis of α -amino acids a process now known as the Strecker reaction bears his name (Strecker, 1850; Masamba, 2021). Multicomponent reactions enable the synthesis of selective compounds via streamlined procedures and offer reduced reaction times compared to conventional methods. Furthermore, the resulting products and the reactions themselves are environmentally friendly and pollutant-free; purification often employs water or ethanol as the solvent (Zaharani et al., 2021; Naidu et al., 2023). Consequently, this class of reactions constitutes a significant component of green chemistry, as it aligns closely with its principles and applications (Calvo-Flores and Mingovance-Sanchez, 2021; Kar et al., 2021). Heterocyclic compounds are among the most significant synthesized chemical compounds with activity across diverse fields; their structures incorporate heteroatoms capable of participating in complex biological mechanisms for treating various medical conditions (Zhang et al., 2014). Prominent examples include pharmaceutical compounds featuring an imidazole ring in their core structure; specifically, fused imidazole derivatives have demonstrated clear efficacy in treating cancer (Al-Kahtani et al., 2012; Akhtar et al., 2017; Taslimi et al., 2021). Furthermore, imidazole derivatives have proven effective in treating bacterial infections, acting as potent antibacterial agents (Ramachandran et al., 2011). Imidazole derivatives have been utilized as anti-obesity agents (Chopra and Sahu, 2020), for treating nerve inflammation (Nascimento et al., 2018), as effective antihypertensives (Siwach and Verma, 2021), and as

antidiabetic agents (Narasimhan et al., 2011). Furthermore, they have been employed as antifungal (Altinadag et al., 2019) and antiparasitic agents (Adeyemi et al., 2020), and have demonstrated significant antitubercular activity (Fassihi et al., 2009; Pandey et al., 2009; Patel et al., 2023). Additionally, imidazole derivatives rich in cyclic substituents have been used in the treatment of HIV-1 (AIDS) (Dong et al., 2022). On the other hand, benzoxanthenes and benzoxanthenes are another biologically active compounds, which exhibiting antibacterial (Devakrishnan et al., 2025), anti-inflammatory (Jeelani et al., 2024), antimicrobial (Li et al., 2025), antiviral (Dean et al., 2023), antifungal (Rzad et al., 2023), and anticancer (Sheng et al., 2023) properties. Xanthone derivatives are found in compounds such as cannabinal present in the cannabis plant and serve as effective treatments for various conditions, including rheumatism and gynecological disorders; one of the most well-known of these compounds is tetrahydrocannabinol (THC) (Maioli et al., 2022). Industrially, xanthenes are utilized as dyes (Farat et al., 2022) and pH-sensitive fluorescent materials (Sun et al., 2024), and they are also employed in laser technologies (Rodrigues et al., 2024). Also, in this work and according to the above advantages, we prepared a supreme type of substituted xanthene involving the imidazole moiety represented by compounds (B₁₋₇)

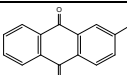
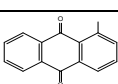
Experimental

The melting Point (M.P) were measured on Electro thermal Stuart SMP 10. melting Point apparatus. The infrared FT-IR spectra were recorded using a Bruker, FT-IR spectrophotometer (Pye unicom SP 2000). The nuclear magnetic resonance spectrometer (¹H-NMR): Measurement of the nuclear magnetic resonance spectrum using Bruker (400 MHz) using DMSO as a solvent and TMS as an internal reference. Spectral regions were expressed in (ppm). Microwave Irradiation apparatus: A Silver crest SMWC, 700 A, Germany domestic oven was used to conduct the microwave irradiation reactions. Then layer chromatography (TLC) was using on silica gel (120 mesh) with (13%) gypsun coated plates (2x10) cm activated at (110-120°C) for one hour before use and the plates were developed with iodine vapor. using benzene:methanol solvent system at ratio of (8:2) .

Synthesis Methods of 2-(4-hydroxyphenyl)-3-aryl-4,5-diphenylimidazole derivatives (A₁₋₇) (Nalage et al., 2010)

Equimolar amounts (0.015 mol) of the substituted amine, benzil, and 4-hydroxybenzaldehyde, along with (0.06 mol) of ammonium acetate in acidic media of (3 mL) of glacial acetic acid, are placed in a ceramic mortar, then mixed thoroughly and grind well for (5 min) . The mixture is transferred to a (100 mL) beaker and subjected to microwave irradiation (MWI) at a power of (270 W) for (8 min) in a domestic microwave oven. After irradiation, the reaction mixture is cooled, and (20 mL) of ice-cold water was added with stirring. The resulting precipitate is filtered off and washed several times with ice-cold water (10 mL) to remove the acid formed during the reaction. Finally, the product is dried and recrystallized from absolute ethanol.

Table (1): The physical properties and spectral data for compounds (A₁₋₇).

Comp. No.	Ar	MP °C	Yield (%)	Colour	R _f	FT-IR (ν cm ⁻¹)				
						OH	C=N	C=C	C-N	Others
A ₁		245-247	91	White	0.714	3527	1612	1491	1245	—
A ₂		239-241	94	Yellow	0.586	3492	1610	1491	1240	NO ₂ assy 1457, sym 1332
A ₃		230-232	89	Brown	0.831	3432	1612	1490	1240	C=O 1671
A ₄		209-211	86	Yellow	0.643	3564	1603	1576	1266	C=O 1661 , 1636

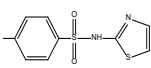
Comp. No.	Ar	MP °C	Yield (%)	Colour	R _f	FT-IR (v cm ⁻¹)				
						OH	C=N	C=C	C-N	Others
A ₅		240-243	92	Yellow	0.561	3360	1612	1490	1239	C-S 770
A ₆		92-95	87	Brown	0.742	3464	1612	1504	1268	NH 3364 , S=O asym 1130, sym 1084
A ₇		263-265	92	Gray	0.475	3566	1611	1490	1240	C-Cl 764

Table (2): ¹H-NMR and ¹³C-NMR spectroscopy for compounds (A₁₋₇).

Comp. No.	¹ H-NMR δ(ppm)	¹³ C-NMR δ(ppm)
A ₁	Ar-H (m, 6.659-9.760, 17H); OH (s, 12.415, 1H)	115.88-158.28
A ₂	Ar-H (m, 6.500-9.788, 17H); OH (s, 12.421, 1H)	107.64-163.74
A ₃	Ar-H (m, 6.357-9.789, 21H); OH (s, 12.433, 1H)	110.18-195.26
A ₄	Ar-H (m, 6.886-9.728, 21H); OH (s, 12.422, 1H)	112.14-195.27
A ₅	S-CH=CH-N (d, 9.732, 2H); Ar-H (m, 6.725-8.108, 14 H); OH (s, 12.427, 1H)	115.88-158.25
A ₆	S-CH=CH-N (d-d, 5.880-6.580, 2H); Ar-H (m, 6.602-7.947, 18 H); HN-SO ₂ (s, 9.811, 1H); OH (s, 10.306, 1H)	107.93-172.56
A ₇	Ar-H (m, 6.859-9.736, 17H); OH (s, 12.432, 1H)	115.88-158.26

Synthesis Methods of 3,3-dimethyl -9-aryl-(1,4,5-tri phenyl-1H-imidazole-2-yl) -2,3,4,9-tetrahydro-1H-xanthen-1-one derivatives (B₁₋₇) (Kumar et al., 2010):

Equimolar amounts (0.0015 mol) of a substituted benzaldehyde, dimedone, and tetra-substituted imidazole (A₁₋₇), with (0.1 g) of boric acid, were placed in a (100 mL) glass flask. The reaction mixture was then heated in an oil bath at (120°C) for (30 min) with continuous stirring. Subsequently, the reaction mixture was cooled, and (10 mL) of ethyl acetate was added to dissolve unreacted materials. The mixture was filtered off, and the precipitate was washed with ice-cold water to remove the acid, dried, and recrystallized from absolute ethanol.

Table (3): The physical properties for compounds (B₁₋₇).

Comp. No.	Ar	X	M.P.C ^o	Yield (%)	Colour	R _f
B ₁		4-NO ₂	128-130	93	Yellow	0.484
B ₂		4-N,N-Dimethyl	194-196	95	Orange	0.615

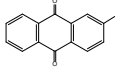
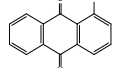
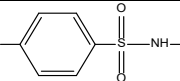
Comp. No.	Ar	X	M.P.C ⁰	Yield (%)	Colour	R _f
B ₃		3-NO ₂	192-195	81	Yellow	0.765
B ₄		3-NO ₂	198-200	86	Red	0.532
B ₅		3-OCH ₃ -4-OH	153-155	82	Yellow	0.817
B ₆		4-NO ₂	212-215	79	Brown	0.473
B ₇		4-N,N-Dimethyl	219-222	78	Orange	0.448

Table (4): FT-IR data for compounds (B₁₋₇).

Comp ·	FT-IR (v cm ⁻¹)												
	C-H	CH ₃		C=O	C=N	C≡C	NO ₂		C=C	C-O-C		C-N	Others
		assy	sym				assy	sym		assy	sym		
B ₁	3058	2926	2871	1650	1591	1596	1537	1342	1488	1380	1179	1289	
B ₂	3054	2954	2869	1650	1592	1507	1538	1338	1489	1371	1168	1239	
B ₃	3061	2952	2868	1672, 1650	1588	1508	1525	1346	1487	1383	1178	1286	
B ₄	3055	2956	2872	1661, 1636	1602	1589	1525	1346	1487	1379	1171	1280	
B ₅	2956	2934	2870	1650	1590	1511	...	...	1465	1370	1151	1266	C-S 811, OH 3341
B ₆	3061	2957	2870	1647	1594	1494	1510	1343	1469	1386	1176	1268	C-S 930, NH 3276, S=O assy 1447, sym 1085
B ₇	3032	2956	2931	1649	1594	1491	...	...	1548	1372	1169	1239	C-Cl 740

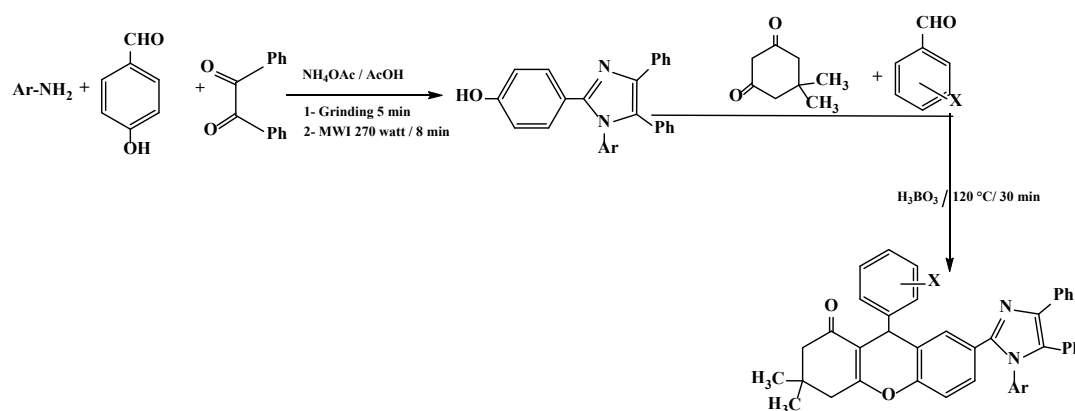
Table (5): ¹H-NMR and ¹³C-NMR spectroscopy for compounds (B₁₋₇).

Comp. No.	¹ H-NMR δ(ppm)	¹³ C-NMR δ(ppm)
B ₁	Dimedone (m, 0.858-1.104, 10H); Ar-H (m, 6.199-8.407, 20H); H-pyran (s, 10.162, 1H)	Dimedone (31.71-33.79); Ar-C (101.60-205.65)
B ₂	Dimedone (m, 0.944-1.040, 10H); 2CH ₃ (s, 3.093, 6H); Ar-H (m,	Dimedone (28.32-39.56); 2CH ₃

Comp . No.	$^1\text{H-NMR } \delta(\text{ppm})$	$^{13}\text{C-NMR } \delta(\text{ppm})$
	6.585-7.970, 20H); H-pyran (s, 9.673, 1H)	(52.19-54.13); Ar-C (111.53-197.48)
B ₃	Dimedone (m, 0.848-1.200, 10H); Ar-H (m, 6.177-8.686, 24H); H-pyran (s, 9.808, 1H)	Dimedone (29.19-33.08); Ar-C (101.75-192.28)
B ₄	Dimedone (m, 0.851-1.122, 10H); Ar-H (m, 6.172-8.206, 24H); H-pyran (s, 9.800, 1H)	Dimedone (31.26-33.06); Ar-C (100.86-195.28)
B ₅	Dimedone (m, 0.840-1.232, 10H); OCH ₃ (s, 3.676, 3H); CH=CH thiazole (d, 5.815-6.376, 2H); Ar-H (m, 6.504-7.527, 16H); H-pyran (s, 7.903, 1H); OH (s, 7.924, 1H)	Dimedone (31.44-33.89); OCH ₃ (59.6); Ar-C (100.77-206.66)
B ₆	Dimedone (m, 0.857-1.230, 10H); Ar-H (m, 6.660-8.179, 21H); CH=CH thiazole (d, 5.501-5.600, 2H); H-pyran (s, 9.810, 1H); NH (s, 10.110, 1H)	Dimedone (31.83-33.79); Ar-C (101.60-192.81)
B ₇	Dimedone (m, 0.846-1.286, 10H); 2CH ₃ (s, 3.096, 6H); Ar-H (m, 6.580-7.968, 20H); H-pyran (s, 9.730, 1H)	Dimedone (28.35-39.55); 2CH ₃ (47.28); Ar-C (111.53-190.33)

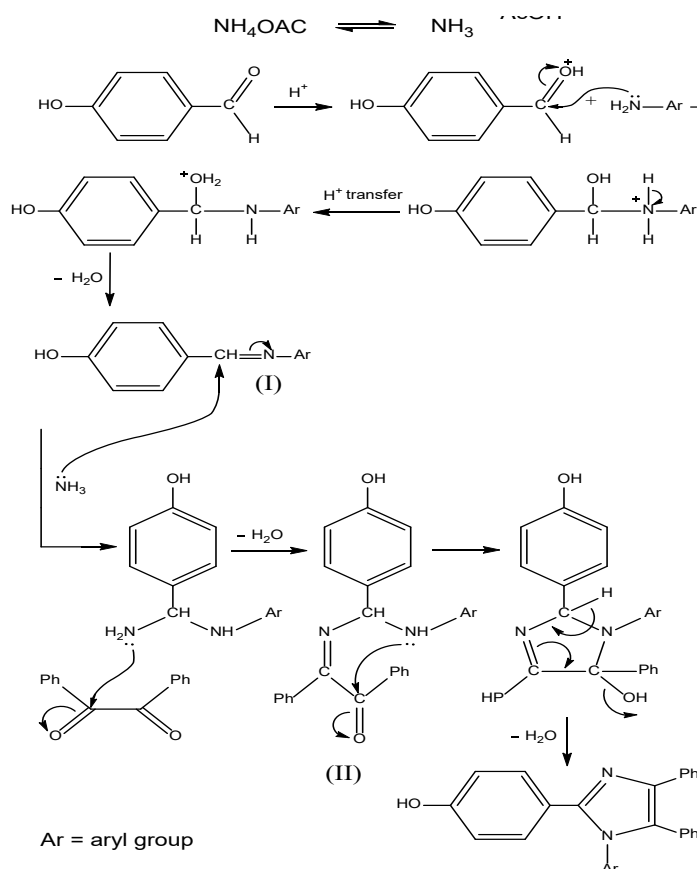
Results and Discussion

The new series of substituted xanthene were prepared according to the following pathway, (Scheme 1)



Scheme (1): The synthesis pathway for compounds (A₁₋₇) and (B₁₋₇).

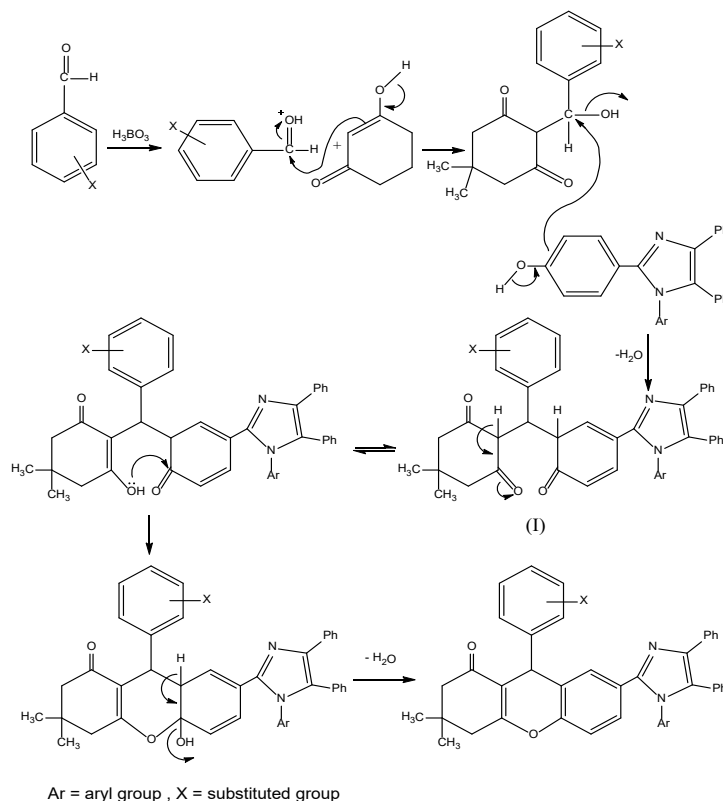
First of all, tetra substituted imidazole compounds were prepared via a one-pot four component green approach utilizing grinding and microwave irradiation (MWI) techniques. The reaction proceeds through a mechanism involving nucleophilic attack of the amine electron pair on the cationic carbon atom (generated by the acid action), followed by the loss of a water molecule to yield the intermediate (I), which then undergoes nucleophilic attack by the electron pair of an ammonia molecule released from ammonium acetate accompanied by the loss of a second water molecule to form the intermediate (II). Finally, the process of intramolecular cyclization with loss of another water molecule to yield the target imidazole compounds (A₁₋₇), Scheme(2). (Mossavi-zere et al., 2015; Hanoon et al., 2019).



Scheme (2): The synthetic mechanism of compounds (A₁₋₇).

The imidazole compounds were characterized using spectroscopic techniques, specifically Fourier-transform infrared FT-IR and nuclear magnetic resonance (¹H-NMR and ¹³C-NMR) spectroscopy. The FT-IR spectra revealed distinct absorption bands in the (1612-1603 cm⁻¹) range, corresponding to the cyclic C=N group, and bands in the (3566-3432 cm⁻¹) range, corresponding to the hydroxyl group, in addition to other absorption bands listed in (Table 1). Regarding the ¹H-NMR spectra, compounds (A₁₋₇) exhibited clear signals in the aromatic region (Table 2). A characteristic signal for the hydroxyl group proton appeared at a chemical shift of (10.306-12.433 (δ) ppm); this significant downfield shift (deshielding) is attributed to the high electronegativity of the aromatic system within the synthesized compounds, thereby supporting the proposed structural formulas. As for the nuclear magnetic resonance spectrum. The ¹³C-NMR data confirmed the proposed structural frameworks of these compounds; the spectra exhibited absorption bands in the aromatic region, as well as distinct bands corresponding to carbonyl and sulfone groups in certain derivatives (Table 2).

The compounds (A₁₋₇) were then used as active precursor to perform the xanthene derivatives via one-pot multicomponent reaction with both of substituted benzaldehyde and dimesone in acidic media of boric acid. The mechanism proceeded through a nucleophilic attack by the enol form of dimesone on the poor carbon atom in aldehyde (generated by the action of the acid) followed by the loss of a water molecule through the addition of the unite building (A₁₋₇) to yield the intermediat (I) which underwent intracyclization reaction with losing another water molecule to yield compound (B₁₋₇), Scheme (3) (Kumar et al., 2010).



Scheme (3): The mechanism of synthetic compounds (B₁₋₇).

The xanthene derivatives (B₁₋₇) were characterized spectroscopically, and their spectra were compared against the proposed chemical structures. In the FT-IR spectra, absorption bands for the methyl groups on the dimedone ring appeared at (2868–2931 cm⁻¹) and (2926–2957 cm⁻¹), corresponding to symmetric and asymmetric vibrations, respectively. Additionally, absorption bands for the C–O–C ether linkage were observed at (1151–1179 cm⁻¹) and (1370–1386 cm⁻¹), representing symmetric and asymmetric stretching vibrations; these, along with other bands listed in (Table 4), provided preliminary evidence supporting the proposed structures. The compounds were further characterized using ¹H and ¹³C-NMR spectroscopy. Distinct absorption bands for the dimedone methyl protons appeared in the (0.840–1.286 (δ) ppm) range; these signals are diagnostic of the expected structure, confirming the successful incorporation of the dimedone ring into the final molecular frameworks. Furthermore, the spectra displayed an absorption band for the pyran ring proton a key indicator for validating the proposed structures within the δ ppm range. ...a singlet signal exhibiting significant shielding due to the fused ring structure, alongside other absorption bands listed in (Table 5). Meanwhile, absorption bands corresponding to the fused dimedone ring appeared clearly in the ¹³C-NMR spectrum (Table 5) within the aliphatic region, in addition to signals from the aromatic system, which appeared distinctly in the aromatic region.

The Molecular Docking

Compounds (B₁₋₃) were subjected to a theoretical molecular docking study with the HOXD13 protein associated with skin cancer. Based on the binding energy values listed in (Table 6), compound B₁ was found to be the most stable upon binding to the protein, with an energy of (-9.8196), compared to compounds B₂ and B₃.

Table (6): Binding Energy data for compounds (B₁₋₃) against the protein HOXD13.

Comp. No.	Higher Swiss Param Score
B ₁	-9.8196
B ₂	-6.6003
B ₃	-6.6151

The Spectral Figures

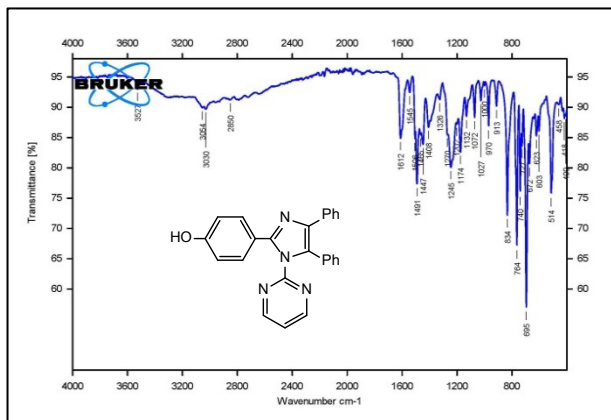


Fig. (1): FT-IR of compound (A₁).

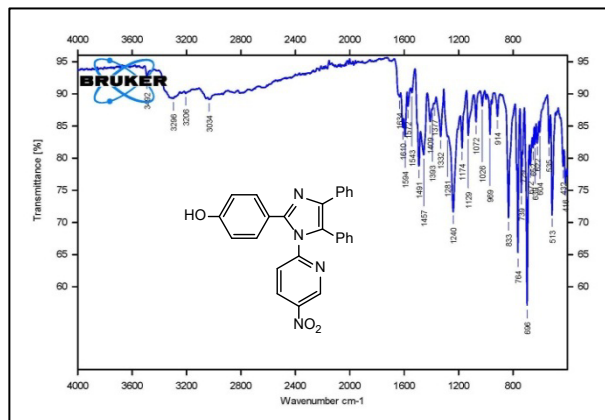


Fig. (2): FT-IR of compound (A_2).

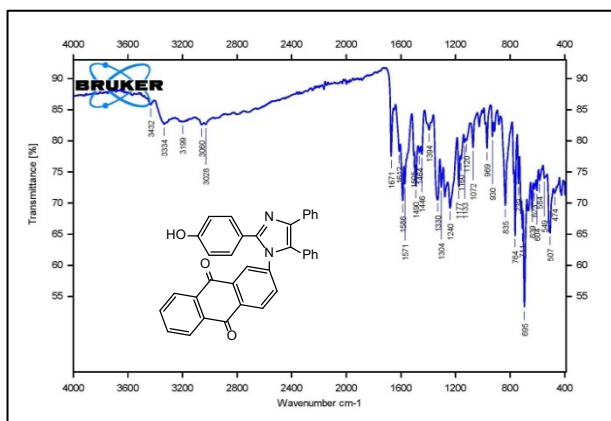


Fig. (3): FT-IR of compound (A_3).

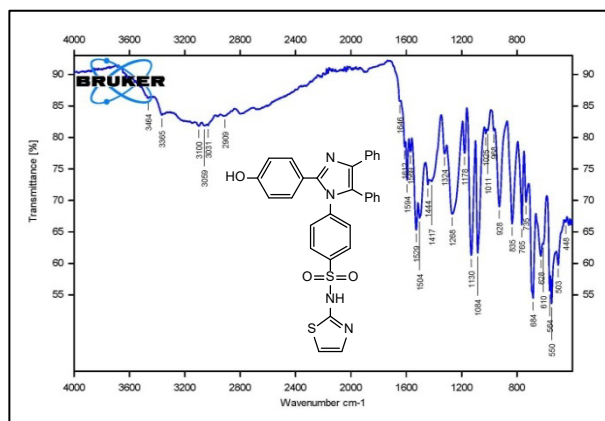


Fig. (4): FT-IR of compound (A_6).

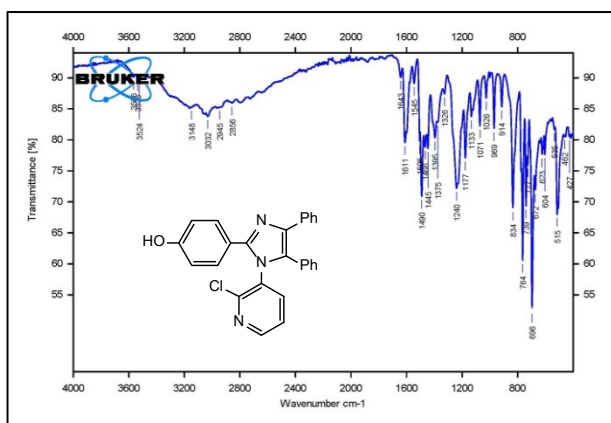


Fig. (5): FT-IR of compound (A₇).

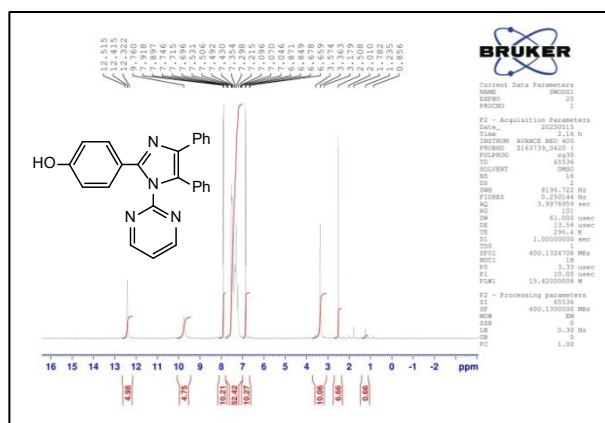


Fig. (6): ^1H -NMR of compound (A_1).

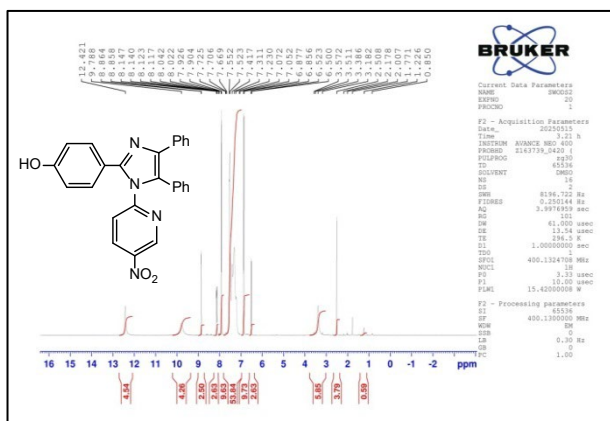


Fig. (7): ¹H-NMR of compound (A₂).

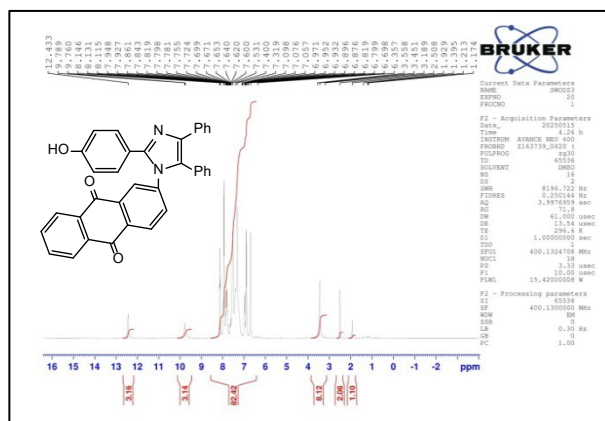


Fig. (8): ¹H-NMR of compound (A₃).

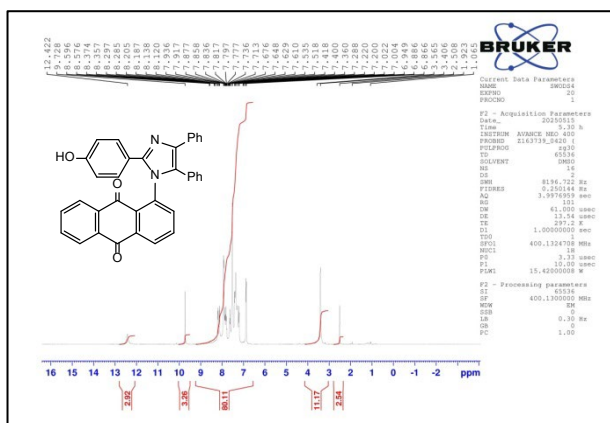


Fig. (9): ¹H-NMR of compound (A₄).

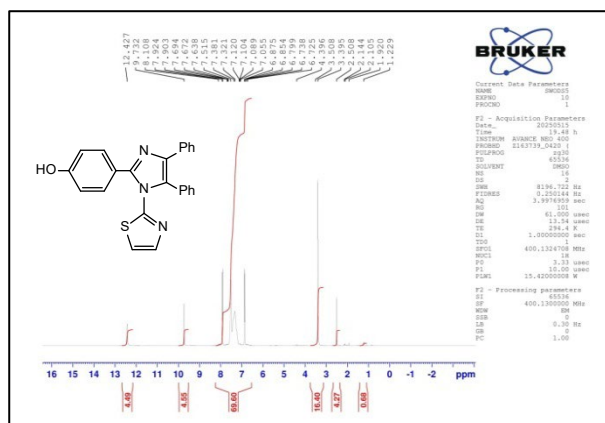


Fig. (10): ¹H-NMR of compound (A₅).

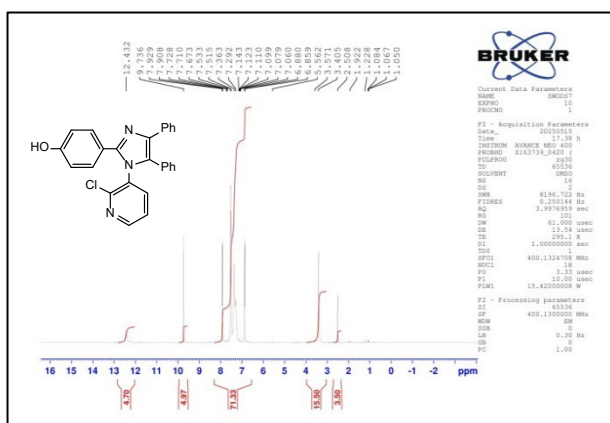


Fig. (11): ¹H-NMR of compound (A₇).

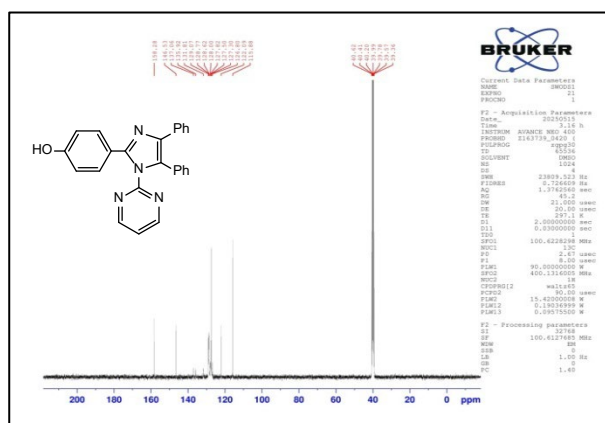


Fig. (12): ¹³C-NMR of compound (A₁).

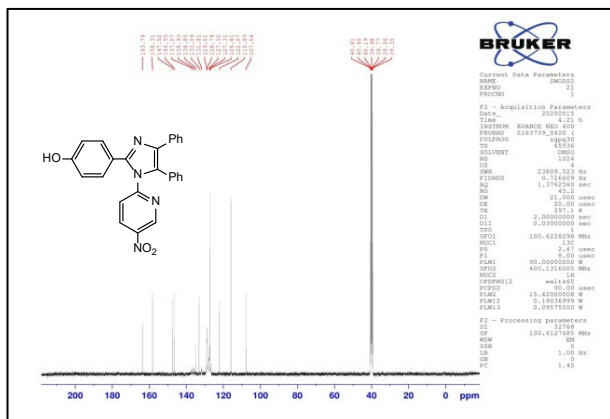


Fig. (13): ^{13}C -NMR of compound (A_2).

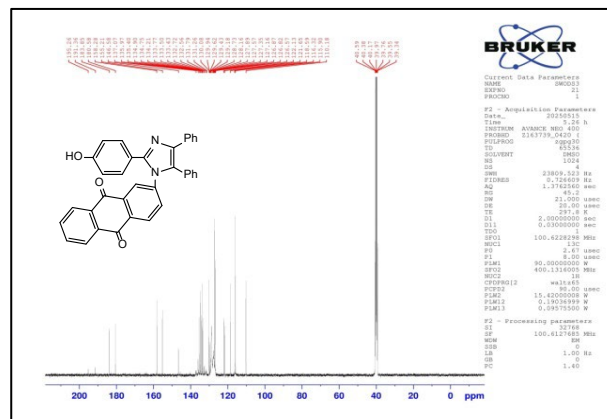


Fig. (14): ^{13}C -NMR of compound (A_3).

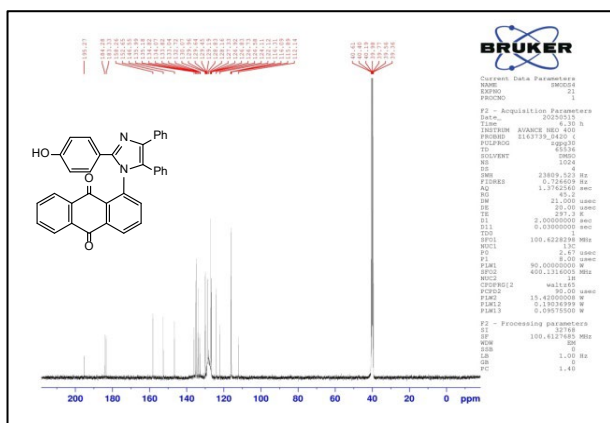


Fig. (15): ^{13}C -NMR of compound (A_4).

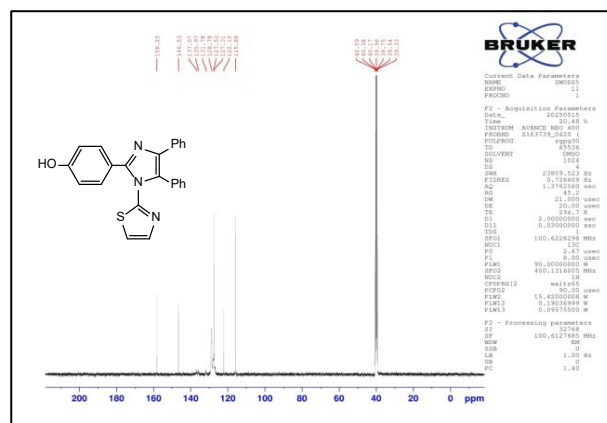


Fig. (16): ^{13}C -NMR of compound (A_5).

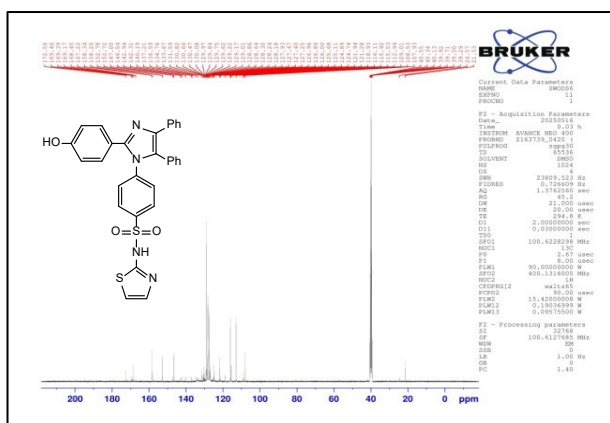


Fig. (17): ^{13}C -NMR of compound (A_6).

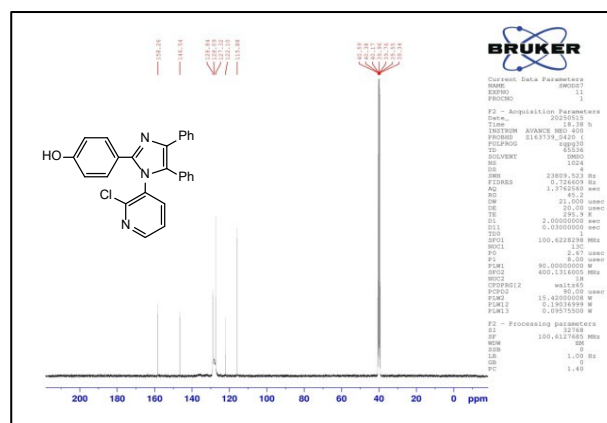


Fig. (18): ^{13}C -NMR of compound (A_7).

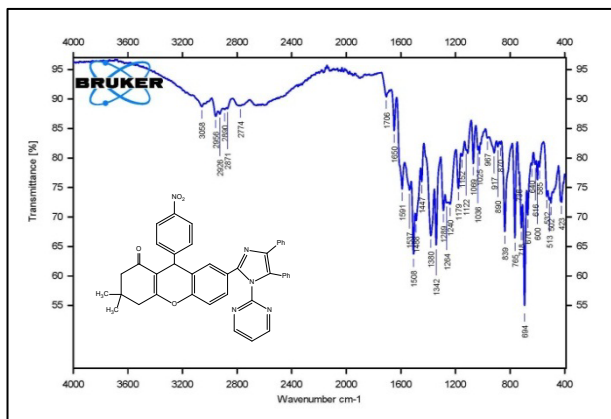


Fig. (19): FT-IR of compound (B₁).

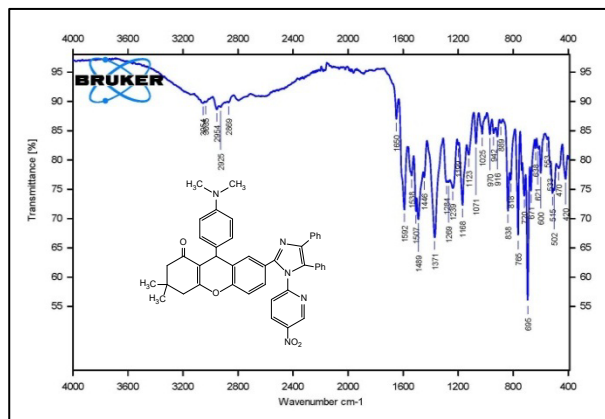


Fig. (20): FT-IR of compound (B₂).

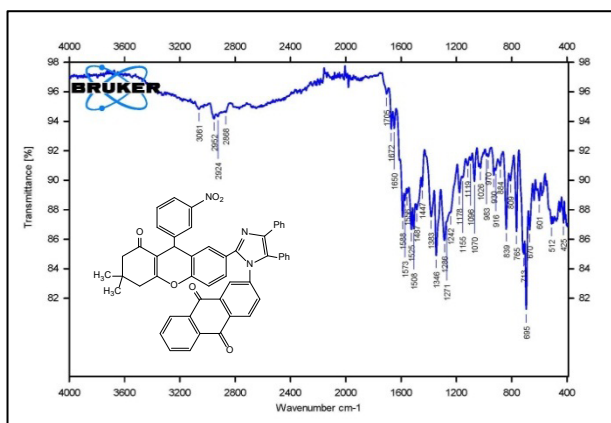


Fig. (21): FT-IR of compound (B₃).

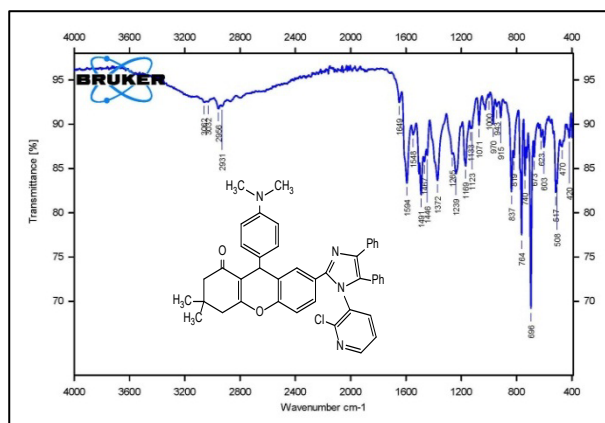
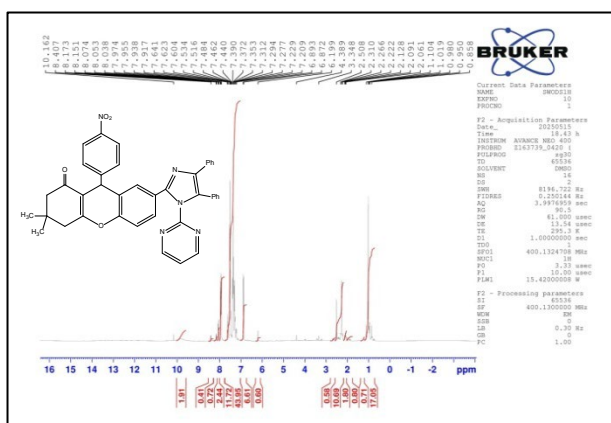
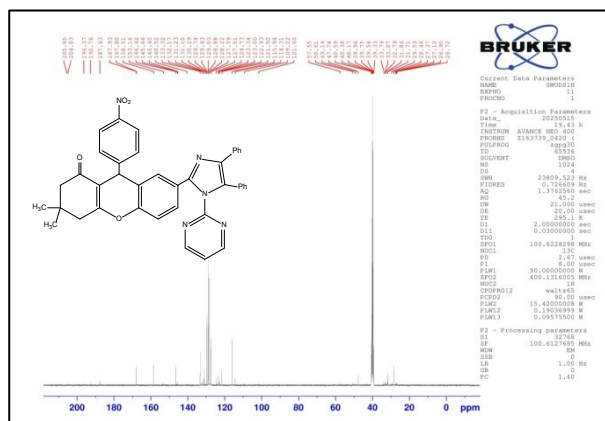
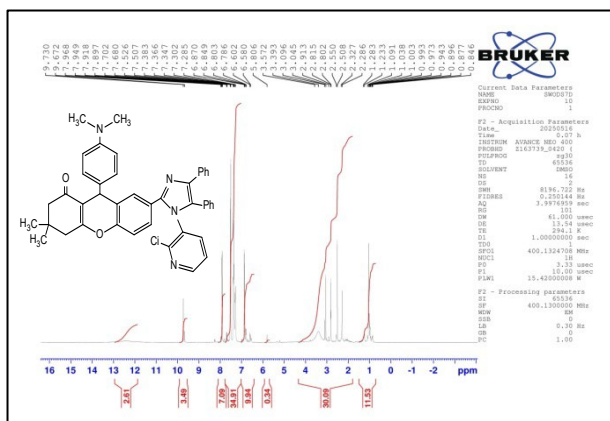
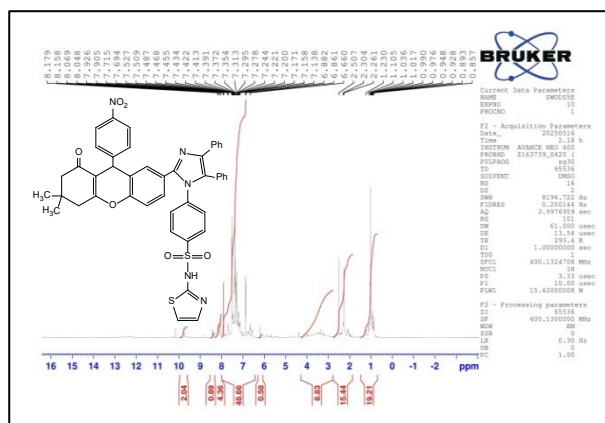
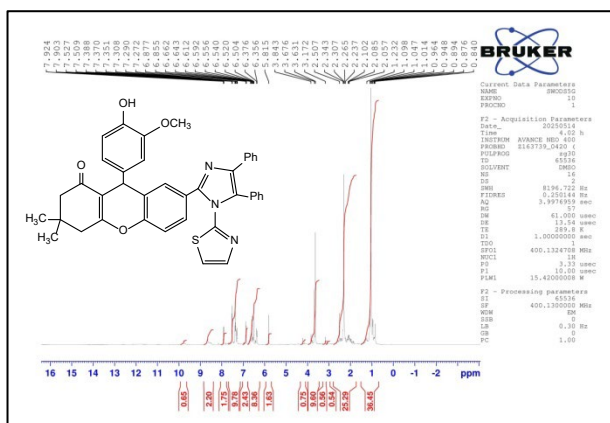
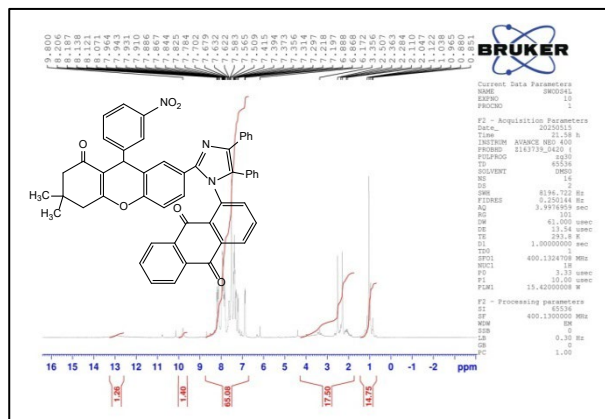
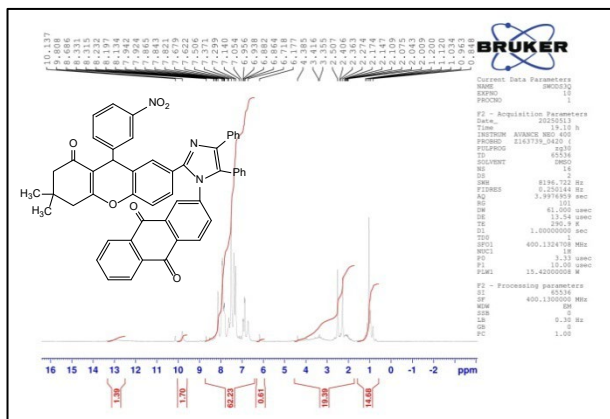


Fig. (22): FT-IR of compound (B₇).





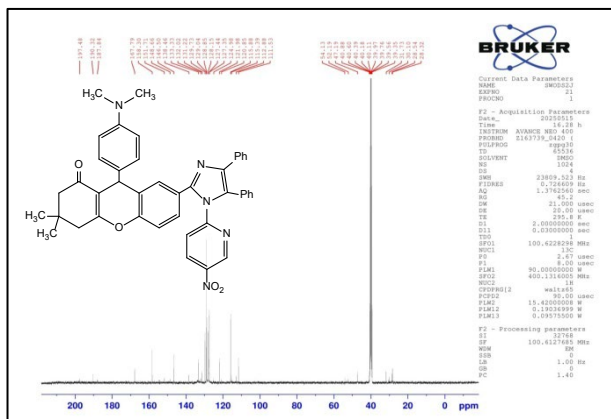


Fig. (31): ^{13}C -NMR of compound (B_2).

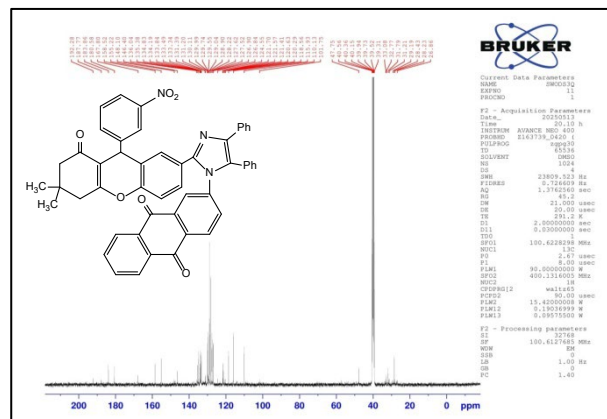


Fig. (32): ^{13}C -NMR of compound (B_3).

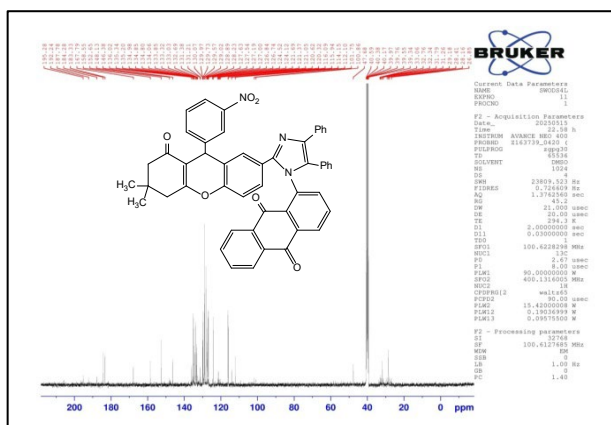
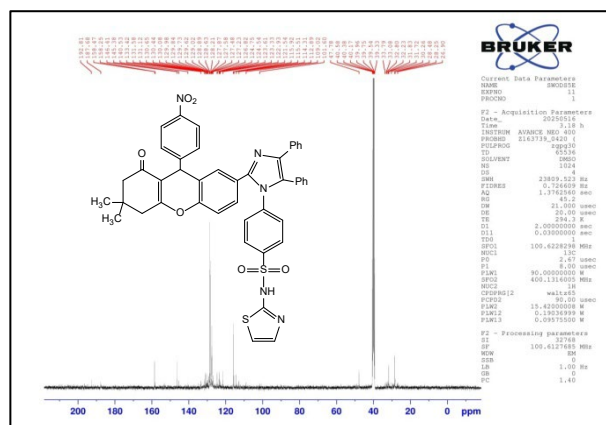


Fig. (33): ^{13}C -NMR of compound (B_4).



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