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Synthesis and Characterization of Some 3,4-Dihydropyrimidine-2-ones Using Tributylborate as a Catalyst

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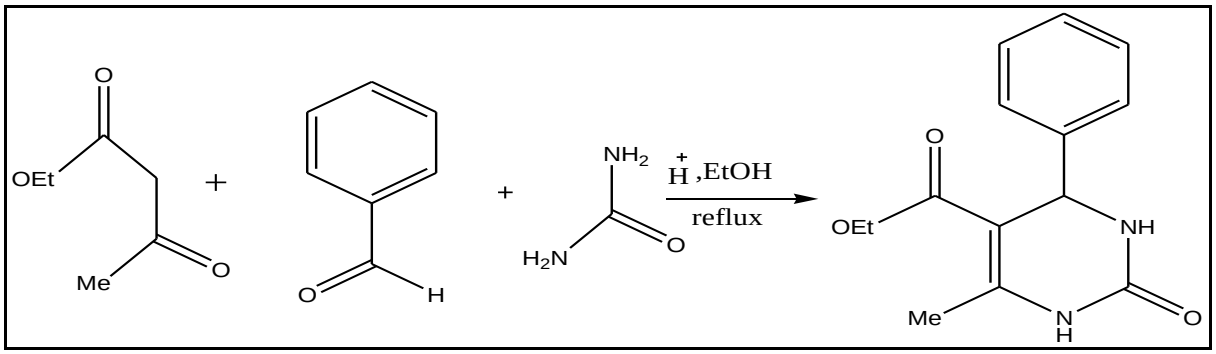
Abstract : We describe here the synthesis of new series of 3,4-dihydropyrimidin-2-ones derivatives from three components viacyclocondensation of ethylacetoacetate, aldehyde and urea or thiourea in the presence of tributylborate as a catalyst. We used here the boron-based catalyst (tributylborate) under a solvent-free, fast, cost effective conditions which offers several advantages including high yields, environmentally friendly procedure, short reaction times and simple work up procedure. Interestingly, reaction of cyclohexanone with urea and 2.0 equiv. of aldehyde furnished a new analogues of pyrimidines. The synthesized compounds have been characterized by spectroscopic study spectra: FTIR, ^{1}H-, ^{13}C NMR and 2D NMR study.
Key words : Biginelli-type reaction; tributylborate ; one-pot; pyrimidinone; solvent-free.

Introduction

Since the late 1980's a tremendous increase in activity has gain occurred, due to the multifunctionalized dihydropyrimidines scaffold DHPMs (Biginelli compounds) represents a heterocyclic system of remarkable pharmacological efficiency. More recently, a very recent highlight in this context was the synthesis of Monastrol as a mitotic kinesin Eg5 motor protein inhibitor and potential new lead for the development of anticancer drugs.

The dihydropyrimidinones (DHPMs) have vary interesting and multifaceted biological activities, such as antiviral, antitumor,antibacterial, and antiflammatory properties as well as calcium channel modulating activity [(1,2)]. The dihydropyrimidinones discovery 120 years ago in 1893 by the Italian chemist Pietro Biginelli[(3,4)]. Among them, the Biginelli multicomponent reaction, involving a multicomponent condensation of aldehyde, β-ketoester, and urea[(6,7)], provides an easy method to the preparation of DHPMs, because multicomponent reactions(MCRs) are considered with high facileness, efficiency and economy in organic chemistry, In recent times,[(8,9)] using bases is increasing with a very fast rate because of their beneficial properties such as undetectable vapor pressure, non-inflammability, and reusability



A new boron-based catalyst, tributyl borate, is introduced for the synthesis of multi-functionalized pharmacologically active dihydropyrimidinones under asolvent-free[10,11] fast, cost effective, and efficient greenerprotocol is described. Herein we report, Catalytic reactions are generally preferred in environmentally friendly green chemistry as they contribute significantly towards reduction in waste generation an efficient and convenient procedure for the synthesis of these arylideneheterobicyclicpyrimidinones by the one-pot three-component condensation of aromatic aldehyde, cyclohaxanone or ethylacetoacetate, and urea or thiourea in the presence of tributylborate, as a green and economical catalystunder solvent-free conditions (Scheme 2)[12,13]

2. Experimental

All reagents were purchased from Merck and used without further purification. All yields refer to the isolated products after purification. The products were characterized by comparison with authentic samples and by spectroscopic data (IR, 1H NMR, 13C NMR spectra and melting point). All melting points were taken on a Gallenkamp melting apparatus and were uncorrected.[14,15] IR spectra were recorded on a JASCO FT/IR-680 PLUS spectrometer. 1H NMR spectra were recorded ona Bruker400MHz

General Procedure for the Synthesis of DHPMs[16]

A mixture of benzaldehyde (3 mmol), ethylacetoacetate or cyclohaxanone (3 mmol), urea (4.5 mmol) and the catalyst (0.6 mmol, 0.2 g) in absolute methanol (50 ml) was heated under reflux for an appropriate period (8-10h)and the reaction progress was monitored by TLC. After cooling to room temperature., the reaction mixture was poured onto crushed ice (50 g) and stirred for 10 min. The precipitate was filtered under suction, washed with cold water(20 ml) to remove excess urea. After then solid was dissolved in ethanol and filtered to remove the catalyst and purified further by recrystallization (hot ethanol).

Spectral data for selected Compounds:

4,5 -Bis(phenyl)-hexahydropyrimido[4,5-d]pyrimidine-2,7(1H,3H)-dione(104 (**6a**).

IR (KBr): υ3487,3224, 2993, 1726, 1705, 1647, 1581, 1362, 1209, 1156, 1037, 952, 843, 756 cm.-1; 1H NMR (DMSO-d6): d .15 (t, 3 H, J = 1.24 Hz), 1.64 (s, 3H), 2.50 (q, 2H, J = 7.0 Hz), 4.77 (s, 1H), 7.30 (d, 2H, J = 8.0 Hz), 7.90 (s, 1H, NH), 8.08 (d, 2H, J = 8.0 Hz) 9.40 (brs, 1H, NH). 13CNMR (DMSO-d6, 75 MHz): d 14.3, 17.9, 53.5, 58.9, 97.4, 124.6, 127.5, 146.8, 149.3, 152.7, 153.1, 164.8. EIMS m/z (%): 306 (m+, 21), 276 (29), 232 (18), 183 (100), 155 (47), 137 (31), 76 (41), 51 (29).

4,5-bis(4-bromophenyl)-hexahydropyrimido[4,5-d]pyrimidine-2,7(1H,3H)-dione(4b)

IR (KBr): υ3409,3340, 2983, , 1681, 1666,1650, 1362, 1209, 1156, 1037, 952, 843, 756 cm.-1; 1H NMR (DMSO-d6): d .1.67 (t, 3 H, J = 6.8 Hz), 1.98 (s, 3H), 2.15 (q, 2H, J = 7.0 Hz), 3.85,. (s, 1H), 7.29 (d, 2H, J = 8.0 Hz), 7.58 (s, 1H, NH), 8.30 (d, 2H, J = 8.0 Hz) 9.40 (brs, 1H, NH). 13CNMR (DMSO-d6, 75 MHz): d 14.3, 17.9, 53.5, 58.9, 97.4, 124.6, 127.5, 146.8, 149.3, 152.7, 153.1, 164.8. EIMS m/z (%): 306 (m+, 21), 276 (29), 232 (18), 183

5-Acetyl-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one (6a).

IR (KBr): υ3241, 2983, 1726, 1705, 1647, 1581, 1362, 1209, 1156, 1037, 952, 843, 756 cm.-1; 1H NMR (DMSO-d6): d .15 (t, 3 H, J = 6.8 Hz), 2.30 (s, 3H), 4.10 (q, 2H, J = 7.0 Hz), 5.22 (s, 1H), 7.50 (d, 2H, J = 8.0

Hz), 7.90 (s, 1H, NH), 8.30 (d, 2H, J = 8.0 Hz) 9.40 (brs, 1H, NH). 13CNMR (DMSO-d6, 75 MHz): d 14.3, 17.9, 53.5, 58.9, 97.4, 124.6, 127.5, 146.8, 149.3, 152.7, 153.1, 164.8. EIMS m/z (%): 306 (m+, 21), 276 (29), 232 (18), 183 (100), 155 (47), 137 (31), 76 (41), 51 (29

5-(Ethoxycarbonyl)-4-(4-diethoxymethylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one(**6b**).

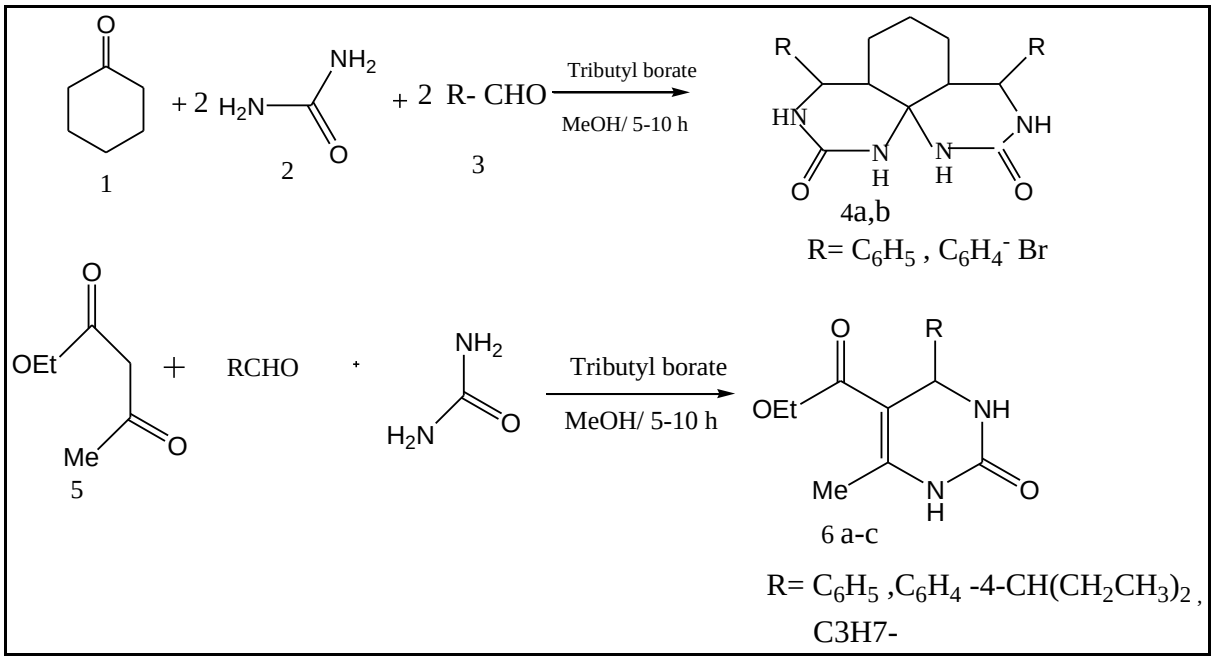
IR (KBr): υ3241, 2983, 1726, 1705, 1647, 1581, 1362, 1209, 1156, 1037, 952, 843, 756 cm.-1; 1H NMR (DMSO-d6): d .15 (t, 3 H, J = 6.8 Hz), 2.30 (s, 3H), 4.10 (q, 2H, J = 7.0 Hz), 5.22 (s, 1H), 7.50 (d, 2H, J = 8.0 Hz), 7.90 (s, 1H, NH), 8.30 (d, 2H, J = 8.0 Hz) 9.40 (brs, 1H, NH). 13CNMR (DMSO-d6, 75 MHz): d 14.3, 17.9, 53.5, 58.9, 97.4, 124.6, 127.5, 146.8, 149.3, 152.7, 153.1, 164.8. EIMS m/z (%): 306 (m+, 21), 276 (29), 232 (18), 183 (100), 155 (47), 137 (31), 76 (41), 51 (29

5-(Ethoxycarbonyl)-6-methyl-4-(n-propyl)-3,4-dihydropyrimidin-2(1H)-one(6c).

IR (KBr): υ3247, 2931, 1720, 1704, 1647, 1581, 1362, 1209, 1156, 1037, 952, 843, 756 cm.-1; 1H NMR (DMSO-d6): d .1.18 (t, 3 H, J = 6.8 Hz), 2.81 (s, 3H), 4.05 (q, 2H, J = 7.0 Hz), 5.22 (s, 1H), 7.50, NH), 8.9 (d, 2H, J = 8.0 Hz) 9.40 (brs, 1H, NH). 13CNMR (DMSO-d6, 75 MHz): d 14.3, 17.9, 53.5, 58.9, 97.4, 124.6, 127.5, 146.8, 149.3, 152.7, 153.1, 164.8. EIMS m/z (%): 306 (m+, 21), 276 (29), 232 (18), 183 (100), 155 (47), 137 (31), 76 (41), 51 (29

Results and Discussion

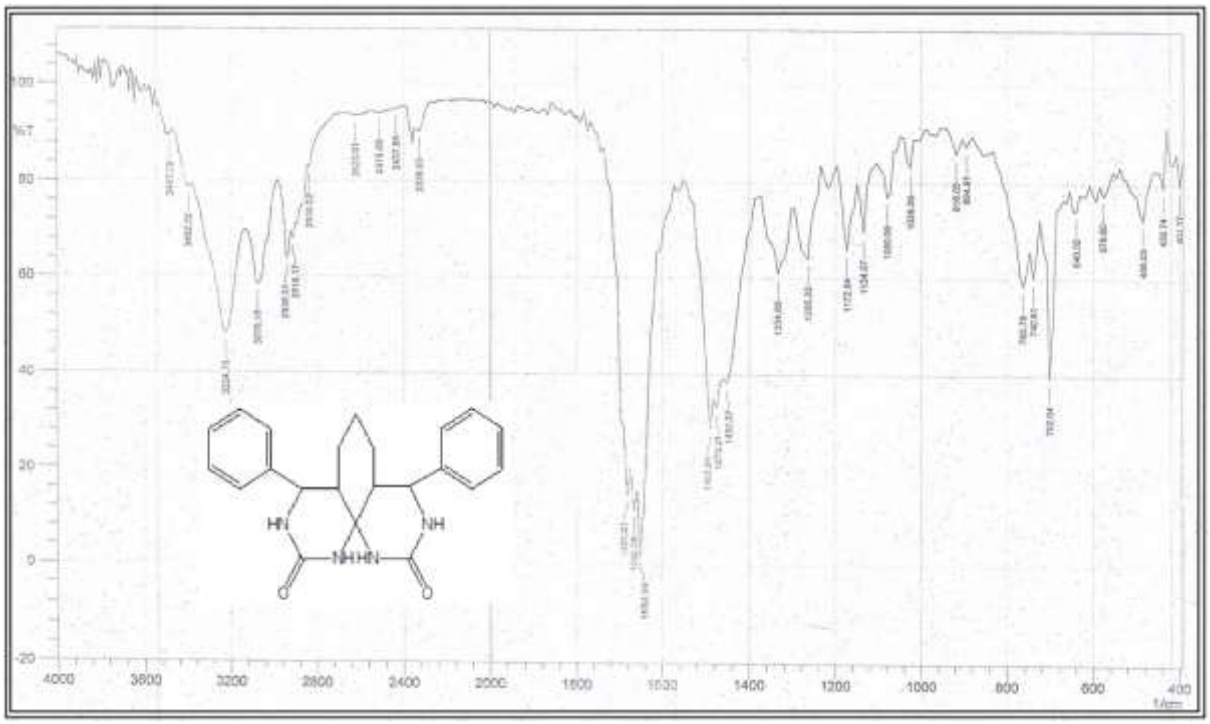
This method employed a one-pot three-component condensation. aldehyde3 reacted with β-diketones or Cyclohaxanone(1,5) namely, and urea 2 in methanol in presence of tributyleborate as a catylast. The mechanism of this reaction was taken place via theknoevenagel condensation of aldehyde 3 and active methylene compound (1,5) to afford the benzylidine as intermediate, In the presence of tributyleborate, urea 2attacked the olefinic double bond, followed by lossed of water as a result of the formation of the enol form 5 togive the dihydropyrimidins 6a-c (scheme 2). (16) The structure of the obtained compounds were confirmed by their analytical and spectroscopic data (cf. Experimental).



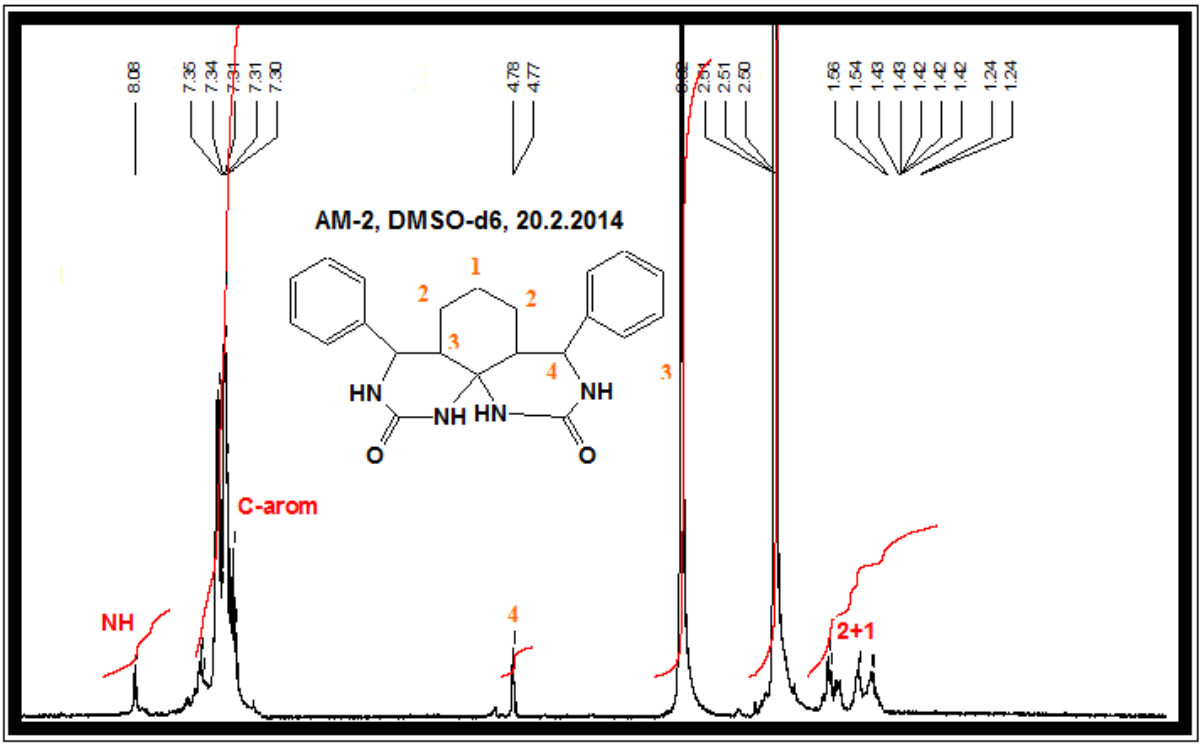
The purity of the crude product was lowered and purification by chromatography or crystallization had tobe carried out. These results promoted us to extended the scope of this environmentally friendly procedure Bignilli procedure and have carried out the synthesis of DHPMs analogue **4a,b**by reacting the aldehyde, urea and cyclohaxanone**1**as an example of non enol form of active methylene compounds in the presence of tributylborate as a catalyst. Unexpectedly, **6a,b**was formed from running the three component reaction **1**, **2**, and **8** in solvent less reactions using silicagel as a catalyst. Structure of **10a,b** was confirmed by its 1H NMR. On the other hand, IR ofcompounds**10a,b**show a peak at 1698cm-1 for (C=O,ester group),(7) in addition to the

disappearance of the CN group. Furthermore, on running this reaction in liquidphase, such as ethanol / HCI or dry acetic acid as medium and catalyst, the same product **9** was isolated (comparative TLC, IR and mixed melting points).(12)

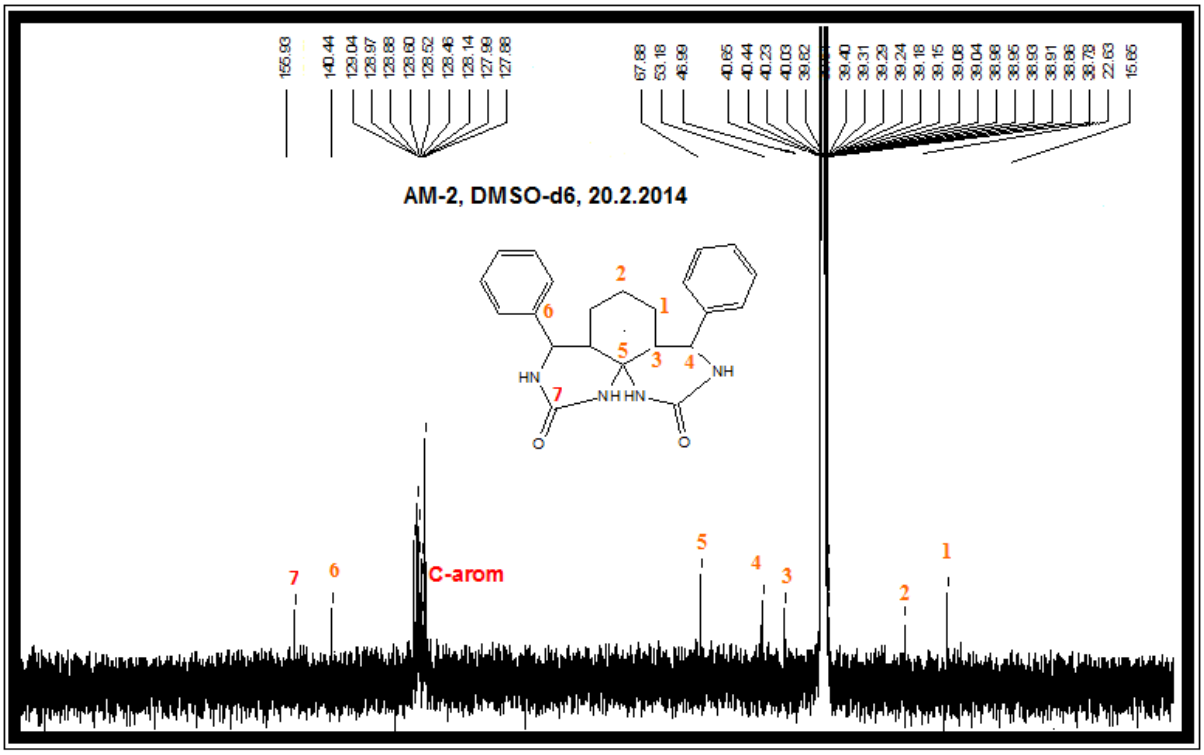
Form of IR (4a)



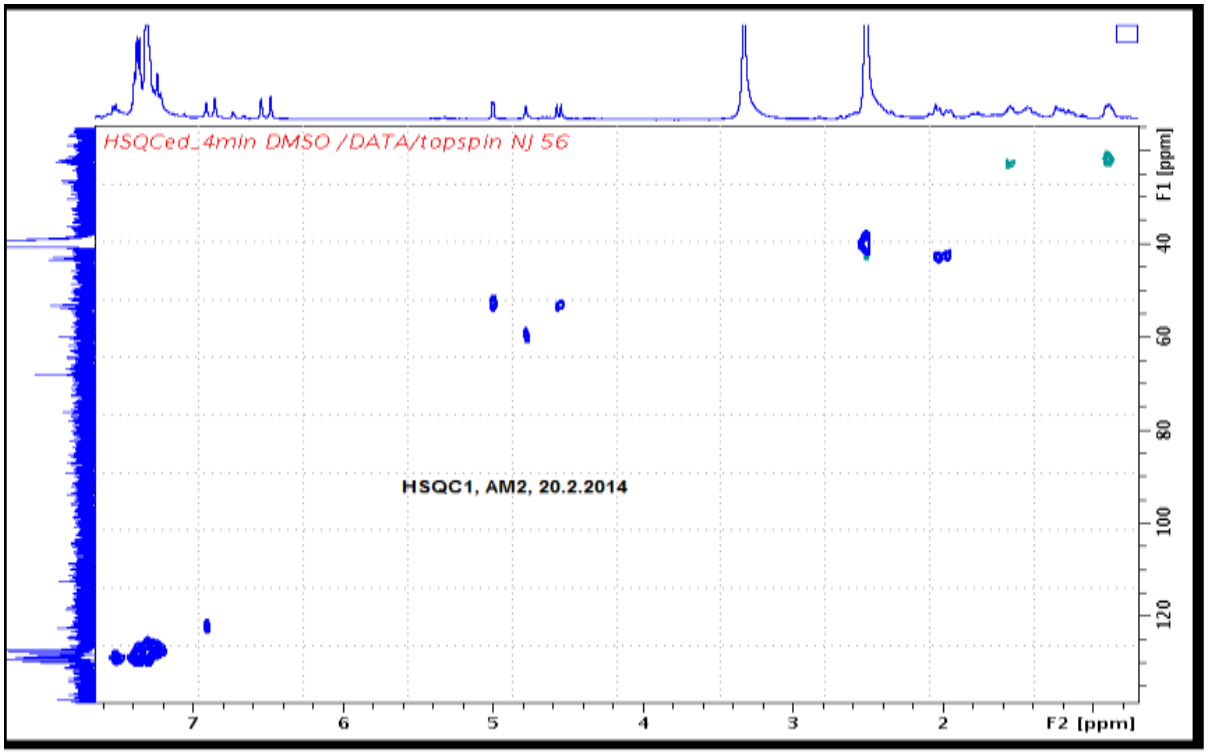
Form of HNMR (4a)

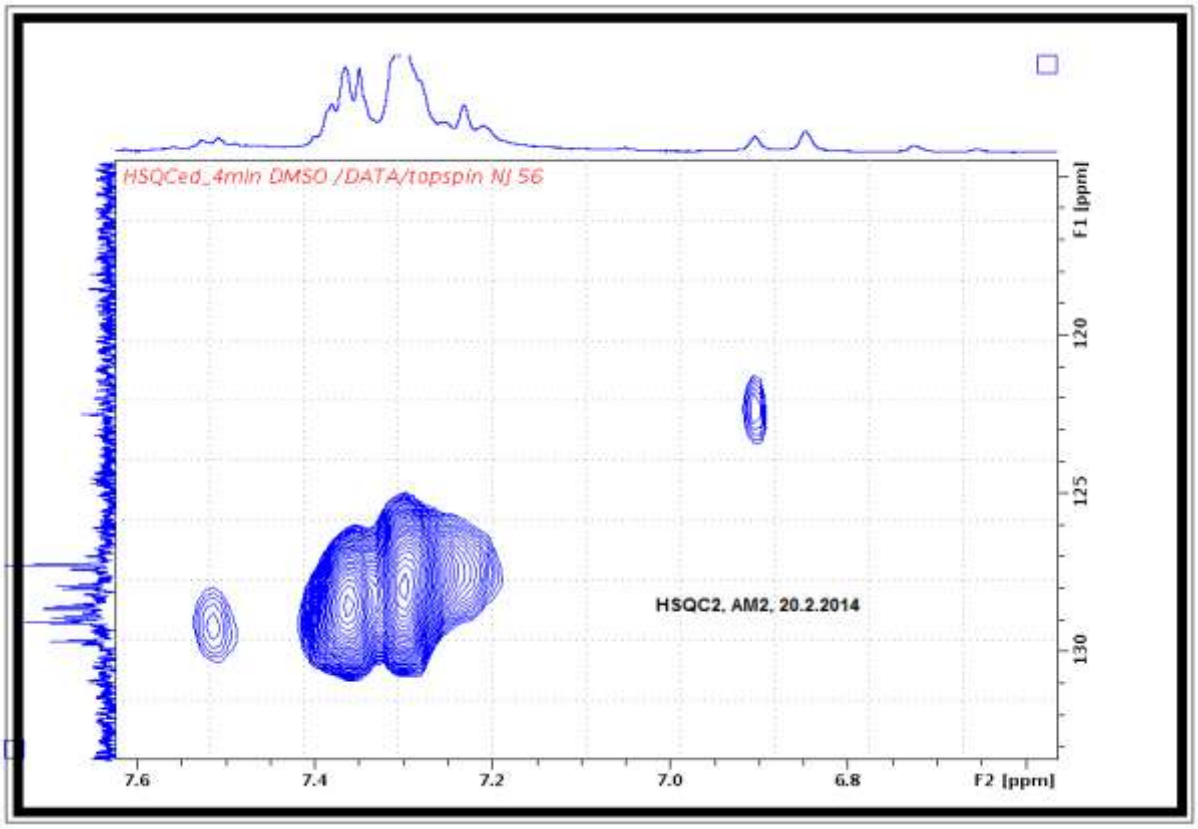


Form of CNMR (4a)



Form of CNMR (4a)

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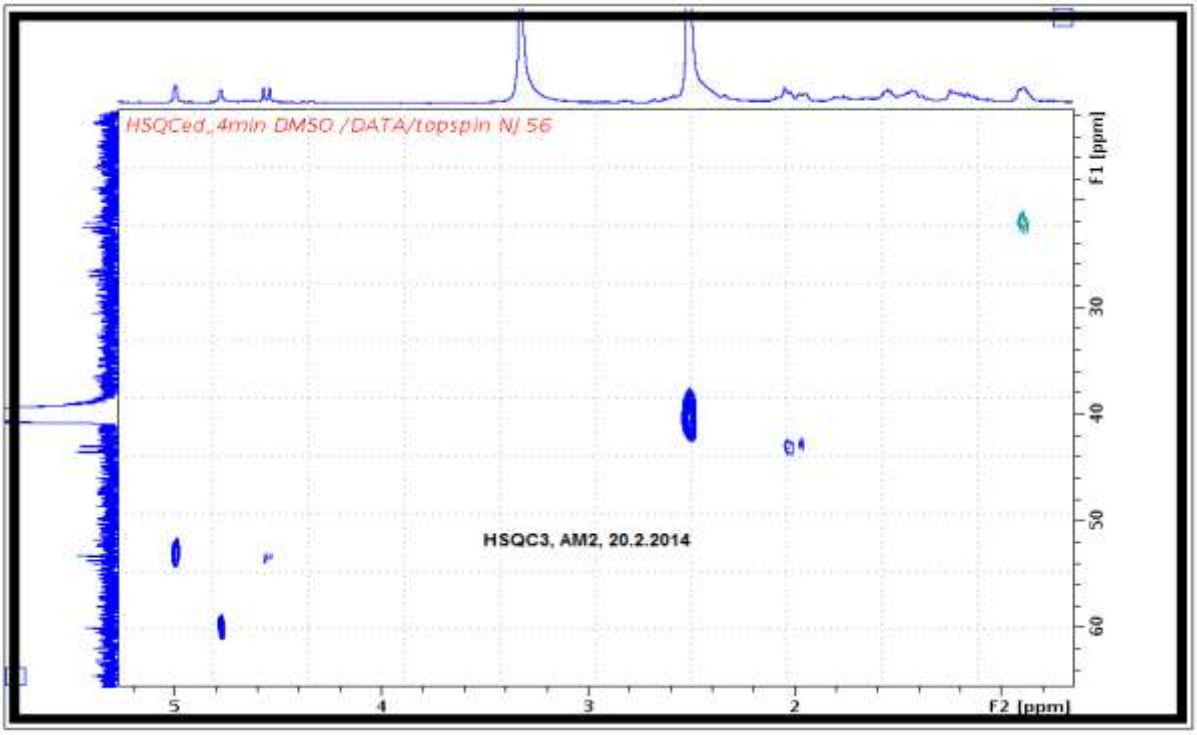
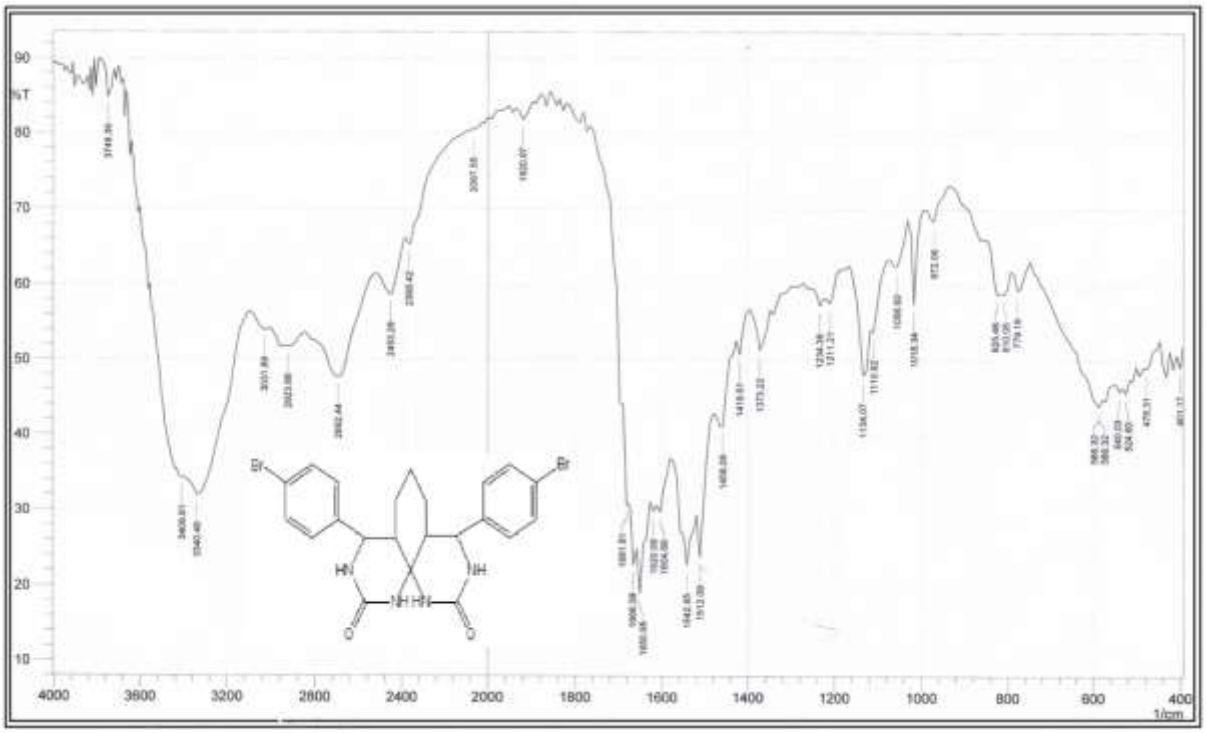
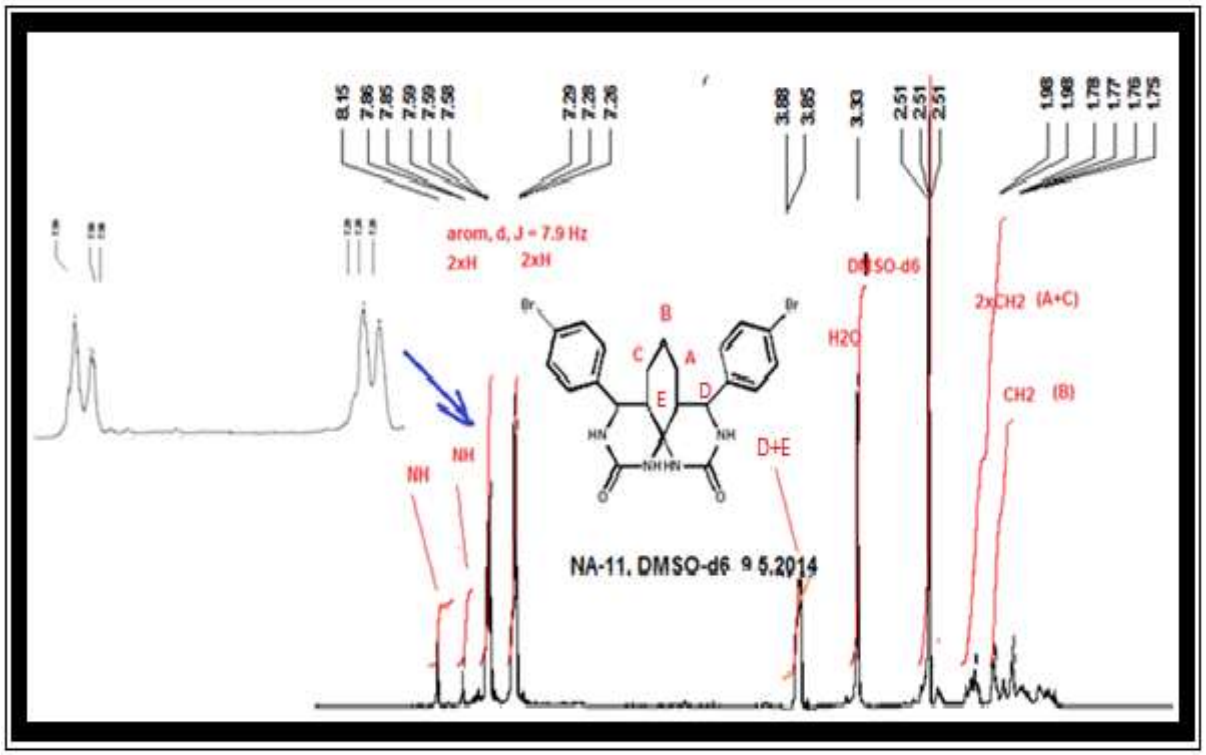
HSQC2, AM2, 20.2.2014
F1 [ppm]
120
125
130
7.6
7.4
7.2
7.0
6.8
F2 [ppm]

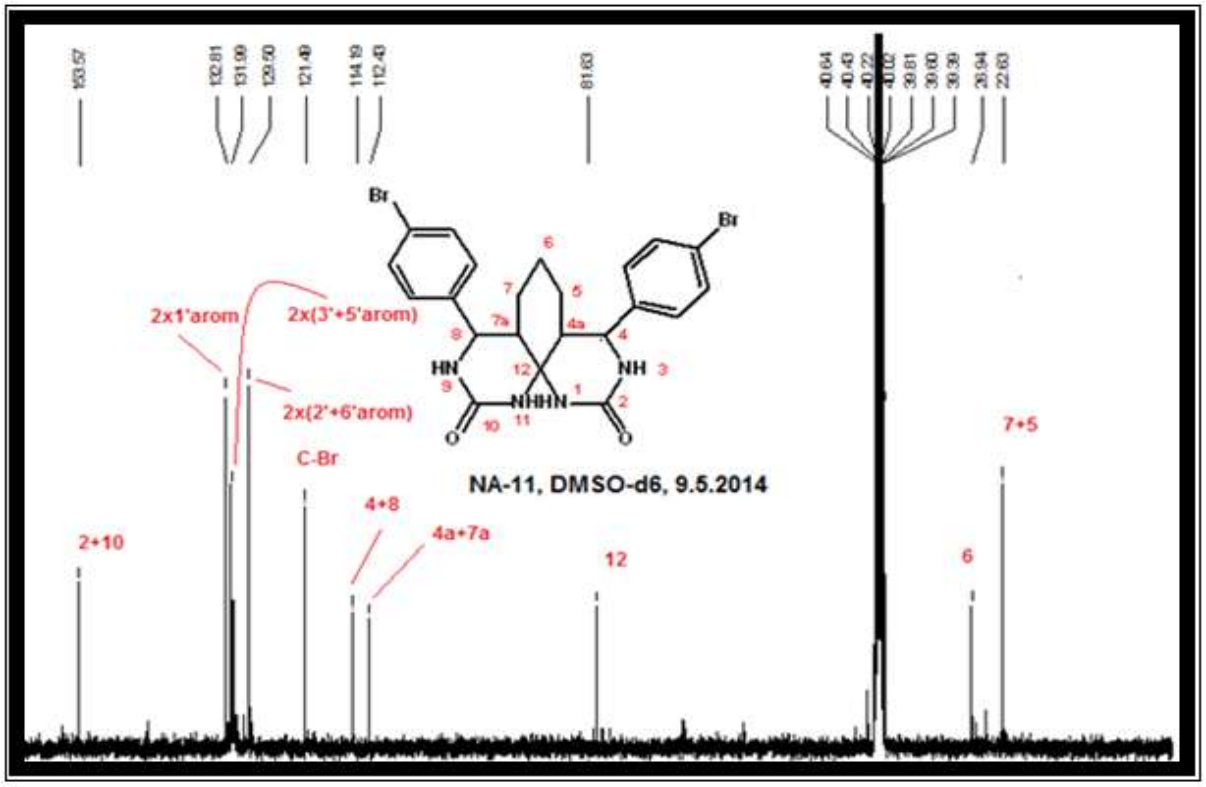

HSQCed_4min DMSO /DATA/topspin NJ 56
HSQC3, AM2, 20.2.2014
F1 [ppm]
30
40
50
60
5
4
3
2
F2 [ppm]


%T
1/cm

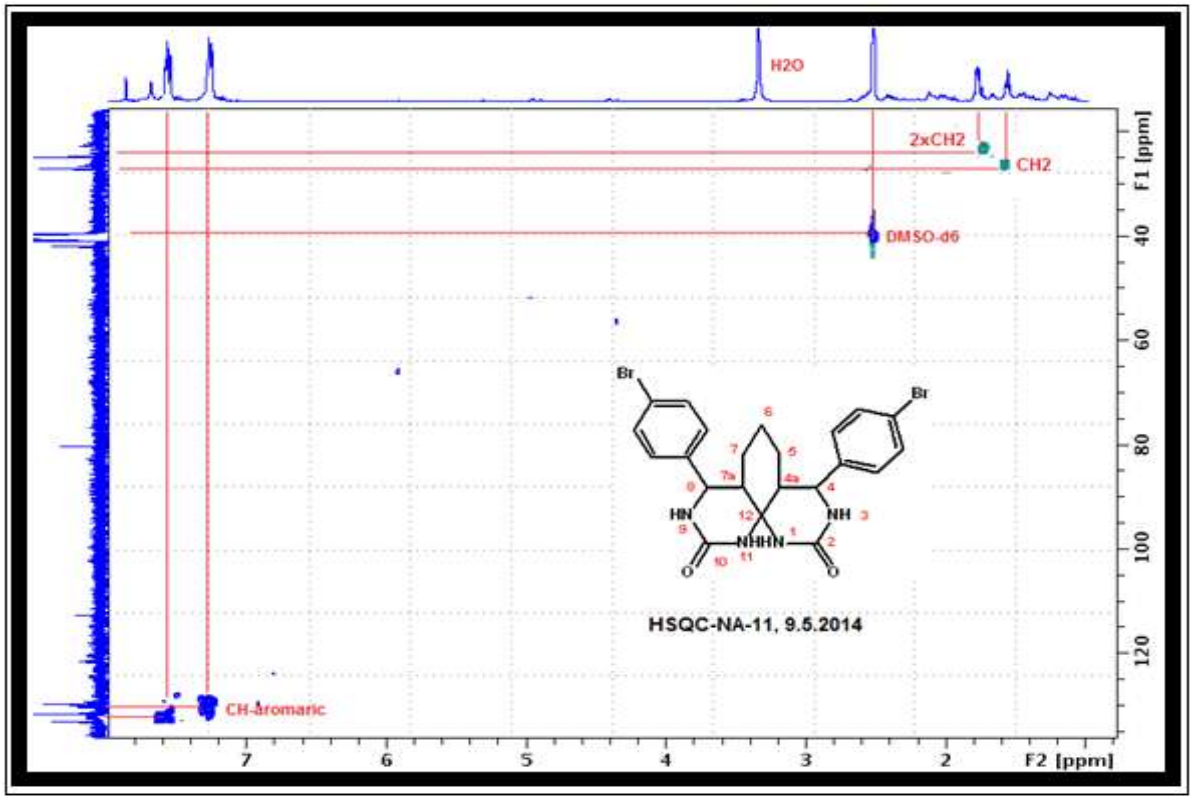
Form of IR (4B)

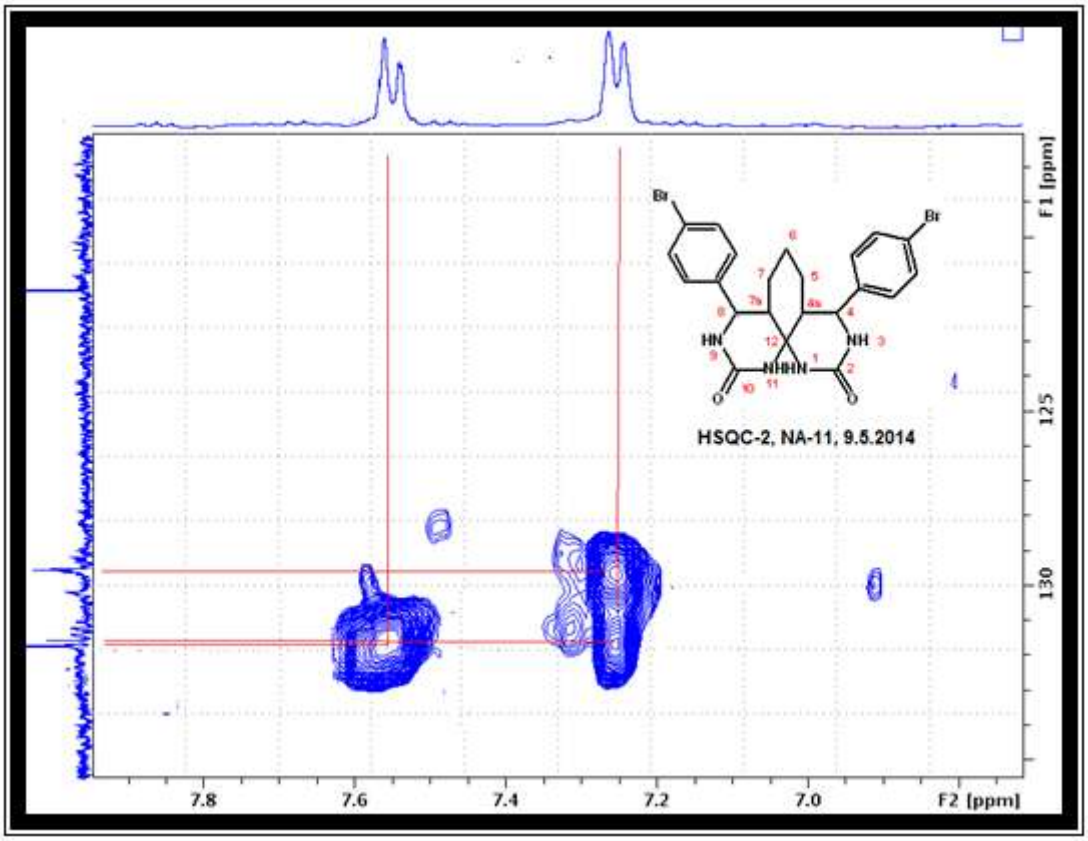

8.15
7.86
7.85
7.59
7.59
7.58
7.29
7.28
7.26
3.88
3.85
3.33
2.51
2.51
2.51
1.98
1.98
1.78
1.77
1.76
1.75
arom, d, J = 7.9 Hz
2xH
2xH
DMSO-d6
H2O
2xCH2 (A+C)
CH2 (B)
NH
NH
D+E
NA-11. DMSO-d6 9 5.2014

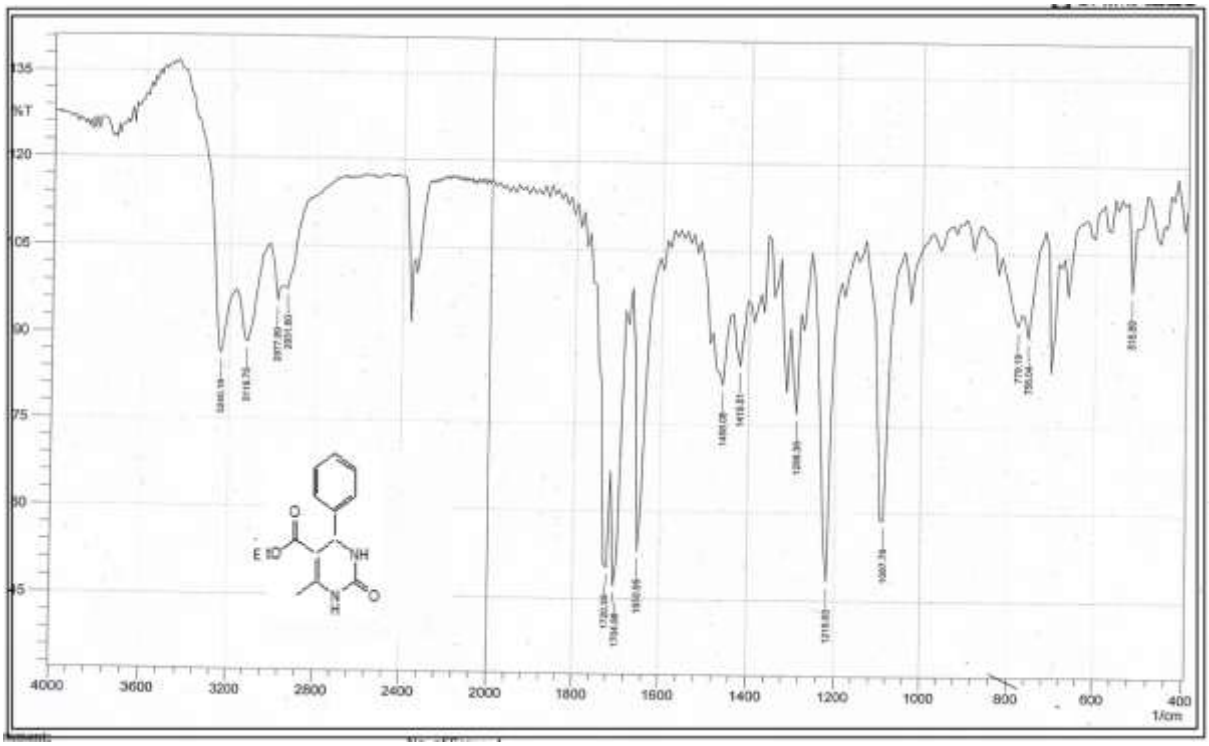
Form of HNMR (4B)



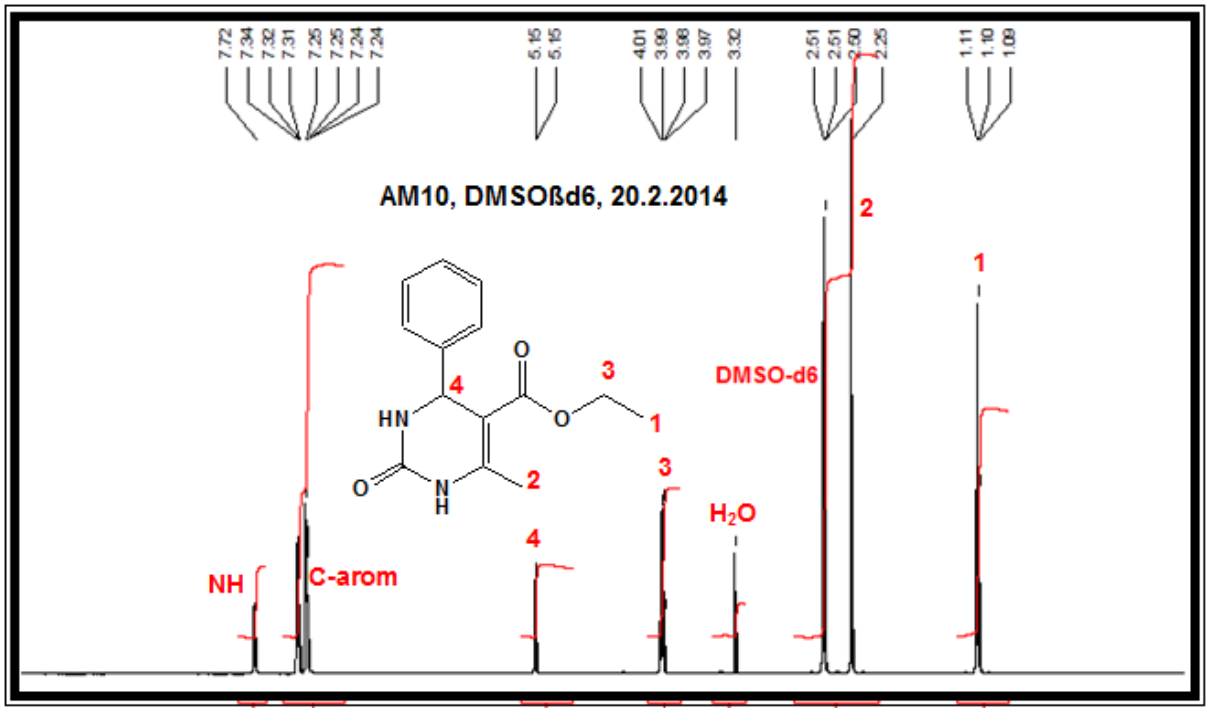
Form of CNMR (4B)



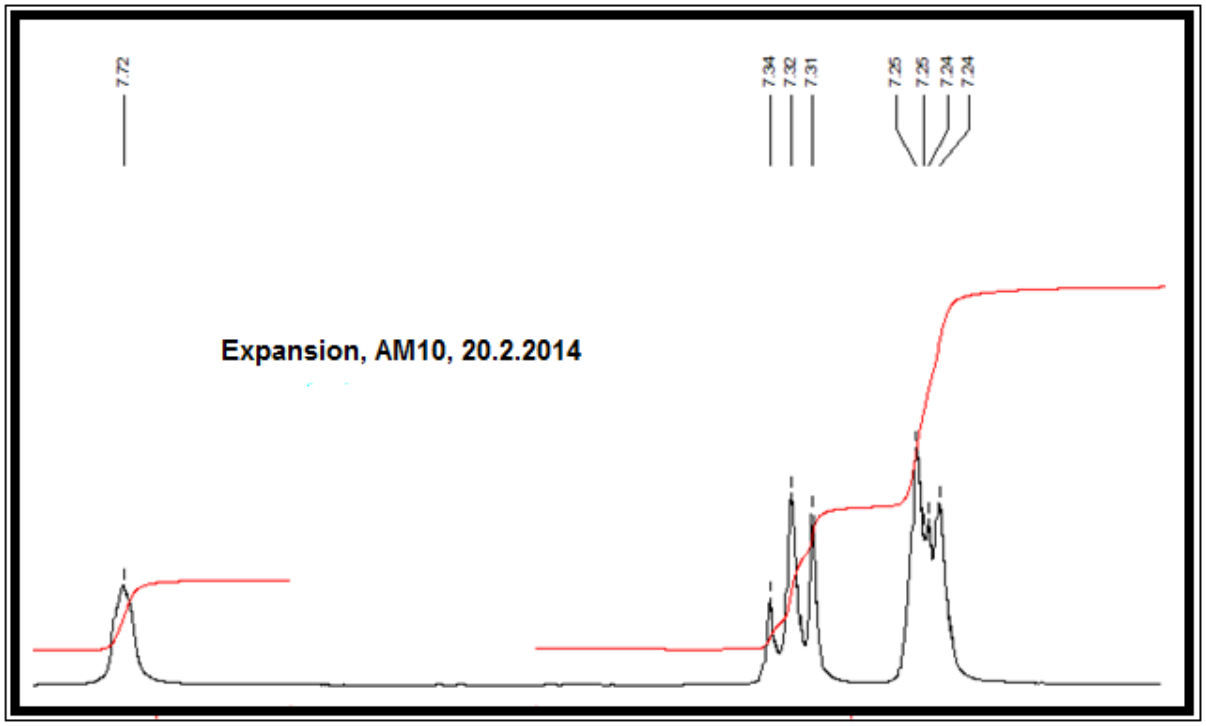

HSQC-2, NA-11, 9.5.2014
F1 [ppm]
F2 [ppm]
7.8
7.6
7.4
7.2
7.0
125
130


%T
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
1/cm

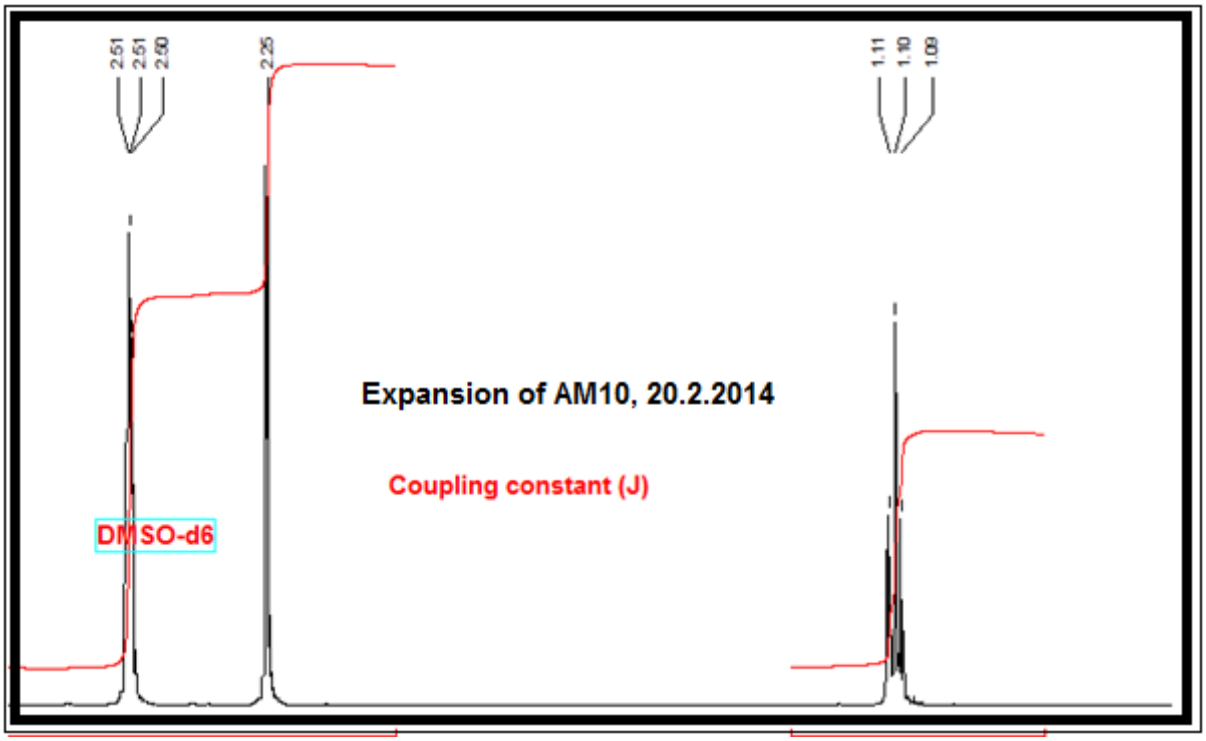
Form of iR (4a)

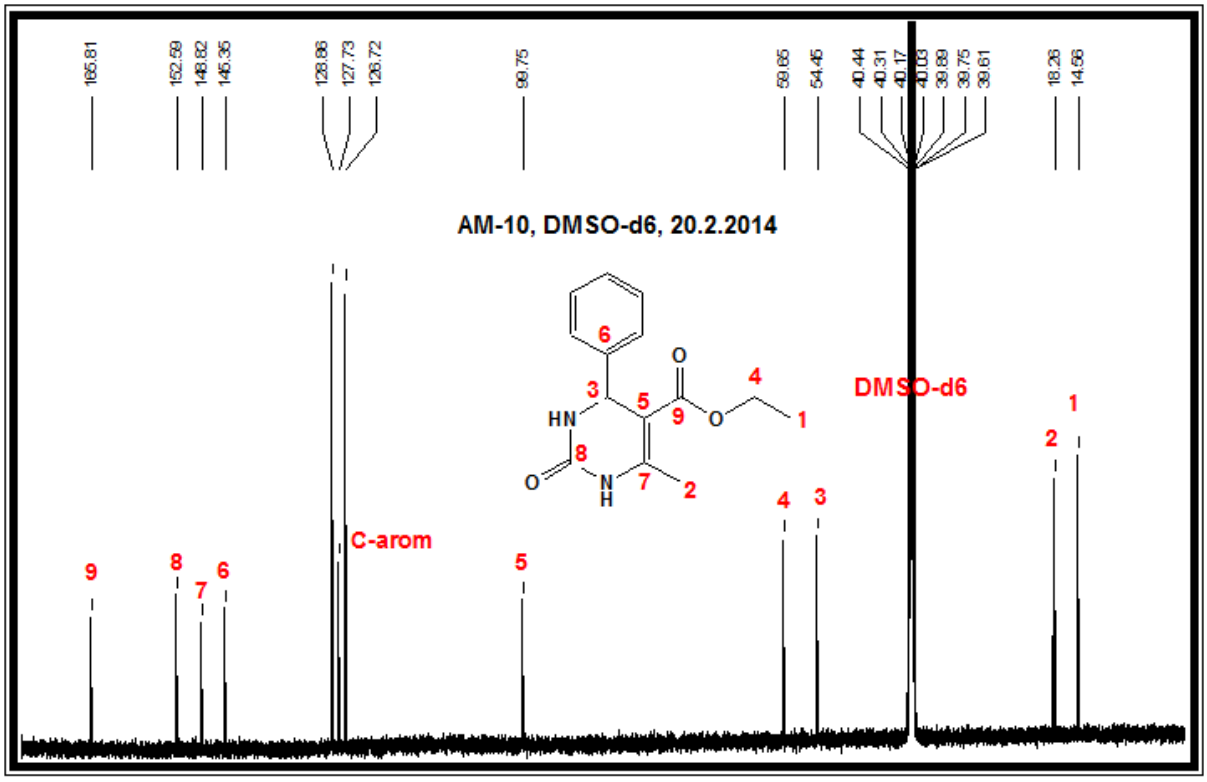


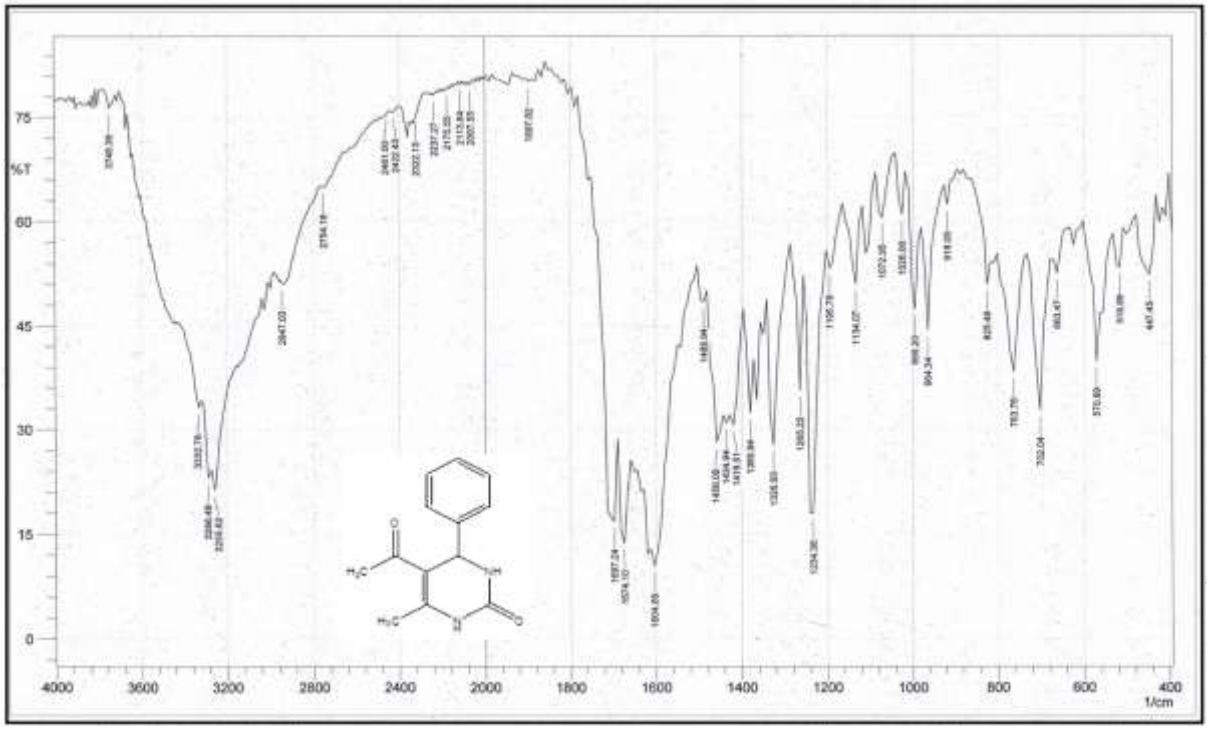
Form of HNMR (4a)



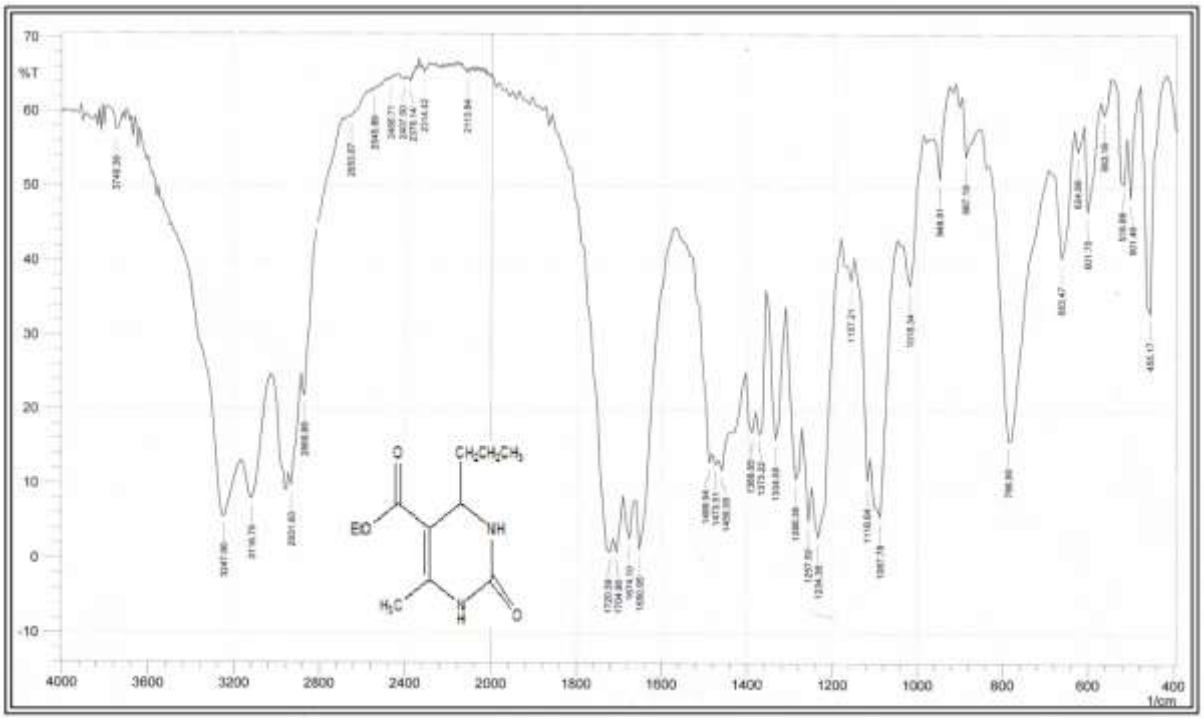
10


2.51
2.51
2.50
2.25
1.11
1.10
1.09
Expansion of AM10, 20.2.2014
Coupling constant (J)
DMSO-d6


165.81
152.59
148.82
145.35
128.86
127.73
126.72
99.75
59.65
54.45
40.44
40.31
40.17
40.03
39.89
39.75
39.61
18.26
14.56
AM-10, DMSO-d6, 20.2.2014
DMSO-d6
C-arom
9
8
7
6
5
4
3
2
1



Form of IR (6a)



Form of IR (6a)

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