SUPPLEMENTARY DATA

# *In vitro* and *in silico* evaluation of new oxadiazole derivatives of pyrrolo[3,4-d]pyridazinone as promising cyclooxygenase inhibitors

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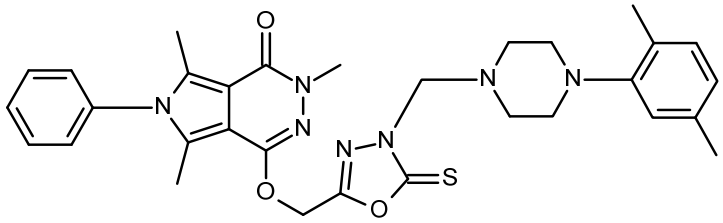
**Table S1.** Structures of new compounds

| |
|---|
|  |
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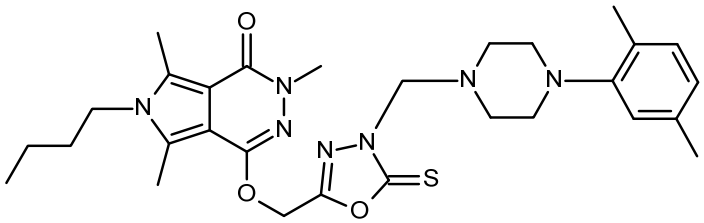
|  |
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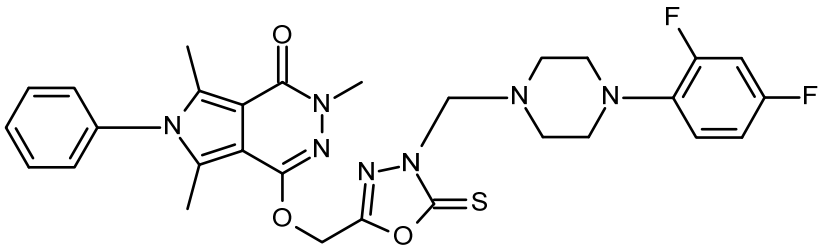
|  |
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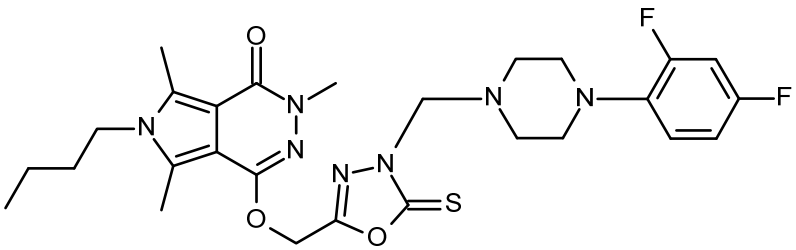
|  |
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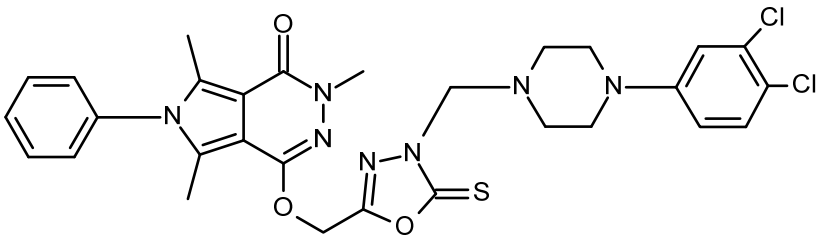
|  |
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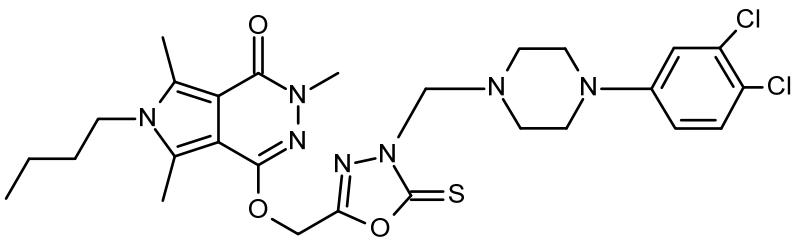

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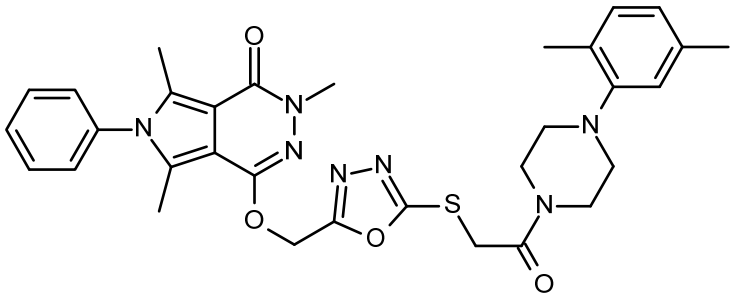

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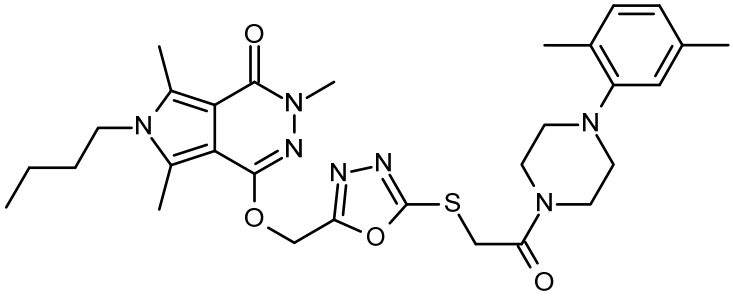

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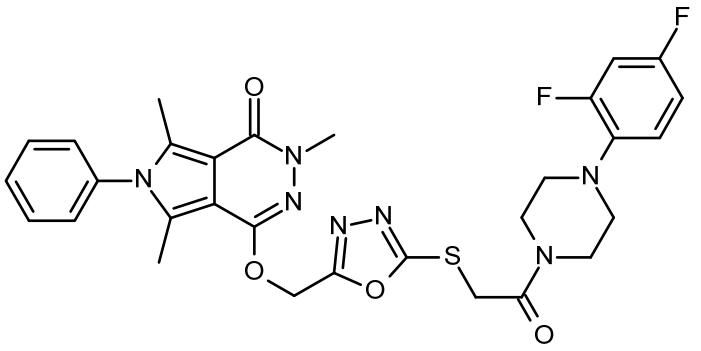

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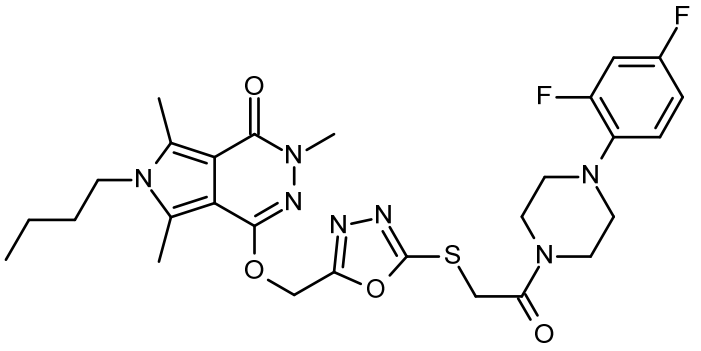

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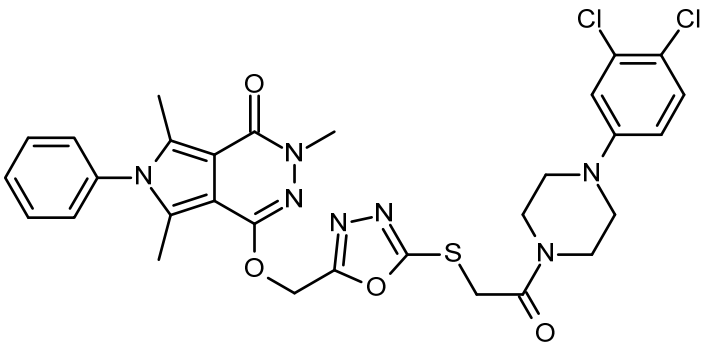


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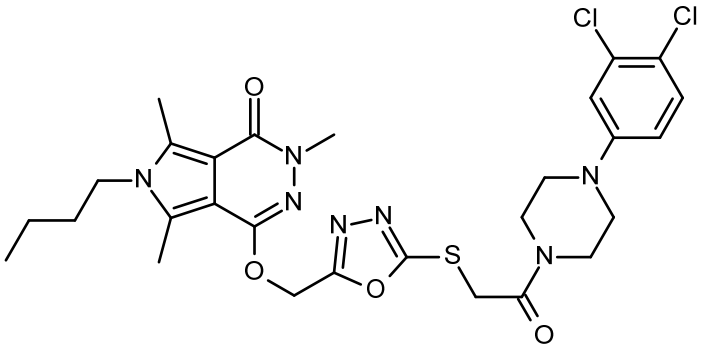


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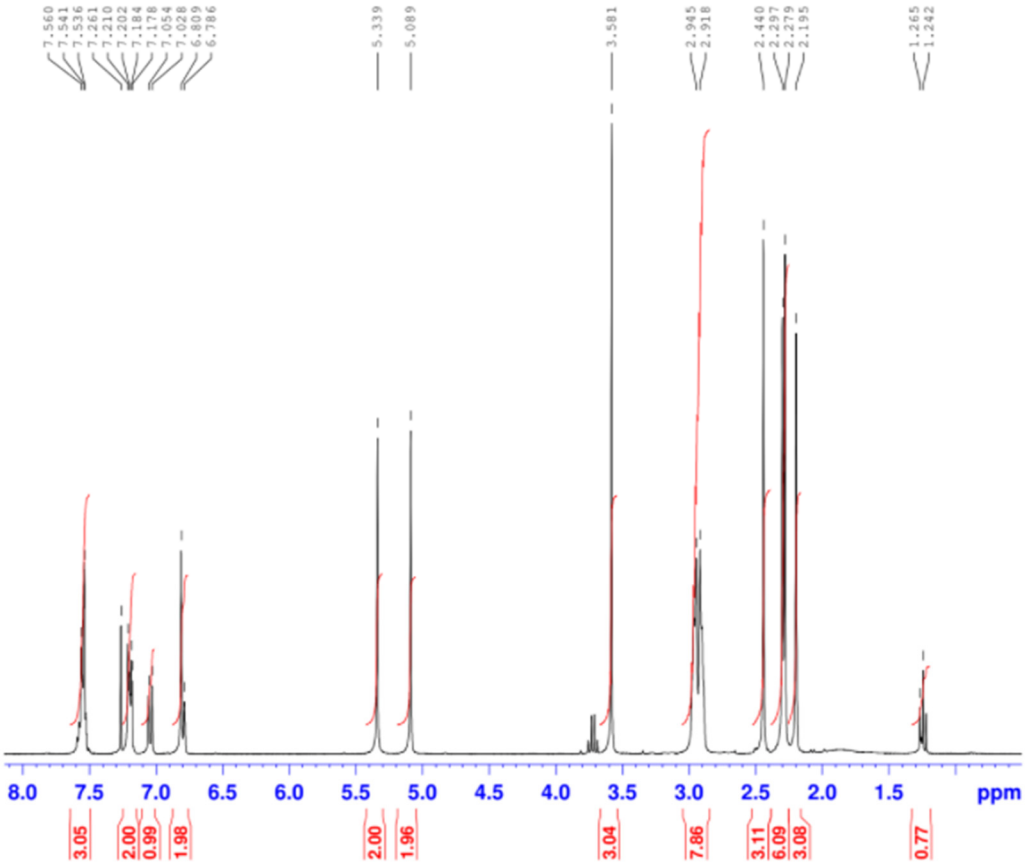
**Table S2.** NMR spectra of new compounds

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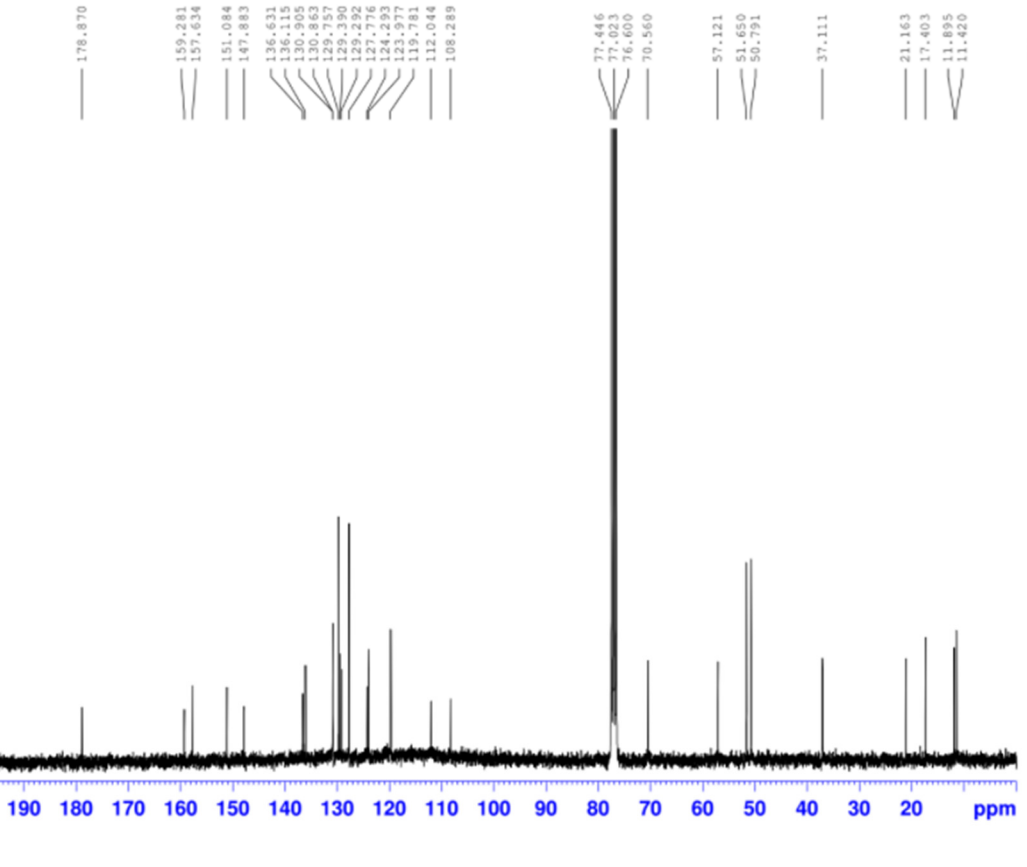


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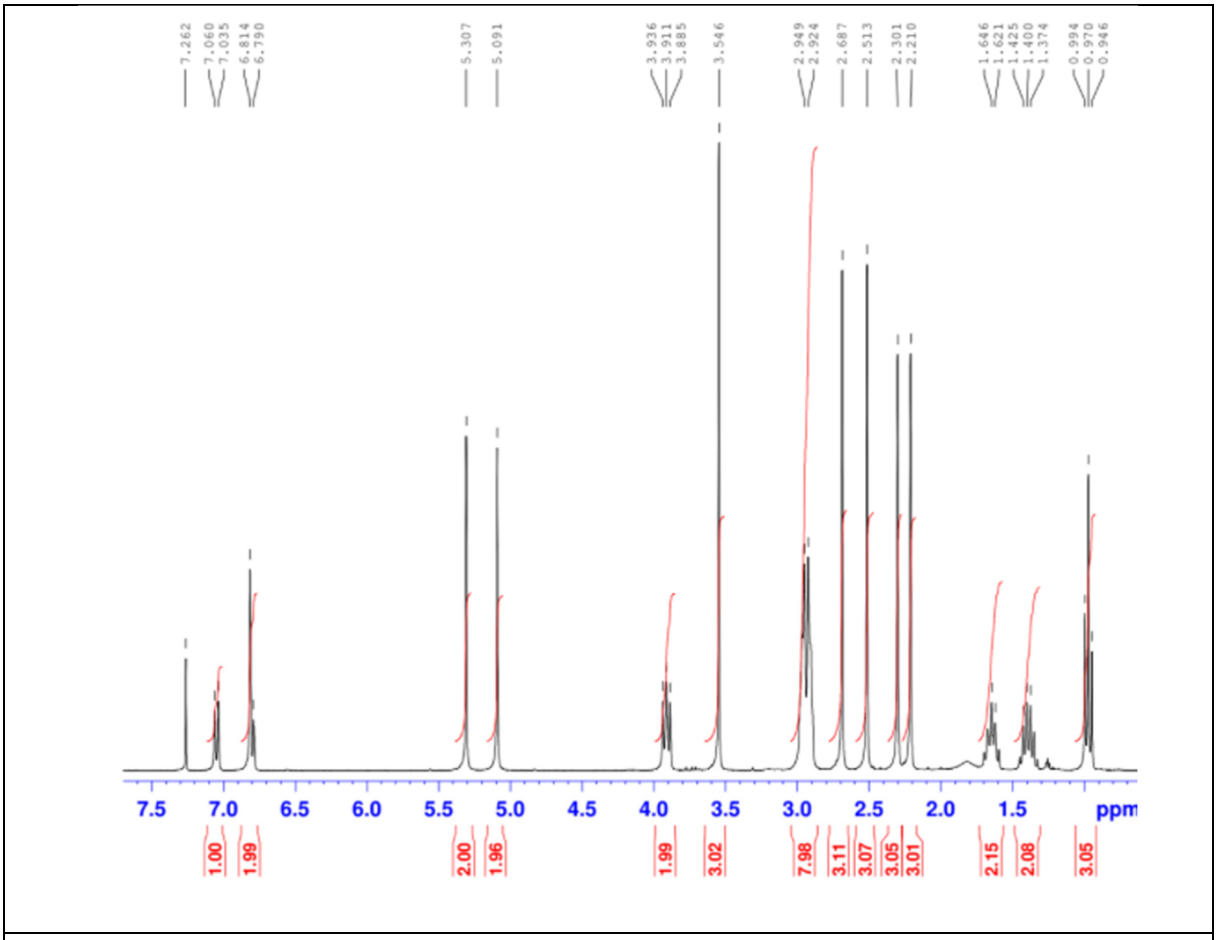
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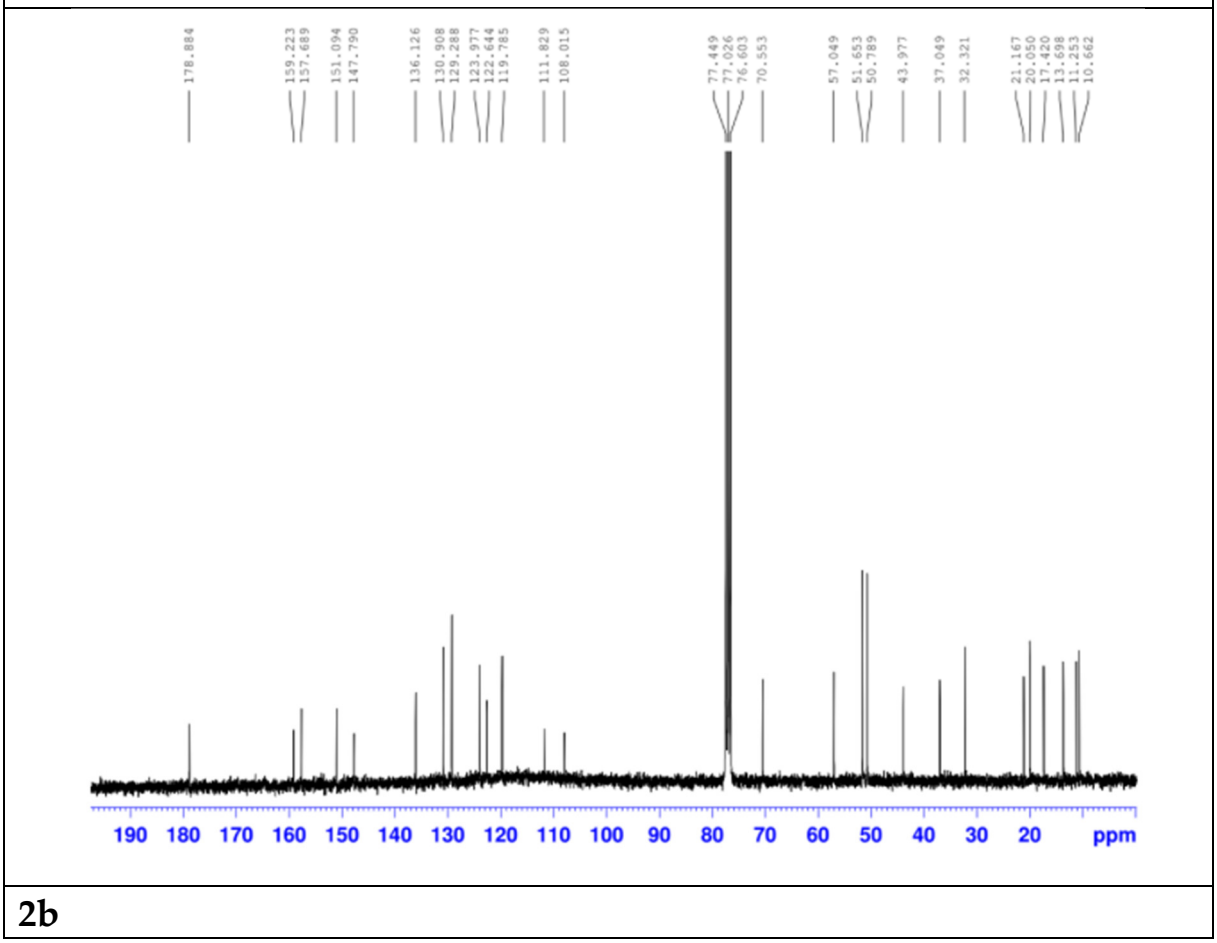
6.814
6.790
5.307
5.091
3.936
3.911
3.885
3.546
2.949
2.924
2.687
2.513
2.301
2.210
1.646
1.621
1.425
1.400
1.374
0.994
0.970
0.946
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
1.99
2.00
1.96
1.99
3.02
7.98
3.11
3.07
3.05
3.01
2.15
2.08
3.05

**2b**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151.094
147.790
136.126
130.908
129.288
123.977
122.644
119.785
111.829
108.015
77.449
77.026
76.603
70.553
57.049
51.653
50.789
43.977
37.049
32.321
21.167
20.050
17.420
13.698
11.253
10.662
190
180
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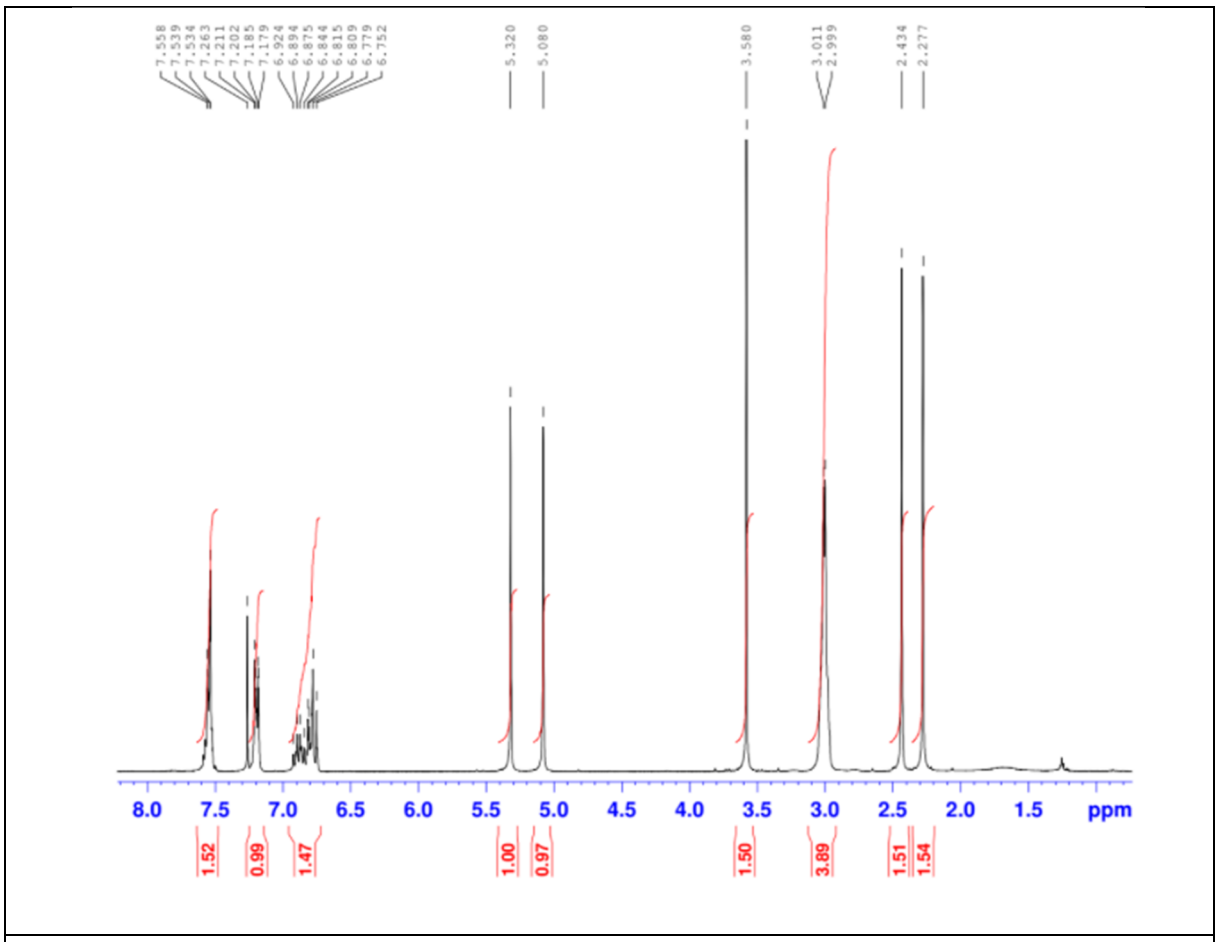
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

**2b**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7.179
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6.815
6.809
6.779
6.752
5.320
5.080
3.580
3.011
2.999
2.434
2.277
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
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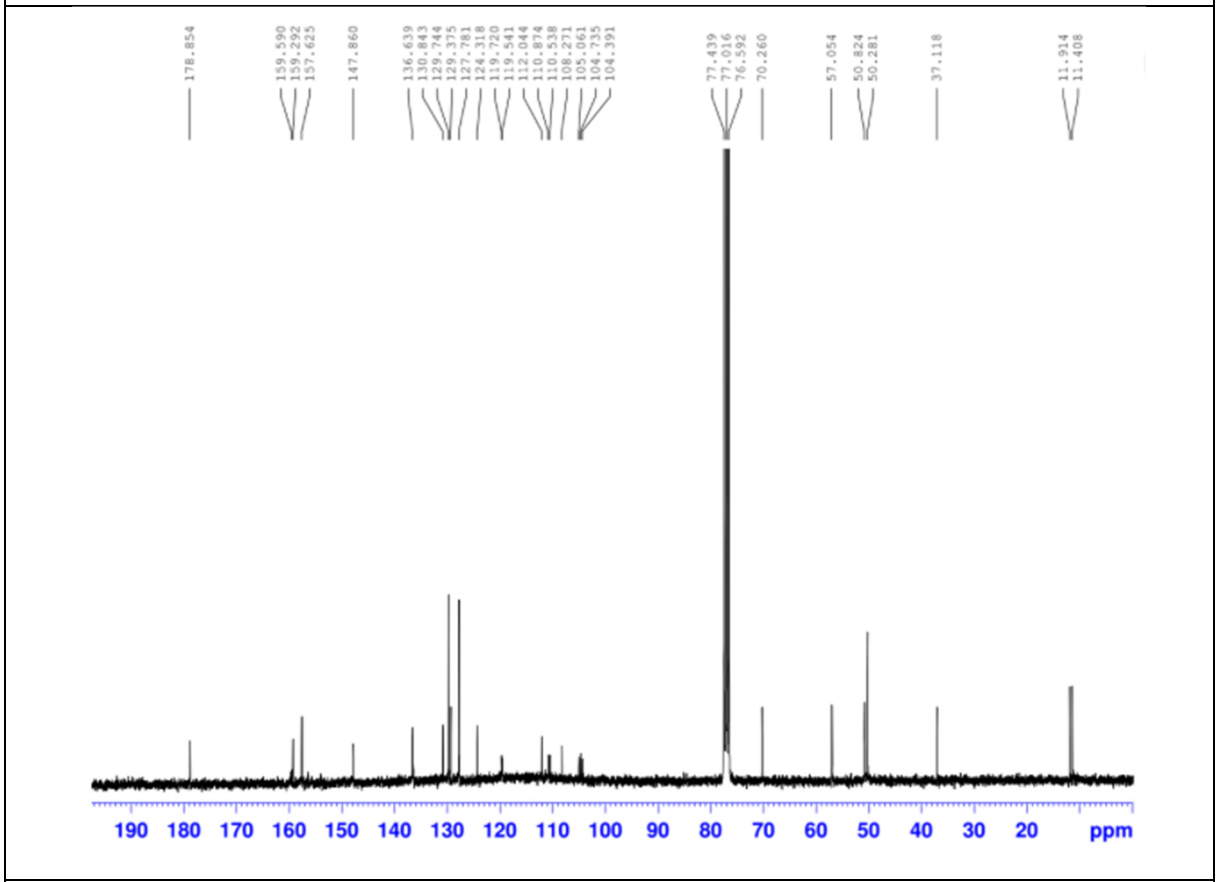
0.99
1.47
1.00
0.97
1.50
3.89
1.51
1.54

**3a**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129.744
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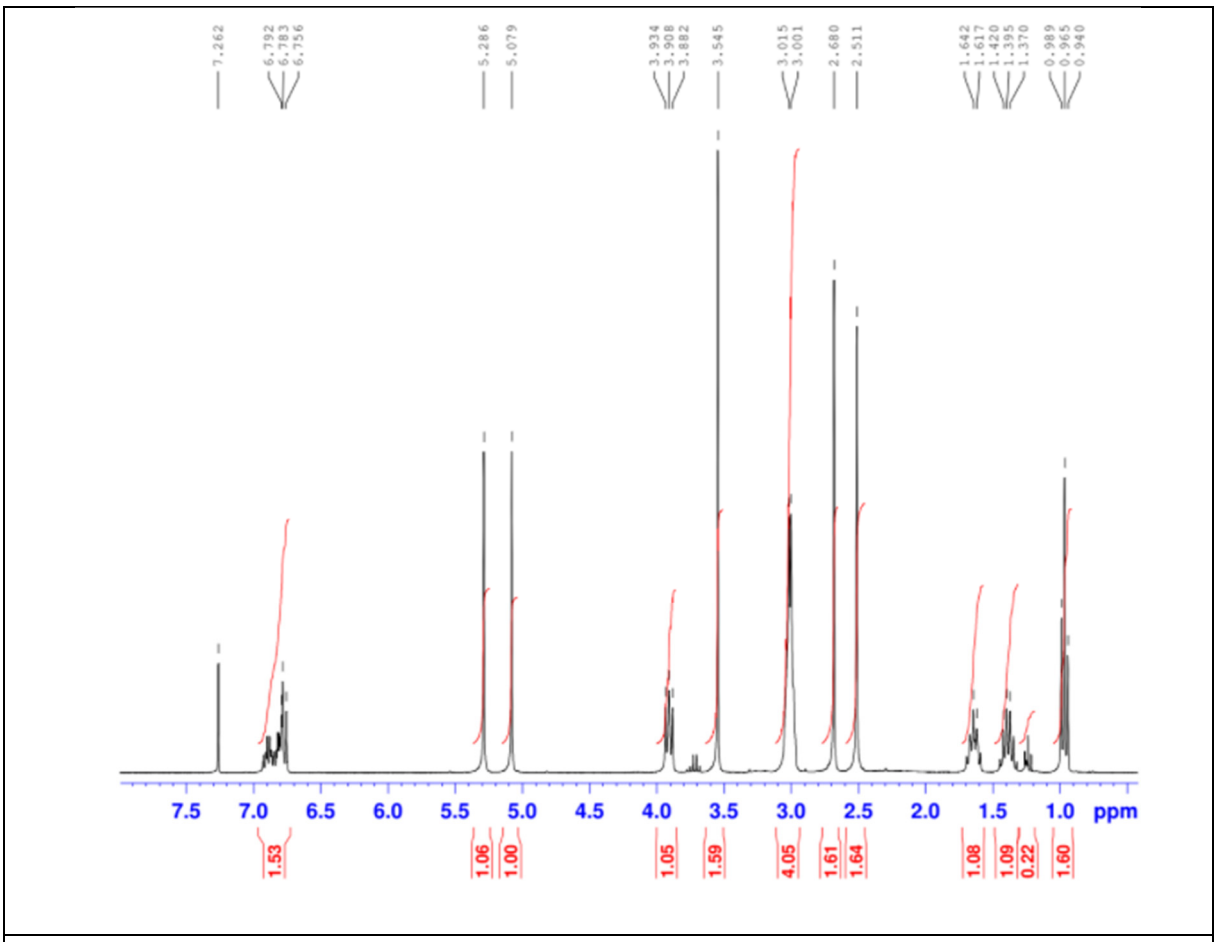
119.541
112.044
110.874
110.538
108.271
105.061
104.735
104.391
77.439
77.016
76.592
70.260
57.054
50.824
50.281
37.118
11.914
11.408
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

**3a**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3.908
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3.545
3.015
3.001
2.680
2.511
1.642
1.617
1.420
1.395
1.370
0.989
0.965
0.940
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.53
1.06
1.00
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1.59
4.05
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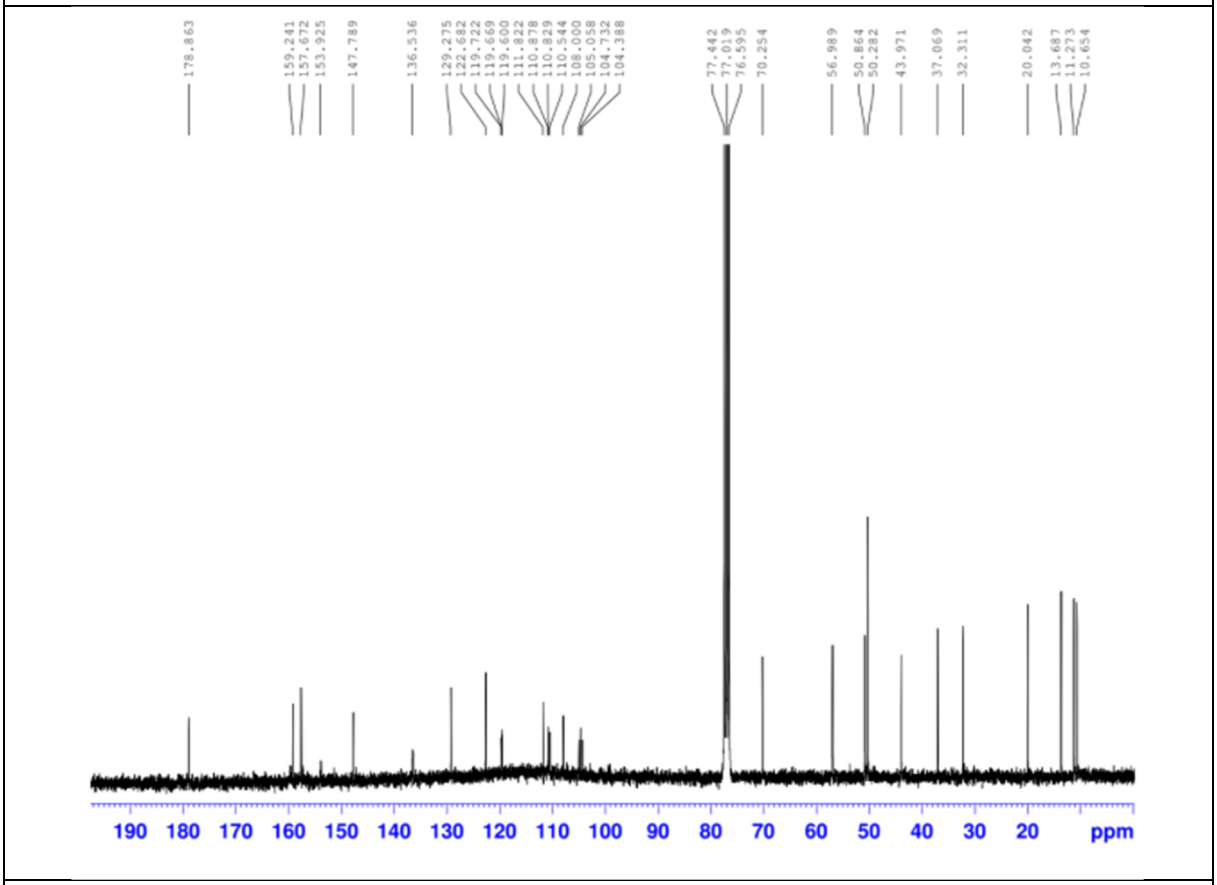
1.64
1.08
1.09
0.22
1.60

**3b**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136.536
129.275
122.682
119.722
119.669
119.600
111.822
110.878
110.829
110.544
108.000
105.058
104.732
104.388
77.442
77.019
76.595
70.254
56.989
50.864
50.282
43.971
37.069
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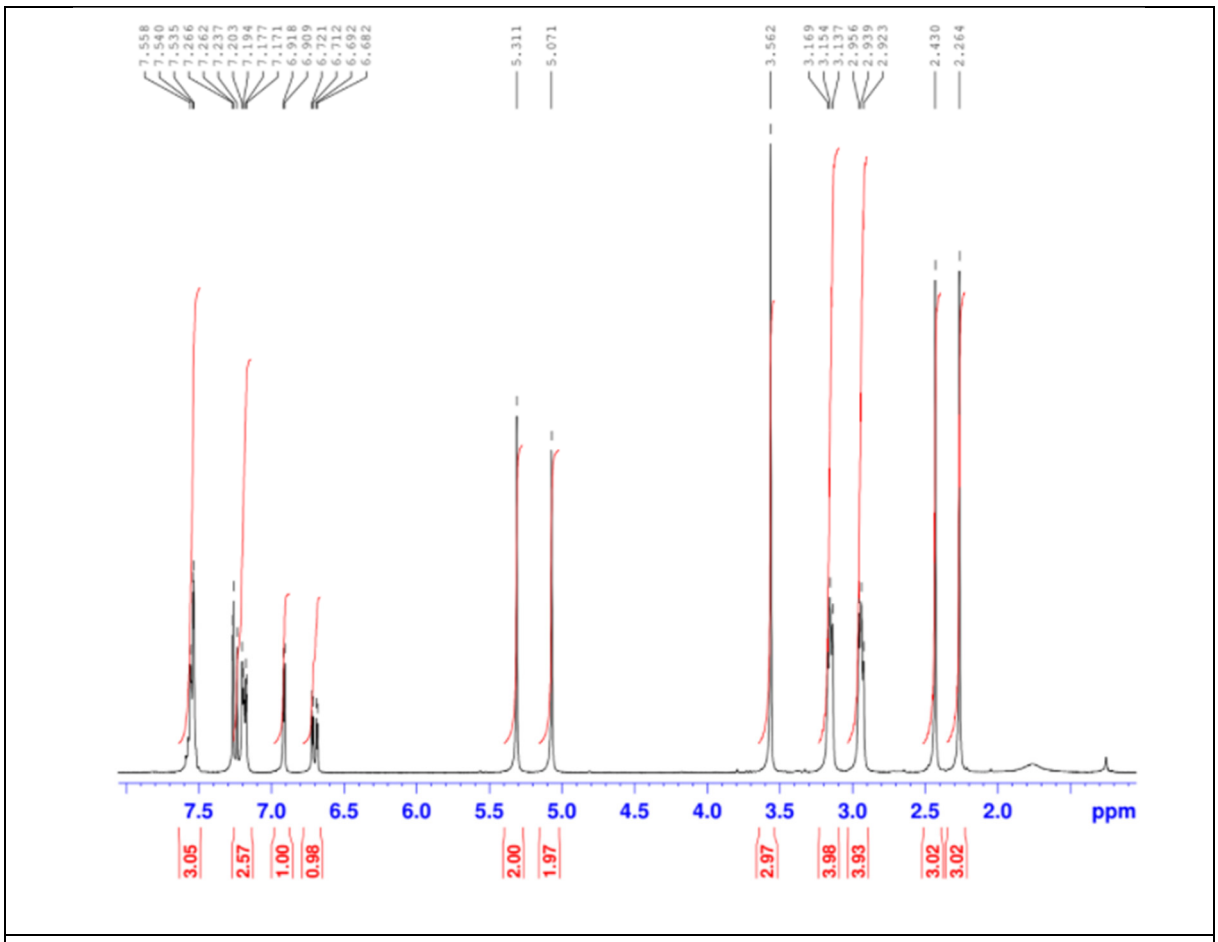
20.042
13.687
11.273
10.654
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

**3b**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7.266
7.262
7.237
7.203
7.194
7.177
7.171
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6.909
6.721
6.712
6.692
6.682
5.311
5.071
3.562
3.169
3.154
3.137
2.956
2.939
2.923
2.430
2.264
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
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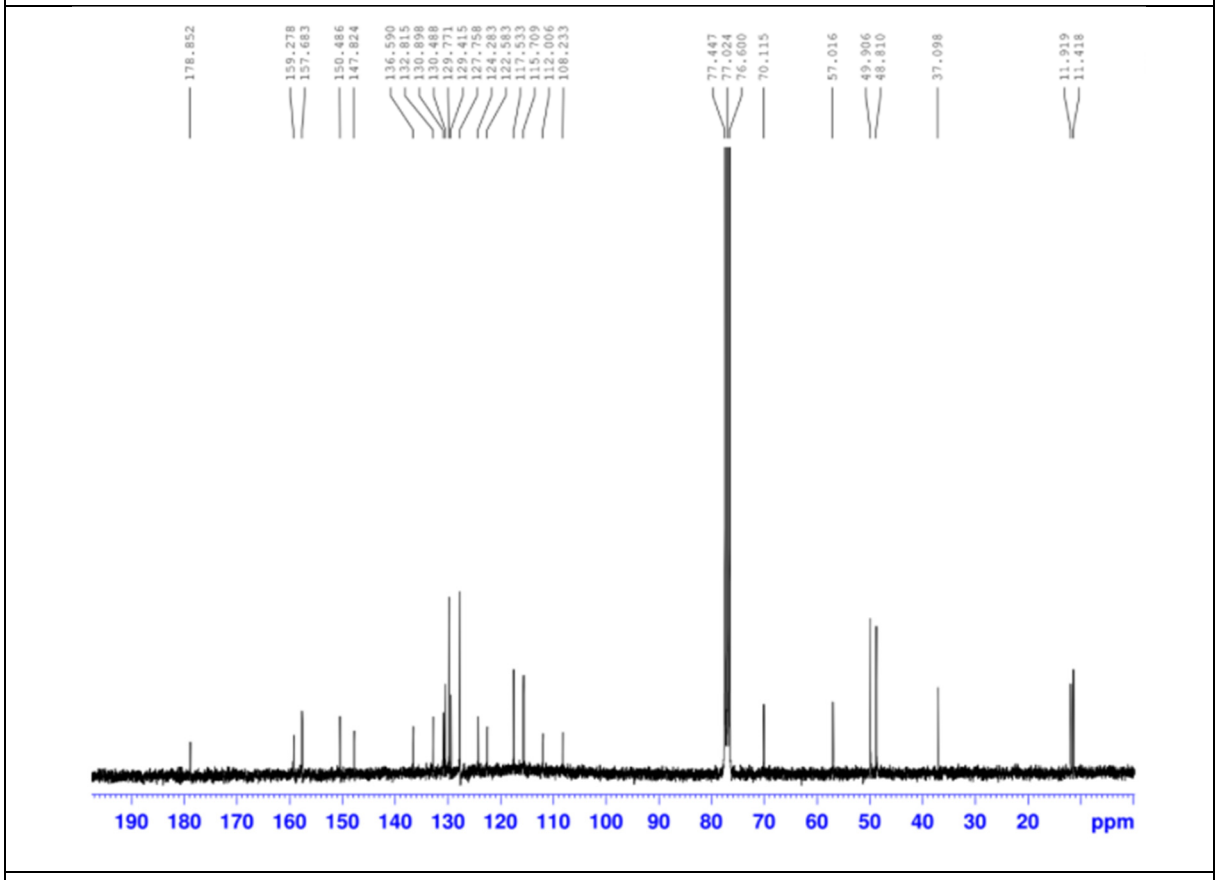
2.97
3.98
3.93
3.02
3.02

**4a**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132.815
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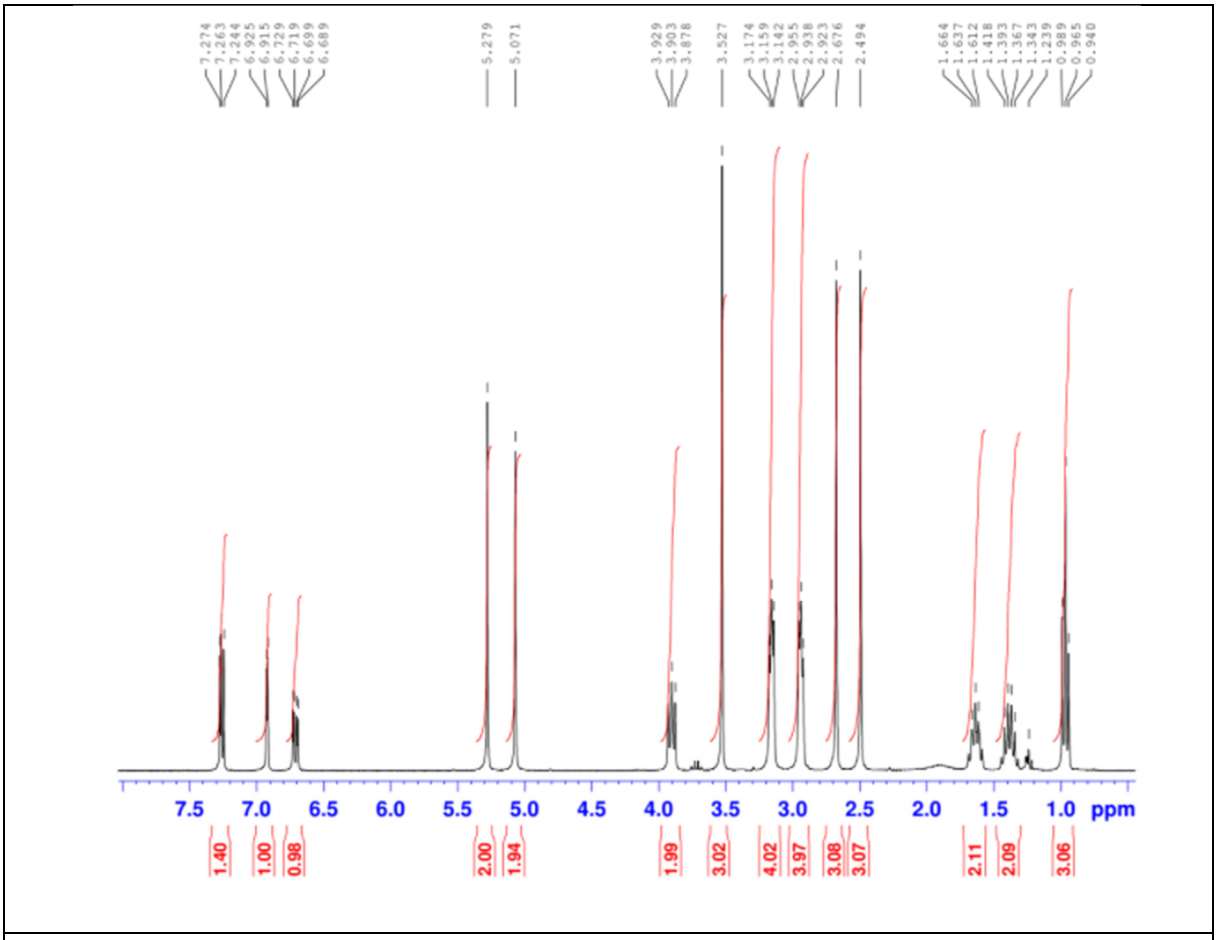
124.283
122.583
117.533
115.709
112.006
108.233
77.447
77.024
76.600
70.115
57.016
49.906
48.810
37.098
11.919
11.418
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

**4a**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3.903
3.878
3.527
3.174
3.159
3.142
2.955
2.938
2.923
2.676
2.494
1.664
1.637
1.612
1.418
1.393
1.367
1.343
1.239
0.989
0.965
0.940
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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2.09
3.06

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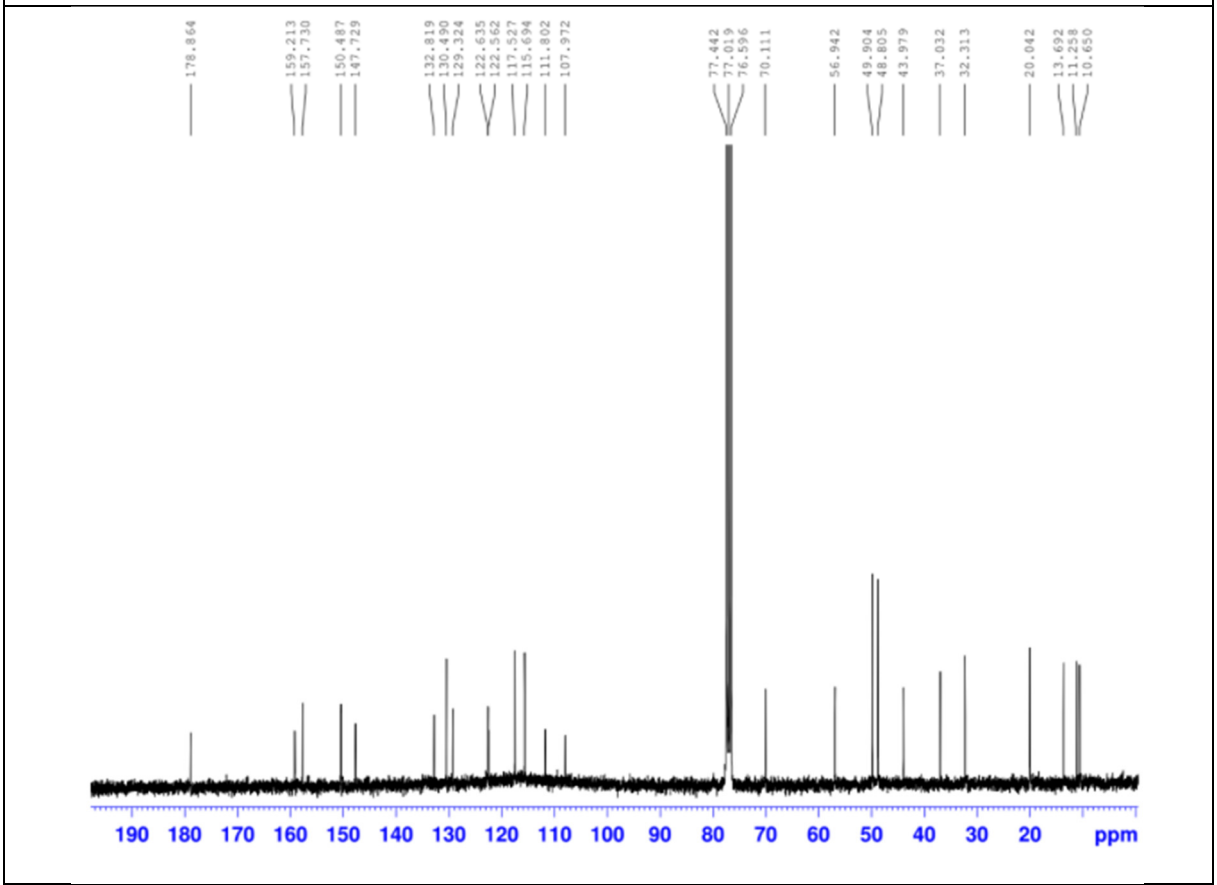
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122.562
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111.802
107.972
77.442
77.019
76.596
70.111
56.942
49.904
48.805
43.979
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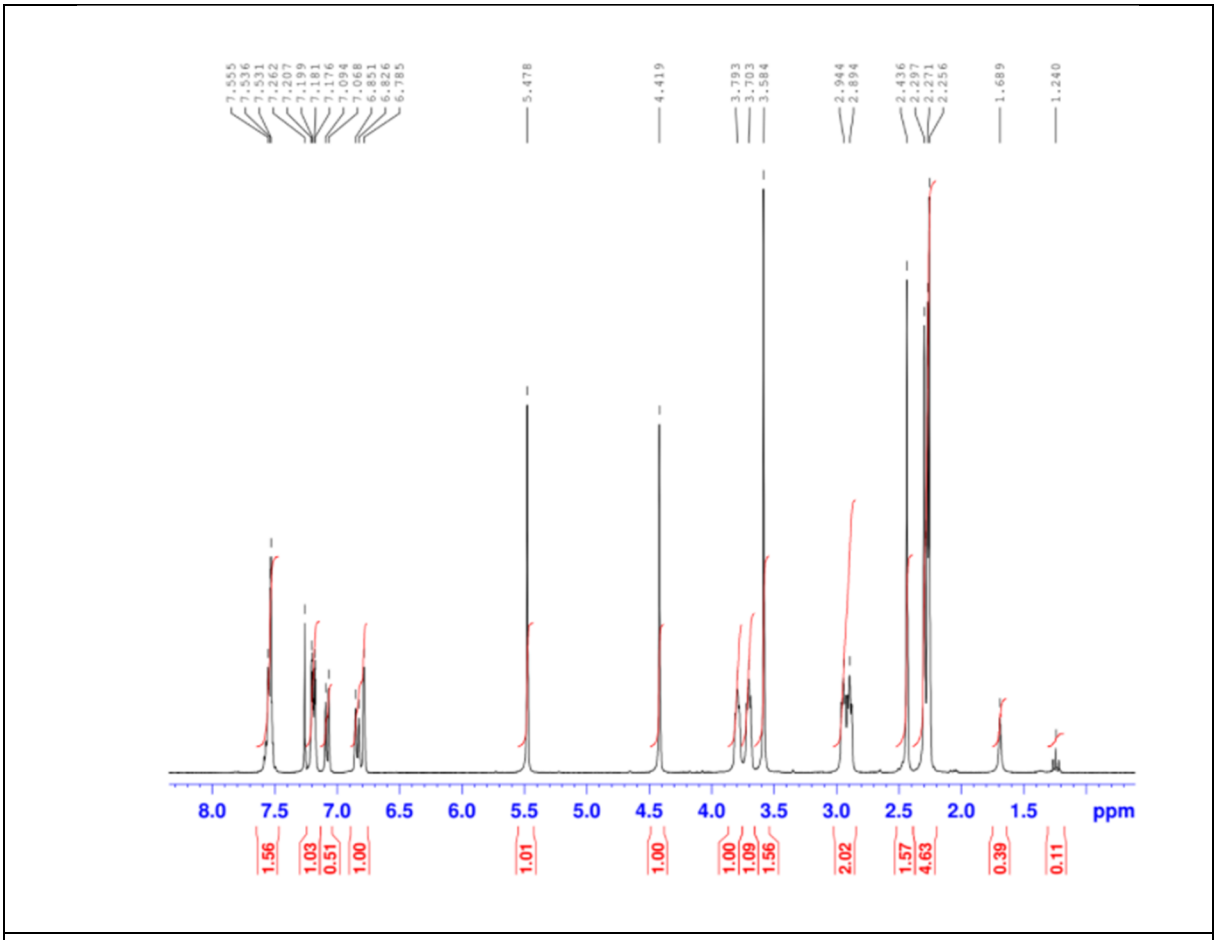
11.258
10.650
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

**4b**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6.785
5.478
4.419
3.793
3.703
3.584
2.944
2.894
2.436
2.297
2.271
2.256
1.689
1.240
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
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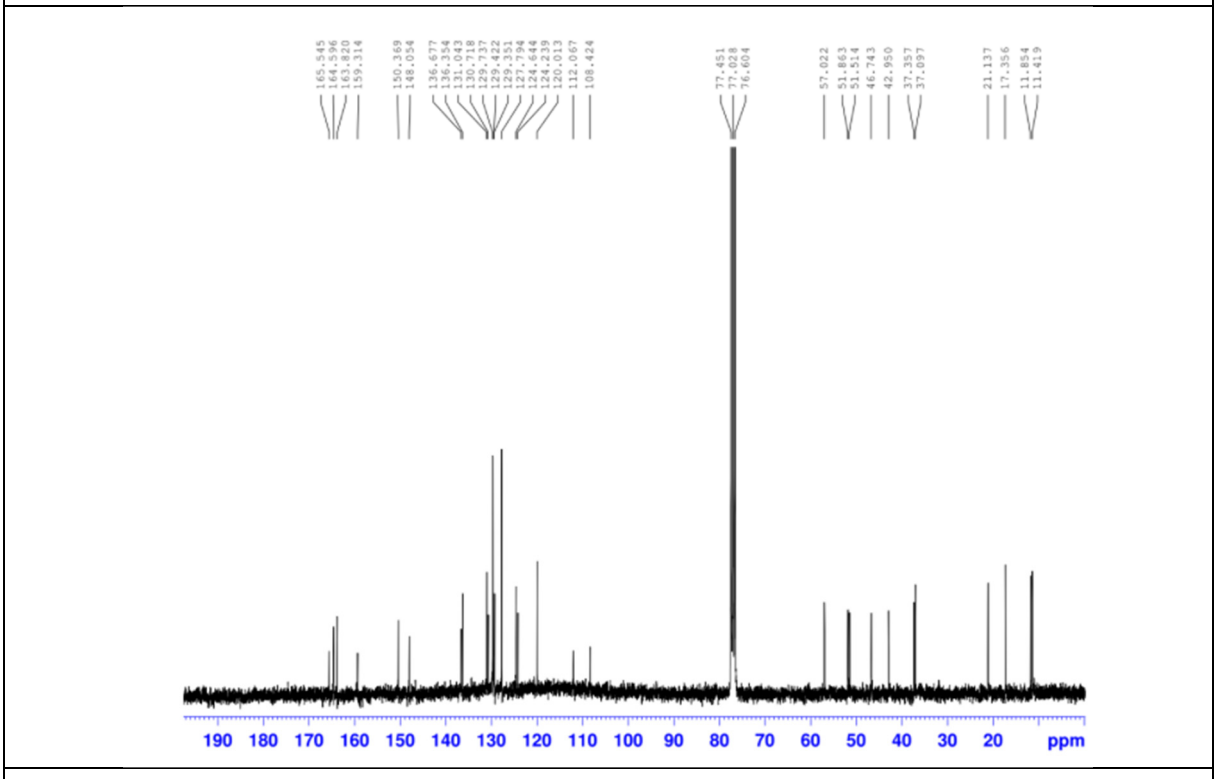
**5a**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163.820
159.314
150.369
148.054
136.677
136.354
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130.718
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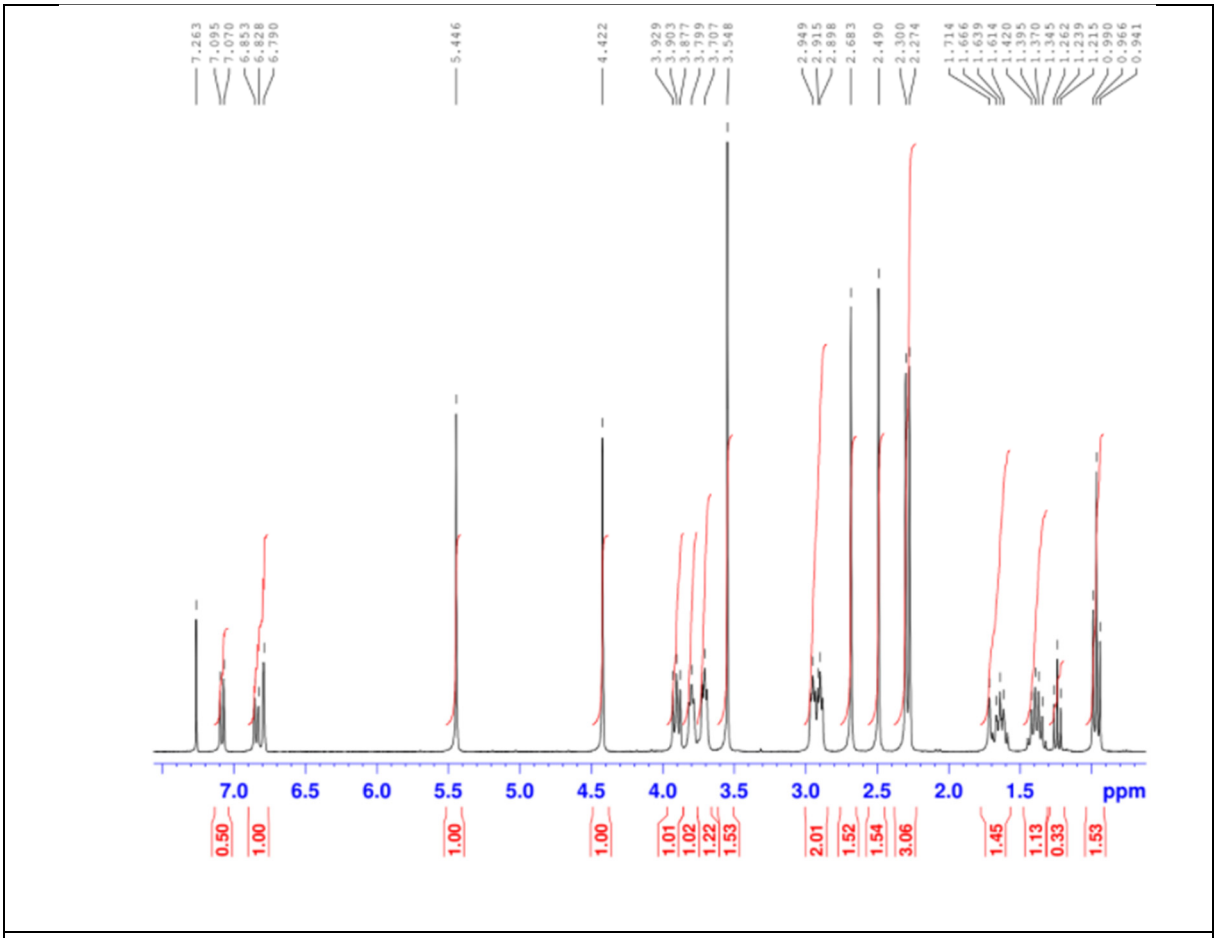
129.351
127.794
124.644
124.239
120.013
112.067
108.424
77.451
77.028
76.604
57.022
51.863
51.514
46.743
42.950
37.357
37.097
21.137
17.356
11.854
11.419
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

**5a**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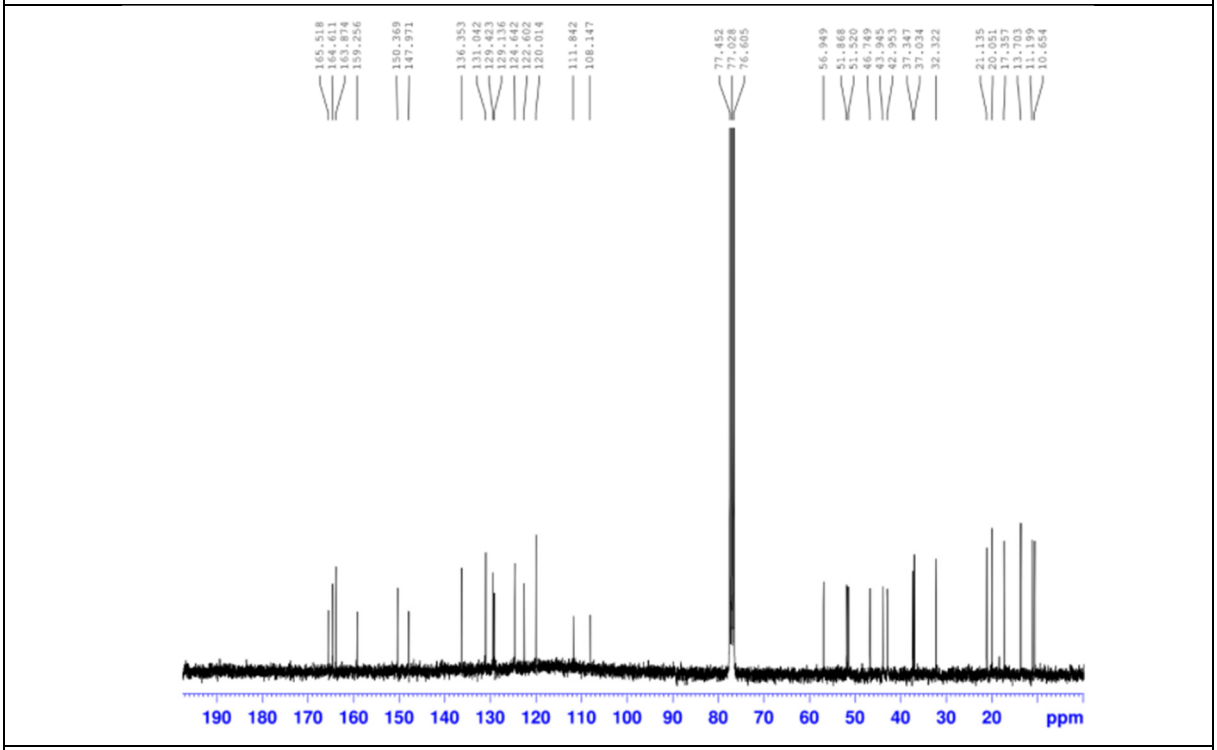
6.828
6.790
5.446
4.422
3.929
3.903
3.877
3.799
3.707
3.548
2.949
2.915
2.898
2.683
2.490
2.300
2.274
1.714
1.666
1.639
1.614
1.420
1.395
1.370
1.345
1.262
1.239
1.215
0.990
0.966
0.941
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.50
1.00
1.00
1.00
1.01
1.02
1.22
1.53
2.01
1.52
1.54
3.06
1.45
1.13
0.33
1.53

**5b**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150.369
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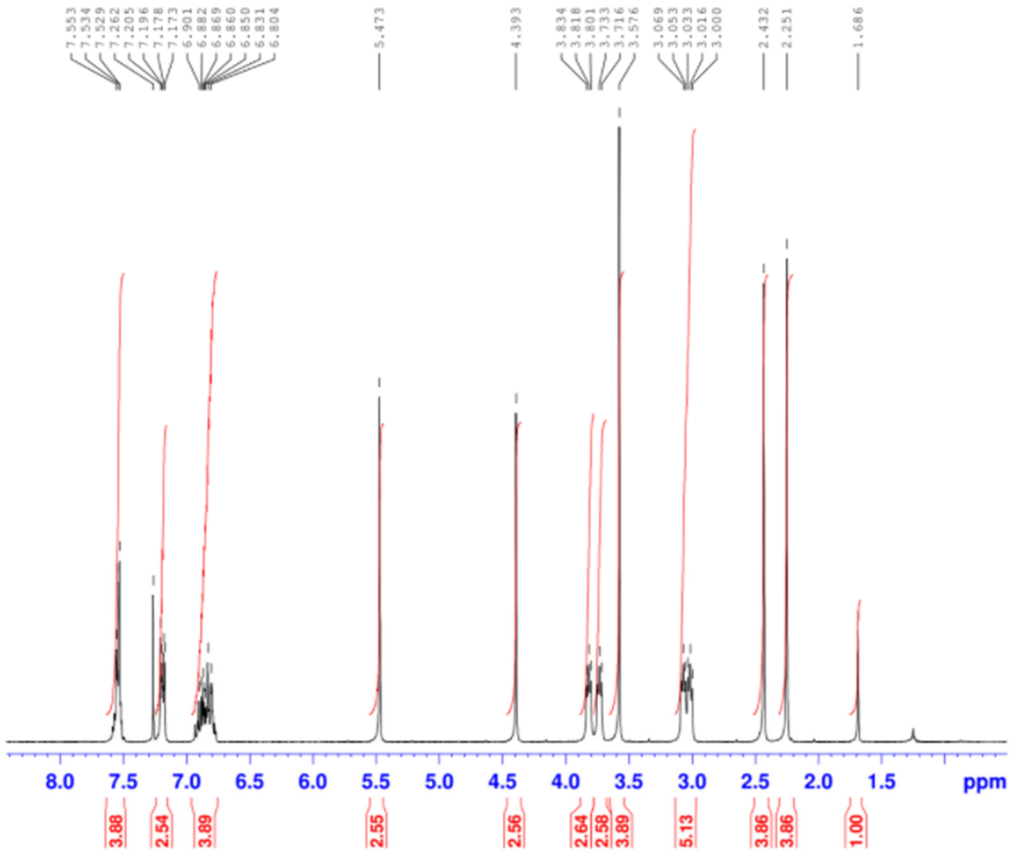
108.147
77.452
77.028
76.605
56.949
51.868
51.520
46.749
43.945
42.953
37.347
37.034
32.322
21.135
20.051
17.357
17.203
11.199
10.654
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

**5b**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7.529
7.262
7.205
7.196
7.178
7.173
6.901
6.882
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6.860
6.850
6.831
6.804
5.473
4.393
3.834
3.818
3.801
3.733
3.716
3.576
3.069
3.053
3.033
3.016
3.000
2.432
2.251
1.686
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
3.88
2.54
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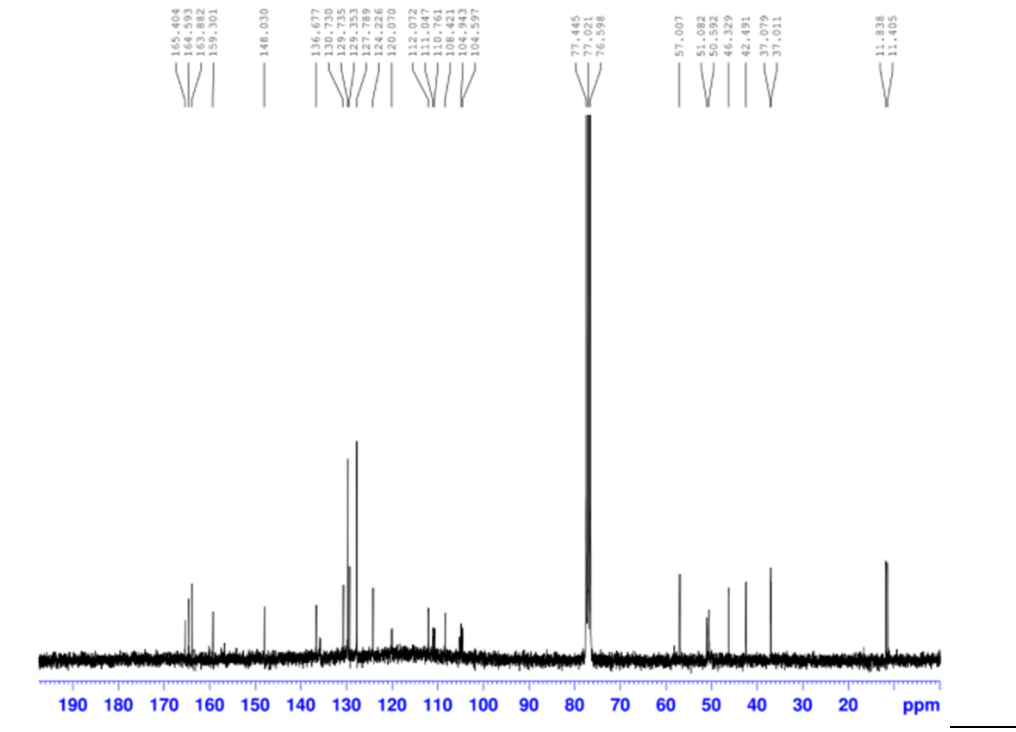
2.56
2.64
2.58
3.89
5.13
3.86
3.86
1.00

**6a**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164.582
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148.030
136.677
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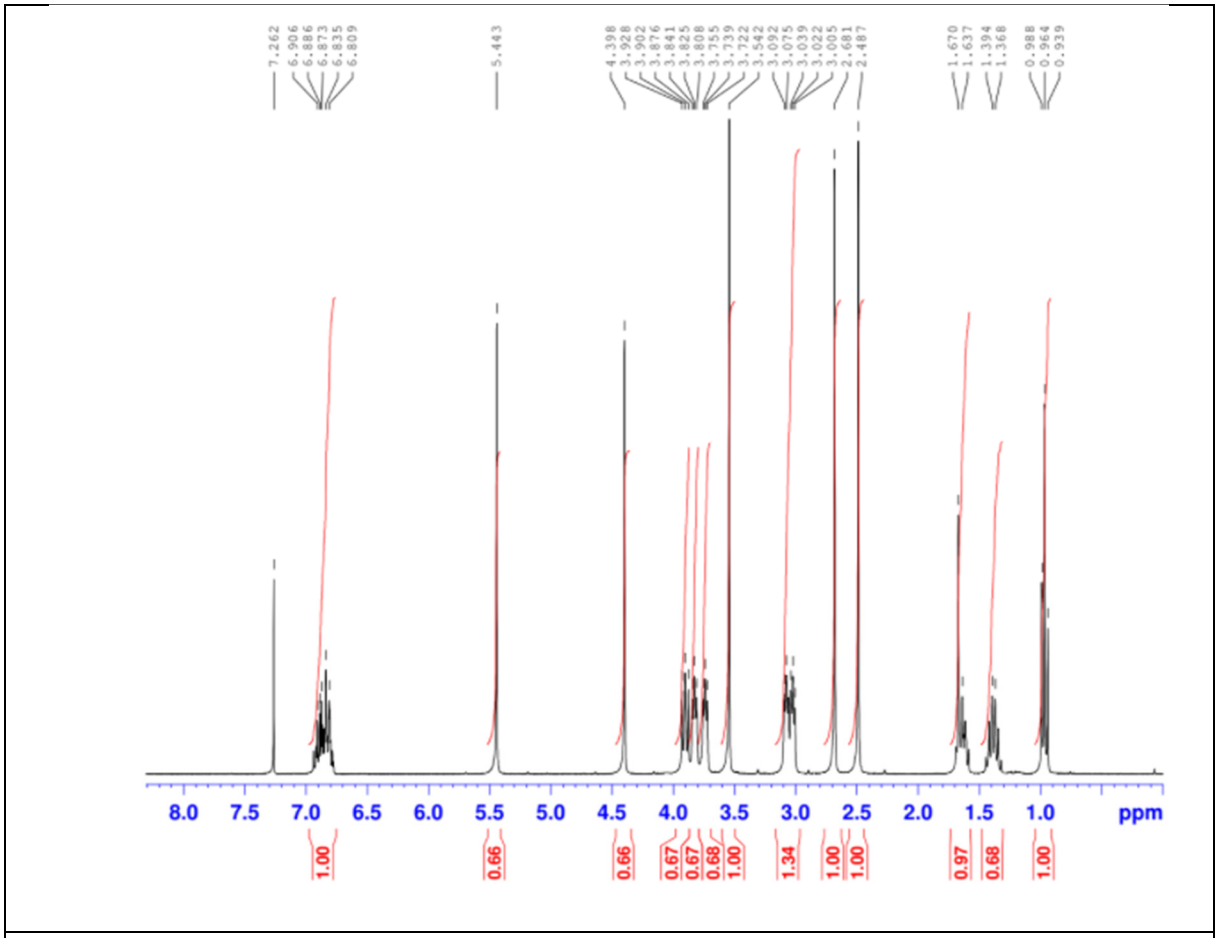
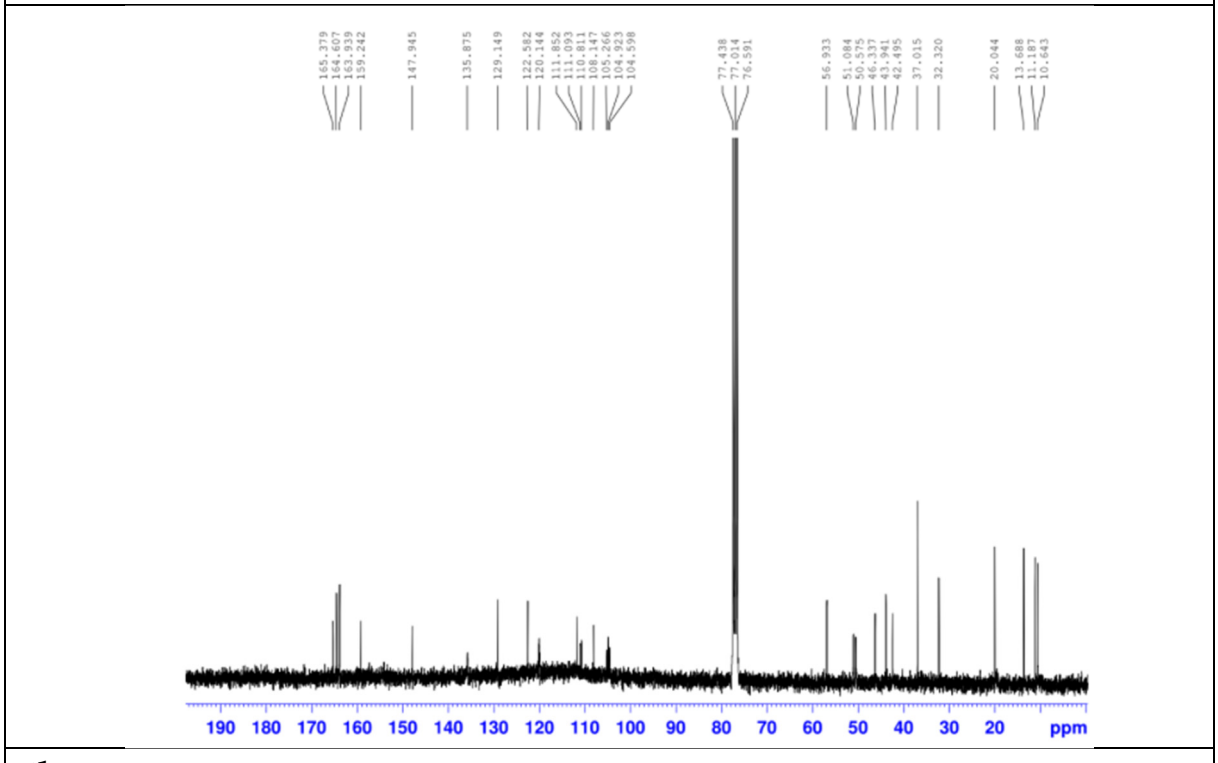
127.789
124.226
120.070
112.072
111.047
110.761
108.421
104.943
104.597
77.445
77.021
76.598
57.007
51.082
50.592
46.329
42.491
37.079
37.011
11.838
11.405
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

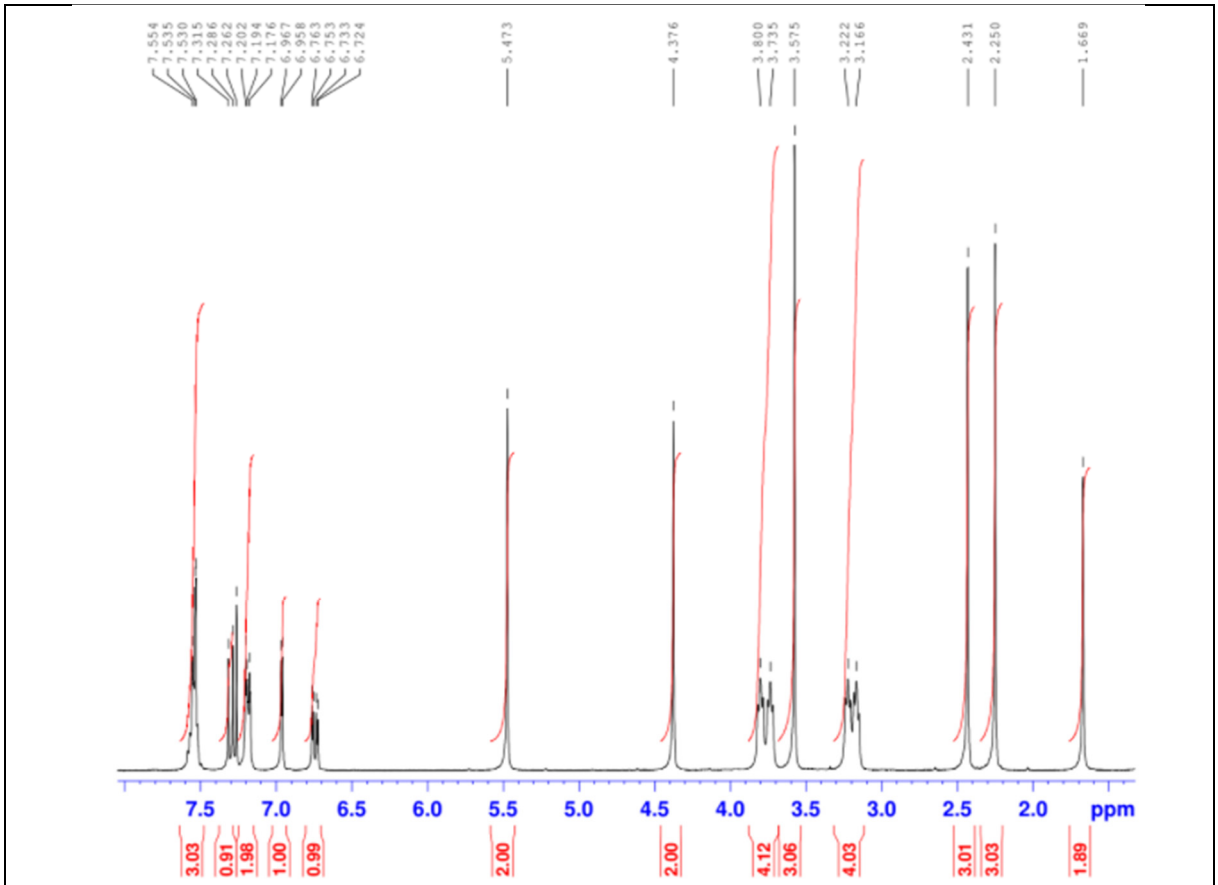
**6a**


7.262
6.906
6.886
6.873
6.835
6.809
5.443
4.398
3.928
3.902
3.876
3.841
3.825
3.808
3.755
3.739
3.722
3.542
3.092
3.075
3.039
3.022
3.005
2.681
2.487
1.670
1.637
1.394
1.368
0.988
0.964
0.939
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00 0.66 0.66 0.67 0.67 0.68 1.00 1.34 1.00 1.00 0.97 0.68 1.00

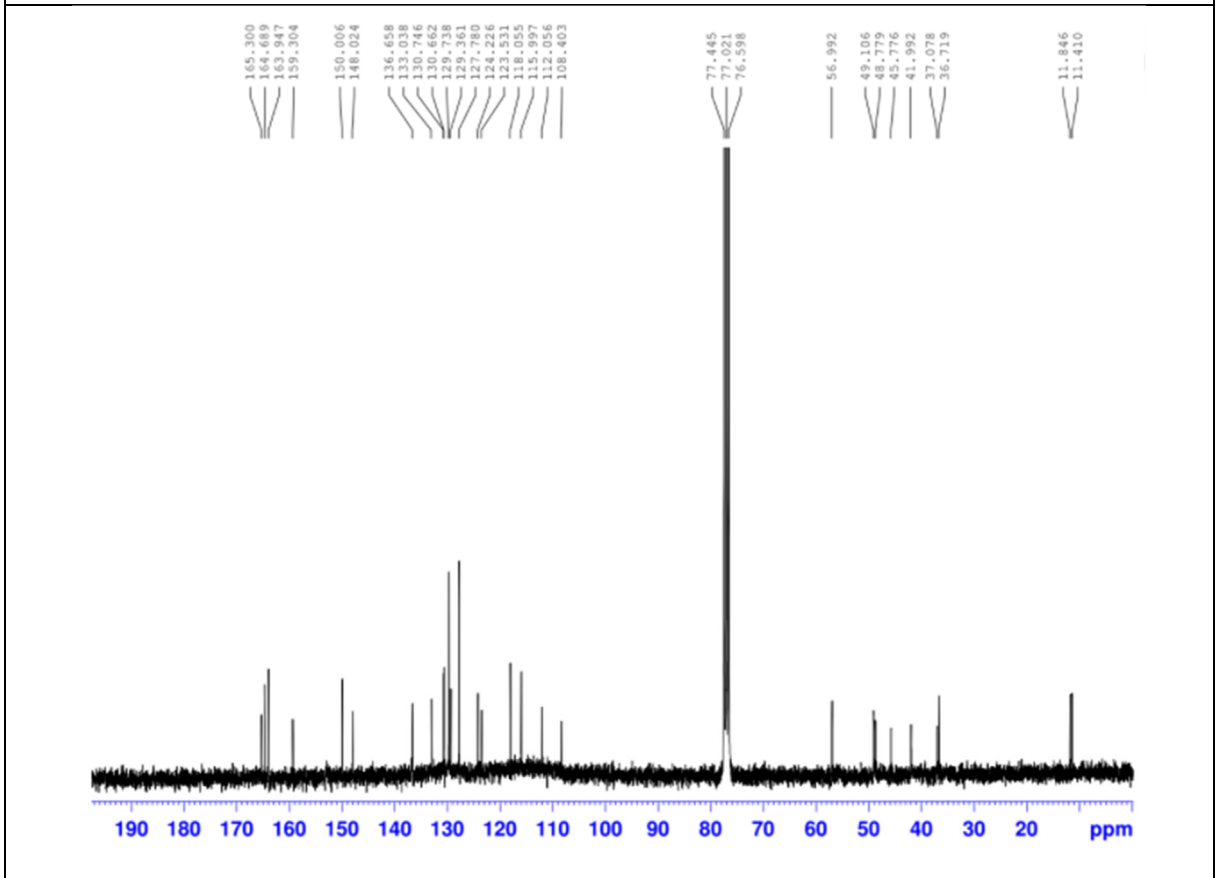
**6b**


165.379
164.607
163.939
159.242
147.945
135.875
129.149
122.582
120.144
111.852
111.093
110.811
108.147
105.266
104.923
104.598
77.438
77.014
76.591
56.933
51.084
50.575
46.337
43.941
42.495
37.015
32.320
20.044
13.688
11.187
10.643
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

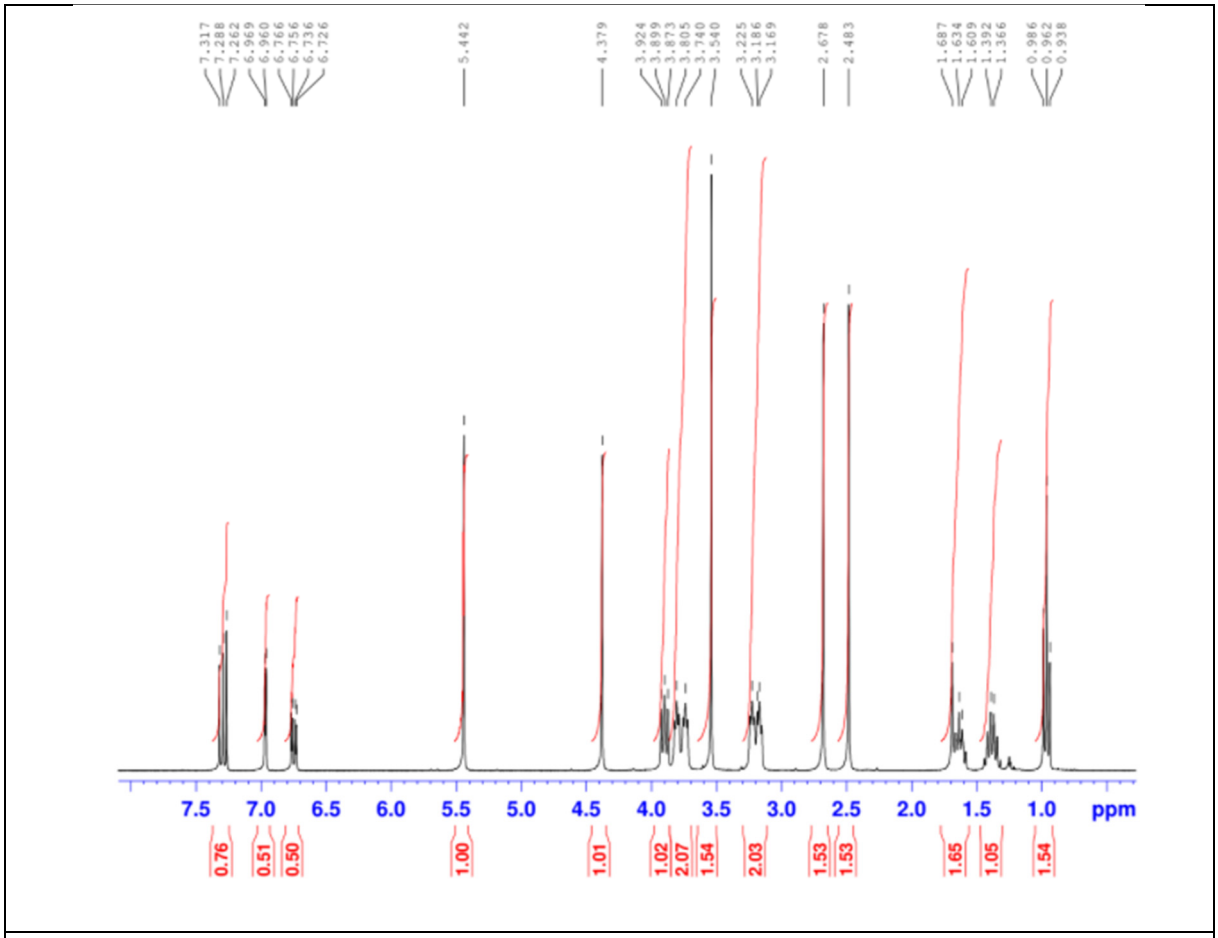
**6b**


7.554
7.535
7.530
7.315
7.286
7.262
7.202
7.194
7.176
6.967
6.958
6.763
6.753
6.733
6.724
5.473
4.376
3.800
3.735
3.575
3.222
3.166
2.431
2.250
1.669
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
3.03
0.91
1.98
1.00
0.99
2.00
2.00
4.12
3.06
4.03
3.01
3.03
1.89

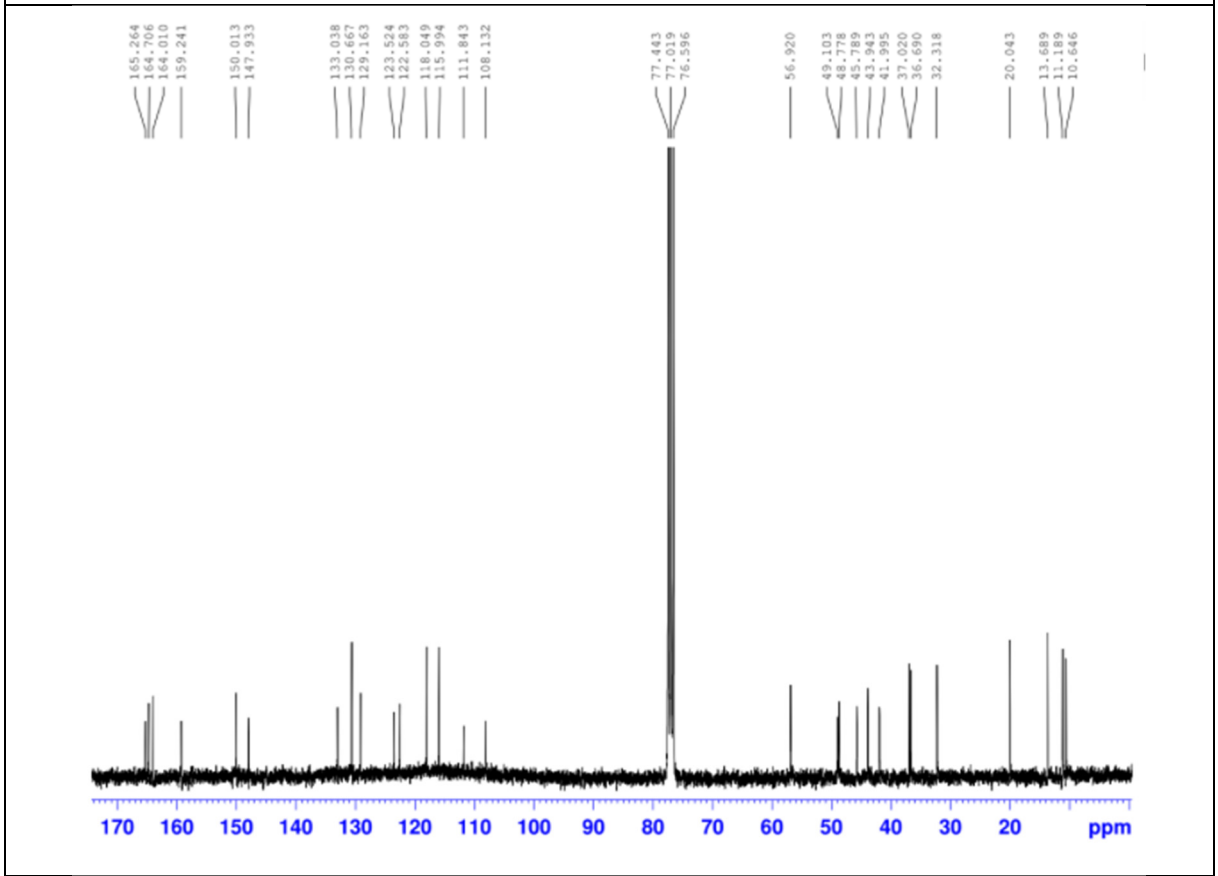
**7a**


165.300
164.689
163.947
159.304
150.006
148.024
136.658
133.038
130.746
130.662
129.738
129.361
127.780
124.226
123.531
118.055
115.997
112.056
108.403
77.445
77.021
76.598
56.992
49.106
48.779
45.776
41.992
37.078
36.719
11.846
11.410
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

**7a**

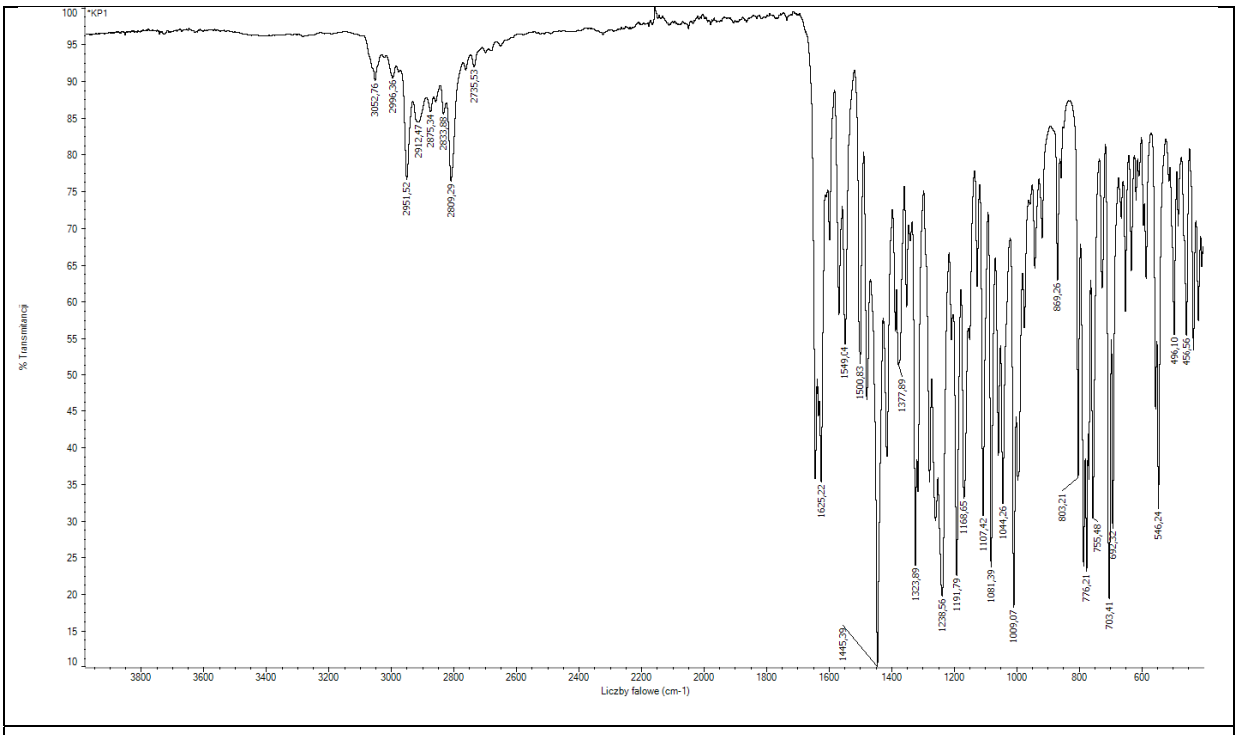

7.317
7.288
7.262
6.969
6.960
6.766
6.756
6.736
6.726
5.442
4.379
3.924
3.899
3.873
3.805
3.740
3.540
3.225
3.186
3.169
2.678
2.483
1.687
1.634
1.609
1.392
1.366
0.986
0.962
0.938
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.76 0.51 0.50 1.00 1.01 1.02 2.07 1.54 2.03 1.53 1.53 1.65 1.05 1.54

**7b**

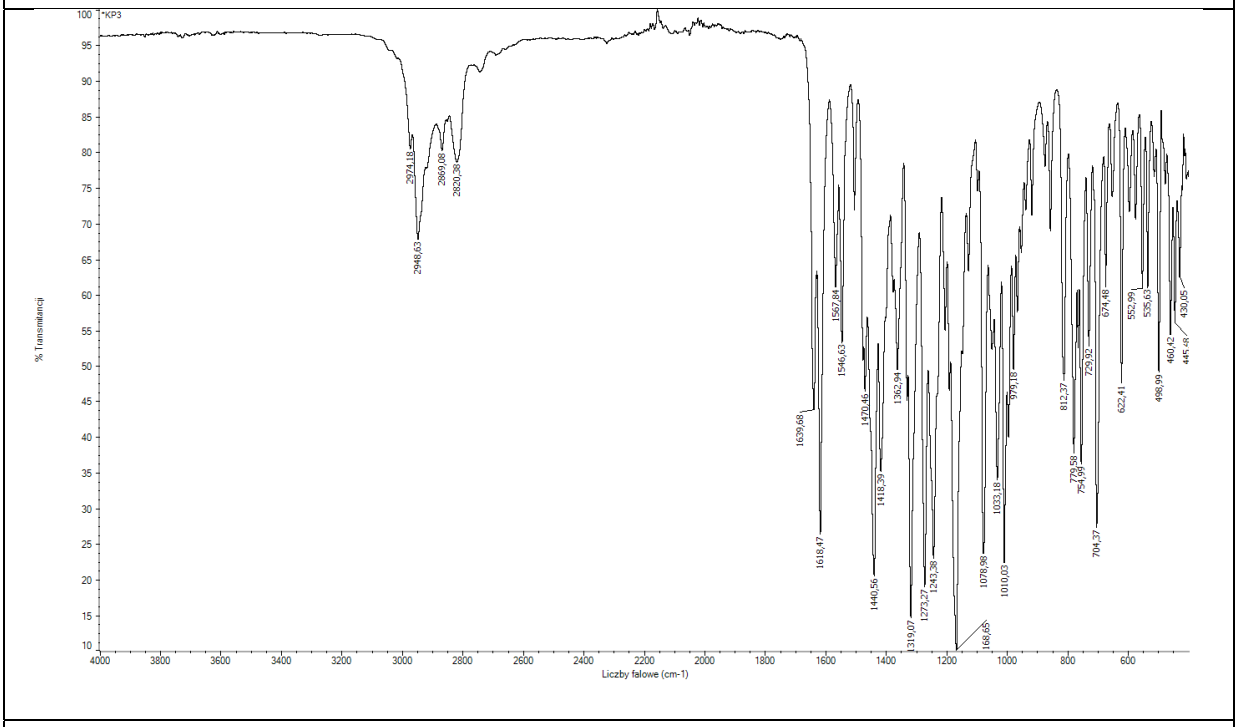

165.264
164.706
164.010
159.241
150.013
147.933
133.038
130.667
129.163
123.524
122.583
118.049
115.994
111.843
108.132
77.443
77.019
76.596
56.920
49.103
48.778
45.789
43.943
41.995
37.020
36.690
32.318
20.043
13.689
11.189
10.646
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

**7b**

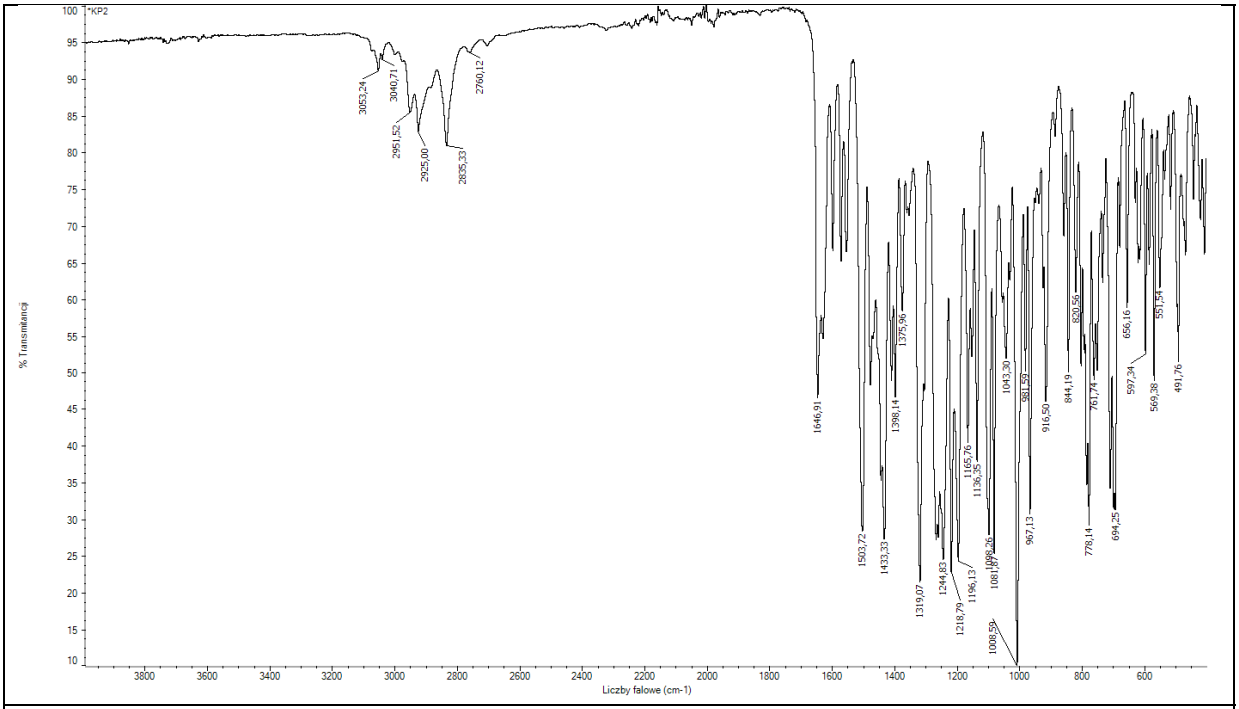
**Table S3.** IR spectra of new compounds



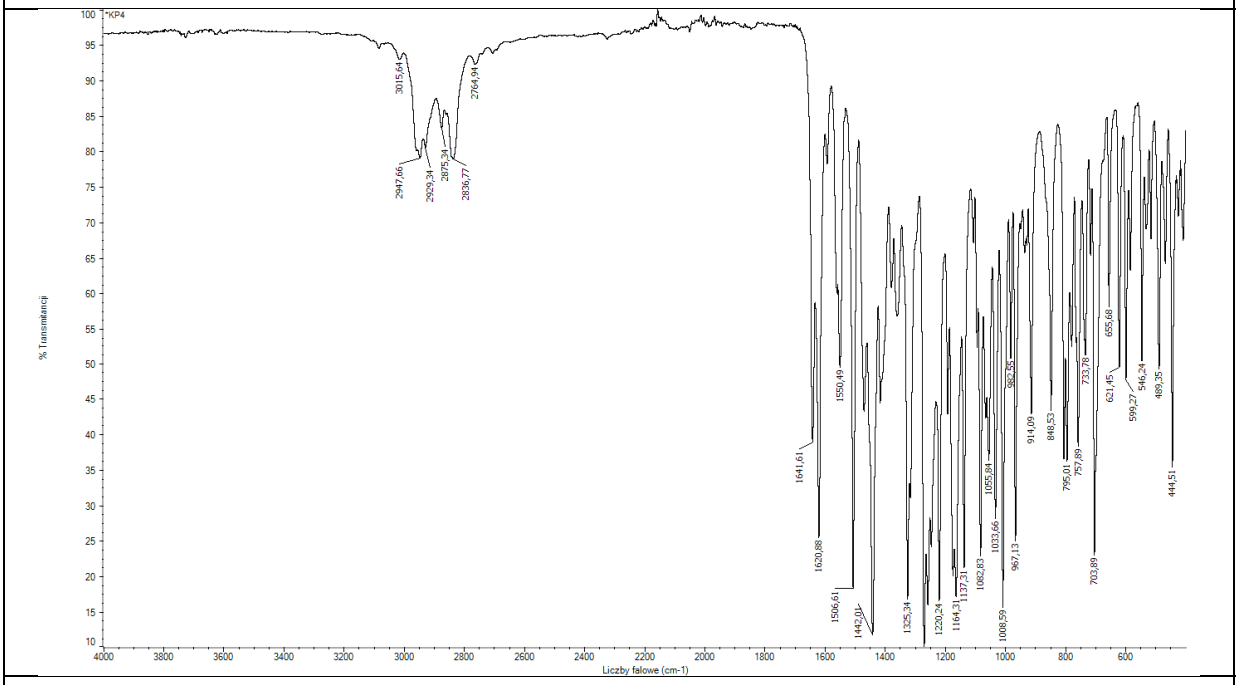

**2a**



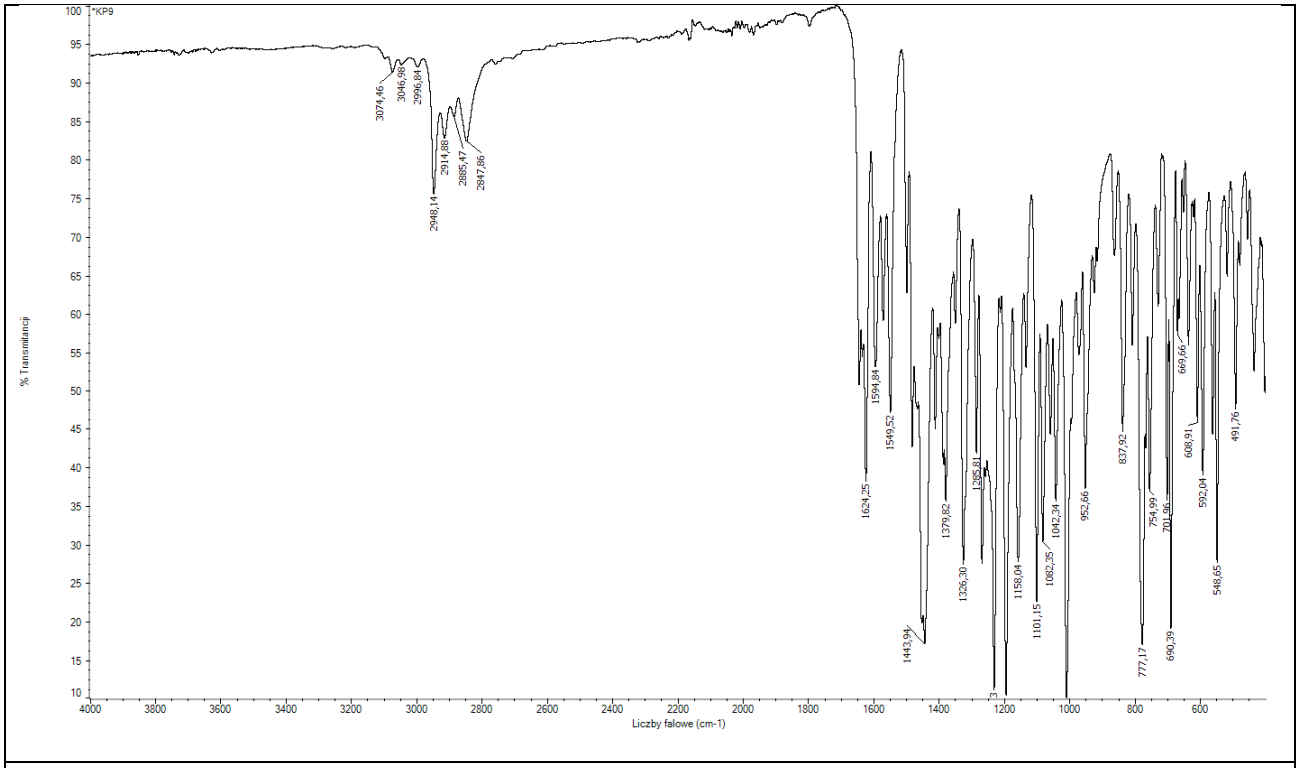

**2b**


*KP2
% Transmitancji
Liczby falowe (cm-1)
3053,24
3040,71
2951,52
2925,00
2835,33
2760,12
1646,91
1503,72
1433,33
1398,14
1375,96
1319,07
1244,83
1218,79
1196,13
1165,76
1136,35
1081,59
1043,30
1008,59
981,59
967,13
916,50
844,19
820,55
778,14
767,74
694,25
656,16
597,34
568,38
551,54
491,76

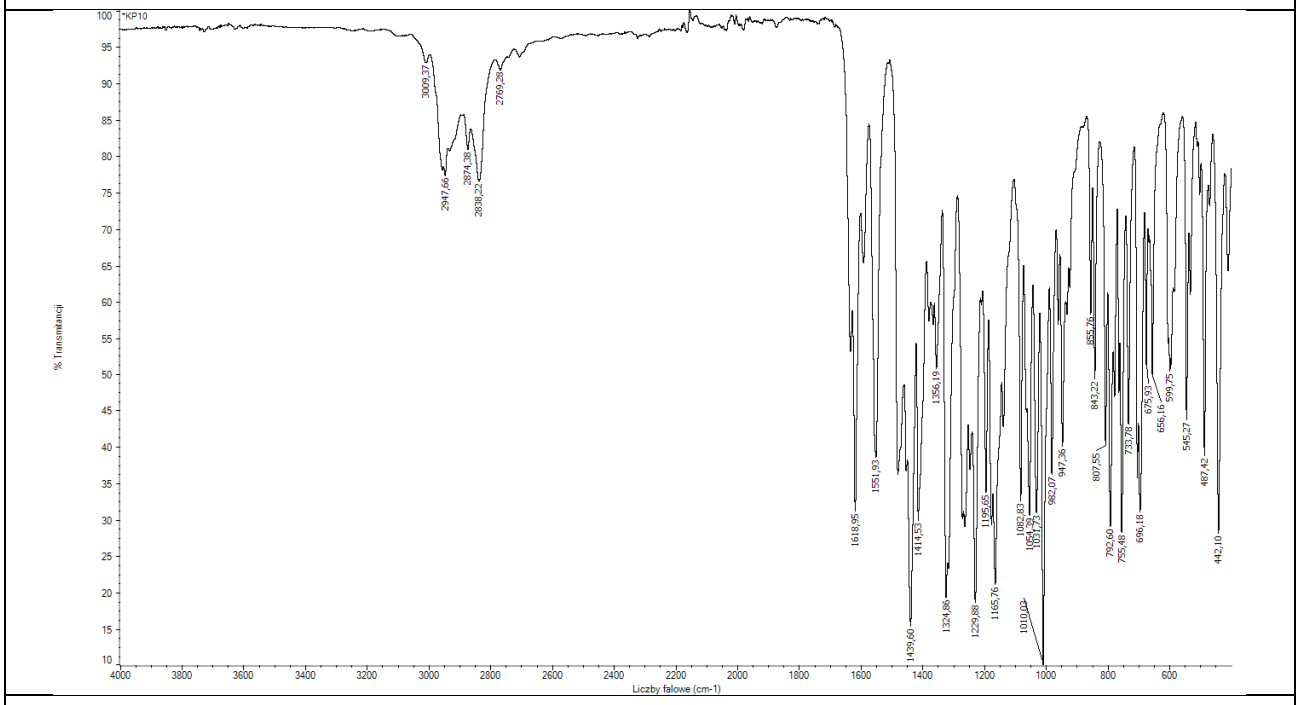
**3a**


*KP4
% Transmitancji
Liczby falowe (cm-1)
3015,64
2947,66
2929,34
2875,24
2836,77
2764,91
1641,61
1620,88
1550,49
1506,61
1442,01
1325,34
1220,24
1164,31
1137,31
1082,83
1055,84
1033,66
1008,59
982,55
967,13
914,09
848,53
795,01
757,89
733,78
703,89
655,68
621,45
599,27
546,24
489,35
444,51

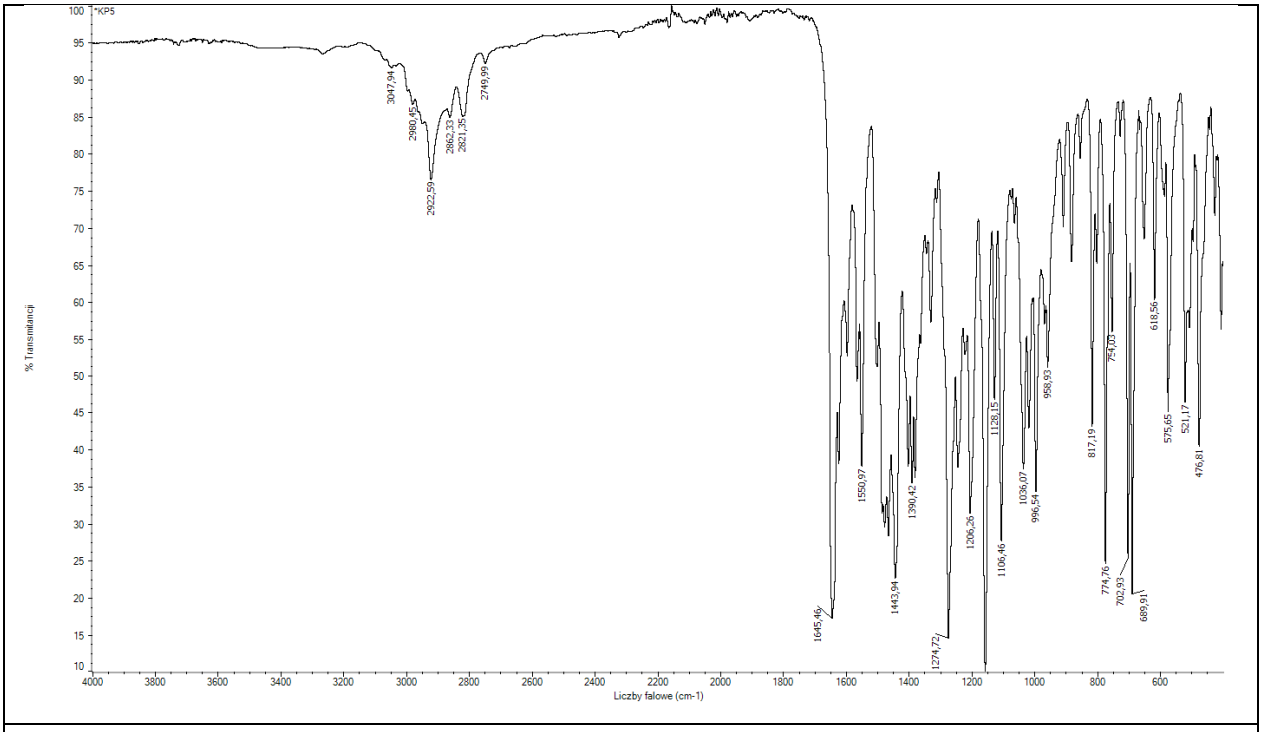
**3b**


*KP9
% Transmitancji
Liczby falowe (cm-1)
3074,46
3046,86
2996,84
2948,14
2914,88
2885,47
2847,86
1624,25
1594,84
1549,52
1443,94
1379,82
1326,30
1305,81
1158,04
1101,15
1082,35
1042,34
952,66
837,92
777,17
754,99
701,96
690,39
669,66
608,91
592,04
548,65
491,76

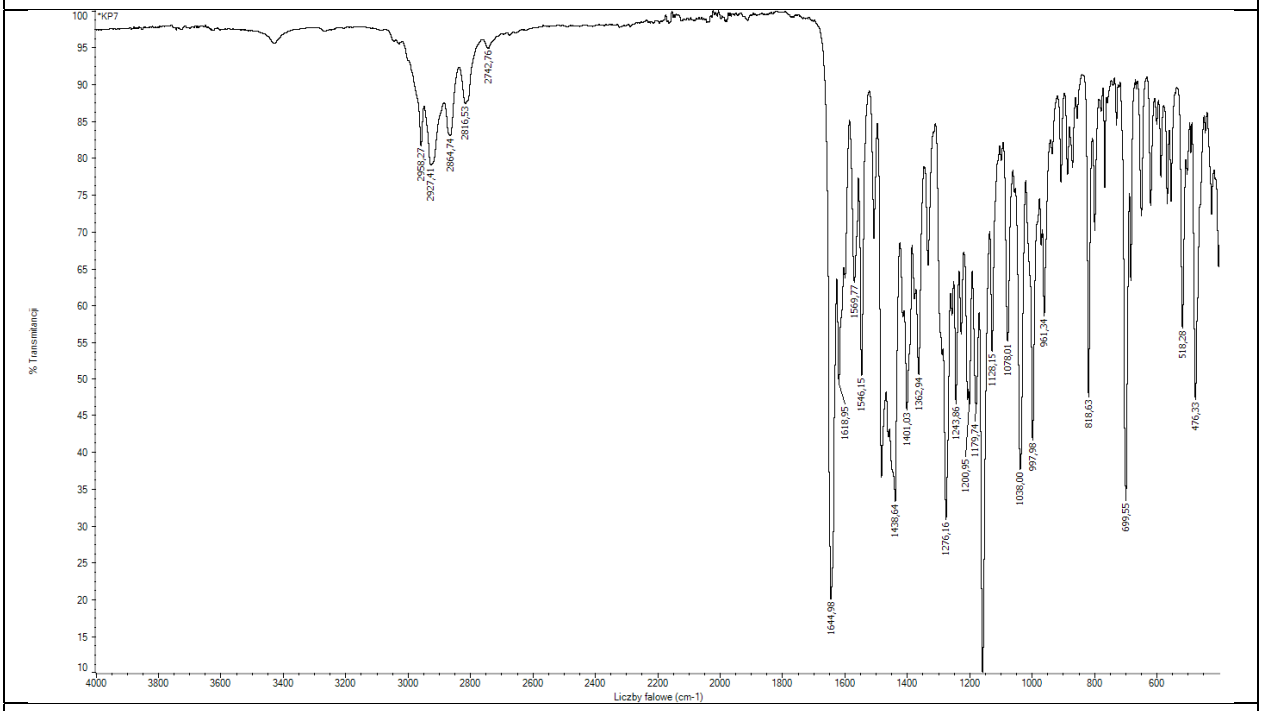
**4a**


*KP10
% Transmitancji
Liczby falowe (cm-1)
3009,37
2947,66
2874,38
2838,22
2769,28
1618,95
1551,93
1439,60
1414,53
1356,19
1324,86
1229,88
1195,65
1165,76
1082,83
1051,73
1010,00
982,07
947,36
855,76
843,22
807,55
792,60
755,48
733,28
696,18
675,93
656,16
599,75
545,27
487,42
442,10

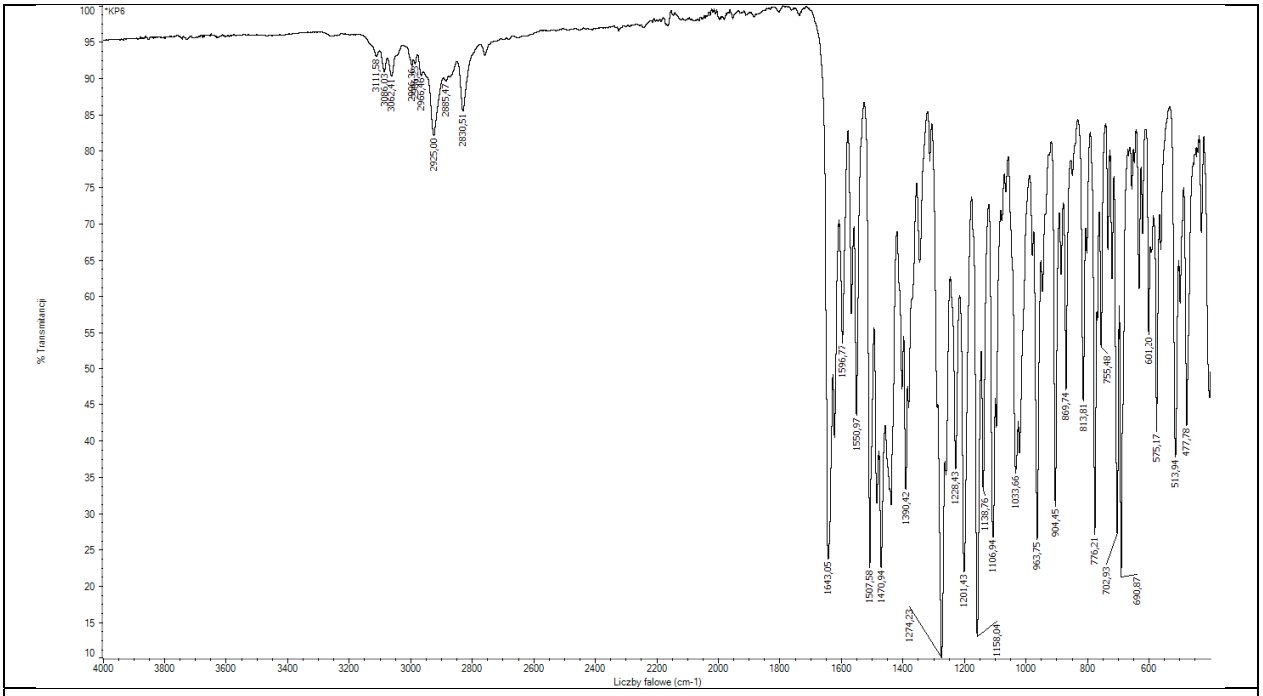
**4b**


*KP5
% Transmitancji
Liczby falowe (cm-1)
3047,94
2980,45
2922,59
2862,33
2821,35
2749,99
1645,46
1550,97
1443,94
1390,42
1274,72
1206,26
1128,15
1106,46
1036,07
996,54
958,93
817,19
774,76
754,03
702,93
689,91
618,56
575,65
521,17
476,81

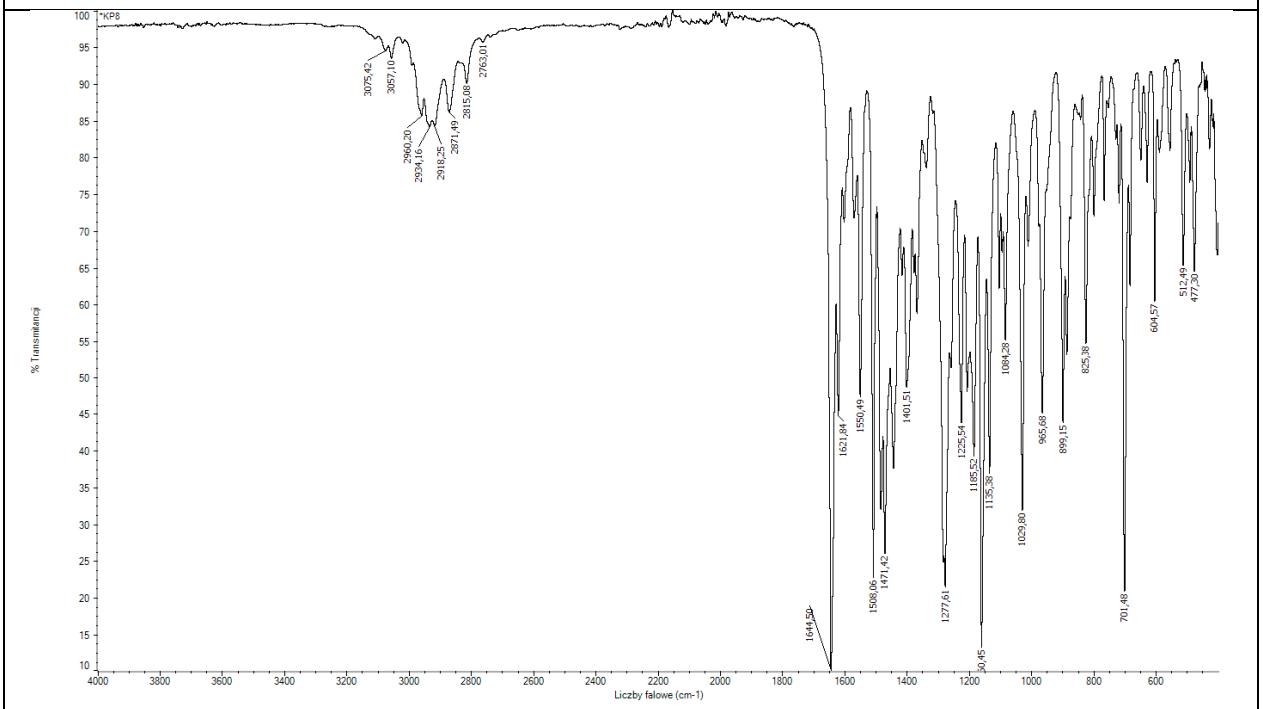
**5a**


*KP7
% Transmitancji
Liczby falowe (cm-1)
2958,27
2927,41
2864,74
2816,53
2742,76
1644,98
1618,95
1569,77
1546,15
1438,64
1401,03
1362,94
1276,16
1243,86
1200,95
1179,74
1128,15
1078,01
1038,00
997,98
961,34
818,63
699,55
518,28
476,33

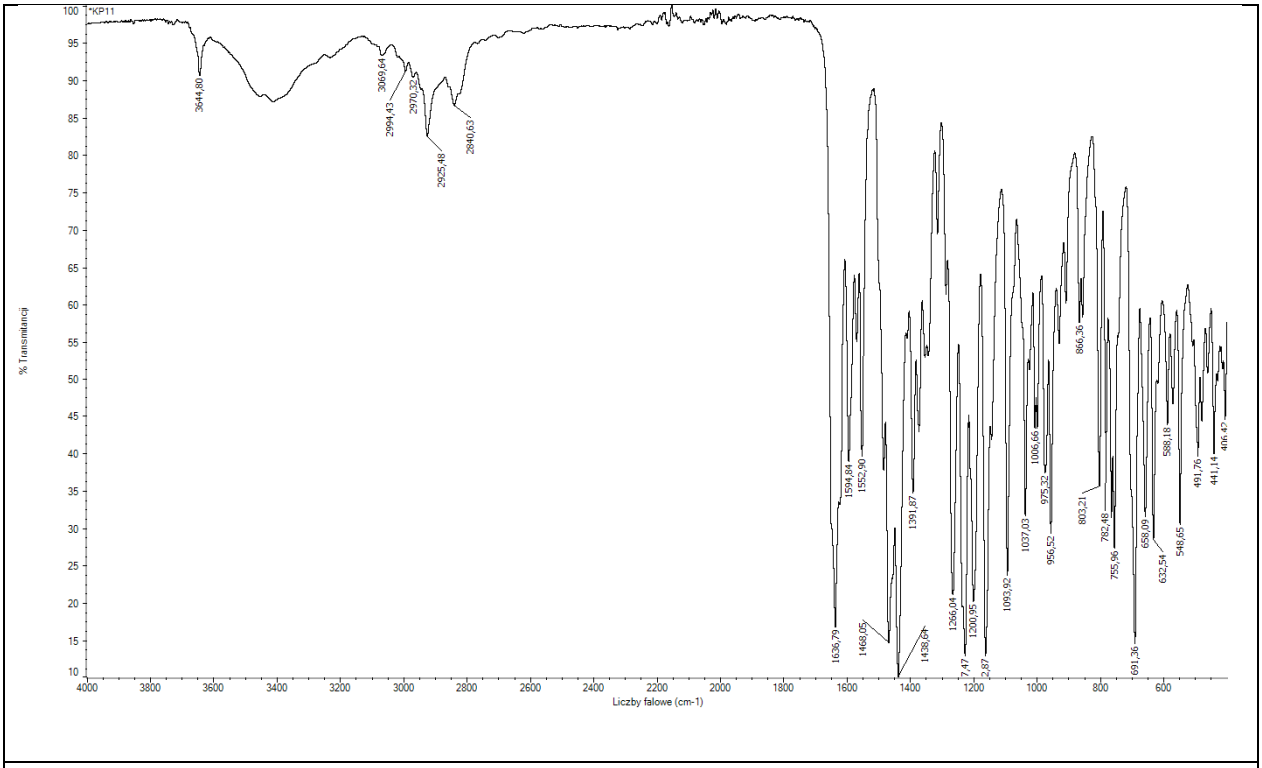
**5b**


*KP6
% Transmitancji
Liczby falowe (cm-1)
3111,58
3075,42
3057,10
3025,41
2966,76
2925,00
2885,47
2830,51
1643,05
1596,71
1550,97
1507,58
1470,94
1390,42
1274,23
1228,43
1201,43
1158,04
1138,76
1106,94
1033,66
963,75
904,45
869,74
813,81
776,21
755,48
702,93
690,87
601,30
575,17
513,94
477,78

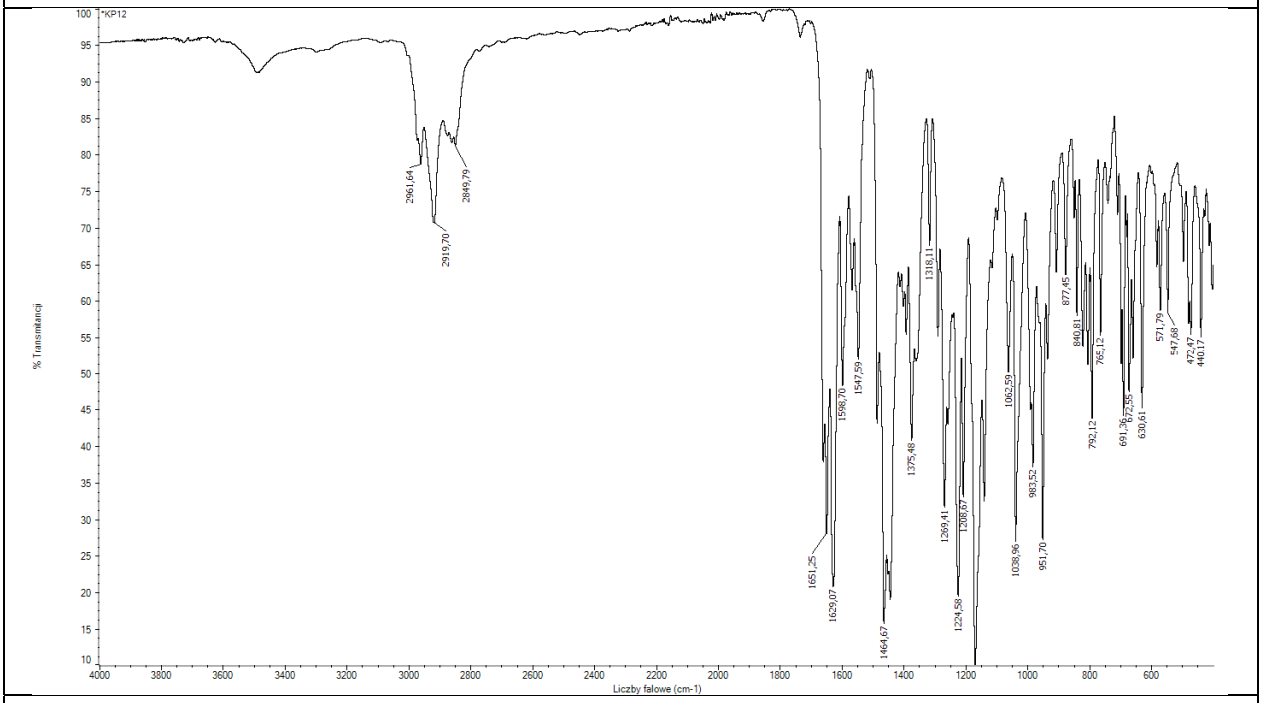
**6a**


*KP8
% Transmitancji
Liczby falowe (cm-1)
3075,42
3057,10
2960,20
2934,16
2918,25
2871,49
2815,08
2763,01
1644,50
1621,84
1550,49
1508,06
1471,42
1401,51
1277,61
1225,54
1185,52
1135,38
1084,28
1029,80
965,68
899,15
825,38
701,48
604,57
512,49
477,30

**6b**

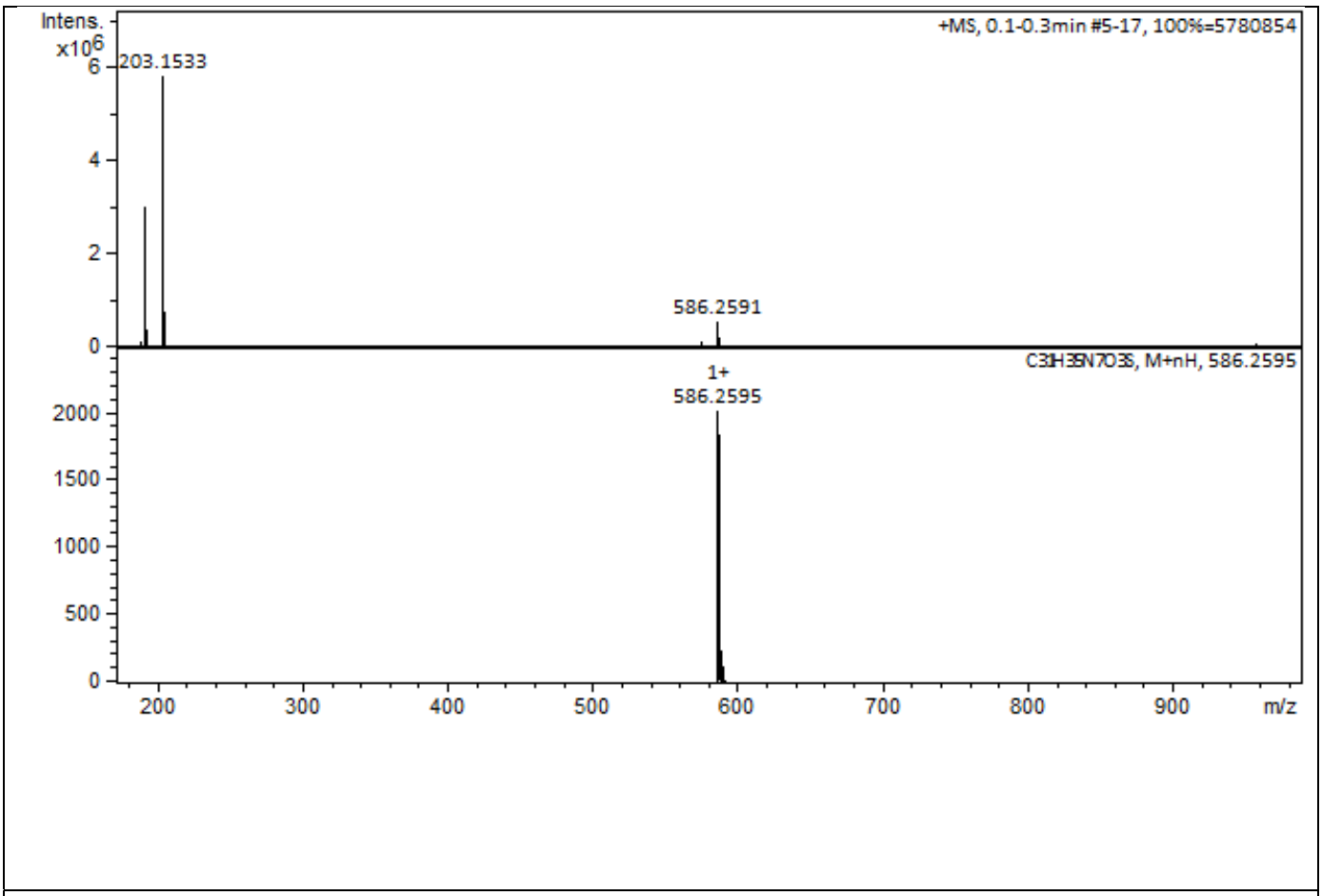

*KP11
% Transmitancji
Liczby falowe (cm-1)
3644,80
3069,64
2994,43
2970,22
2925,48
2840,63
1636,79
1594,84
1552,90
1468,05
1438,64
1391,87
1366,04
1347,47
1320,95
1093,92
1037,03
1006,66
975,52
956,52
866,36
803,21
782,48
755,96
691,36
658,09
632,54
598,18
548,65
491,76
441,14
416,47

**7a**

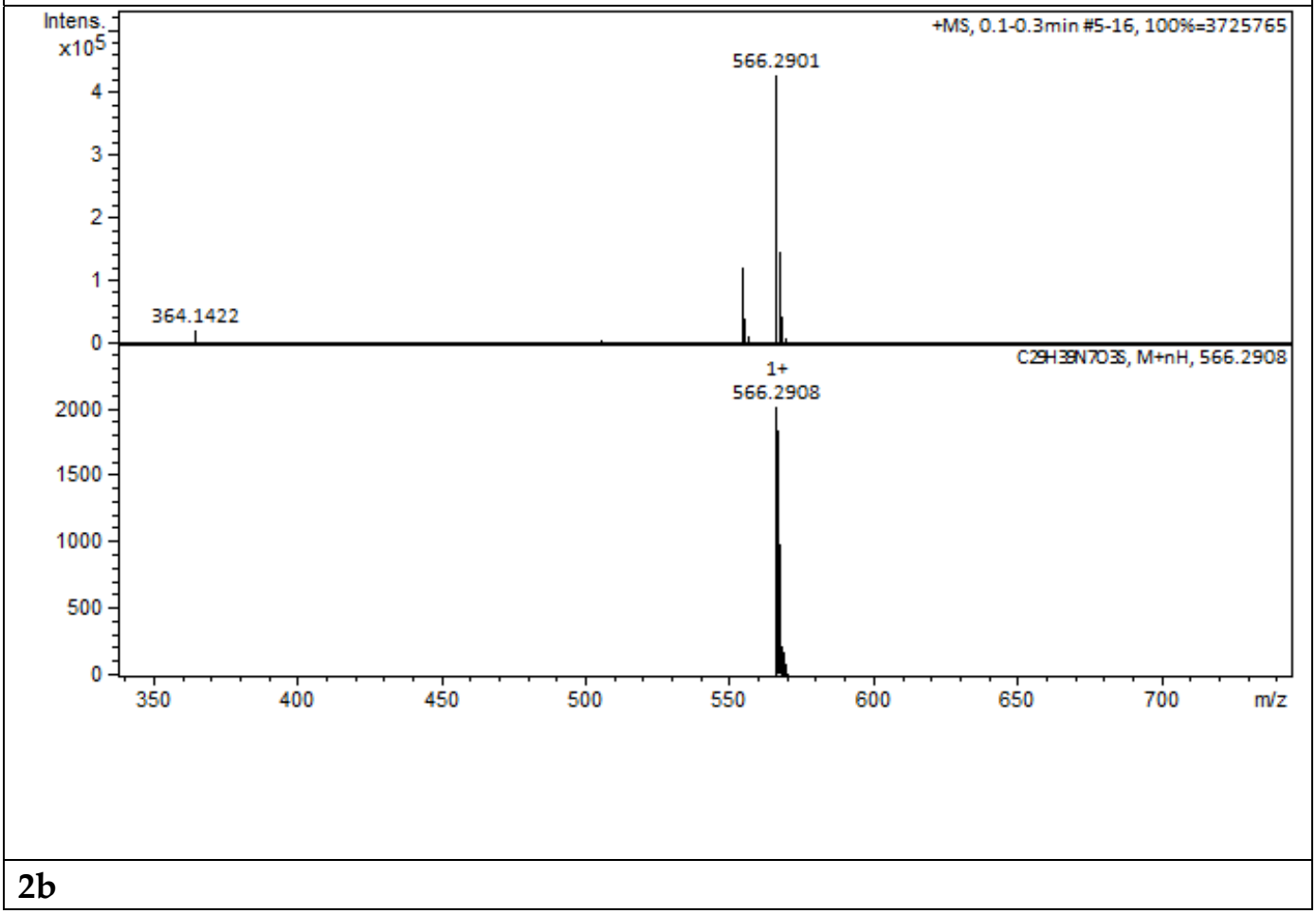

*KP12
% Transmitancji
Liczby falowe (cm-1)
2961,64
2919,70
2849,79
1651,25
1629,07
1598,70
1547,59
1464,67
1375,48
1318,11
1269,41
1206,67
1224,58
1062,59
1038,96
983,52
951,70
877,45
840,81
792,12
765,12
691,36
672,55
630,61
571,79
547,68
472,47
440,17

**7b**

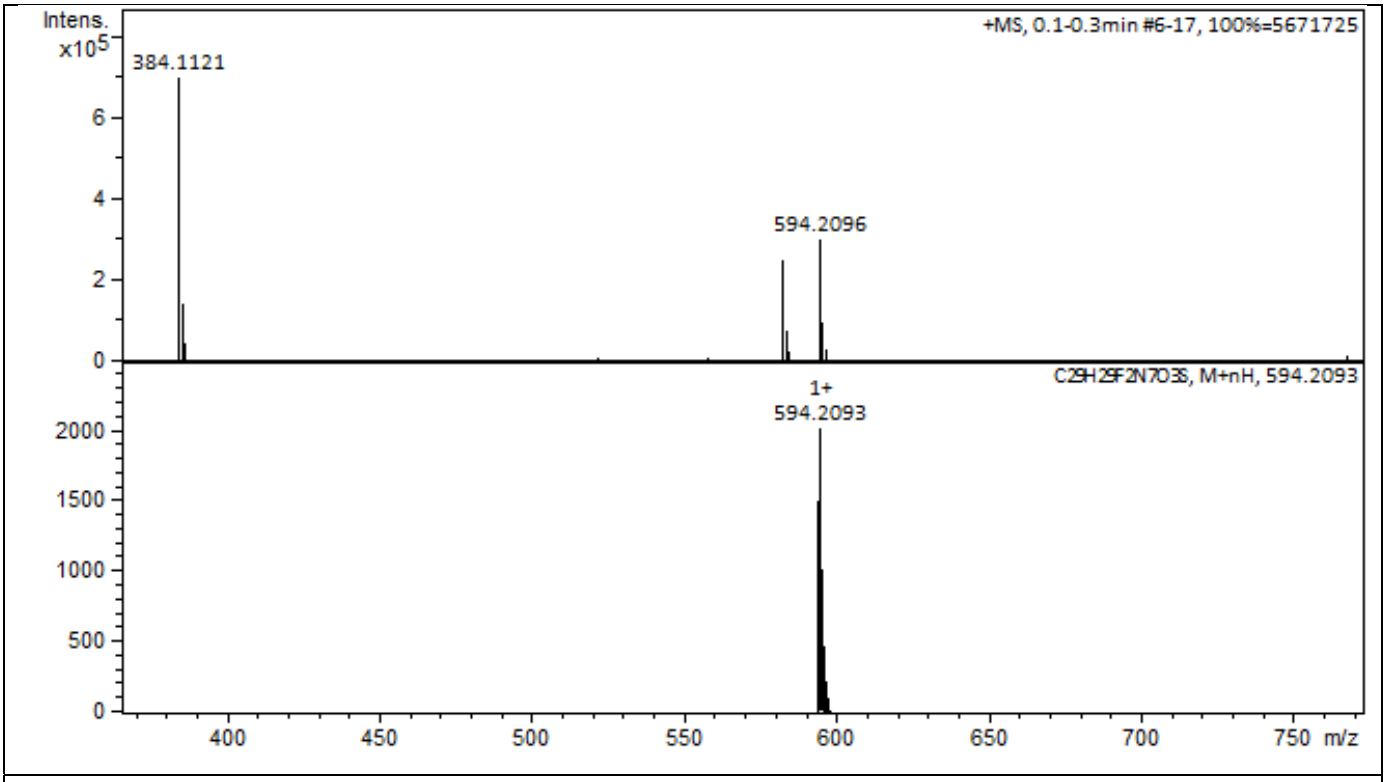
**Table S4.** Mass spectra of new compounds



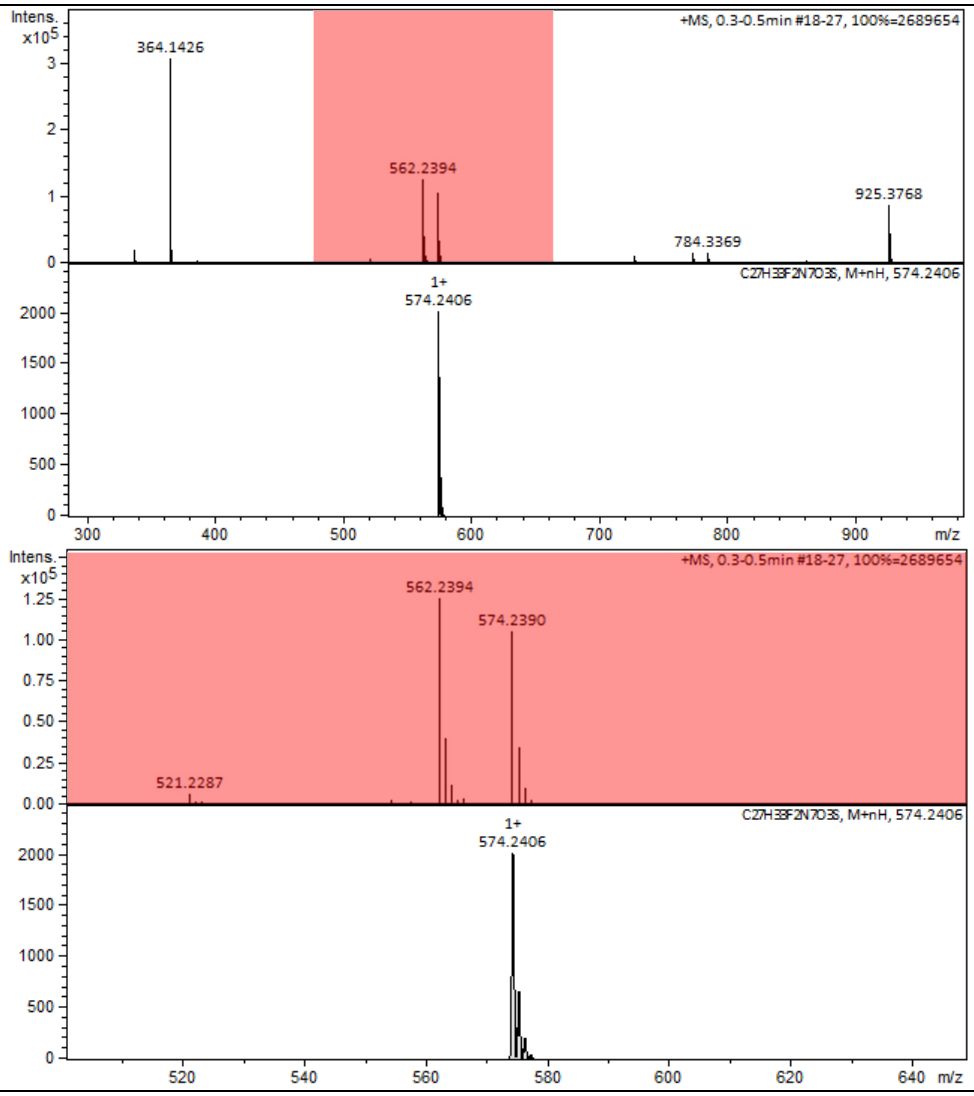

**2a**



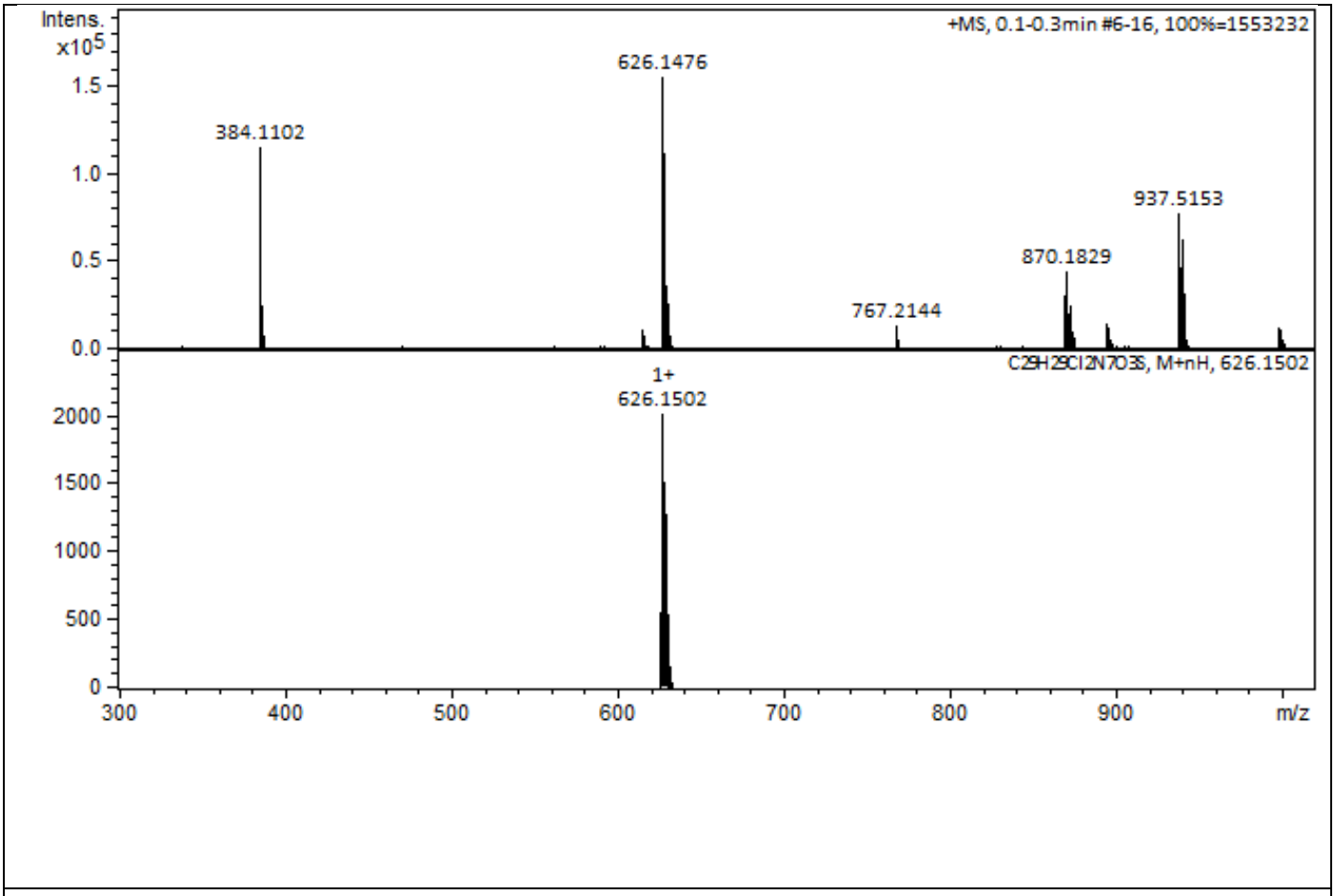

**2b**


Intens.
x10^5
+MS, 0.1-0.3min #6-17, 100%=5671725
384.1121
594.2096
C29H29F2N7O3S, M+nH, 594.2093
1+
594.2093
m/z

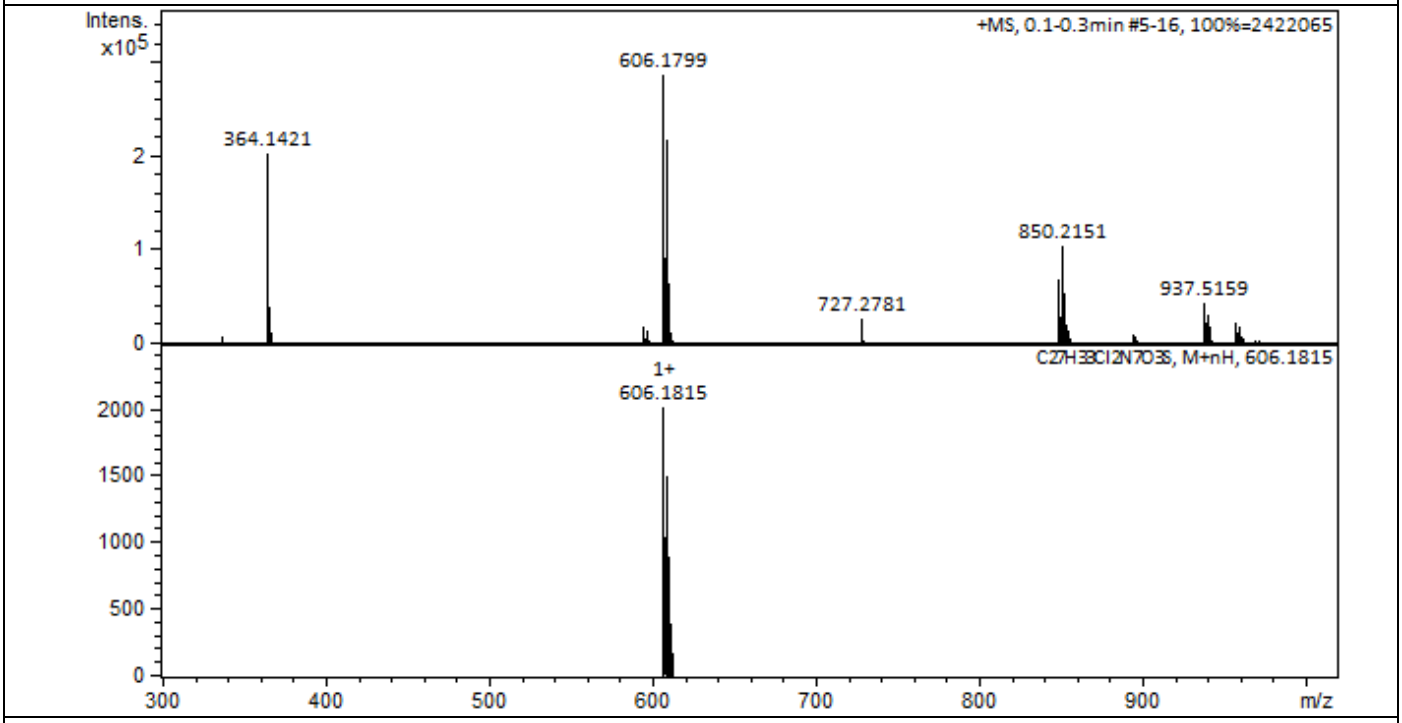
**3a**


Intens.
x10^5
+MS, 0.3-0.5min #18-27, 100%=2689654
364.1426
562.2394
925.3768
784.3369
C27H33F2N7O3S, M+nH, 574.2406
1+
574.2406
m/z
Intens.
x10^5
+MS, 0.3-0.5min #18-27, 100%=2689654
562.2394
574.2390
521.2287
C27H33F2N7O3S, M+nH, 574.2406
1+
574.2406
m/z

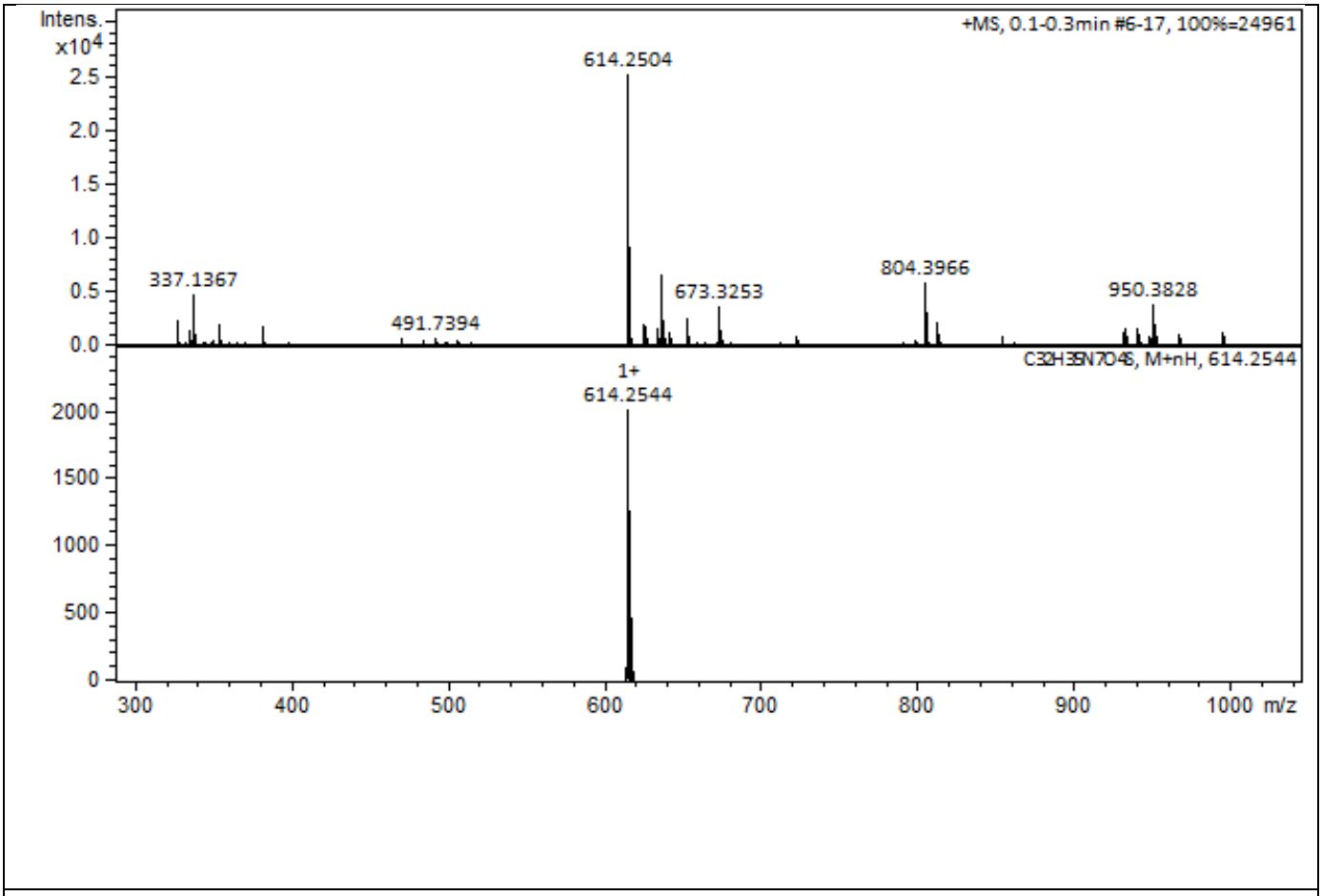
**3b**


Intens.
x10^5
+MS, 0.1-0.3min #6-16, 100%=1553232
626.1476
384.1102
937.5153
870.1829
767.2144
C29H29Cl2N7O3S, M+nH, 626.1502
1+
626.1502
m/z

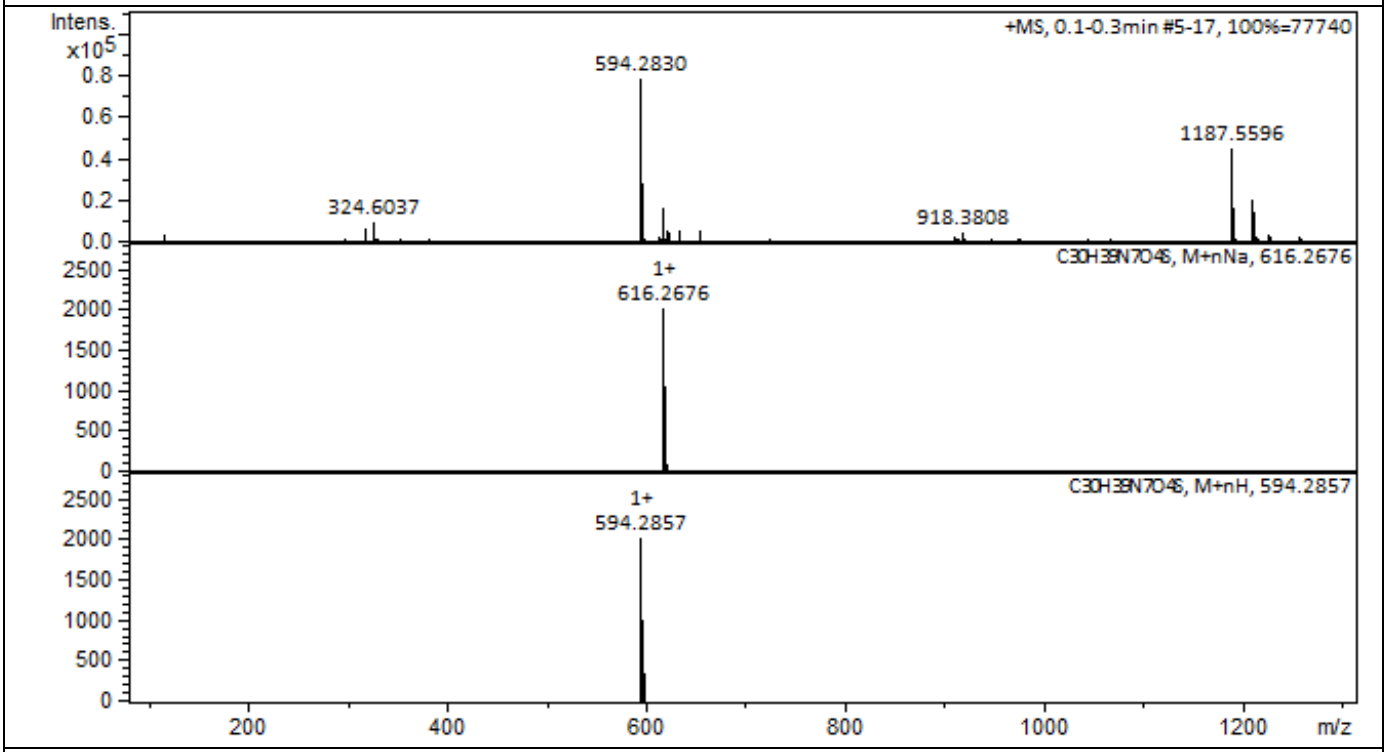
**4a**


Intens.
x10^5
+MS, 0.1-0.3min #5-16, 100%=2422065
606.1799
364.1421
850.2151
937.5159
727.2781
C27H33Cl2N7O3S, M+nH, 606.1815
1+
606.1815
m/z

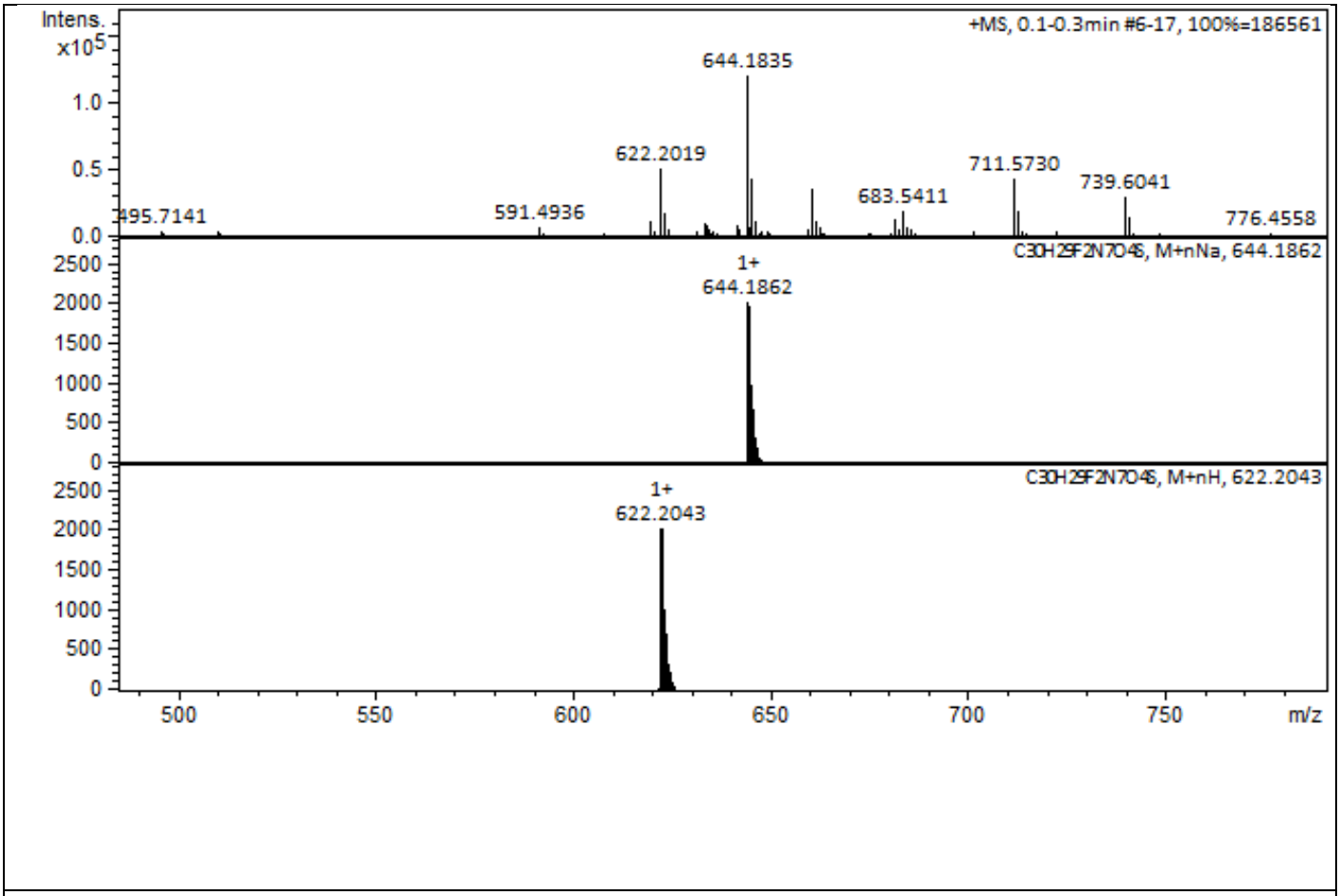
**4b**


Intens.
x10^4
+MS, 0.1-0.3min #6-17, 100%=24961
614.2504
337.1367
491.7394
673.3253
804.3966
950.3828
C32H39N7O4S, M+nH, 614.2544
1+
614.2544
m/z

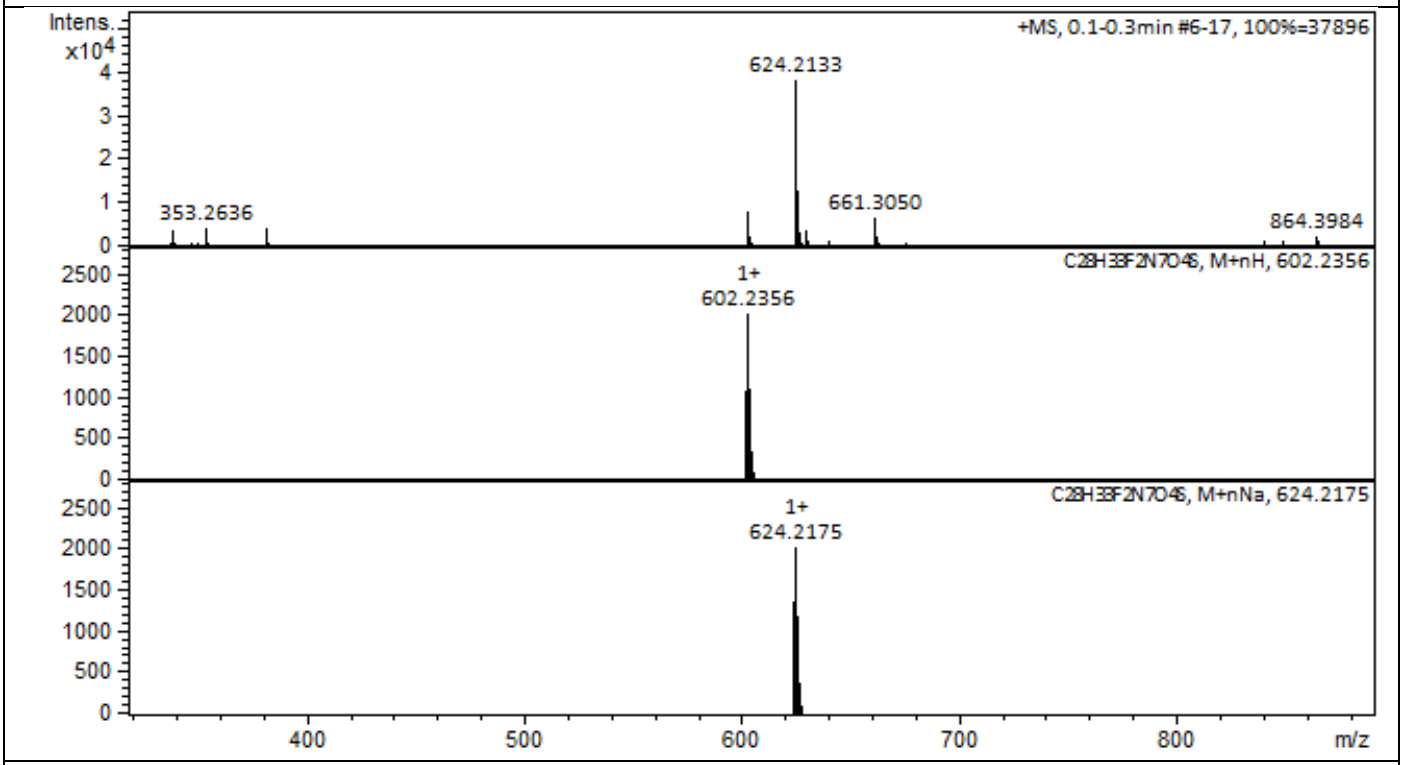
**5a**


Intens.
x10^5
+MS, 0.1-0.3min #5-17, 100%=77740
594.2830
1187.5596
324.6037
918.3808
C30H39N7O4S, M+nNa, 616.2676
1+
616.2676
C30H39N7O4S, M+nH, 594.2857
1+
594.2857
m/z

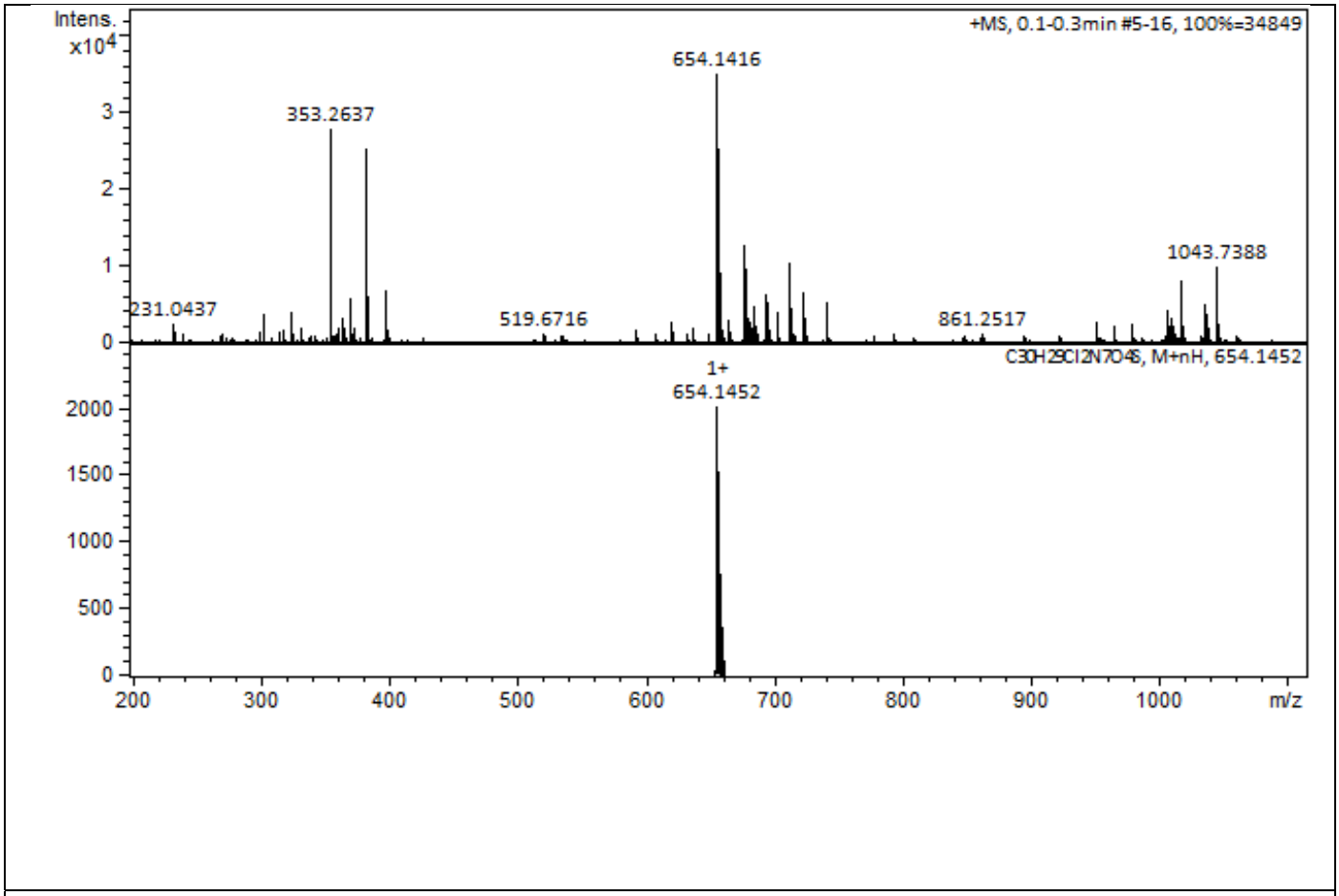
**5b**


Intens.
x10^5
+MS, 0.1-0.3min #6-17, 100%=186561
644.1835
622.2019
711.5730
739.6041
683.5411
591.4936
495.7141
776.4558
C30H29F2N7O4S, M+nNa, 644.1862
1+
644.1862
C30H29F2N7O4S, M+nH, 622.2043
1+
622.2043
m/z

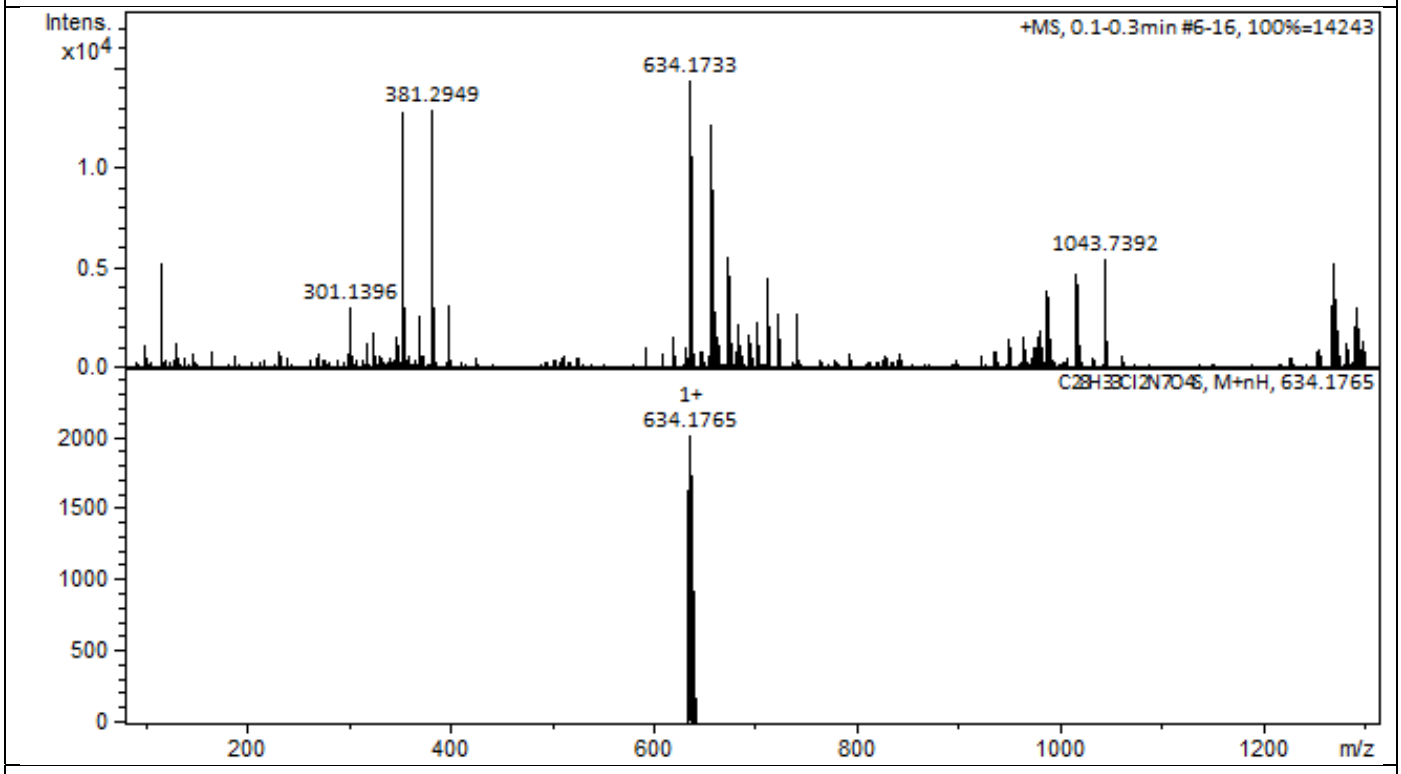
**6a**


Intens.
x10^4
+MS, 0.1-0.3min #6-17, 100%=37896
624.2133
661.3050
353.2636
864.3984
C28H33F2N7O4S, M+nH, 602.2356
1+
602.2356
C28H33F2N7O4S, M+nNa, 624.2175
1+
624.2175
m/z

**6b**


Intens.
x10^4
+MS, 0.1-0.3min #5-16, 100%=34849
654.1416
353.2637
1043.7388
231.0437
519.6716
861.2517
C30H29Cl2N7O4S, M+nH, 654.1452
1+
654.1452
m/z

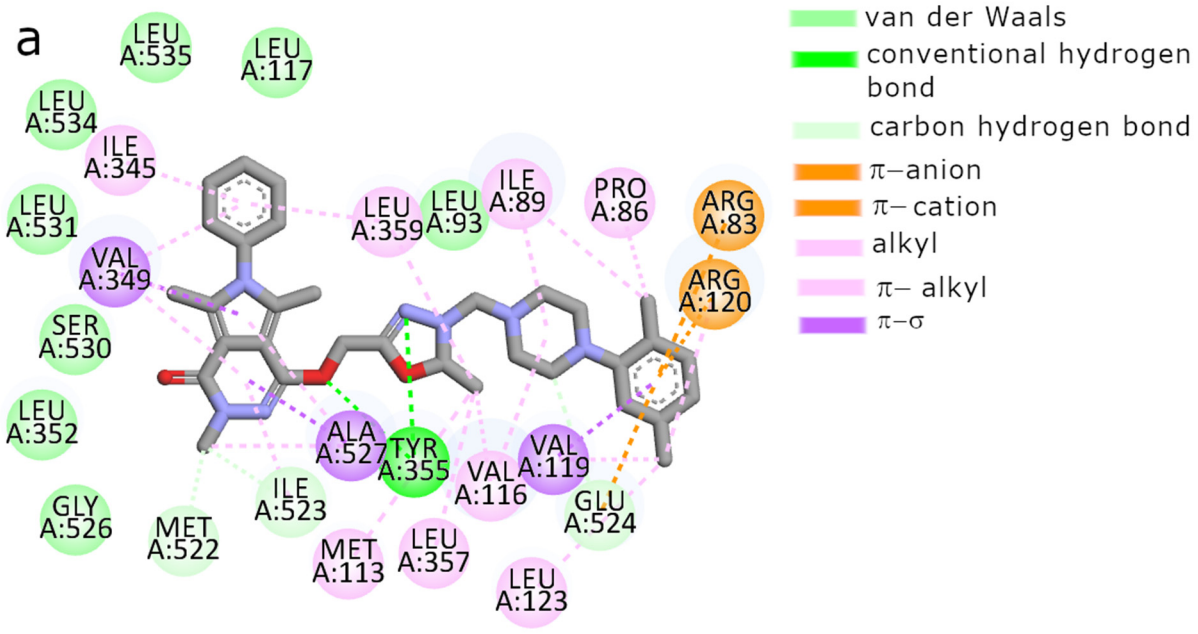
**7a**


Intens.
x10^4
+MS, 0.1-0.3min #6-16, 100%=14243
634.1733
381.2949
1043.7392
301.1396
C28H33Cl2N7O4S, M+nH, 634.1765
1+
634.1765
m/z

**7b**

**Table S5.** The 2D intermolecular interactions of investigated compounds in the active site of COX

**Figure S1**. The intermolecular interactions of **2a** in the active centre of a) COX-1 b) COX-2



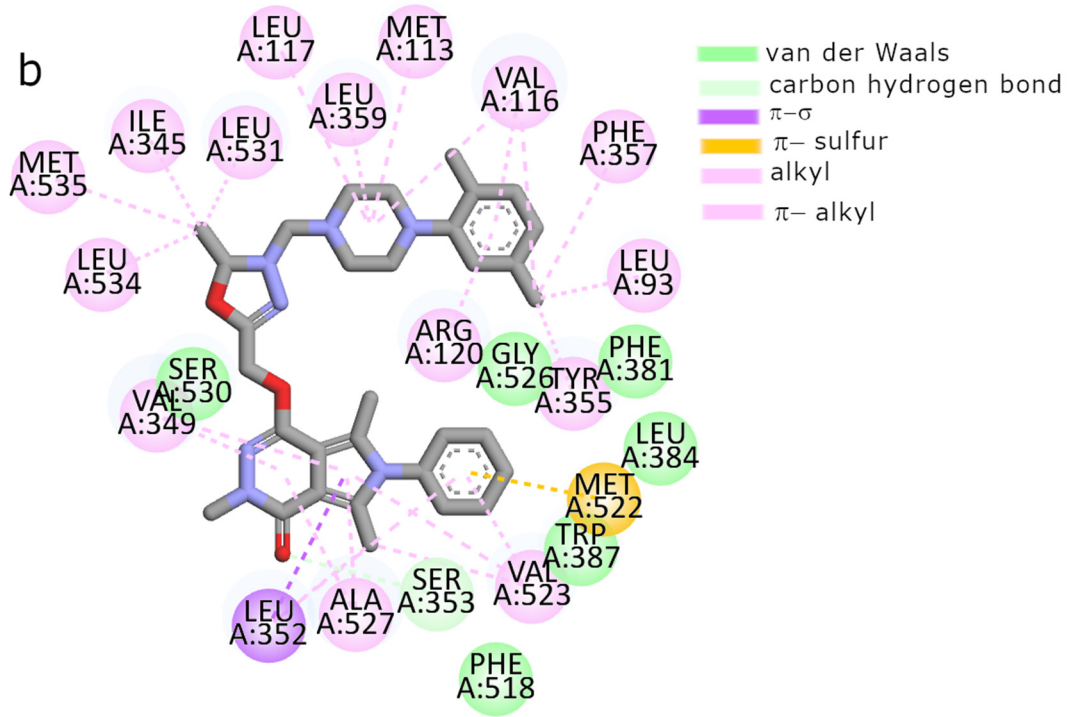



**Figure S2**. The intermolecular interactions of **2b** in the active centre of a) COX-1 b) COX-2

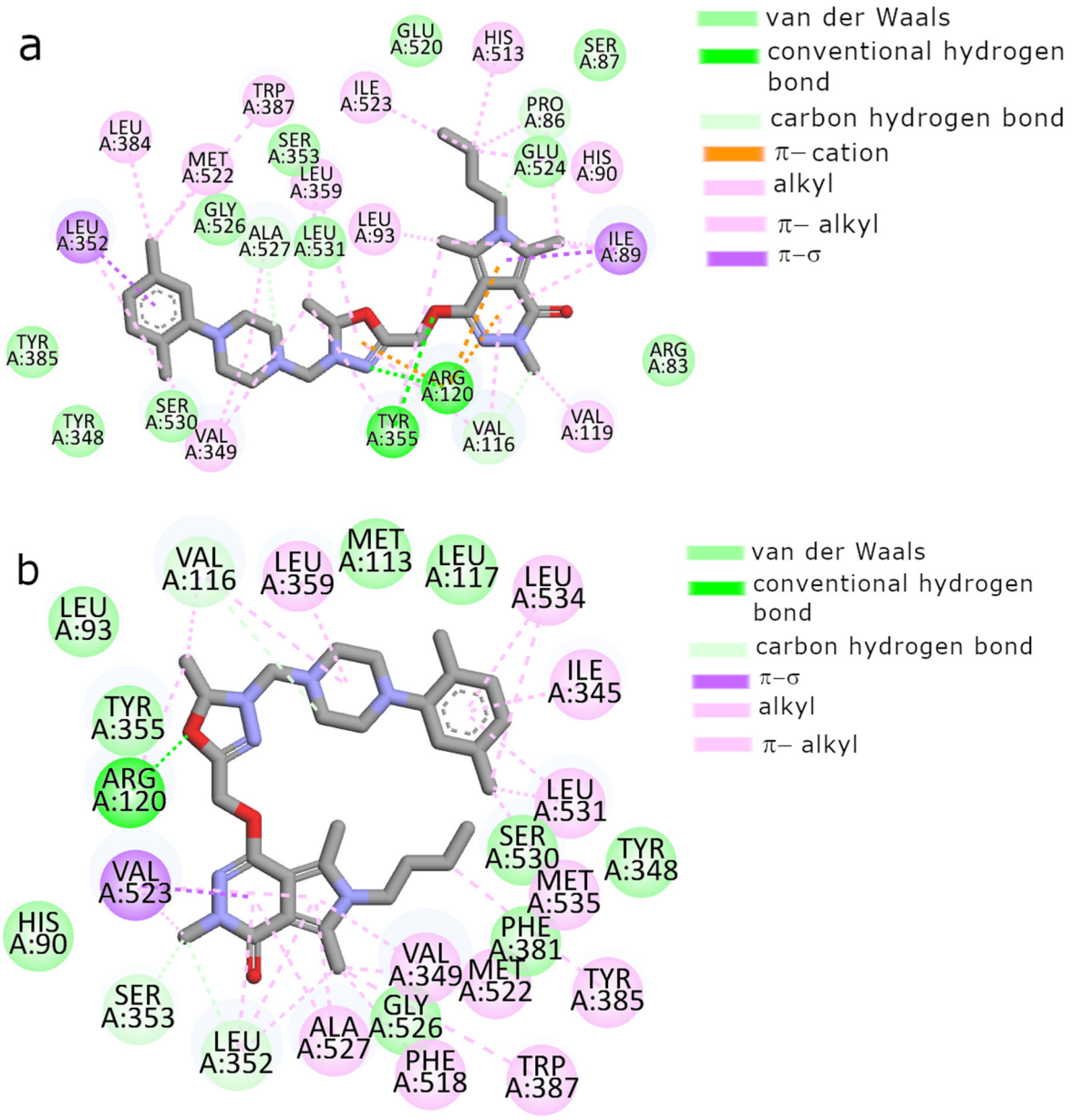


**Figure S3**. The intermolecular interactions of **3a** in the active centre of a) COX-1 b) COX-2

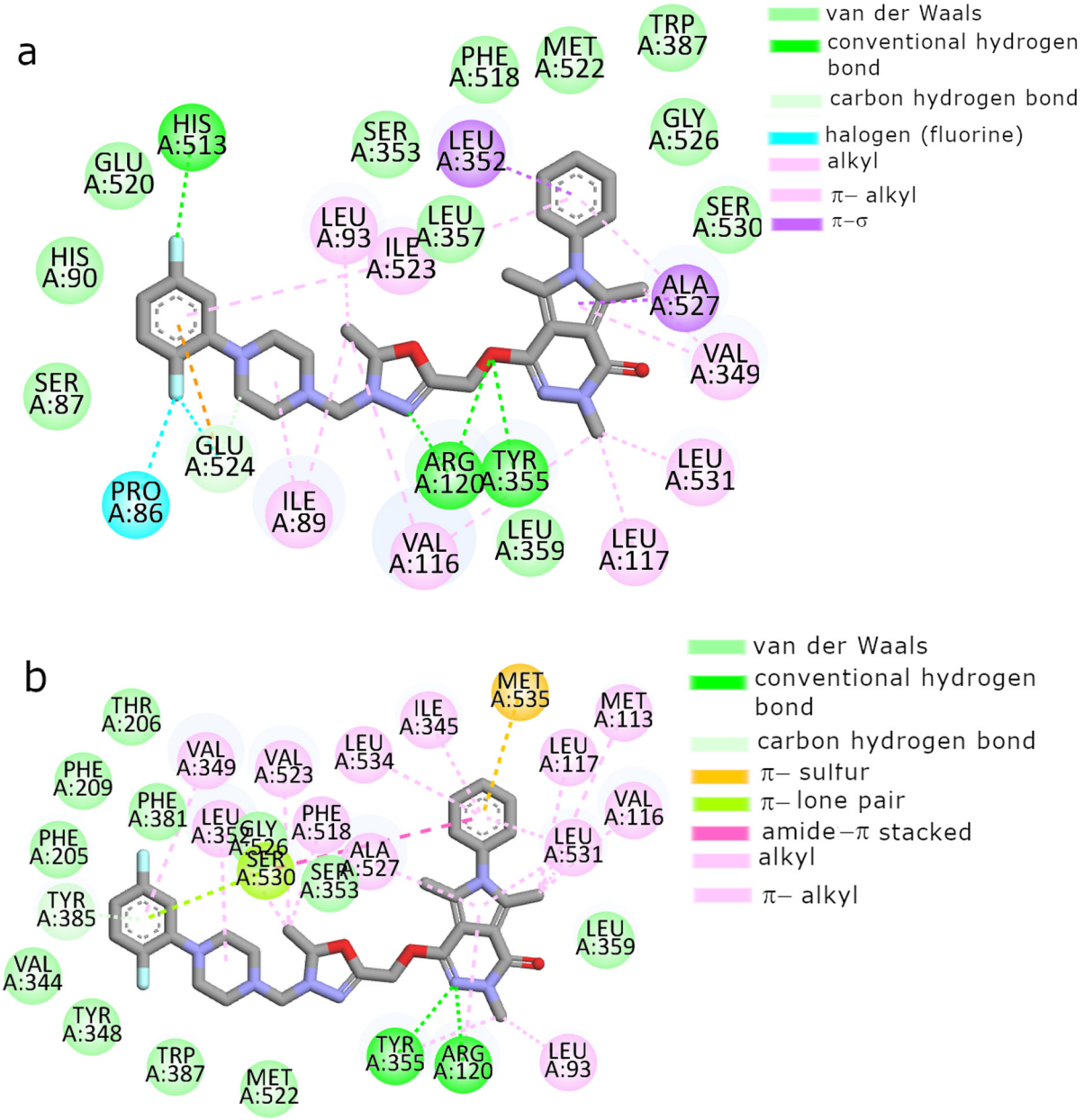


**Figure S4.** The intermolecular interactions of **3b** in the active centre of a) COX-1 b) COX-2

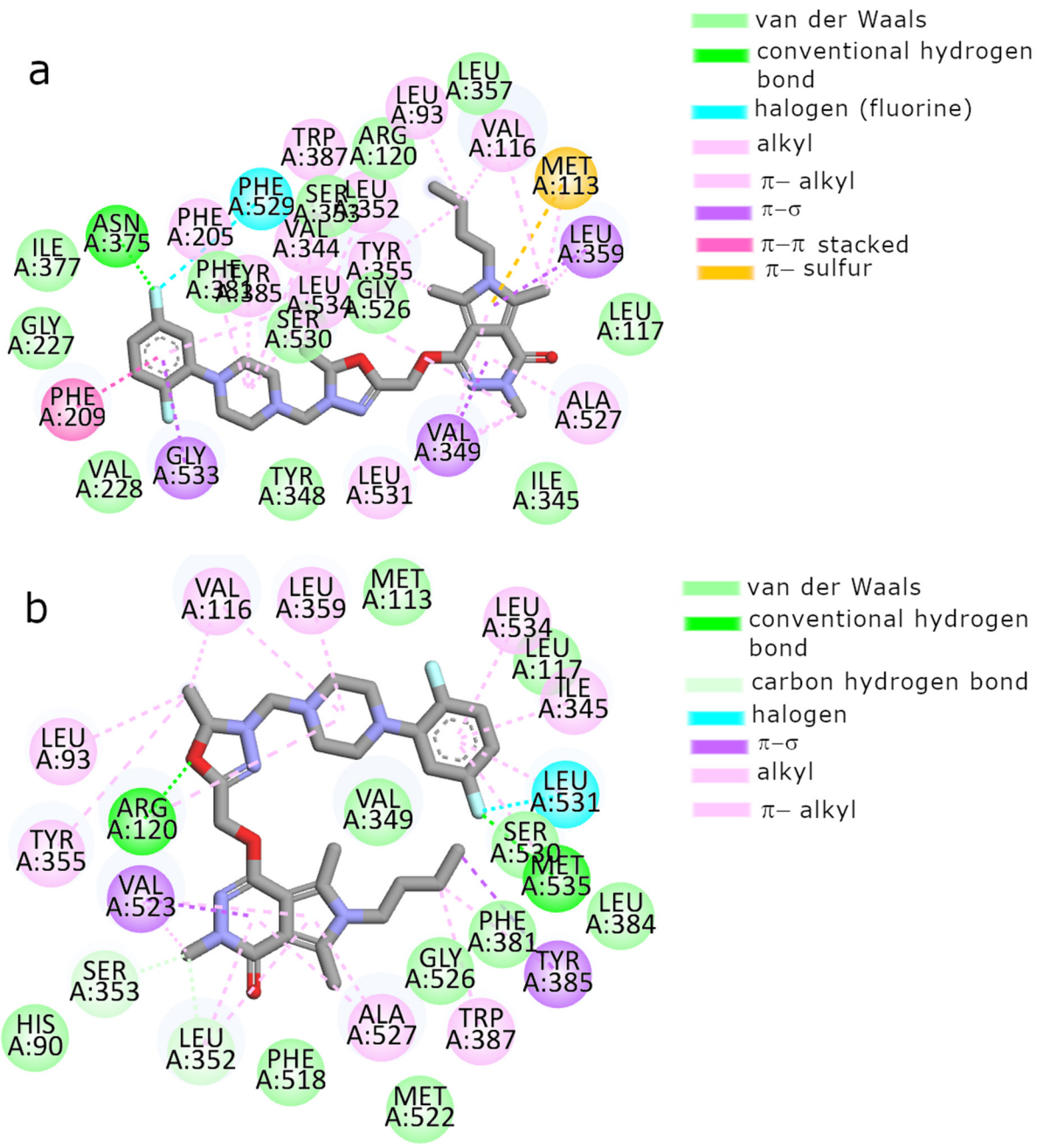


**Figure S5.** The intermolecular interactions of **4a** in the active centre of a) COX-1 b) COX-2

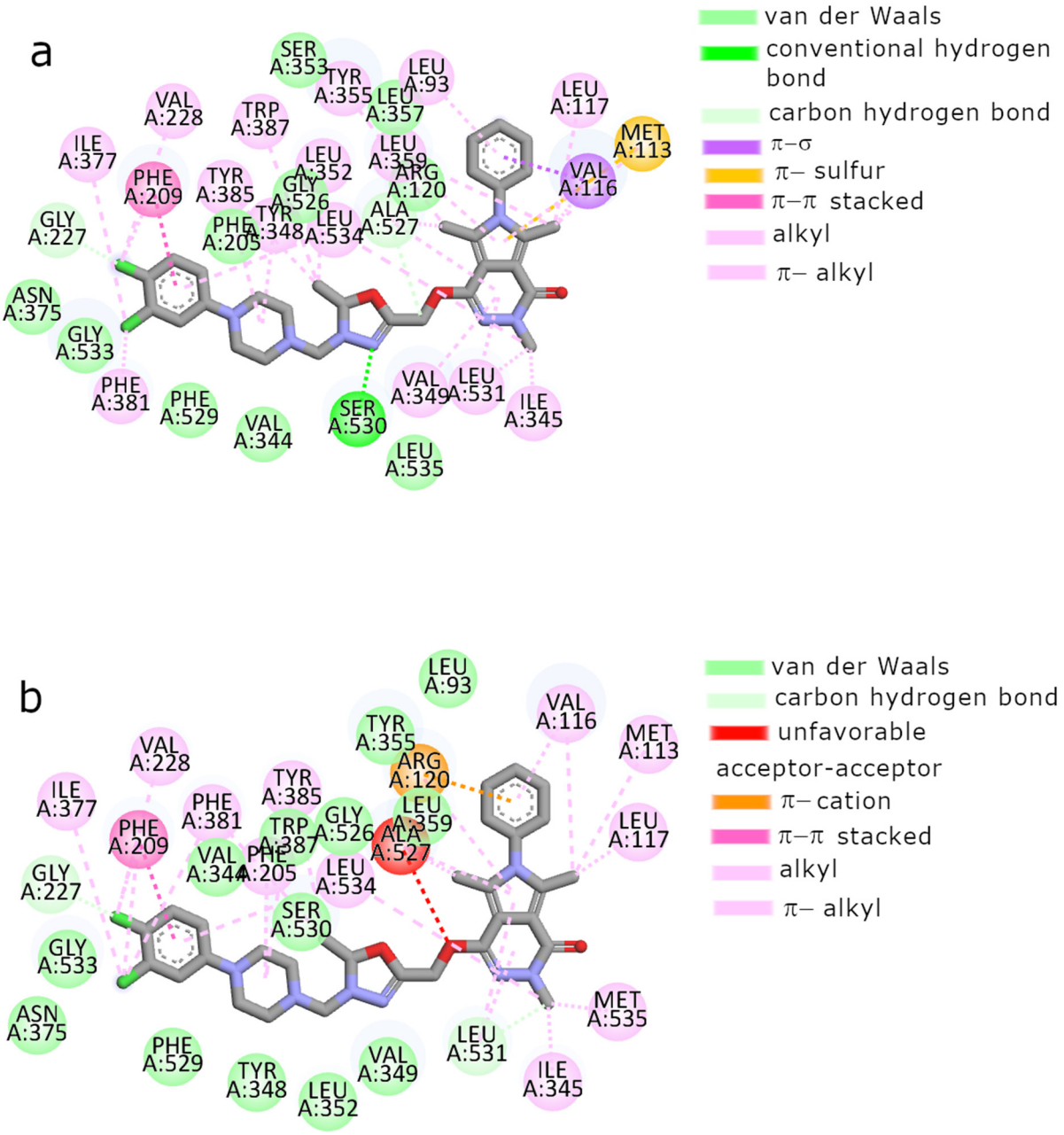


**Figure S6.** The intermolecular interactions of **4b** in the active centre of a) COX-1 b) COX-2

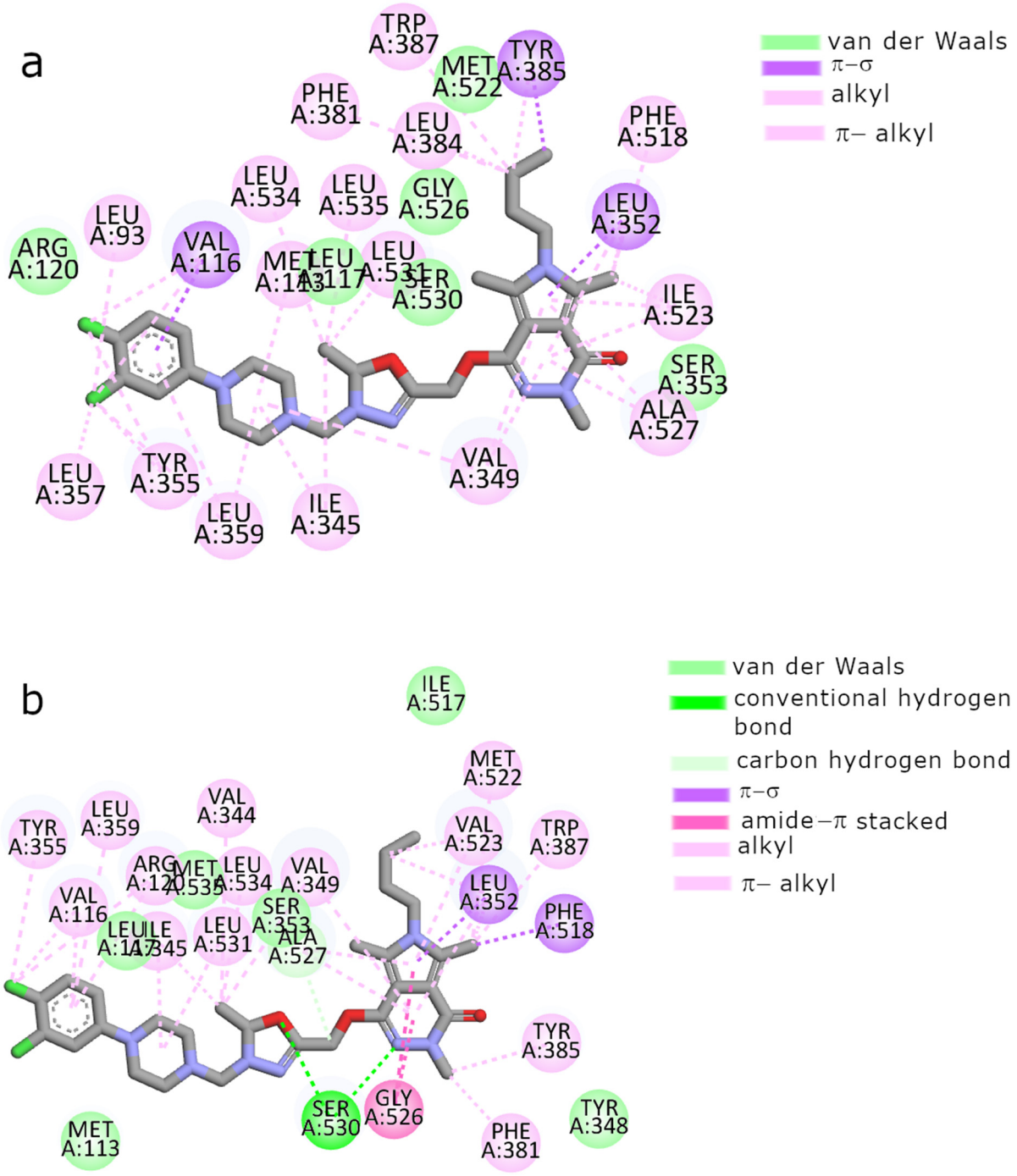


**Figure S7.** The intermolecular interactions of **5a** in the active centre of a) COX-1 b) COX-2

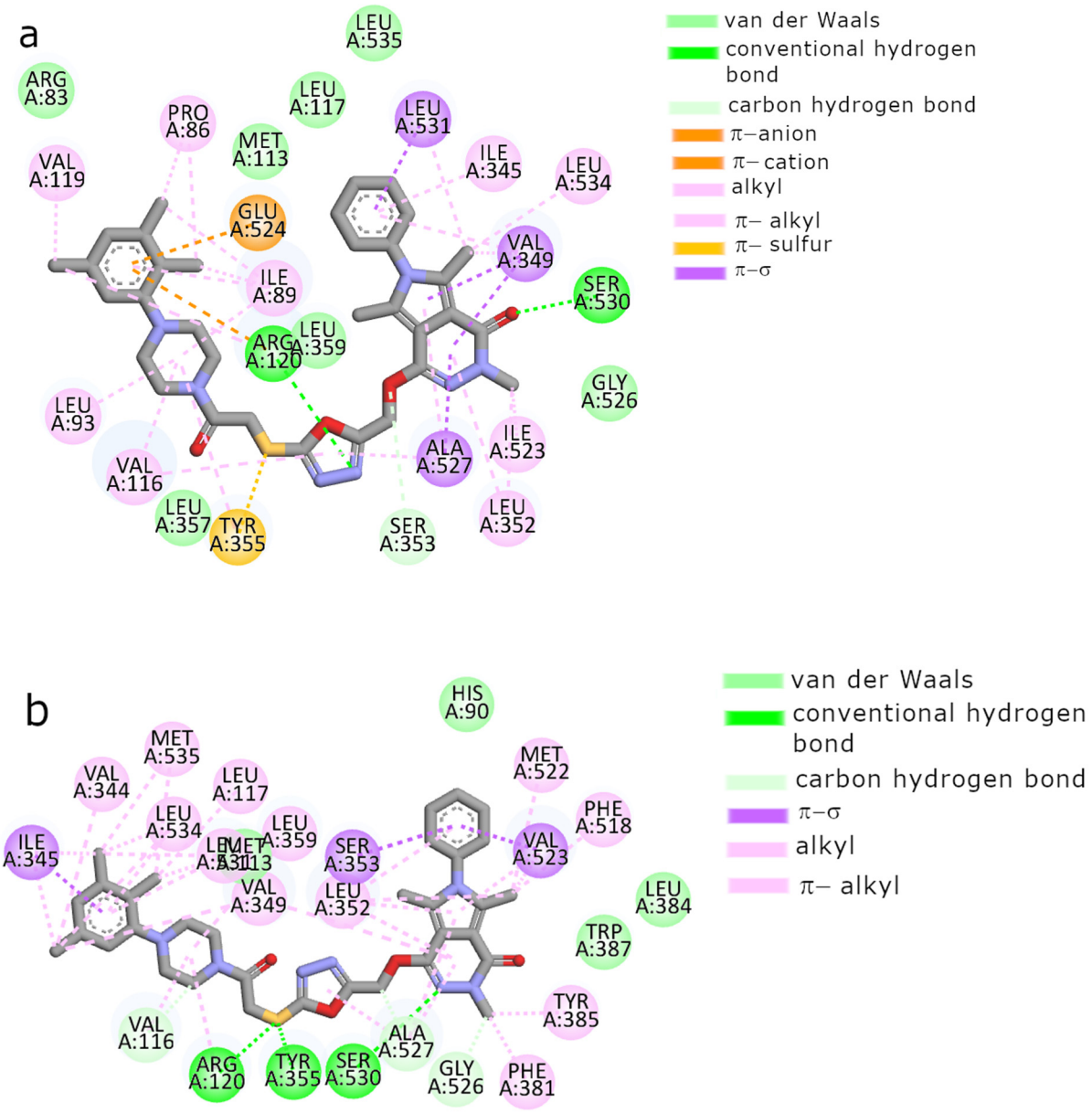


**Figure S8.** The intermolecular interactions of **5b** in the active centre of a) COX-1 b) COX-2

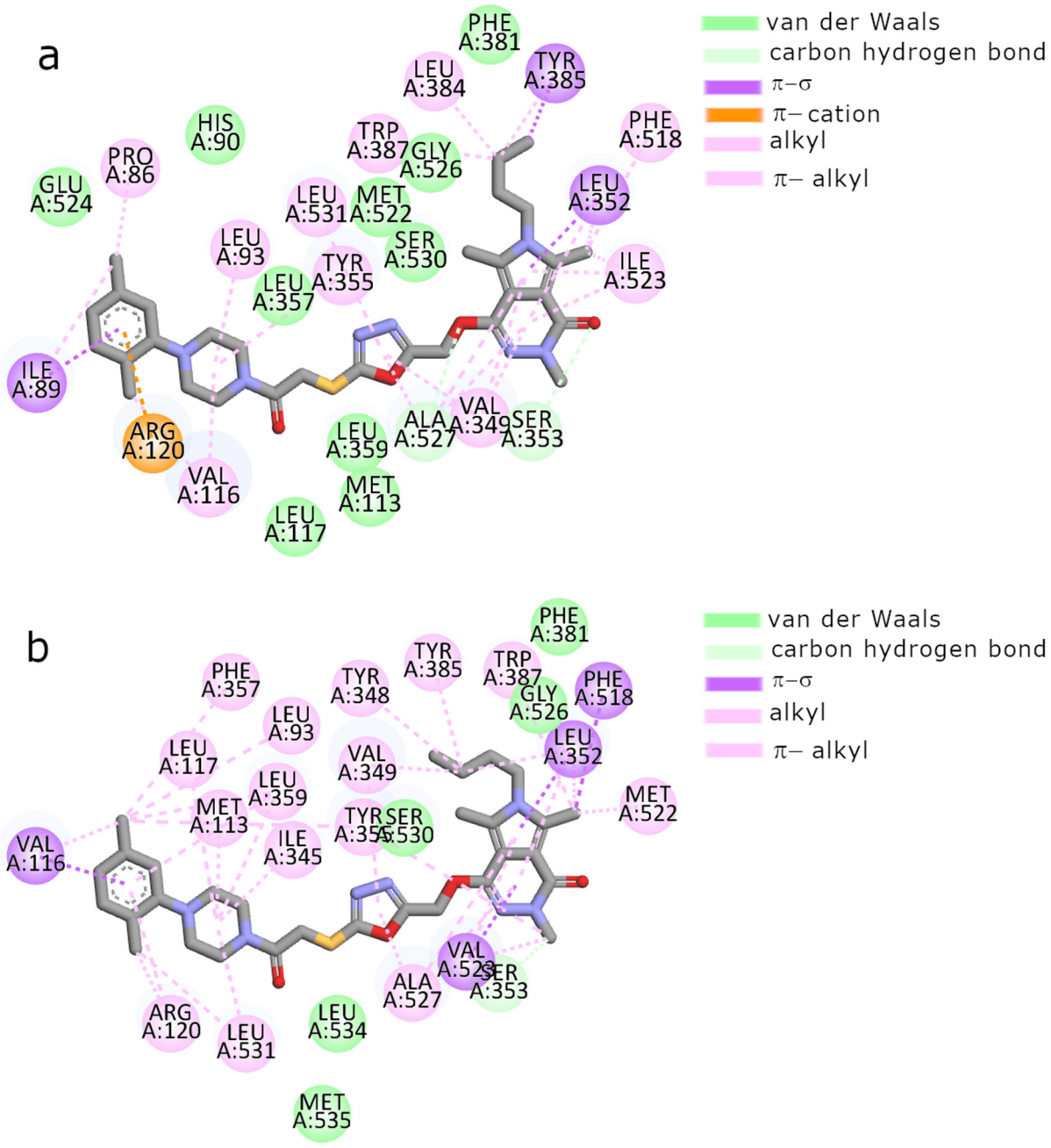


**Figure S9**. The intermolecular interactions of **6a** in the active centre of a) COX-1 b) COX-2

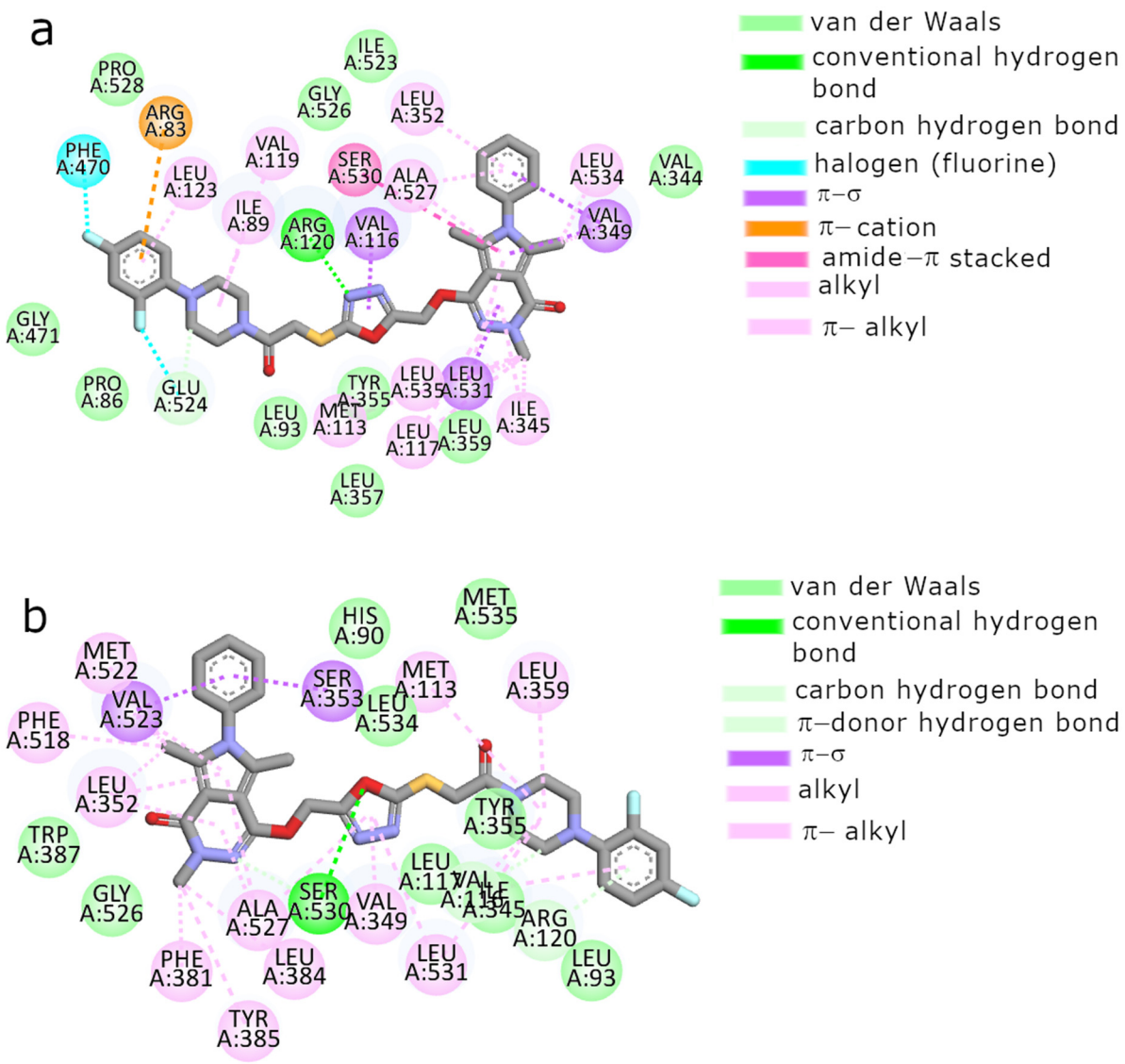


**Figure S10**. The intermolecular interactions of **6b** in the active centre of a) COX-1 b) COX-2

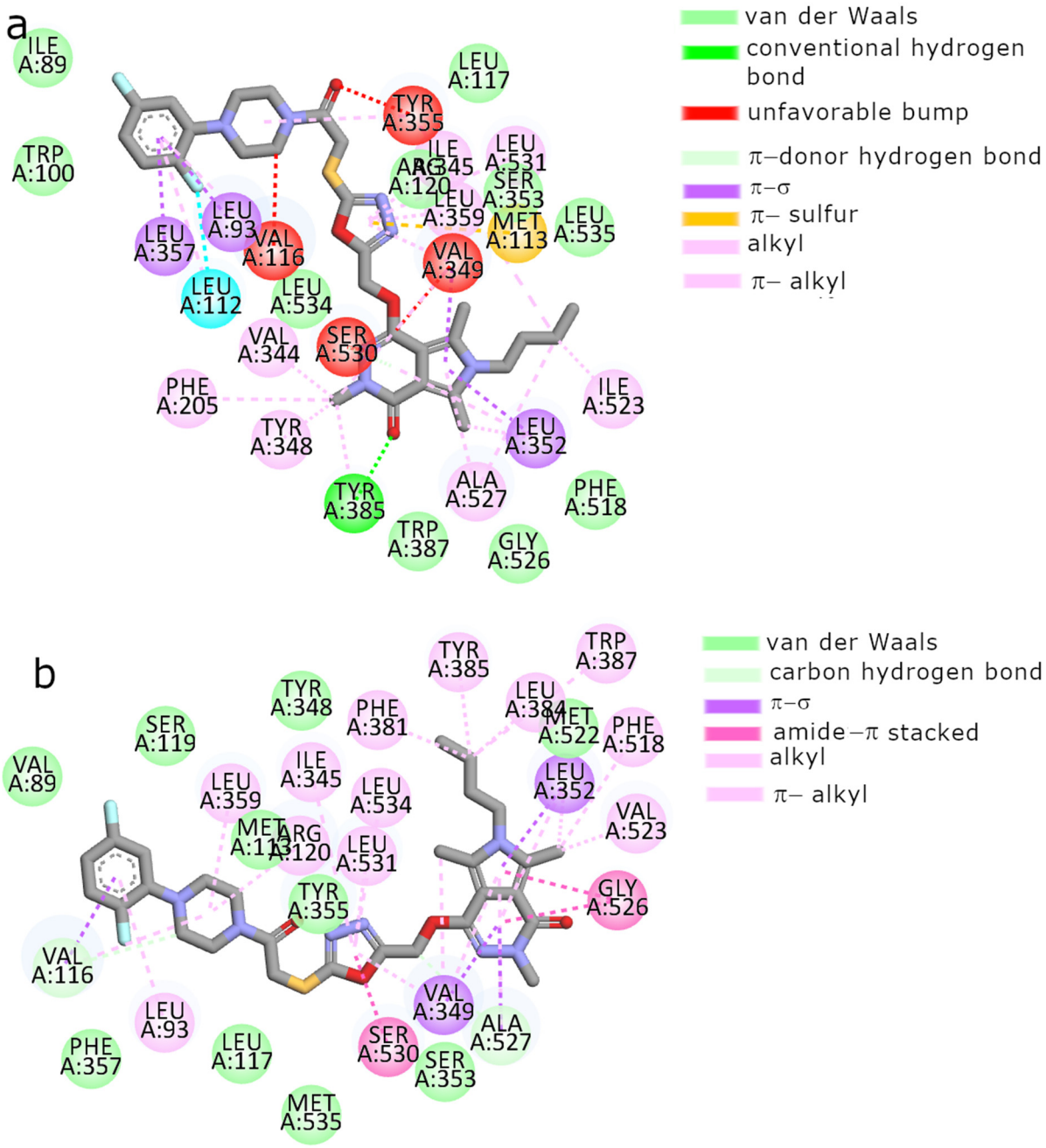


**Figure S11.** The intermolecular interactions of **7a** in the active centre of a) COX-1 b) COX-2

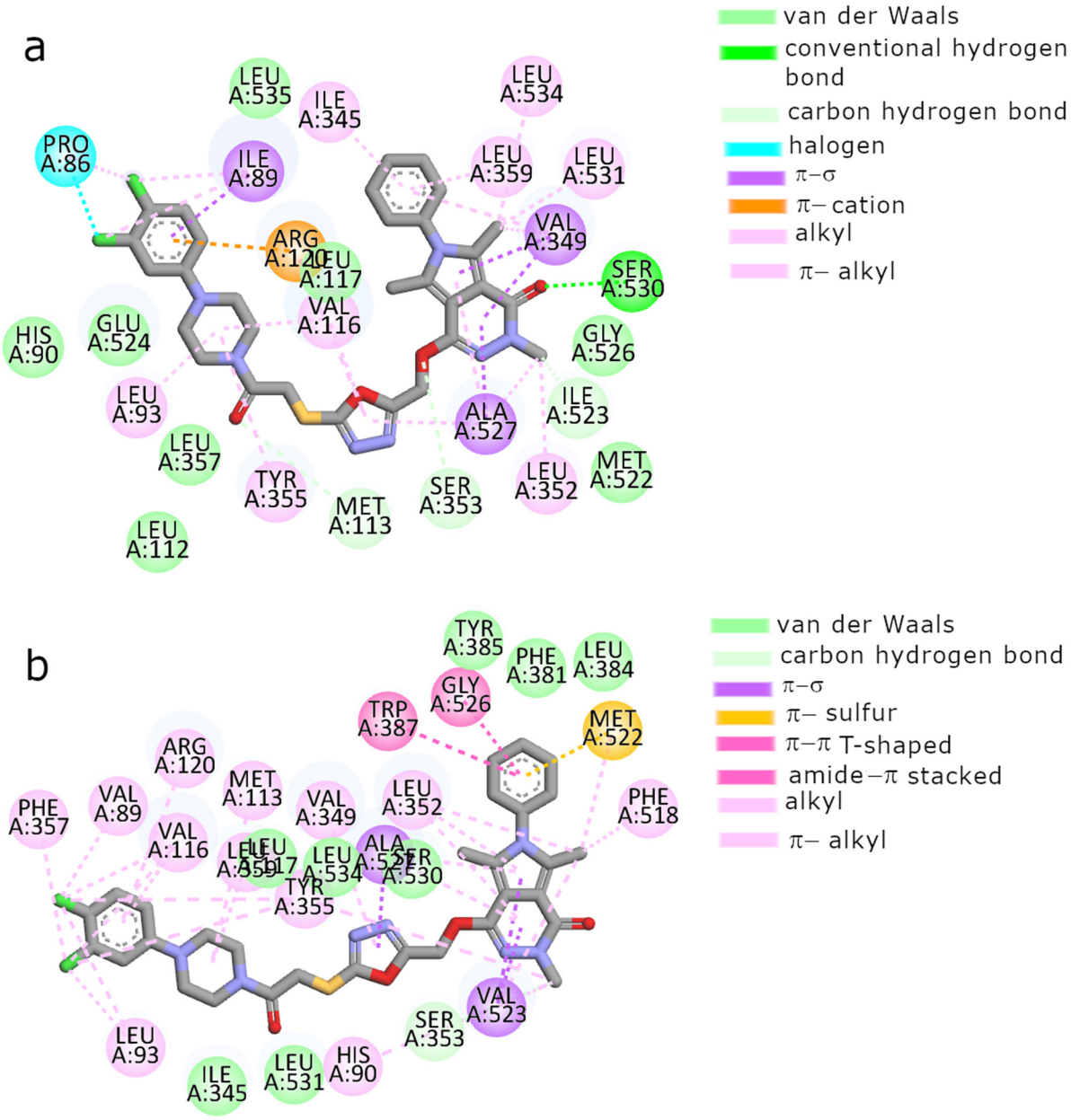
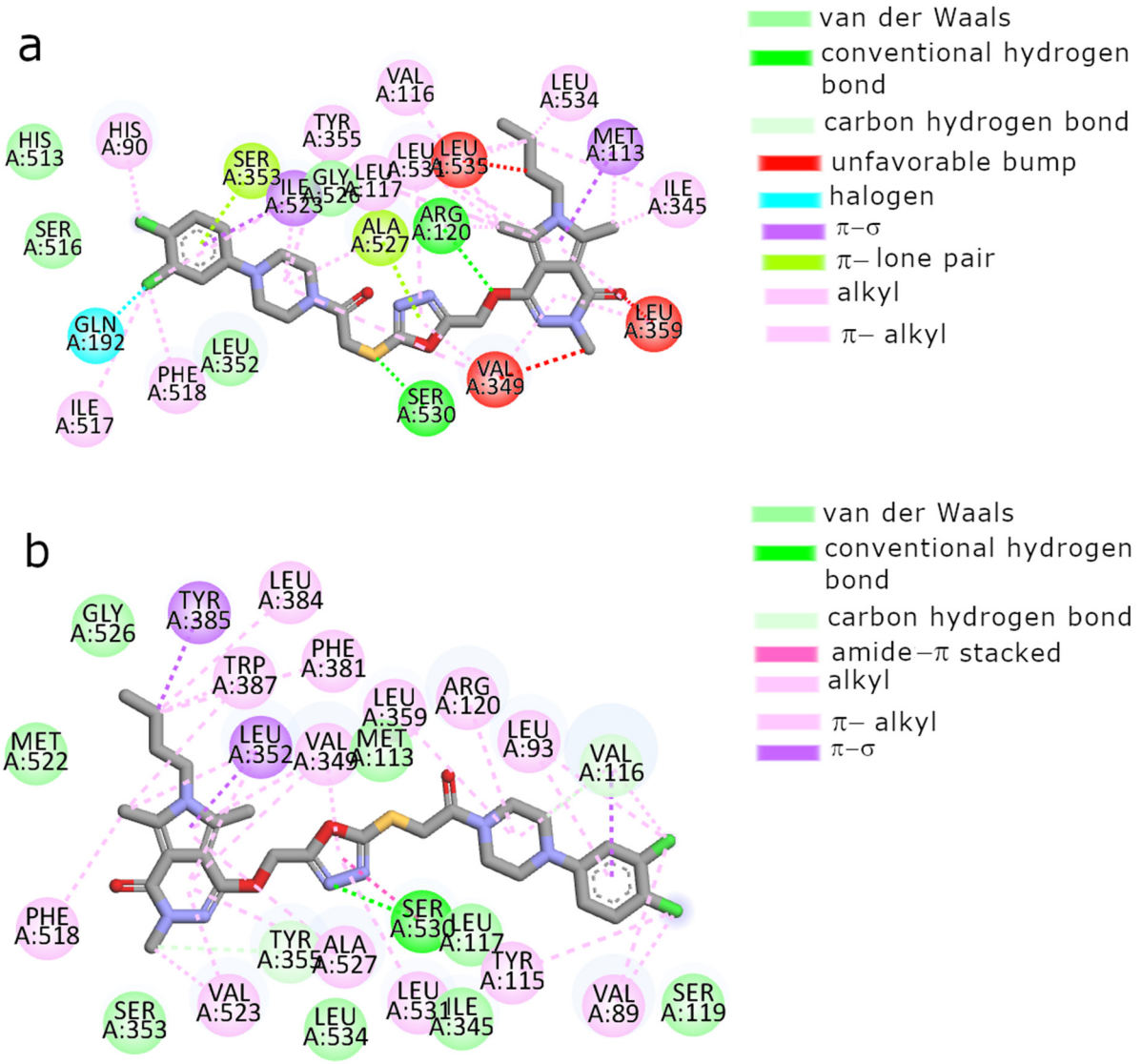
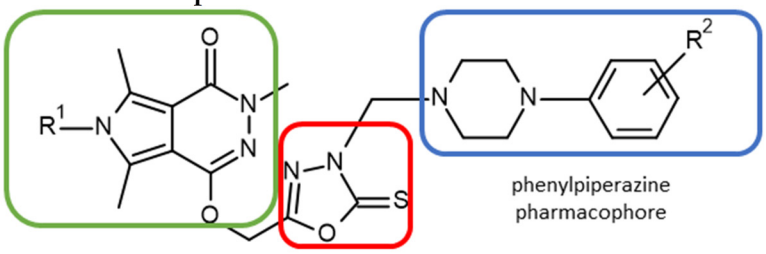


**Figure S12.** The intermolecular interactions of **7b** in the active centre of a) COX-1 b) COX-2



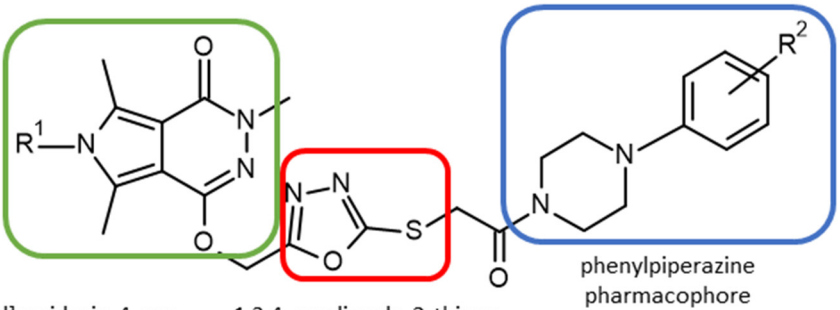
## **Table S6.** Binding mode of investigated compounds with COX-1

Binding mode of compounds **a)** 2a, 2b, 3a, 3b, 4a, 4b; **b)** 5a, 5b, 6a, 6b, 7a, 7b; to the COX-1 obtained from molecular docking (by colour are marked amino acid residues responsible for meloxicam binding)

| | | | |
|---|---|---|---|
| **a**<br>**Compounds 2a 2b 3a 3b 4a 4b**<br>  <br> | | | |
| 2a<br>$R^1$ ($-C_6H_6$) $R^2$ ($-CH_3$, $-CH_3$) | Leu117 Ile345 Val349 Leu352 Leu359 Met522 Gly526 Ala527 Ser530 Ile531 Leu534 Leu535 | Leu93 Met113 Tyr355 Leu357 Leu359 | Arg83 Pro86 Ile89 Val116 Val119 Arg120 Leu123 Glu524 |
| 2b<br>$R^1$ ($-C_4H_9$) $R^2$ ($-CH_3$, - $CH_3$) | Arg83 Pro86 Ser87 Ile89 His90 Leu93 Val116 Val119 Arg120 His513 Glu520 Ile523 Glu524 | Leu93 Arg120 Tyr355 Leu359 Leu531 | Tyr348 Val349 Leu352 Leu384 Tyr385 Trp387 Met522 Gly526 Ala527 Ser530 |
| 3a<br>$R^1$ ($-C_6H_6$) $R^2$ (-F, -F) | Leu117 Val349 Leu352 Leu357 Leu359 Trp387 Phe518 Met522 Gly526 Ala527 Ser530 Leu531 | Ile89 Leu93 Val116 Arg120 Tyr355 Leu359 | Pro86 Ser87 Ile89 His90 His513 Glu520 Ile523 Glu524 |
| 3b<br>$R^1$ ($-C_4H_9$) $R^2$ (-F, -F) | Leu93 Met113 Val116 Leu117 Arg120 Ile345 Val349 Leu352 Leu359 Tyr355 Gly526 Ala527 | Val344 Tyr348 Leu352 Trp387 Ser530 Leu531 Ser353 Leu534 | Phe205 Phe209 Gly227 Val228 Ile337 Asn375 Phe381 Tyr385 Ser530 Gly533 |
| 4a<br>$R^1$ ($-C_6H_6$) $R^2$ (-Cl, -Cl) | Leu93 Met113 Val116 Leu117 Arg120 Ile345 Val349 Leu357 Leu359 Ala527 Leu531 Leu534 | Phe205 Val344 Tyr348 Leu352 Ser353 Leu354 Tyr355 Tyr385 Trp387 Gly526 Ser530 | Phe205 Phe209 Val228 Asn375 Phe381 Tyr385 Gly533 Leu534 |
| 4b<br>$R^1$ ($-C_4H_9$) $R^2$ (-Cl, -Cl) | Val349 Leu352 Ser353 Phe381 Leu384 Tyr385 Trp387 Phe518 Met522 Ile523 Gly526 Ala527 Ser530 Leu351 | Met113 Leu117 Val349 Leu531 Leu534 Leu535 | Leu93 Met113 Val116 Arg120 Ile345 Tyr355 Leu357 Leu359 |
| Meloxicam | Met113 Val116 Leu117 Arg120 Ile345 Val349 Leu352 Ser353 Tyr355 Leu359 Tyr385 Trp387 Phe518 Met522 Ile523 Gly526 Ala527 Ser530 Leu531 Leu534 Leu535 | | |

**b**

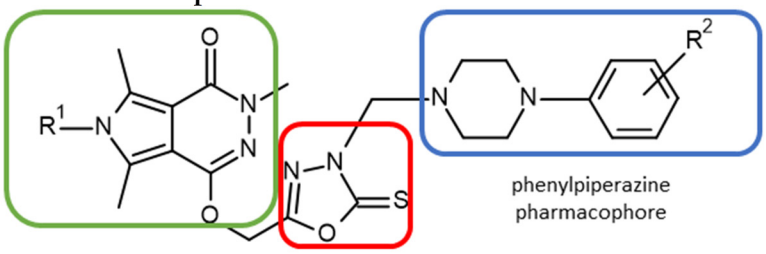
**Compounds 5a 5b 6a 6b 7a 7b**




| | | | |
|---|---|---|---|
| 5a<br>$R^1$ ($-C_6H_6$) $R^2$ ($-CH_3$, $-CH_3$) | Met113 Leu117 Ile345 Val349 Leu352 Ile523 Gly526 Ala527 Ser530 Leu531 Leu534 Leu535 | Arg120 Ser353 Leu359 Ala527 | Arg83 Pro86 Ile89 Leu93 Met113 Val116 Val119 Arg120 Tyr355 Leu357 Glu524 |
| 5b<br>$R^1$ ($-C_4H_9$) $R^2$ ($-CH_3$, - $CH_3$) | Val349 Leu352 Ser353 Leu384 Phe381 Tyr385 Trp387 Phe518 Met522 Ile523 Gly526 Ser530 | Val349 Tyr355 Leu359 Ala527 Leu531 | Pro86 Ile89 His90 Leu93 Val116 leu117 Arg120 Leu357 Glu524 |
| 6a<br>$R^1$ ($-C_6H_6$) $R^2$ (-F, -F) | Ile345 Val344 Val349 Leu352 Ile523 Ala527 Ser530 Leu531 Leu534 | Leu93 Met113 Val116 Leu117 Arg120 Tyr355 Leu357 Gly526 Leu535 | Arg83 Ile89 Leu123 Gly471 Glu524 Pro528 |
| 6b<br>$R^1$ ($-C_4H_9$) $R^2$ (-F, -F) | Met113 Phe205 Val344 Val349 Leu352 Ser353 Tyr385 Trp378 Phe518 Ile523 Ala527 Ser530 Leu531 Ser535 | Arg120 Ile345 Tyr355 Val349 Leu534 Leu359 | Ile89 Leu93 Trp100 Leu112 Val116 Tyr355 Leu357 |
| 7a<br>$R^1$ ($-C_6H_6$) $R^2$ (-Cl, -Cl) | Ile345 Val349 Leu359 Met522 Ile523 Gly526 Ala527 Ser530 Leu531 Leu534 | Met113 Val116 Ser353 Tyr355 Ala527 | Pro86 Ile89 His90 Leu112 Val116 Leu117 Arg120 Leu357 Glu524 Leu535 |
| 7b<br>$R^1$ ($-C_4H_9$) $R^2$ (-Cl, -Cl) | Met113 Val116 Leu117 Arg120 Ile345 Val349 Leu359 Leu531 Leu534 Leu535 | Leu117 Arg120 Val349 Tyr355 Ala527 Ser530 | His90 Gln192 Leu352 Ser353 His513 Ser516 Ile517 Phe518 Ile523 |
| Meloxicam | Met113 Val116 Leu117 Arg120 Ile345 Val349 Leu352 Ser353 Tyr355 Leu359 Tyr385 Trp387 Phe518 Met522 Ile523 Gly526 Ala527 Ser530 Leu531 Leu534 Leu535 | | |

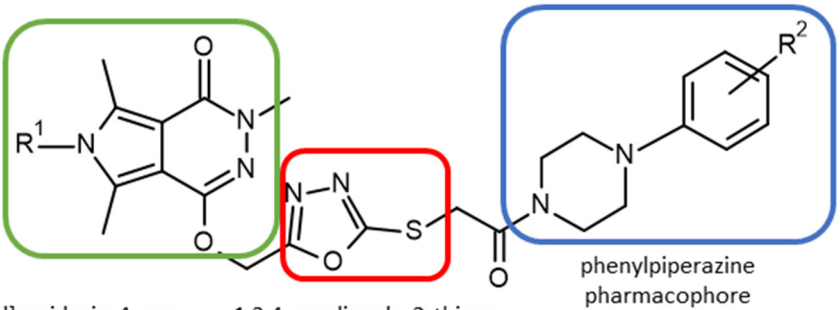
## **Table S7.** Binding mode of investigated compounds with COX-2

Binding mode of compounds **a)** 2a, 2b, 3a, 3b, 4a, 4b; **b)** 5a, 5b, 6a, 6b, 7a, 7b; to the COX-2 obtained from molecular docking (by colour are marked amino acid residues responsible for meloxicam binding)

<table>
<tr><td colspan="4">a<br>Compounds 2a 2b 3a 3b 4a 4b<br>  <br></td></tr>
<tr><td>2a<br>R¹ (-C₆H₆) R² (-CH₃, -CH₃)</td><td>Val349 Leu352 Ser353 Leu384 Trp387 Met522 Val523 Ala527 Ser530 Ser535</td><td>Ile345 Leu531 Leu534 Met535</td><td>Leu93 Met113 Val116 Leu117 Arg120 Tyr355 Phe357 Leu359 Phe381 Gly527</td></tr>
<tr><td>2b<br>R¹ (-C₄H₉) R² (-CH₃, - CH₃)</td><td>His90 Tyr348 Val349 Leu352 Ser353 Phe381 Tyr385 Trp387 Met522 Val523 Gly526 Ala527 Ser530 Leu531</td><td>Leu93 Val116 Arg120 Tyr355</td><td>Met113 Leu117 Ile345 Leu359 Ser530 Leu531</td></tr>
<tr><td>3a<br>R¹ (-C₆H₆) R² (-F, -F)</td><td>Leu93 Met113 Val116 Leu117 Arg120 Tyr355 Ala527 Leu531 Leu534 Met535 Leu359</td><td>Ser353 Phe518 Val523 Gly526 Ser530</td><td>Phe205 Thr206 Phe209 Val344 Tyr348 Val349 Leu352 Phe381 Tyr385 Trp387 Met522 Ser530</td></tr>
<tr><td>3b<br>R¹ (-C₄H₉) R² (-F, -F)</td><td>His90 Val349 Ser352 Ser353 Phe381 Leu384 Tyr385 Trp387 Phe518 Met522 Val523 Gly526 Ala527 Met535</td><td>Leu93 Val116 Arg120 Tyr355</td><td>Met113 Val116 Leu117 Arg120 Ile349 Leu359 Ser530 Leu531 Leu534</td></tr>
<tr><td>4a<br>R¹ (-C₆H₆) R² (-Cl, -Cl)</td><td>Leu93 Met113 Val116 Leu117 Arg120 Ile345 Tyr355 Leu359 Ala527 Leu531 Leu534 Met535</td><td>Val349 Leu352 Gly526 Ser530 Leu531</td><td>Phe205 Phe209 Gly227 Val228 Val344 Tyr348 Asn375 Ile377 Phe381 Tyr385 Trp387 Phe529 Ser530 Gly533</td></tr>
<tr><td>4b<br>R¹ (-C₄H₉) R² (-Cl, -Cl)</td><td>Tyr348 Val349 Leu352 Tyr385 Trp387 Phe381 Ile517 Phe518 Met522 Val532 Gly526 Ala527 Ser530 Ser353</td><td>Val344 Val349 Ser530 Leu531 Ser353 Leu534</td><td>Met113 Leu117 Arg120 Ile345 Tyr355 Leu359 Leu531 Met535</td></tr>
<tr><td>Meloxicam</td><td colspan="3">Met113 Val116 Leu117 Arg120 Ile345 Val349 Leu352 Ser353 Tyr355 Leu359 Tyr385 Trp387 Phe518 Met522 Val523 Ala527 Ser530 Leu531 Leu534 Met535</td></tr>
</table>

**b**

**Compounds 5a 5b 6a 6b 7a 7b**




| | | | |
|---|---|---|---|
| 5a<br>$R^1$ (-$C_6H_6$) $R^2$ (-$CH_3$, -$CH_3$) | His90 Leu352 Ser353 Phe381 Leu384 Tyr385 Trp387 Phe518 Met522 Val523 Gly526 Ala527 Ser530 | Arg120 Tyr355 Ala527 Ser530 | Met113 Val116 Leu117 Arg120 Val344 Ile345 Leu534 Met535 |
| 5b<br>$R^1$ (-$C_4H_9$) $R^2$ (-$CH_3$, - $CH_3$) | Tyr348 Val349 Leu352 Phe381 Tyr385 Trp387 Val523 Phe518 Met522 Gly526 Ala527 Ser530 Ser535 | Tyr355 Ala527 Ser530 | Leu93 Met113 Val116 Leu117 Arg120 Ile345 Phe357 Leu359 Leu531 |
| 6a<br>$R^1$ (-$C_6H_6$) $R^2$ (-F, -F) | Leu352 Ser353 Phe381 Tyr385 Trp387 Met522 Val523 Gly526 Phe518 Ala527 | His90 Val349 Ser530 Leu531 Leu534 | Leu93 Met113 Val116 Leu117 Arg120 Ile345 Tyr355 Leu359 Met535 |
| 6b<br>$R^1$ (-$C_4H_9$) $R^2$ (-F, -F) | Tyr348 Val349 Leu352 Phe381 Leu384 Tyr385 Trp387 Phe518 Met522 Val523 Gly526 Ala527 Leu534 | Arg120 Val349 Tyr355 Ser530 Leu531 Ser353 | Val89 Leu93 Met113 Val116 Leu117 Ser119 Arg120 Phe357 Leu359 |
| 7a<br>$R^1$ (-$C_6H_6$) $R^2$ (-Cl, -Cl) | Phe381 Leu384 Tyr385 Trp387 Leu352 Phe518 Met522 Val523 Gly526 Ser530 | His90 Val349 Tyr355 Ala527 Ser530 Ser353 Leu534 | Val89 Leu93 Met113 Val116 Leu117 Arg120 Ile345 Phe357 Leu359 Leu531 |
| 7b<br>$R^1$ (-$C_4H_9$) $R^2$ (-Cl, -Cl) | Val349 Leu352 Ser353 Tyr355 Phe381 Leu384 Tyr385 Trp387 Peh518 Met522 Val523 Gly526 Leu534 | Met113 Ile345 Leu349 Leu359 Ala527 Ser530 Leu531 | Val89 Leu93 Tyr115 Val116 Leu117 Ser119 Arg120 Ile345 |
| Meloxicam | Met113 Val116 Leu117 Arg120 Ile345 Val349 Leu352 Ser353 Tyr355 Leu359 Tyr385 Trp387 Phe518 Met522 Val523 Gly526 Ala527 Ser530 Leu531 Leu534 Leu535 | | |