Supporting information

Solid-phase rhodium carbenoid reactions: An N-H insertion route to a diverse series of oxazoles

Bruce Clapham, Carsten Spanka and Kim D. Janda*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037

Email Address: kdjanda@scripps.edu

All reagents were purchased from commercial sources and used as received with the following exceptions: Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketal and methylene chloride (CH_2Cl_2) was distilled from calcium hydride. The ion exchange resins used for product purification, Dowex® 50WX2-200 and Dowex® 1X2-400, were washed with distilled water, acetone, methanol and CH_2Cl_2 prior to use. A batch of mixed bed resin was prepared by mixing equal quantities of these acidic and basic resins. The filtration/work-up cartridges were prepared by placing 1.0 g of the mixed bed resin in a 5 mL plastic syringe, equipped with a polyethylene frit; an additional frit was then placed over the top of the resin.

Representative procedures:

Hydroxybutyl *Janda*Jel™ 1

Chloromethyl *Janda*Jel™ (100-200 mesh, 50.0g, ~1.5 $mmolg^{-1}$, ~75 mmol) was placed in a 1 liter flange flask equipped with an overhead stirrer paddle and a nitrogen inlet/bubbler. Toluene (anhydrous, 700ml) was added and the resin was stirred (200 RPM) for 10 minutes. Allylmagnesium chloride (2.0 M in THF, 100 ml, 200 mmol) was

added and the mixture was heated to 60 °C with stirring overnight. The reaction was quenched (*caution exotherm!*) by addition of methanol (50ml) and the resin collected by filtration. The resin was washed with THF/1M HCl_{aq} (9:1), THF ether and hexanes and dried under suction for 20 minutes. The resin was then suspended in THF/1M HCl_{aq} (9:1) (800 ml) and heated to 60 °C with stirring for 4 hours, after which time the washing and drying procedures were repeated; **IR** 1635 cm^{-1} (C=C).

The resin prepared above (50.48 g) was placed in a 1 liter flange flask equipped with a overhead stirrer paddle and a nitrogen inlet/bubbler. THF (500ml) was added and the resin was stirred (200 RPM) for 30 minutes. 9-BBN-H (0.5 M in THF, 400 ml, 200 mmol) was added over 2 h and stirring was continued overnight. $NaOH_{aq}$, (6M, 133ml) and Bu_4NOH (40 wt% in H_2O, 10 ml) were added to the mixture, followed by H_2O_2 (30 wt% in H_20, 35 ml) dropwise (*caution exotherm!*) and stirring was continued for 4 hours. The resin was collected on a filter and washed with THF/1 M HCl_{aq} (9:1), THF, ether and hexanes and dried under suction for 20 min. The resin was split into 2 batches and extracted in a soxhlet using dioxane/water 3:1 for 48 hrs. Washing with dioxane, THF, ether and hexanes followed by re-sieving gave 43 g of resin; **IR** 3400 cm^{-1} (OH).

α-Diazo-β-ketoester 2

A suspension of hydroxybutyl *Janda*Jel™ **1** (10.0 g, ~ 15 mmol) and DMAP (1.83 g, 15.0 mmol) in CH_2Cl_2 (200 ml), cooled to –78 °C was slowly stirred and diketene (1.16 ml, 30 mmol) was added dropwise. After warming to rt over 2 h and stirring for an additional 14 h, the product was collected by filtration and washed with DMF, THF, Et_2O and hexanes to give the product as a free flowing white powder (11.3 g); **IR** 1740 (C=O, ester) 1716cm^{-1} (C=O, ketone).

This resin was swollen in toluene (200 ml) and Et_3N (6.97 ml, 50.0 mmol) and dodecylbenzenesulfonylazide (17.6 g, 50.1 mmol) were added. The vessel was wrapped in aluminum foil and the mixture stirred slowly for 16 h. The product was washed with DMF, THF, Et_2O and hexanes to give **2** as a free flowing off white powder (11.6 g); **IR** 2137 ($=N_2$), 1714 (C=O, ester) and 1655 cm^{-1} (C=O, ketone); loading 1.37 $mmolg^{-1}$ determined by elemental analysis for nitrogen.

α-diazo-β-ketoester 9b

A 50 ml round bottomed flask fitted with a reflux condenser was charged with hydroxybutyl *J*anda*J*el™ **1** (2.00 g, ~3.00 mmol) and acyl-Meldrum's acid adduct **8** (R_1 = Ph) (2.50 g, 7.52 mmol) and purged with argon. THF (40 ml) was added and the mixture was heated to reflux for 16 h. The product was collected in a plastic syringe fitted with a polyethylene frit and washed with DMF, dry THF and toluene. Toluene (20 ml), Et_3N (2.36 ml, 16.9 mmol) and dodecylbenzenesulfonylazide (5.93 g, 16.9 mmol) were added, the vessel was capped and treated as above to give **9b** as a free flowing off white powder (2.46 g); **IR** 2140 (=N_2), 1720 (C=O, ester) and 1689 cm^{-1} (C=O, ketone); loading 1.29 $mmolg^{-1}$ determined by elemental analysis for nitrogen.

Insertion reaction

A 5 ml glass tube fitted with a septa was charged with resin **2** (250 mg, 0.34 mmol) and benzamide (207 mg, 1.71 mmol), purged with argon and toluene (4 ml) was added. This mixture was vigorously stirre, heated in a pre-warmed oil bath (60 °C) for 3 min and a solution of rhodium ocatanoate (~5 mg, ~ 0.7 uM) in toluene (2.00 ml) was added. Nitrogen effervescence was observed and subsided after approximately 30 min. After heating for an additional 1.5 h, the resin was collected in a plastic syringe equipped with a polyethylene frit and washed with DMF, chloroform, Et_2O and hexanes to give **3a** as a off white powder (279 mg, 99%); **IR** 3415 (N-H), 1749 (C=O, ester), 1724 (C=O, ketone) and 1663 cm^{-1} (C=O, amide).

Dichlorotriphenylphosphorane cyclodehydration

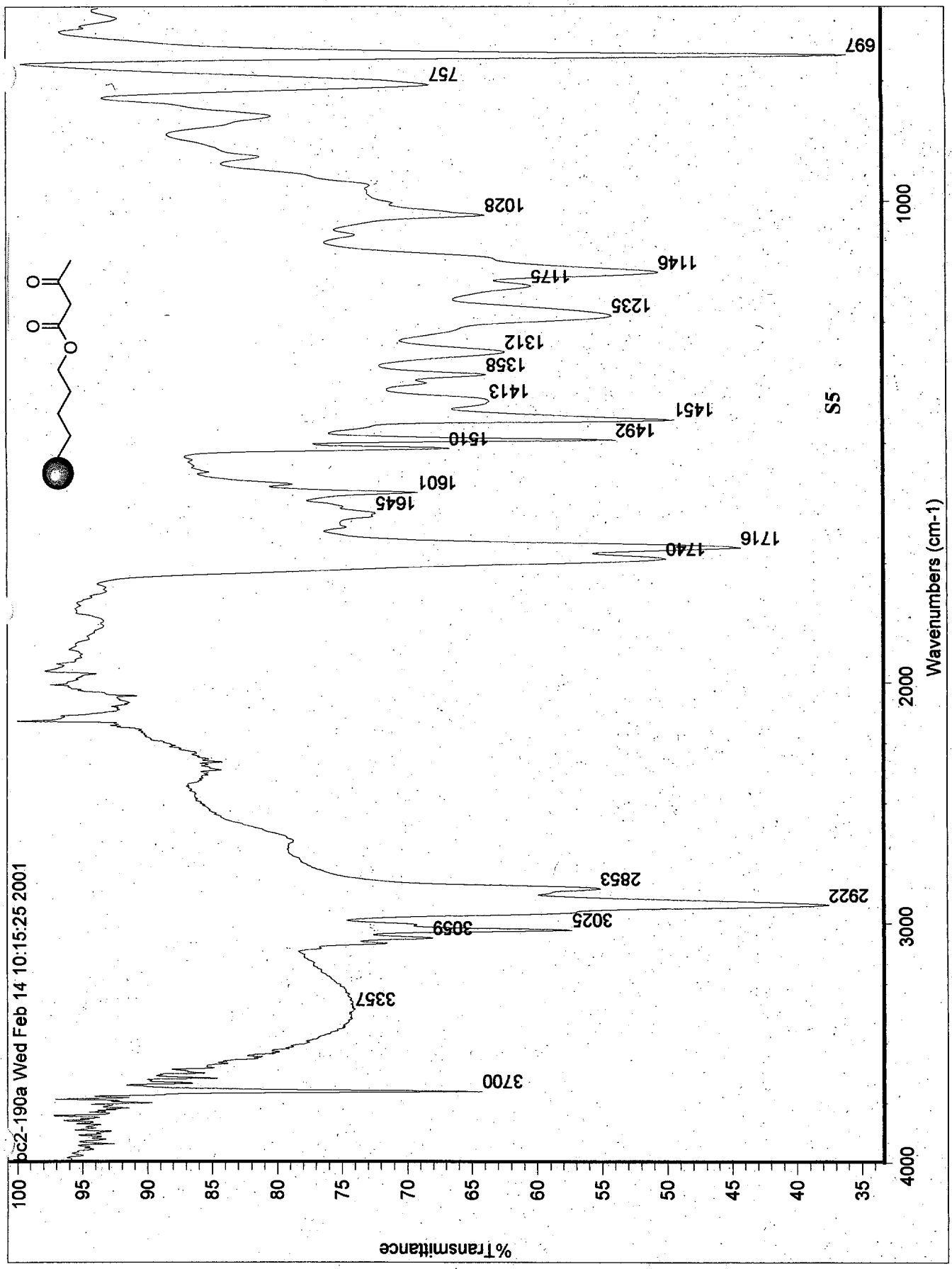
To a solution of Cl_2PPh_3 (226 mg, 0.68 mmol) in CH_2Cl_2 (2 ml) was added Et_3N, (0.57 ml, 4.08 mmol) and the mixture was stirred for 5 min. This solution was then drawn into the plastic syringe containing product **3a**, the syringe was then capped and shaken for 16 h. The product was washed with DMF, chloroform, Et_2O and hexanes and obtained as a light brown powder (285 mg); **IR** 1713 cm^{-1} (C=O, ester).

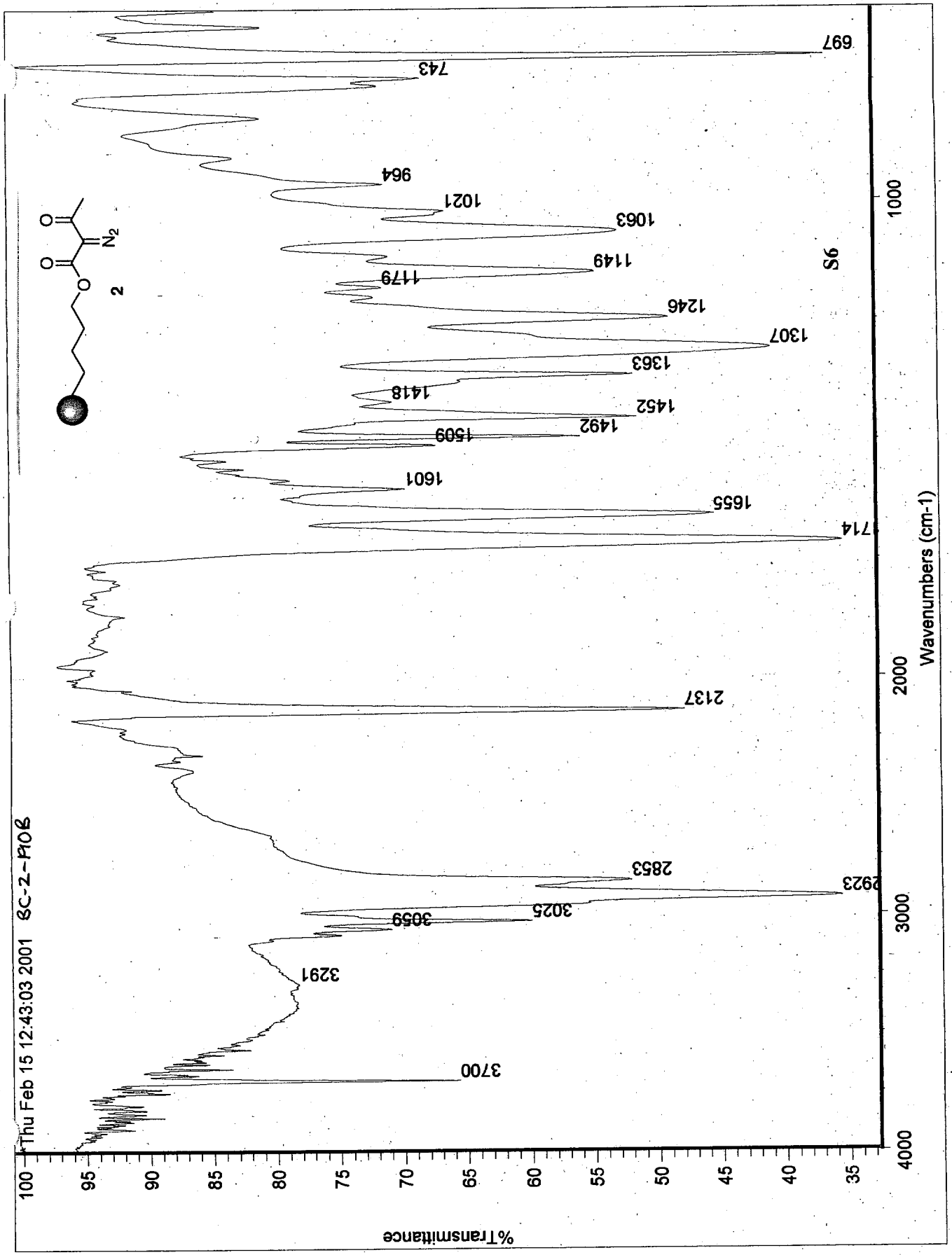
Burgess reagent cyclodehydration

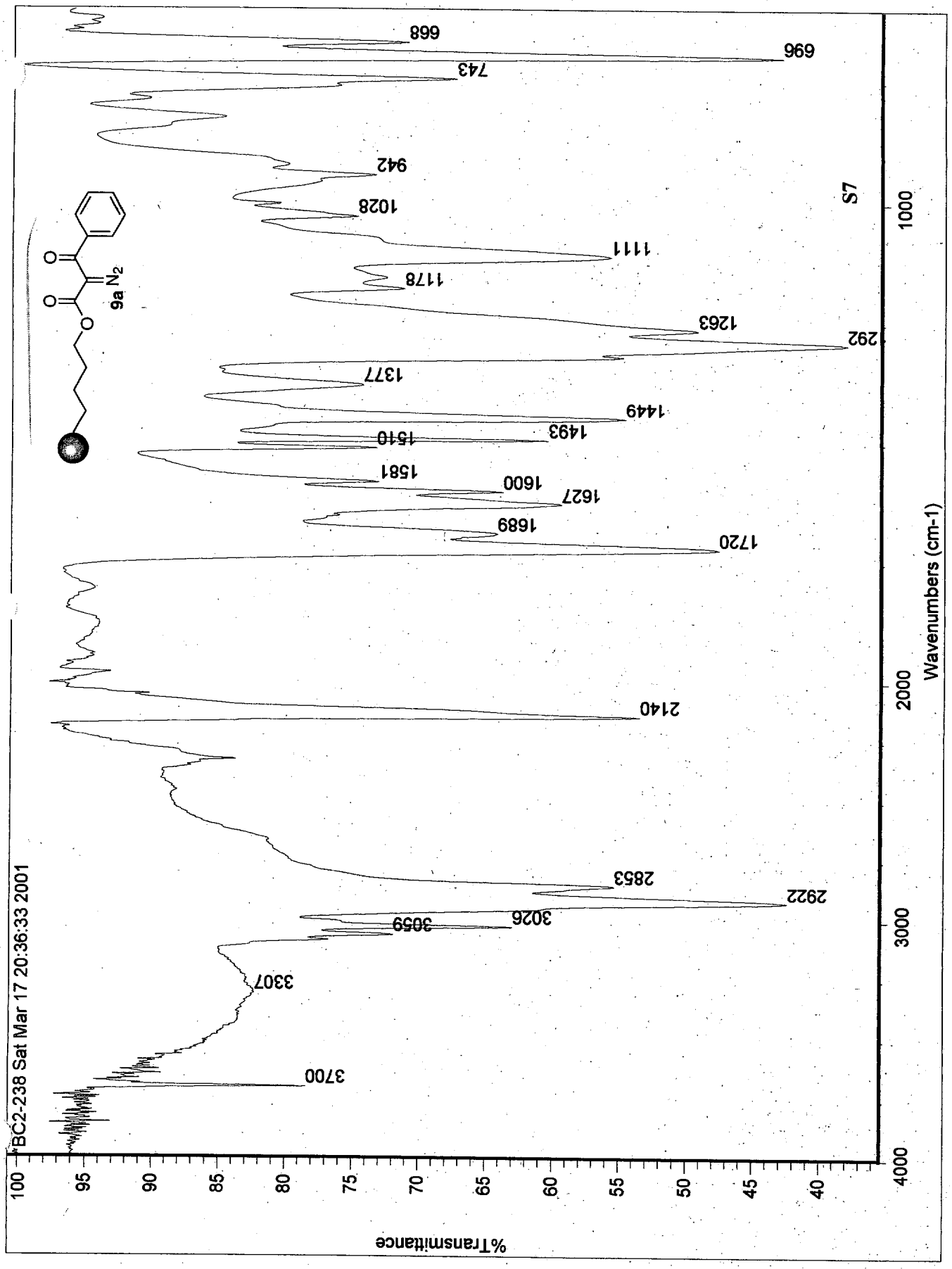
A 5 ml vial equipped with a small stir bar and a PTFE septum cap was charged with resin **10** R_1 = Ph, R_2 = tBu (117 mg, 0.14 mmol) and purged with argon. A solution of Burgess reagent (2.00 ml, 85 mg/ ml, 0.71 mmol) in THF was added, the vial was sealed and immersed in an oil bath at 70 °C. After stirring for 6 h, the resin was collected in a plastic syringe equipped with a polyethylene frit and washed with DMF, chloroform, Et_2O and hexanes to give oxazole **11** (R_1 = Ph, R_2 = ^{t}Bu) (111 mg) as a off white powder; **IR** 1716 cm^{-1} (C=O, ester).

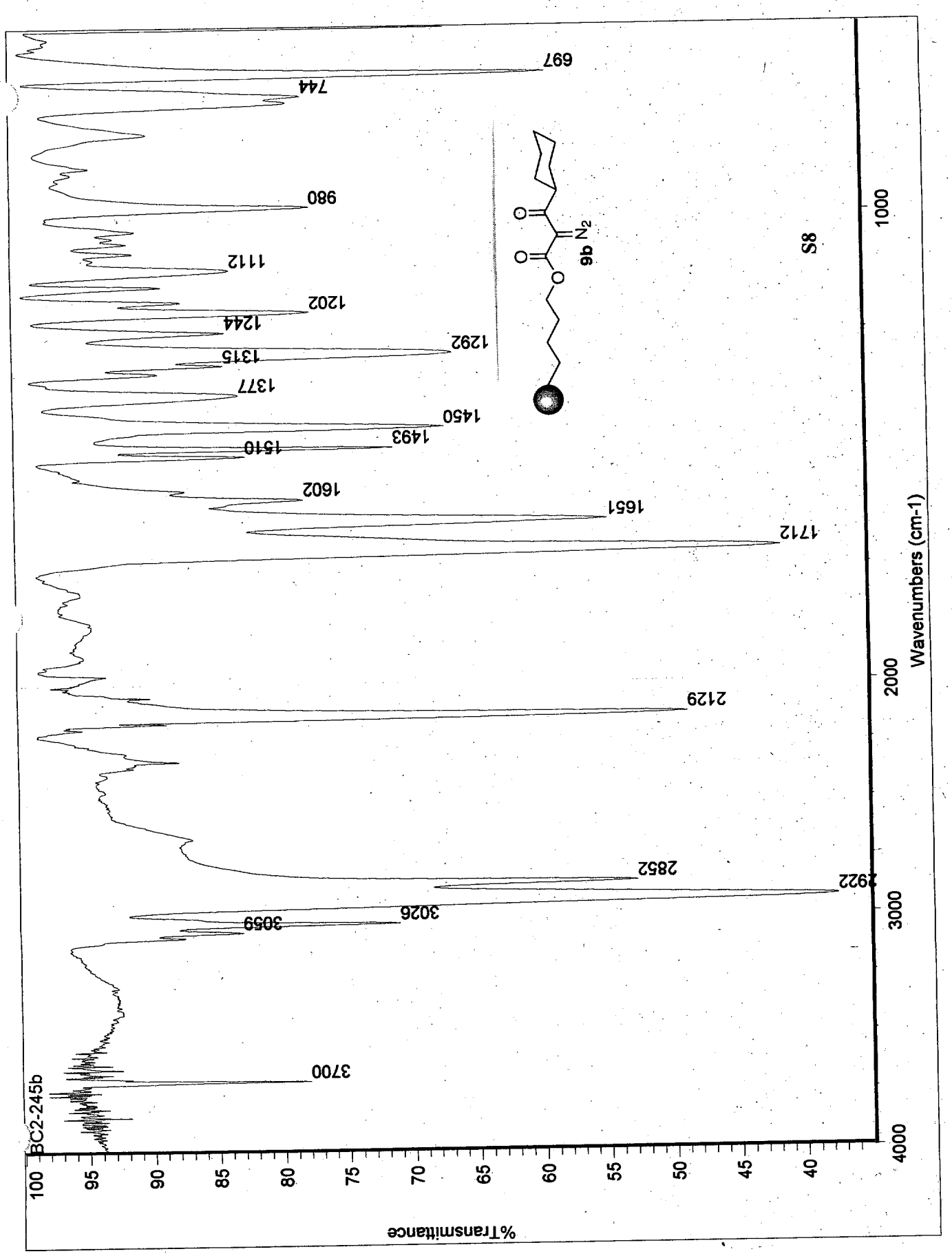
Cleavage reaction

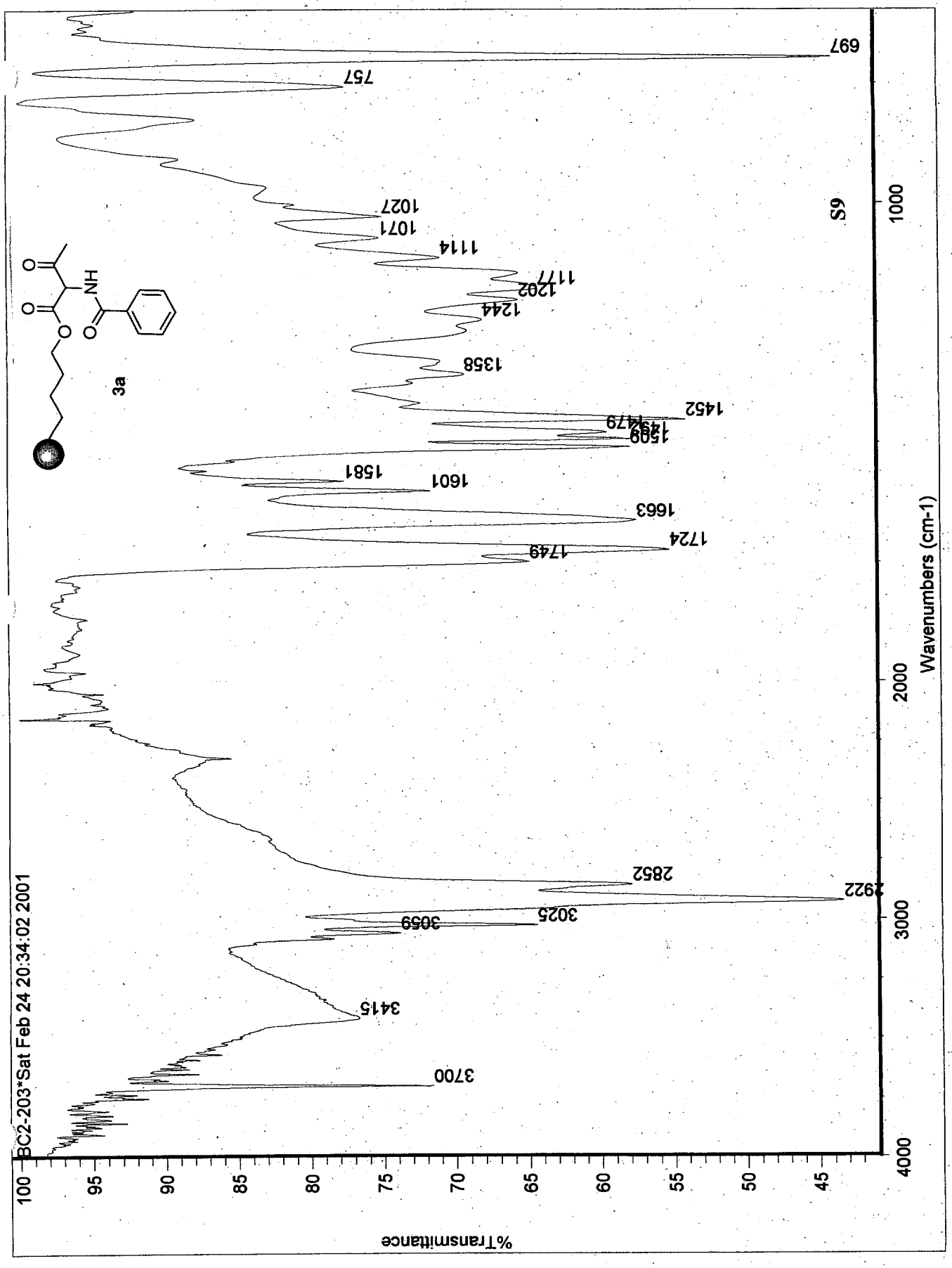
To a suspension of aluminum chloride (81.0 mg, 0.61 mmol) in CH_2Cl_2 (3.00 ml) was added piperidine (0.24 ml, 2.43 mmol) dropwise. After stirring for 10 min. the solution was added to resin **3a** (245 mg, 0.30 mmol) and the resulting suspension was stirred overnight. Saturated Na_2CO_3 (0.10 ml) and THF (1.00 ml) were added and the mixture was stirred for an additional 10 min. Na_2SO_4 (~50 mg) was added to the mixture which was then filtered through a mixed bed ion exchange resin and concentrated *in vacuo* to give the crude product. Purification by preparative TLC (25% ethyl acetate in hexanes) gave **7a** (43 mg, 54%) as a white solid.

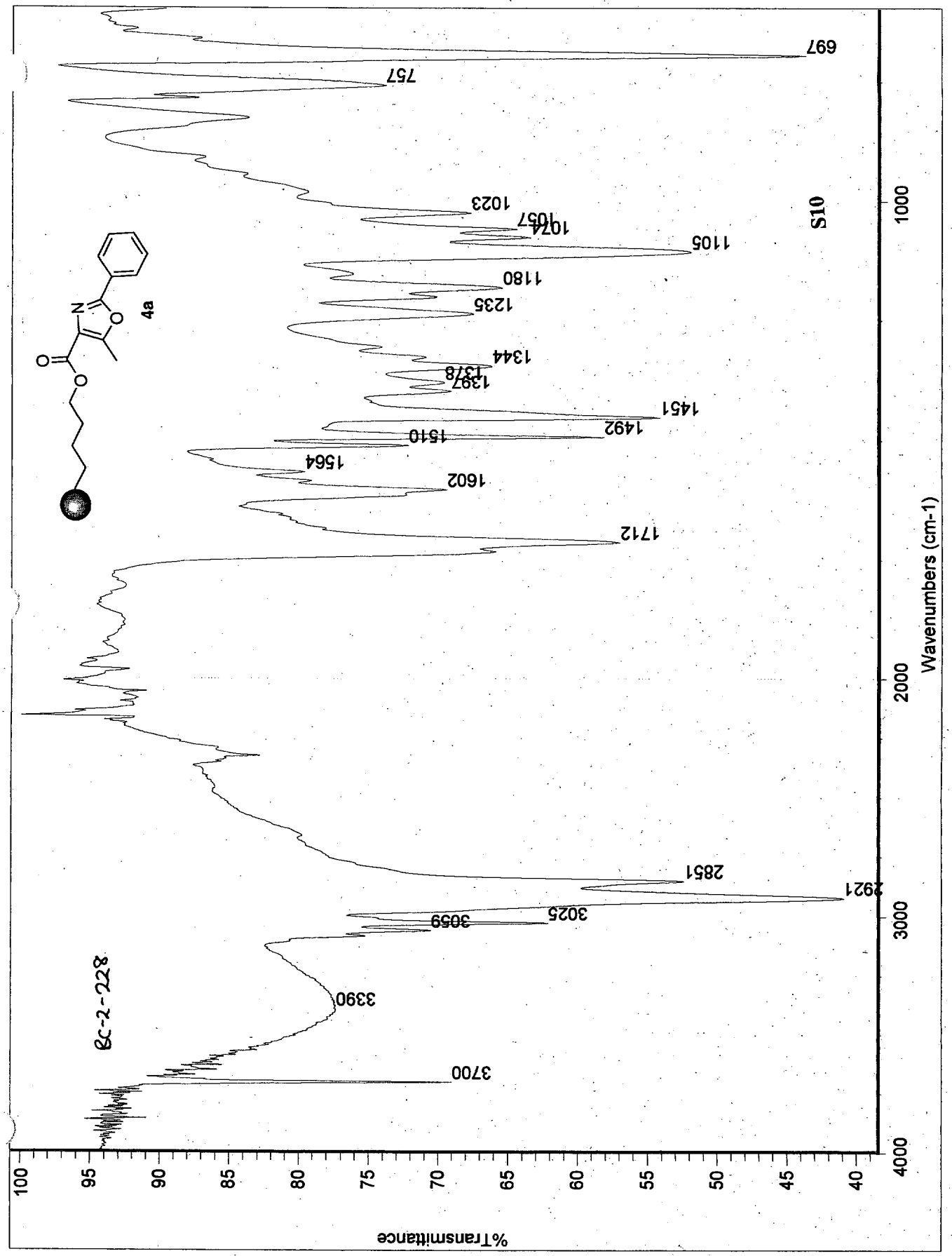

697
757
1028
1146
1175
1235
1312
1358
1413
1451
1492
1510
1601
1645
1716
1740
2853
2922
3025
3059
3357
3700
S5
bc2-190a Wed Feb 14 10:15:25 2001
%Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3000
2000
1000

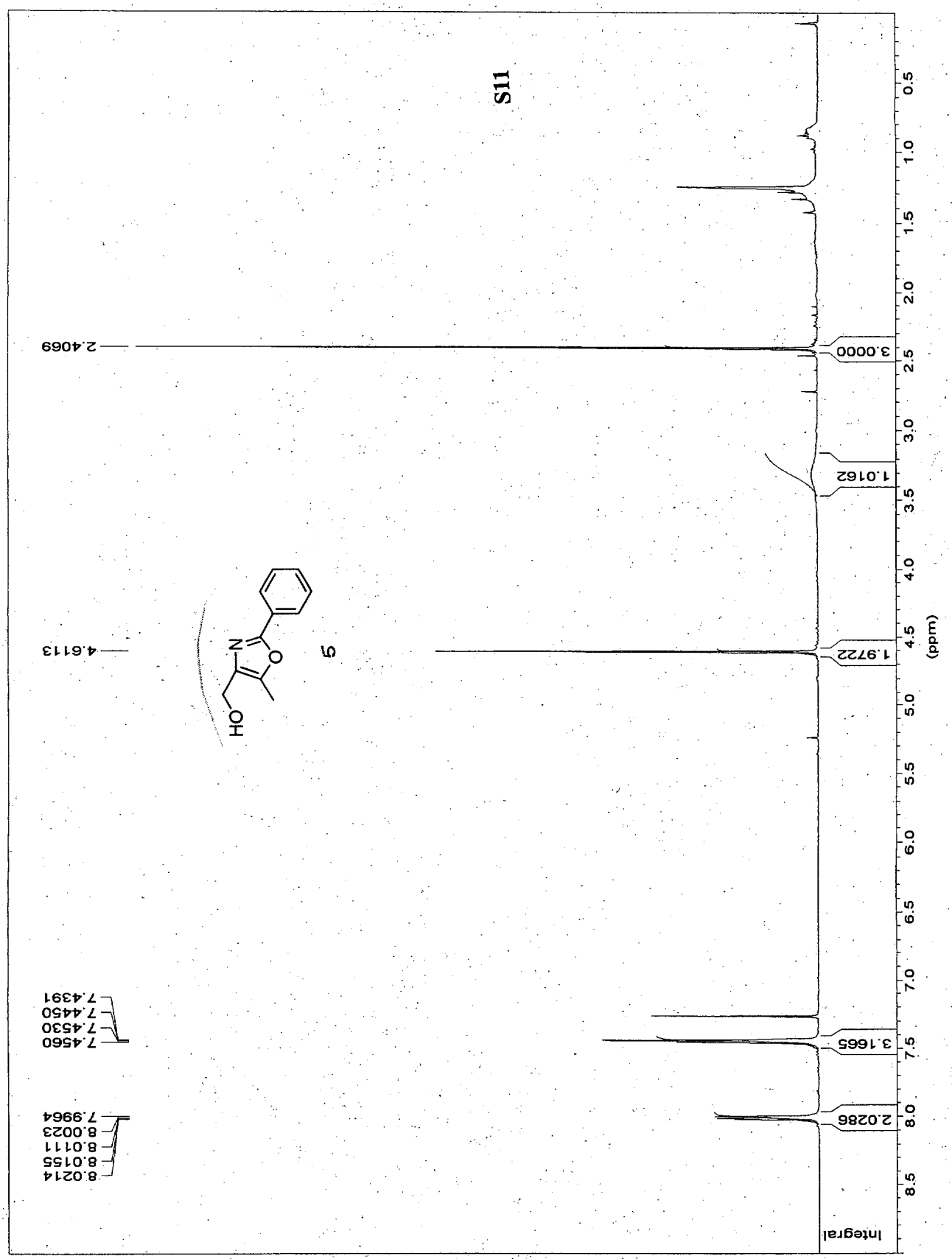

Thu Feb 15 12:43:03 2001 BC-2-PAGE
%Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3000
2000
1000
3700
3291
3059
3025
2923
2853
2137
1714
1655
1601
1509
1492
1452
1418
1363
1307
1246
1179
1149
1063
1021
964
743
697
S6
2

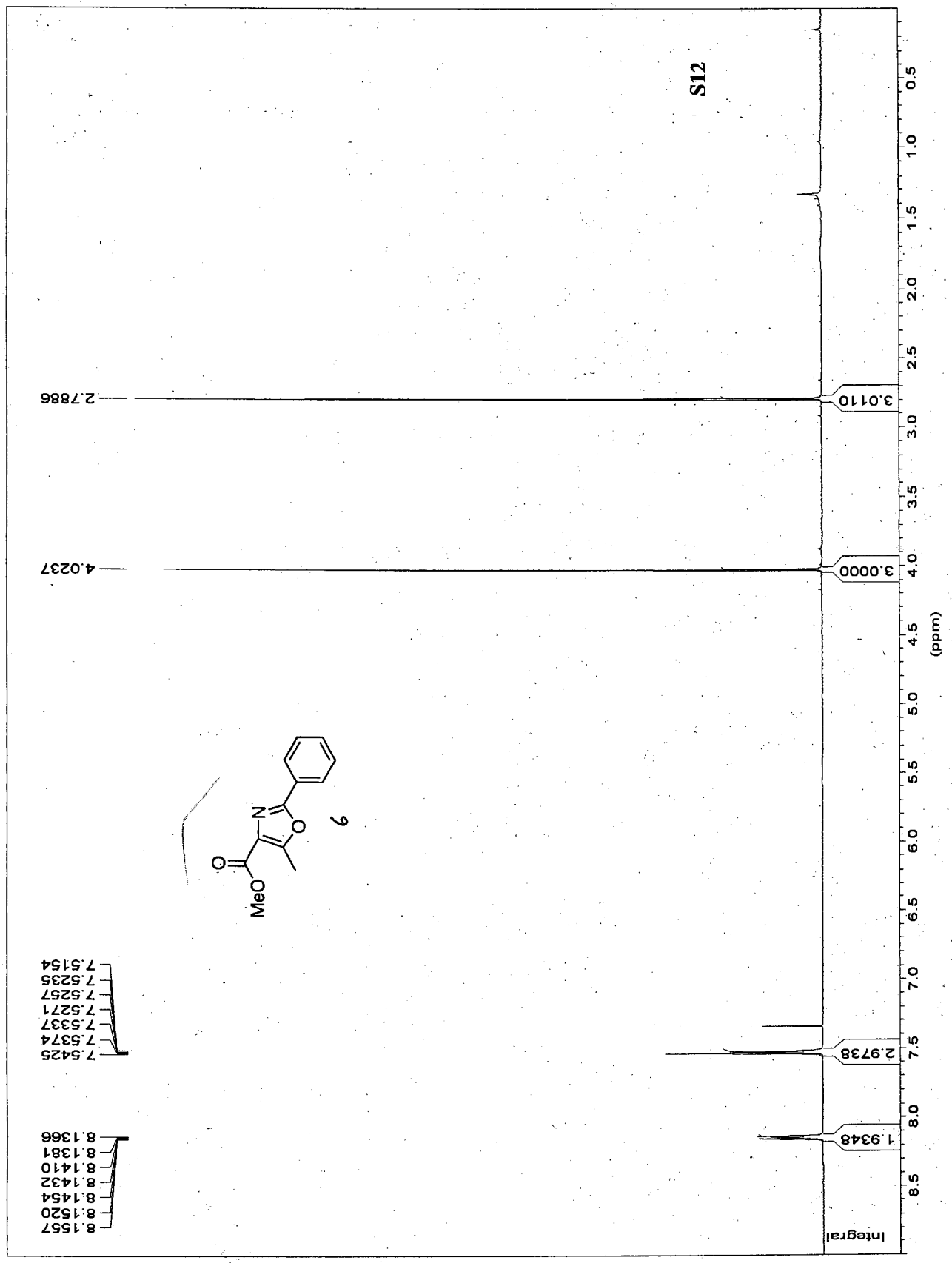

668
696
743
942
1028
1111
1178
1263
292
1377
1449
1493
1510
1581
1600
1627
1689
1720
2140
2853
2922
3026
3059
3307
3700
S7
9a
N_2
O
O
O
O
100
95
90
85
80
75
70
65
60
55
50
45
40
%Transmittance
4000
3000
2000
1000
Wavenumbers (cm-1)
*BC2-238 Sat Mar 17 20:36:33 2001

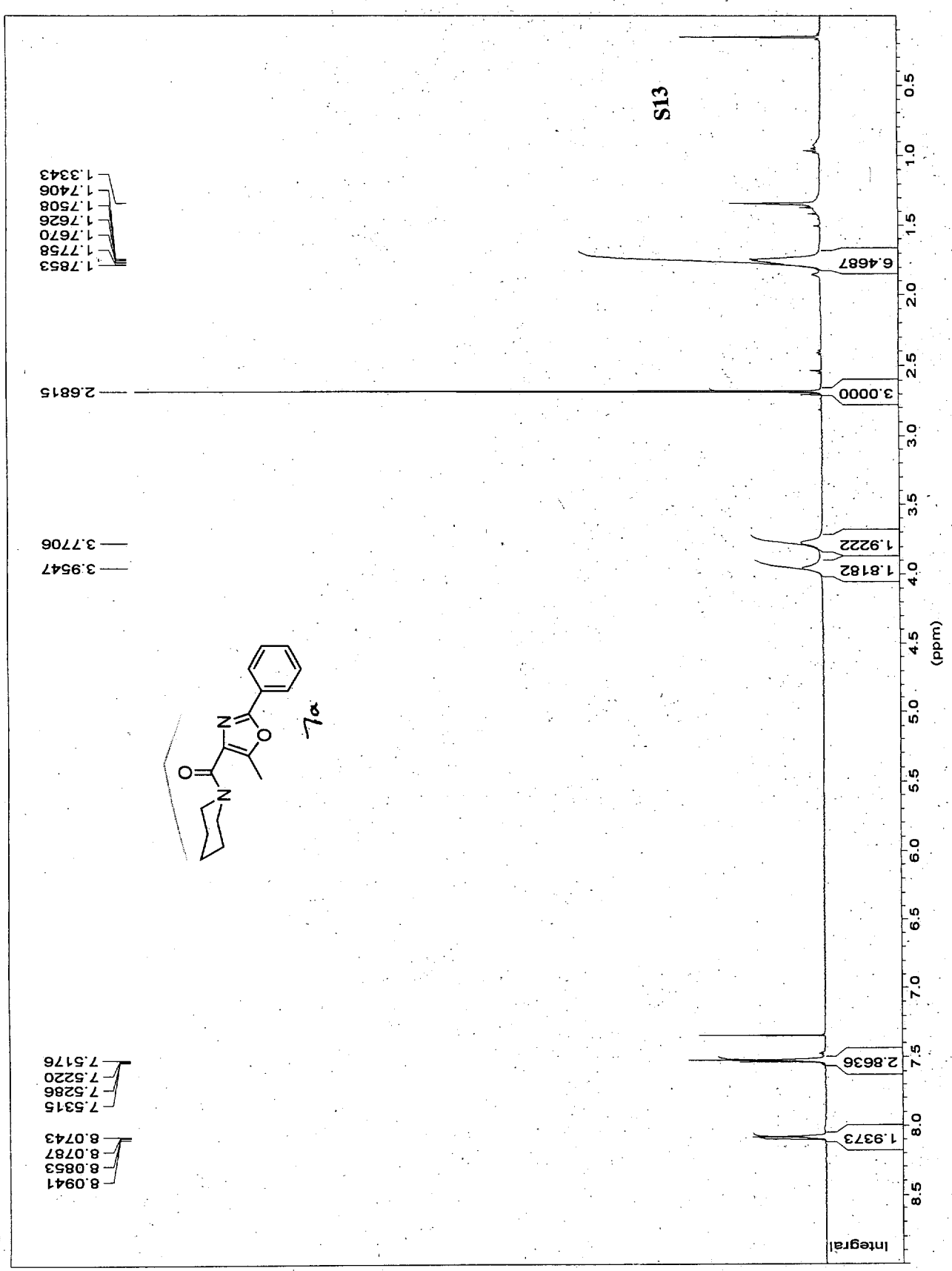

S8
9b
BC2-245b
%Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
4000
3000
2000
1000
3700
3059
3026
2922
2852
2129
1712
1651
1602
1510
1493
1450
1377
1315
1292
1244
1202
1112
980
744
697

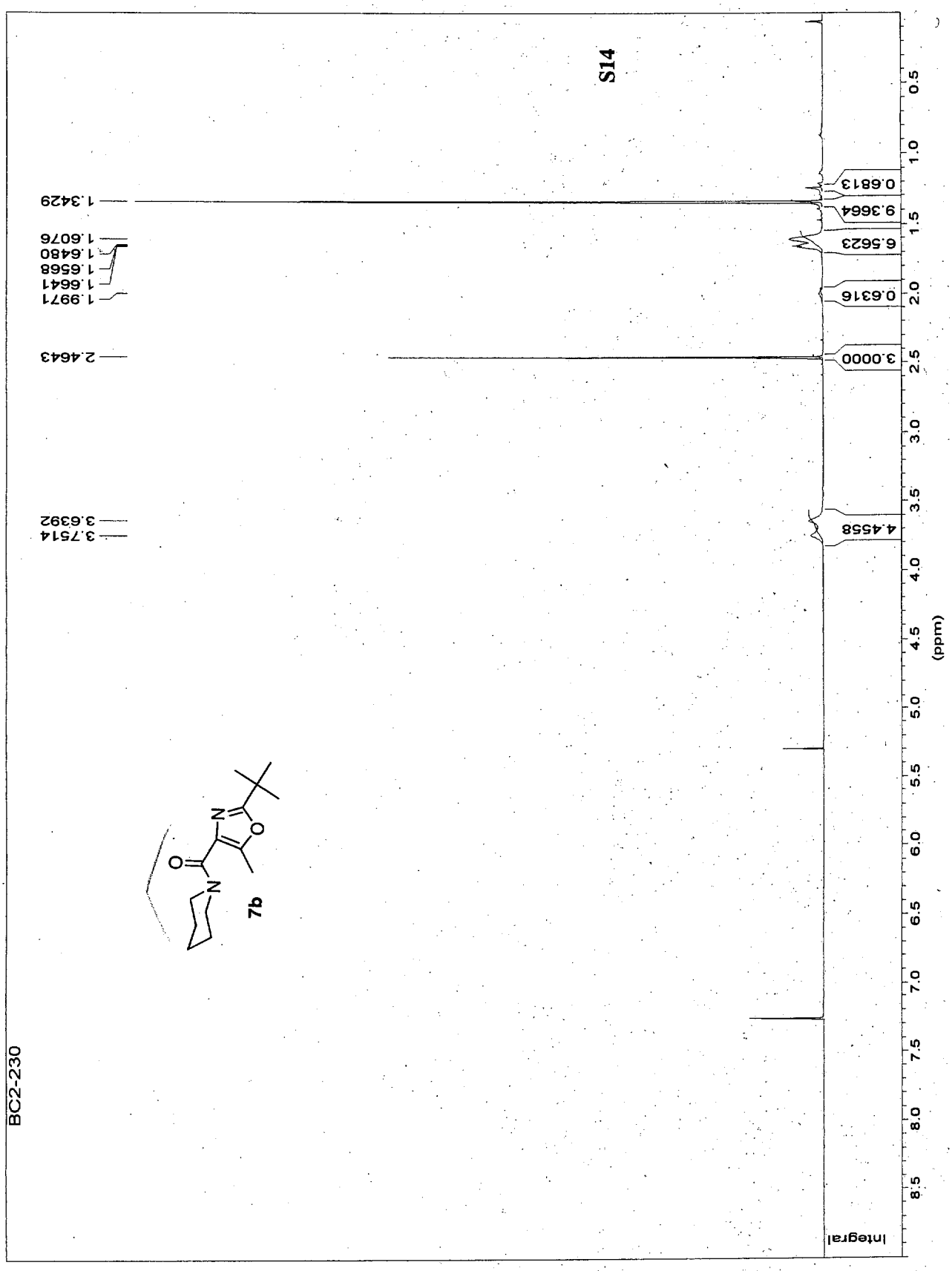


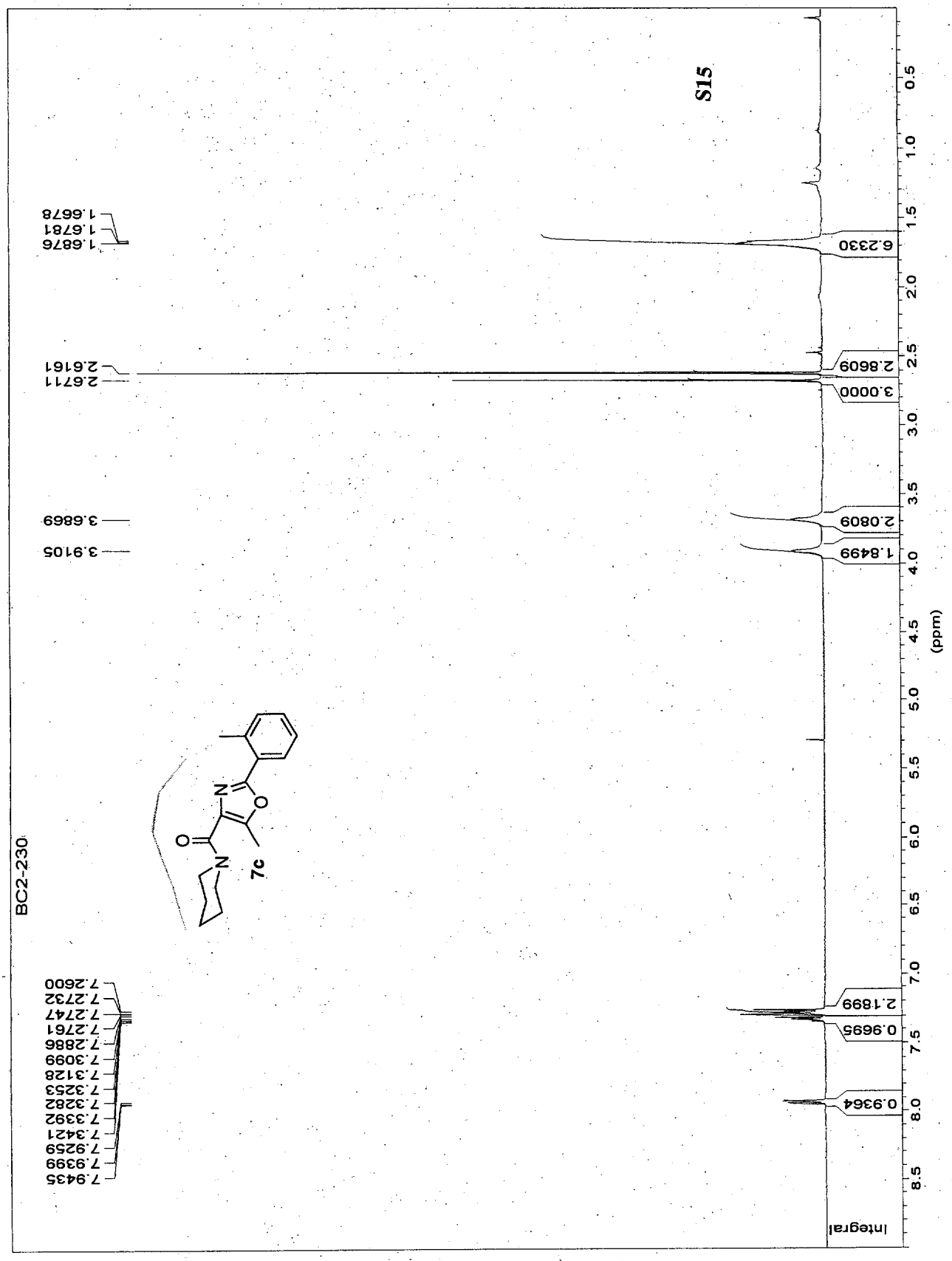

BC-2-228
S10
4a
%Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
4000
3000
2000
1000
3700
3390
3059
3025
2921
2851
1712
1602
1564
1510
1492
1451
1397
1378
1344
1235
1180
1105
1074
1057
1023
757
697

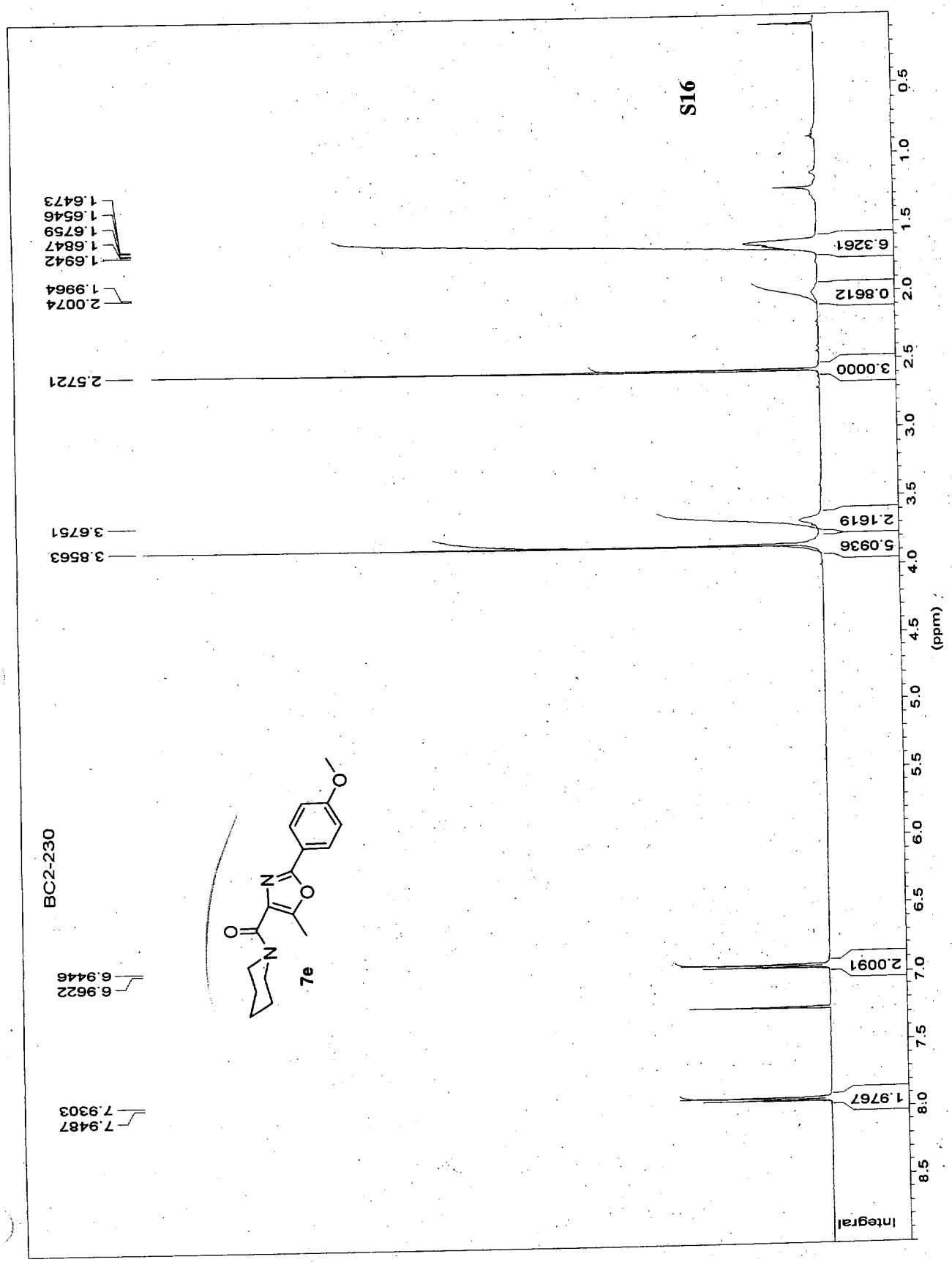


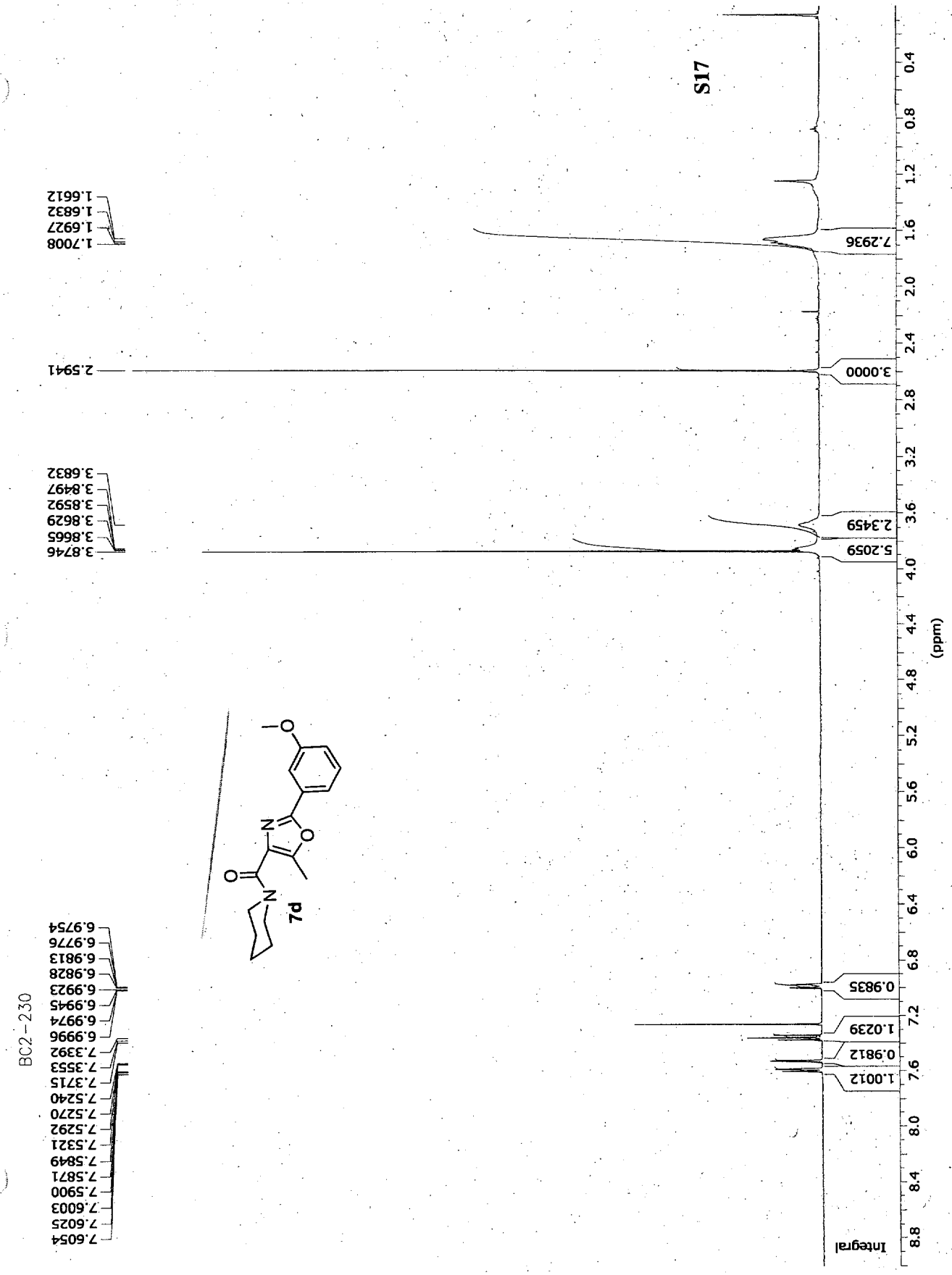

S12
2.7886
4.0237
7.5425
7.5374
7.5337
7.5271
7.5257
7.5235
7.5154
8.1366
8.1381
8.1410
8.1432
8.1454
8.1520
8.1557
MeO
9
3.0110
3.0000
2.9738
1.9348
Integral
(ppm)

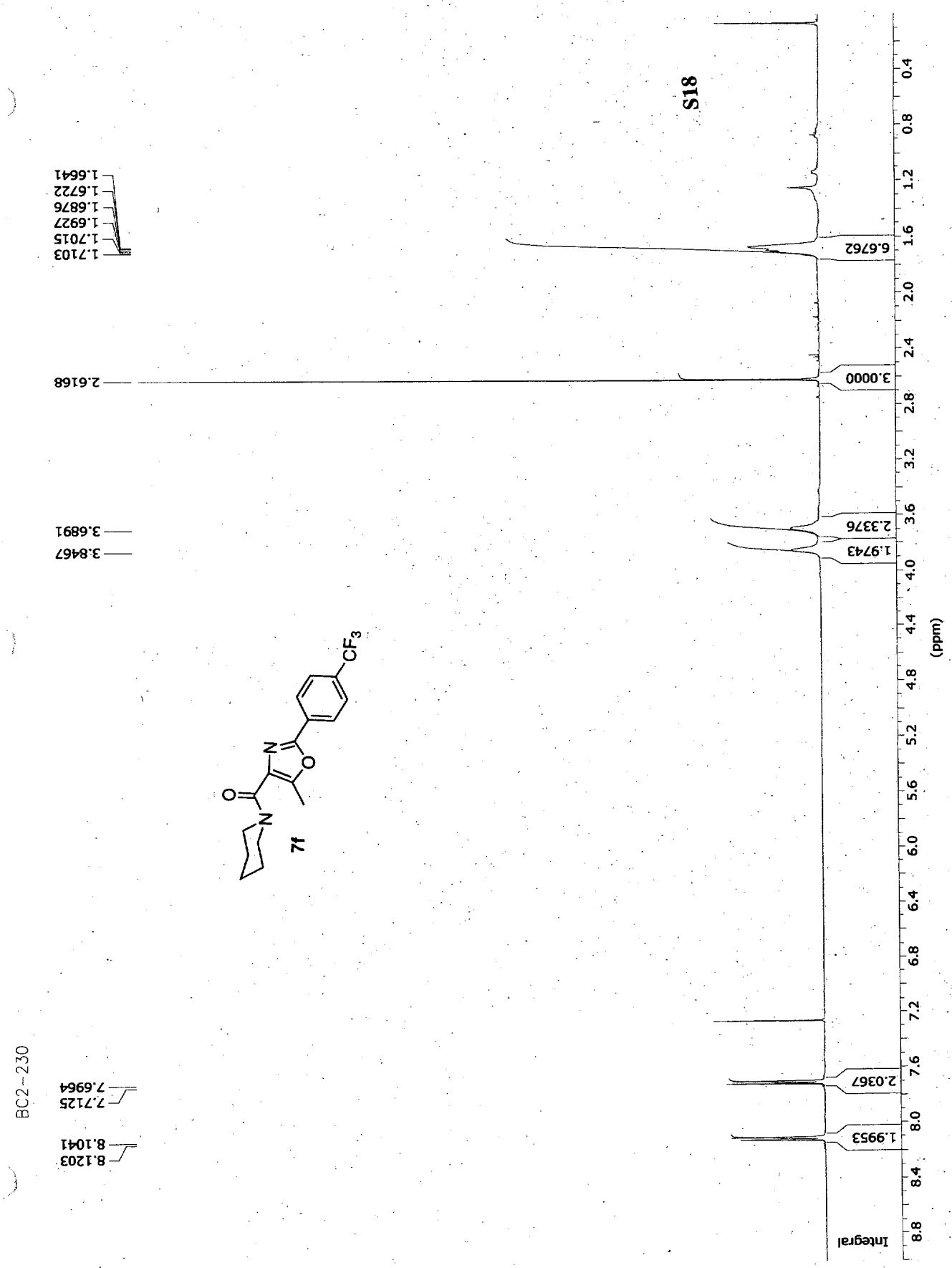

S13
8.0941
8.0853
8.0787
8.0743
7.5315
7.5286
7.5220
7.5176
3.9547
3.7706
2.6815
1.7853
1.7758
1.7670
1.7626
1.7508
1.7406
1.3343
1.9373
2.8636
1.8182
1.9222
3.0000
6.4687
Integral
(ppm)

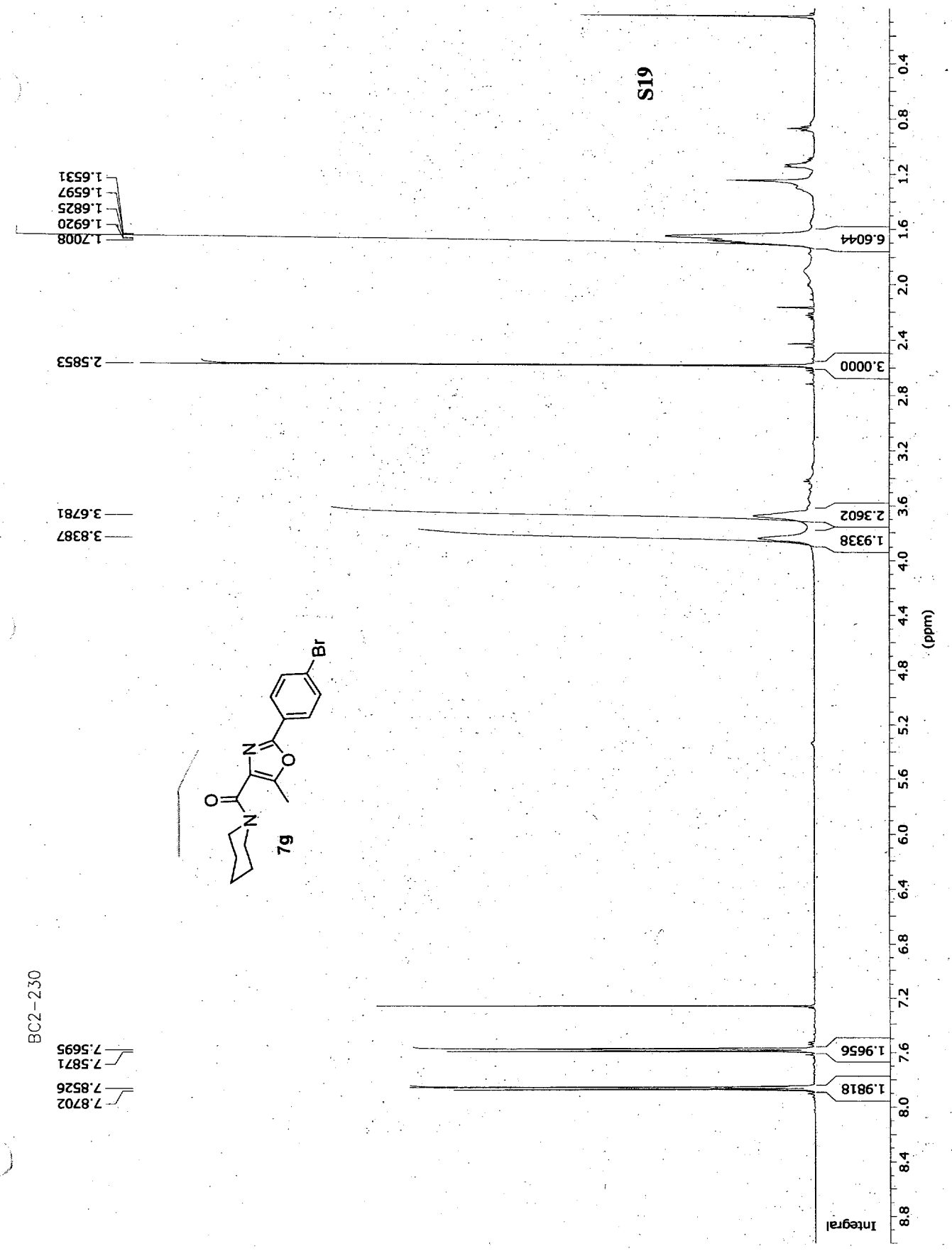


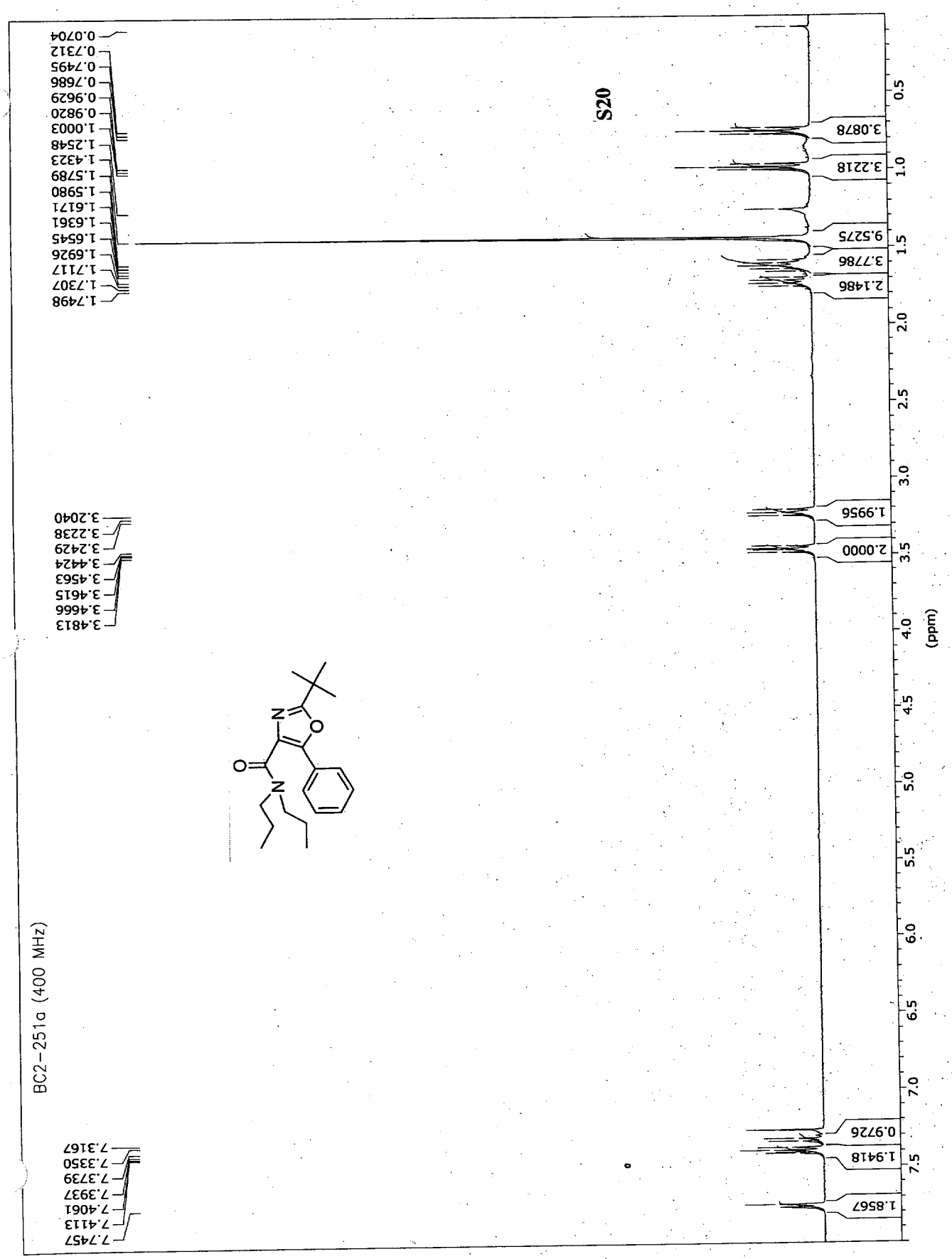

S15
BC2-230
7c
1.6678
1.6781
1.6876
2.6161
2.6711
3.6869
3.9105
7.2600
7.2732
7.2747
7.2761
7.2886
7.3099
7.3128
7.3253
7.3282
7.3392
7.3421
7.9259
7.9399
7.9435
6.2330
2.8609
3.0000
2.0809
1.8499
2.1899
0.9695
0.9364
Integral
(ppm)

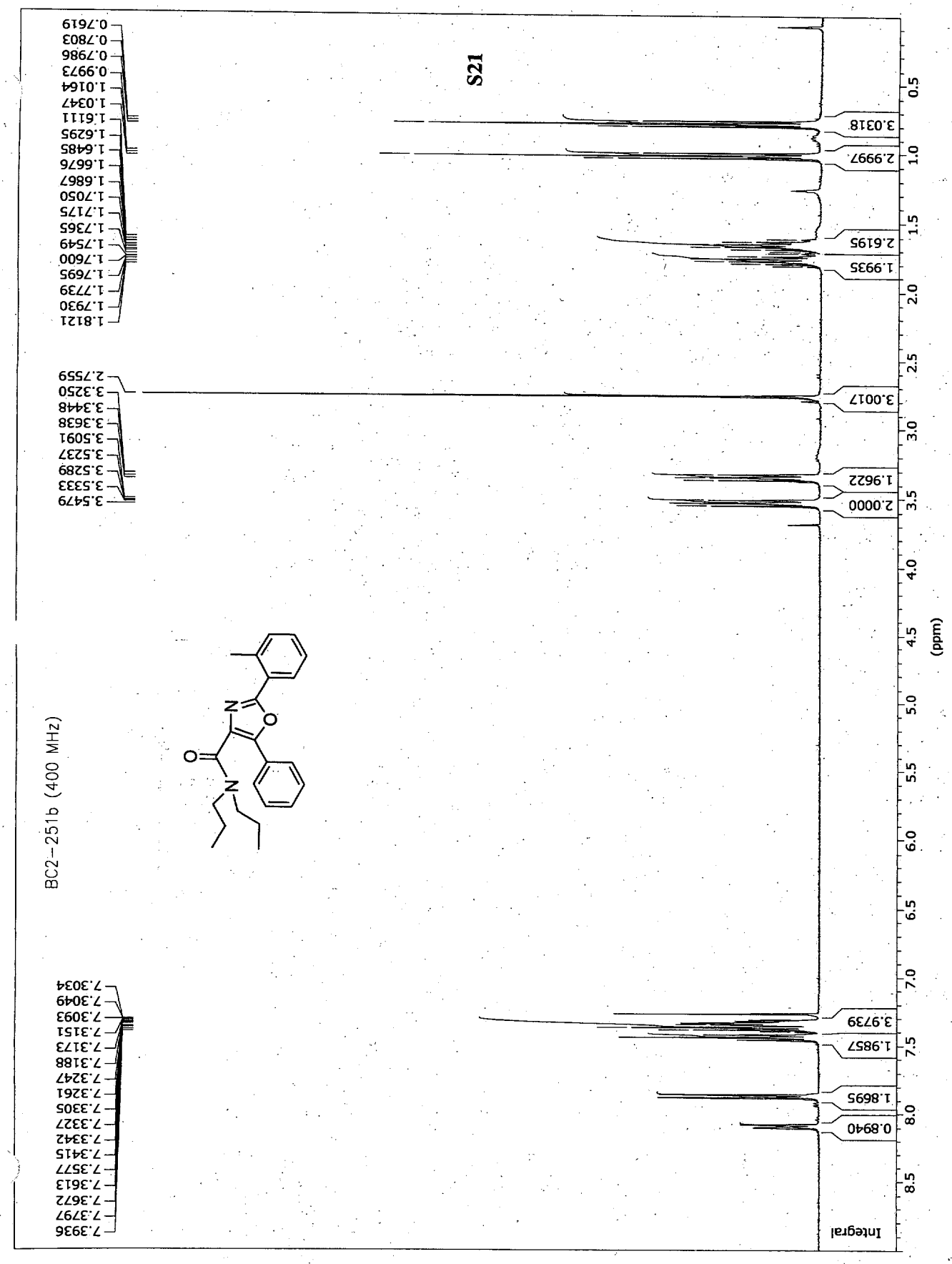

S16
BC2-230
7e
7.9487
7.9303
6.9622
6.9446
1.6473
1.6546
1.6759
1.6847
1.6942
1.9964
2.0074
2.5721
3.6751
3.8563
6.3261
0.8612
3.0000
2.1619
5.0936
2.0091
1.9767
Integral
(ppm)

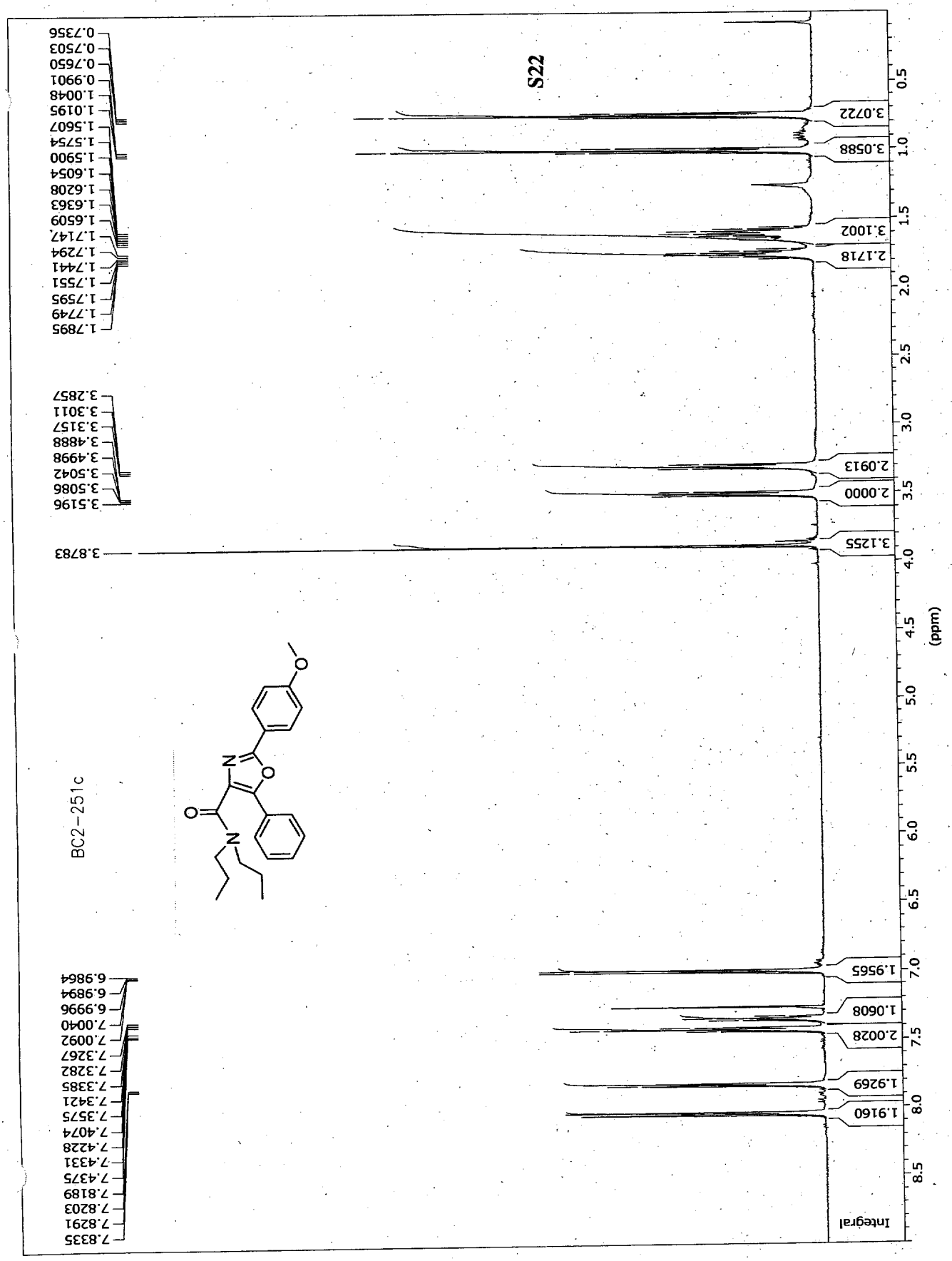


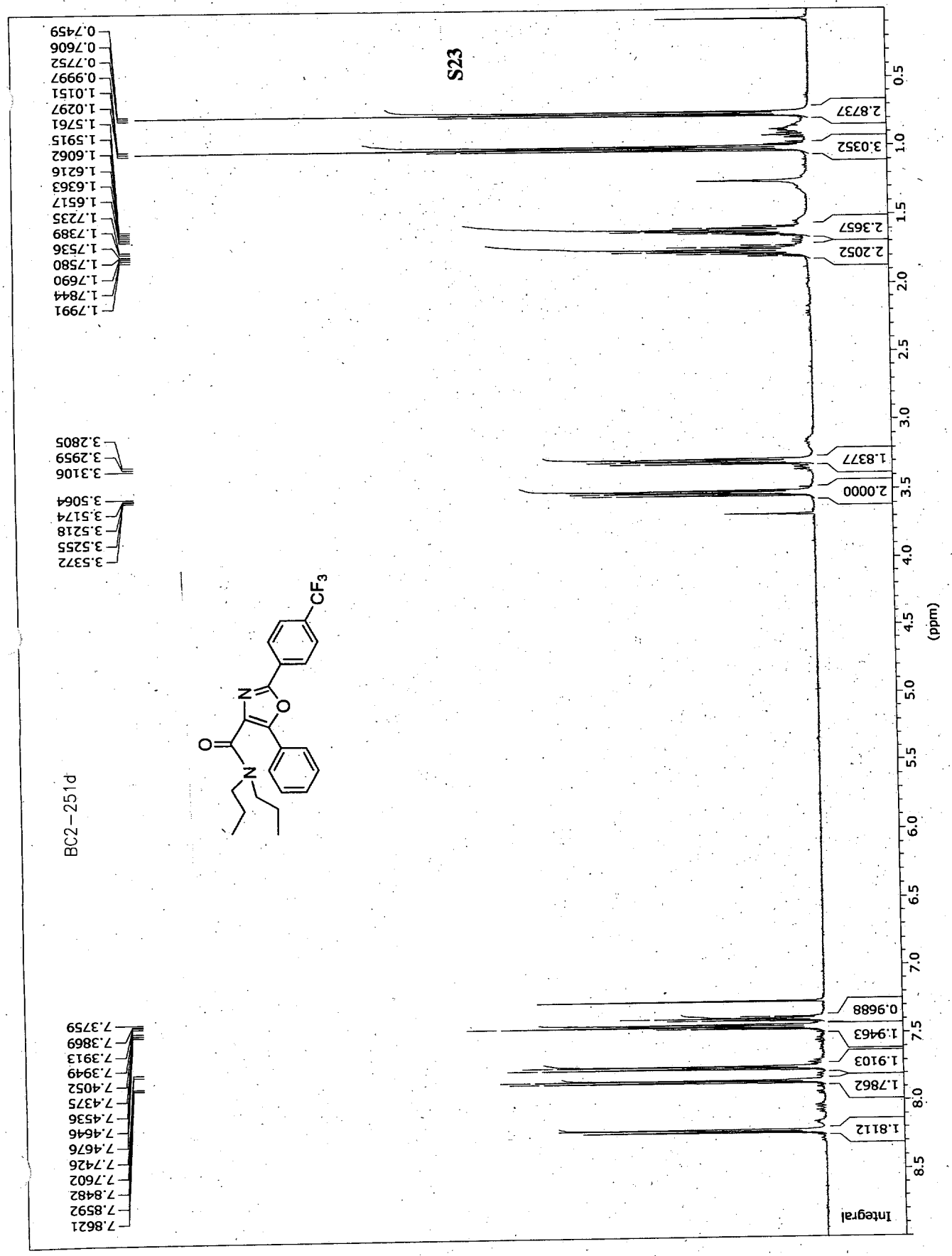


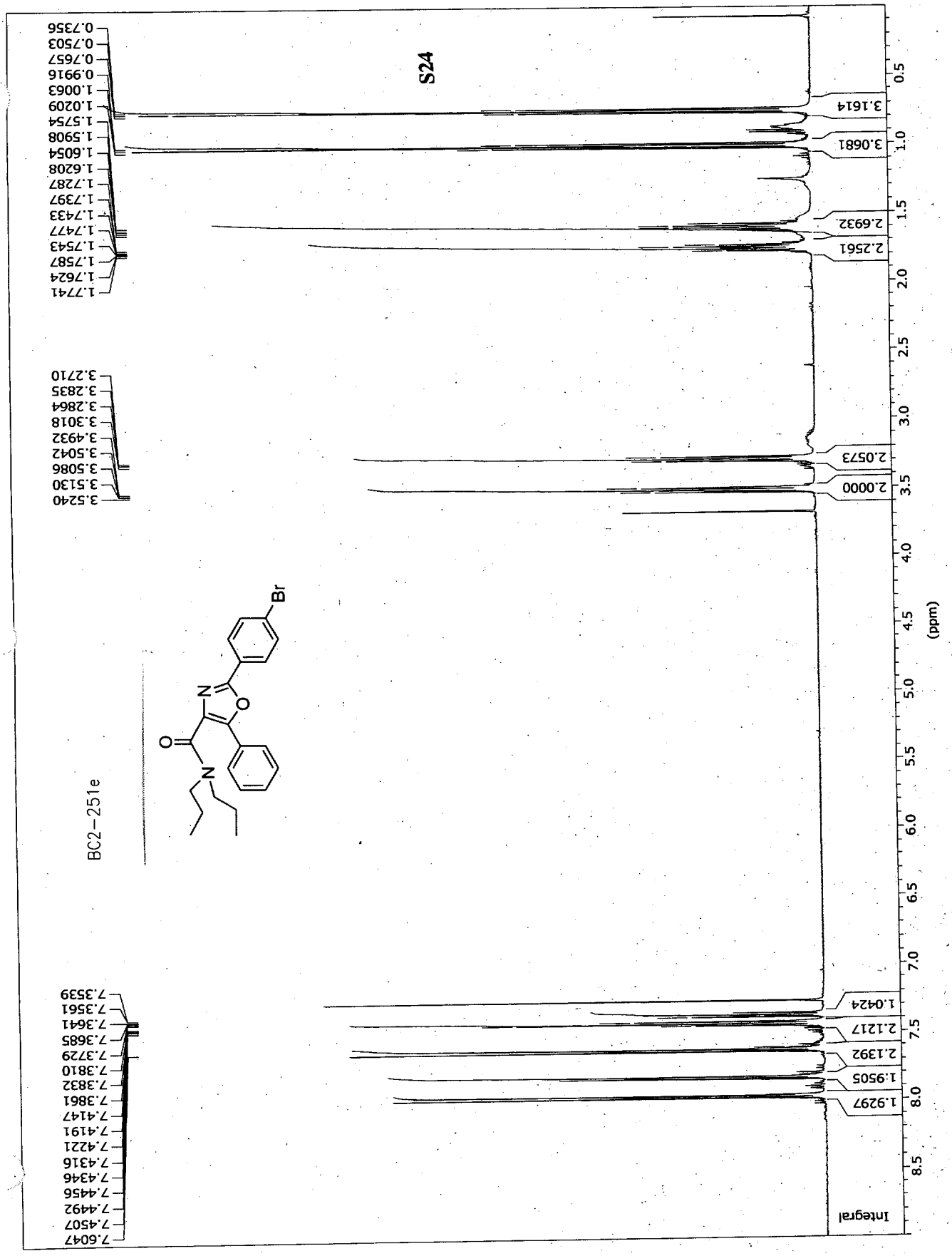

S19
BC2-230
7g
Br
N
O
O
N
1.7008
1.6920
1.6825
1.6597
1.6531
6.6044
2.5853
3.6781
3.8387
3.0000
2.3602
1.9338
1.9656
1.9818
7.8702
7.8526
7.5871
7.5695
Integral
(ppm)

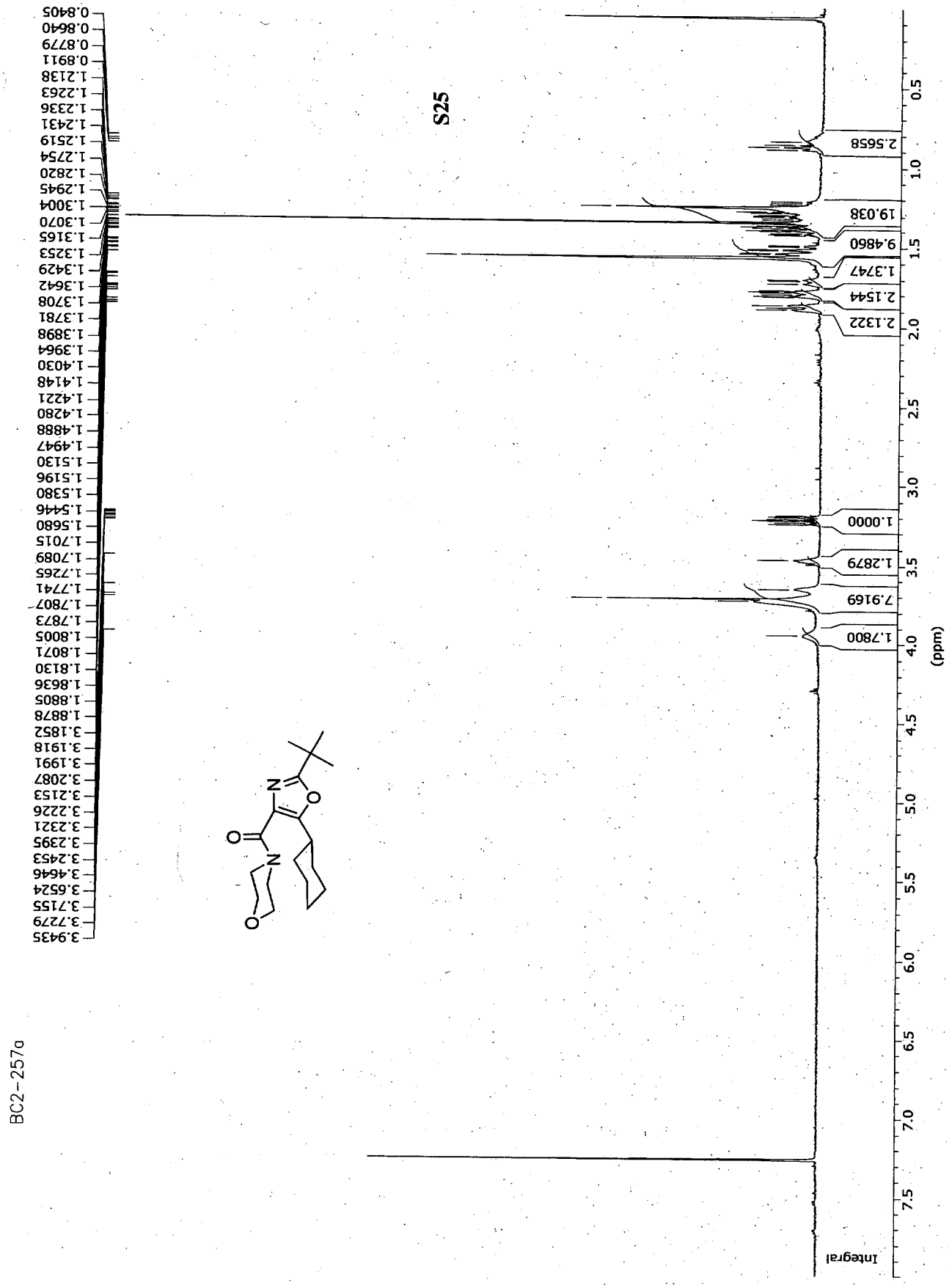

S20
BC2-251a (400 MHz)
(ppm)
0.0704
0.7312
0.7495
0.7686
0.9629
0.9820
1.0003
1.2548
1.4323
1.5789
1.5980
1.6171
1.6361
1.6545
1.6926
1.7117
1.7307
1.7498
3.0878
3.2218
9.5275
3.7786
2.1486
1.9956
2.0000
3.2040
3.2238
3.2429
3.4424
3.4563
3.4615
3.4666
3.4813
0.9726
1.9418
1.8567
7.3167
7.3350
7.3739
7.3937
7.4061
7.4113
7.7457

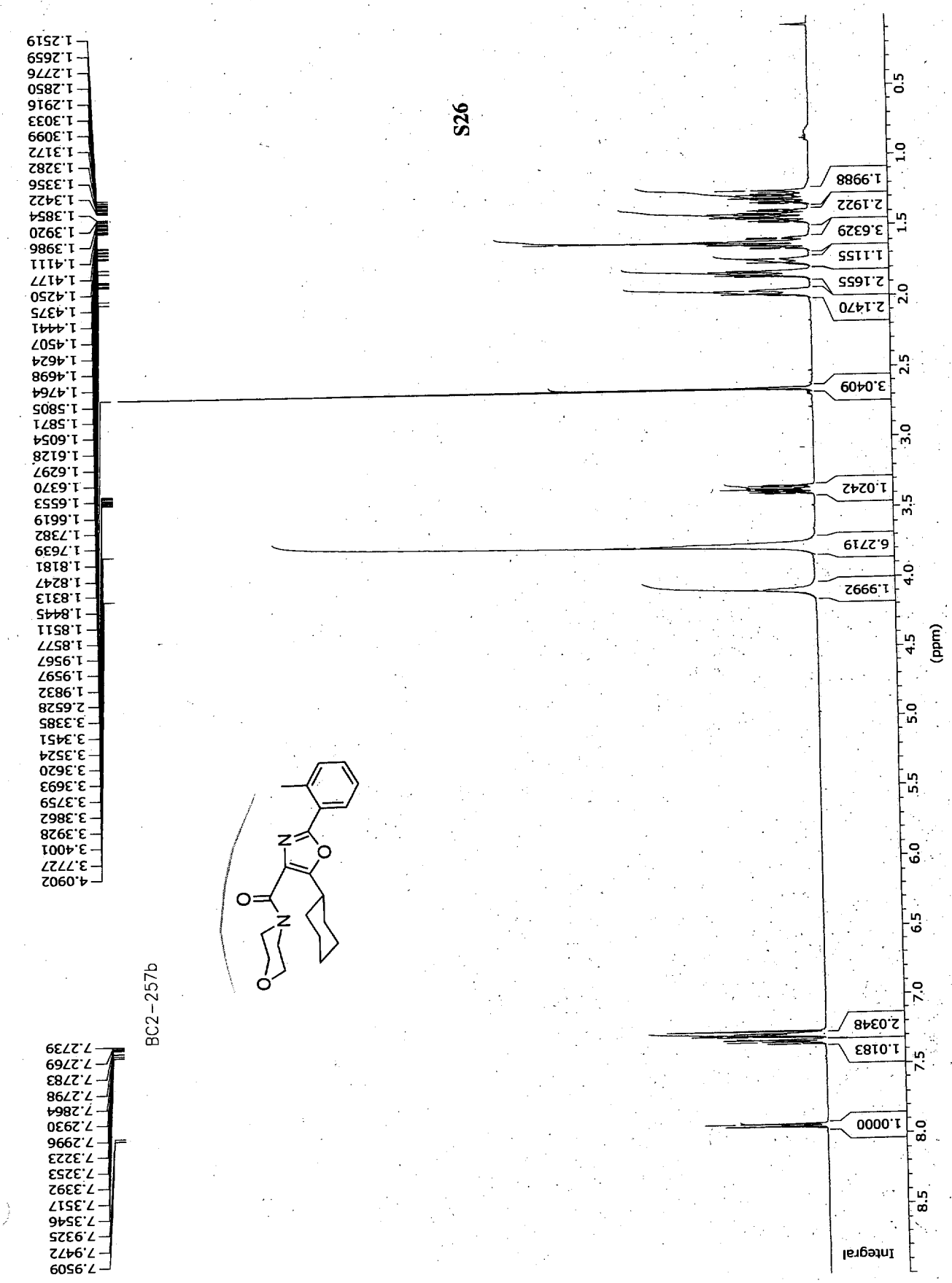

S21
BC2-251b (400 MHz)
Integral
(ppm)
3.0318
2.9997
2.6195
1.9935
3.0017
1.9622
2.0000
3.9739
1.9857
1.8695
0.8940
0.7619
0.7803
0.7986
0.9973
1.0164
1.0347
1.6111
1.6295
1.6485
1.6676
1.6867
1.7050
1.7175
1.7365
1.7549
1.7600
1.7695
1.7739
1.7930
1.8121
2.7559
3.3250
3.3448
3.3638
3.5091
3.5237
3.5289
3.5333
3.5479
7.3034
7.3049
7.3093
7.3151
7.3173
7.3188
7.3247
7.3261
7.3305
7.3327
7.3342
7.3415
7.3577
7.3613
7.3672
7.3797
7.3936


S22
BC2-251c
(ppm)
Integral
3.0722
3.0588
3.1002
2.1718
2.0913
2.0000
3.1255
1.9565
1.0608
2.0028
1.9269
1.9160
3.8783
3.5196
3.5086
3.5042
3.4998
3.4888
3.3157
3.3011
3.2857
1.7895
1.7749
1.7595
1.7551
1.7441
1.7294
1.7147
1.6509
1.6363
1.6208
1.6054
1.5900
1.5754
1.5607
1.0195
1.0048
0.9901
0.7650
0.7503
0.7356
7.8335
7.8291
7.8203
7.8189
7.4375
7.4331
7.4228
7.4074
7.3575
7.3421
7.3385
7.3282
7.3267
7.0092
7.0040
6.9996
6.9894
6.9864


S23
BC2-251d
CF3
N
O
O
N
0.7459
0.7606
0.7752
0.9997
1.0151
1.0297
1.5761
1.5915
1.6062
1.6216
1.6363
1.6517
1.7235
1.7389
1.7536
1.7580
1.7690
1.7844
1.7991
3.2805
3.2959
3.3106
3.5064
3.5174
3.5218
3.5255
3.5372
7.3759
7.3869
7.3913
7.3949
7.4052
7.4375
7.4536
7.4646
7.4676
7.7426
7.7602
7.8482
7.8592
7.8621
2.8737
3.0352
2.3657
2.2052
1.8377
2.0000
0.9688
1.9463
1.9103
1.7862
1.8112
Integral
(ppm)


S24
BC2-251e
Br
N
O
O
N
0.7356
0.7503
0.7657
0.9916
1.0063
1.0209
1.5754
1.5908
1.6054
1.6208
1.7287
1.7397
1.7433
1.7477
1.7543
1.7587
1.7624
1.7741
3.2710
3.2835
3.2864
3.3018
3.4932
3.5042
3.5086
3.5130
3.5240
7.3539
7.3561
7.3641
7.3685
7.3729
7.3810
7.3832
7.3861
7.4147
7.4191
7.4221
7.4316
7.4346
7.4456
7.4492
7.4507
7.6047
3.1614
3.0681
2.6932
2.2561
2.0573
2.0000
1.0424
2.1217
2.1392
1.9505
1.9297
Integral
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
(ppm)


S25
BC2-257a
(ppm)
Integral
2.5658
19.038
9.4860
1.3747
2.1544
2.1322
1.0000
1.2879
7.9169
1.7800
O
N
O
N
O


S26
BC2-257b
(ppm)
Integral
1.9988
2.1922
3.6329
1.1155
2.1655
2.1470
3.0409
1.0242
6.2719
1.9992
2.0348
1.0183
1.0000