Scope and Limitations of γ-Valerolactone (GVL) as a Green Solvent to be Used with Base for Fmoc Removal in Solid Phase Peptide Synthesis

Ashish Kumar [1,2], Anamika Sharma [1,2], Beatriz G. de la Torre [2,* and Fernando Albericio [1,3,4,*]

[1] Peptide Science Laboratory, School of Chemistry and Physics, University of KwaZulu-Natal, Durban 4001, South Africa; ashishpy12@gmail.com (A.K.); anamika.aug14@gmail.com (A.S.)

[2] KwaZulu-Natal Research Innovation and Sequencing Platform (KRISP), School of Laboratory Medicine and Medical Sciences, College of Health Sciences, University of KwaZulu-Natal, Durban 4041, South Africa

[3] Department of Organic Chemistry, University of Barcelona, Martí i Franqués 1-11, Barcelona 08028, Spain

[4] CIBER-BBN, Networking Centre on Bioengineering, Biomaterials and Nanomedicine, Barcelona Science Park, Baldiri Reixac 10, Barcelona 08028, Spain

* Correspondence: garciadelatorreb@ukzn.ac.za (B.G.d.l.T.); Albericio@ukzn.ac.za (F.A.)

Figure 1. ^{1}H NMR of GVL

Figure 2. ^{13}C NMR of GVL

Figure 3. ^1H NMR of PIP

Figure 4. ^{13}C NMR of PIP
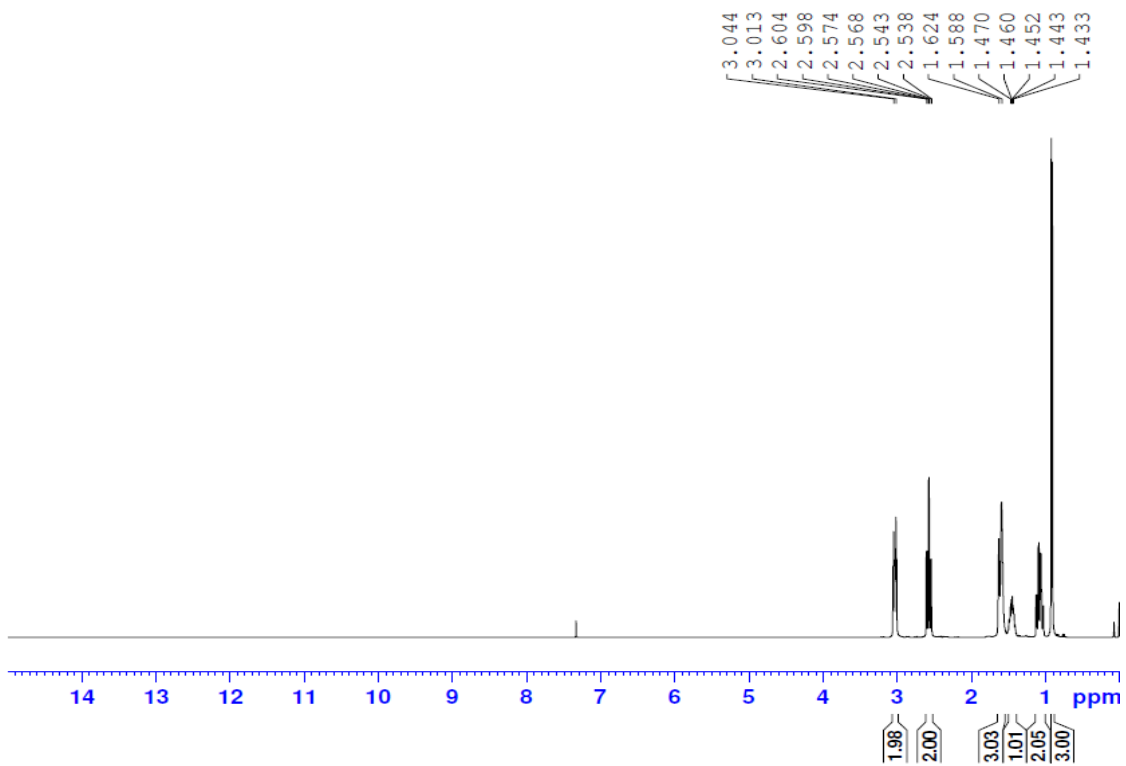
Figure 5. ^{1}H NMR of 4-MP
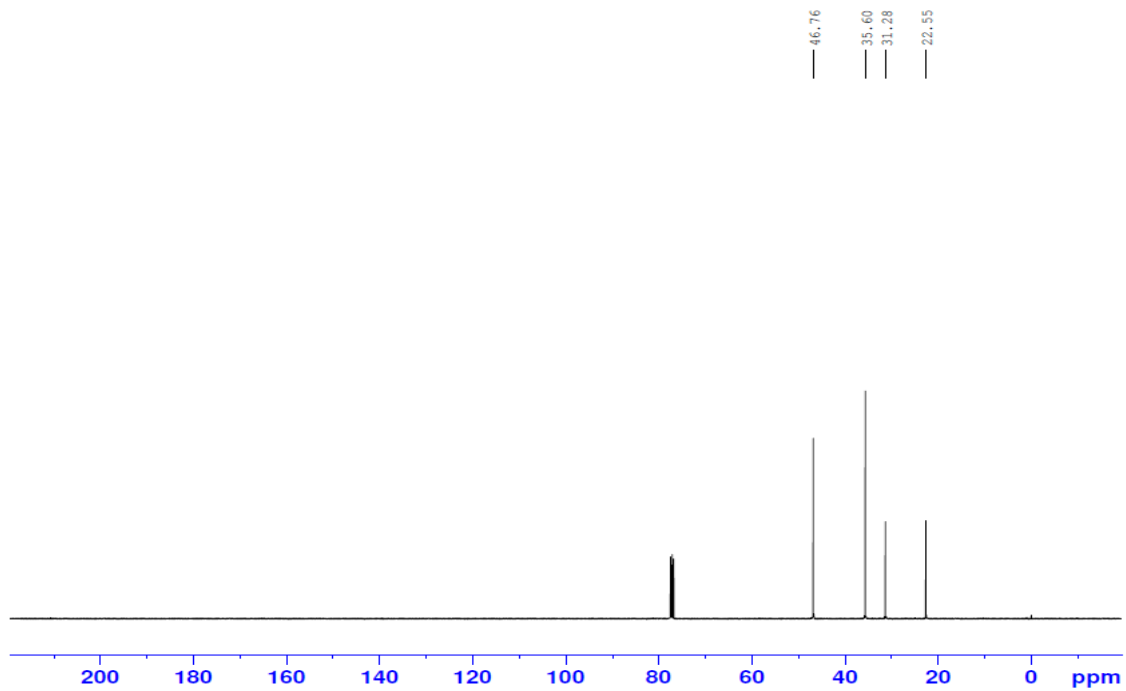
Figure 6.^{13}C NMR of 4-MP
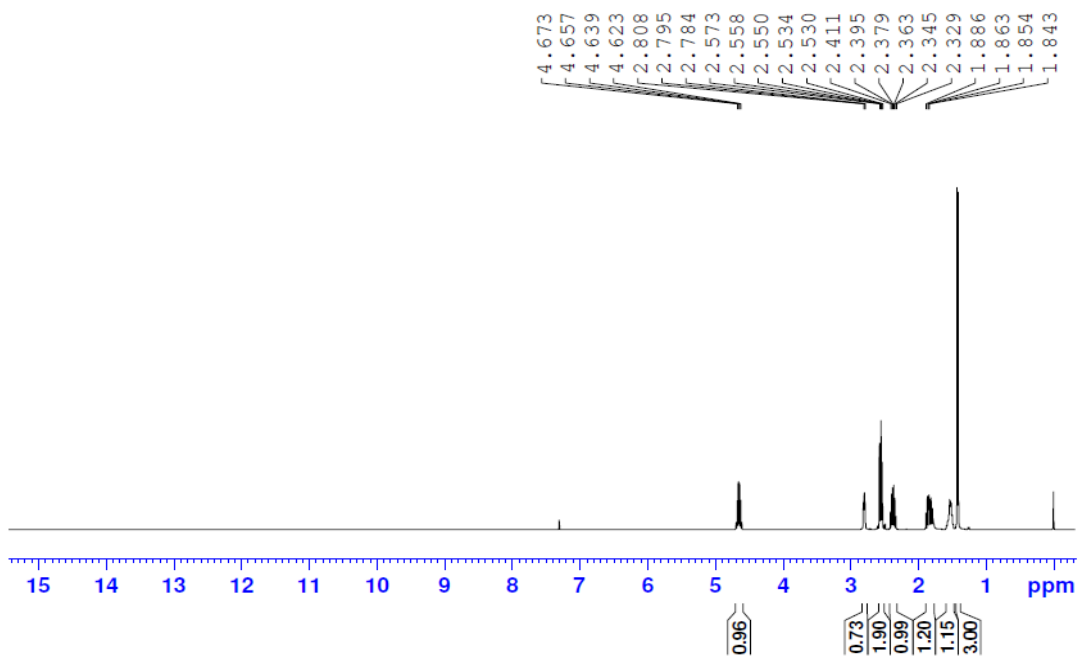
Figure 7.^{1}H NMR of 20% PIP in GVL at 0 min
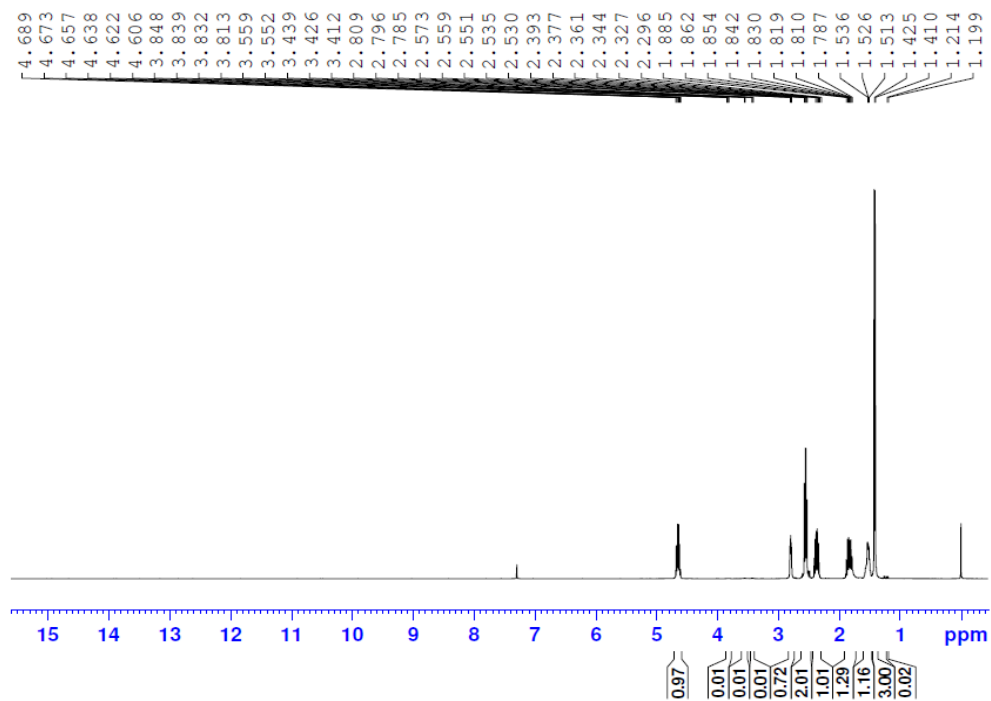
Figure 8. ^{1}H NMR of 20% PIP in GVL after 2 h
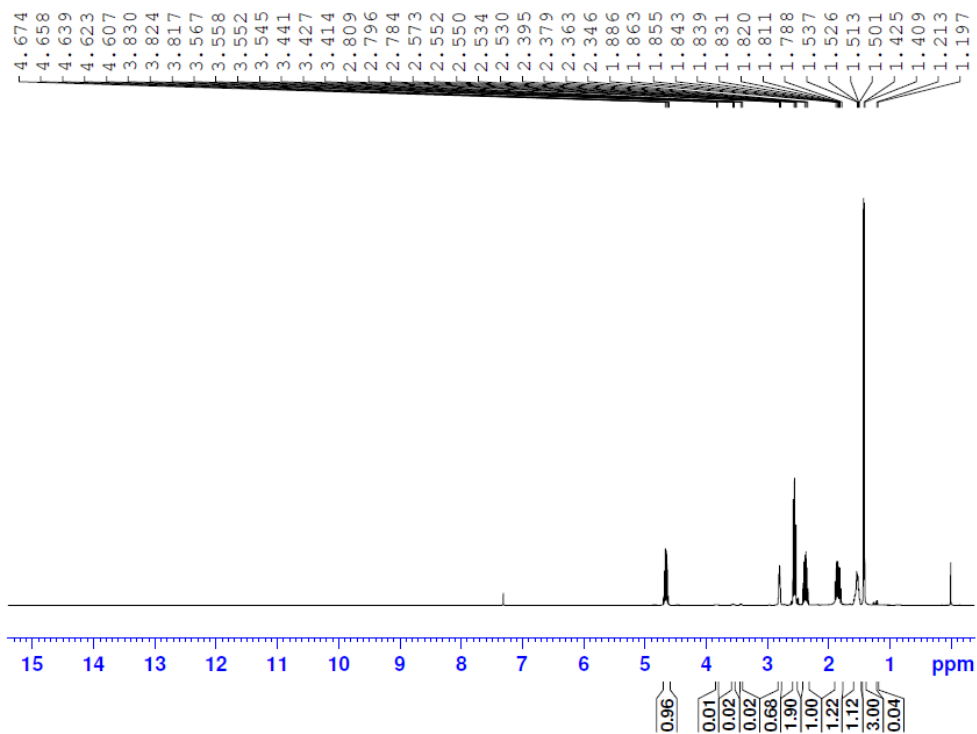
Figure 9. ^{1}H NMR of 20% PIP in GVL after 4 h
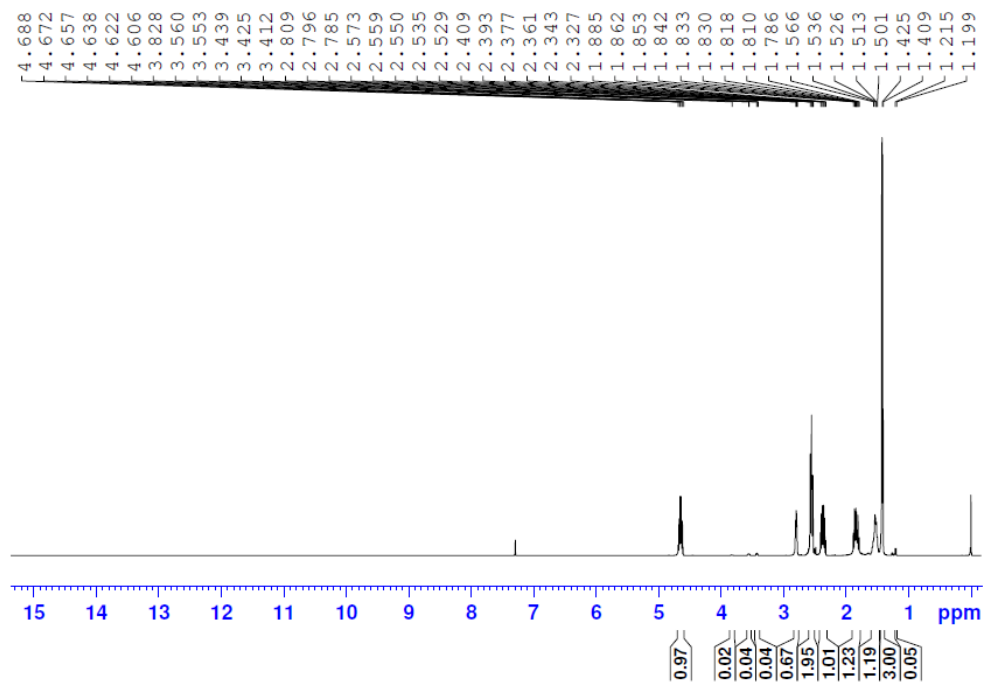
Figure 10. ^{1}H NMR of 20% PIP in GVL after 6 h
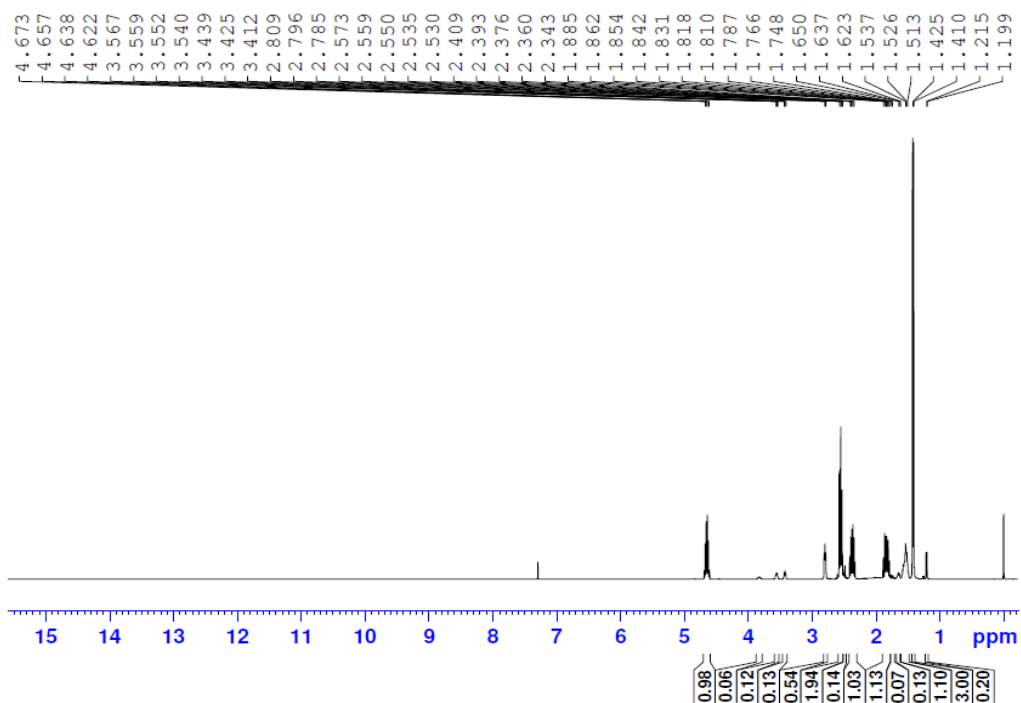
Figure 11. ^{1}H NMR of 20% PIP in GVL after 24 h
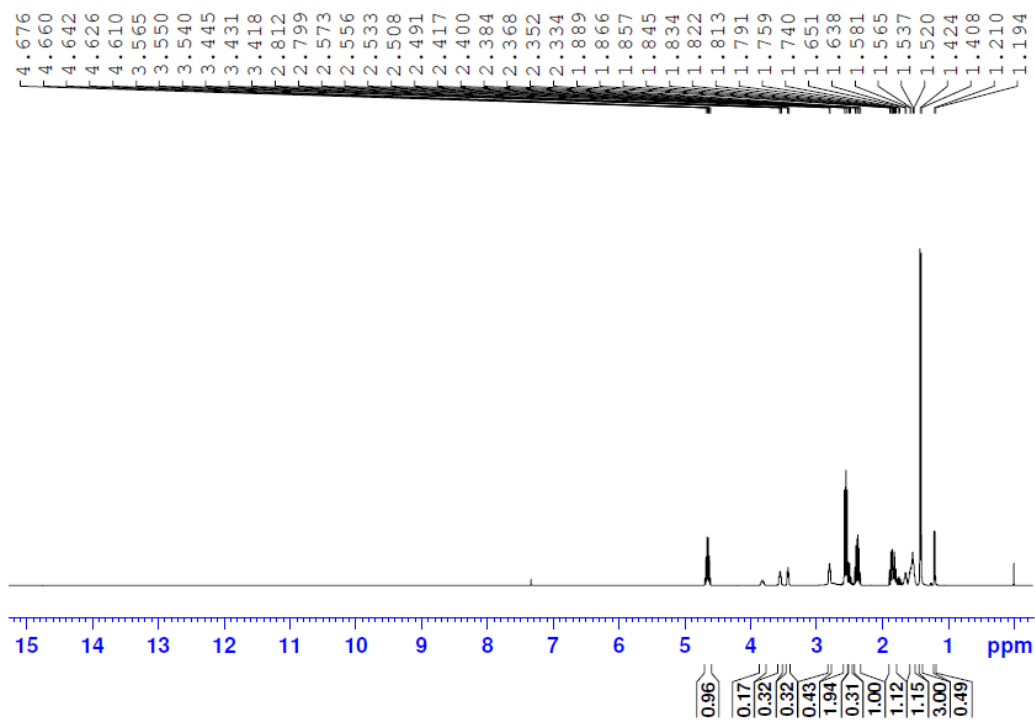
Figure 12. ^{1}H NMR of 20% PIP in GVL after 48 h
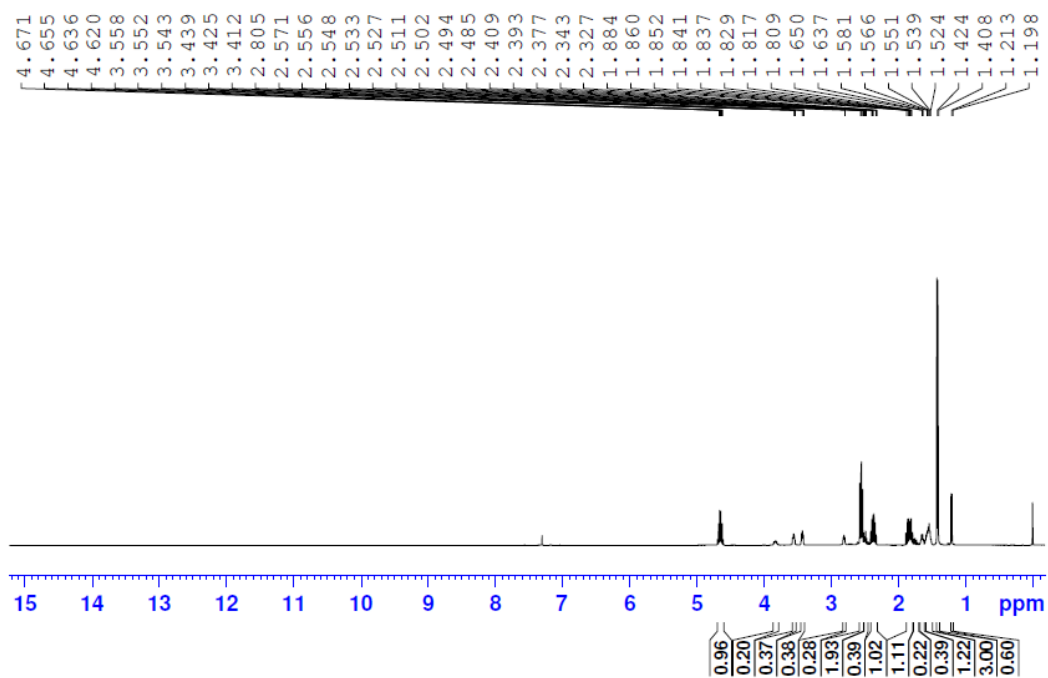
Figure 13. ^{1}H NMR of 20% PIP in GVL after 72 h
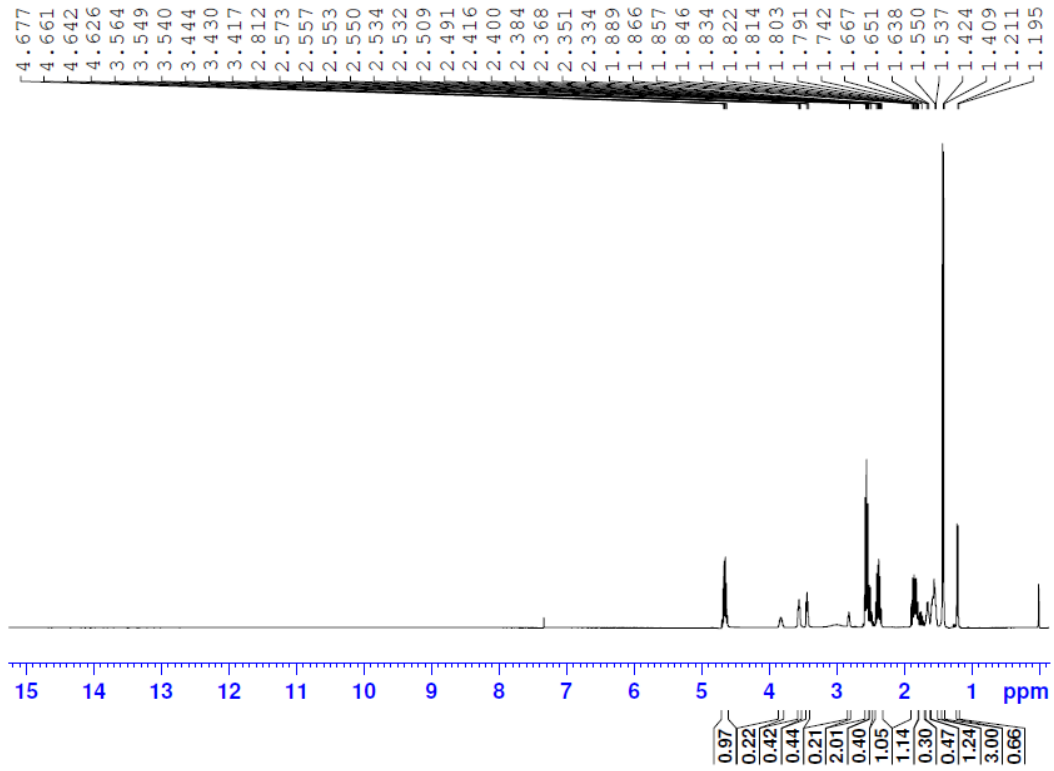
Figure 14. ^{1}H NMR of 20% PIP in GVL after 96 h
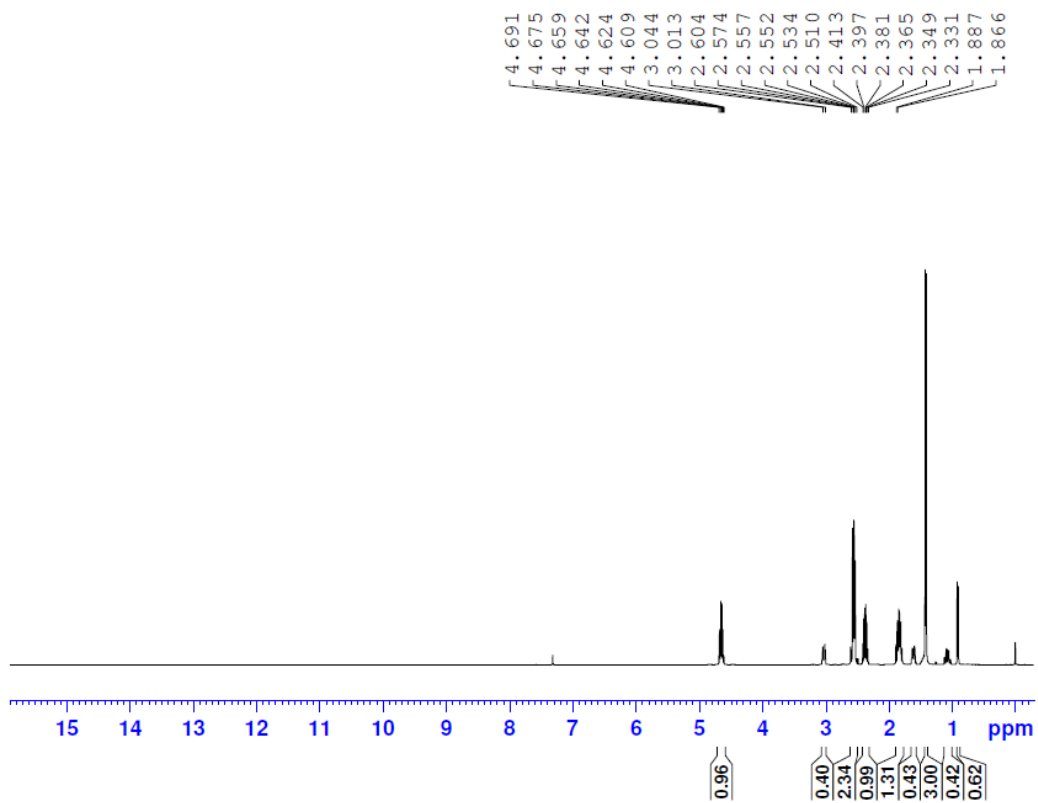
Figure 15. ^{1}H NMR of 20% 4-MP in GVL at 0 min
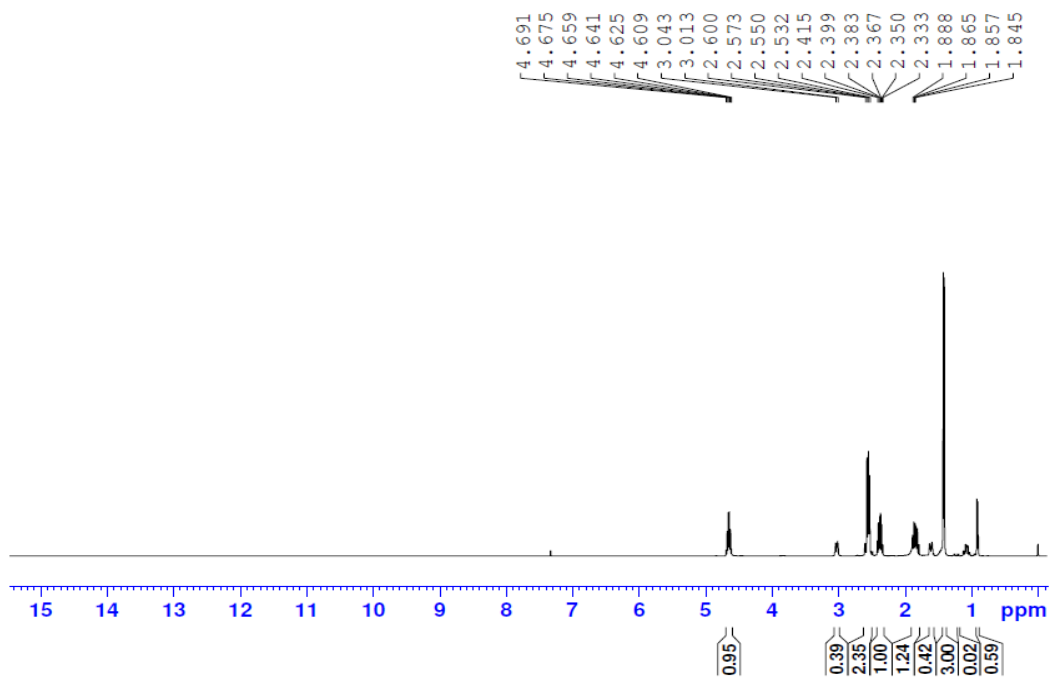
Figure 16.[^1]H NMR of 20% 4-MP in GVL after 2 h
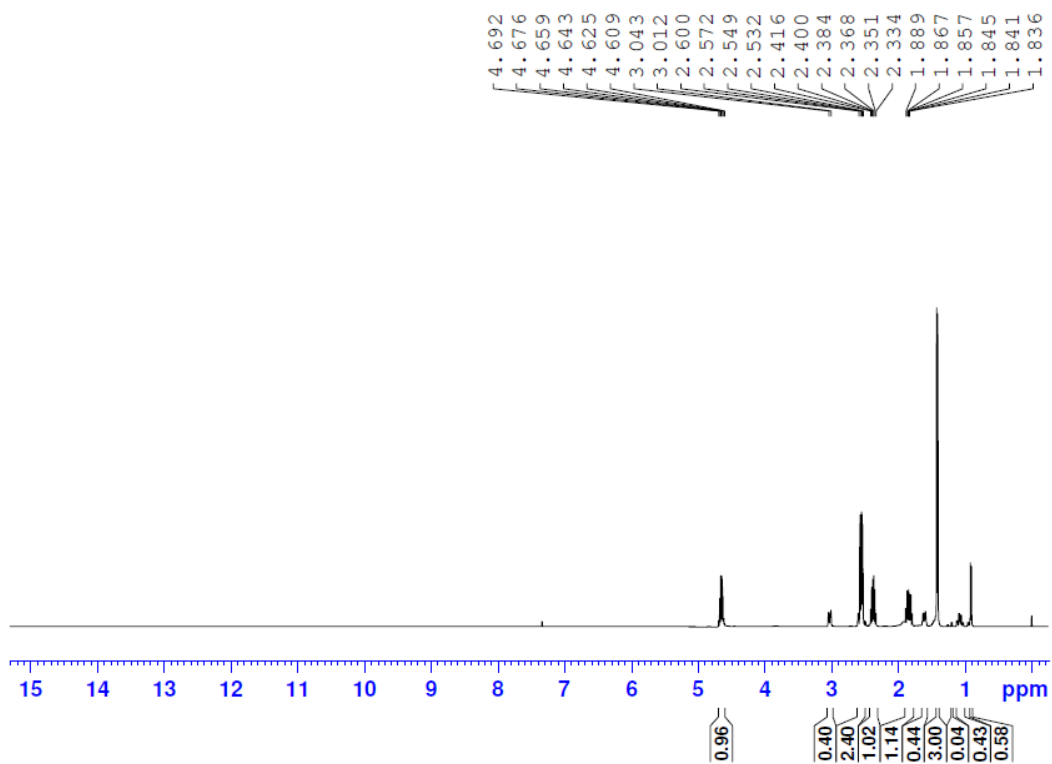
Figure 17.[^1]H NMR of 20% 4-MP in GVL after 4 h
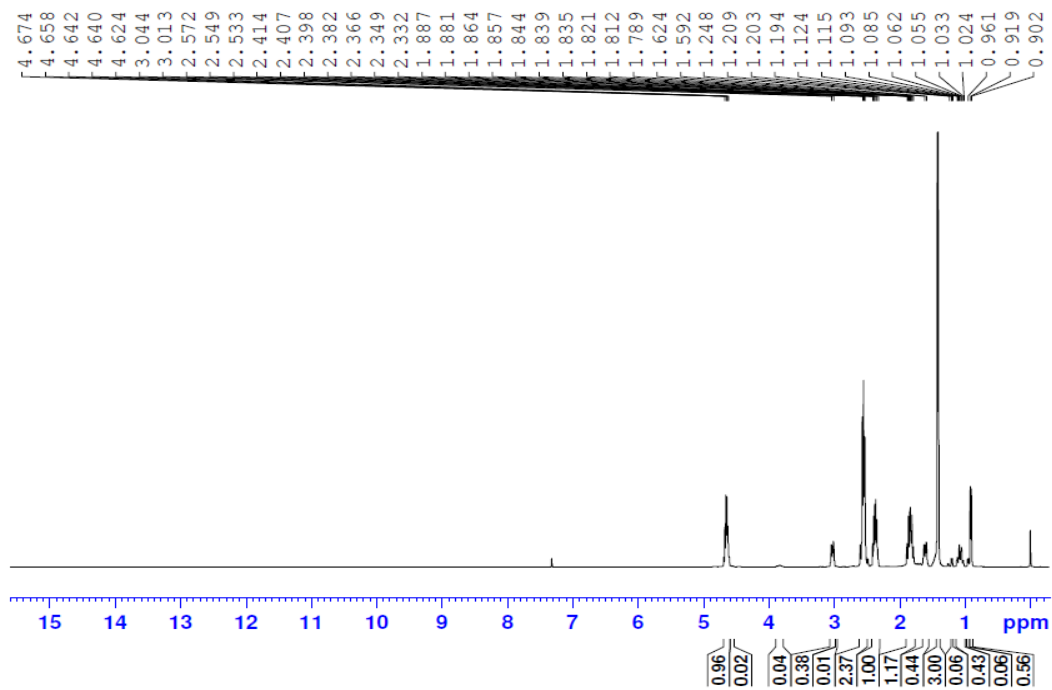
Figure 18. ^{1}H NMR of 20% 4-MP in GVL after 6 h
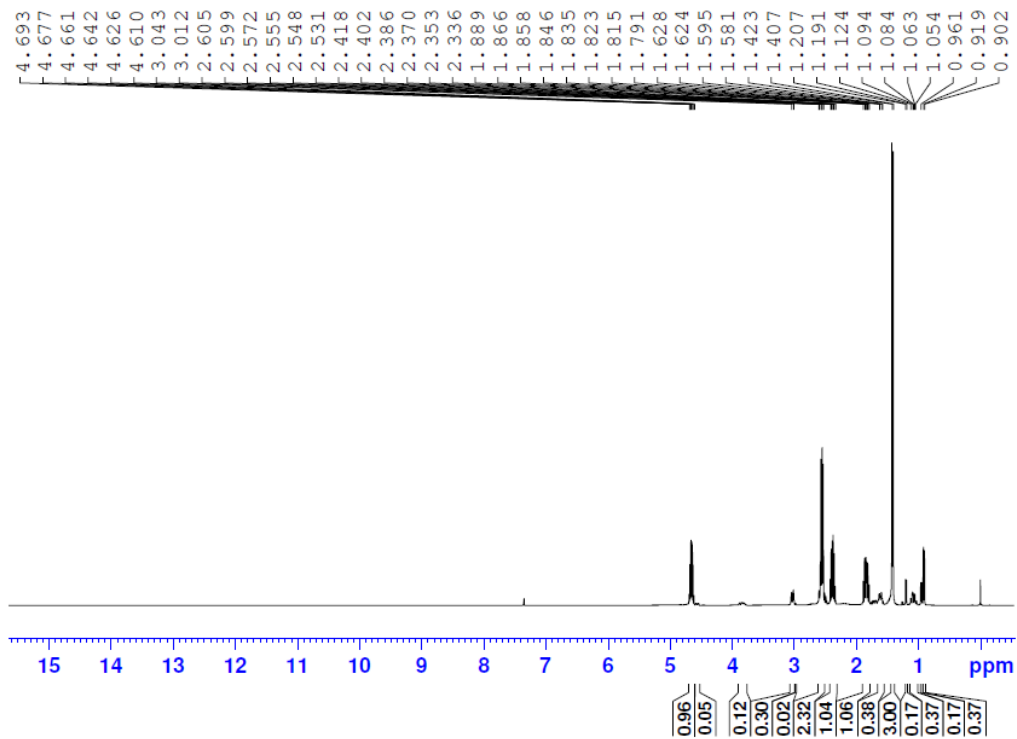
Figure 19. ^{1}H NMR of 20% 4-MP in GVL after 24 h
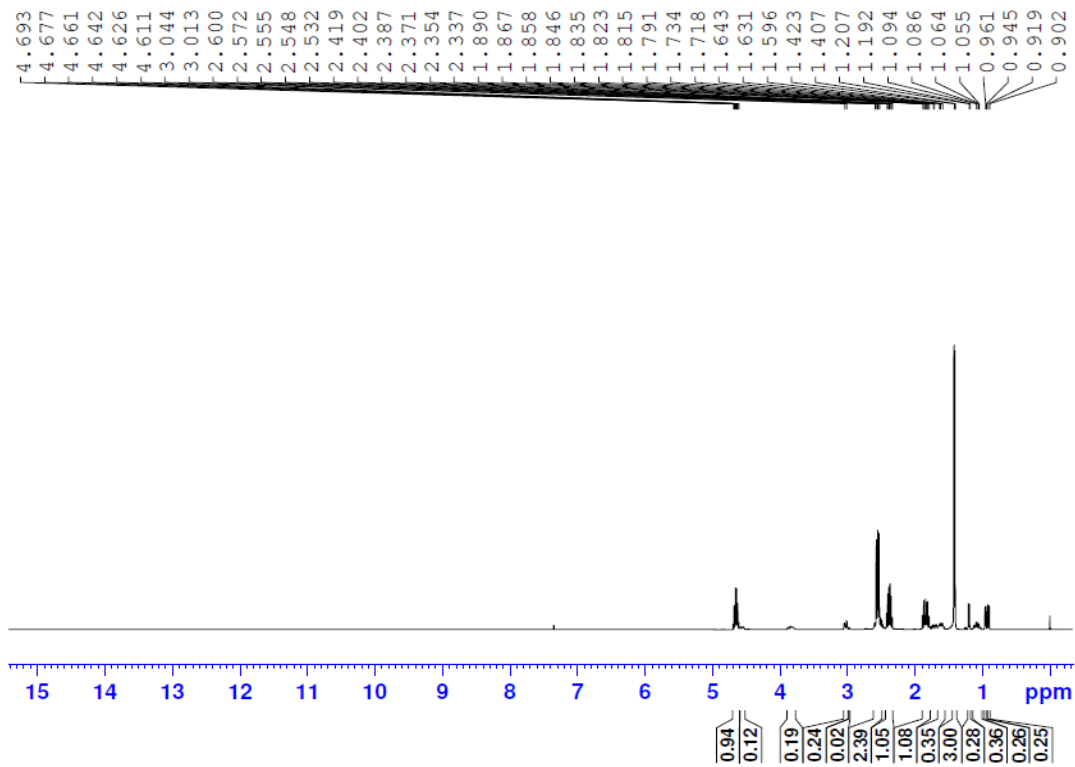
Figure 20. [^1]H NMR of 20% 4-MP in GVL after 48 h
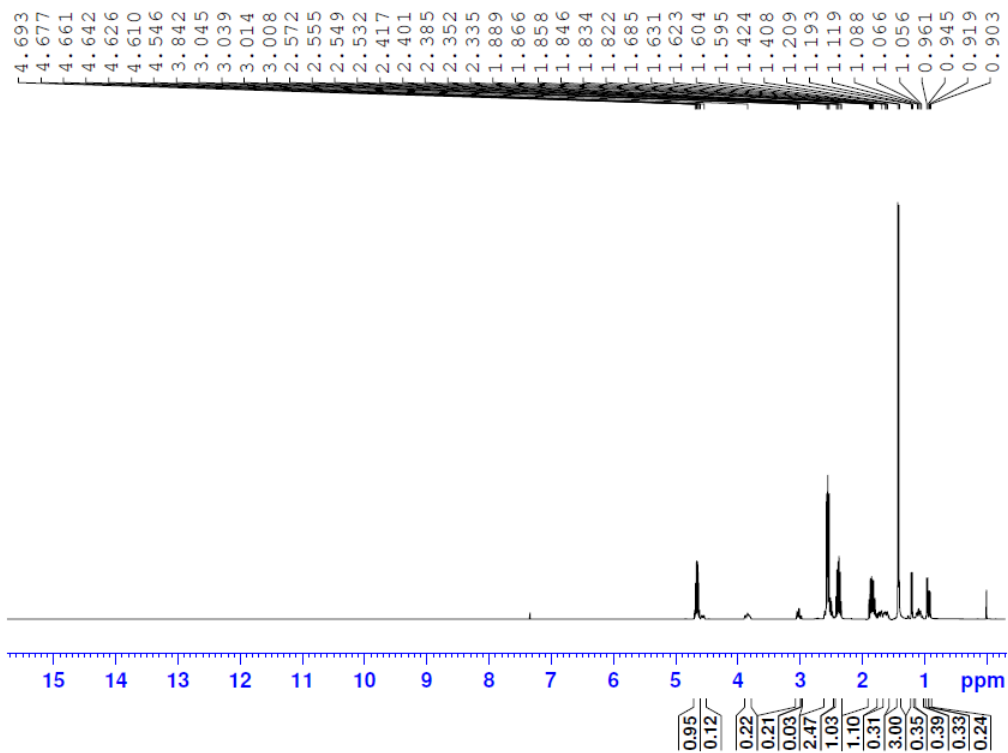
Figure 21. [^1]H NMR of 20% 4-MP in GVL after 72 h
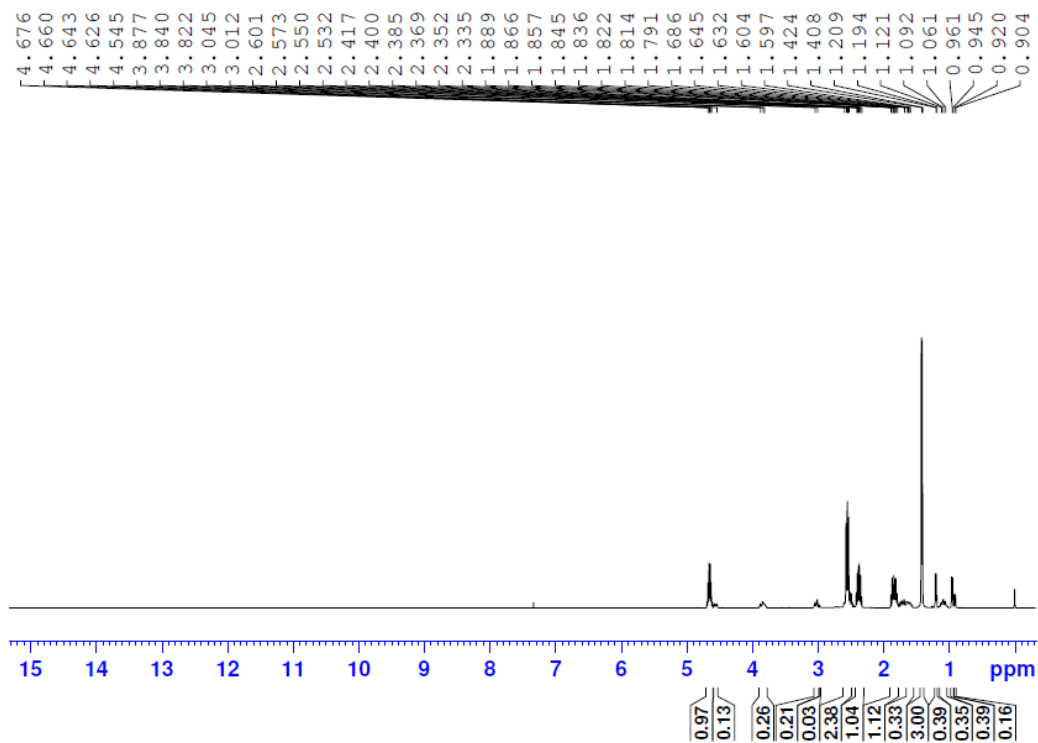
Figure 22.^{1}H NMR of 20% 4-MP in GVL after 96h
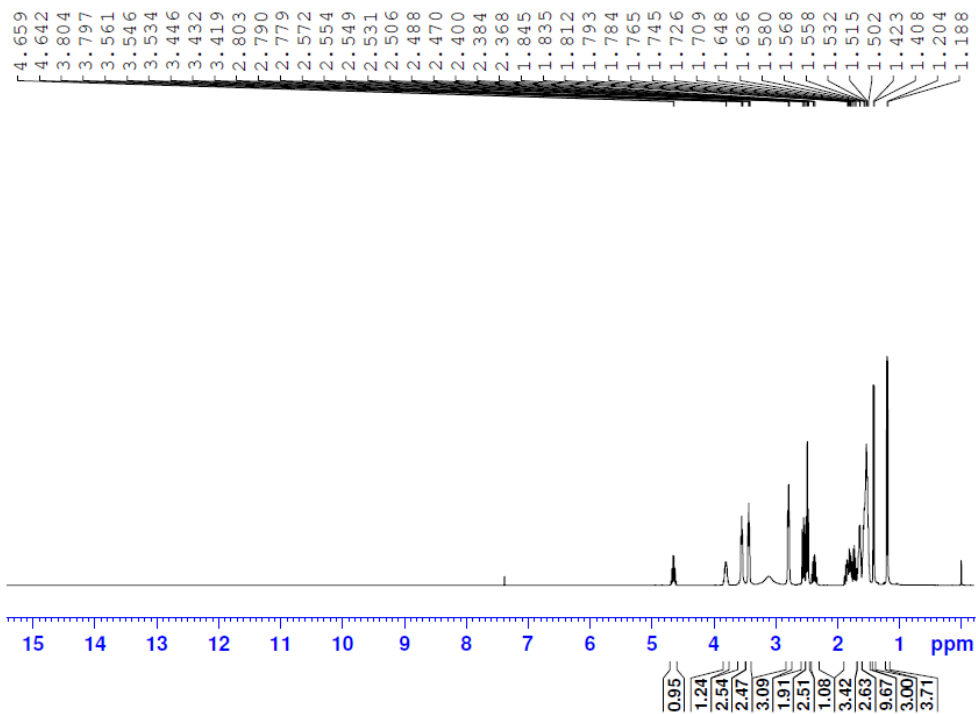
Figure 23.^{1}H NMR of equimolar solution of GVL and PIP after 1h MW at 90 °C
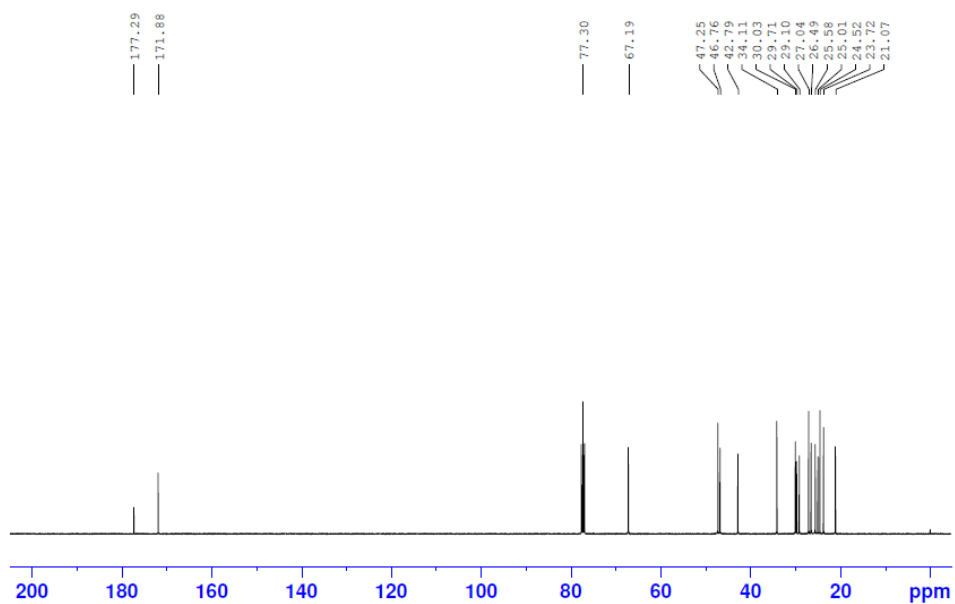
Figure 24. ^{13}C NMR of equimolar solution of GVL and PIP after 1h MW at 90 °C
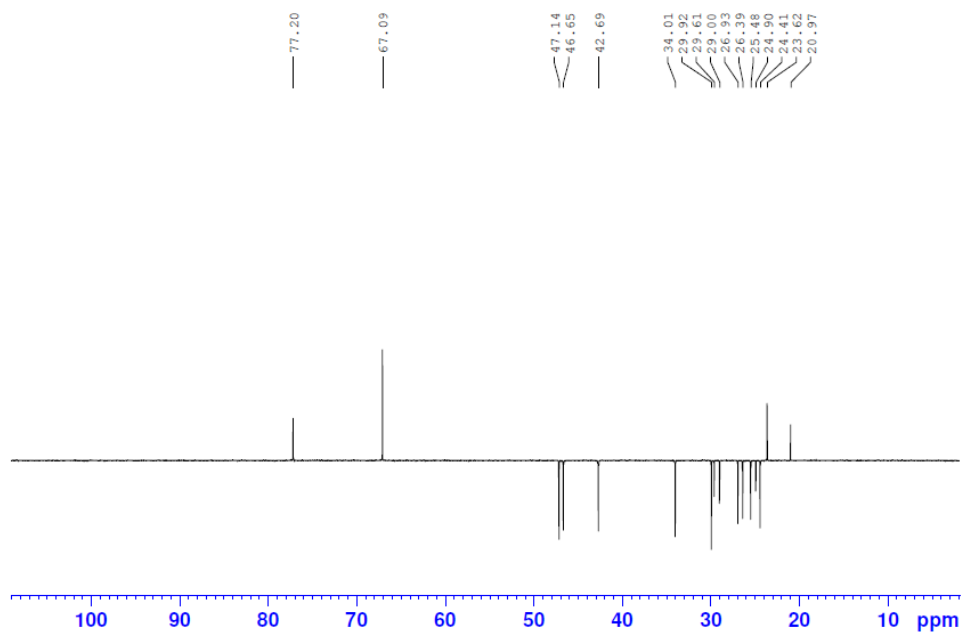
Figure 25. DEPT 135 NMR of equimolar solution of GVL and PIP after 1h MW at 90 °C
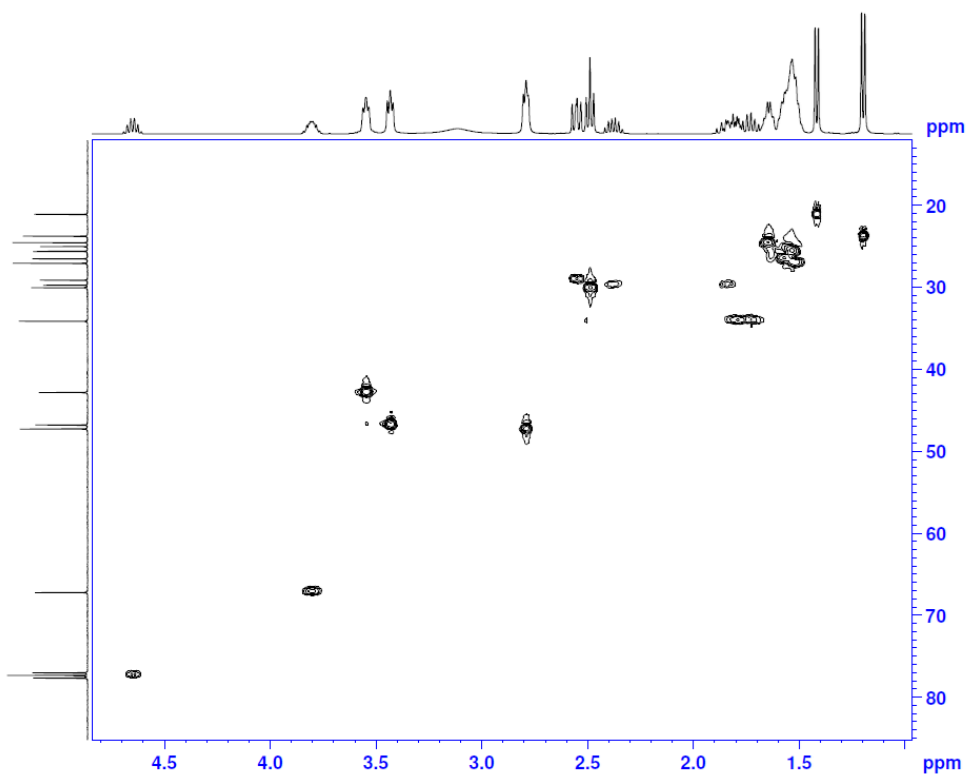
Figure 26. HSQC of equimolar solution of GVL and PIP after 1h MW at 90 °C
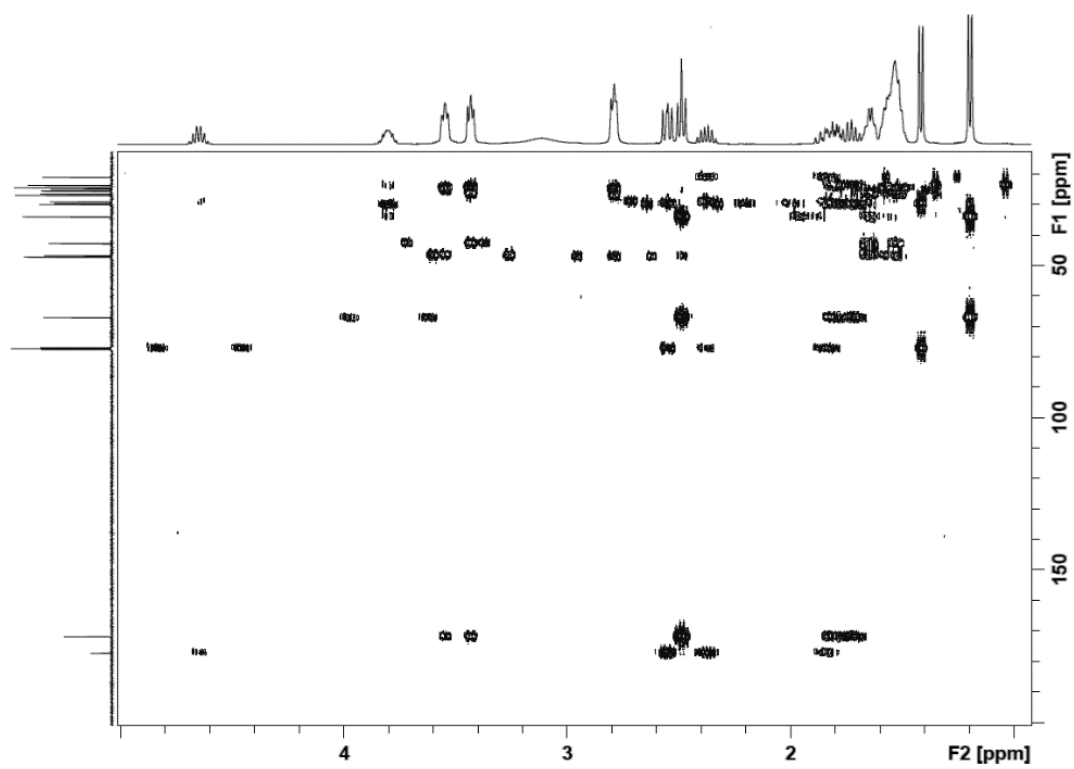
Figure 27. HMBC of equimolar solution of GVL and PIP after 1h MW at 90 ℃

1;1pIP;GVL,MW90-1h
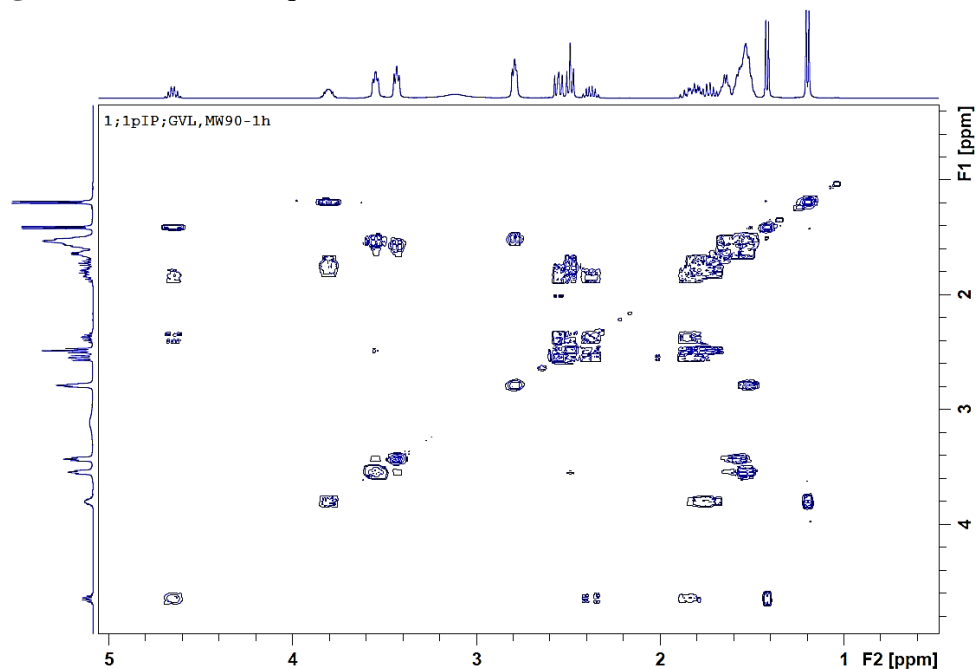
Figure 28. COSY of equimolar solution of GVL and PIP after 1h MW at 90 ℃
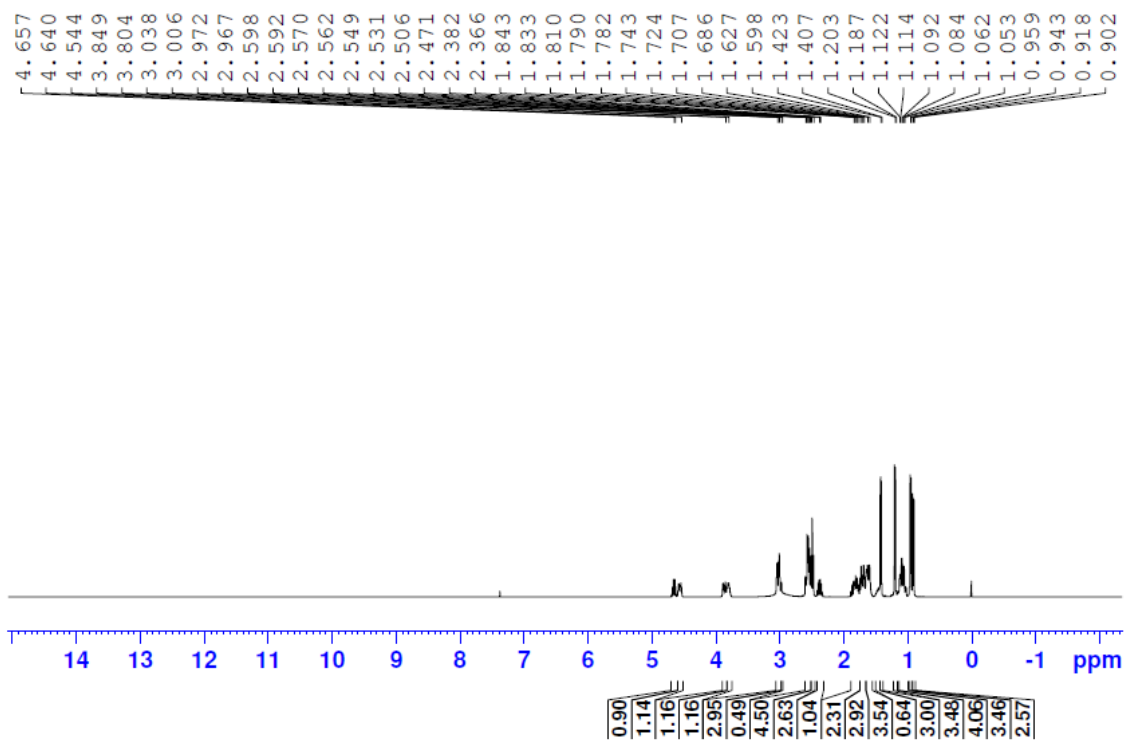
Figure 29. ¹H NMR of equimolar solution of GVL and 4-MP after 1h MW at 90 ℃
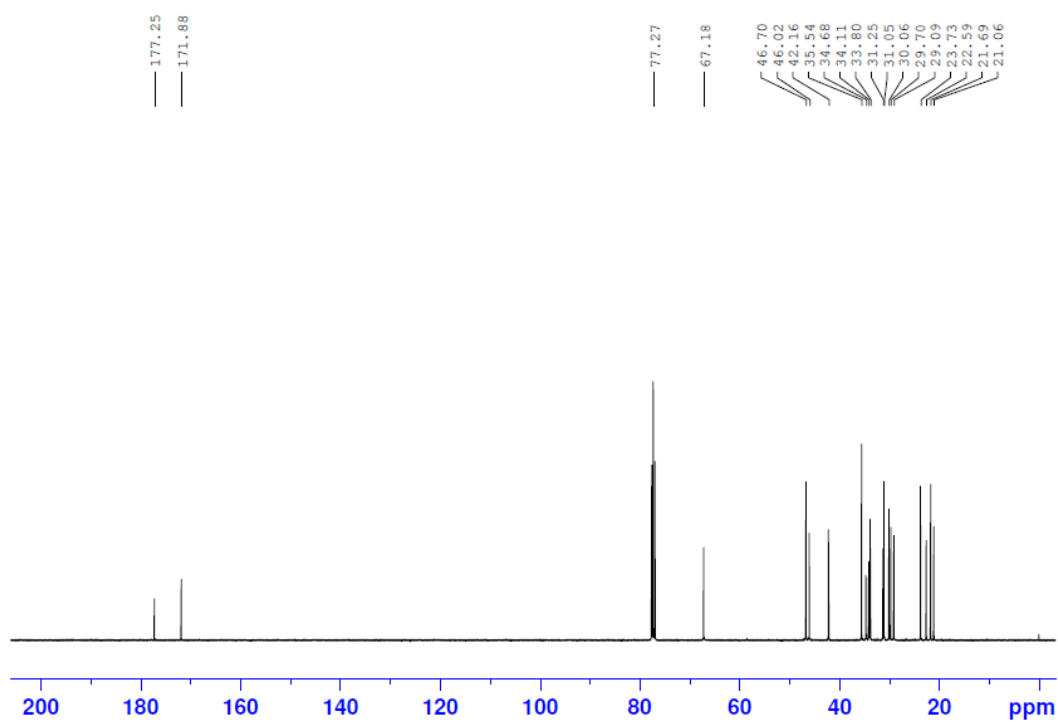
Figure 30. ¹³C NMR of equimolar solution of GVL and 4-MP after 1h MW at 90 ℃
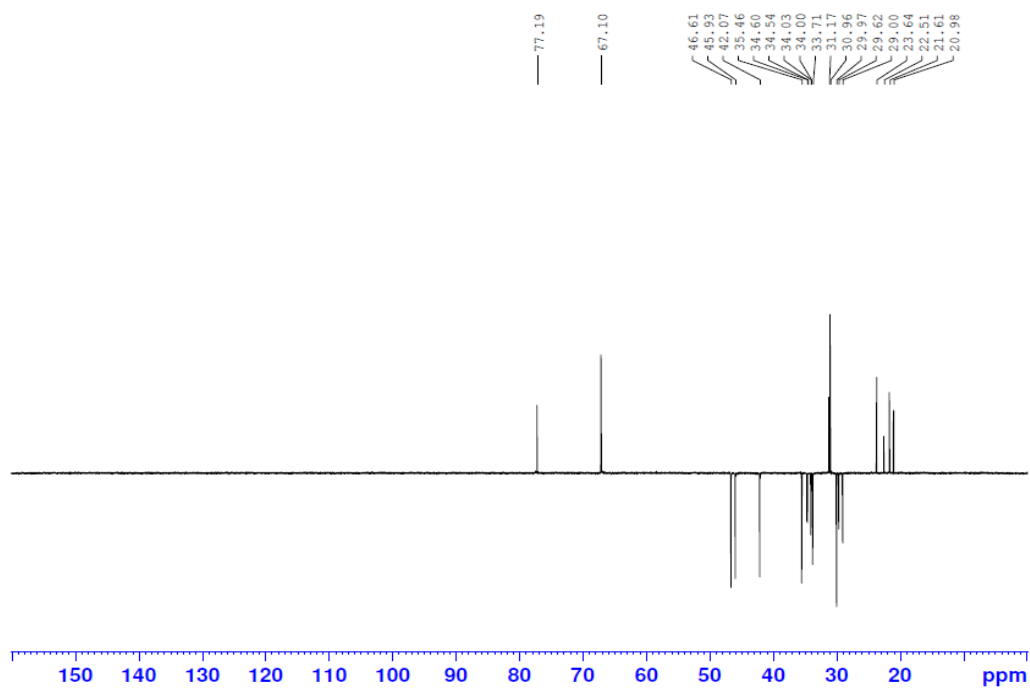
Figure 31. DEPT 135 of equimolar solution of GVL and 4-MP after 1h MW at 90 ℃

31. Table 1. ^{1}H (400MHz), ^{13}C (100MHz) NMR and HBMC correlation of mixture of Product (**3a)** GVL and PIP

S.N.	[13]C	HSQC	HMBC
1	177.2, C		
2	171.8, C		
3	77.2, CH_2	4.64	177.2, 29.0
4	67.3, CH_2	3.80	30.0
5	47.3, CH_2	2.78	47.3, 25.1
6	46.7, CH_2	3.42	171.8, 42.8, 26.4, 24.5
7	42.8, CH_2	3.54	171.8, 46.7, 24.5
8	34.0, CH_2	1.80, 1.73	171.8, 67.3, 23.7
9	30.0, CH_2	2.48	171.8, 67.3, 34.0
10	29.7, CH_2	2.37, 1.83	177.2, 29.1, 21.0
11	29.0, CH_2	2.54	177.2, 77.3, 29.7
12	27.1, CH_2	1.51	47.3, 27.2
13	26.4, CH_2	1.56	46.7, 25.5
14	25.5, CH_2	1.53	42.8, 26.4
15	25.0, CH_2	1.54	47.3
16	24.5, CH_2	1.64	46.7, 42.8, 26.4, 25.5
17	23.7, CH_3	1.20	67.3, 34.0
18	21.0, CH_3	1.42	77.2, 29.7

32. Cartesian Coordinates for GVL

```
# opt freq b3lyp/6-311++g(d,p) geom=connectivity

Title Card Required

0 1
 C                 -0.46421691    -2.02938416     0.16968728
 C                  1.03212722    -1.77689887     0.32857778
 C                 -0.03308555     0.20830045     0.55725610
 C                 -0.86904336    -0.68113472    -0.36423812
 H                 -0.72143220    -2.84260435    -0.47638795
 H                 -0.90564501    -2.21791732     1.12598038
 H                  1.47580639    -1.60517197    -0.62983689
 H                 -1.92352816    -0.50271869    -0.33062974
 H                 -0.54567284    -0.55801271    -1.37674613
 O                 -0.26438007     1.42309043     0.79040567
 O                  1.07112529    -0.55847077     1.13135974
 C                  1.76866489    -2.94920086     1.00298145
 H                  1.67844658    -3.82457648     0.39431227
 H                  2.80290308    -2.70088169     1.11955309
 H                  1.33639520    -3.13666592     1.96365818

 1 2 1.0 4 1.0 5 1.0 6 1.0
 2 7 1.0 11 1.0 12 1.0
 3 4 1.0 10 2.0 11 1.0
 4 8 1.0 9 1.0
 5
 6
 7
 8
 9
 10
 11
 12 13 1.0 14 1.0 15 1.0
 13
 14
 15
```

33. Coordinates for PIP

```
# opt freq b3lyp/6-311++g(d,p) geom=connectivity

Title Card Required

0 1
 C                 -2.67620952    -2.84380601     0.04207373
 C                 -1.12628081    -2.88283691    -0.03726108
 C                 -0.56947933    -1.43538667    -0.10783526
 C                 -1.46586451    -0.58547088     0.73225457
 C                 -3.12274320    -1.68343399    -0.78602352
 H                  0.44888390    -1.44294393     0.22046219
 H                 -0.79496123    -3.40780391     0.83425311
 H                 -0.77289576    -3.38270760    -0.91484201
 H                 -2.61672628    -1.73768905    -1.72724786
 H                 -3.01700505    -2.65852499     1.03928451
 H                 -1.60411163    -1.08132762     1.67029179
```

```
H                    -1.06280140    0.39016604    0.90710517
H                    -4.17927336   -1.68092073   -0.95525029
H                    -3.06083158   -3.78476272   -0.29194174
H                    -0.61575042   -1.04149819   -1.10162139
N                    -2.75750696   -0.44130670   -0.02264446
H                    -2.70323162    0.28353416   -0.70941947


1 2 1.0 5 1.0 10 1.0 14 1.0
2 3 1.0 7 1.0 8 1.0
3 4 1.0 6 1.0 15 1.0
4 11 1.0 12 1.0 16 1.0
5 9 1.0 13 1.0 16 1.0
6
7
8
9
10
11
12
13
14
15
16 17 1.0
17
```

34. Coordinates of 4-MP

```
# opt freq b3lyp/6-311++g(d,p) geom=connectivity

Title Card Required

0 1
 C                   -2.67620952   -2.84380601    0.04207373
 C                   -1.12628081   -2.88283691   -0.03726108
 C                   -0.56947933   -1.43538667   -0.10783526
 C                   -1.46586451   -0.58547088    0.73225457
 C                   -3.12274320   -1.68343399   -0.78602352
 H                    0.44888390   -1.44294393    0.22046219
 H                   -0.79496123   -3.40780391    0.83425311
 H                   -2.61672628   -1.73768905   -1.72724786
 H                   -3.01700505   -2.65852499    1.03928451
 H                   -1.60411163   -1.08132762    1.67029179
 H                   -1.06280140    0.39016604    0.90710517
 H                   -4.17927336   -1.68092073   -0.95525029
 H                   -3.06083158   -3.78476272   -0.29194174
 H                   -0.61575042   -1.04149819   -1.10162139
 N                   -2.75750696   -0.44130670   -0.02264446
 H                   -2.70323162    0.28353416   -0.70941947
 C                   -0.61767055   -3.60227697   -1.30032149
 H                    0.43902485   -3.75229351   -1.22423023
 H                   -1.10666592   -4.54952456   -1.39254699
 H                   -0.83198569   -3.00488329   -2.16176784


1 2 1.0 5 1.0 9 1.0 13 1.0
2 3 1.0 7 1.0 17 1.0
3 4 1.0 6 1.0 14 1.0
4 10 1.0 11 1.0 15 1.0
```

```
5 8 1.0 12 1.0 15 1.0
6
7
8
9
10
11
12
13
14
15 16 1.0
16
17 18 1.0 19 1.0 20 1.0
18
19
20
```

35. Coordinates for TS for GVL+PIP

```
# opt=(calcfc,ts) freq b3lyp/6-31++g(d,p) geom=connectivity

Title Card Required

0 1
 C                     2.79608000    -0.82937400    -0.32050900
 C                     1.44727700    -1.56441900    -0.33516800
 C                     0.53133000    -0.89183200     0.67448300
 C                     2.48434900     0.64629800    -0.66384300
 H                     3.23037700    -0.89631700     0.68468400
 H                     3.50016100    -1.28877700    -1.02539800
 H                     1.54896100    -2.61330200    -0.03679900
 H                     1.03362800    -1.53058200    -1.34890900
 H                     2.35779300     0.70605100    -1.76738200
 C                    -1.49493800     0.53204000     1.14975700
 C                    -2.62791700     1.36409100     0.54767600
 C                    -3.57592700     0.50352900    -0.29943100
 C                    -2.78373800    -0.26835700    -1.36291700
 C                    -1.64245200    -1.07361700    -0.73496100
 H                    -3.17029500     1.85092200     1.36590200
 H                    -1.86864700    -0.21329100     1.85862200
 H                    -0.76080500     1.15124100     1.66503400
 H                    -4.10612600    -0.20767900     0.34933100
 H                    -4.33994600     1.12811500    -0.77507300
 H                    -3.43263600    -0.95771400    -1.91513200
 H                    -2.36547900     0.43282500    -2.09737900
 H                    -2.03430500    -1.85136900    -0.06736400
 H                    -1.04082500    -1.55949400    -1.50479300
 H                    -2.20028700     2.16602400    -0.06850600
 O                     1.29437100     0.97910500    -0.01299900
 O                     0.54479200    -1.10103100     1.86622200
 N                    -0.75132600    -0.19761000     0.07707000
 H                    -0.12781400     0.52763800    -0.43940200
 C                     3.63020500     1.58704000    -0.27556700
 H                     4.56779600     1.30914000    -0.77518200
 H                     3.38266000     2.61647000    -0.55337100
 H                     3.78616700     1.55638500     0.80872000
```

```
1 2 1.0 4 1.0 5 1.0 6 1.0
2 3 1.0 7 1.0 8 1.0
3 26 2.0
4 9 1.0 25 1.0 29 1.0
5
6
7
8
9
10 11 1.0 16 1.0 17 1.0 27 1.0
11 12 1.0 15 1.0 24 1.0
12 13 1.0 18 1.0 19 1.0
13 14 1.0 20 1.0 21 1.0
14 22 1.0 23 1.0 27 1.0
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29 30 1.0 31 1.0 32 1.0
30
31
32
```

36. Coordinates for TS for GVL+PIP

```
# opt=(calcfc,ts) freq b3lyp/6-31++g(d,p) geom=connectivity

Title Card Required

0 1
 C                  3.20123400   -0.55953500   -0.54521600
 C                  1.92665300   -1.41165300   -0.64044400
 C                  1.01366600   -1.02797200    0.51301800
 C                  2.73681400    0.91495800   -0.59630400
 H                  3.69769900   -0.76299100    0.41175600
 H                  3.90204400   -0.81117600   -1.35091000
 H                  2.14156800   -2.48136900   -0.54530700
 H                  1.45150500   -1.23855800   -1.61237200
 H                  2.54061800    1.15951900   -1.66352800
 C                 -1.09904700    0.08299400    1.32379600
 C                 -2.33252900    0.89417900    0.92976700
 C                 -3.26888300    0.11956100   -0.01309700
 C                 -2.46268600   -0.37775200   -1.22486400
 C                 -1.21920900   -1.16824900   -0.80888000
 H                 -2.86379100    1.17921100    1.84567800
 H                 -1.36336000   -0.80806800    1.90137000
 H                 -0.39430500    0.67061300    1.91194000
```

```
H                        -3.63642700    -0.76525700     0.53005400
H                        -3.08212800    -1.01708200    -1.86558200
H                        -2.15543200     0.48155600    -1.83751400
H                        -1.49827800    -2.08751200    -0.27889600
H                        -0.62752300    -1.44803900    -1.68215900
H                        -2.01509800     1.82918900     0.44730300
O                         1.56152900     1.00348700     0.15275500
O                         1.11532800    -1.44658200     1.64379700
N                        -0.35863000    -0.36930000     0.10685800
H                         0.16439800     0.49453700    -0.29426100
C                         3.81232800     1.88103100    -0.08737900
H                         4.74110600     1.79383500    -0.66677200
H                         3.45556700     2.91333400    -0.16001500
H                         4.03279200     1.67176800     0.96549000
C                        -4.47920300     0.95749800    -0.43899100
H                        -5.14743600     0.38782500    -1.09436300
H                        -5.05996400     1.28188200     0.43139000
H                        -4.16282500     1.85628500    -0.98215200

1 2 1.0 4 1.0 5 1.0 6 1.0
2 3 1.0 7 1.0 8 1.0
3 25 2.0
4 9 1.0 24 1.0 28 1.0
5
6
7
8
9
10 11 1.0 16 1.0 17 1.0 26 1.0
11 12 1.0 15 1.0 23 1.0
12 13 1.0 18 1.0 32 1.0
13 14 1.0 19 1.0 20 1.0
14 21 1.0 22 1.0 26 1.0
15
16
17
18
19
20
21
22
23
24
25
26
27
28 29 1.0 30 1.0 31 1.0
29
30
31
32 33 1.0 34 1.0 35 1.0
33
34
35
```
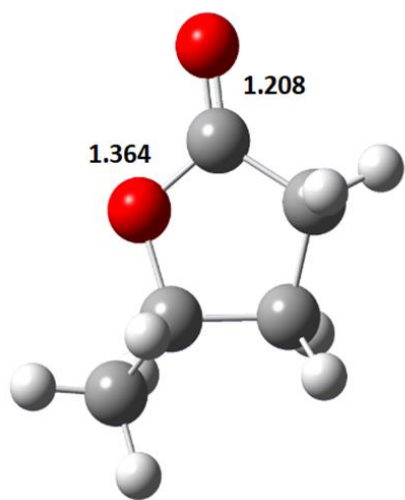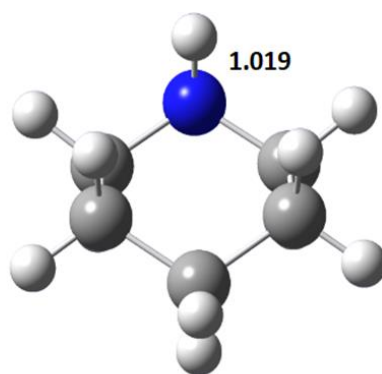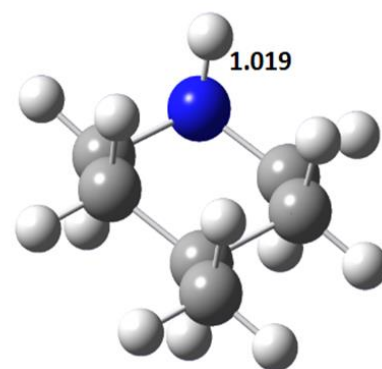
Figure 31: Optimized geometry of GVL, PIP and 4-MP with bond lengths

GVL   **PIP**   **4-MP**