Synthesis and Identification of some new Five and Six Membered Rings Compounds from Sulfadiazine Drug

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ABSTRACT:

A series of five and six member rings has been synthesized from Sulfadiazine drug. In the present investigation sulfadiazine has been taken as initial material and treated with acetyl acetone to prepare new azo compound. then azo compound reacts with different aromatic aldehydes in absolute ethanol to prepare chalcone derivatives. then chalcone derivatives react with various compounds such as urea, thiourea, hydroxyl amine hydrochloride, 2,4-dinitrophenyl hydrazine and hydrazine hydrate to prepare new heterocyclic compounds.

KEYWORDS: sulfadiazine , azo compound, chalcone derivatives, heterocyclic compounds.

INTRODUCTION:

Heterocyclic derivatives having nitrogen attached to sulfonamide moieties have received a large amount of attention in the literature, . Sulfadiazine drug includes sulfonamide functional group which have wide biological activities revolutionized the field of medical sciences**[1]** .

Heterocyclic sulfonamides are used as carbonic anhydrase inhibitors **[2–4]**, antibacterial agents **[5],** anticancer, anti-inflammatory and analgesic agents **[6],** β3-adrenergic receptor agonists **[7],** PC-1 inhibitors **[8],** antifungal agents and antiviral agents [9]. Azo dye, aromatic rings associated together through azo(-N=N) chromophores represent the largest category of dyes used in textile processing and other industries like food colorant, printing, cosmetic, and pharmaceutical industries **[10,11].** Chalcone derivatives have α,β-unsaturated carbonyl moiety have wide spectrum of biological activity in both medicinal and pharmaceutical, for example antimicrobial **[12],** anti-inflammatory **[13],** antitubercular **[14],** antioxidant **[15]** and anticancer **[16].**

The SO_2NH moiety as a toxophoric function in many sulfa drugs like sulfadiazine, sulfamethoxa-zole, and sulfamerazine play important roles in its antimicrobial activity **[17]**, Sulfadiazine exhibits in vitro inhibitory activity against several aerobic gram-positive and gram-negative bacteria **[18]**, Sulfadiazine is one of the medication populace of barbituric acids has concern**[19]**.

MATERIAL AND METHODS:

Reagents and reactants are used like obtained from commercial companies without further purification. Solvents were purified beforehand. The purity of derivatives and path of reaction were monitored using thin layer chromatography on silica gel-G (Merck grade) with ethanol and benzene mixture as mobile phase. The Melting points were measured in open capillaries, with the help of (Stuart) melting point (SMP30, England) melting point apparatus are expressed in °C and are uncorrected. Infrared spectra (FT-IR) were recorded on Shimadzu Prestige-21 Spectrophotometer by using potassium bromide (KBr pellets) and the values are expressed in cm^{-1}, ^{1}H NMR and ^{13}CNMR spectra of the derivatives were recorded on Bruker (Avance III, Bruker 400MHz NMR spectrophotometer using TMS as an interior standard and the values are expressed in ppm in university of Behshti in Iran

EXPERIMENTAL:

Preparation of Azo compounds (S_1)[20]

Sulfadiazine (3gm,0.012 mole) has been liquefied in (4 ml) of concentrated hydrochloric acid in addition to (20 ml) of purified water. The solution has been under (0 – 5) °C in ice-water bath. About 0.012 mole of sodium nitrite has been liquefied in 10 ml of purified water with adding drop by drop to a solution with stirring. Also, 0.012 mole of Acetyl acetone has been liquefied in 20 ml of ethanol and 5 ml (10 %) sodium hydroxide and cooled under (0 – 5) °C with addition of diazonium solution in droopingly wise with stirring under (0 – 5) °C for two hours for getting the coupling agent. The precipitate found was filtered, washed and recrystallized from ethanol.

Preparation of Chalcone (S_2, S_3)[21]

S_1 compound (1gm,0.002 mol) with(0.596gm,0.002mol) N,N-di methylbenzaldehyde and Vanillin respectively (0.01 mol) were dissolved in absolute ethanol (30 mL).Sodium hydroxide solution 10% (5 ml) was added gradually and the mixture stirred for 8 hrs then it was constant stirring and put overnight in Refrigerator. The precipitate found was filtered, washed and recrystallized from ethanol.

Preparation of Isoxazole derivatives (S2a, S3a)[22]

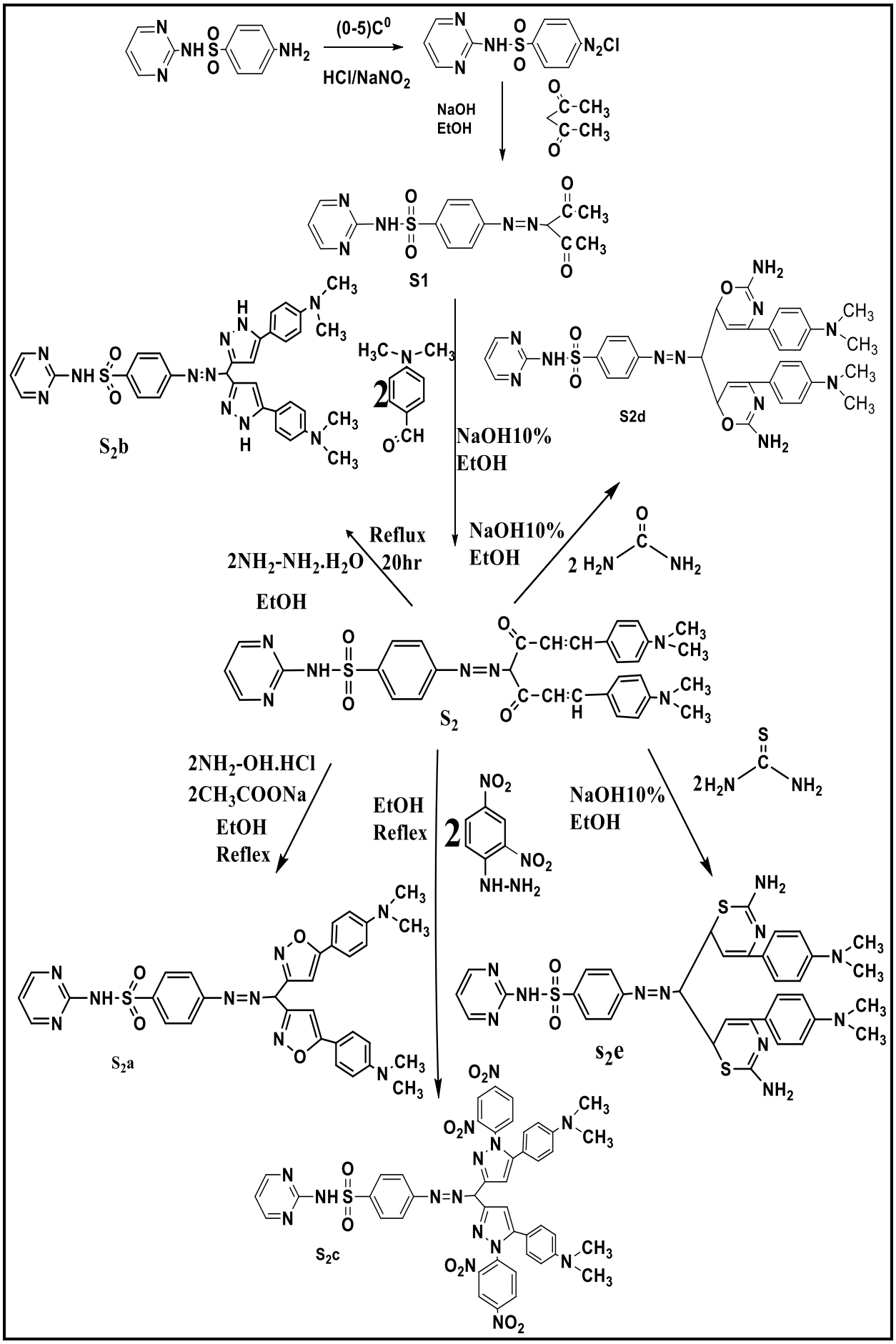
A compound of Chalcone [S_2,S_3] (0.36 gm,0.0004 mol), hydroxylamine hydrochloride (0.06gm, 0.0004 mol) and sodium acetate in ethanol (30 ml) was refluxed for 16 hrs, then the reaction mixture was cooled. The precipitate obtained was filtered, washed and recrystallized from ethanol.

Preparation of pyrazole derivatives (S_2b, S_2C, S_3b, S_3C)[23]

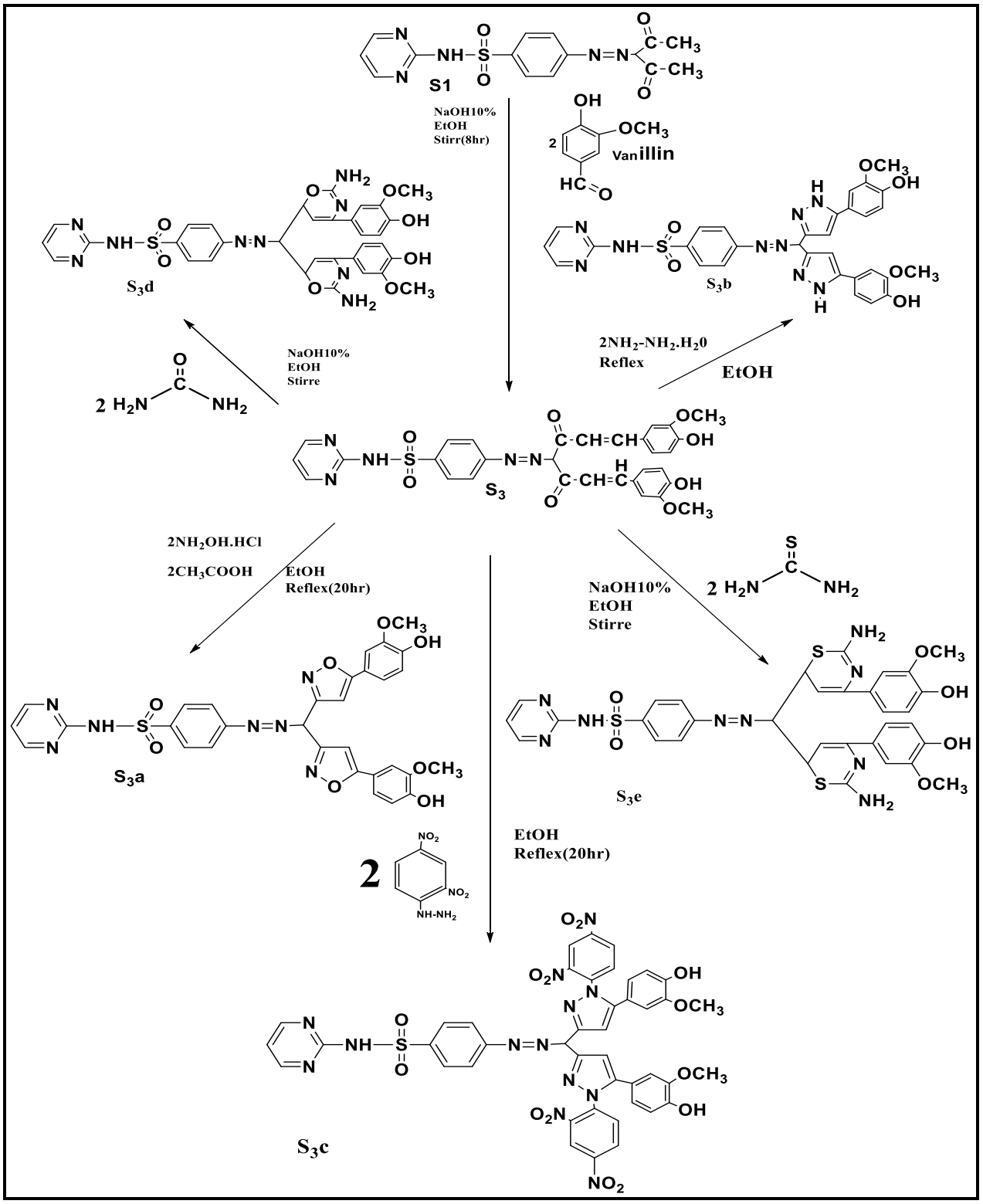
A mixture of Chalcone **[S_2-S_3]** (0.3gm,0.0004 mol) with hydrazine hydrate (0.05 ,0.0004 mol)and 2,4-di nitro phenyl hydrazine (0.2gm ,0.0004mol) respectively in ethanol (25 ml) was refluxed for 20 hrs. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice water. The precipitate obtained was filtered, washed and recrystallized from ethanol. The completion of the reaction was monitored by TLC .

Preparation of Oxazine and Thiazine derivatives (S_2d, S_2e, S_3d, S_3e)[24]

A mixture of chalcone **[S_2,S_3]** (0.3gm , 0.0004 mol), urea / thiourea (0.06gm ,0.0004 mol) were dissolved in (30 ml) of absolute ethanol and sodium hydroxide solution 10% (5 ml) was stirred for 4 hrs, after that it was transferred into 20 ml of ice water with continuous stirring for 1 hrs, then left overnight. The precipitate made was filtered, washed and recrystallized from ethanol.



Scheme (1):Synthesis of Heterocyclic compounds (five and six) membered rings from chalchone (S_2)



Scheme (2):Synthesis of Heterocyclic compounds (five and six) membered rings from chalchone (S_3)

Result and discussion:

S: 4-amino-N-phenylbenzenesulfonamide: m. p (90-95) C^0 ,yield 90%, FT-IR(KBr) cm^{-1} v3493-3358 (NH_2) , v 3325($NH_{pyrimidine}$) , v3076 ($CH_{aromatic}$) , v1585 (C=C), v1323(SO_2).

S_1: 4-((2,4-dioxopentan-3-yl)diazenyl)-N-(pyrimidin-2-yl)benzenesulfonamide: m.p (98-100)C^0,yield 70%, FT-IR(KBr)cm^{-1}, v3091 ($CH_{aromatic}$) , v3358(NH), v2939($CH_{aliphatic}$), v1635 ($C=O_{ketone}$), v1583 $(C=C)_{aromatic}$,v1678 $(C=N)_{pyrimidine}$, v1440 (N=N)' v1317 (SO_2) : ^{1}H-NMR(DMSO),: δ 11.2 (s,1H, $NH)_{Sulfonamide}$, δ 2.3(s,3H,$CH_3)_{Methyl\ group}$, δ6.9-7.3(m,4H, aromatic rings): ^{13}CNMR(DMSO) : δ 198(C 0f $C=O)_{ketone}$, δ 158 (C of $C=N)_{pyrimidine}$, δ 111-156(C of phenyl groups), δ 23 (C of CH_3).

S_2: 4-((1,7-bis(4-(dimethylamino)phenyl)-3,5-dioxohepta-1,6-dien-4-yl)diazenyl)-N-(pyrimidin-2-yl)benzenesulfonamide: m .p (113-117)C^0,yield 87%, FT-IR(K Br) cm^{-1}, v3431$(NH)_{Sulfadiazine}$, v2920($CH_{aromatic}$), v2818 ($CH_{aliphatic}$), v1670 ($C=O_{ketone}$), v1593 $(CH=CH)_{alkene}$, v1419 (N=N), v1367 (SO_2): ^{1}H-NMR(DMSO) , : δ 11.4(s,1H, $NH)_{Sulfadiazine}$, δ 6.8 (d,2H, $CH=CH)_{Alkene}$, δ7.2-8.3(m, 7H ,Aromatic rings) δ 2.0(s,6H,2CH3)$_{Methyl\ group}$, δ2.5 (DMSO) : ^{13}C NMR(DMSO): δ 199(C of $C=O)_{ketone}$, δ160-162 (C of CH=CH) , δ 158(C of $C=N)_{pyrimidine}$, δ 106-142 (C of aromatic rings), δ, δ 23 (C of CH_3).

S_3: 4-((1,7-bis(3-hydroxy-4-methoxyphenyl)-3,5-dioxohepta-1,6-dien-4-yl)diazenyl)-N-(pyrimidin-2-yl)benzenesulfonamide, m .p (139-140)C^0 , yield 81% , FT-IR(K Br) cm^{-1},v3421(OH), v3288$(NH)_{sulfadiazine}$, v2970($CH_{aromatic}$) , v2835 ($CH_{aliphatic}$), v1658 ($C=O_{ketone}$) v1583$(CH=CH)_{Alkene}$, v1564$(C=C)_{aromatic}$, , v1417 (N=N), v1361 (SO_2), v1126 (OCH_3):^{1}H-NMR(DMSO), δ 11.4 (s,1H, NH), δ 11.7 (s,1H, OH), δ7.4-8.1(m,8H, aromatic ring), δ 6.7 (d, ,2H, $CH=CH)_{Alkene}$, δ 3.4 (s,3H,OCH_3): ^{13}CNMR(DMSO) δ198 (C of $C=O)_{ketone}$, δ 156(C of $C=N)_{pyrimidine}$, δ 117- 131 (C of aromatic rings) , δ 55(C of OCH_3).

S_2a : 4-((bis(5-(4-(dimethylamino)phenyl)isoxazol-3-yl)methyl)diazenyl)-N-(pyrimidin-2-yl)benzenesulfonamide, m .p(145-148)C^0, yield 87% , FT-IR(K Br) cm^{-1} v3251$(NH)_{sulfadiazine}$, v3043($CH_{aromatic}$), v2831 ($CH_{aliphatic}$), 1583 $(C=C)_{aromatic}$, v1600 $(C=N)_{isoxazole}$, v1483 (N=N) , v1340(SO_2): ^{1}H-NMR(DMSO), δ 11.5 (s, 1H, NH $)_{sulfadiazine}$, δ2.0 (s,6H,2CH_3) , δ7.4-7.9 (m,8H, aromatic rings): ^{13}C NMR(DMSO): δ 158(C of C=N) $_{isoxazole}$, δ157 (C of C=N) $_{pyrimidine}$, 116-131 (C of aromatic rings) , δ 23(C of CH_3).

S_2b: 4-((bis(5-(4-(dimethylamino)phenyl)-1H-pyrazol-3-yl)methyl)diazenyl)-N-(pyrimidin-2-yl)benzenesulfonamide, m .p(158-160)C^0,yield 88% , FT-IR(K Br) cm^1, v 3417 (NH) $_{pyrazole\ ring}$,v3352(NH) $_{sulfadiazine}$, v3047 ($CH_{aromatic}$),v2918 ($CH_{aliphatic}$), v 1602 (C=N) $_{pyrazole\ ring}$, v1546$(C=C)_{aromatic}$, v1419(N=N) , v1361(SO_2): ^{1}H-NMR(DMSO), δ11.8 (s, 1H, NH) $_{pyrazole\ ring}$, δ 9.5 (s,NH,1H) $_{sulfadiazine}$,δ7.0-7.9 (m,7H,

aromatic rings) , δ2.0 (s,6H,2CH_3): ^{13}C NMR(DMSO): δ 159(C of C=N) $_{pyrazole\ ring}$, δ 158(C of C=N) $_{pyrimidine}$, δ 116 -131 (C of phenyl ring), δ 23(C of CH_3).

S_2c: 4-((bis(5-(4-(dimethylamino)phenyl)-1-(2,4-dinitrophenyl)-1H-pyrazol-3-yl) methyl)diazenyl)-N-(pyrimidin-2-yl)benzene sulfonamide, m .p (188-190)C^0,yield 85% , FT-IR(K Br) cm^{-1}, ν3585 $(NH)_{sulfadiazine}$, ν3043$(CH_{aromatic})$,ν2912 $(CH_{aliphatic})$,ν1512 $(C=C)_{aromatic}$, ν1593 $(C=N)_{pyrazole\ ring}$, ν1419(N=N) , ν1344(SO_2).

S_2d: 4-((bis(2-amino-4-(4-(dimethylamino)phenyl)-6H-1,3-oxazin-6-yl)methyl)diazenyl)-N-(pyrimidin-2-yl)benzenesulfonamide, m .p(150-152)C^0,yield 84%,FT-IR(K Br) cm^{-1}, ν3441-3402 $(NH_2)_{Oxazine\ ring}$, ν 3124(NH) $_{sulfadiazine}$, ν 3010$(CH_{aromatic})$ ν2920$(CH_{aliphatic})$,ν1541$(C=C)_{aromatic}$, ν1599 $(C=N)_{Oxazine\ ring}$, ν1502(N=N) , ν1325(SO_2) ν1170(C-O-C).

S_2e:4-((bis(2-amino-4-(4-(dimethylamino)phenyl)-6H-1,3-thiazin-6-yl)methyl)diazenyl)-N-(pyrimidin-2-yl)benzenesulfonamide, m. p(148-150)C^0,yield 87% , FT-IR(K Br)cm^{-1} , ν3400-3352$(NH_2)_{Thiazine\ ring}$,ν3112$(NH)_{sulfadiazine}$,ν3039$(CH_{aromatic})$, ν2870 $(CH_{aliphatic})$, ν1577$(C=C)_{aromatic}$, ν1614 $(C=N)_{Thiazine\ ring}$, ν1479(N=N) , ν1373(SO_2) ν,1267$(C-S-C)_{Thiazine\ ring}$.

S_3a: 4-((bis(5-(4-hydroxy-3-methoxyphenyl)isoxazol-3-yl)methyl)diazenyl)-N-(pyrimidin-2-yl)benzenesulfonamide : m .p(156-158)C^0, yield 90%, FT-IR(K Br)cm^{-1},ν3446$(OH)_{hydroxyl\ group}$, ν3196$(NH)_{sulfadiazine}$,ν3097 $(CH_{aromatic})$,ν2939 $(CH_{aliphatic})$, ν1516 $(C=C)_{aromatic}$,ν1585$(C=N)_{isoxazole\ ring}$, ν1436(N=N) , ν1338(SO_2), ν1159$(C-O-C)_{isoxazole\ ring}$: ^{1}H-NMR(DMSO), δ 11.4 (s,OH,1H), δ11 (s,NH,1H), δ 6.5(s,1H,C=N) $_{isoxazole}$, δ7.0-7.6 (m,7H, aromatic ring), δ 3.6 (s,3H,OCH_3): ^{13}CNMR(DMSO), δ 159(C of C=N) $_{isoxazole\ ring}$, δ129-105(C ,aromatic rings) , δ 57(C of OCH_3), δ 157 (C of C=N) $_{pyrimidine}$.

S_3b: 4-((bis(5-(4-hydroxy-3-methoxyphenyl)-1H-pyrazol-3-yl)methyl)diazenyl)-N-(pyrimidin-2-yl)benzenesulfonamide, M.P(158-160)C^0,yield 88% ,FT-IR(KBr)cm^{-1},ν3585(OH) ν3429(NH) $_{pyrazolering}$, ν3109(NH) $_{sulf}$,ν3043 $(CH_{aromatic})$,ν2821 $(CH_{aliphatic})$, ν1593 $(C=N)_{pyrazolering}$,ν1512 $(C=C)_{aromatic}$,ν1449(N=N) , ν1344(SO_2), ν1240(OCH_3), ν1161 $(C-N)_{pyrazolering}$.

S_3c: 4-((bis(1-(2,4-dinitrophenyl)-5-(4-hydroxy-3-methoxyphenyl)-1H-pyrazol-3-yl)methyl)diazenyl)-N-(pyrimidin-2-yl)benzenesulfonamide, m. p(198-200)C^0,yield 85% ,FT-IR(K Br)cm^{-1},ν3585(OH), ν3429(NH) $_{pyrazole\ ring}$, ν $(NH)_{sulfadiazine}$, ν3111 $(CH_{aromatic})$, ν1514(C=C) $_{aromatic}$, ν1589 $(C=N)_{pyrazole\ ring}$, ν1419(N=N) , ν1346(SO_2), ν1201(OCH_3), ν1134 $(C-N)_{pyrazole\ ring}$, ν1298 (NO_2).

S_3d: 4-((bis(2-amino-4-(4-hydroxy-3-methoxyphenyl)-6H-1,3-oxazin-6-yl)methyl)diazenyl)-N-(pyrimidin-2-yl)benzenesulfonamide, m .p(155-157)C^0,yield

86% ,FT-IR(K Br)cm^{-1}, ν3581 (OH), ν 3478-3392 $(NH_2)_{Oxazine\ ring}$,ν3163(NH) $_{sulfadiazine}$, ν3039 (CH $_{aromatic}$), ν2858(CH $_{aliphatic}$),ν1512 $(C=C)_{aromatic}$, ν1584 $(C=N)_{Oxazine\ ring}$, ν1436(N=N) , ν1344 (SO_2), ν1155(OCH_3), ν1229$(C\text{-}O\text{-}C)_{Oxazine\ ring}$.

S_3e: 4-((bis(2-amino-4-(4-hydroxy-3-methoxyphenyl)-6H-1,3-thiazin-6-yl)methyl)diazenyl)-N-(pyrimidin-2-yl)benzenesulfonamide, m. p(150-152)C^0,yield 90% ,FT-IR(K Br)cm^{-1}, ν3542 (OH), ν3371-3319 $(NH_2)_{Thiazine\ ring}$,ν3105(NH) $_{sulfadiazine}$, ν2981 (CH $_{aromatic}$), ν1544 $(C=C)_{aromatic}$, ν1595 $(C=N)_{Thiazine\ ring}$, ν1465(N=N) , ν1344(SO_2), ν1253(OCH_3), ν1105$(C\text{-}S\text{-}C)_{Thiazine\ ring}$, ^{1}H-NMR(DMSO): δ 11.9 (s,1H,OH) , δ 11.3 (s,1H,NH)$_{sulfadiazine}$, δ 3.5 (s,3H,OCH_3), δ7.6-7.1 (m,8H, aromatic rings), δ 6.6 (s, 2H,NH_2)$_{thiazine}$: ^{13}C NMR(DMSO): δ 158(C of C=N) $_{Thiazine\ ring}$, δ 154 (C of C=N) $_{pyrimidine}$, δ 116-130 (C of phenyl group) , δ 54(C of OCH_3) .

Table-1- The physical properties of the prepared compounds:

No.	M.F	M.wt	m.p^{0}C	Color	R_f	Yield%
S_1	$C_{15}H_{15}N_5O_4S$	361.38	98-100	Orange	0.59	70
S_2	$C_{33}H_{33}N_7O_4S$	623.73	113-117	Light brown	0.83	87
S_3	$C_{31}H_{27}N_5O_8S$	629.64	139-140	Dark Brown	0.82	81
S_2a	$C_{33}H_{31}N_9O_4S$	649.73	145-148	Light yellow	0.47	87
S_3a	$C_{31}H_{25}N_7O_8S$	655.64	156-158	Orange	0.47	87
S_2b	$C_{33}H_{33}N_{11}O_2S$	647.76	158-160	Light brown	0.67	88
S_3b	$C_{31}H_{27}N_9O_6S$	653.67	150-152	Dark brown	0.62	85
S_3c	$C_{43}H_{31}N_{13}O_{14}S$	985	198-200	Red	0.61	85
S_2d	$C_{35}H_{37}N_{11}O_4S$	707.81	150-152	Dark Yellow	0.68	84
S_2e	$C_{35}H_{37}N_{11}O_2S_3$	739.49	148-150	Brown	0.64	90
S_3d	$C_{33}H_{31}N_9O_8S$	713.73	155-157	Light red	0.71	86
S_3e	$C_{33}H_{31}N_9O_6S_3$	745.85	150-152	Brown	0.62	90
S_2c	$C_{45}H_{37}N_{15}O_{10}S$	979.95	188-190	Black	0.72	85

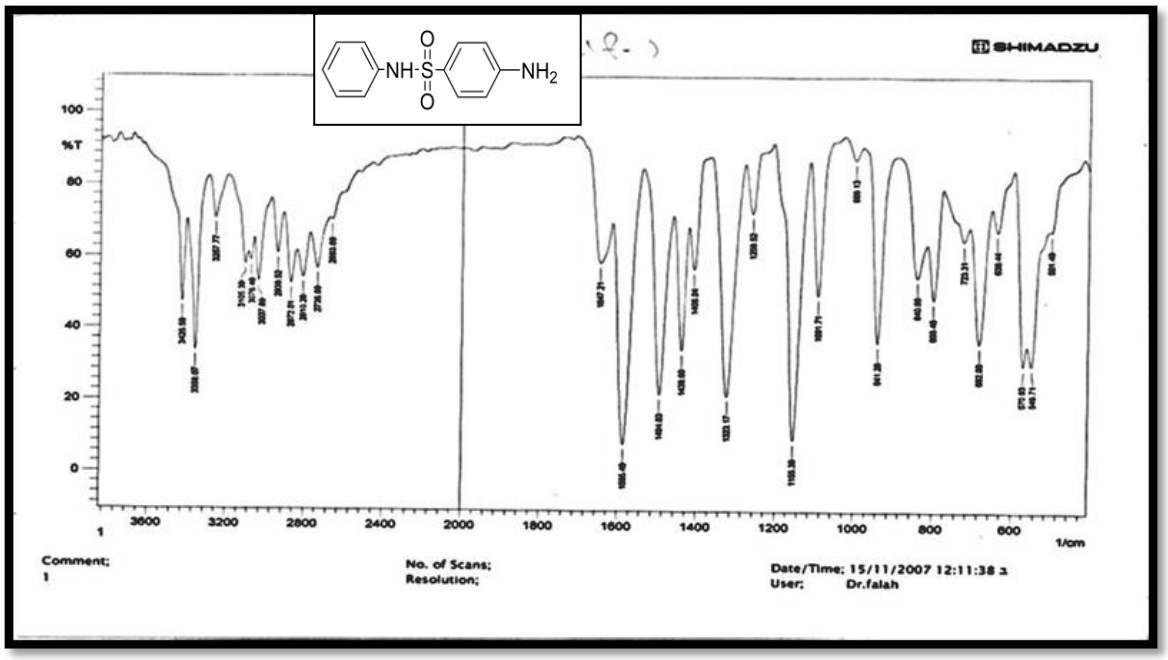


Fig.1:FT-IR Spectrum of compound (Sulfadiazine)

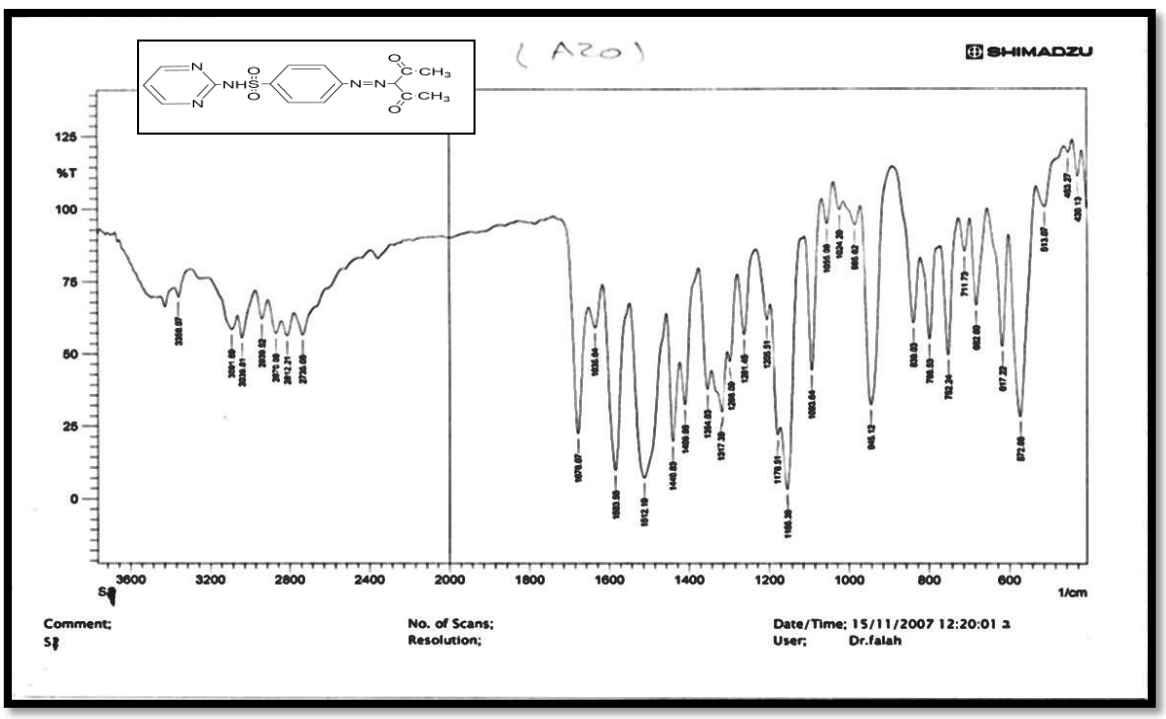


Fig.2:FT-IR Spectrum of compound (S_1)

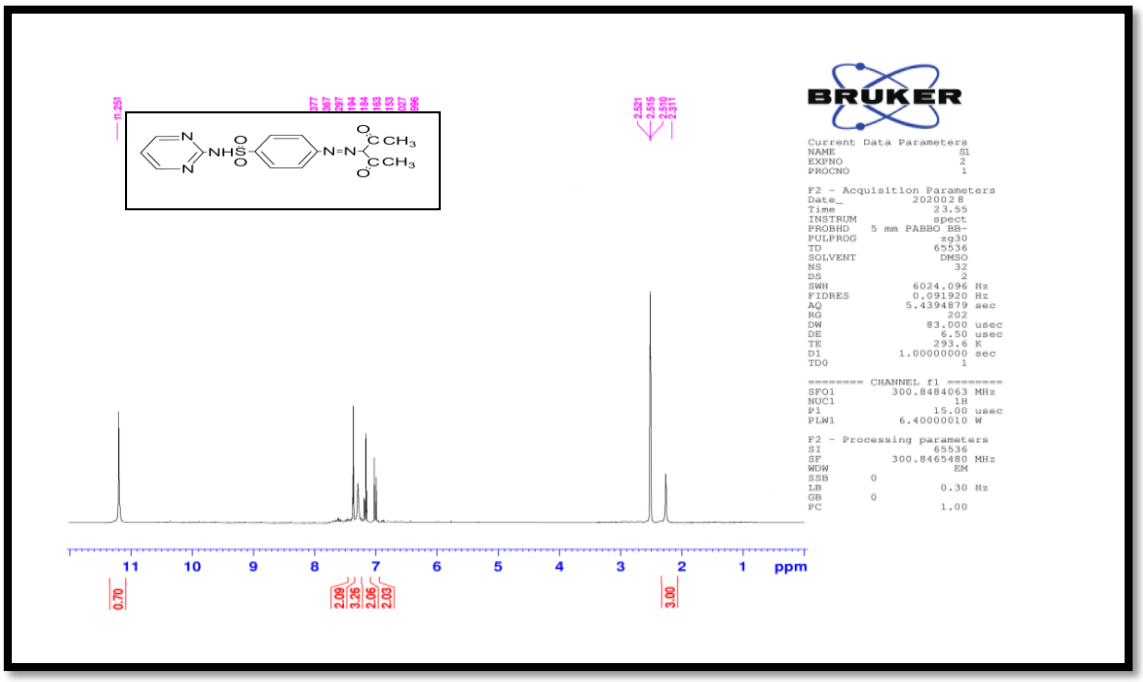


Fig.3:[1]H-NMR Spectrum of compound (S_1)

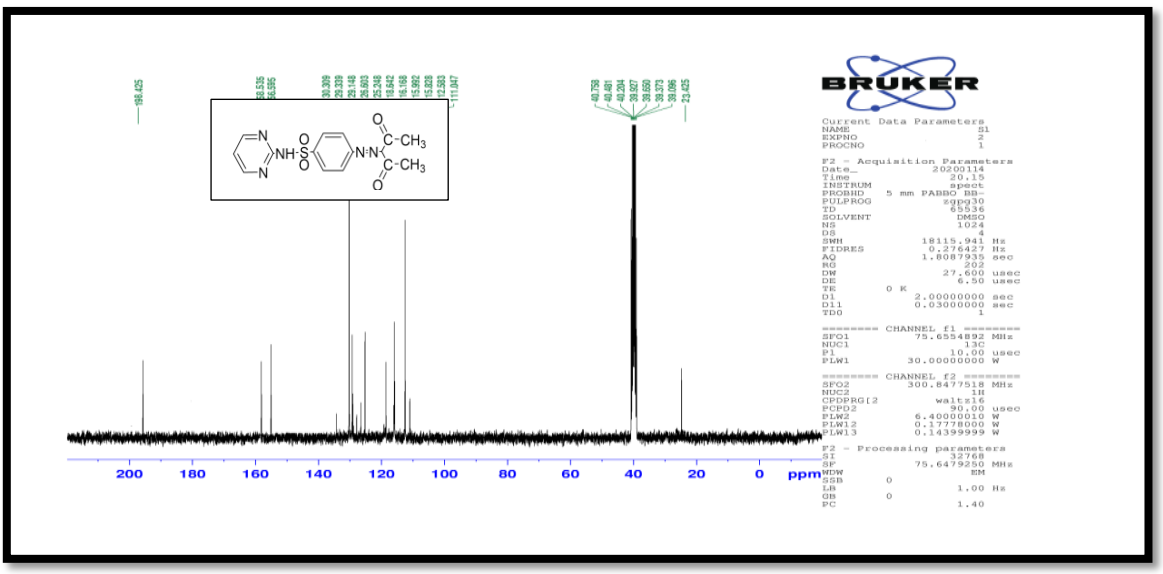


Fig.4:[13]C-NMR Spectrum of compound (S_1)

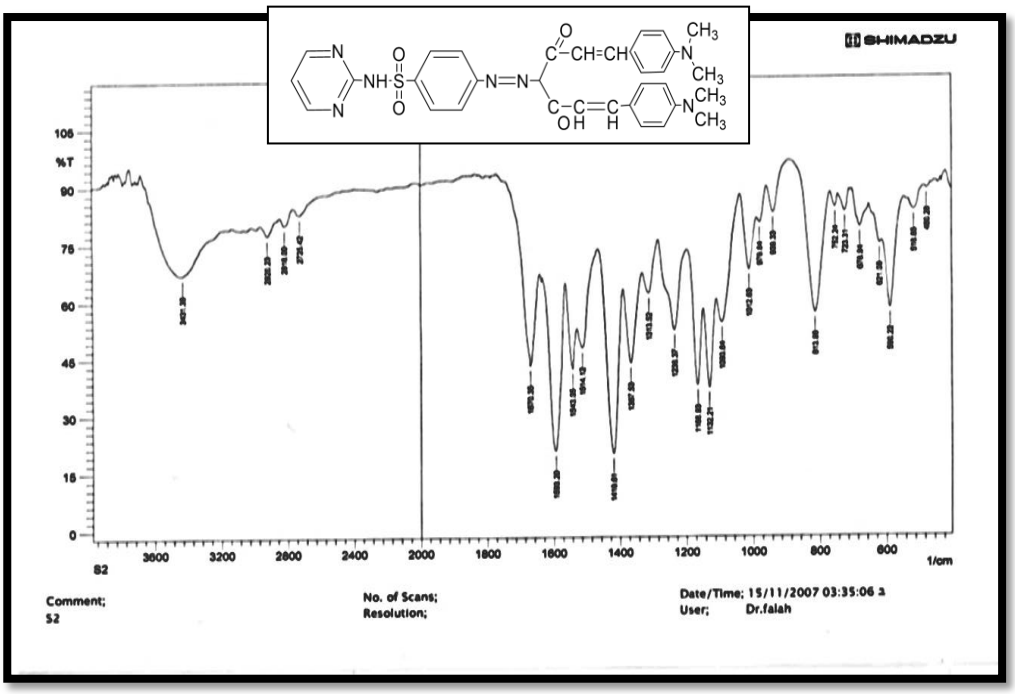


Fig.5:FT-IR Spectrum of compound (S_2)

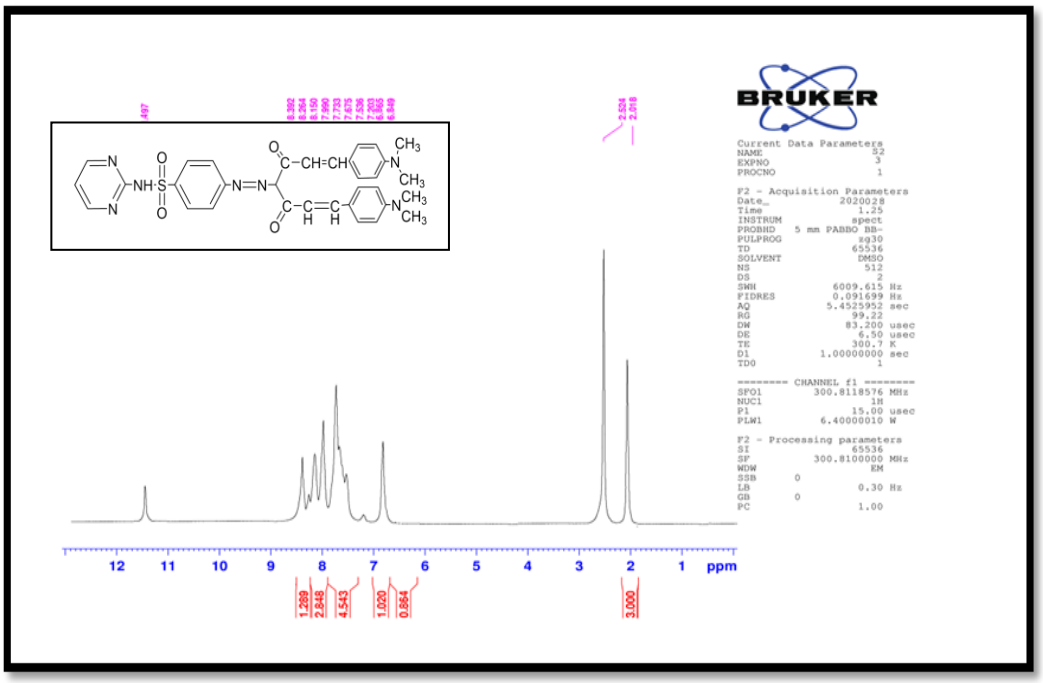


Fig.6:^{1}H-NMR Spectrum of compound (S_2)

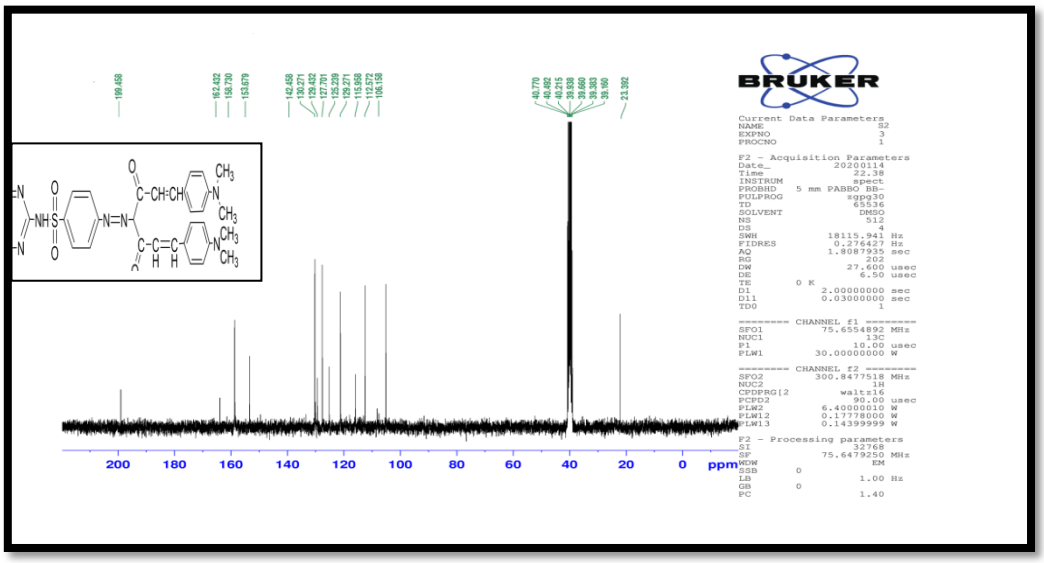


Fig.7:^{13}C-NMR Spectrum of compound (S_2)

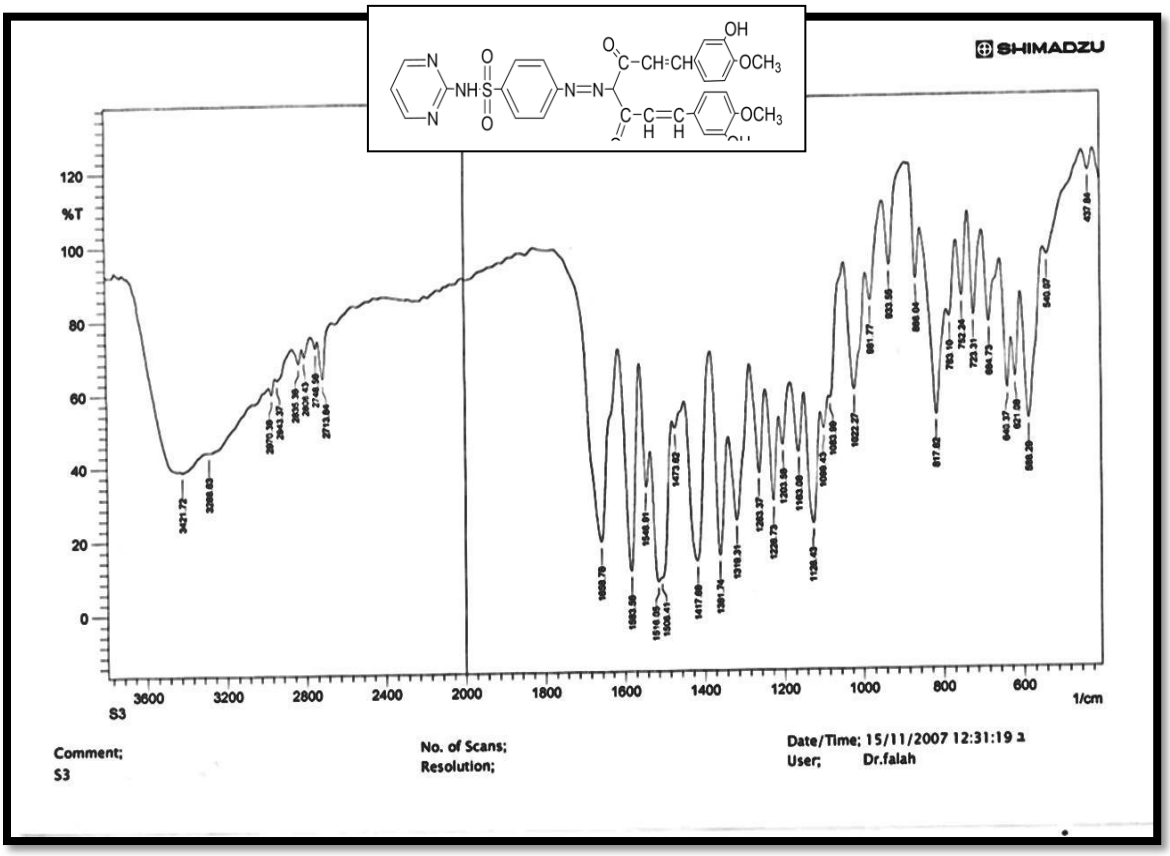


Fig.8:FT-IR Spectrum of compound (S_3)

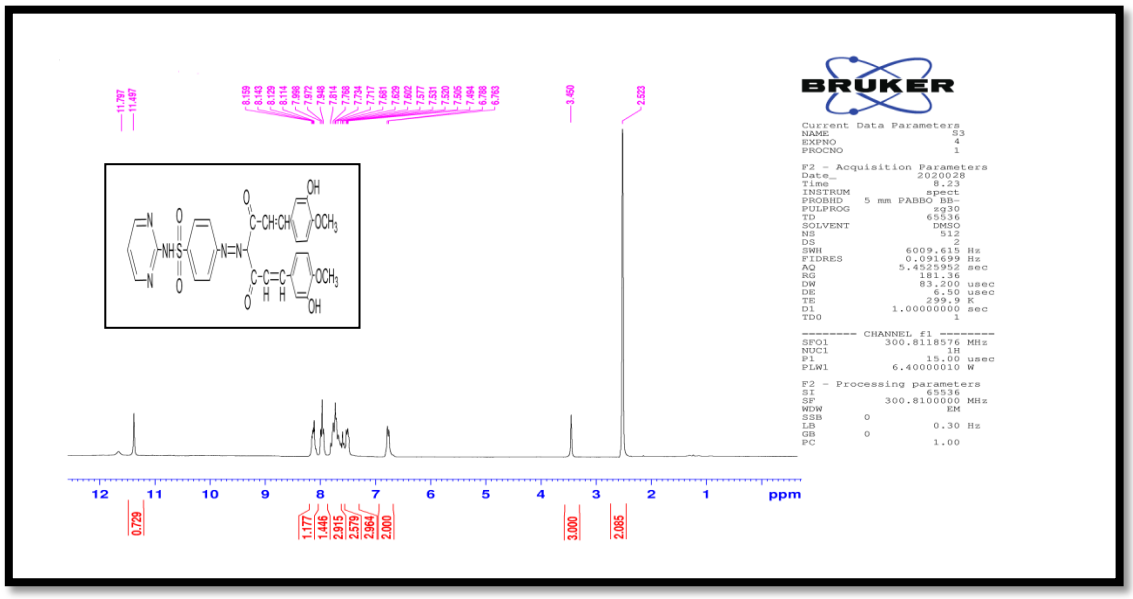


Fig.9:[1]H-NMR Spectrum of compound (S_3)

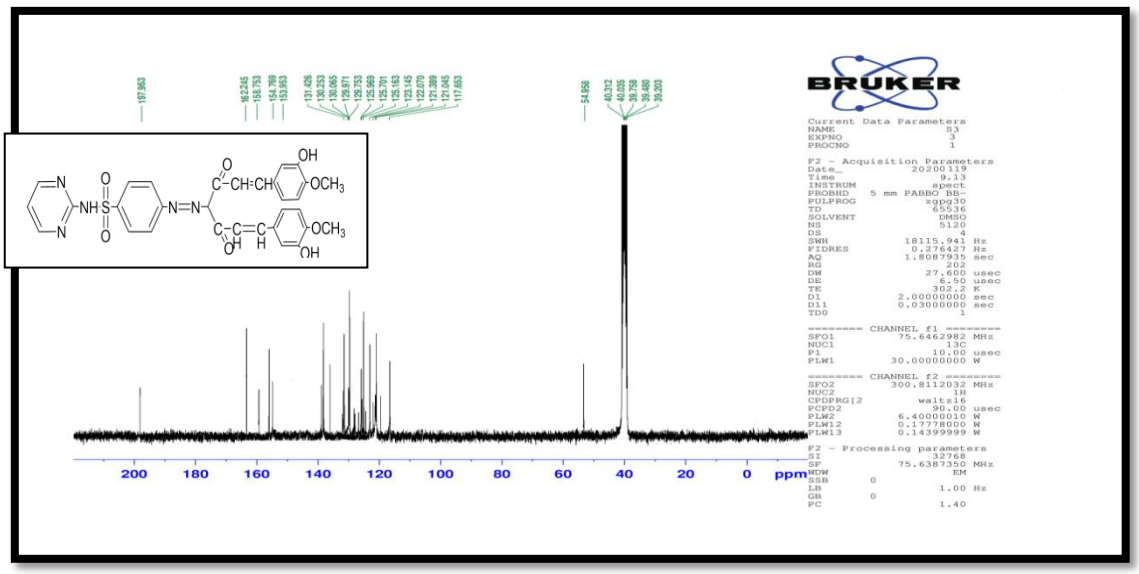


Fig.10:[13]C-NMR Spectrum of compound (S_3)

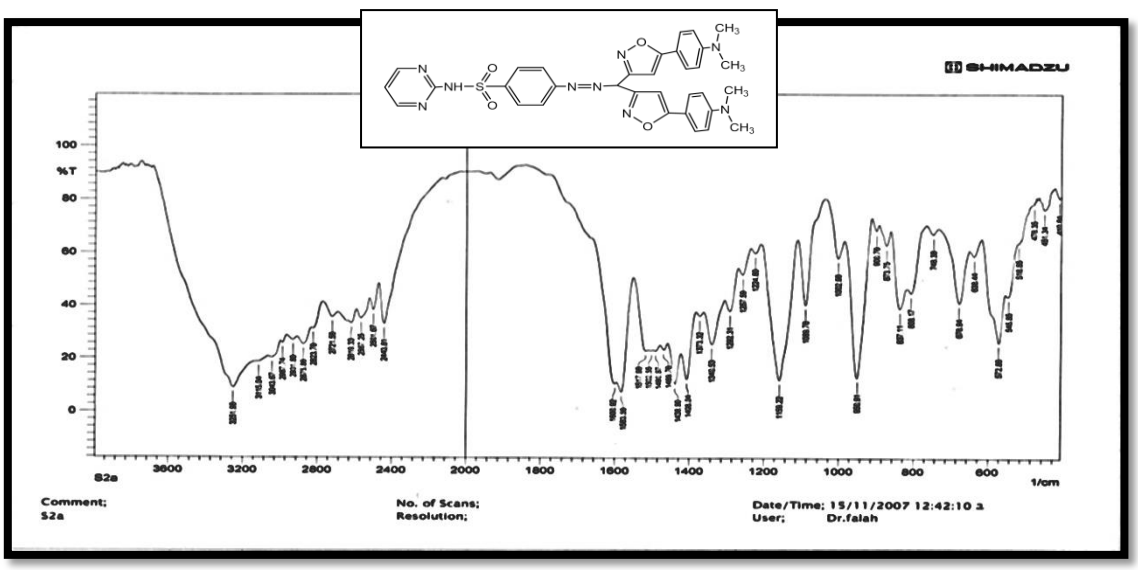


Fig.11:FT-IR Spectrum of compound (S_2a)

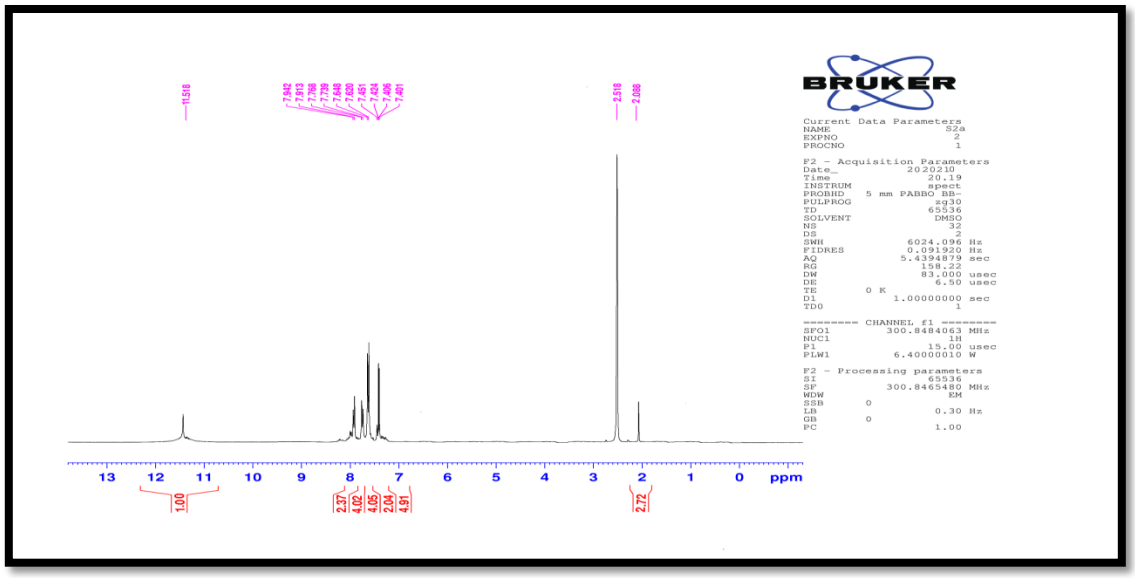


Fig.12:^{1}H-NMR Spectrum of compound (S_2a)

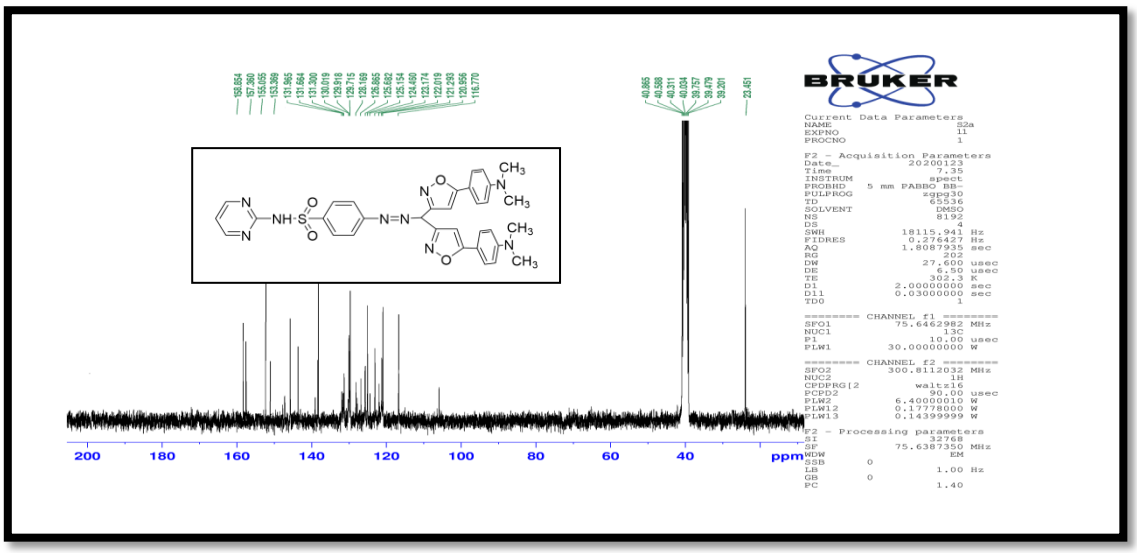


Fig.13:^{13}C-NMR Spectrum of compound (S_2a)

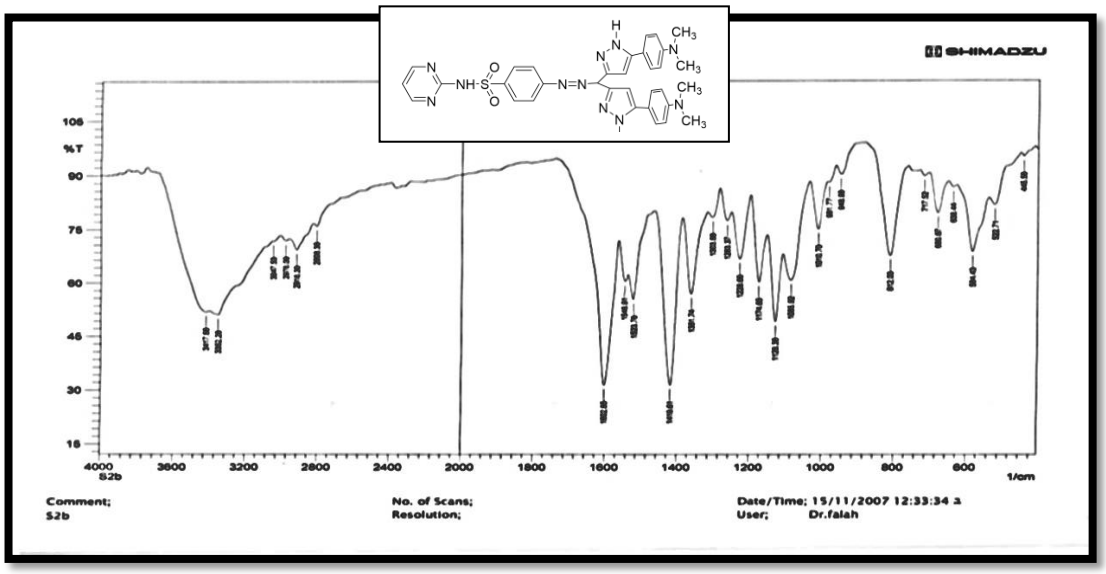


Fig.14:FT-IR Spectrum of compound (S_2b)

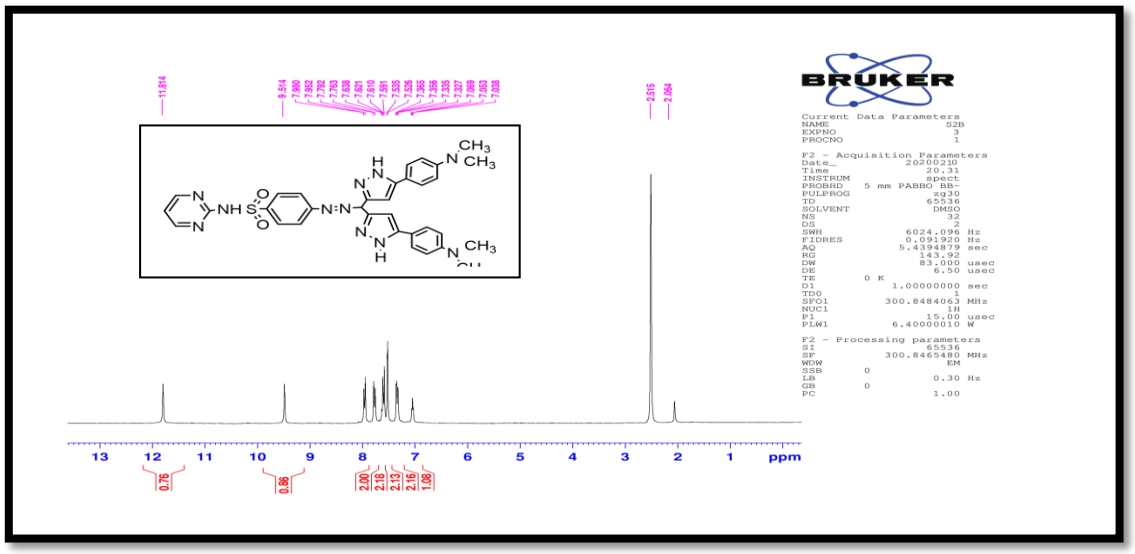


Fig.15:^{1}H-NMR Spectrum of compound (S_2b)

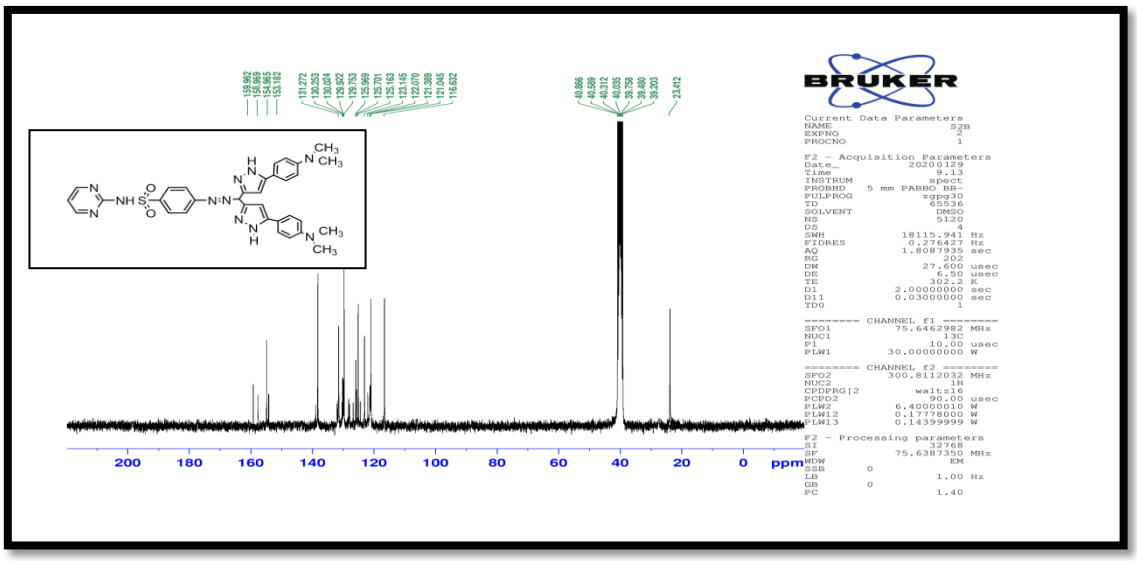


Fig.16:^{13}C-NMR Spectrum of compound (S_2b)

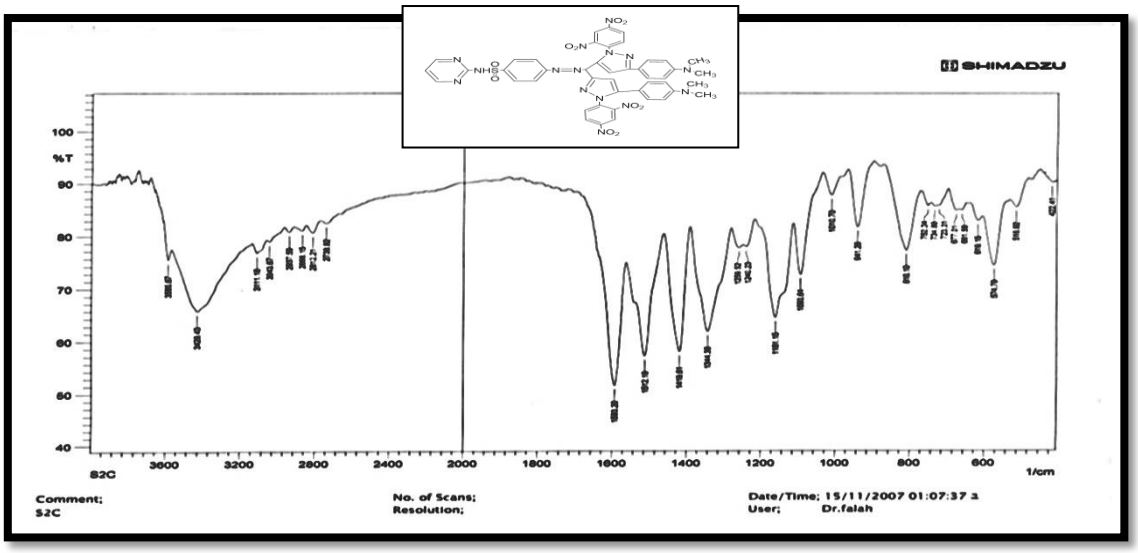


Fig.17:FT-IR Spectrum of compound (S_2c)

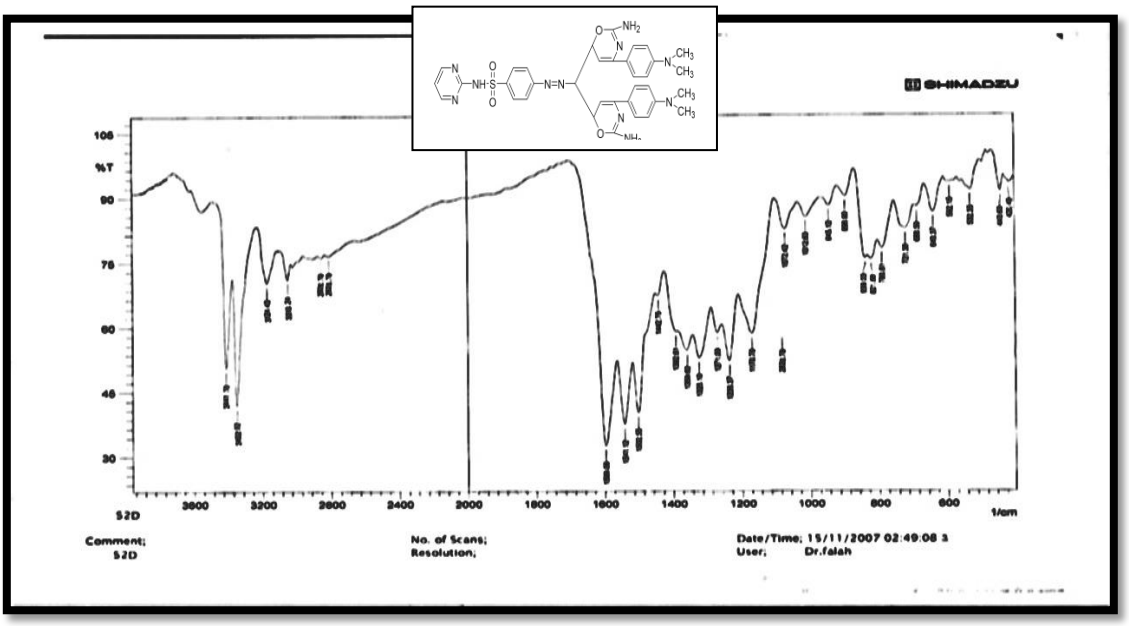


Fig.18:FT-IR Spectrum of compound (S_2d)

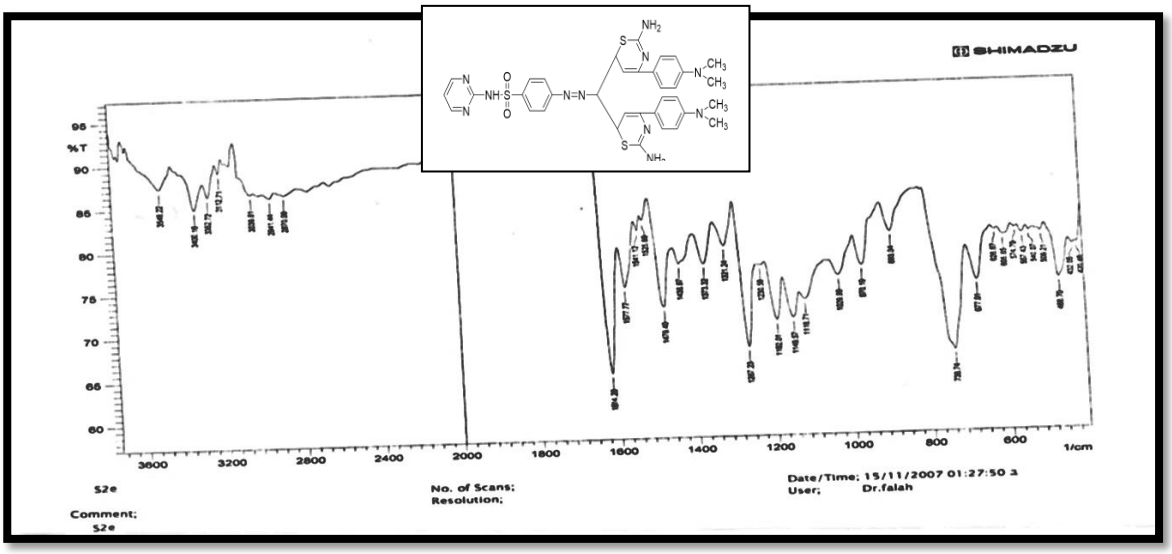


Fig.19:FT-IR Spectrum of compound (S_2e)

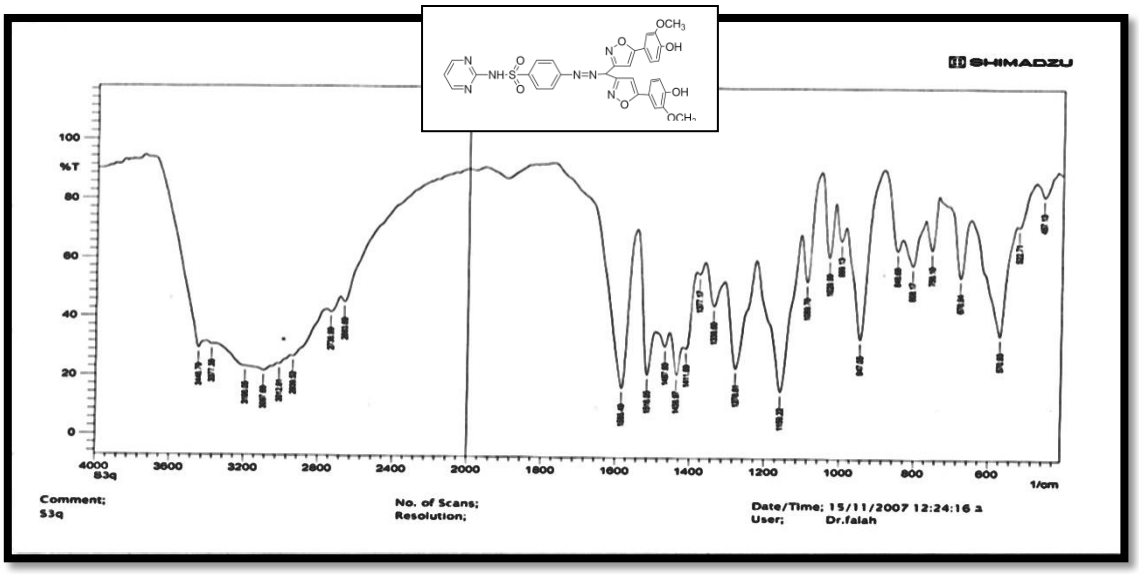


Fig.20:FT-IR Spectrum of compound (S_3a)

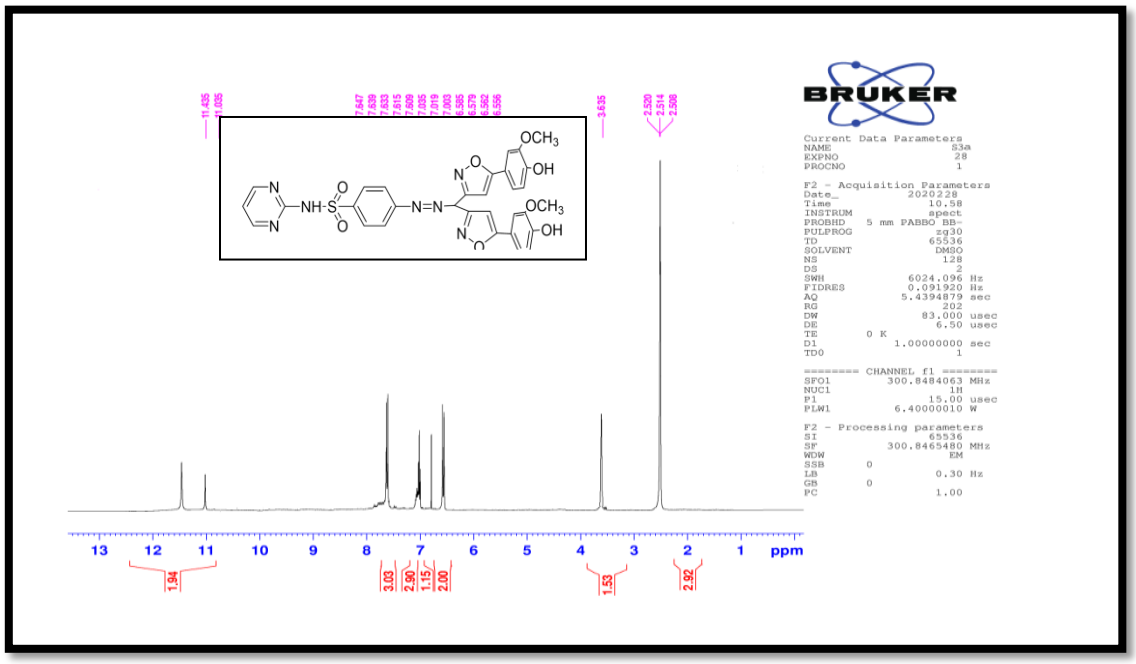


Fig.21:[1]H-NMR Spectrum of compound (S_3a)

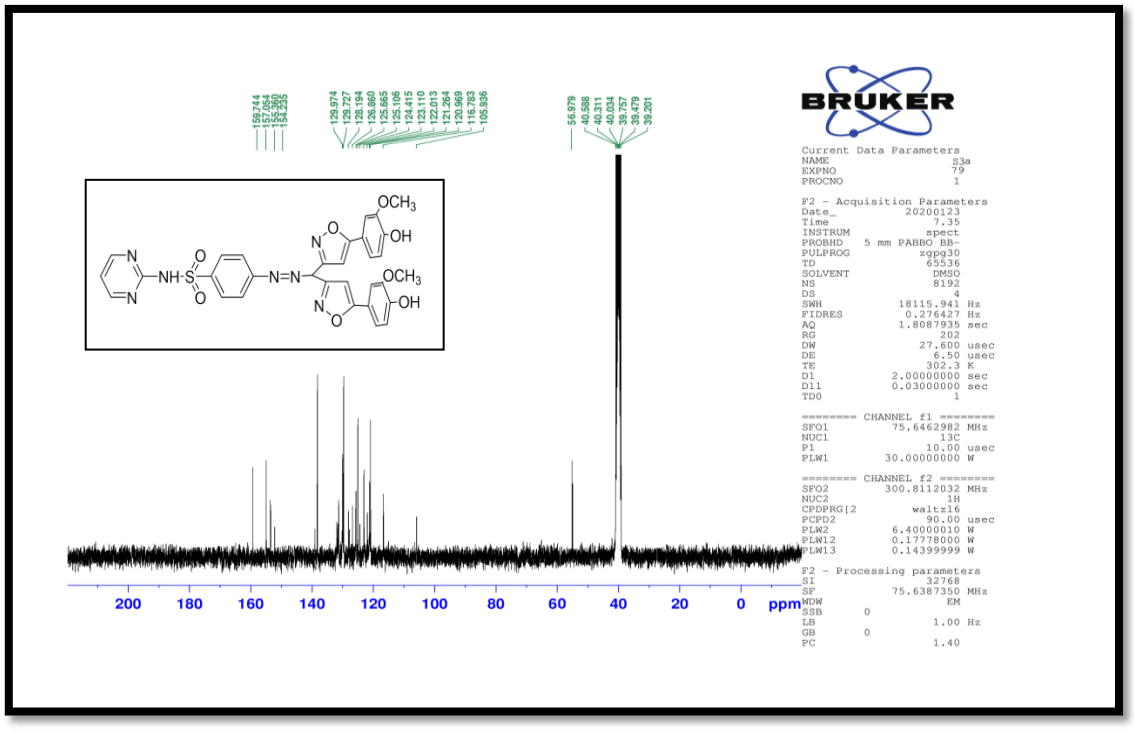


Fig.22:[13]C-NMR Spectrum of compound (S_3a)

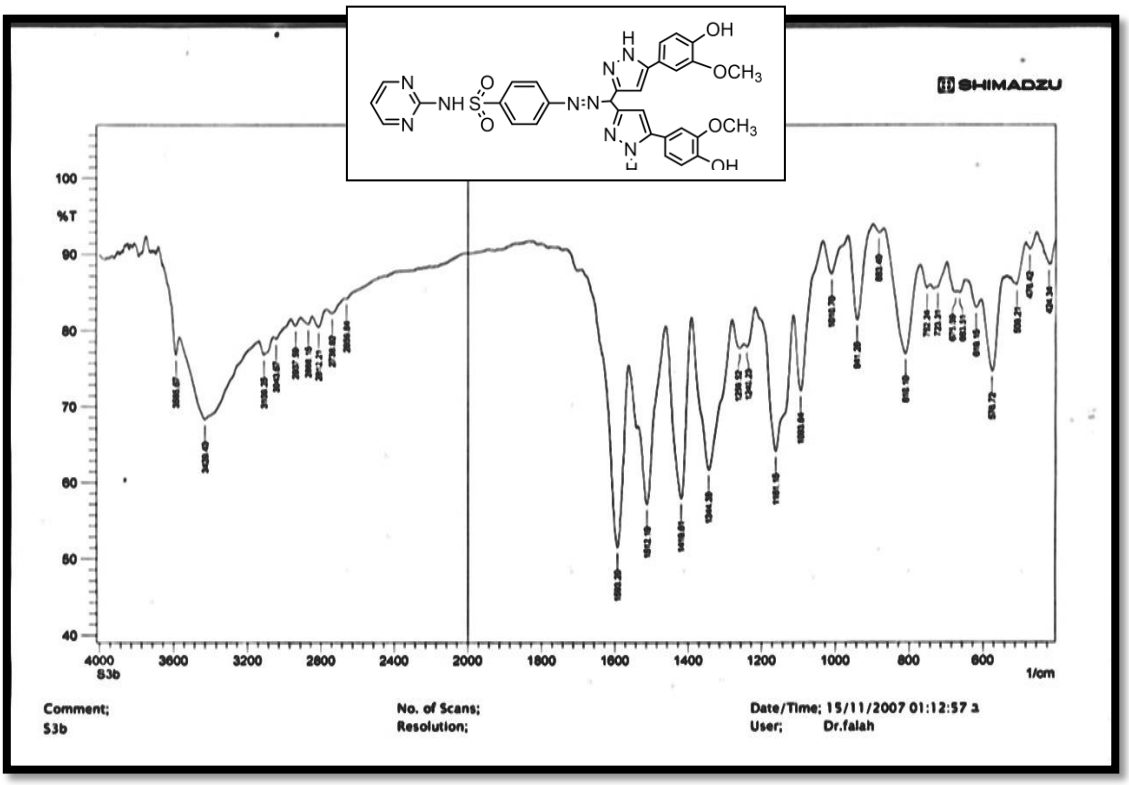


Fig.23:FT-IR Spectrum of compound (S_3b)

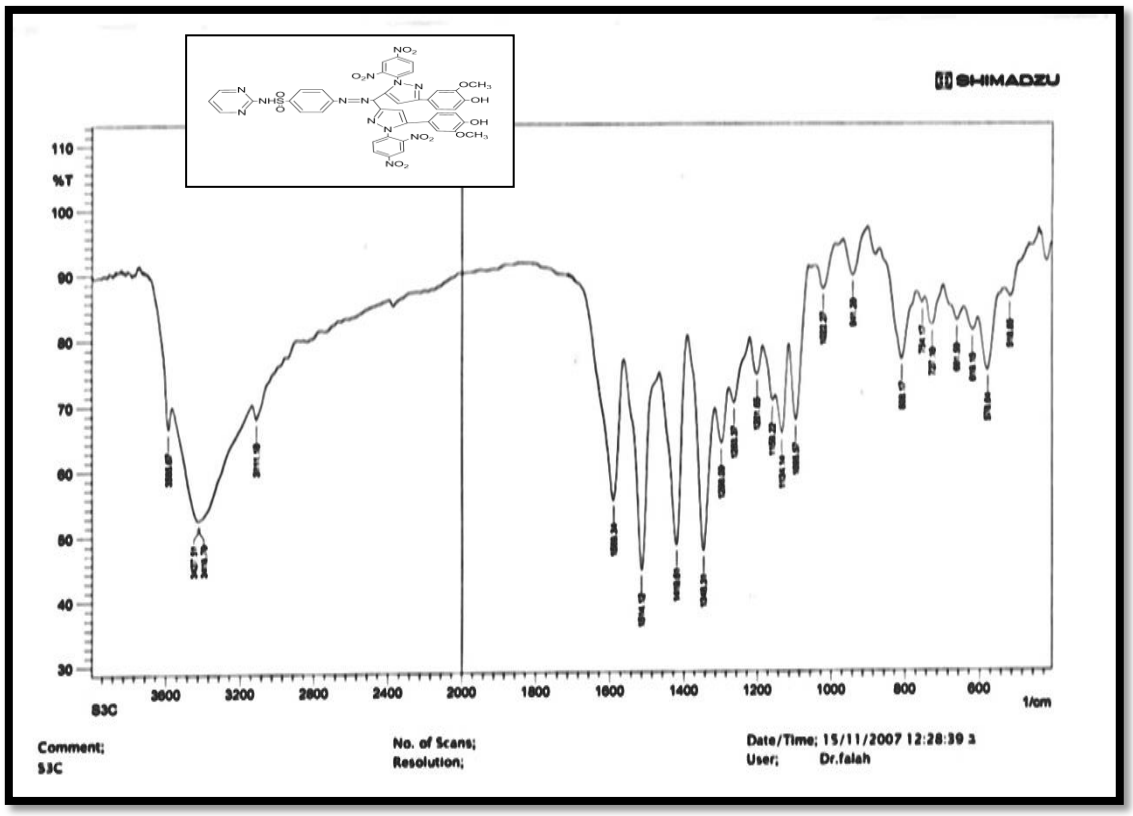


Fig.23:FT-IR Spectrum of compound (S_3c)

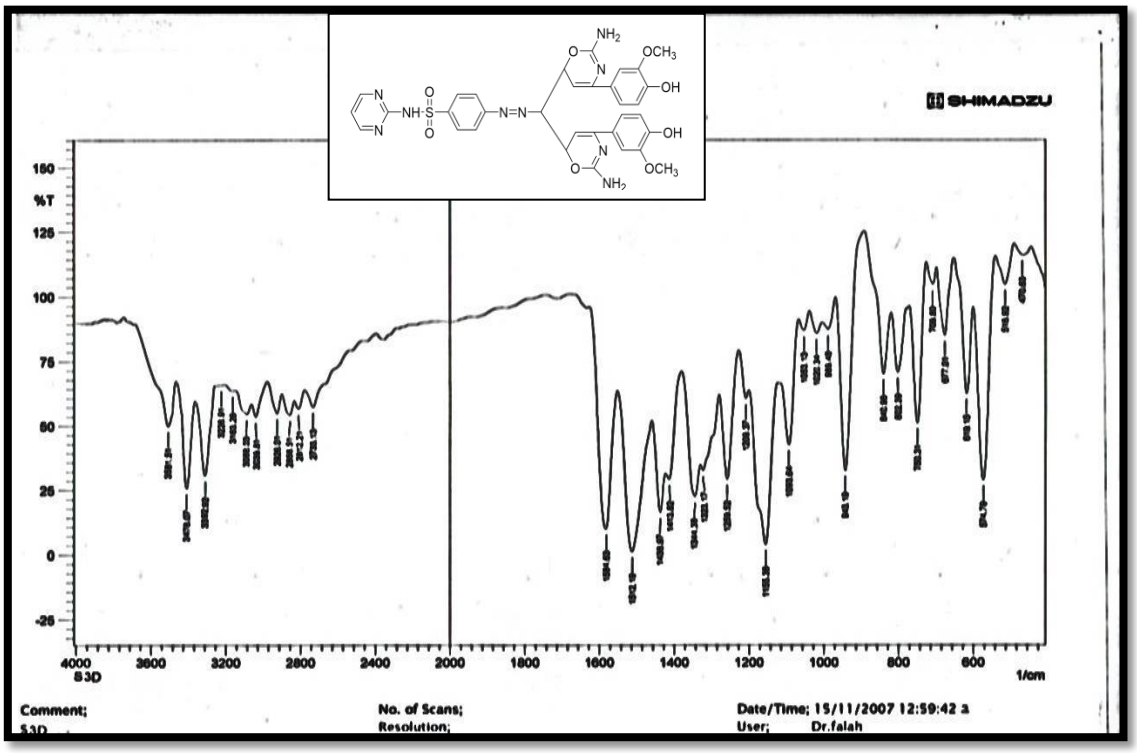


Fig.24:FT-IR Spectrum of compound (S_3d)

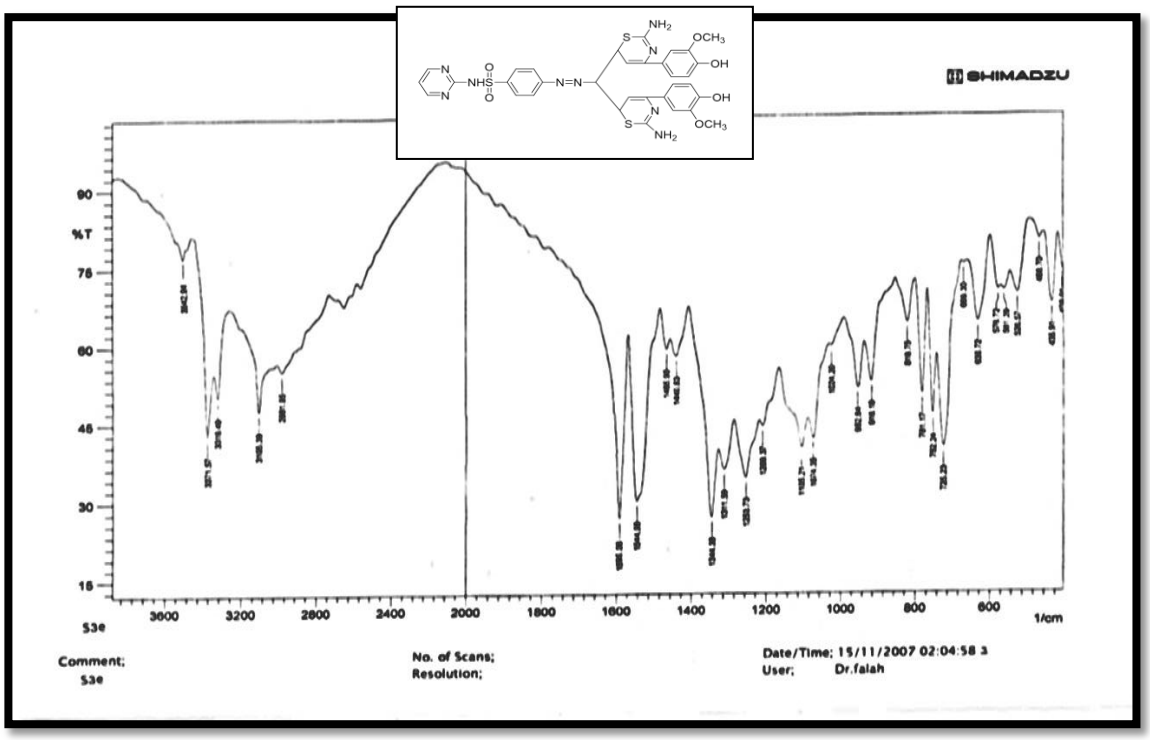


Fig.25:FT-IR Spectrum of compound (S_3e)

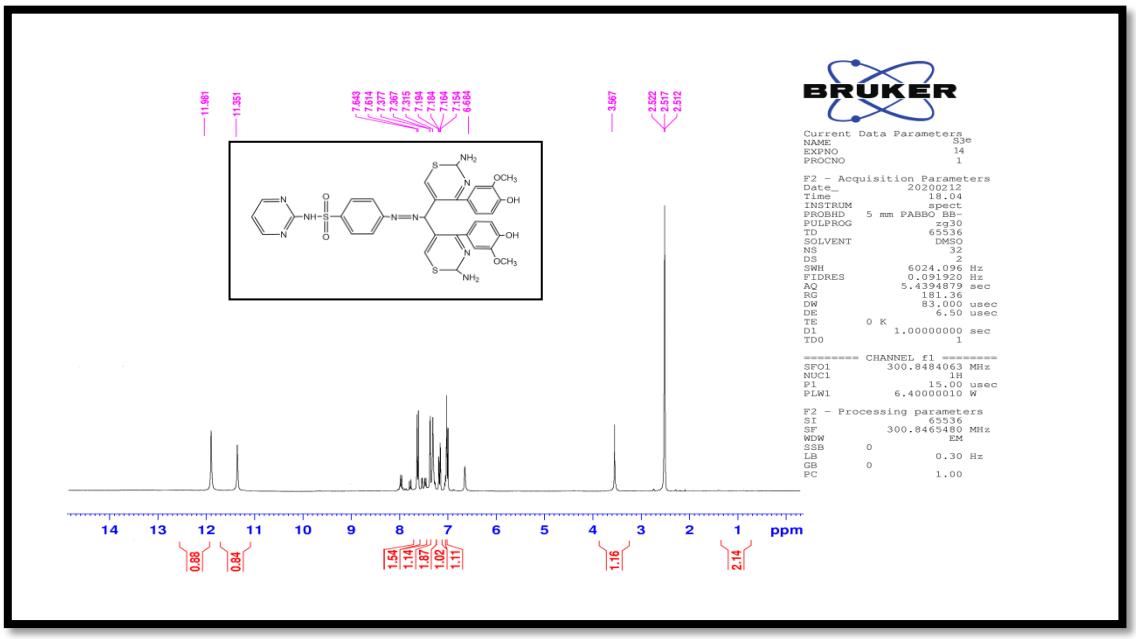


Fig.26:^{1}H-NMR Spectrum of compound (S_3e)

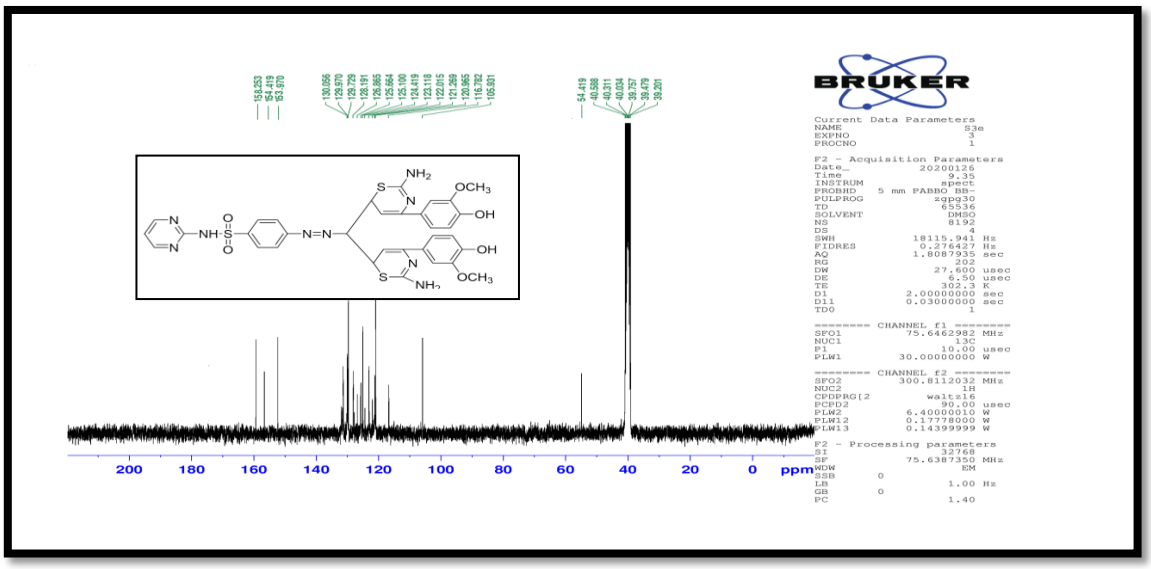


Fig.27:^{13}C-NMR Spectrum of compound (S_3e)

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