ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Synthesis of new quinoline derivatives from methylene Meldrum's acid and screening the biological properties.

Hanan F Mohssen[1], Naji M Ali[2]*, and Hanaa A Ali[3].

[1]Chemistry Department, Faculty of Education , Kufa University ,Iraq
[2]Pharmaceutical Chemistry Department ,Faculty of Pharmacy ,Kufa University ,Iraq
[3]Chemistry Department ,Faculty of Science , Kufa University , Iraq

ABSTRACT

The present work includes synthesis of new quinoline derivatives of methylene Meldrum's acid through reaction with substituted aniline and methylene Meldrum's acid to produce Phenylamine(methylene Meldrum's acid)derivatives , which was converted to substitute quinolone. The quinolone reaction with($POCl_3$) gives substituted 4-chloro quinoline. The reaction of 4-chloro quinoline with different aromatic amines produce 4-aminophenylquinoline derivatives and in the other side 4-chloroquinoline reaction with different boronic acids in the presence of Tetrakis (triphenylphosphine) palladium (0) gives the 4-phenylquinolines .Then the study of biological activity of some new compounds . the structure of these compounds were characterized by (H^1-NMR, C^{13}-NMR, H-HCOSY NMR, FT-IR) Techniques , melting points and other physical studies.

Keywords: Methylene Meldrum's acid , Quinoline , 4-aminophenylquinoline

Corresponding author

ISSN: 0975-8585

INTRODUCTION

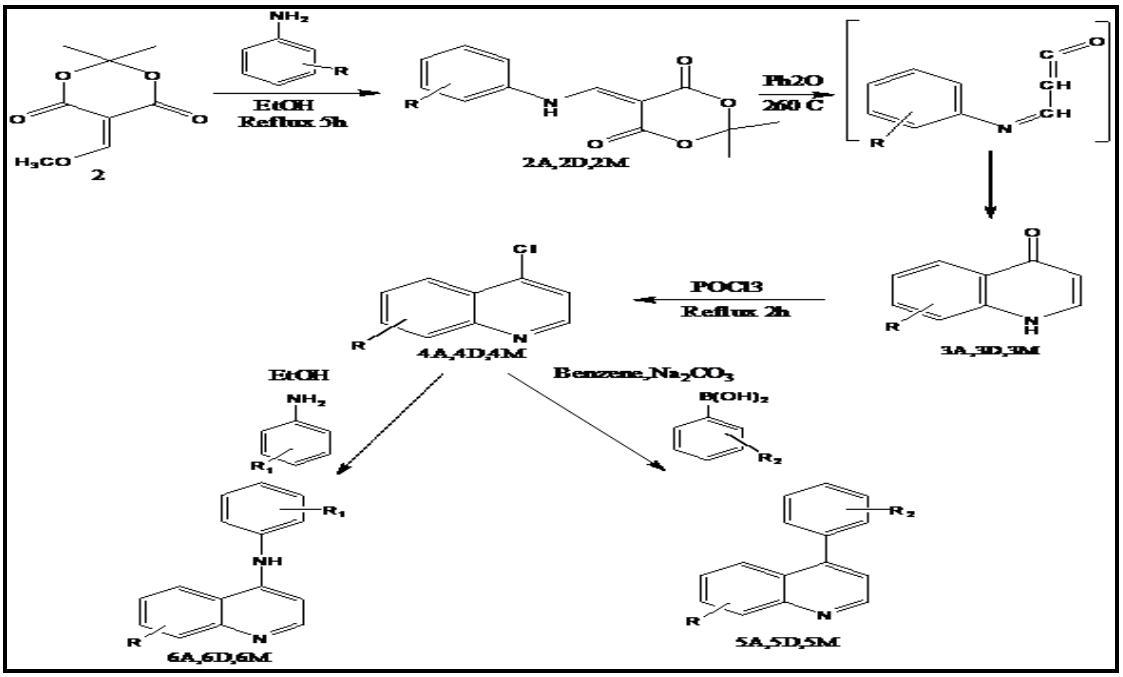
Quinoline is characterized by a double ring structure consists of benzene and pyridine ring fused at two adjacent carbons atom. Whereas the pyridine ring contains five carbon atoms and a nitrogen atom having molecular formula of C9H7N[1,2]. Quinoline is one of the most popular N-hetero aromatic compounds included into the structures of many pharmaceuticals Predominantly the quinoline skeleton used for the design of many synthetic compounds with diverse pharmacological properties[3-10] Quinoline derivatives also have been shown to view a wide variety of pharmacological activities including effects on cancer and nowadays it is mentioned that the merge of quinoline nucleus could alter the course of reaction as well as the biological properties of the synthesized compounds[11]. Compounds containing quinoline motif are most widely used as antibacterials, [12] antifungals [13] and Antimicrobial [14-16]. Anti-inflammatory [17-18] , antileishmanial [19-21] , antimalarial [22-23] , antitoxidant [24] , cytotoxicity [25-27] and HIV-1 Integrase Inhibitors [28-30] . Some 4-substituted quinoline derivatives showed enhanced activity against gram-negative bacteria [31]. Sulfonamide are drugs of certain therapeutic importance and used against a wide spectrum of bacterial ailments . Some sulfonamide quinoline derivatives have been found to be biological active. Some are useful as chemotherapeutic agent [32]

RESULT AND DISCUSSION

Chemistry

For the synthesis of new quinoline derivatives , the reaction sequence is out lined in **Scheme 1**, started from 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane -4,6-dione (2) .

Scheme 1: Reaction sequences of the synthesized compounds



R	R2	R1
2A= Sulfa pyridine	5A= Phenyl boronic acid	6A= 2-nitro-4-methoxyaniline
2D= Sulfadiazine	5D= Phenyl boronic acid	6D= Pyrimidine-2-amine
2M= Benzidine	5M= 4-Chloro phenyl boronic acid	6M= 3-hydroxy aniline
		7M= 2-aminobenzothiazole

Compounds **2A,2D,2M** ,4-((2,2dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methylamino)-N-pyridin-2-yl) , 4-((2,2dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methylamino)-N-pyrimidin-2-yl)benzenesulfonamide,5,5'-

ISSN: 0975-8585

(biphenyl-4,4'-diylbis (ananediyl)) bis (methan-1-yl-1-ylidene) bis (2,2dimethyl-1,3-dioxane-4,6-dione benzenesulfonamide was obtained by the reflux of Sulfapyridine, Sulfadiazine ,benzidine with 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane -4,6-dione (**2**) in the presence of ethanol absolute. Cyclazation of compound **2A,2D,2M**, with diphenyl ether in 260^{o}C afforded **3A,3D,3M** in good yield. The FT-IR spectrum of compound **2A,2D,2M** showed absorption bands in the 3244 , 3356 , 3201 cm−1 (NH-CH=), 1739-1687, 1734-1685,1724-1678 cm−1 (Ketone C=O carbonyl stretching), and 1602, 1602 , 1624 cm-1 (alkene C=C stretching). The 1H-NMR spectrum exhibited a singlet due to the -CH=C proton at δ 8.58 , δ 8.50 , δ 8.63 ppm and a singlet due to the(–NH) proton at δ11.29, δ 11.94, δ 11.32 respectively . compound **3A,3D,3M** react with oxyphosphoril chloride to yield compound **4A,4D,4M** that can react with substituted phenyl boronic acid to yield compounds **5A,5D,5M**, or react with substituted aromatic amine to yield compound **6A,6D,6M**. For compounds **3**, the IR spectrum has the following characteristic absorption bands: vN-H (3282 , 3383, 3410 cm−1); vC=O (1687 , 1668 , 1656 Ketone cm−1), . In the IR spectrum of compounds **4**, no absorption band was detected about (1687-1656 cm−1) indicating the absence of the ketone carbonyl group, which is evidence for the conversion of compounds **3** to compounds **4**. Also, in the IR spectrum of the new heterocyclic compound **5** a stretching band characteristic of the C=N group from heterocyclic nucleus was seen at 1631 , 1643 , 1641 cm−1 (from quinoline).

From the react with substituted aromatic amine of compound **4A ,4D, 4M**, in ethanol absolute type compound **6A, 6D , 6M , 7M** was observed. Existence of the 4-aminoquinoline form predominantly in the solid state is demonstrated by the presence of absorption band at 3373 , 3142 ,3385, 3240 cm−1 belonging to the ν NH groups, respectively, and by absence of ν C-Cl.

Anti bacterial Activity Assay[33]

An antibacterial activity has been conducted according to Piercing method, Some of prepare compounds were tested by the method against four types of bacteria gram negative such as Escherichiacoli , and gram positive like Staphylococcus aureus , Granuticetell aadiacens , Streptococcus pneumonia . All compounds were dissolved in 3 dissimilar concentration 5mg , 10mg , 15mg in 5ml DMSO, the surface of solid culture media (Nutrient Agar) dried and applied on the plates which had been streaked with standardized bacterial inoculums and incubated at 37 ^{o}C for 24h. This technique is based on the determination of an inhibited zone (in mm) proportional to the bacteria in the plates .

Table 1: Zone inhibition (mm) of some of prepared compounds against various microorganisms

Comp. No.	Inhibition zone (mm)									Conc. µg/L
	Escherichia coli			Staphylococcus aureus			Streptococcus pneumonia			
2A	9	11	13	4	5	8	-	-	-	1 2 3
2M	6	7	9	8	9	11	-	-	-	1 2 3
3A	10	13	17	11	13	16	6	8	11	1 2 3
3D	10	15	19	13	16	20	-	-	-	1 2 3
3M	8	9	11	10	11	14	-	-	-	1 2 3
4D	10	14	17	6	7	9	-	-	-	1 2 3
4M	11	14	18	10	13	17	-	-	-	1 2 3
7M	-	-	-	12	14	18	4	5	7	1 2 3
6D	11	13	17	10	12	15				

EXPERIMENTAL

General

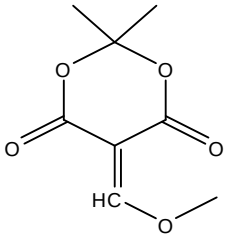
All chemicals were of highest purity and used as supplied by Fluka and Sigma-company . Measurements melting points, electro thermal 9300 , melting point engineering LTD , U.K of the synthesized compounds were determined in open capillary tube , All measurements were carried out by: FT-IR spectra ,Fourier transform infrared shimadzu (8400),H1-NMR&C13-NMR-spectra in (ppm) –unit were obtained in

ISSN: 0975-8585

DMSO solution using (Bruker , Ultra Shield 300 MHz Switzerland) , (Iran). Thin layer chromatography(T.L.C)was performed on silica gel for (T.L.C) and spots were visualized by Iodine vapors.

5-(methoxy methylene)-2, 2-dimethyl-1,3-dioxane -4,6-dione (2)[34] .

Mixture of Meldrum's acid (0.85 g, 6 mmol)and HC(OMe)3 (1.5 mL, 12.5 mmol) was heated under reflux for 4 h, and the reaction mixture was then evaporated to dryness. m.p. 99.0 °C; IR: 2951.09-2991.59 cm−1 (C-H, aliphatic), 3057.17 cm−1 (C-H, alkene), 1747.51-1705.07 cm−1 (C=O, ketone), 1681.93 cm−1 (C=C, alkene), 1176.58 cm−1 (C-O).



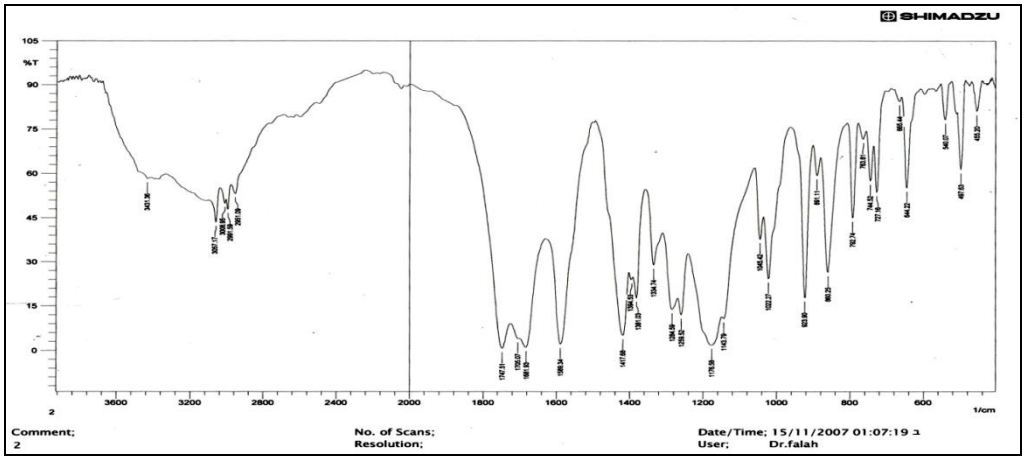


Fig 1 : FT-IR Spectrum of Comp. 2

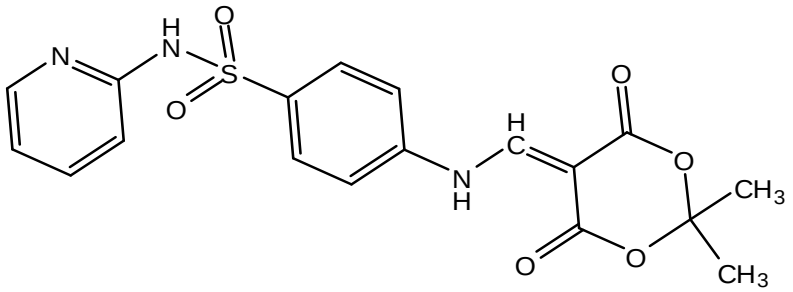
General produce for preparation of compounds (2A, 2D, 2M)[34]

A solution of compound 2 in ethanol (10 mL) was refluxed with sulfa pyridine, sulfadiazine, benzedine (1.25g, 1.25g , 0.46g , 5 mmol) respectively and the reaction mixture was stirred at ambient temperature overnight, After concentrating the reaction mixture a solid mass separated out and recrystallized using ethanol.

((2, 2 dimethyl-4, 6-dioxo-1,3-dioxan-5-ylidene)methyl amino)-N-pyridin-2-yl) benzene sulfonamide (2A)

yield 78.9 %, Rf = 0.65 , m. p 228-230°C; 1H-NMR (DMSO): δ 1.65 (s, 3H, CH3), δ 6.89-8.07 (m,7H) for aromatic ring, δ 11.29 (s, 1H, NH), δ 11.25 (s, 1H, NH Sulfa pyridine) , δ 8.58 (s, 1H) for (HC=C-C) ; 13C-NMR (DMSO): C13-NMR : 104.29,112.35,117.08,117.11,119.15,-128.86(C)Phenyl ring , 141.43,152.71,153.16 (C)Pyridine ring , 87.84 C-12 , 152.71 C-8 ,138.69 C-9 , 162.57-163.63(C-10 & C-14) , 26.48 (C-15 & C-16) ; IR: 3244.27, 3415.93 cm−1 (N-H), 2993.52-2937.59 cm−1 (C-H, aliphatic), 3037.89cm−1 (C-H, aromatic), 3103.46 cm−1 (C-H, alkene), 1739.79,1687.71 cm−1 (C=O), 1637.56 cm−1 (C=C) 1583.56,1523.76 cm−1(C=C, aromatic)

ISSN: 0975-8585



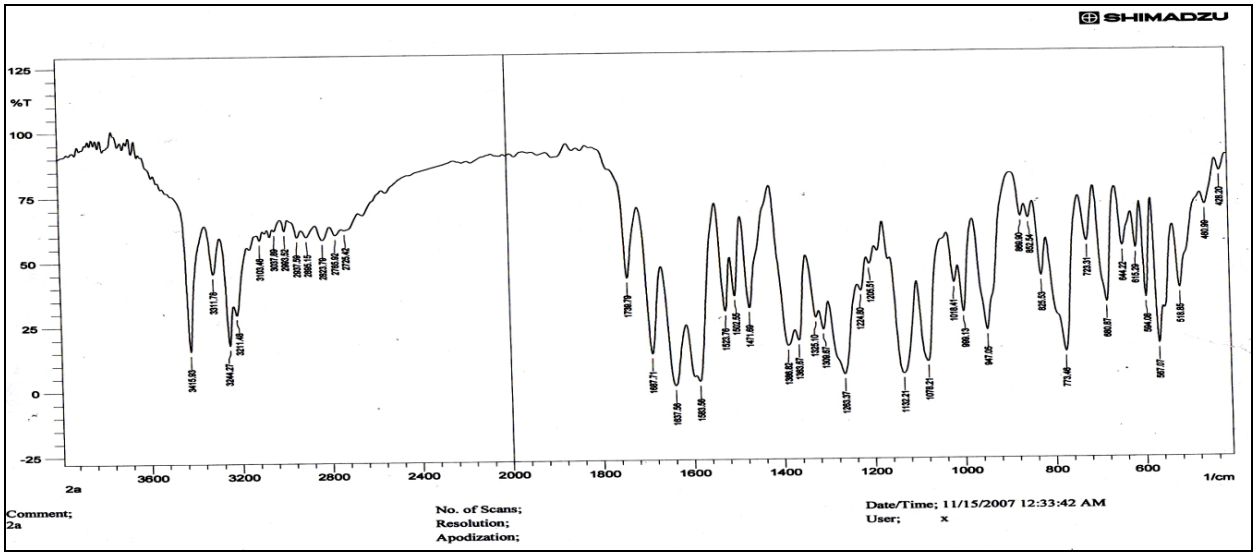


Fig 2: FT-IR Spectrum of Comp. 2A

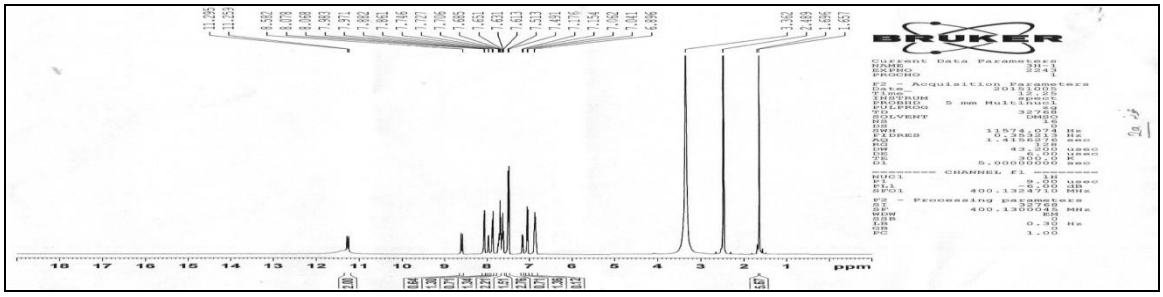


Fig 18: 1H-NMR Spectrum of Comp. 2A

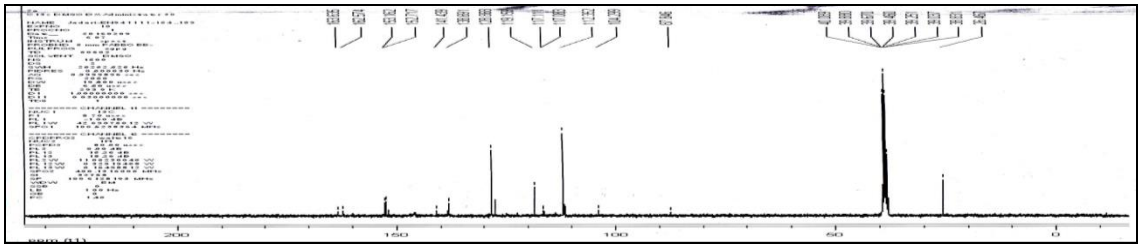
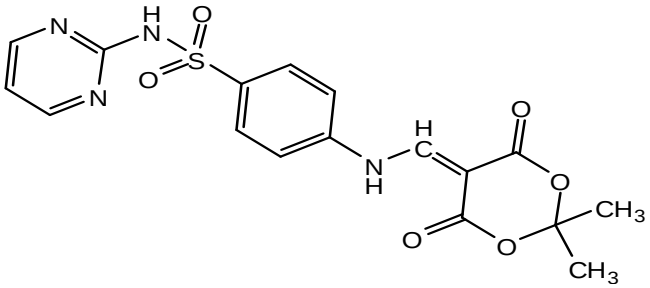


Fig 38: 13C-NMR Spectrum of Comp. 2A

((2, 2dimethyl-4, 6-dioxo-1, 3-dioxan-5-ylidene) methyl amino)-N-pyridin-2-yl benzene sulfonamide (2D)

yield 76 %, Rf = 0.8 , m. p 274-276°C; 1H –NMR (DMSO) : δ 1.65-1.66 (s,6H,CH3) , δ 6.00-8.49 (m,7H) , δ 8.50 (s,1H,CH=C) , δ 11.30 (1H,NHSulfadiazine),δ 11.94 (1H,NH) ; 13C -NMR (DMSO) : 104.33,106.34,

112.07,115.49,118.99,124.76 (C)Phenyl ring ,153.14, 157.18,158.22,160.94 (C)Pyridine ring ,103.84 C-12 , 153.00 C-8 ,129.79 C-9 , 162.60-163.60 (C-10& C-14) , 26.47 (C-15&C-16) ; IR (KBr , cm-1) : 1734-1685(υC=O) , 1643(υC=N), 1585 (υC=C)Alkene , 1492-1442 (υC=C)Aromatic , 1236(υC-O) ,2939(υC-H)Aliphatic , 3356 , 3423 (υN-H) , 1271(υC-N).



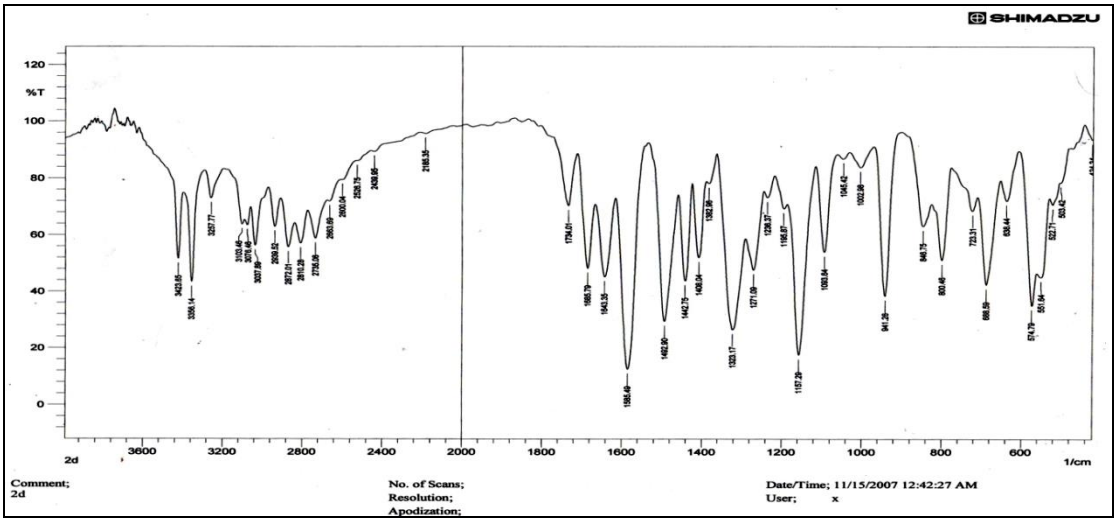


Fig 3: FT-IR Spectrum of Comp. 2D

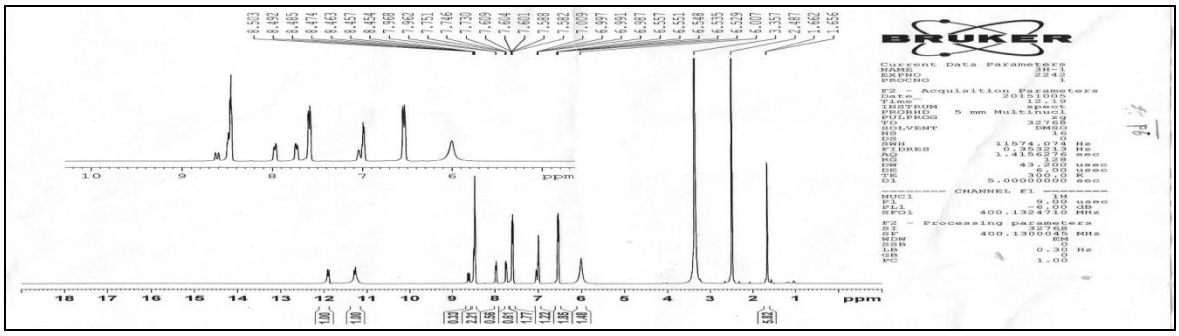


Fig 19: 1H-NMR Spectrum of Comp. 2D

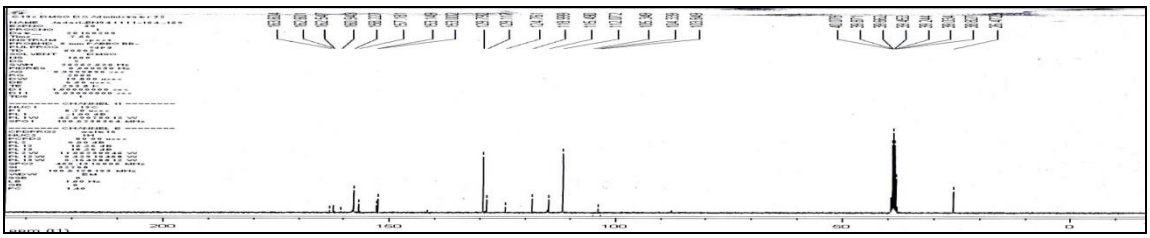
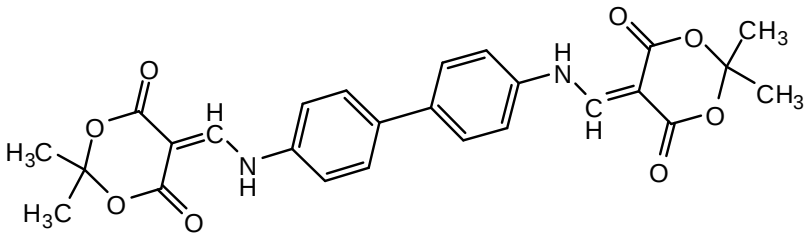


Fig 39: 13C-NMR Spectrum of Comp. 2D

ISSN: 0975-8585

5,5'-(biphenyl-4,4'-diylbis(ananediyl))bis(methan-1-yl-1-ylidene)bis(2,2dimethyl-1,3-dioxane-4,6-dione (2M)

Yield 81 %, Rf = 0.72 , m. p 212-214°C; 1H –NMR (DMSO) : δ 1.67 (s,6H,CH3) , δ 7.18-8.59 (m,7H) , δ 8.62-8.63 (s,1H,CH=C) , δ 11.29-11.32 (1H,NH) ; 13C -NMR (DMSO) : 114.46,119.55, 125.97,126.73,127.47, 136.62,136.80 , 138.65 (C)Phenyl ring , 87.30 C-12 , 152.91 C-8 ,148.53 C-9 , 163.85-163.92 (C-10& C-14) , 26.44 (C-15&C-16) ; IR (KBr , cm-1) : 1724-1678 (υC=O) , 1624 (υC=C)Alkene ,1590-1500 (υC=C)Aromatic , 1230 (υC-O) ,2991(υC-H)Aliphatic , 3201 (υN-H) , 1273(υC-N).



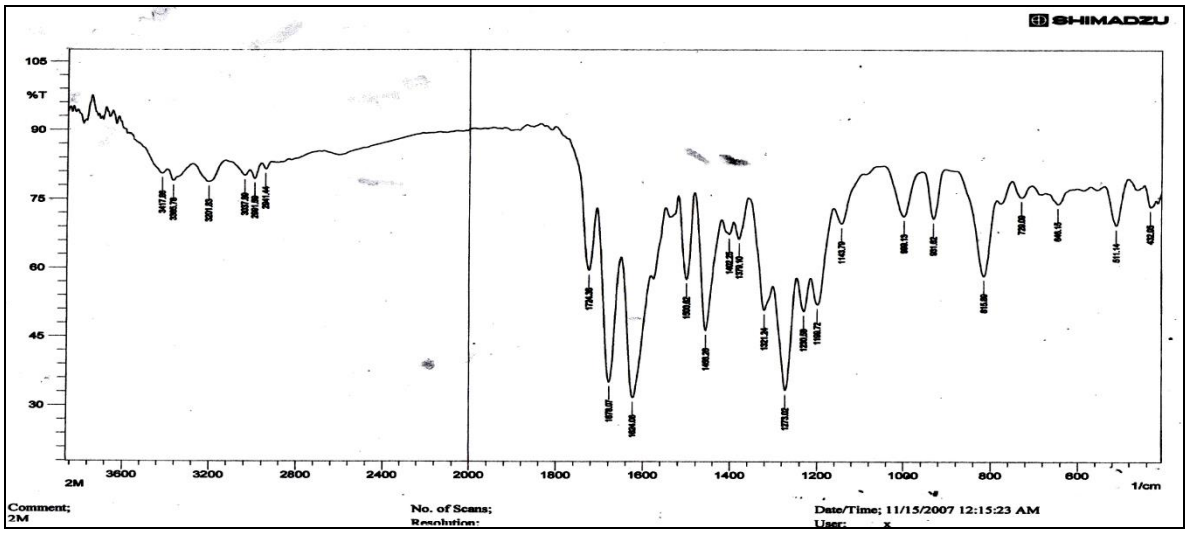


Fig 4: FT-IR Spectrum of Comp. 2M

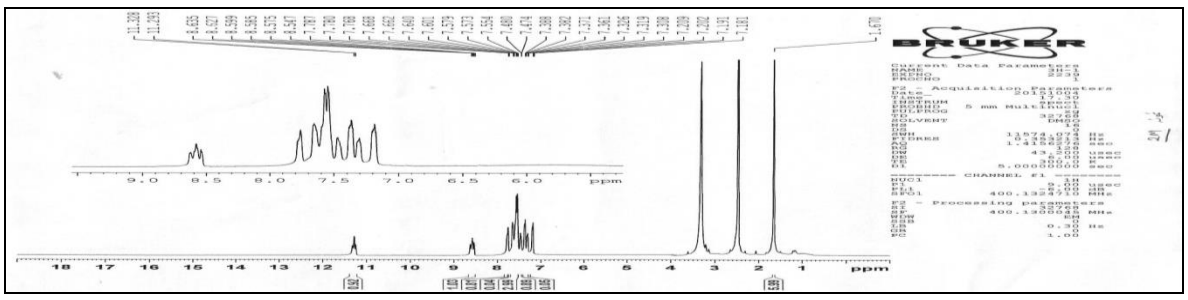
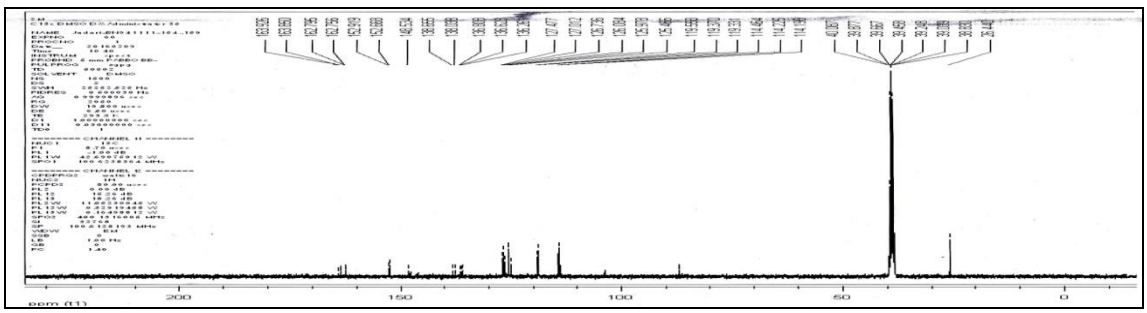


Fig 20: 1H-NMR Spectrum of Comp. 2M



ISSN: 0975-8585

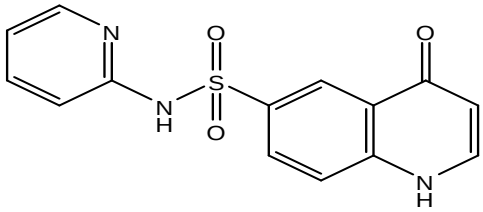
Fig 40: 13C-NMR Spectrum of Comp. 2M

General produce for preparation of compounds (3A,3D,3M and 4A,4D,4M)(35)

(1 m mol) of (2A, 2D, 2M) was added to Ph2O (15ml) . The reaction mixture was heated at 260 ◦ C for 30 min, and then quickly cooled to room temperature, and the precipitate was filtered off and washed with n-hexane. And add to phosphoryl chloride (4 ml) . the resulting mixture was reflux for (2 h) poured onto ice and water (40 ml) , neutralized with 10% NaOH extracted with CH2Cl2 (3× 20 mL) and the combined organic layers dried (MgSO4) .

4-oxo-N-(pyridine-2-yl)-1,4-dihydroquinoline-6-sulfonamide (3A)

yield 65.9 %, m. p 198-200°C; 1H-NMR (DMSO): δ 7.12-8.16 (m,7H) for aromatic ring, δ 11.76 (s, 1H, NH), δ 10.71-10.74 (s, 1H, NH Sulfa pyridine) , δ 7.00-7.03 (d, 2H) for (HC=CH) ; IR: 3248.13, 3375.43 cm−1 (N-H), 3039.81cm−1 (C-H, aromatic), 1687.71 cm−1 (C=O) ketone ,1635−1 cm (C=N) , 1595.13 cm−1 (C=C) 1531.48 cm−1(C=C, aromatic)



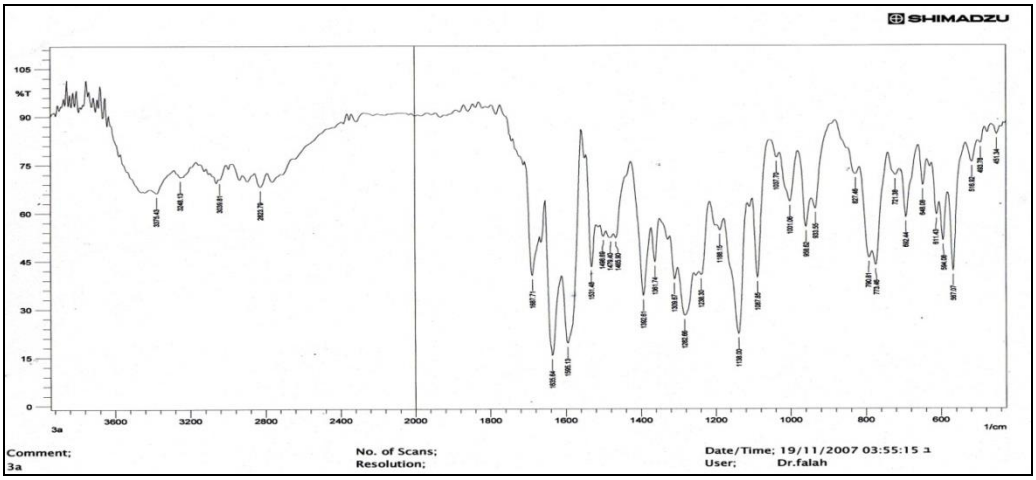


Fig 5: FT-IR Spectrum of Comp. 3A

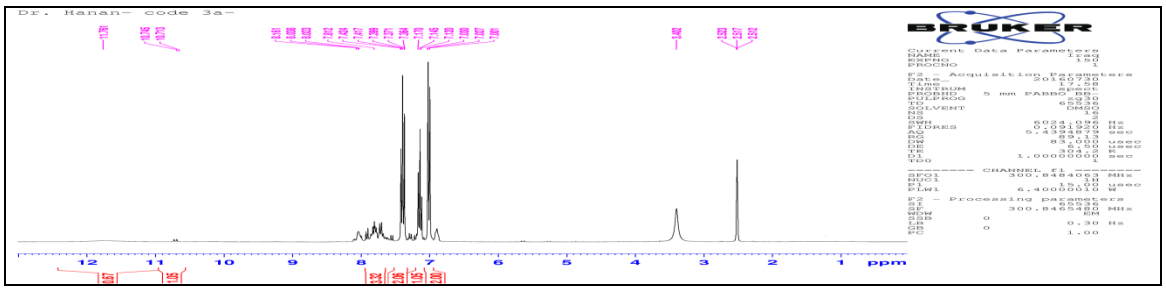


Fig 21: 1H-NMR Spectrum of Comp. 3A

ISSN: 0975-8585

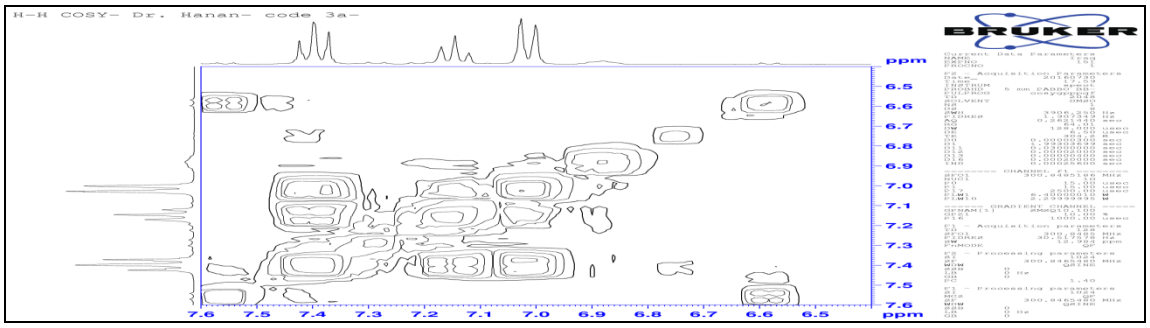


Fig 22: 2D H-HCOSY-NMR Spectrum of Comp. 3A

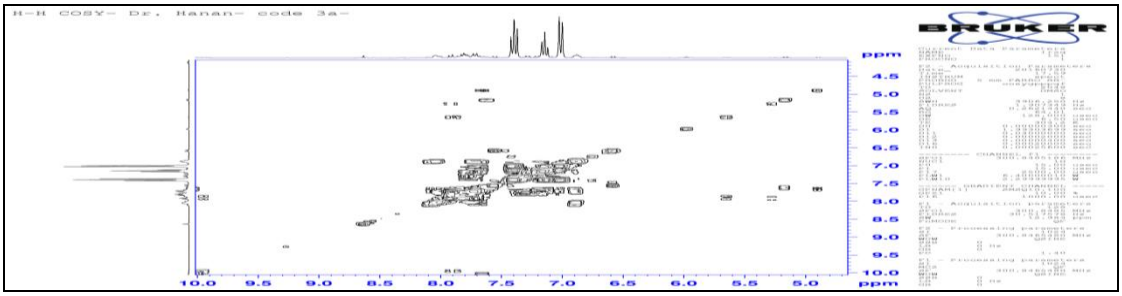
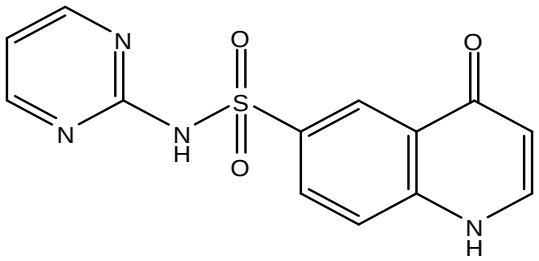


Fig 23: 2D H-HCOSY-NMR (2) Spectrum of Comp. 3A

4-oxo-N-(pyrimidin-2-yl)-1,4-dihydroquinoline-6-sulfonamide (3D)

yield 73 %, m. p 161-163 °C; 1H –NMR (DMSO) : δ 7.15-8.50 (m,7H) , δ 7.00-7.07 (d,2H,CH=CH) , δ 11.48 (1H,NHSulfadiazine),δ 11.65 (1H,NH) ; 13C -NMR (DMSO) : 164.32 (C-4) , 111.63(C-3) , 145.52(C-2), 116.97, 120.44, 123.90, 124.23, 127.43, 128.61 ,157.11 (C) Phenyl ring . ; IR (KBr , cm-1) :1668.43(υC=O), 1637.56 (υC=N), 1585.49 (υC=C)Alkene , 1489.05 (υC=C)Aromatic , 3383.14 , 3448.72 (υN-H) , 1238.30(υC-N).



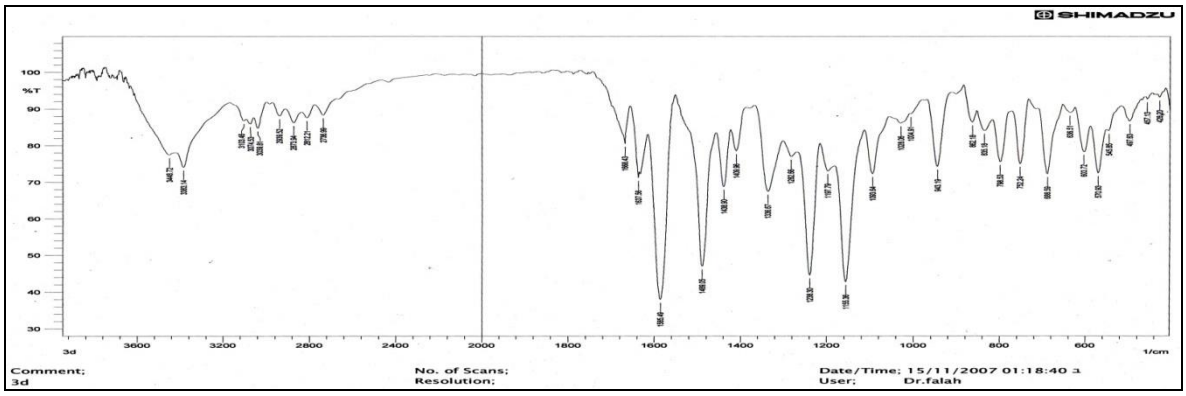


Fig 6: FT-IR Spectrum of Comp. 3D

ISSN: 0975-8585

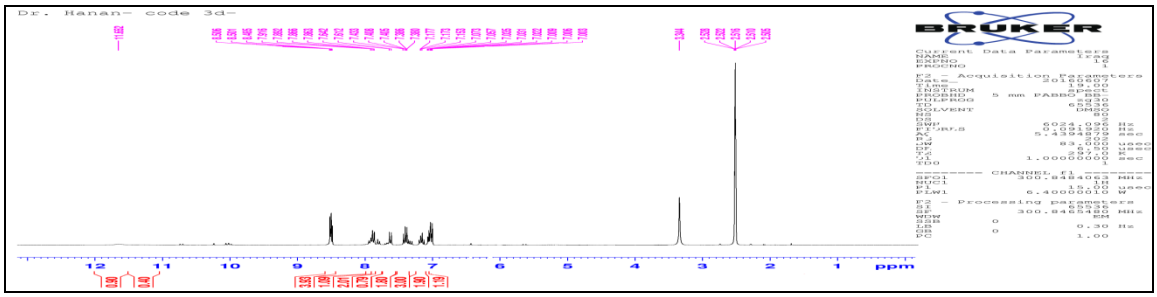


Fig 24: 1H-NMR Spectrum of Comp. 3D

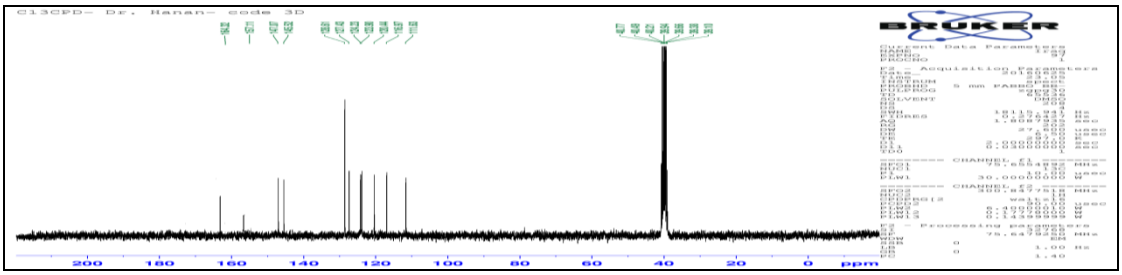


Fig 41: 13C-NMR Spectrum of Comp. 3D

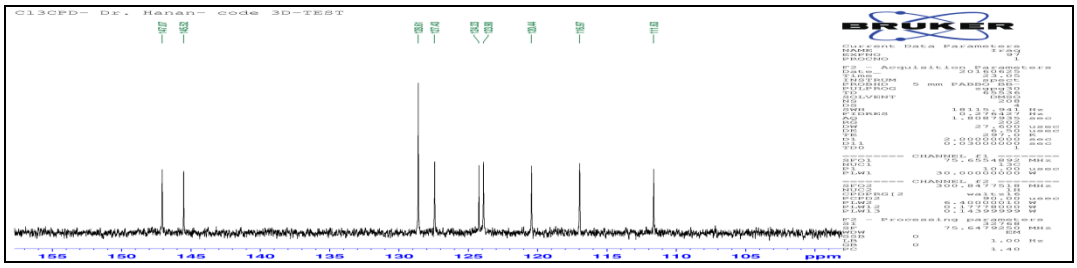
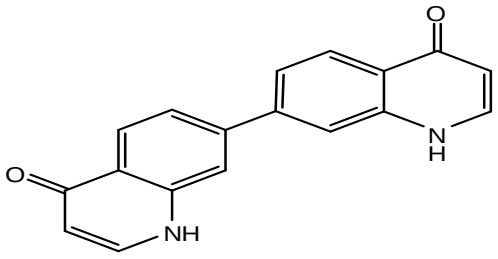


Fig 42: 13C-NMR (2) Spectrum of Comp. 3D

7,7' biquinoline-4,4'(1H,1H')-dione (3M)

yield 70 %, m. p 280-281°C; 1H–NMR (DMSO) : δ 7.25-7.78 (m,4H) , δ 7.00-7.02 (d,2H,CH=CH) , δ 11.37 (1H,NH) ; IR (KBr , cm-1) : 1656.85 (υC=O)ketone ,1600.92 (υC=C)Alkene ,1589(υC=C)Aromatic ,3073.89(υC-H)Aromatic , 3410.15 (υN-H) , 1238.30 (υC-N).



ISSN: 0975-8585

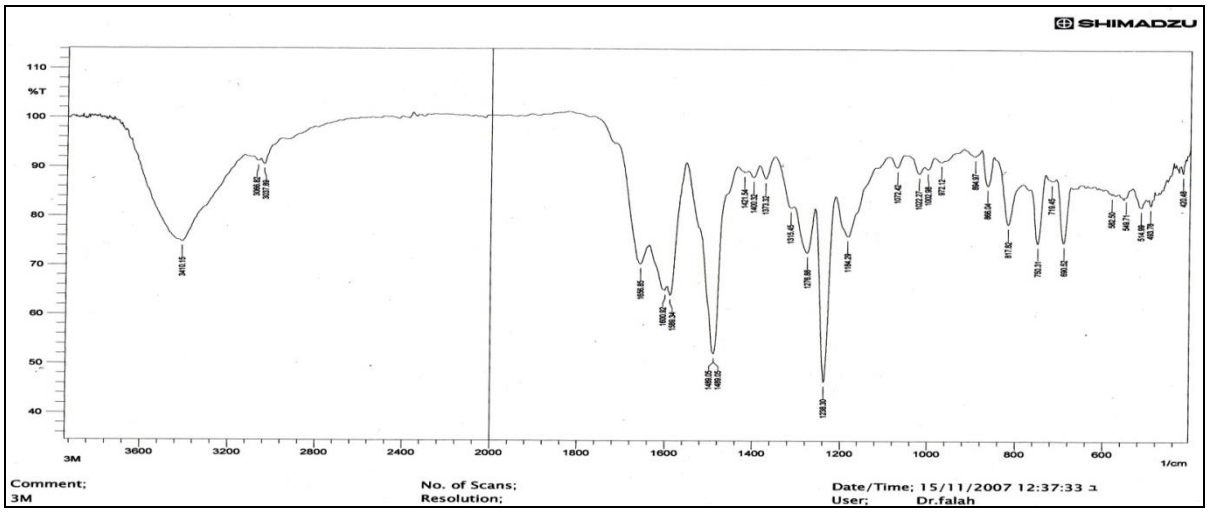


Fig 7: FT-IR Spectrum of Comp. 3M

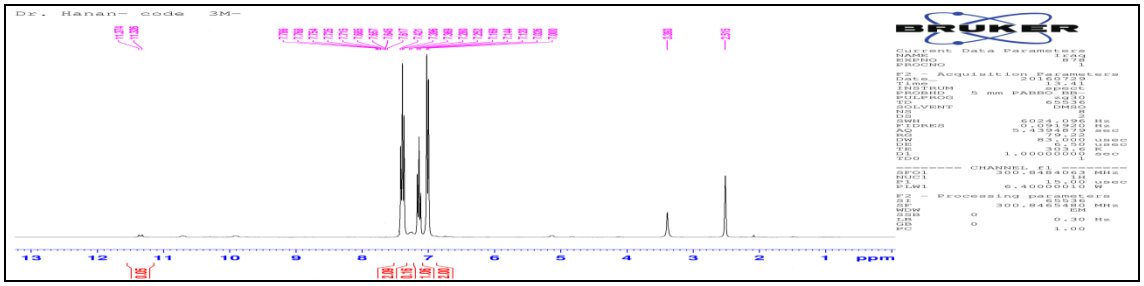
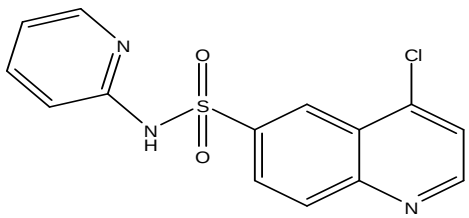


Fig 25: 1H-NMR Spectrum of Comp. 3M

4-chloro-N-(pyridine-2-yl) quinoline-6-sulfonamide(4A)

yield 60.6 %, m. p 221- 223 °C; 1H-NMR (DMSO): δ 7.01 H-3 ,7.79 H-2, , δ 7.74 -7.75 – 8.00 (H-8, H-7 ,H-5) , δ 6.87-7.72 (H-3'-H-6')Pyridine ring , δ10.68 (1H,NHSulfapyridin); IR: 3433.29 cm−1 (N-H), 1261.45 cm−1 (C-N), 835.18 cm−1 (C-Cl) ,1631.78−1 cm (C=N) , 1593.20 cm−1(C=C ,aromatic)



ISSN: 0975-8585

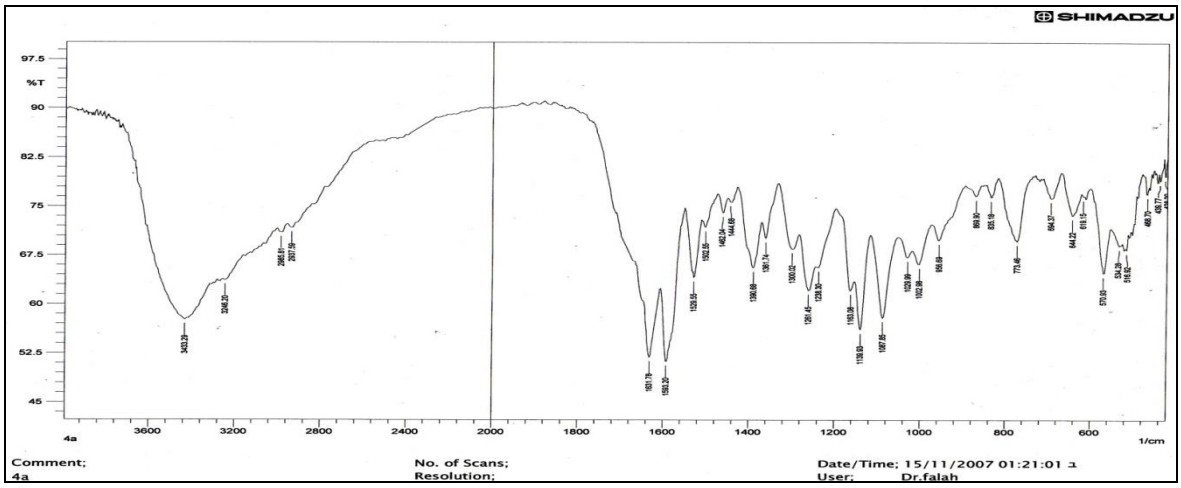


Fig 8: FT-IR Spectrum of Comp. 4A

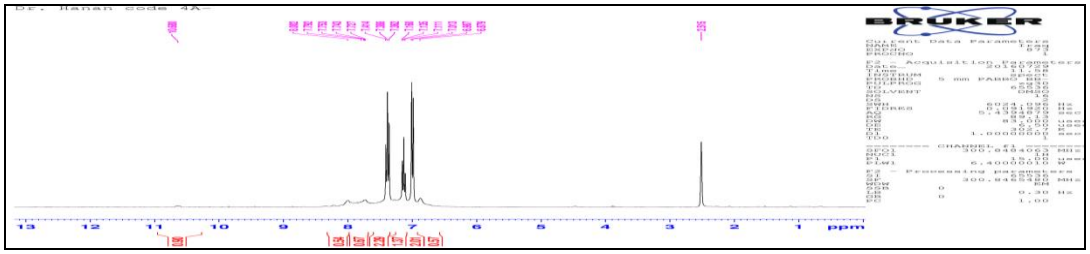


Fig 26: 1H-NMR Spectrum of Comp. 4A

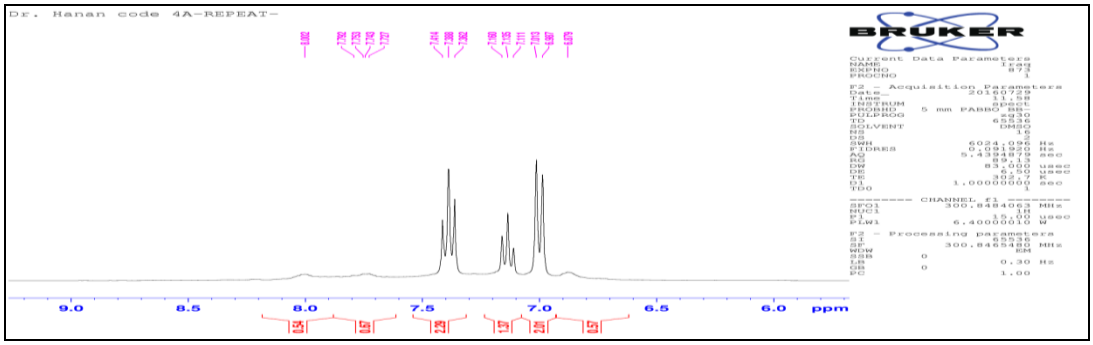
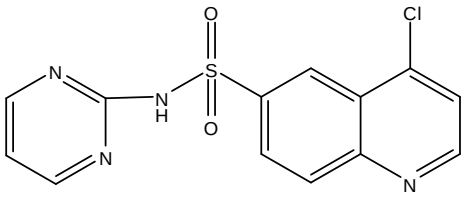


Fig 27: 1H-NMR Spectrum of Comp. 4A

4-chloro-N-(pyrimidin-2-yl) quinoline-6-sulfonamide (4D)

yield 56 %, m. p 215-217°C; 1H-NMR (DMSO): δ 7.34 H-3, 8.50 H-2, **,** δ 7.82 -7.90 – 8.56 (H-8, H-7, H-5) , δ 7.00-7.65 (H-2'-H-4')Pyrimidine ring , δ11.26 (1H,NHSulfadiazine); 13C-NMR (DMSO) : 119.22C-3 ,145.59C-2 , 140.26 C-4, 119.07 C-5 , 131.49 C-6 , 130.25 C-7, 130.52 C-8 , 123.91 C-4' , 152.60 C-8' , 157.11(C-4''& C-6') , 158.84 C-2' , 116.25 C-5' ;IR: 3336.85 cm−1 (N-H), 1232.51 cm−1 (C-N), 866.04 cm−1 (C-Cl) ,1632 −1 cm (C=N) , 1585.49 cm−1 (C=C, aromatic) .

ISSN: 0975-8585



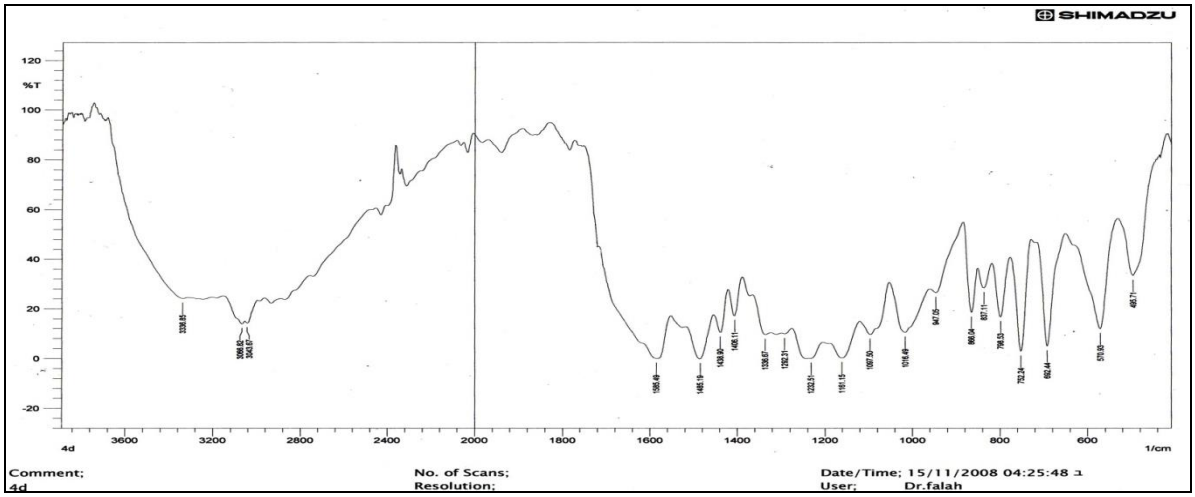


Fig 9: FT-IR Spectrum of Comp. 4D

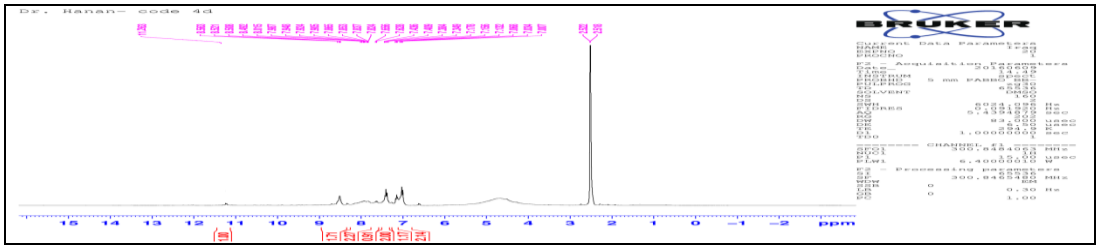


Fig 28: 1H-NMR Spectrum of Comp. 4D

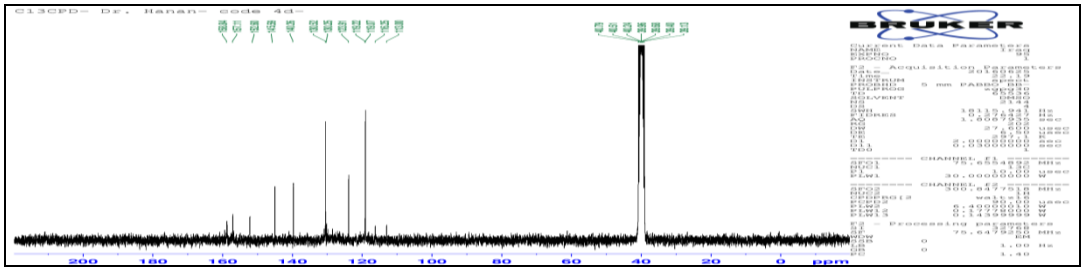
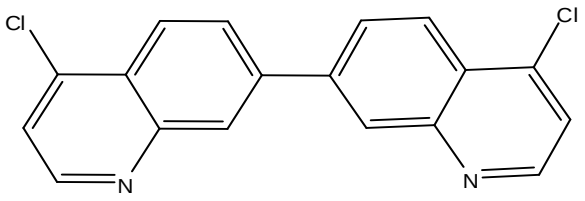


Fig 43: 13C-NMR Spectrum of Comp. 4D

4,4'dichloro-7,7'biquinoline (4M)

yield 67 %, m. p 220-221 °C; IR: 3050 cm−1 (C-H, aromatic), 869.90 cm−1 (C-Cl) ,1639.49 cm−1(C=N) , 1587.42 cm−1(C=C, aromatic).

ISSN: 0975-8585



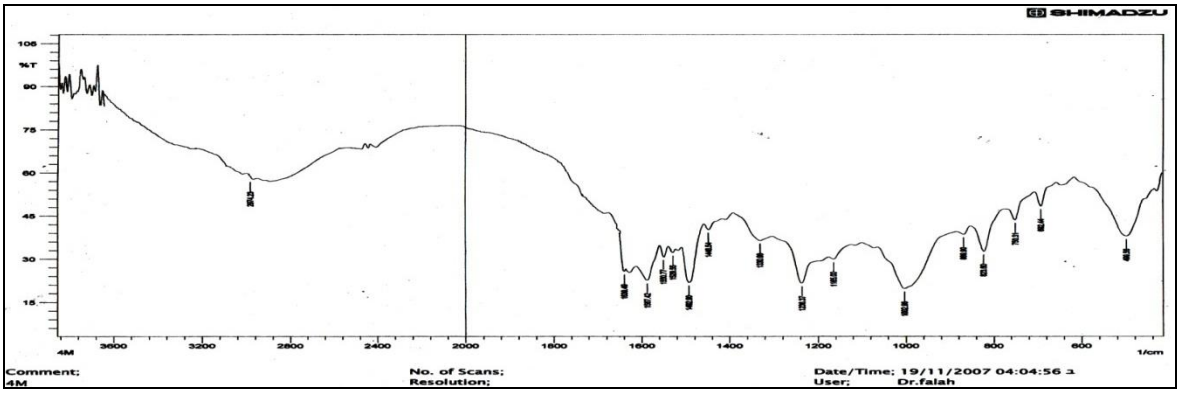


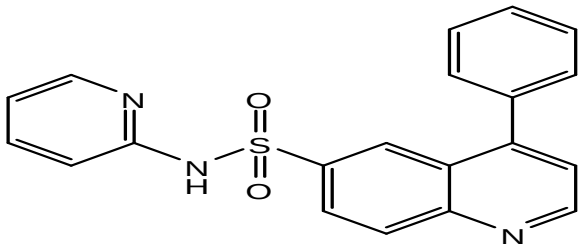
Fig 10: FT-IR Spectrum of Comp. 4M

General produce for preparation of compounds (5A,5D,5M)(34)

To a solution of the (4A, 4D, 4M) compounds (0.5 mmol) , boronic acid (0.5 mmol) in benzene (10 ml) and 1M Na2CO3 solution (1.2 ml) were introduced . The mixture was heated to 55°C , after which Pd(pph3)4 (0.02 mmol) was add. After stirring at 55°C for 20h , the mixture was allowed to cool to RT , and was then poured into water (6 ml), and extracted with CH2Cl2 (3×3 mL) . The combined organic layers were dried over Na2SO4 and evaporated to dryness .

4-phenyl-N-(pyridin-2-yl)quinoline-6-sulfonamide (5A)

yield 58.65 %, m. p 264-265 °C; 1H-NMR (DMSO): δ 7.36 H-3, δ 8.09 H-2 , δ 8.02 -7.82 – 7.81 (H-5, H-7,H-8) , δ 7.79- 7.43-7.39 (H-2'& H-6' , H-3',H-5'& H-4')Phenyl ring ,7.78-7.40- 7.34-7.30(H-3''& H-6'')Pyridine ring, δ10.74 (1H,NHSulfapyridin). ; IR: 3250.06 cm−1 (N-H), 1274.95 cm−1 (C-N), 1631.78−1 cm (C=N) , 1600.92 cm−1(C=C,aromatic) .



ISSN: 0975-8585

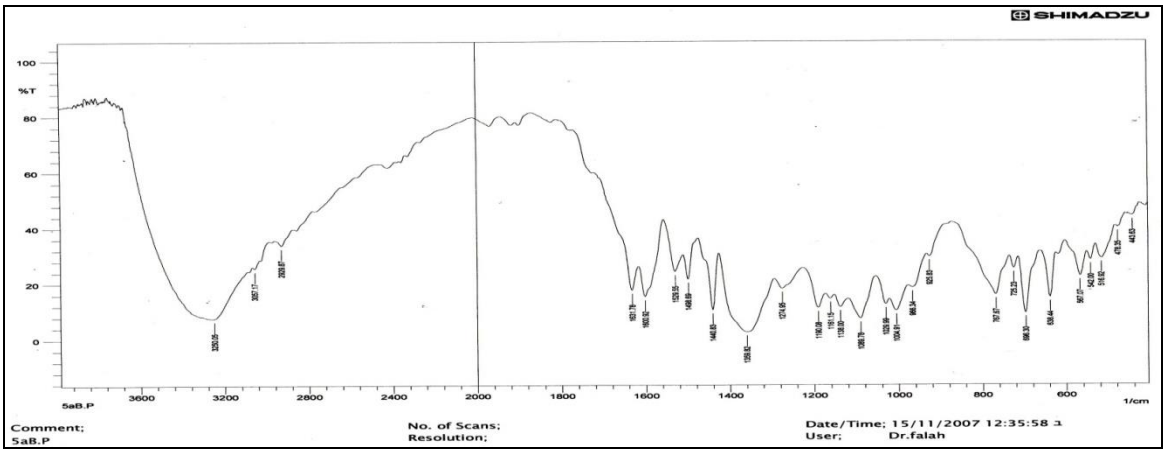


Fig 11: FT-IR Spectrum of Comp. 5A

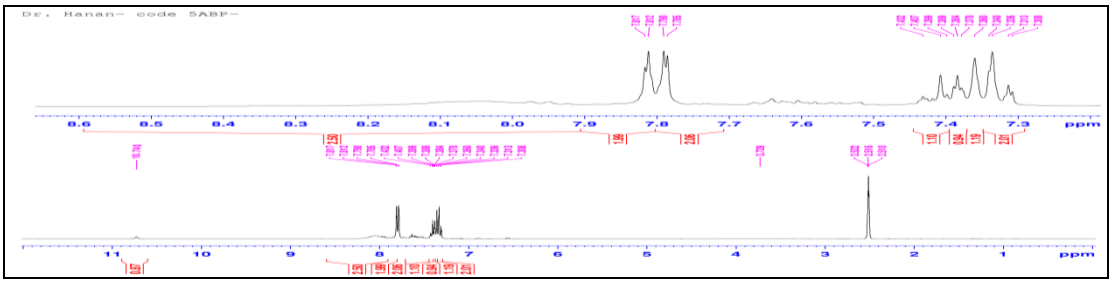
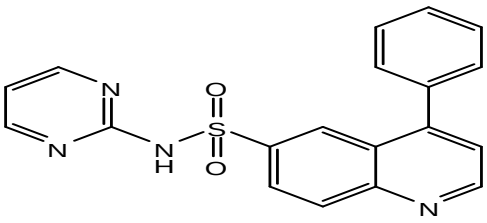
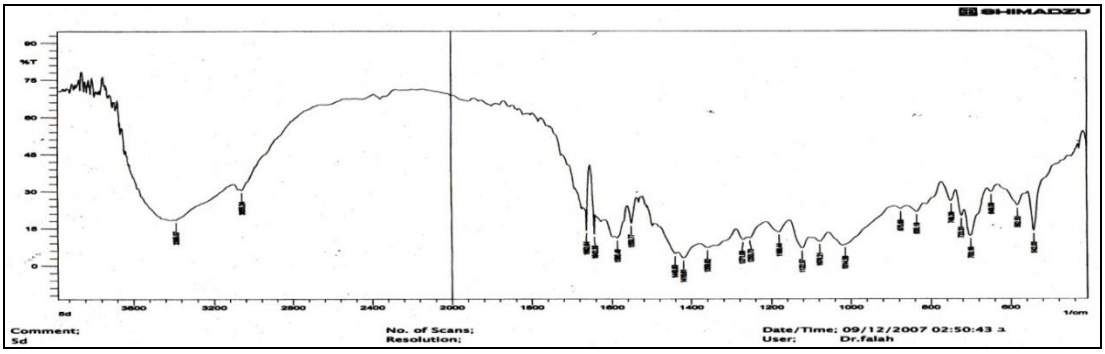


Fig 29: 1H-NMR Spectrum of Comp. 5A

4-phenyl-N-(pyrimidin-2-yl) quinoline-6-sulfonamide (5D)

yield 57.9 %, m. p 256-257 °C; 1H-NMR (DMSO): δ 7.48 H-3, δ 8.11 H-2 , δ 7.94 -7.83 – 7.81 (H-5, H-7,H-8) , δ 7.04- 7.97 (5H, Phenyl ring) , δ 8.09-6.78 (H3''& H-5'',H-4'')Pyrimidine ring, δ10.55 (1H,NHSulfadiazine). ; 13C-NMR (DMSO) : 150.09 C-2 , 112.37 C-3 , 133.73 C-4 , 126.91 C-4' , 134.79 C-8' , 132.58 C-1' , 128.00-128.75-129.01 (C-3'& C4''& C-5') , 130.29 C-8 , 127.58 C-7 ,127.76 C-5, 131.90 C-6 , 164.81 C-1'' , 157.81 C-3''& C-5'' , 115.76 C-4'''. ; IR: 3385.07 cm−1 (N-H), 1271.09 cm−1 (C-N), 1662.64-1643.35 cm −1 (C=N) , 1585.49 cm−1(C=C,aromatic).





ISSN: 0975-8585

Fig 12: FT-IR Spectrum of Comp. 5D

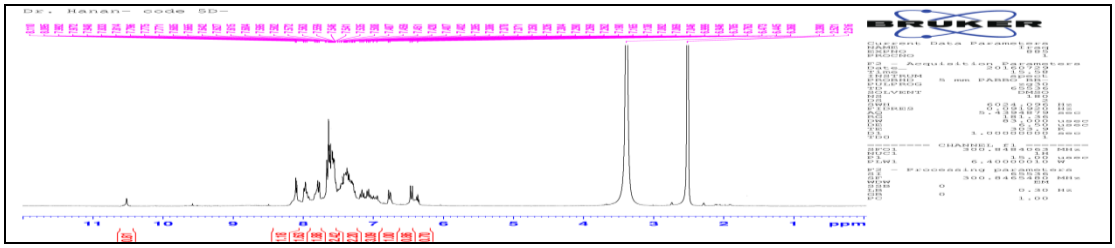


Fig 30: 1H-NMR Spectrum of Comp. 5D

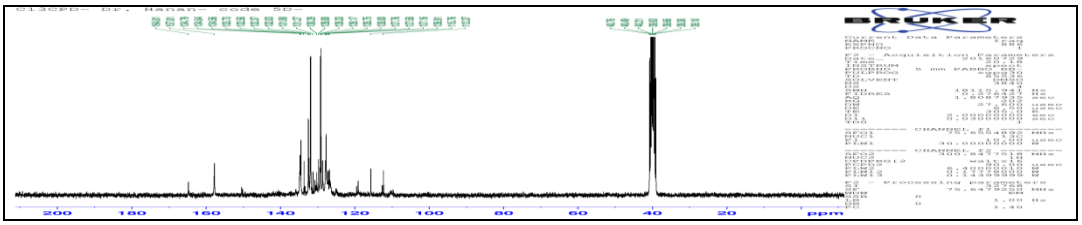
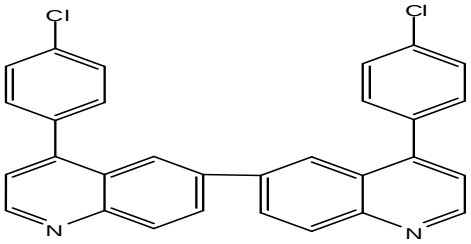


Fig 44: 13C-NMR Spectrum of Comp. 5D

4,4'-bis(4-chlorophenyl)-7,7'biquinoline (5M)

yield 73 %, m. p >300°C decomp.; 1H-NMR (DMSO): δ 7.21 H-3, δ 8.75 H-2 , δ 7.72 -7.69 – 7.58(H7, H-8,H-5), δ 6.77-6.80-7.40-7.43 (H-2'& H-6',H-3'& H-5') .; 13C-NMR (DMSO) : 156.81C-2,117.40 C-3 ,133.82 C-4 , 131.89 C-4' ,138.11 C-8' ,133.18 C-1' , 128.92 C-2''& C-6'' ,129.16 C-7 ,132.55 C-6, 122.74 C-5 ,130.52 C-8, 132.02C-4'' ,129.58 C-3'& C-5' . ;IR: 3070.68-3001.24 cm−1 (C-H,aromatic), 817.82 cm−1 (C-Cl) ,1641.42 cm−1(C=N) , 1589.34 cm−1(C=C,aromatic)



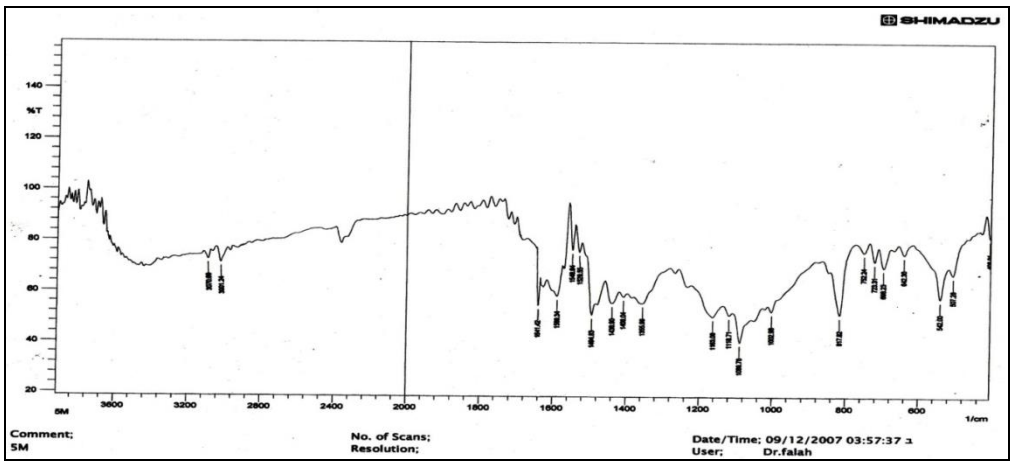


Fig 13: FT-IR Spectrum of Comp. 5M

ISSN: 0975-8585

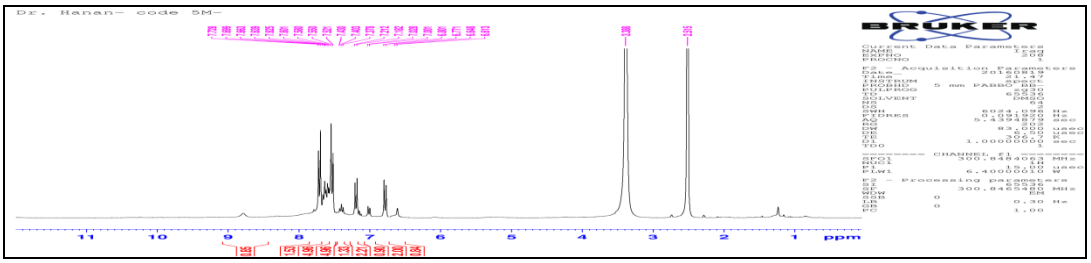


Fig 31: 1H-NMR Spectrum of Comp. 5M

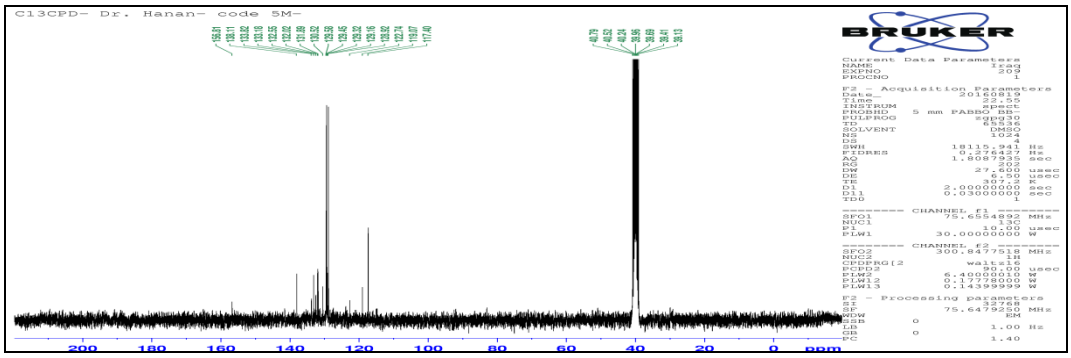


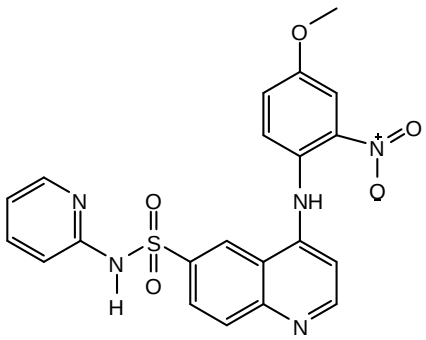
Fig 45: 13C-NMR Spectrum of Comp. 5M

General produce for preparation of compounds (6A, 6D, 6M, 7M) (36)

Treatment of **4A,4D,4M** (10 mmole) with different aromatic amines (10 mmol.) in ethanol absolute (20 mL) at 80 oC , (5-6)h produced **6A,6D,6M** . The reaction completion was monitored by TLC. The reaction mixture was cooled, poured into ice cold water , filtered and dried.

4-(4-methoxy-2-nitrophenylamino)-N-(pyridine-2-yl)quinoline-6-sulfonamide (6A) .

yield 60 %, m. p 165-167 °C; Rf =0.63 1H-NMR (DMSO): δ (7.01-7.36)Phenyl ring , δ 3.72 (3H, OCH3) , δ 11.05 (1H,NHSulfapyridin) , 9.82 (1H,NH) **,** δ 5.23 expect it back to the hydrogen bond (OH) between nitro group and (NH) group ,δ 55.92 for a methoxy group (Ar-OCH3) ; 13C-NMR (DMSO) : δ 159.09 for (C-4') , signal at 157.18 for (C-2 & C-1'') , 149.63 (C-4) and 142.45 (C-8a), 133.44 (C-2') ,129.50 (C-1'& C-5'') , 127.59 (C-6) , 121.27 (C-8) ,118.20 (C-6') , 114.54 (C-4a & C-5') , 113.89 (C-5 & C-4'') , 113.02 (C-3) , 105.26 (C-3' & C-6'') .; IR: 3489.23,3373.50 cm−1 (N-H), 1510.26-1382.96 cm−1 (NO2), 1641.42 cm−1 (C=N), 1597.06cm−1(C=C, aromatic)



ISSN: 0975-8585

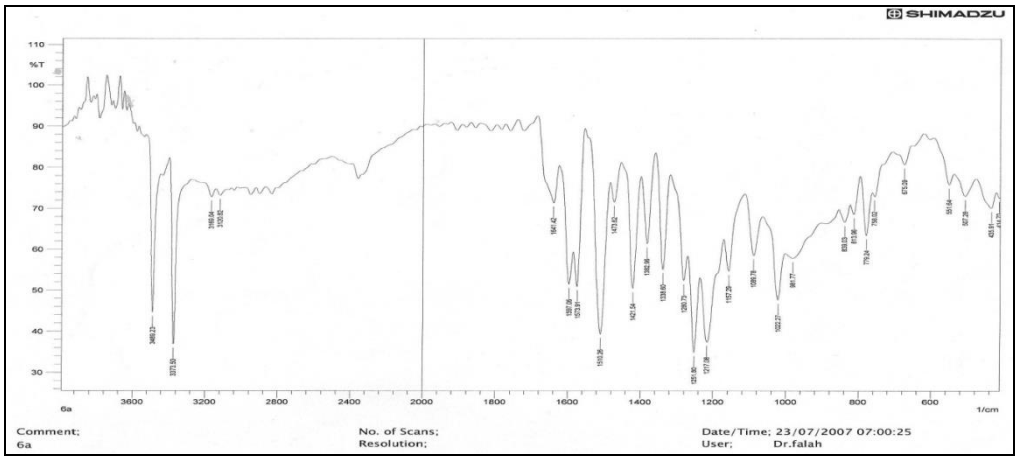


Fig 14: FT-IR Spectrum of Comp. 6A

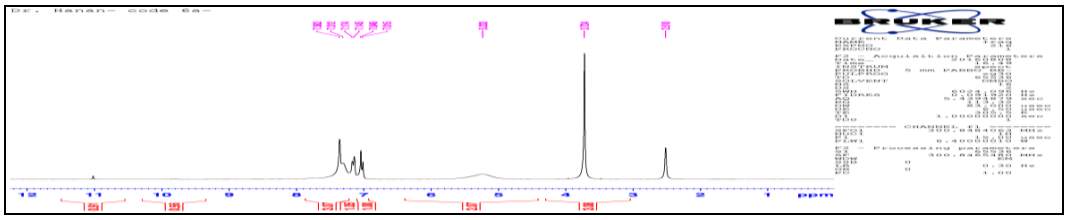


Fig 32: 1H-NMR Spectrum of Comp. 6A

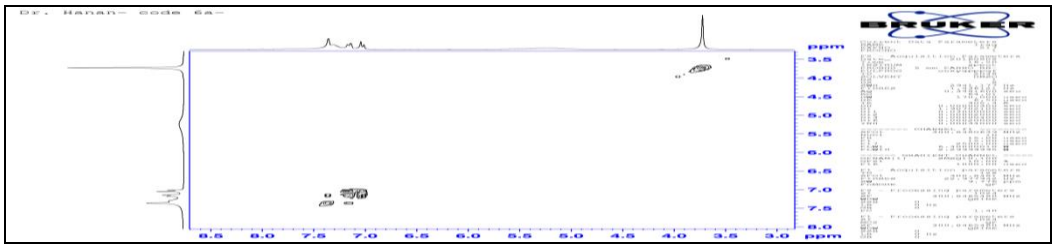


Fig 33: H-HCOSY-NMR Spectrum of Comp. 6A

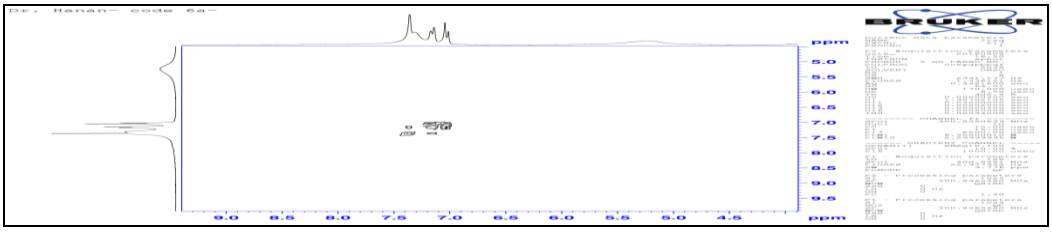


Fig 34: H-HCOSY-NMR (2) Spectrum of Comp. 6A

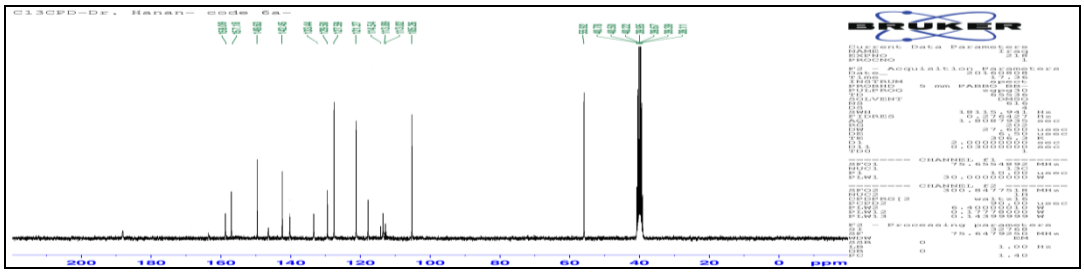
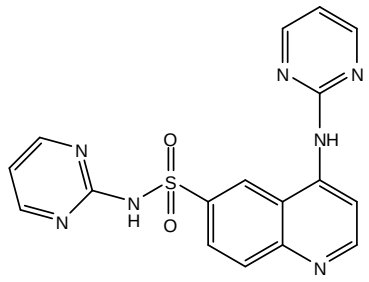


Fig 46: 13C-NMR Spectrum of Comp. 6A

ISSN: 0975-8585

N-(pyrimidin-2-yl)-4-(pyrimidin-2-ylamino)quinoline-6-sulfonamide (6D).

yield 61.3 %, m. p 181-183 °C; Rf =0.75 1H-NMR (DMSO): δ 6.97 (H-3), δ 7.00 (H-4' & H-4'') , δ 8.14 (H-8) , δ 8.16 (H-7) , δ 8.18 (H-5) , 8.64 (H-2) , δ 8.65 (H-3',H-5' & H-3'',H-5'') δ 9.62 (1H,NH) . δ 10.71 (1H,NHSulfadiazine) . ; .; IR: 3338.78 ,3142.04 cm−1 (N-H), 1286.52 cm−1 (C-N), 1674.21-1637.56 cm−1 (C=N), 1595-1541.12 cm−1(C=C, aromatic)



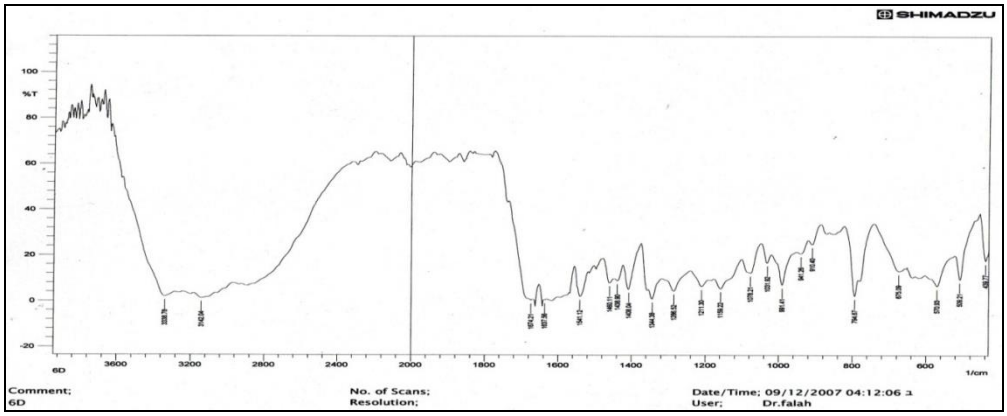


Fig 15: FT-IR Spectrum of Comp. 6D

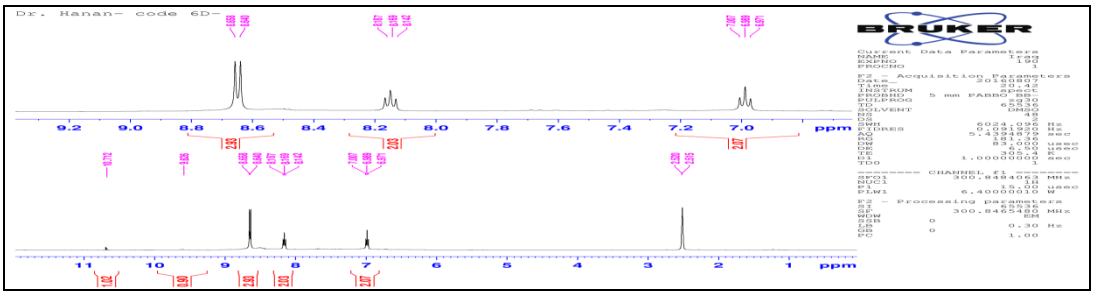
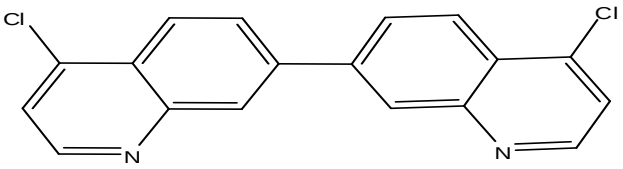


Fig 35: 1H-NMR Spectrum of Comp. 6D

3,3'-(6,6'-biquinoline-4,4'-diyl)diphenol (6M)

yield 74.25 %, m. p 249-251 °C; Rf =0.8 1H-NMR (DMSO): δ 10.10 (OH) , δ 6.14 (H-2'), δ 7.00 (H-4') , δ 7.69 (H-8) , δ 7.76 (H-7) , δ 7.59 (H-5) ,7.81 (H-2) , δ 7.38 (H-5') , δ 7.15 (H-3) , δ 7.50 (H-6') , δ 8.65 (1H,NH) . ; .; IR: 3385.07 cm−1(OH) ,3250 cm−1 (N-H), 1236.37 cm−1 (C-N),1635.67 cm−1 (C=N), 1598.99-1525.69 cm−1(C=C, aromatic) .

ISSN: 0975-8585



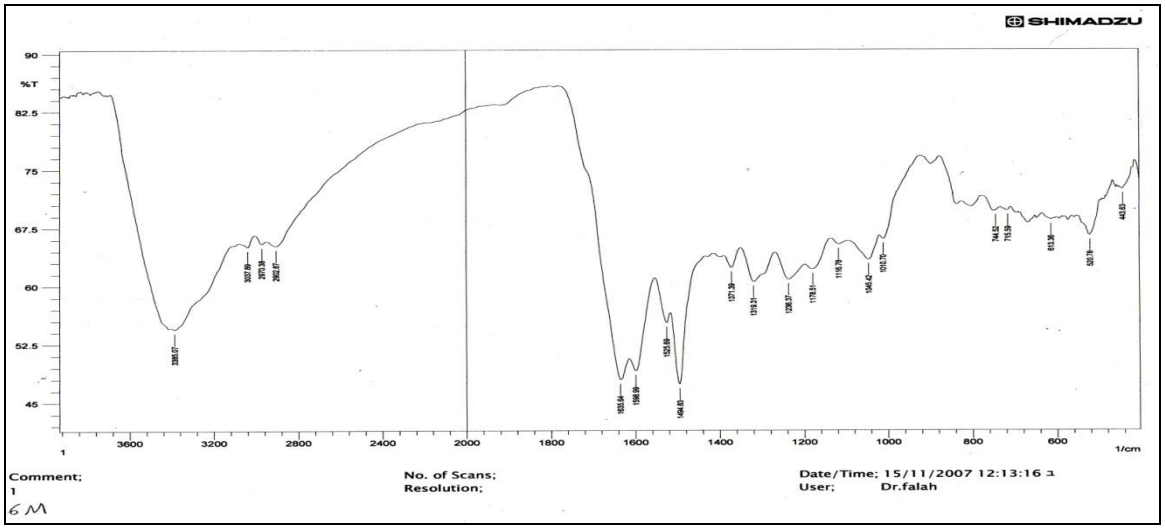


Fig 16: FT-IR Spectrum of Comp. 6M

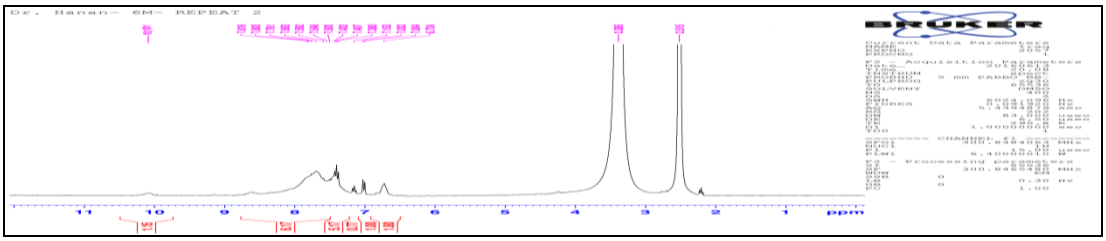


Fig 36: 1H-NMR Spectrum of Comp. 6M

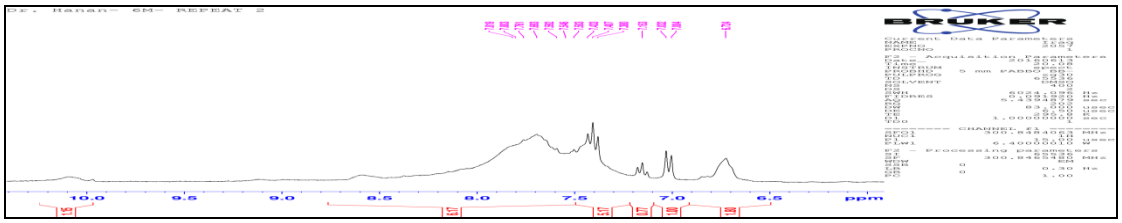
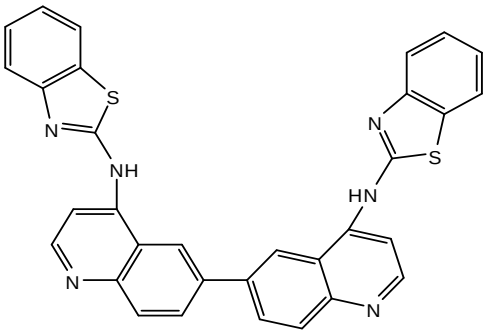


Fig 37: 1H-NMR (2) Spectrum of Comp. 6M

N4,N4'-di(benzo[d]thiazol-2-yl)-6,6'biquinoline-4,4'-diamine (7M)

yield 68.7 %, m. p 260 decomp. °C; Rf =0.7 .; IR: 3240.41 cm−1 (N-H), 1220.94 cm−1 (C-N),1660.71 cm−1 (C=N), 1602.85-1531.48 cm−1(C=C, aromatic) , 659.66 cm−1 (C-S).

ISSN: 0975-8585



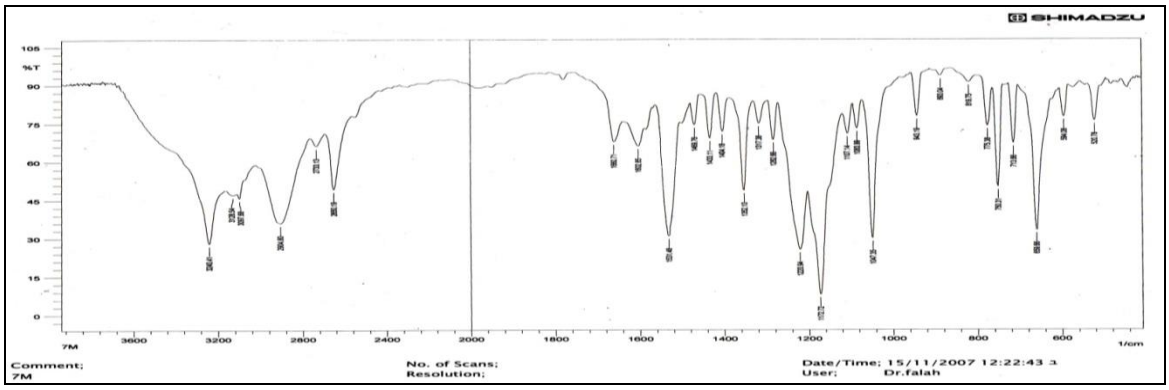


Fig 17: FT-IR Spectrum of Comp. 7M

CONCLUSION

According to the result of biological activity the compound (3A, 3D ,3M, 4D ,4M ,7M , 6D) show high activity and we believed that these compounds contain the groups such as sulfonamide , chlorine , thiazol heterocyclic ring , pyrimidine ring .

REFERENCES

[1] R. Kharab, H. Kaur, , "Therapeutic Significance of quinoline derivatives as antimicrobial agents". Indian Research journal of pharmacy.4(3), 63-69, (2013).

[2] A. Marella, O.P Tanwar., R Saha, MR. Ali , S. Srivastava, M. Akhter, M. Shaquiquzzaman, M.M. Alam, "Quinoline: A versatile heterocyclic". Saudi Pharmaceutical Journal, 21 (1), 1-12 , (2013) .

[3] H. Amii, Y. Kishikaws and K. Umeyama ," Rh(I)-Catalyzed Cyclaziation coupling of N-Aryl Trifluoroacetimidoyl Chlorides with alkynes :One-Pot Synthesis of Fluororinated Quinoline " , Organic Letters Vol.3 , No. 8 , pp. 1109-1112 , (2001) .

[4] C. S. Cho, B. H. Oh, J. S. Kim, T. S. Kim and S. C. Shim , " Synthesis of Quinolines via Ruthenium-catalysed Amines Exchange Reaction between Anilines and Trialkylamines " Chemical Communications No. 19, pp. 1885-1886, (2000) .

[5] N. D. Obushak , N. T. Pokhodylo, I. T. Krupa and V. S. Matiichuk , " Synthesis of Substituted 4-([1,2,4]Triazolo-[3,4-b]-[1,3,4]thiadiazol-6-yl)quinolines," Russian Journal of Organic Chemistry Vol. 43, No. 8 ,pp. 1223-1227, (2007) .

[6] M. G. Shevelhgeimer and N. N. Kondrashora , " Synthesis of New Derivatives of 4-Quinolinecarboxylic acid " Heterocyclic Chemistry , Vol. 38 , No. 2 , pp. 253-254, (2002).

[7] X. Y. Yu , J. M. Hil, G. Yang, Y. Yu , A. F. Kluge , D. Keith, J. Finn, P. Gallant, J. Silverman, and A. Lim, " A Series of Quinoline Analogues as Potent Inhibitors of C.albicans Prolyl t RNA Synthesis " Bioorganic & Medicinal Chemistry Letters , Vol. 11 , No. 4 , pp. 541-544 , (2001) .

[8] Y.K urasawa , K. Yoshida, N. Yamazaki , E. Kaji, K. Sasaki, Y. Zamami, Y. Sakai, T. Fujii, and H. Ito, " Quinolone Analogs 11: Synthesis of novel 4-Quinolone 3-Carbohydrizide Derivatives with antimalarial Activity " , Journal of Heterocyclic Chemistry , (2011) .

[9] A. Wube , F. Bucar , C. Hochfellener, M. Blunder , R. Bauer, and A. Hüfner, " Synthesis of N-Substituted 2-[(1E)-Alkenyl]-4-(1H)-Quinoline Derivatives as Antimycrobacterial Agents against Non-Tubercular Mycrobacteria " , European Journal of Medicinal Chemistry , Vol. 46, No. 6, pp. 2091-2101 , (2011) .

[10] M. A. Ibrahim , H. M. Hassanin, Y. A. Gabr, Y. Al-Namer, " Novel Heterocyclic Derivatives of Pyrano[3,2-c] quinolinone from 3-(1-Ethyl-4-hydroxy-2-oxo-2(1H)-quinolin-3-yl)-3-oxopropanoic acid " European Journal of Chemistry , Vol. 1 , No. 3 , pp. 195-199, (2010) .

[11] A. Chawla , P. Chawla , K. Kaur , M. Singh , P. Sunaina , K. Singh , " A Review: Chemistry of Antimicrobial and Anticancer Quinolines " , Canadian Open Pharmacy Journal , Vol. 1, No. 1, pp. 1 - 12 , (2014) .

[12] Sagheer, O.M., Saour, K.Y., and Ghareeb, M.M., "Synthesis of oxoquinoline derivatives coupled to different amino acids esters and studying their biological activity as cytotoxic agents". International Journal of Pharmacy and Pharmaceutical Sciences. , 5(4) 464-469 , (2013).

[13] Phan, L. T.; Jian, T.; Chen, Z.; Qiu, Y. -L.; Wang, Z.; Beach, T.; Polymeropoulos, A.; Or, Y. S. J. Med. Chem. 47, 2965-2968 , (2004)

[14] SB. Singh , JF. Barrett, " Emperica antibacterial drug discovery- Foundation in natural products " , Bio. Chem. Pharm. , 71, 1006-1015 , (2006) .

[15] K. Bush , MJ. Pucci , " New antimicrobial agents on the horizon " , Bio. Chem. Pharmacol , 82, 1528-1539 , (2011).

[16] N. Pramod , and S. Jayakumar , " Synthesis and antimicrobial activity of fluroquinolines " Ind. J. of heterocyclic Chem. , 21, 61-64 , (2011).

[17] J. Azimvand , " Synthesis of some new analogs of quinoline containing imine bond form the initial composition of aniline" , J. Chem. Pharm. Res., 4(8):3905-3908 , (2012) .

[18] N. P. Dhammika Nanayakkara; Arba L. Ager; Jr Marilyn S. Bartlett;Vanessa Yardley; Simon L. Croft, ; Agents Chemother., ,52(17) , 2130 – 2137 , (2008) .

[19] H. Nakayama , PM. Loiseau, C. Bories , O. Torres , A. Schinini , E. Serna , A. Rojas , MA. Fakhfakh , X. Franck, B. Figadere , R. Hocquemiller , A. Fouurnet , " Efficacy of orally administered 2-substituted quinolines in experimental murine cutaneous and visceral leishmaniases " , Dec , 49 (12) : 4950-4956 , (2005) .

[20] NC. Vieira , C. Herrenknecht , J. Vacus , A. Fournet , C. Bories , et al. " Selection of the most promising 2-substituted quinoline as antileishmanial candidate for clinical trials " , Biomed Pharmacother , 62:684-689 , (2008) .

[21] A. A. Essa , A. Mohammad , A. I. Mohammad , " Antileishmanial Activity and Computational Studies of Some Hydrazone Derivatives Possessing Quinoline Nucleus " , Eur. J. of Pharm. And Med. Res. , 2(7) , 324-338 , (2015) .

[22] R. Vlabhov , S. Parushev , J. Vlahov , P. Nickle, G. Snatzke , " Synthesis of some new quinoline derivatives-potential ant malarial drugs " , Pure Appl. Chem. 62(7) , 1303-1306, (1990) .

[23] B. H. M. Jayakumar , P.N.Balaji, N. Pramod, E.Jajuri, R. N. Rao, " Novel Quinoline Thiosemicarbazone derivatives as potential anti microbial activity " Int. J. of Pharmacy & Therapeutics , 3(3) , 276-281, (2012) .

[24] A. H. Plate , S. B. Jayakumar , B. D. Sanjaykumar, N. Pramod , " Synthesis and characterization of Thiadiazole-Quinoline derivatives as potent antioxidant agents" RRBB. 2, 44-52, (2011) .

[25] YL. Chen, YL. Zhao, CM. Lu , CC. Tzeng , JP. Wang , " Synthesis Cytotoxicity , and anti-inflammatory evaluation of 2-(furan-2-yl)-4-(phenoxy)quinoline derivatives " , Bio.Org. Med. Chem. , 14 :4373-4378 , (2006) .

[26] Theodouli Stergiopoulou; Joseph Meletiadis; Tin Sein, Paraskevi Papaioannidou; Ioannis Tsiouris; Emmanuel Roilides, J. Antimicrob. Chemother., 63(11), 343 – 348 , (2009).

[27] Richard D. Cannon;Erwin Lamping; Ann R. Holmes; Kyoko Niimi; Philippe V. Baret, Clin. Microbiol. Rev., 22(8), 291 – 321 , (2009).

[28] C. Benard , F. Zovhin , " Linker modified quinoline derivatives targeting HIV-1integrase :synthesis and biological activity " , Bio. Org. Med. Chem. Letters , 14: 2473-2476 , (2004) .

[29] SA. Mehanna , " Rationale of design of anti HIV Drugs , In Burgers medicinal chemistry and drug discovery. " Abraham D. J. Ed. Vol. 5, 6th , Virginia . Jhon Viley and Sons ; 458-479 , (2003) .

[30] Shabana I. Khan; Alison C. Nimrod; Mohammed Mehrpooya;John L. Nitiss; Larry A. Walker , Antimicrob. Agents Chemother., 46(17), 1785 – 1792, (2002) .

[31] Ishac Nazi; Adam Scott; Anita Sham; Laura Rossi; Peter R. Williamson; James W. Kronstad, Antimicrob. Agents Chemother., 51(13), 1731 – 1736 ,(2007).

[32] P. J. Vora , A. G. Mehta, " Synthesis and Characterization of Some Quinoline Azosulphonanides Clubbed Molecule " , Journal of Applied Chemistry , Vol. 1, 49- 54 , (2012) .
[33] M. Pechiamma , S. Leena , S. Ravichandran , " Synthesis ,Characterization and screening of antimicrobial activity of metal complexes derived from the Mannich base N-[1-morpholino(4-nitrobenzyl)]benzamide " Int. J. of Chem. Tech. Res. 7 , 287-292 , (2015) .
[34] M. Annam'aria , K. Anita, P. Laszlo , M. Zoltan , V.Gabor , H. Istvan , " Suzuki-Miyaura cross-coupling reactions of halo derivatives of 4H-pyrido[1,2-a]pyrimidin-4-ones" ,. Org. Biomol. Chem. , 9, 6559 , (2011) .
[35] G. I. Graf , H. Daniel , E. Luiz, A. R. Ricardo , G. M. Antonio , M. Alexander , " The Synthesis of aromatic diazatricycles from phenylenediamine-bis(methylene Meldrums acid) derivatives" , Tetrahedron. 58 , 9095- 9100 , (2002) .
[36] M. Alka , S. N. Villendra R. Uma, " Synthesis and antimycobacterial activities of certain trifluoromethyl-aminoquinoline derivatives" , ARKIVOC , 220-227 , (2006) .