Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(11):48-56

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis and characterization of some new thioxanthone derivatives

Nabeel A. A. Al-Radha* and Asmaa J. Kadhim

Chemistry Department, College of Science, AL-Qadisiya University, AL Diwaniyah City of AL-Qadisiya Provence, Republic of Iraq

---

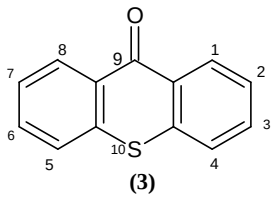
ABSTRACT

This study mainly targets a number of derivatives of thioxanthone, taking advantage of the Schiff base reaction which includes the reaction of 2-bromo thioxanthone which reaction with amines compound in the presence of glacial Acetic acid and absolute ethanol as a solvent . The preparation of compound 2-bromo thioxanthone (3), is to be used as a compound acid. The compound having heterocyclic ring is expected to have various important biological and therapeutic application. This demonstrates structural formula for each of new synthesis compound on the basis of chemical reaction , analysis of the elements, the infrared spectra and nuclear magnetic resonance .(1H NMR and 13 C NMR)

Keywords: Schiff's base, Thioxanthone Derivatives, Quantitative analysis.

INTRODUCTION

Thioxanthone (Figure 1) belong to a unique member of the large group of benzoannelated heterocycles [1]. They are found extensively in biomedical applications (drugs and other bioactive compounds [2-3] and material sciences, e.g., as photosensitizers (e.g., isopropylthioxanthone or diethylthioxanthone) [4-5] or as ligands [6, 7] and derivatives are an important class of molecules and are a common heterocyclic scaffold in biologically active and medicinally significant compounds [8,9]. The thioxanthone and derivatives are the core structure of a wide variety of naturally occurring and synthetic compounds that exhibit extraordinary anti-tumor [10,11,12], anti-parasitic [13,14], anti-cancer activity [15,16], antihypertensive, anti-oxidative, antithrombotic [17,18] and are potential anti-cancer drugs and some thioxanthones containing plant extract are directly used in traditional medicine [11,12]. The thioxanthone [19,20]possess a number of interesting pharmacological activities [21,22]. Certain members of these classes of compounds exhibit significant anti-tumor and cytotoxic effects [23,24]

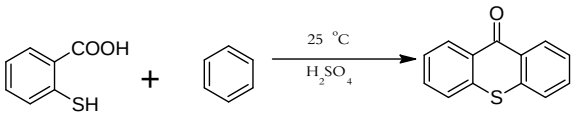


(3)

9*H*-thioxanthen-9-one

Figure -I-

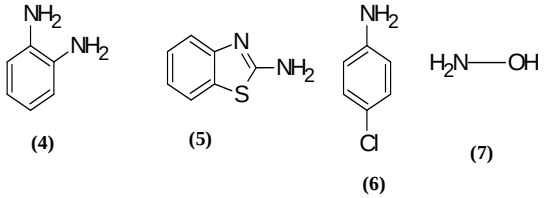
Several methods were used for the synthesis of thioxanthones[25,26]. One method used for preparation thioxanthone from reaction dray benzene and thiosylcilic acid in the presence of H2SO4. According to the following equation:



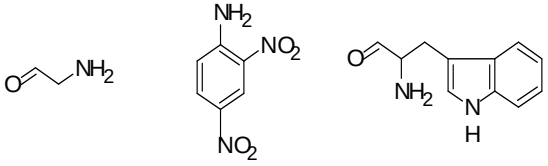
(1) **(2)** **(3)**

EXPERMENTAL SECTION

The chemical used in the synthesis of all compounds were purchased from Aldrich, Merck and BDH Chemical Companies and used without further purification. The melting points were measured on an Electro thermal Melting point / SMP (Gallenkamp) and are uncorrected.



(4) **(5)** **(6)** **(7)**



(8) **(9)** (10)

The spectral measurements are infrared spectroscopy of type FT-IR spectrophotometry (Broker). Nuclear magnetic resonance spectroscopy of the proton and carbon –type Biospin Auance III and 400 MHz (Germany) 600 MHz using (DMSO-d_6) as solvent and TMS as a reference . Thin layer chromatography (TLC) was performed on Alumina plates covered with silica gel layer and the spots were developed with iodine vapor. Element analyses (CHN) ,were carried out by using Vario Element Analyzer 3000(Shimadzu, Japan).

Preparation of a series of compound 2-bromo thioxanthone by Schiff base reaction : A mixture of 2-bromr-9H-thioxanthen-9-one(0.6mg ,0.2mmol) and concentrated amine compound in absolut ethanol (15ml) containing glacial acetic acid (5 drops) was reflux for 8- 10h. The progress of reaction was monitored by TLC . After the completion of reaction ,the reaction mixture was allowed to reach ambient temperature and then the precipitate formed was filtered , dried and from recrystallization by ethanol to get pure powder.

Synthesis of N-[(9Z)-2-Bromo-9H-thioxanthen-9-ylidene]benzene-1,2-diamine (11) : the compound **4** was prepared according to general method where taking (0.6mg ,0.2mmol) of compound **3** with (0.2mmol,2.5mg) of 1,2 di amino phenyl and then add (5) drops from catalyst (glacial acetic acid).After reflex the mix for 10 h , the compound was obtained as brown precipitate after recrystallization. Yield 43mg (30%), m.p.= 67-69 ˚ C , R_f =0.78. Anal.calc (%) for $C_{19}H_{13}BrN_2S$ (324.34) : C ,59.85; H ,3.44; N, 7.35 Found (%) : C ,59.66; H, 3.37; N ,7.28.

Synthesis of *N*-[(9*Z*)-2-Bromo-9*H*-thioxanthen-9-ylidene]-1,3-benzothiazol-2-amine(12) : the compound **5** was prepared according to general method where taking (0.6mg ,0.2mmol) of compound **3** with (0.2mmol ,3mg) of 2 amino benzothiazol and then add (5) drops from catalyst (glacial acetic acid).After reflex the mix for 10 h , the compound was obtained yellow as precipitate after recrystallization. Yield 61 mg (73%), m.p =116 -118˚ C, R_f =0.85. Anal.calc (%) for $C_{19}H_{11}FOS$(306.35): C,56.74 ;H, 2.62 ;N,6.62 Found (%) : C ,56.53 ;H,2.57;N ,6.47.

Synthesis of 3- *N*-[(9*Z*)-2- bromo-9*H*-thioxanthen-9-ylidene]-4-chloroaniline (13) : the compound **4** was prepared according to general method where taking (0.6mg ,0.2mmol) of compound **3** with (0.2mmol, 3mg) of Bara –Cloro aniline and then add (5) drops from catalyst (glacial acetic acid).After reflex the mix for 10 h , the compound was obtained as brown precipitate after recrystallization. Yield 42mg (10%), m.P =86-88˚ C, R_f = 0.71 .Anal.calc (%)C, 56.95; H, 2.77; N 3.50, Found(%) C, 56.76; H, 2.70; N,3.39

Synthesis of 4-(9*Z*)-2-bromo-*N*-hydroxy-9*H*-thioxanthen-9-imine (14) : the compound **4** was prepared according to general method where taking (0.6mg ,0.2mmol) of compound **3** with (0.2mmol ,4.5mg) of hydroxyl amine and then add (5) drops from catalyst (glacial acetic acid).After reflex the mix for 10 h , the compound was obtained as

yellow precipitate after recrystallization. Yield 15mg(48%), m.p =124-122 ˚ C, R_f = 0.71. Anal.calc.(%) for $C_{13}H_8BrNOS$ **(**306.17) :C, 56.76; H, 2.70; N .4.57 ,Found (%) C, 56.54; H, 2.62; N,4.39

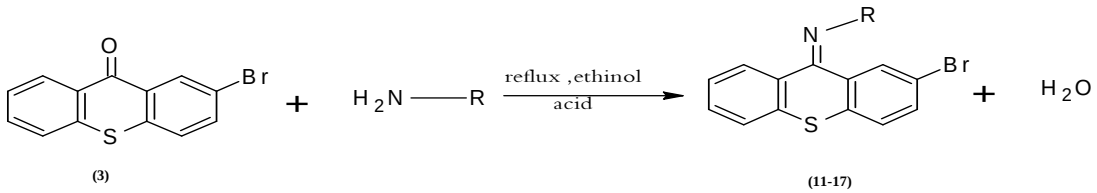
Synthesis of 2-{[(9*E*)-2-bromo-9*H*-thioxanthen-9-ylidene]amino}-3-(1*H*-indol-3-yl) propanal(15) : the compound **4** was prepared according to general method where taking (0.6mg ,0.2mmol) of compound **3** with (0.2mmol ,4mg) of tryptophan and then add (5) drops from catalyst (glacial acetic acid). After reflex the mix for 10 h , the compound was obtained as yellow precipitate after recrystallization. Yield 9.2 mg (19%), m.p = 98-100 ˚ C, R_f = 0.76. Anal.calc.(%) for $C_{24}H_{17}BrN_2O_2S$ (477.38) :C,60.39;H,3.59 ;N,5.87,Found (%) C,60.18 ;H,3.50 ;N,5.72.

Synthesis of N-[(9E)-2-bromo-9H-thioxanthen-9-ylidene]-2,4-dinitroaniline(16) : the compound **4** was prepared according to general method where taking (0.6mg ,0.2mmol) of compound **3** with 2,4 di nitro phenyl hydrazine and then add (5) drops from catalyst (glacial acetic acid).After reflex the mix for 10 h , the compound was obtained as precipitate after recrystallization. Yield 8mg (14%), m.p =135-133°C ,R_f = 0.71 , Anal.calc (%) for $C_{19}H_{10}BrN_3O_4S$ (456.27) :C, 50.02; H, 2.21, N, 9.21, Found C, 49.89; H ,2.16; N ,9.08

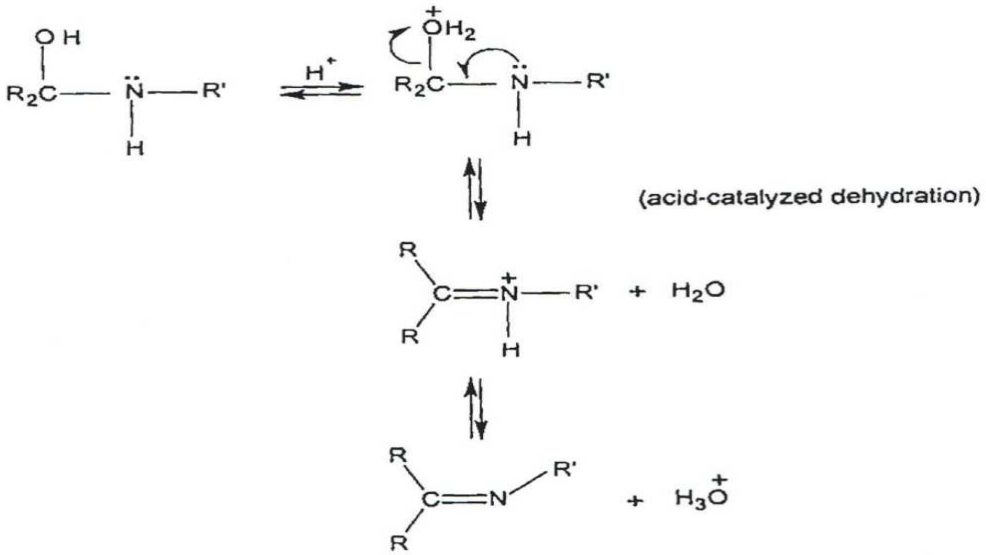
Synthesis of [(2-Bromo-9*H*-thioxanthen-9-ylidene)amino]acetic acid (17) : the compound **4** was prepared according to general method where taking (0.6mg ,0.2mmol) of compound **3** with (2mg,0.2mmol) of glassine and then add (5) drops from catalyst (glacial acetic acid).After reflex the mix for 10 h , the compound was obtained as precipitate after recrystallization. Yield 9mg (27%), m.p = 110-112°C ,R_f = 0.79 . Anal.calc (%) for $C_{15}H_{10}BrNO_2S$ (348.21): C, 51.74; H, 2.89; N, 4.02, Found C, 51.59;H, 2.78, N3.91

RESULTS AND DISCUSSION

Thioxanthone derivatives (**11-17**) were synthesized through the condition 2-bromo thioxanthone (3) with number of amino compound with 5 drops from glacial acetic acid as catalyst and ethanol absolute as solvent .According to the following equation:



R =alkyl or aryl group



R and R[1] = alkyl or aryl group

Scheme I: Mechanism for acid catalyzed Schiff base synthesis

The mechanism of Schiff base formation is another variation on the theme of neucleophilic addition to the carbonyl group. In this case, the nucleophile is the amine. In the first part of the mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine. The carbinolamine loses water by

either acid or base catalyzed pathways. Since the carbinolamine is an alcohol, it undergoes acid catalyzed dehydration.

Typically the dehydration of the carbinolamine is the rate-determining step of Schiff base formation and that is why the reaction is catalyzed by acids. Yet the acid concentration cannot be too high because amines are basic compounds. If the amine is protonated and becomes non-neucleophilic, equilibrium is pulled to the left and carbinolamine formation cannot occur. Therefore, many Schiff bases synthesis are best carried out at mildly acidic pH. The dehydration of carbinolamines is also catalyzed by base. This reaction is somewhat analogous to the E2 elimination of alkyl halides except that it is not a concerted reaction. It proceeds in two steps through an anionic intermediate. The corresponding Schiff base at room temperature within 10 to 8 hours **(Scheme-I).**

The melting point was uncorrected which determine by open capillary tube and was listed in the Table -1 as well as other physical properties.

The synthesized compound was characterization by their element analysis, IR, 1H NMR, 13C NMR. The IR spectra of compound 11-17.

TABLE-1 PHYSICAL –CHEMICAL DATA OF THE COMPOUNDS 11-17

Comp. No	m.p. (°C)	Yield(%)	Colour	R_f
11	67- 69	30	brown powder	0.78
12	116-118	14	yellow powder	0.91
13	86 -88	10	brown powder	0.71
14	122-124	48	yellow powder	0.71
15	98- 100	19	yellow powder	0.76
16	135-133	14	yellow powder	0.71
17	110-112	27	white powder	0.79

TABLE-2 FT-IR SPECTRA DATA (cm^{-1}) OF THE COMPOUNDS 11-17

Comp. No.	C=N	C=C	C-Br	C-N	C-H	C-C	Other
11	1612	1489	734	1435	3200	1285	NH_2 3083
12	1636	1524	718	1120	3067	1283	___
13	1636	1589	639	1313	3000	1162	C-Cl 1091
14	1637	1436	639	___	2800	1274	OH 3000
15	1715	1453	644	1015	2150	1114	OH 2600, NH_2 3100, C=O 1596
16	1636	1435	734	1285	3100	1285	C-NO_2 1389
17	1715	1443	644	1353	3000	1114	C=O 1596, OH 2600, C-Hsp_3 1307

TABEL-3 ^{1}HNMR SPECTRA DATA (ppm) OF COMPOUNDS 11-17

Comp. No.	H-1	H-3+H-6+H-7	H-8	Other
11	8.51	7.95	8.46	NH_2 5.24, H-3'H-6' 6.51, H-4'+H-5' 7.1, H-5+H-4+H-6+H-7 7.9
12	8.50	7.9	8.45	___
13	8.50	7.9	8.45	H-3'+H-5' 7.00 , H-2'+H-6' 6.54
14	8.49	7.9	8.44	N-OH 10.36
15	8.51	7.9	8.46	CH_2CHCO_2H 2.51, NH 10.94 ,$CHCO_2H$ 3.4
16	8.48	7.84	8.43	C-5' 8.79 ,C-3' 9.97
17	8.51	7.8	8.46	CH_2 4.35 ,CO_2H 11.99

TABLE-4 13C NMR SPECTRA DATA (ppm) OF COMPOUNDS 11-17

Comp. No.	C-2	C-2'	C-9	C-4a+C-5a	Other
11	120.2	148.53	165.34	136.4	C-3'116.3 , C-1+C-4 131.78
12	120.2	178.2	166.9	136.8	C-3a' 153.3
13	120.2	___	163.9	136.8	C2'+C-6'122.6 , Caro.-1' 149.5
14	120.7	___	164.3	136.8	____
15	120.2	127.6	155.7	141.9	CH2 (26.8-27.6), $CHCO_2$ (55.2-55.8)CO_2H 178.2
16	120.2	143.75	163.9	136.8	C-6' 116.0 , C-1' 151.9 , C-4' 149.6
17	120.2	___	154.4	136.8	CH_2 53.7, CO_2H 178.2 , C-9a 143.9

TABLE -5 ELEMENT ANALYSIS OF COMPOUND 11-17

Comp. No.	Element analysis (%) : Calc , (Fond)		
	C	H	N
11	59.85(59.66)	3.44(3.37)	7.35(7.28)
12	56.74(56.53)	2.62(2.57)	6.62(6.47)
13	56.95(56.76)	2.27(2.70)	3.50(3.39)
14	56.76(56.54)	2.70(2.62)	4.57(4.39)
15	60.39(60.18)	3.59(3.50)	5.87(5.72)
16	50.02(49.89)	2.21(2.16)	9.21(9.08)
17	51.74(51.59)	2.89(2.78)	4.02(3.91)

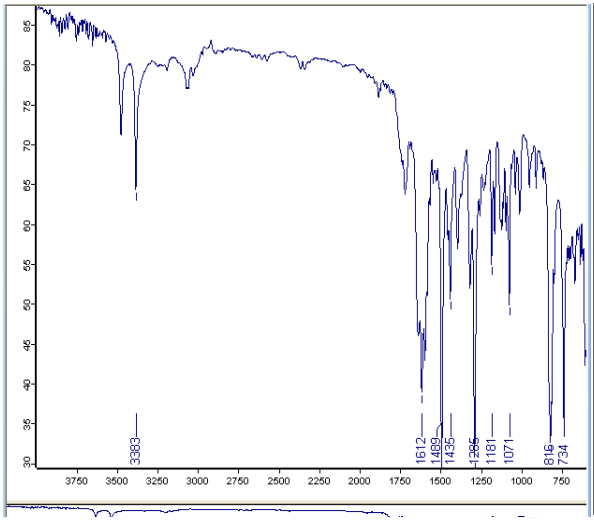


Figure (1): FT-IR spectrum for compound (11)

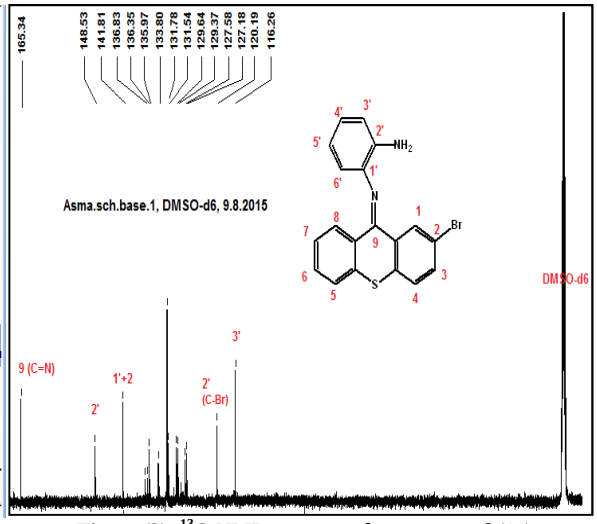


Figure.(2): ^{13}C-NMR spectrum for compound (11)

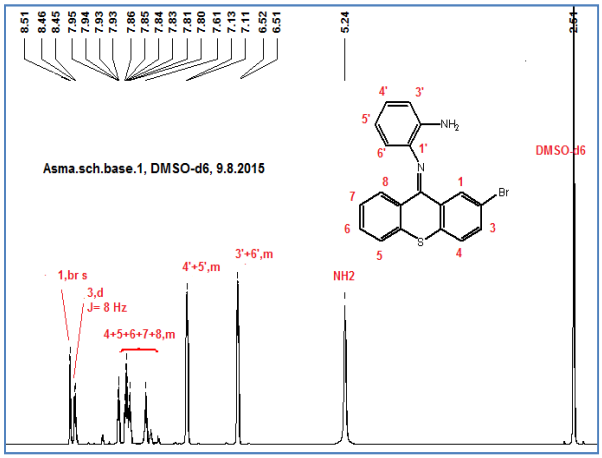


Figure (3): 1H-NMR spectrum for compound (11)

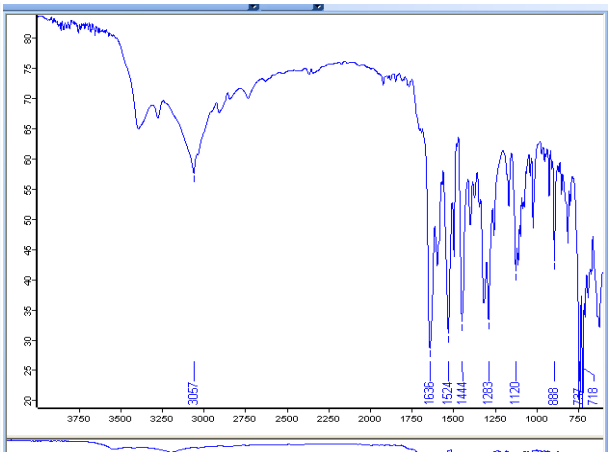


Figure (4): FT-IR spectrum for compound (12)

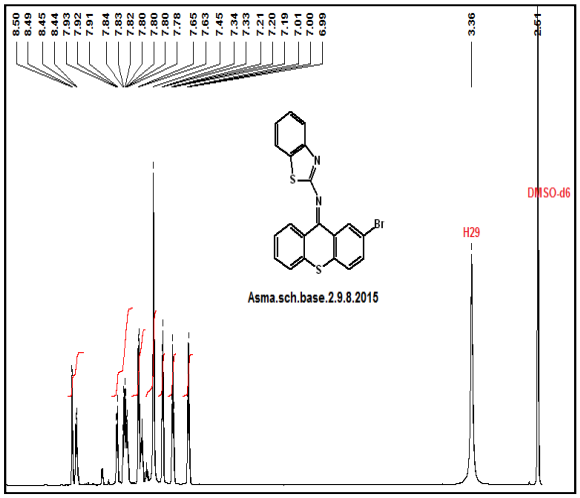


Figure (5): 1H-NMR spectrum for compound (12)

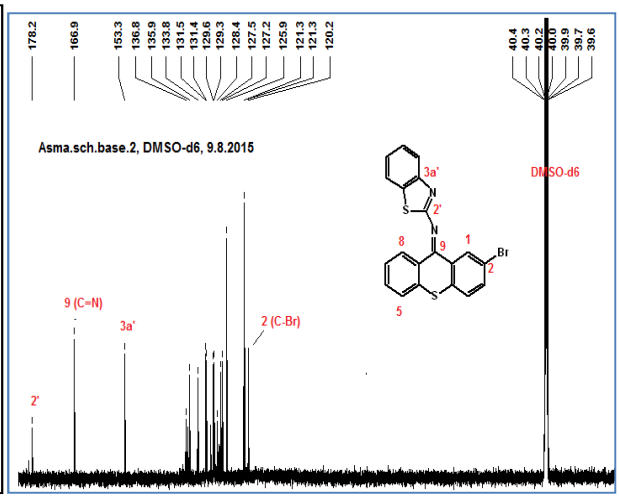


Figure (6) 1C-NMR spectrum for compound (12)

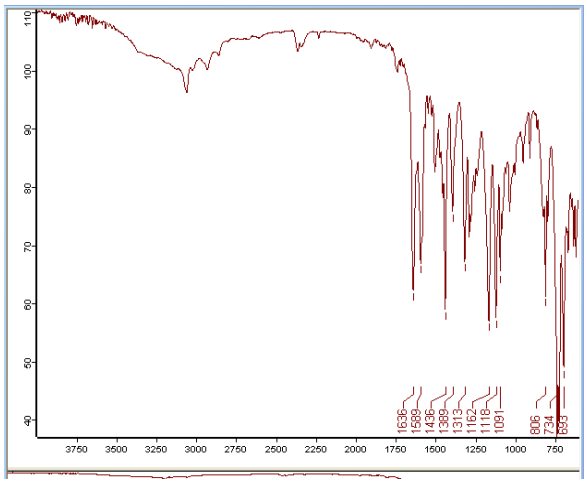


Figure (7): FT-IR spectrum for compound (13)

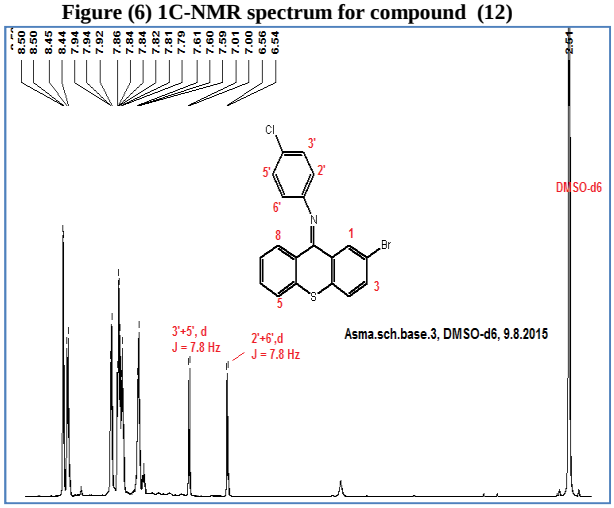


Figure (8): 1H-NMR spectrum for compound(13)

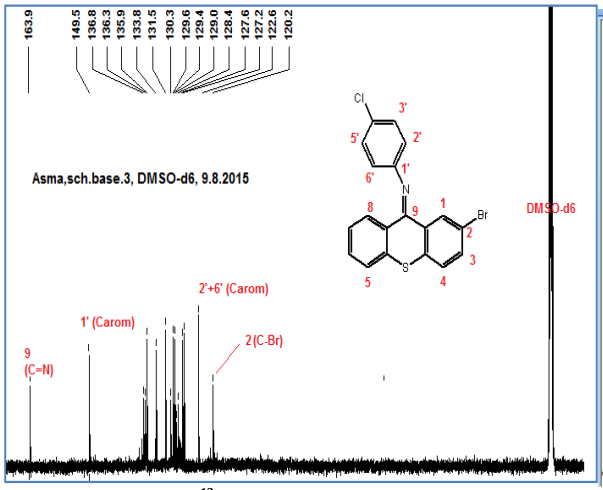


Figure (9): ^{13}C-NMR spectrum for compound(13)

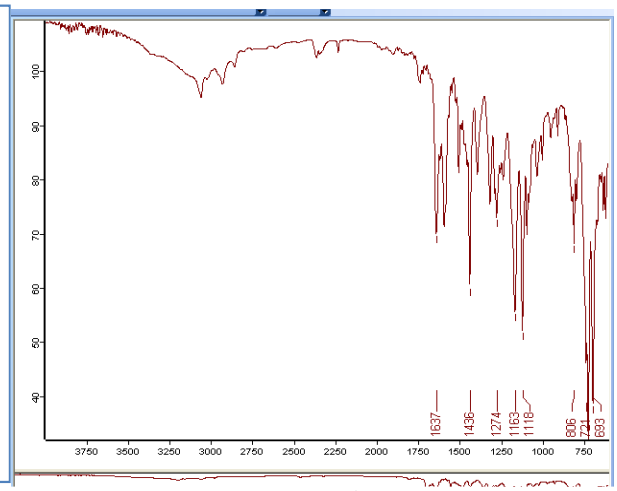


Figure (10): FT-IR spectrum for compound (14)

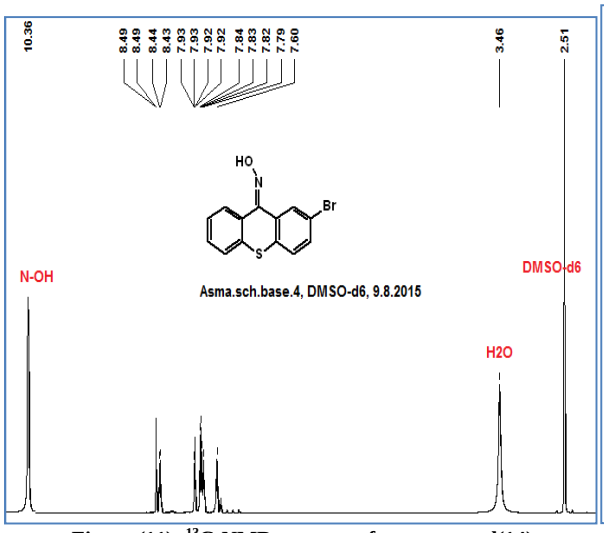


Figure (11): ^{13}C-NMR spectrum for compound(14)

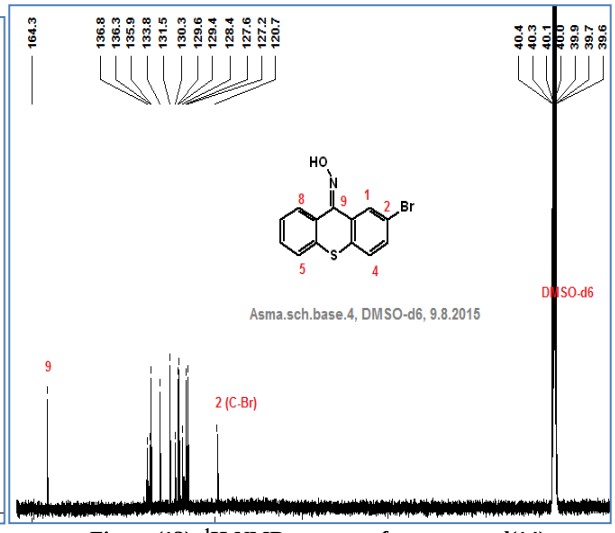


Figure (12): ^{1}H-NMR spectrum for compound(14)

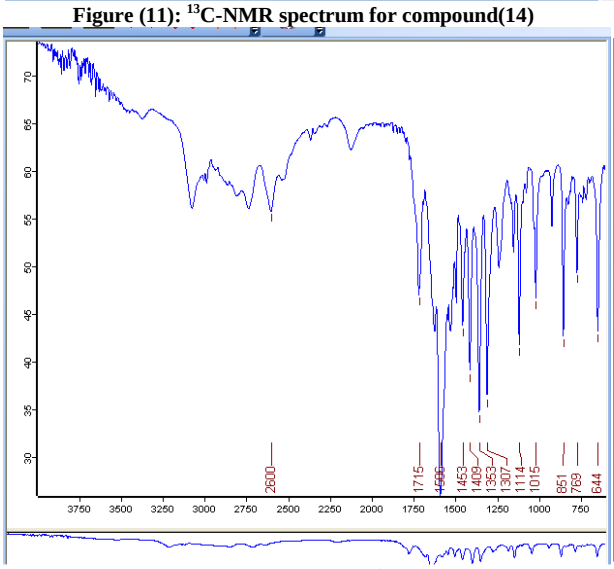


Figure (13): FT-IR spectrum for compound (15)

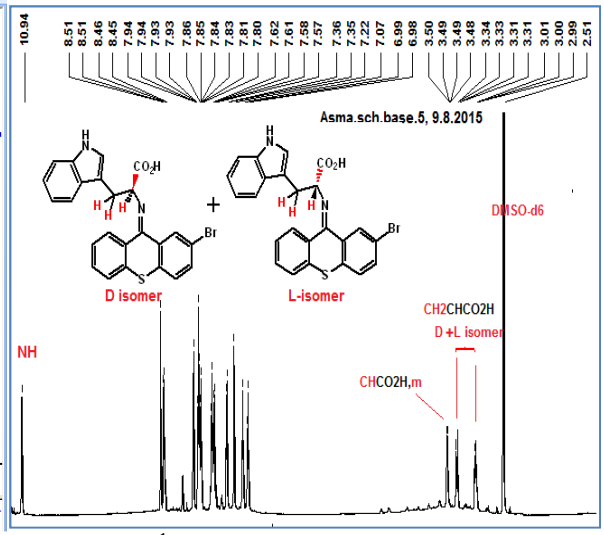


Figure (14): ^{1}H-NMR spectrum for compound(15)

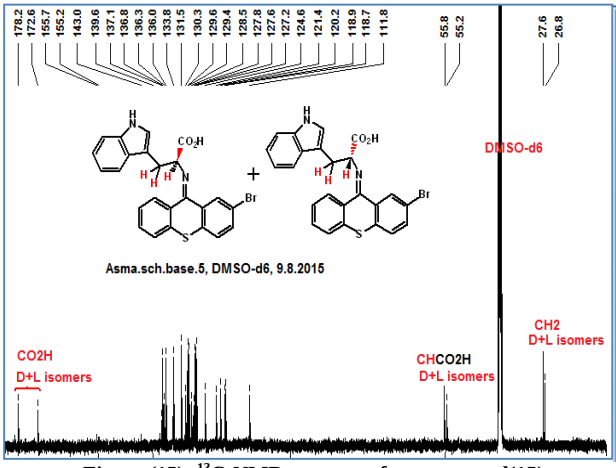


Figure (15): ^{13}C-NMR spectrum for compound(15)

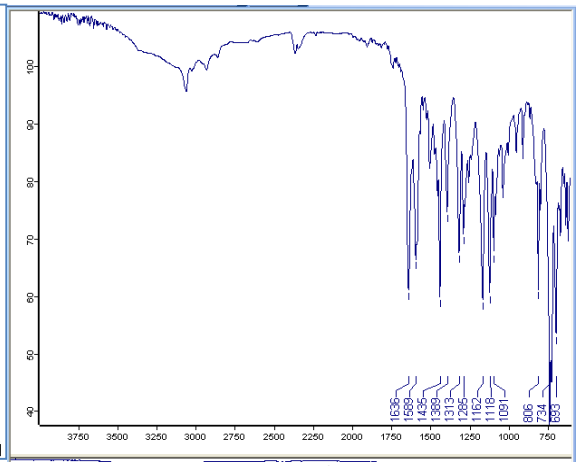


Figure (16): FT-IR spectrum for compound (16)

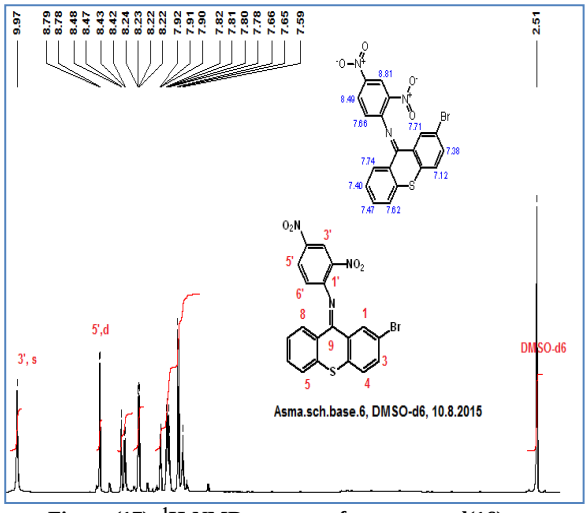


Figure (17): ^{1}H-NMR spectrum for compound(16)

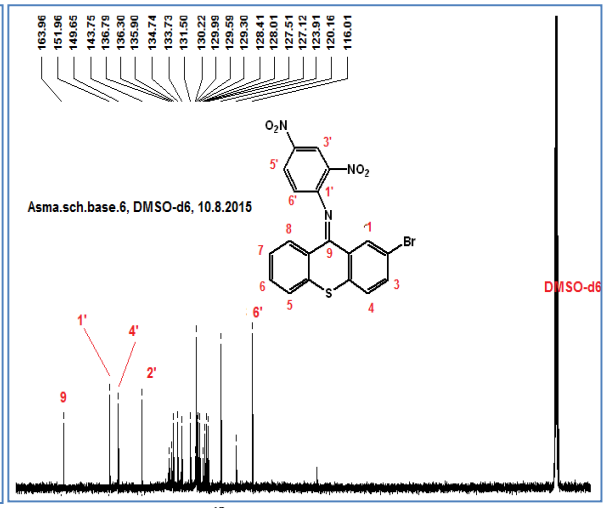


Figure (18): ^{13}C-NMR spectrum for compound(16)

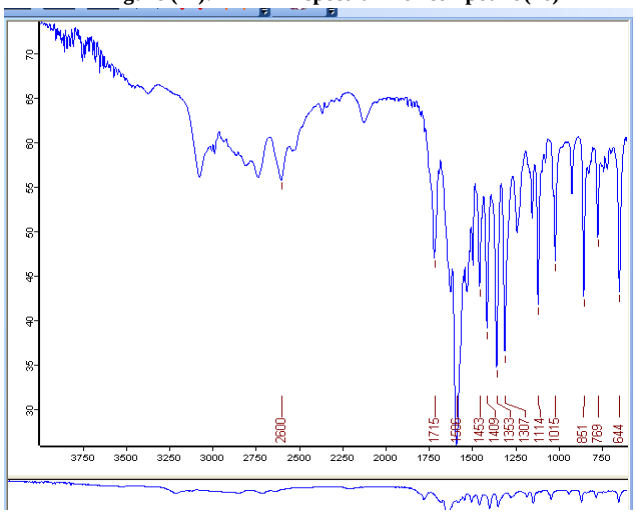


Figure (19): FT-IR spectrum for compound (17

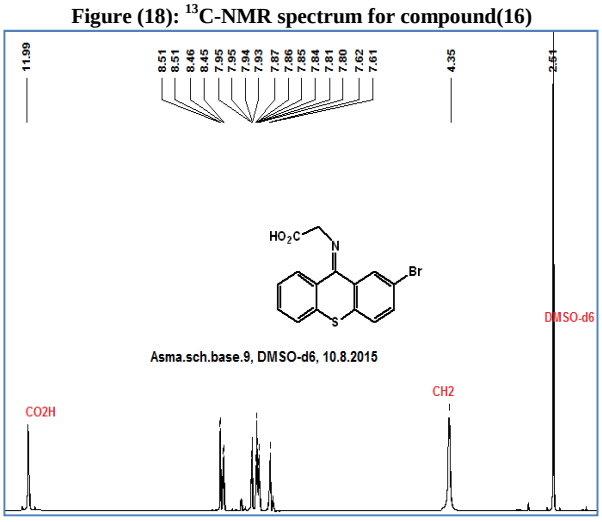


Figure (20): ^{1}H-NMR spectrum for compound(17)

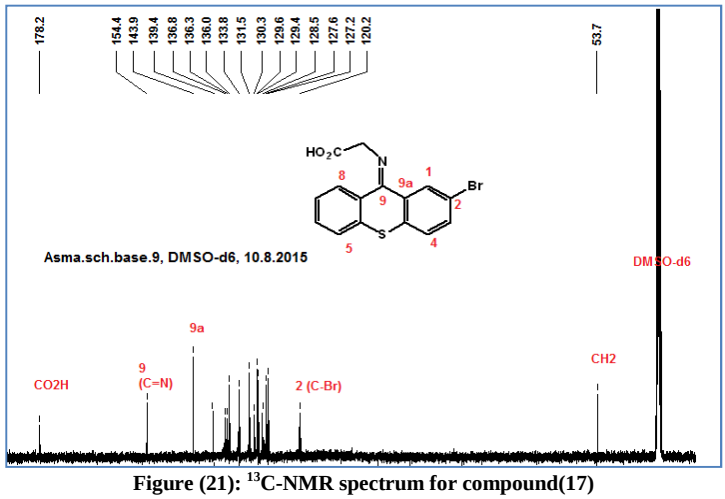


Figure (21): ^{13}C-NMR spectrum for compound(17)

Acknowledgements

The authors would like to express their gratitude to Prof Dr. Najim A.Al-Masoudi for providing the required facilities, conducting spectral measurements with interpretation and for encouraging us.

REFERENCES

[1] Nelson, A. *Sci. Synth*. **2003**, **14**, 787.

[2] Woo, S.-W.; Kang, D.-H.; Kim, J.-S.; Lee, C.-S.; Lee, E.-S.; Jahng, Y.-D.; Kwon, Y.-J.; Na, Y.-H. *Bull. Korean Chem. Soc*., **29**, 471(**2008**)
[3] Paiva, A. M.; Pinto, M. M.; Sousa, E. *Curr. Med. Chem.,* **20**, 2438(**2013**).
[4] Karasu, F.; Arsu, N.; Jockusch, S.; Turro, N. J. *J. Org. Chem.* **2013**, **78**,(9161).
[5] Malval, J.-P.; Jin, M.; Morlet-Savary, F.; Chaumeil, H.; Defoin, A.; Soppera, O.; Scheul, T.; Bouriau, .; Baldeck, P. L. *Chem. Mater*., **23**, 3411 (**2011**).
[6] Breslow, R.; Mehta, M. P. *J. Am. Chem. Soc*., **108**, 6417(**1986**).
[7] Breslow, R.; Guo, T. *Tetrahedron Lett*., **28**, 3187(**1987**).
[8] Moon. J. K, Park. J. W, Lee. W. S. and Yoon. Y. *J. Heterocyclic. Chem.,* 36(**3**): 793-798. (**1999**)
[9] Fioster. B. J, Wiegand. R. A, Pugh. S. and Corbett. T. H. *Clin. Cancer. Res*., 3(**11**): 2047-2053(**1997**).
[10] Wentland. M. P, Perni. R. B, Hlavac. A. G, Coughlin. T. H. and Rake. J. B. *Bioorg. Med. Chem. Lett*4, . (**4**): 609-614 (**1994**).
[11] Showalter. H. D. H, Angelo. M. M. and Berman. E. M. *J. Med. Chem.,* 31(**8**):1527-1539(**1988**)
[12] Archer. S, Abdel-Hadi. Z, Rabindra. R. and Thomas. A. R. *J. Med. Chem.,* 26(**9**):1240-1246(**1983**) .
[13] Watanade. M, Pate. M, Tsukazaki. M. and Furukawa. S. "Regioselective Synthesis of substituted Thioxanthene- and selenoxanthen-9-one Derivatives .(**1989**).
[14] Chem. Pharm. Bull., 37(1): 36-41. Archer. S, Mattoccia. L. P, Cioli. D, Seyed-Mozaffari. A. and Zayed. A. H. *J. Med. Chem.,* 31(**1**): 254-260(**1988**).
[15] Davis. S, Weiss. M. J, Wong. J. R, Lampidis. T. J. and Chen. L. B. 1985. *J. Biol. Chem.,* 260(**25**): 13844-13850.
[16] Sun. Z. Y, Botros. E, Su. A. D, Kim. Y, Wang. E, Baturay. N. J. and Kwon. C.H. *J. Med. Chem*., 43(**22**): 4160-4186(**2000**).
[17] Pinto. M. M. M, Sousa. M. E. and Nascimento. M.. *J. Curr. Med. Chem.*,12(**21**): 2517-2538(**2005**).
[18] Wang. L. W, Kang. J. J, Chen. I. J, Teng. C. M. and Lin. C. N. *Bioorg. Med. Chem*., 10(**3**): 567-572(**2002**).
[19] Kostakis. I. K, Pouli. N. and Mikros. E. *Bioorg. Med. Chem*., 9(**11**): 27932802(**2001**).
[20] Siavash. R, Parvis. N, Abdolmajid. B. M, Mohammad. R. G, Gholam. R. K. and Hashem. S. *Chemical Physics*., 337(1): 33-38 (**2007**) .
[21] Horwits. J. P, Massova. I, Wiese. T. E, Besler. B. H. and Corbett. T. H. *J. Med. Ch*em., 37(**6**): 781- 786 (**1994**).
[22] Gannon. M. K, Holt. J. J, Bennett. S. M, Wetzel. B. R, Loo. T. W. and Bartlett. M. C. *J. Med. Chem.,* 52(**10**): 3328- 3341(**2009***).*
[23] Berberian. D. A, Freele. H, Rosi. D, Dennis. E. W. and Archer. S. J. *Parasitol*., 53(**2**): 306- 311(**1967**).
[24] Turner. S, Bases. R, Pearlman. A, Nobler. M. and Kabakow. B. *Radiology*., 114(**3**): 729 -731 (**1975**).
[25] Zhao, J.; Larock, R. C. *J. Org. Chem*., **72**, 583 (**2007**).
[26] Ran, R.; Pittman, U. C. *J. Heterocycl. Chem*., **30,** 1673 (**1993**).