Electronic Supporting Information (ESI)

Design, synthesis and biological activity of 4′-[(benzimidazol-1-yl)methyl] biphenyl-2-sulphonamides as dual angiotensin II and endothelin A receptor antagonists

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CONTENTS

1.Chemistry

The biphenyl intermediate A was prepared according to the procedure described by Reference 1.
All benzimidazole precursors B were prepared according to the procedure described by Reference 2.

1.1 General Procedure for Preparation of Compounds C_1-C_{22}

To a solution of compound **B** (0.24 mmol) in 1 mL DMF was added NaH (0.228 mmol, 60%) at 0℃. After stirring for 0.5 h, compound **A** (0.24 mmol) was added at 0 ℃,then the mixture was stirred for 3 h at rt. the mixture was diluted with EtOAc, washed with brine, the organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford an alkylation product **C** as colorless oil.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-N-(2-morpholinoethyl)-2-propyl-1H-benzo[d]imidazole-6-carboxamide(C_1)
Colorless oil, 122.1 mg, 60.5 %. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.95 (t, J = 7.2 Hz, 3H), 1.74 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.36 (t, J = 7.2 Hz, 4H), 2.55 (s, 3H), 2.79 (t, J = 7.2 Hz, 2H), 2.84 (t, J = 7.1 Hz, 2H), 3.32 (s, 3H), 3.45 (m, 2H), 3.47 (m, 2H), 3.68 (m, 6H), 4.21 (s, 2H), 4.78 (s, 2H), 7.09-7.93 (m, 10H), 8.45 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-N-(2-(4-methylpiperazin-1-yl)ethyl)-2-propyl-1H-benzo[d]imidazole-6-carboxamide (C_2)
Colorless oil, 120.1 mg, 59.5 %. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.95 (t, J = 7.2 Hz, 3H), 1.74 (m, 2H), 1.88 (s, 3H), 2.15 (s, 3H), 2.30 (s, 3H), 2.46 (t, J = 7.3 Hz, 4H), 2.56 (s, 3H), 2.67 (t, J = 7.2 Hz, 4H), 2.78 (t, J = 7.2 Hz, 2H), 2.83 (t, J = 7.2 Hz, 2H), 3.32 (s, 3H), 3.46 (m, 2H), 3.48 (m, 2H), 3.69 (m, 2H), 4.21 (s, 2H), 4.80 (s, 2H), 7.06-7.91 (m, 10H), 8.44 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-N-(2-(piperidin-1-yl)ethyl)-2-propyl-1H-benzo[d]imidazole-6-carboxamide (C_3)
Colorless oil, 123.2 mg, 61.4 %. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.94 (t, J = 7.2 Hz, 3H), 1.58 (m, 6H), 1.75 (m, 2H), 1.89 (s, 3H), 2.14 (s, 3H), 2.40 (t, J = 7.2 Hz, 4H), 2.55 (s, 3H), 2.78 (t, J = 7.2 Hz, 2H), 2.85 (t, J = 7.2 Hz, 2H), 3.32 (s, 3H), 3.45 (m, 2H), 3.49 (m, 2H), 3.67 (m, 2H), 4.22 (s, 2H), 4.81 (s, 2H), 7.10-7.94 (m, 10H), 8.45 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-

[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-N-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazole-6-carboxamide(C_4)

Colorless oil, 126.3 mg, 62.5 %. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.58 (t, J = 7.2 Hz, 4H), 1.74 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.26 (t, J = 7.2 Hz, 4H), 2.55 (s, 3H), 2.86 (t, J = 7.2 Hz, 2H), 2.95 (t, J = 7.2 Hz, 2H), 3.32 (s, 3H), 3.45 (m, 2H), 3.51 (m, 2H), 3.68 (m, 2H), 4.23 (s, 2H), 4.79 (s, 2H), 7.09-7.91 (m, 10H), 8.43 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-N,2-dipropyl-1H-benzo[d]imidazole-6-carboxamide(C_5)

Colorless oil, 132.1 mg, 65.3 %.^{1}H NMR (400MHz, $CDCl_3$) δ: 0.91 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.23 Hz, 3H), 1.58 (m, 2H), 1.75 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.55 (s, 3H), 2.77 (t, J = 7.2 Hz, 2H), 3.20 (t, J = 7.2 Hz, 2H), 3.32 (s, 3H), 3.45 (m, 2H), 3.68 (m, 2H), 4.23 (s, 2H), 4.79 (s, 2H), 7.07-7.89 (m, 10H), 8.45 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-isopropyl-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (C_6)

Colorless oil, 122.2 mg, 60.3 %.^{1}H NMR (400MHz, $CDCl_3$) δ: 0.94 (t, J = 7.2 Hz, 3H), 1.25 (d, J = 7.2 Hz, 6H), 1.76 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.55 (s, 3H), 2.79 (t, J = 7.2 Hz, 2H), 3.31 (s, 3H), 3.44 (m, 2H), 3.67 (m, 2H), 3.95 (m, 1H), 4.24 (s, 2H), 4.82 (s, 2H), 7.08-7.89 (m, 10H), 8.44 (s, 1H).

N-butyl-1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (C_7)

Colorless oil, 138.3 mg, 68.4 %.^{1}H NMR (400MHz, $CDCl_3$) δ: 0.91 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H), 1.32 (m, 2H), 1.59 (m, 2H), 1.75 (m, 2H), 1.87 (s, 3H), 2.14 (s, 3H), 2.56 (s, 3H), 2.81 (t, J = 7.2 Hz, 2H), 3.33 (s, 3H), 3.42 (m, 2H), 3.53 (m, 2H), 3.68 (m, 2H), 4.23 (s, 2H), 4.79 (s, 2H), 7.11-7.92 (m, 10H), 8.45 (s, 1H).

N-(tert-butyl)-1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (C_8)

Colorless oil, 118.2 mg, 58.6 %.^{1}H NMR (400MHz, $CDCl_3$) δ: 0.95 (t, J = 7.2 Hz, 3H), 1.39 (s, 9H), 1.85 (m, 2H), 1.88 (s, 3H), 2.16 (s, 3H), 2.58 (s, 3H), 2.97 (t, J = 7.2 Hz, 2H), 3.31 (s, 3H), 3.43 (m, 2H), 3.66 (m, 2H), 4.21 (s, 2H), 4.77 (s, 2H), 7.09-7.94 (m, 10H), 8.43 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-N-phenyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (C_9)

Colorless oil,127.1 mg, 69.3 %.^{1}H NMR (400MHz, $CDCl_3$) δ: 0.96 (t, J = 7.2 Hz, 3H),

1.74 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.55 (s, 3H), 2.78 (t, J = 7.2 Hz, 2H), 3.30 (s, 3H), 3.45 (m, 2H), 3.68 (m, 2H), 4.23 (s, 2H), 4.76 (s, 2H), 7.07-7.95 (m, 15H), 8.45 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(2-methoxyphenyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(C_{10})
Colorless oil, 131.1 mg, 64.8 %.^{1}H NMR (400MHz, $CDCl_3$) δ: 0.95 (t, J = 7.2 Hz, 3H), 1.78 (m, 2H), 1.89 (s, 3H), 2.14 (s, 3H), 2.55 (s, 3H), 2.80 (t, J = 7.2 Hz, 2H), 3.31 (s, 3H), 3.45 (m, 2H), 3.65 (s, 3H), 3.68 (m, 2H), 4.23 (s, 2H), 4.77 (s, 2H), 7.09-7.92 (m, 14H), 8.44 (s, 1H).

N-benzyl-1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(C_{11})
Colorless oil ,129.2 mg, 63.9 %. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.75 (m, 2H), 1.87 (s, 3H), 2.15 (s, 3H), 2.56 (s, 3H), 2.81 (t, J = 7.2 Hz, 2H), 3.34 (s, 3H), 3.47 (m, 2H), 3.69 (m, 2H), 4.23 (s, 2H), 4.31 (s, 2H), 4.79 (s, 2H), 7.09-7.91 (m, 15H), 8.43 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(2-methoxybenzyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(C_{12})
Colorless oil, 132.3 mg, 65.1 %.^{1}H NMR (400MHz, $CDCl_3$) δ: 0.97 (t, J = 7.2 Hz, 3H), 1.74 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.55 (s, 3H), 2.78 (t, J = 7.2 Hz, 2H), 3.32 (s, 3H), 3.43 (m, 2H), 3.47 (s, 3H), 3.69 (m, 2H), 4.22 (s, 2H), 4.45 (s, 2H), 4.79 (s, 2H), 7.12-7.86 (m, 14H), 8.45 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(3-methoxybenzyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (C_{13})
Colorless oil, 136.3 mg, 67.1 %. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.95 (t, J = 7.2 Hz, 3H), 1.76 (m, 2H), 1.88 (s, 3H), 2.14 (s, 3H), 2.56 (s, 3H), 2.79 (t, J = 7.2 Hz, 2H), 3.31 (s, 3H), 3.42 (m, 2H), 3.68 (m, 2H), 3.73 (s, 3H), 4.21 (s, 2H), 4.41 (s, 2H), 4.78 (s, 2H), 7.08-7.92 (m, 14H), 8.43 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(4-methoxybenzyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(C_{14})
Colorless oil, 122.2 mg, 60.3 %.^{1}H NMR (400MHz, $CDCl_3$) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.75 (m, 2H), 1.86 (s, 3H), 2.15 (s, 3H), 2.55 (s, 3H), 2.79 (t, J = 7.2 Hz, 2H), 3.33 (s, 3H), 3.44 (m, 2H), 3.67 (m, 2H), 3.77 (s, 3H), 4.21 (s, 2H), 4.46 (s, 2H), 4.77 (s, 2H), 7.09-7.90 (m, 14H), 8.44 (s, 1H).

N-(3,4-dimethoxybenzyl)-1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(C_{15})
Colorless oil, 138.1 mg, 68.2 %.^{1}H NMR (400MHz, $CDCl_3$) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.75 (m, 2H), 1.86 (s, 3H), 2.15 (s, 3H), 2.55 (s, 3H), 2.79 (t, J = 7.2 Hz, 2H), 3.32 (s, 3H), 3.44 (m, 2H), 3.68 (m, 2H), 3.72 (s, 3H), 3.80 (s, 3H), 4.21 (s, 2H), 4.42 (s, 2H), 4.79 (s, 2H), 7.07-7.93 (m, 13H), 8.43 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-N-phenethyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(C_{16})
Colorless oil, 136.2 mg, 67.7 %. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.94 (t, J = 7.2 Hz, 3H), 1.73 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.56 (s, 3H), 2.79 (t, J = 7.2 Hz, 2H), 2.83 (t, J = 7.1 Hz, 2H), 3.31 (s, 3H), 3.45 (m, 2H), 3.47 (m, 2H), 3.68 (m, 2H), 4.22 (s, 2H), 4.79 (s, 2H), 7.09-7.99 (m, 15H), 8.45 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(3-methoxyphenethyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(C_{17})
Colorless oil, 131.1 mg, 64.8 %. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.86 (t, J = 7.2 Hz, 3H), 1.75 (m, 2H), 1.84 (s, 3H), 2.14 (s, 3H), 2.50 (s, 3H), 2.81 (t, J = 7.2 Hz, 2H), 2.88 (t, J = 7.2 Hz, 2H), 3.33 (s, 3H), 3.46 (m, 2H), 3.65 (m, 2H), 3.68 (m, 2H), 3.76 (s, 3H), 4.22 (s, 2H), 4.76 (s, 2H), 7.05-7.94 (m, 14H), 8.44 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(4-methoxyphenethyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (C_{18})
Colorless oil, 130.2 mg, 64.5 %. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.97 (t, J = 7.2 Hz, 3H), 1.73 (m, 2H), 1.88 (s, 3H), 2.15 (s, 3H), 2.56 (s, 3H), 2.78 (t, J = 7.2 Hz, 2H), 2.87 (t, J = 7.1 Hz, 2H), 3.31 (s, 3H), 3.40 (m, 2H), 3.47 (m, 2H), 3.66 (m, 2H), 3.69 (s, 3H), 4.21 (s, 2H), 4.77 (s, 2H), 7.10-7.90 (m, 14H), 8.45 (s, 1H).

N-(2,5-dimethoxyphenethyl)-1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(C_{19})
Colorless oil, 128.3 mg, 63.7 %. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.96 (t, J = 7.3 Hz, 3H), 1.75 (m, 2H), 1.87 (s, 3H), 2.15 (s, 3H), 2.55 (s, 3H), 2.80 (t, J = 7.2 Hz, 2H), 2.85 (t, J = 7.2 Hz, 2H), 3.32 (s, 3H), 3.45 (m, 2H), 3.48 (m, 2H), 3.67 (m, 2H), 3.71 (s, 3H), 3.77 (s, 3H), 4.23 (s, 2H), 4.78 (s, 2H), 7.07-7.87 (m, 13H), 8.43 (s, 1H).

N-(3,4-dimethoxyphenethyl)-1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(C_{20})
Colorless oil, 127.2 mg, 63.3 %. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.94 (t, J = 7.2 Hz,

3H), 1.77 (m, 2H), 1.86 (s, 3H), 2.16 (s, 3H), 2.56 (s, 3H), 2.77 (t, J = 7.2 Hz, 2H), 2.87 (t, J = 7.2 Hz, 2H), 3.33 (s, 3H), 3.46 (m, 2H), 3.49 (m, 2H), 3.68 (m, 2H), 3.73 (s, 3H), 3.79 (s, 3H), 4.22 (s, 2H), 4.79 (s, 2H), 7.10-7.91 (m, 13H), 8.44 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(2-fluorophenethyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(C_{21})
Colorless oil, 130.1 mg, 64.2 %. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.95 (t, J = 7.2 Hz, 3H), 1.74 (m, 2H), 1.84 (s, 3H), 2.15 (s, 3H), 2.55 (s, 3H), 2.79 (t, J = 7.2 Hz, 2H), 2.85 (t, J = 7.1 Hz, 2H), 3.32 (s, 3H), 3.44 (m, 2H), 3.53 (m, 2H), 3.68 (m, 2H), 4.21 (s, 2H), 4.78 (s, 2H), 7.13-7.85 (m, 14H), 8.44 (s, 1H).

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)-N-((2-methoxyethoxy)methyl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(4-fluorophenethyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(C_{22})
Colorless oil, 132.3 mg, 65.7 %. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.73 (m, 2H), 1.87 (s, 3H), 2.16 (s, 3H), 2.56 (s, 3H), 2.78 (t, J = 7.2 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H), 3.31 (s, 3H), 3.47 (m, 2H), 3.56 (m, 2H), 3.67 (m, 2H), 4.23 (s, 2H), 4.79 (s, 2H), 7.08-7.96 (m, 14H), 8.45 (s, 1H).

1.2 General Method for Preparation of Compounds 1-22

To a solution of compound **C** (0.161mmol) in EtOH (2 mL) was added 6N HCl (1mL), then the mixture refluxed for 1 h. The solvent was removed in vacuo, and the pH was adjusted to 8 by saturated aqueous of $NaHCO_3$, then acidified with AcOH to pH=5. The mixture was extract with EtOAc, the combined organic layers were washed with brine, dried over anhydrous $NaSO_4$ and concentrated. The residue was separated by flash column chromatography (MeOH:Water =1:9) to afford the product as yellow solid.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-N-(2-morpholinoethyl)-2-propyl-1H-benzo[d]imidazole-6-carboxamide (1)

Yellow solid, 48.8 mg, 40 %, m.p. 103-105 ℃.^{1}H NMR (400MHz, DMSO) δ: 0.95 (t, J = 7.2 Hz, 3H), 1.74 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.36 (t, J = 7.2 Hz, 4H), 2.55 (s, 3H), 2.79 (t, J = 7.2 Hz, 2H), 2.84 (t, J = 7.1 Hz, 2H), 3.47 (m, 2H), 3.68 (m, 4H), 4.78 (s, 2H), 7.09-7.93 (m, 10H), 8.45 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 6.6, 10.3, 13.9, 16.5, 20.8, 28.8, 38.1, 46.6, 49.5, 53.3, 68.6, 108.5, 109.5, 123.4, 124.4, 127.7, 128.7, 128.8, 128.9, 123.0, 132.7, 133.0, 134.8, 135.5, 138.1, 138.5, 141.5, 142.8, 154.4, 156.3, 161.9, 169.7; MS (ESI), m/z: 671.3 (M+H); Anal. Calcd. For ($C_{36}H_{42}N_6O_5S$)(%): C, 64.47; H, 6.31; N, 12.53; Found(%): C, 64.42; H, 6.30; N, 12.54.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-N-(2-(4-methylpiperazin-1-yl)ethyl)-2-propyl-1H-benzo[d]imidazole-6-

carboxamide (2)

Yellow solid, 58.3 mg, 47.8 %, m.p. 101-103 ℃.^{1}H NMR (400MHz, DMSO) δ: 0.95 (t, J = 7.2 Hz, 3H), 1.74 (m, 2H), 1.88 (s, 3H), 2.15 (s, 3H), 2.30 (s, 3H), 2.46 (t, J = 7.3 Hz, 4H), 2.56 (s, 3H), 2.67 (t, J = 7.2 Hz, 4H), 2.78 (t, J = 7.2 Hz, 2H), 2.83 (t, J = 7.2 Hz, 2H), 3.48 (m, 2H), 4.80 (s, 2H), 7.06-7.91 (m, 10H), 8.44 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 6.2, 9.9, 13.6, 16.2, 20.4, 28.4, 38.2, 43.2, 46.2, 49.5, 52.4, 53.1, 108.1, 109.1, 123.0, 124.0, 127.3, 128.3, 128.4 , 128.5, 129.5, 132.4, 132.7, 134.4, 135.1, 137.7, 138.1, 141.1, 142.5, 154.1, 155.9, 161.5, 169.4; MS (ESI), m/z: 684.3 (M+H); Anal. Calcd. For ($C_{37}H_{45}N_7O_4S$)(%): C, 64.98; H, 6.63; N, 14.34; Found(%): C, 64.93; H, 6.63; N, 14.33.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-N-(2-(piperidin-1-yl)ethyl)-2-propyl-1H-benzo[d]imidazole-6-carboxamide (3)

Yellow solid, 65.4 mg, 53.6 %, m.p. 107-108 ℃.^{1}H NMR (400MHz, DMSO) δ: 0.94 (t, J = 7.2 Hz, 3H), 1.58 (m, 6H), 1.75 (m, 2H), 1.89 (s, 3H), 2.14 (s, 3H), 2.40 (t, J = 7.2 Hz, 4H), 2.55 (s, 3H), 2.78 (t, J = 7.2 Hz, 2H), 2.85 (t, J = 7.2 Hz, 2H), 3.49 (m, 2H), 4.81 (s, 2H), 7.10-7.94 (m, 10H), 8.45 (s, 1H); ^{13}C NMR (400MHz, , $CDCl_3$) δ: 6.2, 9.8, 13.5, 16.1, 20.4, 25.5, 27.3, 28.4, 38.0, 46.1, 47.6, 53.4, 108.0, 109.0, 122.9, 123.9, 127.2, 128.2, 128.4 128.4, 129.4, 132.3, 132.6, 134.3, 135.0, 137.6, 138.0, 141.1, 142.4, 154.0, 155.8, 161.4, 169.3; MS (ESI), m/z: 669.3 (M+H); Anal. Calcd. For ($C_{37}H_{44}N_6O_4S$)(%): C, 66.44; H, 6.63; N, 12.56; Found(%): C, 66.46; H, 6.62; N, 12.55.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-N-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazole-6-carboxamide (4)

Yellow solid, 68.4 mg, 56.1 %, m.p. 105-107 ℃.^{1}H NMR (400MHz, DMSO) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.58 (t, J = 7.2 Hz, 4H), 1.74 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.26 (t, J = 7.2 Hz, 4H), 2.55 (s, 3H), 2.86 (t, J = 7.2 Hz, 2H), 2.95 (t, J = 7.2 Hz, 2H), 3.51 (m, 2H), 4.79 (s, 2H), 7.09-7.91 (m, 10H), 8.43 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 6.9, 10.5, 14.2, 16.8, 21.1, 25.8, 29.1, 38.6, 46.8, 47.2, 53.4, 108.7, 109.7, 123.6, 124.6, 127.9, 128.9, 129.0, 129.1, 130.2, 133.0, 133.4, 135.0, 135.7, 138.3, 138.7, 141.8, 143.1, 154.7, 156.5, 162.1, 170.0; MS (ESI), m/z: 655.3 (M+H); Anal. Calcd. For ($C_{36}H_{42}N_6O_4S$)(%): C, 66.03; H, 6.46; N, 12.83; Found(%): C, 66.06; H, 6.45; N, 12.84.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-N,2-dipropyl-1H-benzo[d]imidazole-6-carboxamide(5)

Yellow solid, 70.2 mg, 57.5 %, m.p. 113-115 ℃.^{1}H NMR (400MHz, DMSO) δ: 0.91

(t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H), 1.58 (m, 2H), 1.75 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.55 (s, 3H), 2.77 (t, J = 7.2 Hz, 2H), 3.20 (t, J = 7.2 Hz, 2H), 4.79 (s, 2H), 7.07-7.89 (m, 10H), 8.45 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 6.5, 10.1, 11.3, 13.8, 16.4, 20.7, 23.2, 28.7, 43.4, 46.4, 108.3, 109.3, 123.3, 124.2, 127.5, 128.5, 128.6, 128.7, 129.8, 132.6, 132.9, 134.6, 135.3, 138.0, 138.3, 141.4, 142.7, 154.3, 156.1, 161.7, 169.6; MS (ESI), m/z: 600.3 (M+H); Anal. Calcd. For ($C_{33}H_{37}N_5O_4S$)(%): C, 66.09; H, 6.22; N, 11.68; Found(%): C, 66.12; H, 6.21; N, 11.67.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-isopropyl-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(6)

Yellow solid, 66.8 mg, 54.8 %, m.p. 111-113 ℃.^{1}H NMR (400MHz, DMSO) δ: 0.94

(t, J = 7.2 Hz, 3H), 1.25 (d, J = 7.2 Hz, 6H), 1.76 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.55 (s, 3H), 2.79 (t, J = 7.2 Hz, 2H), 3.95 (m, 1H), 4.82 (s, 2H), 7.08-7.89 (m, 10H), 8.44 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 6.9, 10.6, 14.3, 16.9, 21.1, 23.8, 29.1, 41.6, 46.9, 108.8, 109.9, 123.7, 124.7, 128.1, 129.0, 129.1, 129.2, 130.2, 133.1, 133.4, 135.1, 135.8, 138.4, 138.8, 141.8, 143.2, 154.8, 156.6, 162.2, 170.1; MS (ESI), m/z: 600.3 (M+H); Anal. Calcd. For ($C_{33}H_{37}N_5O_4S$)(%): C, 66.09; H, 6.22; N, 11.68; Found(%): C, 66.06; H, 6.21; N, 11.68.

N-butyl-1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (7)

Yellow solid, 72.2 mg, 59.2 %, m.p. 116-118 ℃.^{1}H NMR (400MHz, DMSO) δ: 0.91

(t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H), 1.32 (m, 2H), 1.59 (m, 2H), 1.75 (m, 2H), 1.87 (s, 3H), 2.14 (s, 3H), 2.56 (s, 3H), 2.81 (t, J = 7.2 Hz, 2H), 3.53 (m, 2H), 4.79 (s, 2H), 7.11-7.92 (m, 10H), 8.45 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 6.0, 9.6, 13.3, 13.9, 15.9, 19.6, 20.2, 28.2, 32.2, 40.6, 45.9, 107.9, 108.8, 122.7, 123.8, 127.1, 128.0 128.1, 128.2, 129.3, 132.1, 132.4, 134.1, 134.8, 137.4, 137.9, 140.9, 142.2, 153.8, 155.6, 161.2, 169.1; MS (ESI), m/z: 614.3 (M+H); Anal. Calcd. For ($C_{34}H_{39}N_5O_4S$)(%): C, 66.53; H, 6.40; N, 11.41; Found(%): C, 66.56; H, 6.40 ; N, 11.40.

N-(tert-butyl)-1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (8)

Yellow solid, 70.6 mg, 57.9 %, m.p. 114-116 ℃.^{1}H NMR (400MHz, DMSO) δ: 0.95

(t, J = 7.2 Hz, 3H), 1.39 (s, 9H), 1.85 (m, 2H), 1.88 (s, 3H), 2.16 (s, 3H), 2.58 (s, 3H), 2.97 (t, J = 7.2 Hz, 2H), 4.77 (s, 2H), 7.09-7.94 (m, 10H), 8.43 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 7.0, 10.6, 14.3, 16.9, 21.2, 29.2, 30.8, 46.9, 47.8, 108.8, 109.8, 123.7, 124.7, 128.0, 129.0, 129.1, 129.2, 130.2, 133.1, 133.4, 135.2, 135.8, 138.4, 138.2, 141.9, 143.2, 154.8, 156.6, 162.2, 170.1; MS (ESI), m/z: 614.3 (M+H); Anal. Calcd. For ($C_{34}H_{39}N_5O_4S$)(%): C, 66.53; H, 6.40; N, 11.41; Found(%): C, 66.50; H, 6.39; N, 11.42.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-N-phenyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (9)

Yellow solid, 67.8 mg, 55.6 %, m.p. 109-111 ℃.^{1}H NMR (400MHz, DMSO) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.74 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.57 (s, 3H), 2.83 (t, J = 7.2 Hz, 2H), 4.46 (s, 2H), 6.82-7.95 (m, 15H), 8.85 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 6.1, 9.7, 13.4, 16.0, 20.2, 28.3, 46.0, 107.9, 108.9, 121.6, 122.8, 123.8, 124.5, 127.1, 128.1, 128.2, 128.3, 129.0, 129.3, 132.2, 132.5, 134.2, 134.9, 135.6, 137.5, 137.9, 141.0, 142.3, 153.9, 155.7, 161.3, 169.2; MS (ESI), m/z: 634.2 (M+H); Anal. Calcd. For ($C_{36}H_{35}N_5O_4S$)(%): C, 68.23; H, 5.57; N, 11.05; Found(%): C, 68.18; H, 5.57; N, 11.05.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(2-methoxyphenyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (10)

Yellow solid, 69.3 mg, 56.8 %, m.p. 107-108 ℃.^{1}H NMR (400MHz, DMSO) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.77 (m, 2H), 1.89 (s, 3H), 2.14 (s, 3H), 2.55 (s, 3H), 2.84 (t, J = 7.2 Hz, 2H), 3.81 (s, 3H), 4.54 (s, 2H), 7.09-7.92 (m, 14H), 8.44 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 7.1, 10.7, 14.4, 17.0, 21.2, 29.3, 47.1, 56.0, 108.9, 109.9, 114.5, 121.3, 122.5, 123.8, 124.8, 125.8, 128.1, 129.1, 129.2, 129.3, 130.3, 133.2, 133.5, 135.2, 135.9, 138.5, 138.9, 142.0, 143.3, 152.6, 154.9, 156.7, 162.3, 170.2; MS (ESI), m/z: 664.3 (M+H); Anal. Calcd. For ($C_{37}H_{37}N_5O_5S$)(%): C, 66.95; H, 5.62; N, 10.55; Found(%): C, 66.97; H, 5.62; N, 10.54.

N-benzyl-1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(11)

Yellow solid , 66.2 mg, 54.3 %, m.p. 112-114 ℃. ^{1}H NMR (400MHz, DMSO) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.75 (m, 2H), 1.87 (s, 3H), 2.15 (s, 3H), 2.57 (s, 3H), 2.84 (t, J = 7.2 Hz, 2H), 4.41 (s, 2H), 4.79 (s, 2H), 6.89-7.91 (m, 15H), 8.83 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 6.3, 9.9, 13.6, 16.2, 20.5, 28.5, 44.4, 46.2, 108.1, 109.1, 123.0, 124.0, 126.9, 127.1, 127.3, 128.3, 128.4, 128.5, 128.7, 129.6, 132.4, 132.7, 134.4, 135.1, 137.8, 138.1, 141.2, 141.7, 142.5, 154.1, 155.9, 161.5, 169.4; MS (ESI), m/z: 648.3 (M+H); Anal. Calcd. For ($C_{37}H_{37}N_5O_4S$) (%): C, 68.60; H, 5.76; N, 10.81; Found (%): C, 68.63; H, 5.76; N, 10.82.

N-(2-methoxybenzyl)-1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (12)

Yellow solid , 65.5 mg, 53.7 %, m.p. 108-109 ℃. ^{1}H NMR (400MHz, DMSO) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.77 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.58 (s, 3H), 2.84 (t, J = 7.2 Hz, 2H), 3.81 (s, 3H), 4.54 (s, 2H), 4.79 (s, 2H), 6.88-7.86 (m, 14H), 8.71 (s, 1H);

^{13}C NMR (400MHz, $CDCl_3$) δ: 7.3, 11.0, 14.7, 17.2, 21.5, 29.5, 35.7, 47.3, 55.3, 109.2, 110.2, 114.4, 120.9, 124.1, 125.1, 127.4, 127.8, 128.0, 128.4, 129.4, 129.5, 130.0, 130.6, 133.5, 133.8, 135.5, 136.2, 138.8, 139.2, 142.2, 143.5, 155.1, 156.4, 157.0, 162.6, 170.5; MS (ESI), m/z: 678.3 (M+H); Anal. Calcd. For ($C_{38}H_{39}N_5O_5S$) (%): C, 67.34; H, 5.80; N, 10.33; Found (%): C, 67.39; H, 5.79; N, 10.35

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(3-methoxybenzyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (13)

Yellow solid , 69.4 mg, 56.9 %, m.p. 106-107 ℃. ^{1}H NMR (400MHz, DMSO) δ: 0.95 (t, J = 7.2 Hz, 3H), 1.76 (m, 2H), 1.88 (s, 3H), 2.14 (s, 3H), 2.56 (s, 3H), 2.83 (t, J = 7.2 Hz, 2H), 3.83 (s, 3H), 4.51 (s, 2H), 4.78 (s, 2H), 6.88-7.92 (m, 14H), 8.73 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 7.3, 10.9, 14.6, 17.2, 21.5, 29.5, 43.7, 47.2, 54.9, 109.1, 109.7, 110.1, 112.6, 119.5, 124.0, 125.0, 128.3, 129.3, 129.4, 129.5, 129.8, 130.6, 133.4, 133.7, 135.4, 136.1, 138.8, 139.1, 142.2, 142.8, 143.5, 155.1, 157.0, 160.4, 162.5, 170.4; MS (ESI), m/z: 678.3 (M+H); Anal. Calcd. For ($C_{38}H_{39}N_5O_5S$) (%): C, 67.34; H, 5.80; N, 10.33; Found (%): C, 67.29; H, 5.80; N, 11.31.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(4-methoxybenzyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (14)

Yellow solid , 65.4 mg, 53.6 %, m.p. 103-105 ℃. ^{1}H NMR (400MHz, DMSO) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.75 (m, 2H), 1.86 (s, 3H), 2.15 (s, 3H), 2.57 (s, 3H), 2.82 (t, J = 7.2 Hz, 2H), 3.70 (s, 3H), 4.41 (s, 2H), 4.77 (s, 2H), 6.89-7.90 (m, 14H), 8.44 (s, 1H); 13C NMR (400MHz, $CDCl_3$) δ: 6.0, 9.6, 13.3, 15.9, 20.1, 28.2, 44.4, 45.9, 55.9, 107.8, 108.8, 114.3, 122.7, 123.7, 127.0, 128.0, 128.1, 128.2, 129.2, 132.1, 132.4, 134.1, 134.8, 137.4, 137.8, 140.9, 142.2, 153.8, 155.6, 158.6, 161.2, 169.1; MS (ESI), m/z: 678.3 (M+H); Anal. Calcd. For ($C_{38}H_{39}N_5O_5S$) (%): C, 67.34; H, 5.80; N, 10.33; Found (%): C, 67.38; H, 5.80; N, 11.36.

N-(3,4-dimethoxybenzyl)-1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (15)

Yellow solid , 63.2 mg, 51.8 %, m.p. 101-103 ℃. ^{1}H NMR (400MHz, DMSO) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.75 (m, 2H), 1.86 (s, 3H), 2.15 (s, 3H), 2.57 (s, 3H), 2.83 (t, J = 7.2 Hz, 2H), 3.70 (s, 3H), 3.72 (s, 3H), 4.42 (s, 2H), 4.79 (s, 2H), 6.87-7.93 (m, 13H), 8.83 (s, 1H); ^{13}C NMR (400MHz,$CDCl_3$) δ: 7.1, 10.7, 14.4, 17.0, 21.3, 29.3, 44.0, 47.1, 55.8, 56.2, 109.0, 110.0, 112.6, 115.4, 120.6, 123.8, 124.9, 128.2, 129.2, 129.3, 129.4, 130.4, 133.2, 133.5, 134.7, 135.3, 136.0, 138.5, 139.0, 142.0, 143.3, 147.6, 149.6, 154.9, 156.7, 162.4, 170.2; MS (ESI), m/z: 708.3 (M+H); Anal. Calcd. For ($C_{39}H_{41}N_5O_6S$) (%): C, 66.18; H, 5.84; N, 9.89; Found (%): C, 66.13; H, 5.83; N, 9.90.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-

methyl-N-phenethyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (16)

Yellow solid, 72.3 mg, 59.3 %, m.p. 107-108 ℃. ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.94

(t, J = 7.2 Hz, 3H), 1.73 (m, 2H), 1.89 (s, 3H), 2.15 (s, 3H), 2.56 (s, 3H), 2.79 (t, J = 7.2 Hz, 2H), 2.83 (t, J = 7.1 Hz, 2H), 4.79 (s, 2H), 7.09-7.99 (m, 15H), 8.45 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 6.3, 10.0, 13.6, 16.2, 20.1, 28.5, 35.6, 41.6, 46.3, 108.2, 109.2, 123.1, 124.1, 126.2, 127.4, 127.9, 128.4, 128.5, 128.6, 128.8, 129.7, 132.4, 132.7, 134.5, 135.2, 137.8, 138.2, 139.4, 141.2, 142.5, 154.1, 156.0, 161.6, 169.4; MS (ESI), m/z: 662.3 (M+H); Anal. Calcd. For ($C_{38}H_{39}N_5O_4S$) (%): C, 68.96; H, 5.94; N, 10.58; Found (%): C, 68.92; H, 5.94; N, 10.58.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(3-methoxyphenethyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(17)

Yellow solid , 70.8 mg,58.0 %, m.p. 101-103 ℃. ^{1}H NMR (400MHz, DMSO) δ: 1.06

(t, J = 7.2 Hz, 3H), 1.77 (m, 2H), 1.84 (s, 3H), 2.14 (s, 3H), 2.56 (s, 3H), 2.81 (t, J = 7.2 Hz, 4H), 3.45 (m, 2H), 3.70 (s, 3H), 4.76 (s, 2H), 7.05-7.84 (m, 14H), 8.43 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 6.9, 10.5, 14.2, 16.8, 21.1, 29.1, 36.3, 41.1, 46.8, 53.6, 108.8, 109.7, 111.4, 112.0, 120.4, 123.6, 124.7, 128.0, 129.06, 129.0, 129.1, 129.8, 130.2, 133.0, 133.3, 135.0, 135.7, 138.3, 138.8, 140.5, 141.8, 143.1, 154.8, 156.5, 160.5, 162.1, 170.0; MS (ESI), m/z: 692.3 (M+H); Anal. Calcd. For ($C_{39}H_{41}N_5O_5S$) (%): C, 67.71; H, 5.97; N, 10.12; Found (%): C, 67.75; H, 5.97; N, 10.12.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(4-methoxyphenethyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(18)

Yellow solid, 67.3 mg, 55.2 %, m.p. 98-100 ℃. ^{1}H NMR (400MHz, DMSO) δ: 1.07

(t, J = 7.2 Hz, 3H), 1.77 (m, 2H), 1.88 (s, 3H), 2.15 (s, 3H), 2.56 (s, 3H), 2.83 (t, J = 7.2 Hz, 2H), 2.87 (t, J = 7.1 Hz, 2H), 3.47 (m, 2H), 3.69 (s, 3H), 4.77 (s, 2H), 7.10-7.90 (m, 14H), 8.45 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 6.4, 10.1, 13.7, 16.3, 20.6, 28.6, 35.2, 41.5, 46.3, 55.7, 108.2, 109.2, 114.9, 123.2, 124.1, 127.4, 128.4, 128.5, 128.6, 129.7, 131.4, 132.5, 132.8, 134.5, 135.2, 137.8, 138.2, 141.3, 142.6, 154.2, 156.0, 158.0, 161.6, 169.5; MS (ESI), m/z: 692.3 (M+H); Anal. Calcd. For ($C_{39}H_{41}N_5O_5S$) (%): C, 67.71; H, 5.97; N, 10.12; Found (%): C, 67.76; H, 5.97; N, 10.11.

N-(2,5-dimethoxyphenethyl)-1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(19)

Yellow solid, 68.7 mg, 56.3 %, m.p. 95-96 ℃. ^{1}H NMR (400MHz, DMSO) δ: 0.96 (t,

J = 7.3 Hz, 3H), 1.75 (m, 2H), 1.87 (s, 3H), 2.15 (s, 3H), 2.55 (s, 3H), 2.80 (t, J = 7.2 Hz, 2H), 2.85 (t, J = 7.2 Hz, 2H), 3.48 (m, 2H), 3.71 (s, 3H), 3.77 (s, 3H), 4.78 (s, 2H), 7.07-7.87 (m, 13H), 8.43 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 5. 9, 9.5, 13.2, 15.8,

20.1, 26.5, 28.1, 42.5, 45.8, 55.6, 107.8, 108.7, 112.5, 121.4, 122.1, 122.6, 123.7, 127.0, 128.0, 128.0, 128.1, 129.2, 132.0, 132.3, 134.0, 134.7, 137.3, 137.8, 140.8, 142.2, 149.1, 149.8, 153.7, 155.5, 161.1, 169.0; MS (ESI), m/z: 722.3 (M+H); Anal. Calcd. For ($C_{40}H_{43}N_5O_6S$) (%): C, 66.55; H, 6.00; N, 9.70; Found (%): C, 66.54; H, 6.00; N, 9.70.

N-(3,4-dimethoxyphenethyl)-1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(20)

Yellow solid, 66.0 mg, 54.1 %, m.p. 96-97 ℃. ^{1}H NMR (400MHz, DMSO) δ: 0.94 (t, J = 7.2 Hz, 3H), 1.77 (m, 2H), 1.86 (s, 3H), 2.16 (s, 3H), 2.56 (s, 3H), 2.77 (t, J = 7.2 Hz, 2H), 2.83 (t, J = 7.2 Hz, 2H), 3.45 (m, 2H), 3.68 (s, 6H), 4.79 (s, 2H), 6.73-7.87 (m, 13H), 8.44 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 6.2, 9.8, 13.5, 16.1, 20.4, 28.4, 36.3, 41.6, 46.1, 55.7, 56.4, 108.0, 109.0, 112.2, 112.8, 115.34, 122.9, 123.9, 127.2, 128.2, 128.4, 128.5, 129.4, 132.3, 132.6, 133.0, 134.3, 135.1, 137.6, 138.0, 141.1, 142.4, 147.6, 149.5, 154.0, 155.8, 161.4, 169.3; MS (ESI), m/z: 722.3 (M+H); Anal. Calcd. For ($C_{40}H_{43}N_5O_6S$) (%): C, 66.55; H, 6.00; N, 9.70; Found (%): C, 66.59; H, 6.00; N, 9.70.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(2-fluorophenethyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide(21)

Yellow solid , 69.3 mg, 56.8 %, m.p. 104-106 ℃. ^{1}H NMR (400MHz, DMSO) δ: 0.95 (t, J = 7.2 Hz, 3H), 1.74 (m, 2H), 1.84 (s, 3H), 2.15 (s, 3H), 2.55 (s, 3H), 2.84 (t, J = 7.2 Hz, 2H), 2.87 (t, J = 7.1 Hz, 2H), 3.53 (m, 2H), 4.78 (s, 2H), 7.03-7.85 (m, 14H), 8.46 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 6.9, 10.5, 14.2, 16.8, 21.2, 24.6, 29.1, 41.1, 46.9, 108.8, 109.8, 115.7, 123.6, 124.1, 124.7, 128.0, 129.0, 129.1, 129.2, 130.2, 133.0, 133.3, 135.1, 135.8, 138.3, 138.8, 141.8, 143.1, 154.7, 156.5, 160.4, 162.2, 170.0; MS (ESI), m/z: 680.3 (M+H); Anal. Calcd. For ($C_{38}H_{38}FN_5O_4S$) (%): C, 67.14; H, 5.63; N, 10.30; Found (%): C, 67.11; H, 5.63; N, 10.31.

1-((2'-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(4-fluorophenethyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (22)

Yellow solid, 70.6 mg, 57.9 %, m.p. 106-108 ℃. ^{1}H NMR (400MHz, DMSO) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.77 (m, 2H), 1.87 (s, 3H), 2.16 (s, 3H), 2.56 (s, 3H), 2.86 (t, J = 7.2 Hz, 4H), 3.46 (m, 2H), 4.79 (s, 2H), 7.06-7.86 (m, 14H), 8.42 (s, 1H); ^{13}C NMR (400MHz, $CDCl_3$) δ: 7.3, 11.0, 14.7, 17.3, 21.5, 29.5, 35.4, 41.3, 47.3, 109.3, 110.2, 115.8, 124.1, 125.1, 128.5, 129.4, 129.5, 129.6, 130.6, 133.5, 133.8, 135.0, 135.5, 136.2, 138.8, 139.3, 142.2, 143.6, 155.2, 157.0, 160.1, 162.6, 170.5; MS (ESI), m/z: 680.3 (M+H); Anal. Calcd. For ($C_{38}H_{38}FN_5O_4S$)(%):C, 67.14; H, 5.63; N, 10.30; Found(%): C, 67.11; H, 5.63; N, 10.30.

2. Molecular Modelling Experiments

2.1. Generation of DARAs pharmacophore mode

The DARAs pharmacophore model for AT_1 and ET_A receptor antagonists was gen -erated using the HipHop module of the CATALYST soft. six training set molecules (Figure 1) were built in a 3D window, and conformational models for each molecule were generated using the diverse conformation module. Then the resulting SD files were used for common features hypothesis generation using the HipHop module by default, and 10 pharmacophore model were selected according to their ranking scores in HipHop scores.

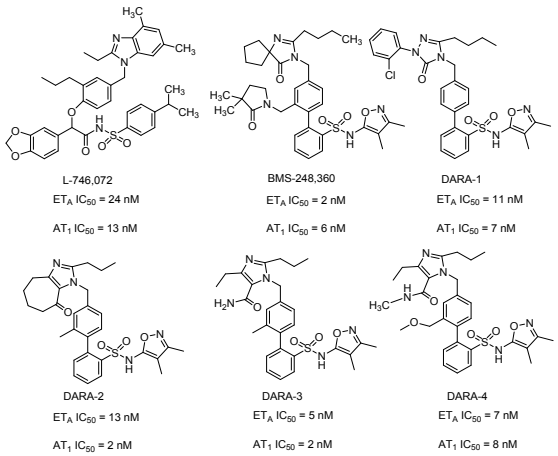

Figure 1. Structures and observed activities of DARAs for the HipHop training set

2.2. DARAs test set selection

Five DARAs (Figure 3) were selected as the traning set, Molecules were built in a 3D window, and conformational models for each molecule were generated using the diverse conformation module. Then the resulting SD files were built in a 3D window. The hypothesis Hypo-DARA-4 aligned to the test set SD files by using “ligand pharmacophore comparison” module.

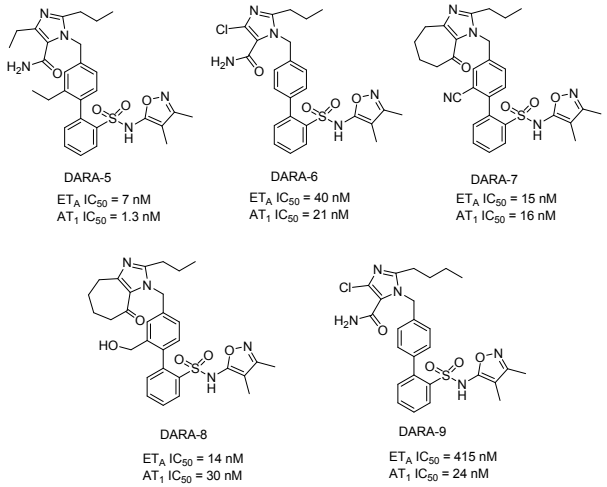

Figure 3. Structures and observed activities of DARAs for the test set

3. Pocedure for Receptor Binding Aassay

3.1. Angiotensin II. AT_1 receptor binding assay was carried out by competitive displacementof the binding of 0.2 nM ^{125}I-labeled Sar^1-Ile^8-angiotensin II with human

angiotensin AT_1 receptor according to Reference 1. Each 180 mL incubate contained the following: [125I] Sar1 Ile8-Ang II (25pM), AT_1 receptor (25 mg) and standard or test compounds. The binding was performed at 37 ℃ for 2h in 96-well filtration plates (Costar, USA) and was terminated by rapid vacuum filtration using a vacuum device; dried filters disks were punched out and counted in a gamma counter. IC_{50} value was calculated by Sars 2.0 software.

3.2. Endothelin. Binding to the human ET_A receptor was evaluated by incubating test compounds with CHO-K1 cells expressing the human ET_A receptor in the presence of 0.05 nM ^{125}I-labelled endothelin 1 according to Reference 1.

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4. Procedure for Oral Activity in the Spontaneously Hypertensive Rats (SHR)

All experiments involving the use of live animals in this study were performed in compliance with Beijing Administration Rule of Laboratory Animal and the Guide for Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH publication No. 85-23, revised 1996) and the Policy of Animal Care and Use Committee of Institute of Chinese Materia Medica China Academy of Chinese Medical Science.

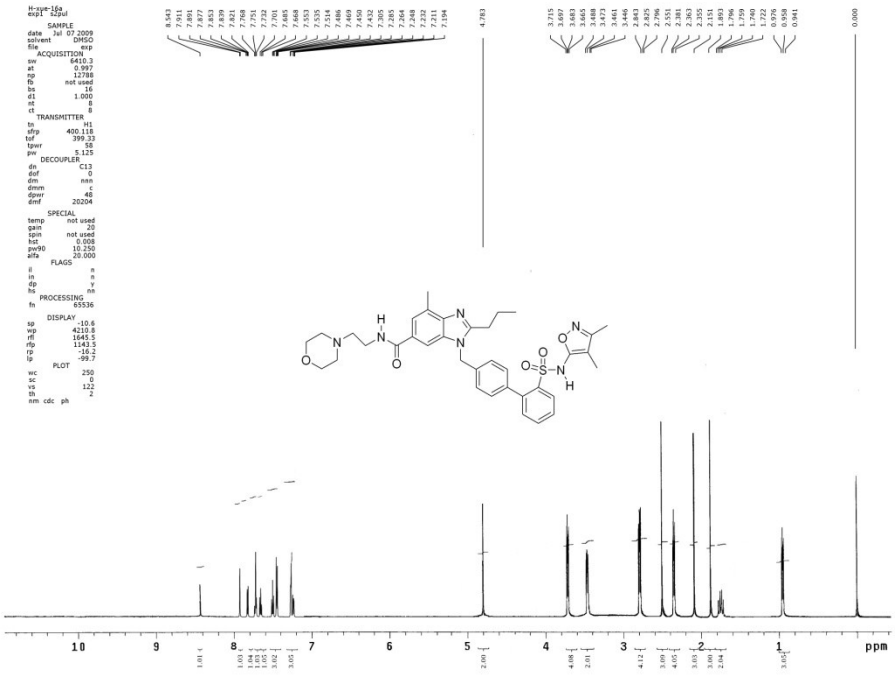
Male SHR, 12 to 13 weeks old. Six animals served as controls and received the vehicle treatment (20 mL/kg). Hypertensive animals were divided into two groups (*n* = 6). Group 1 was administered with Irbesartan, whereas group 2 was given the same dose of the tested compound 11. The vehicle and test compounds were orally administered. Blood pressure and heart rate were measured by tail plethysmography (BP-98A, Softron, Japan) after a warming period in unanesthetized rats. The BP measurements only required a few minutes per individual rat. All data were analyzed by SPSS (Statistical Product and Service Solutions)13.0 and expressed as mean±SEM.

5. references

1. N. Murugesan, J. E. Tellew, Z. Gu, B. L. Kunst, L. Fadnis, L. A. Cornelius, R. A. F. Baska, Y. Yang, S. M.; Beyer, H. Monshizadegan, K. E.; Dickinson, B.; Panchal, M. T. Valentine, S. Chong, R. A. Morrison, K. E. Carlson, J. R. Powell, S. Moreland, J. C. Barrish, M. C.; Kowala, J. E. Macor, *J. Med. Chem.* 2002, **45**, 3829.

2. S. Ficht, L. Roeglin, M.; Ziehe, D. Breyer, O. Seitz, *Synlett*, 2004, **14**, 2525.

6. ^{1}H NMR & MS Spectra Attached



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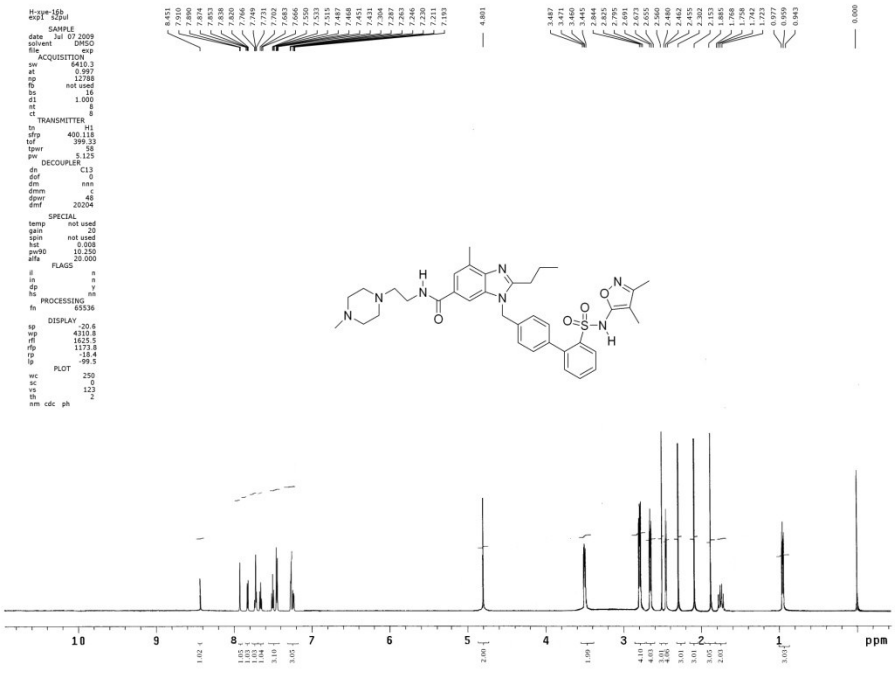

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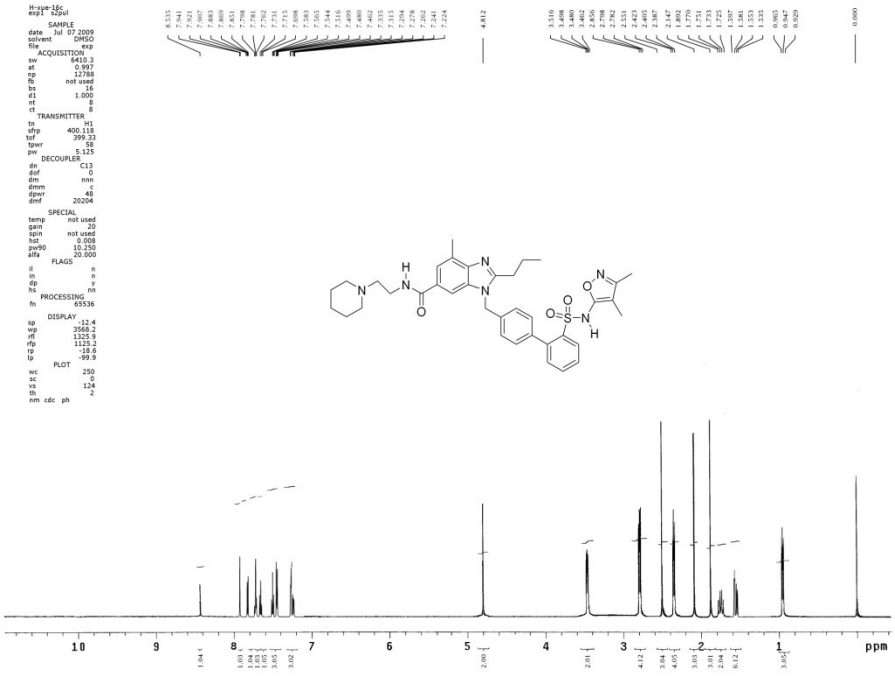

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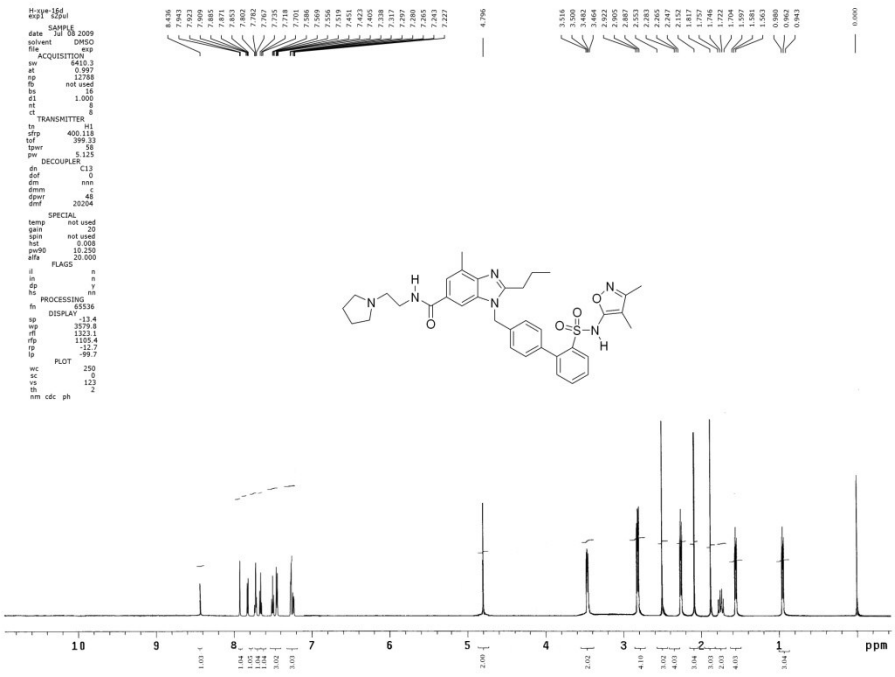

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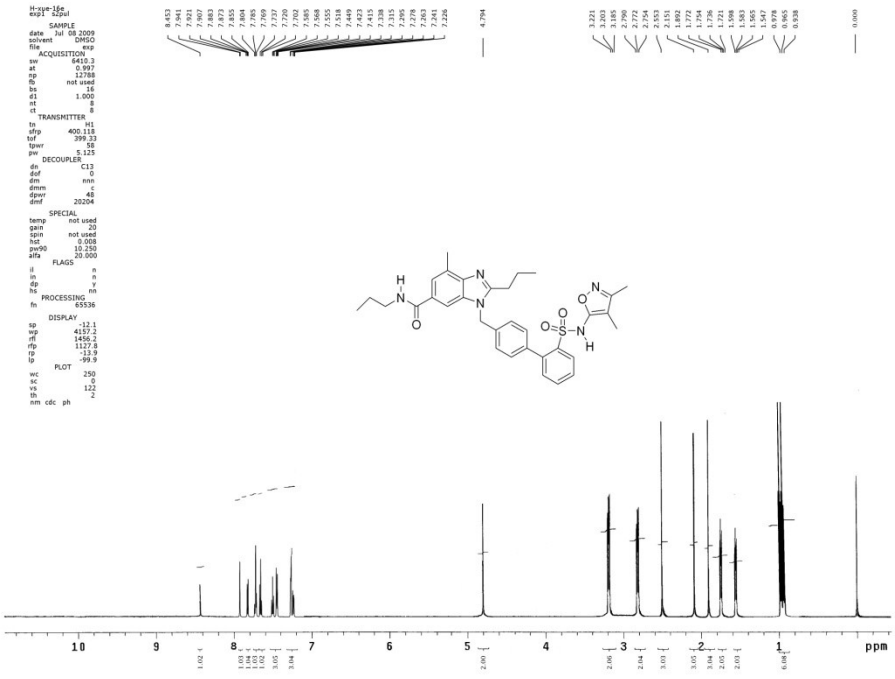

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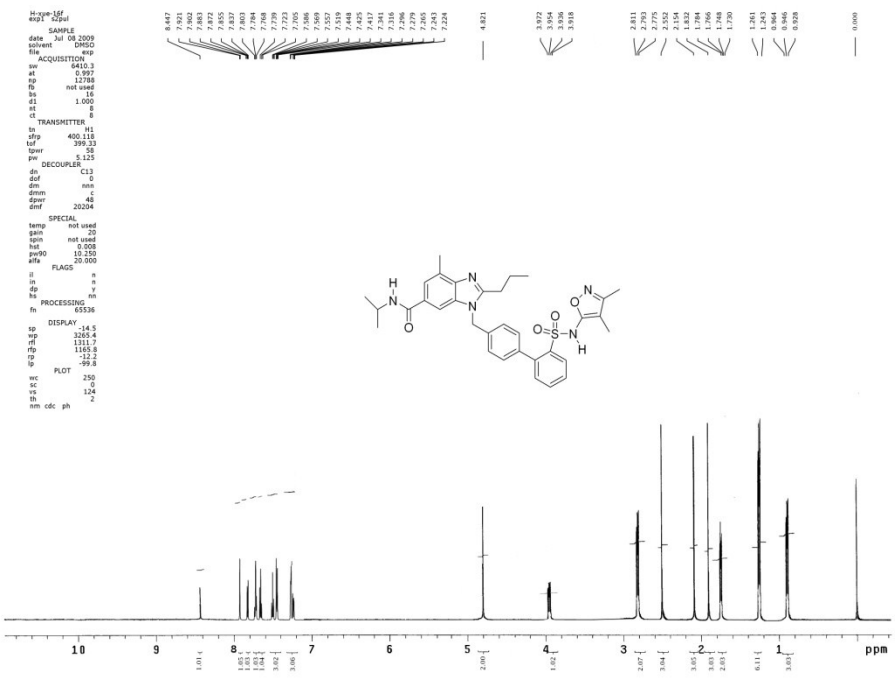

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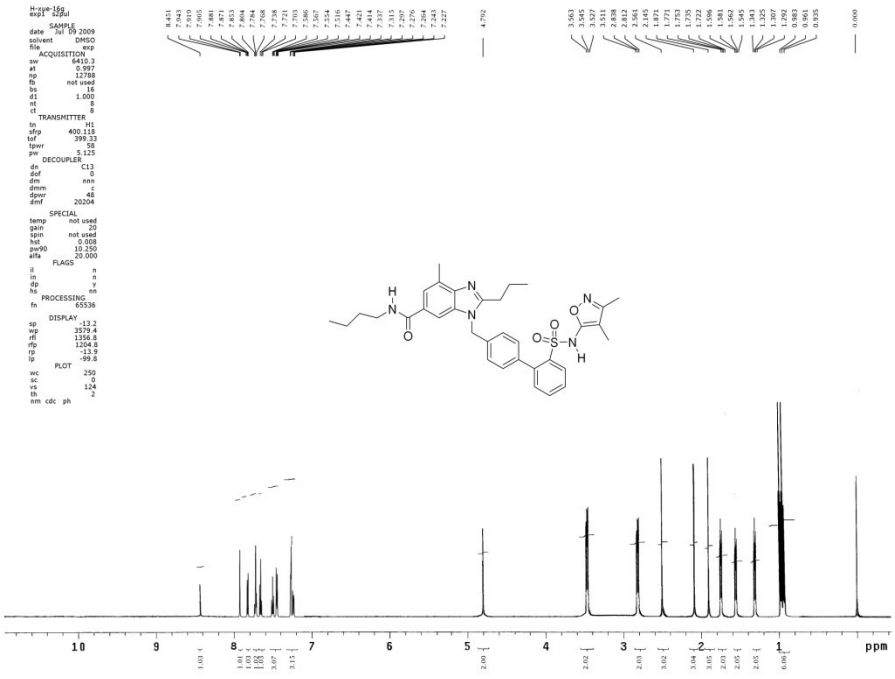

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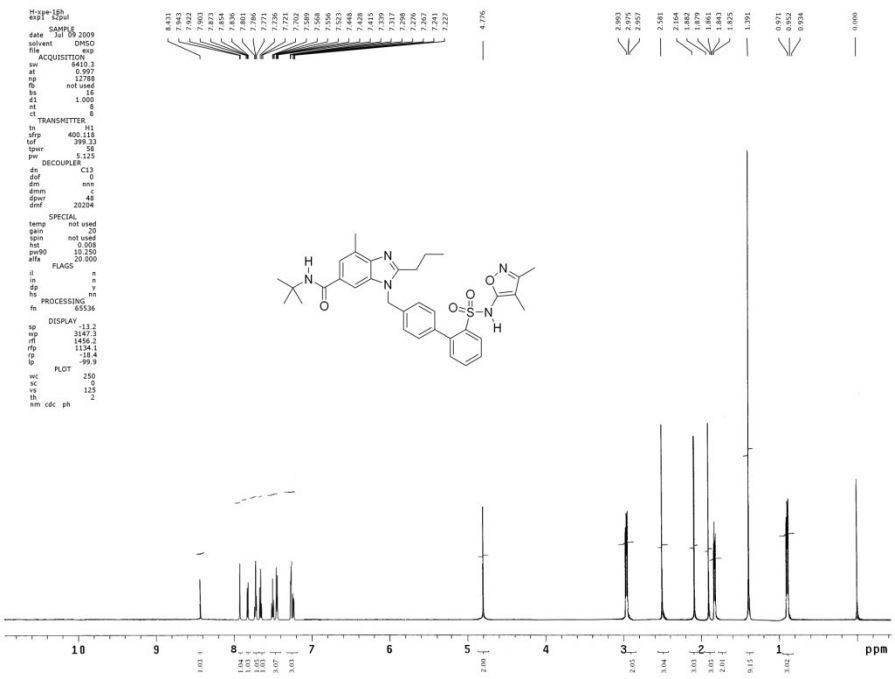

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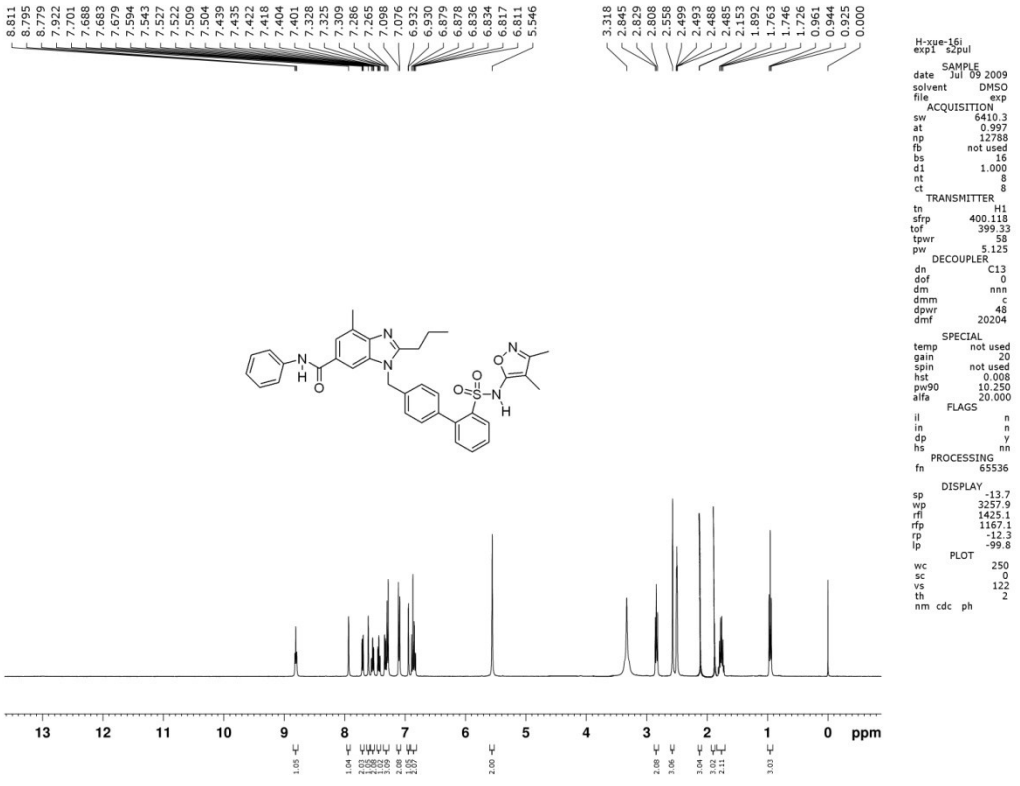

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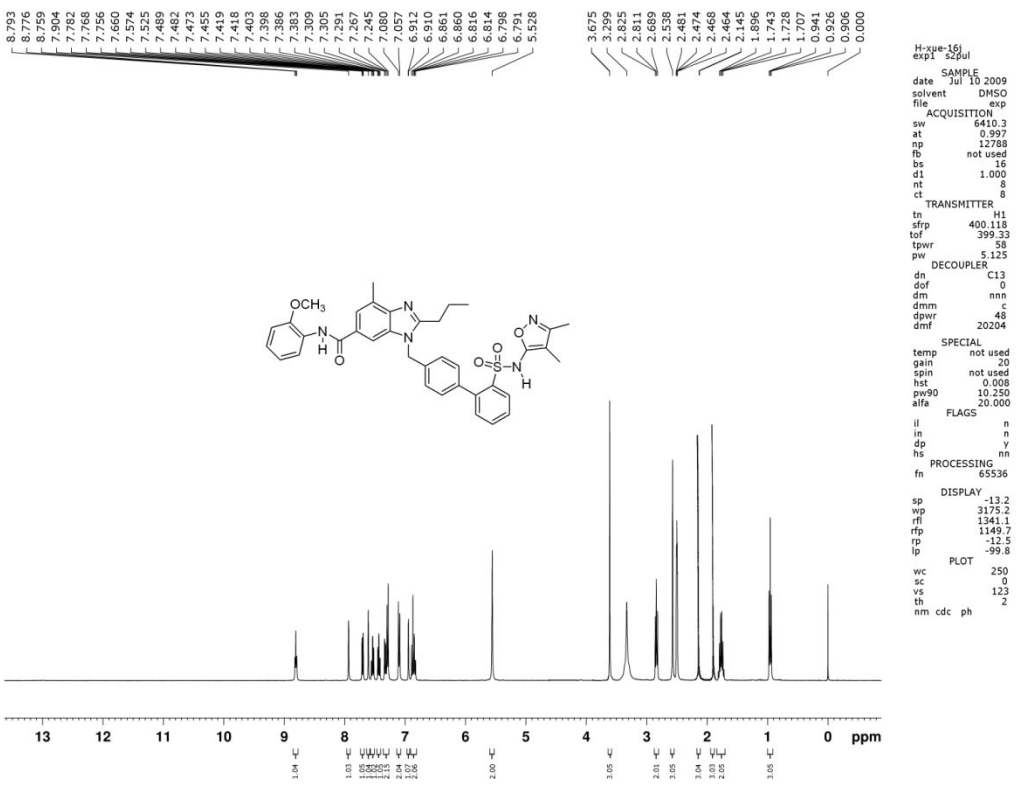

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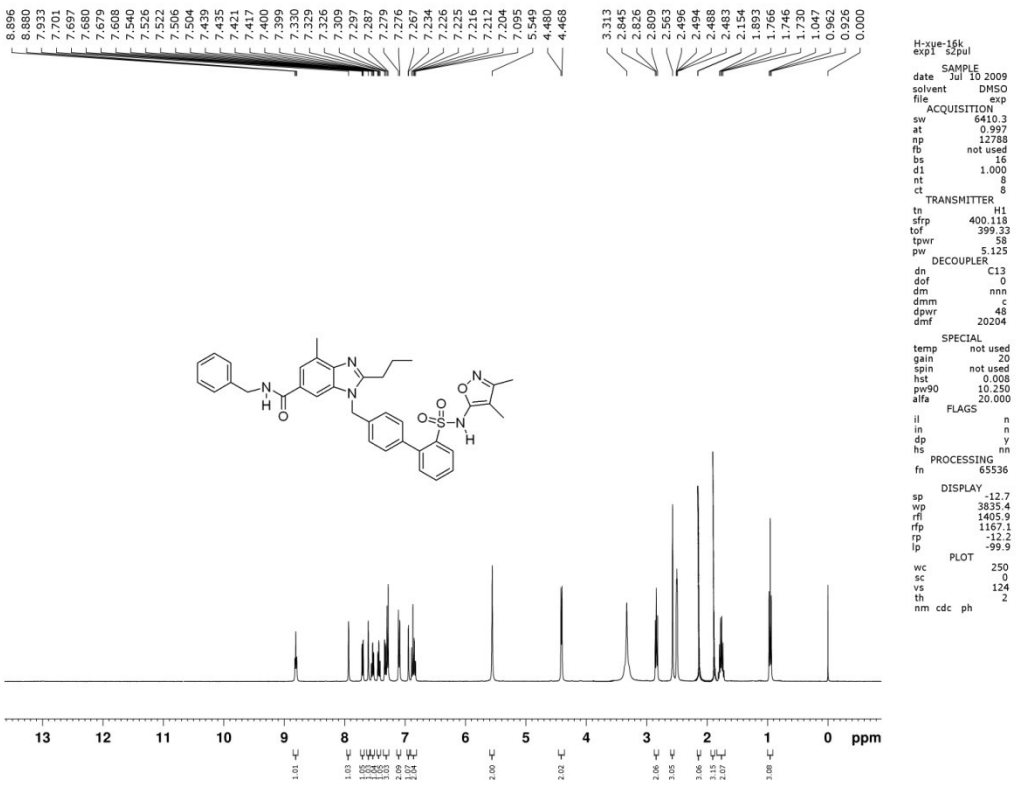

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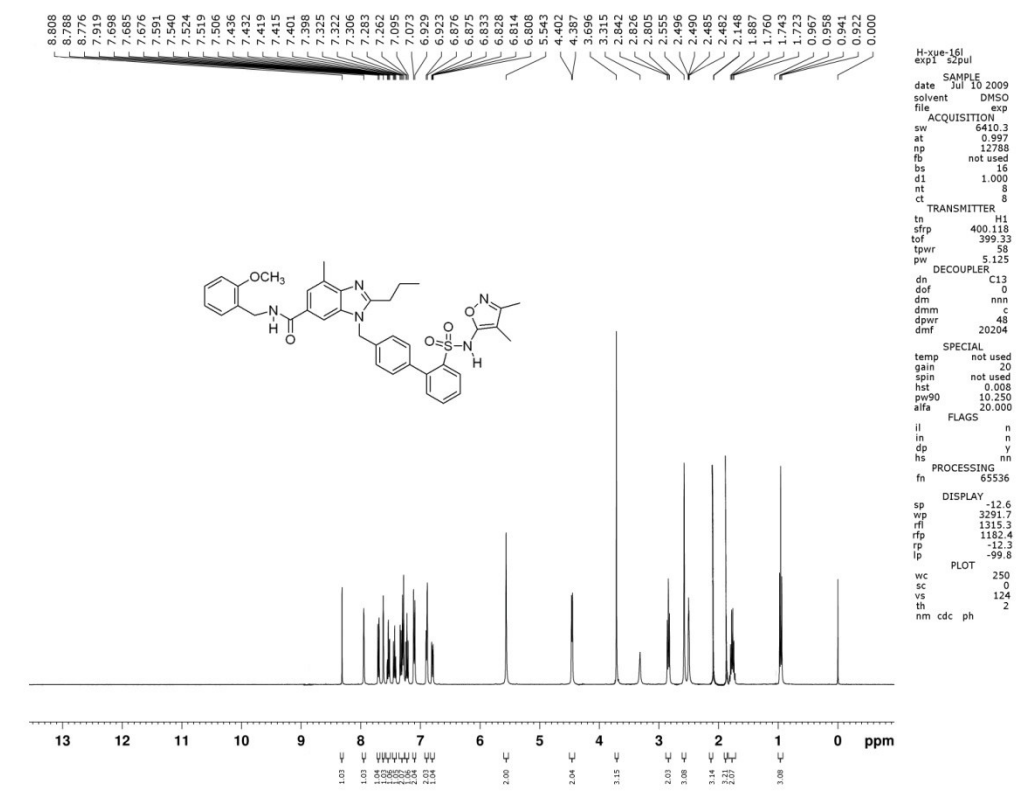

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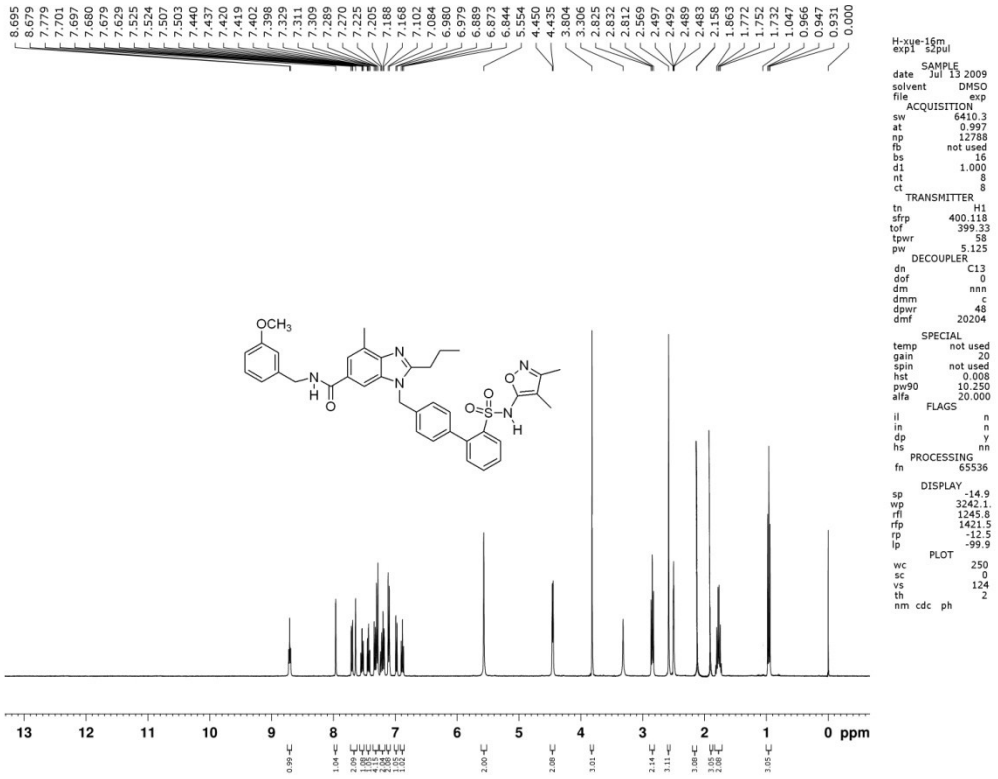

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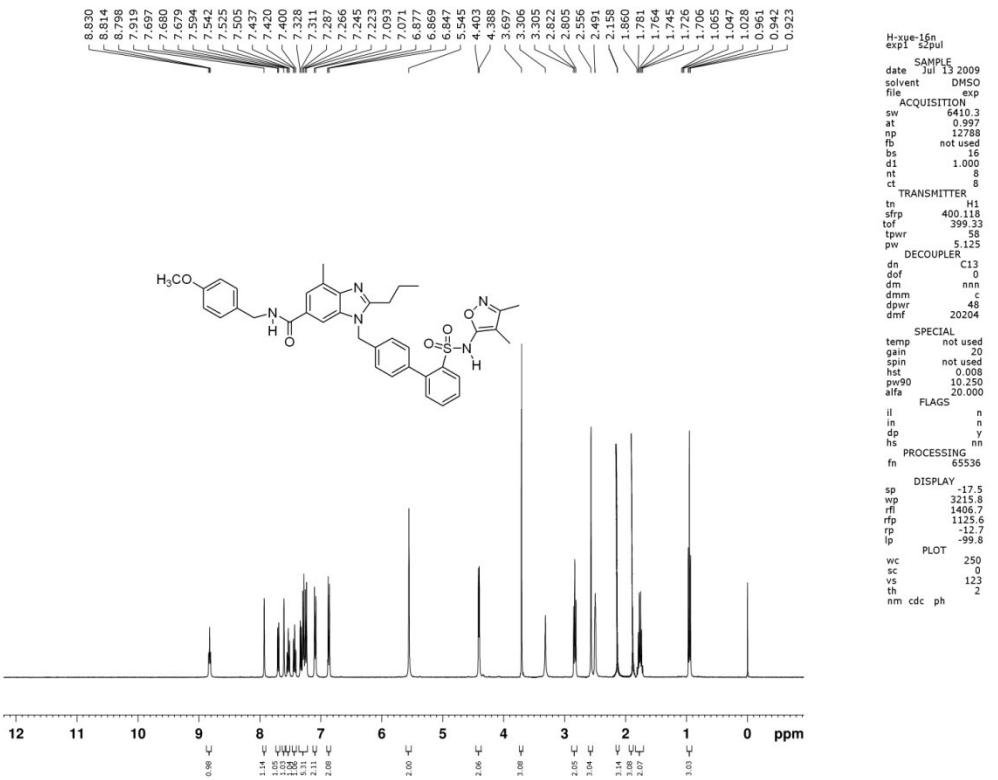

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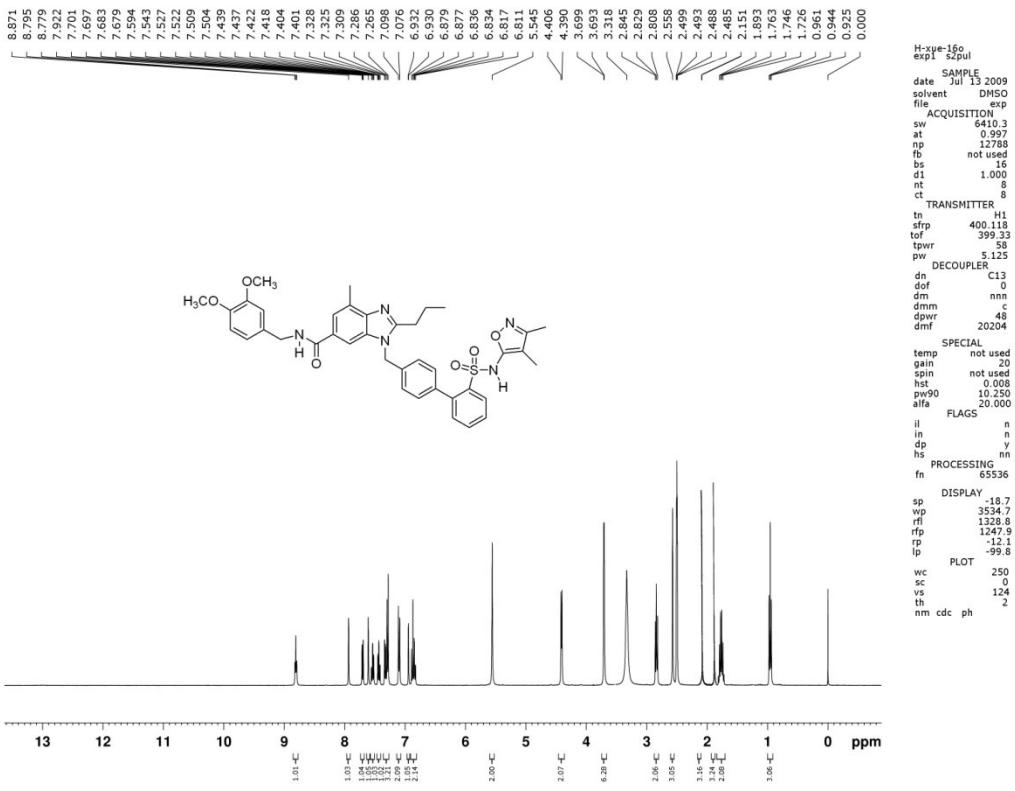

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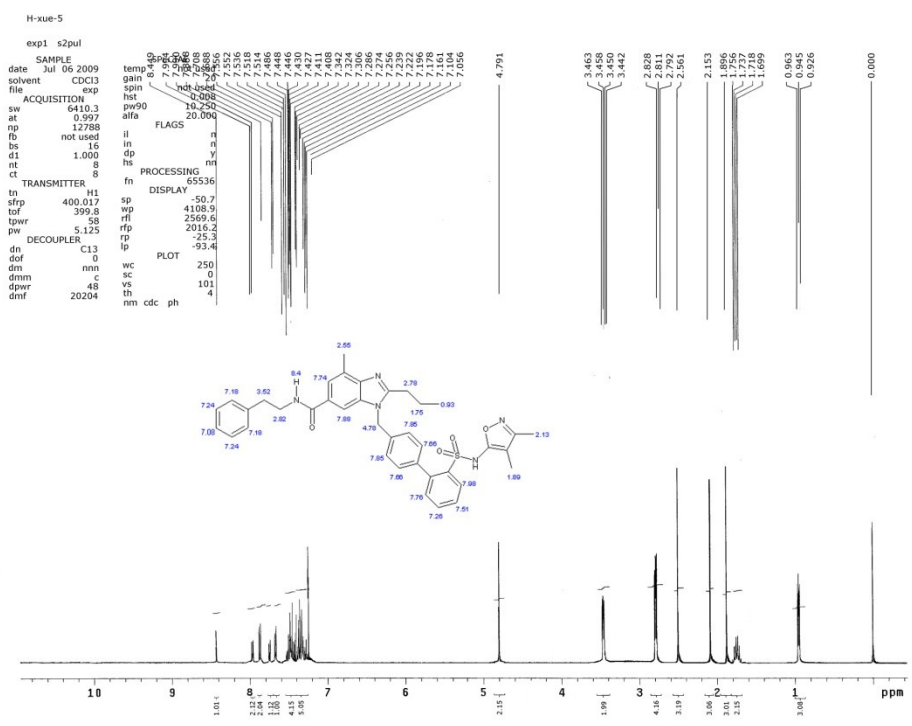

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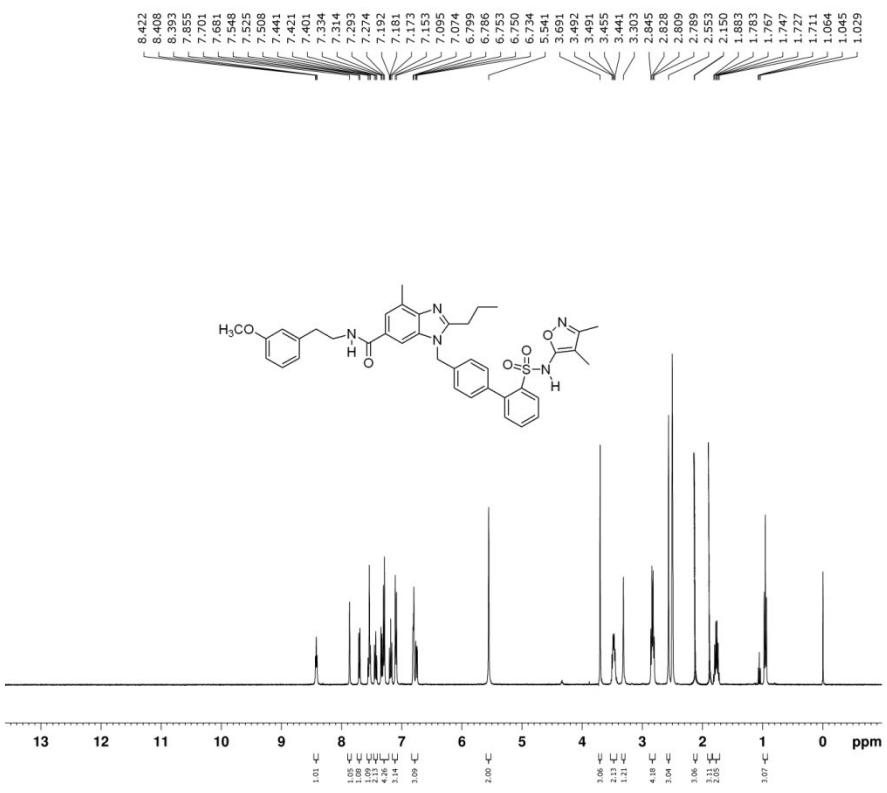


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ct                8
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in                n
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hs               nn
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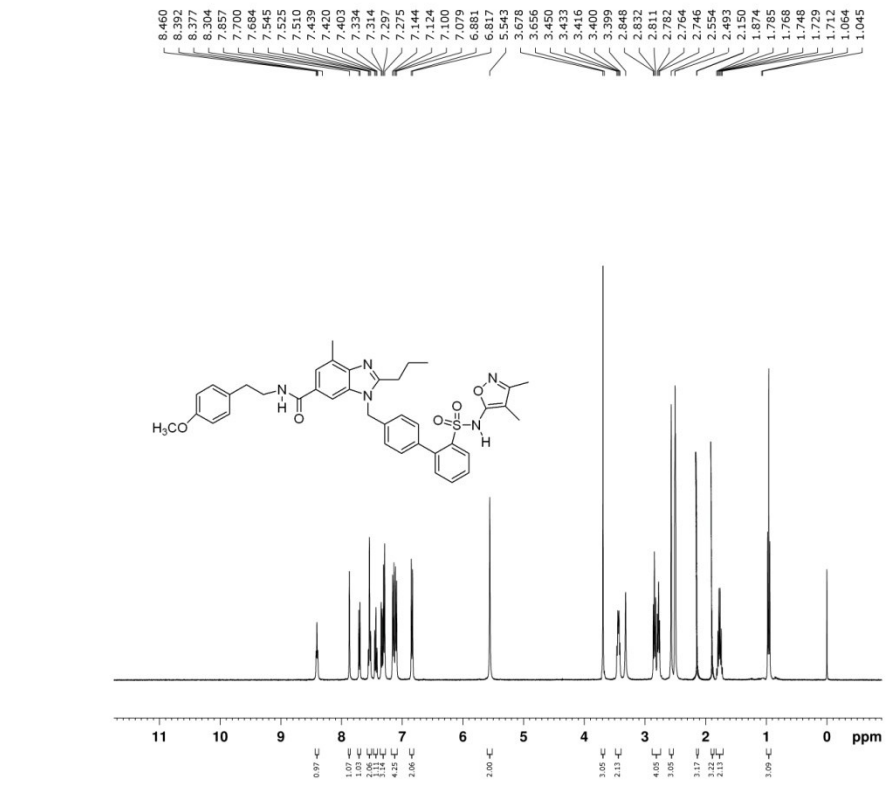


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np            12788
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bs               16
d1            1.000
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ct                8
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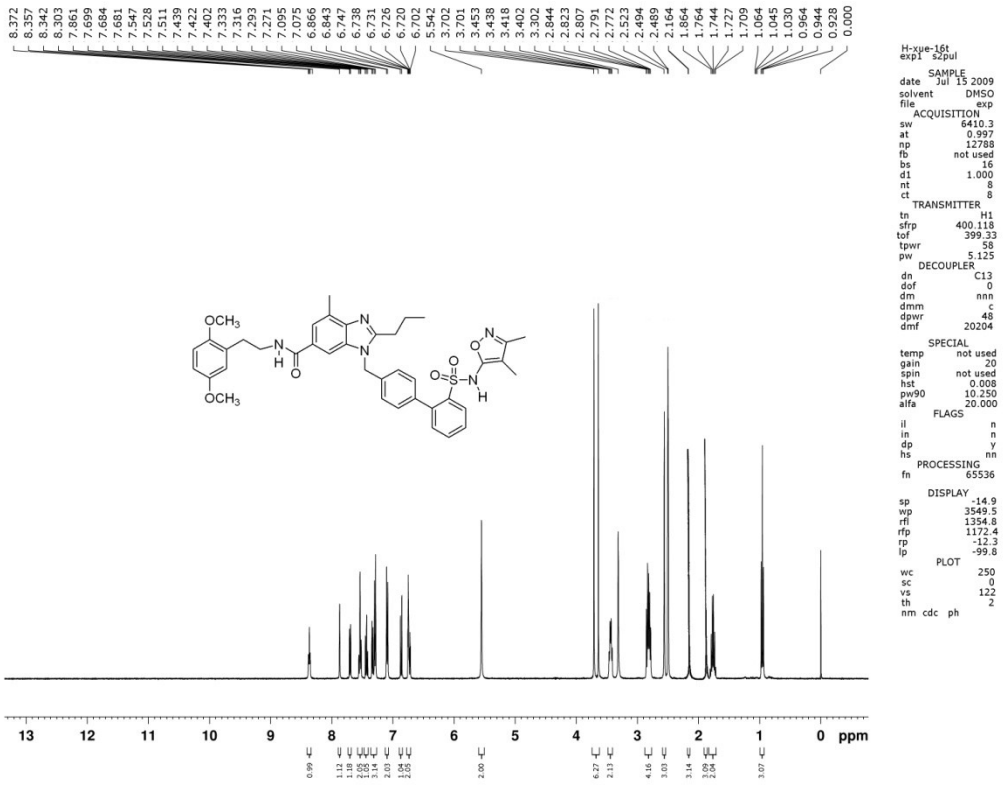

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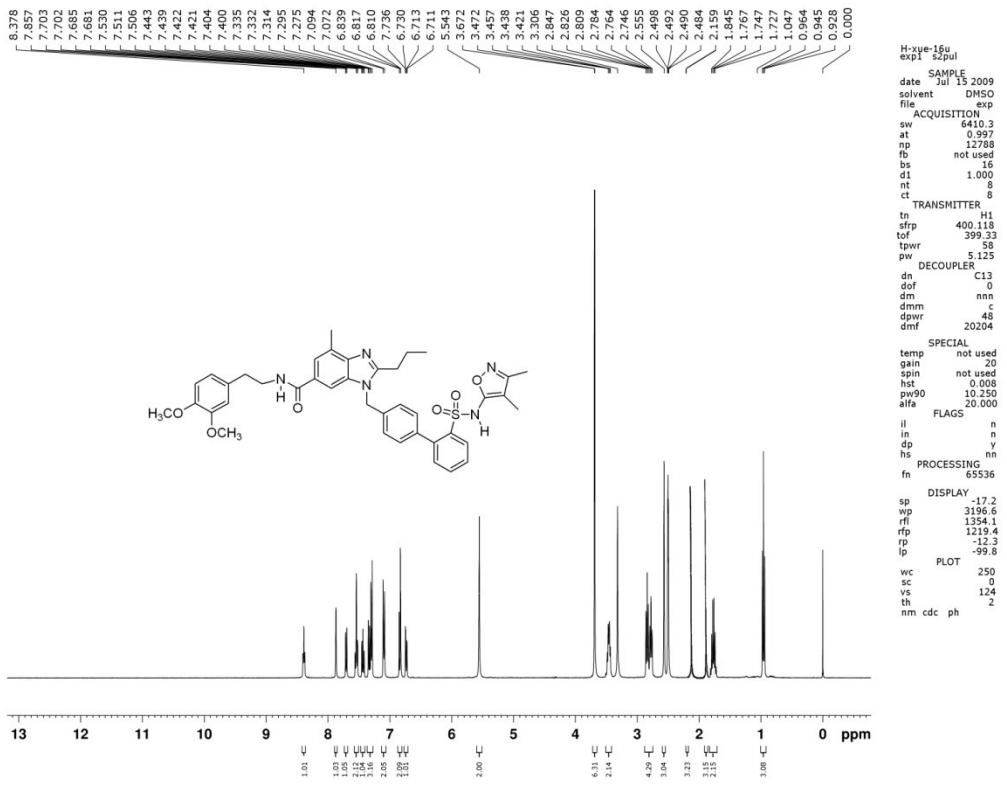

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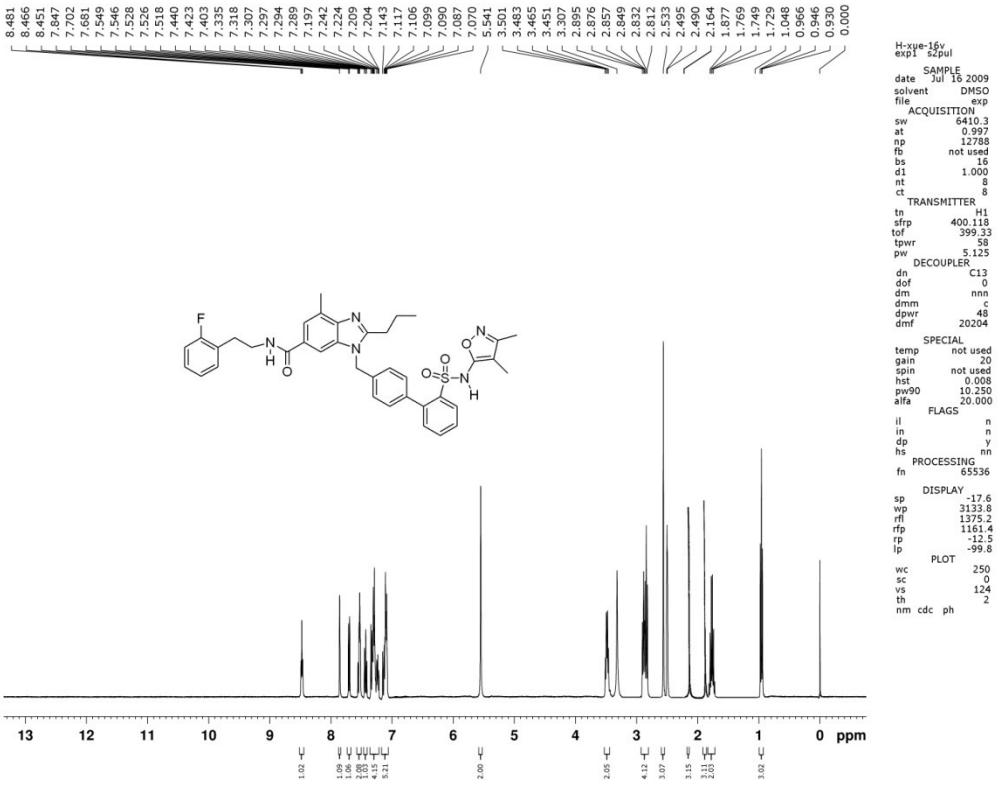

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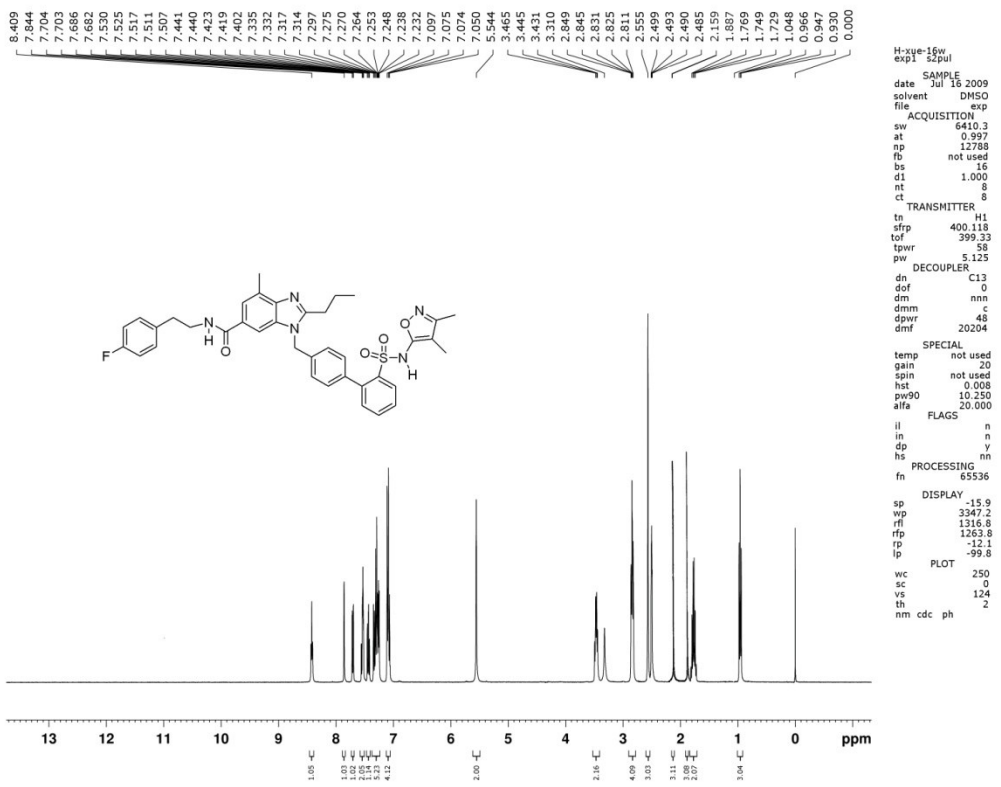

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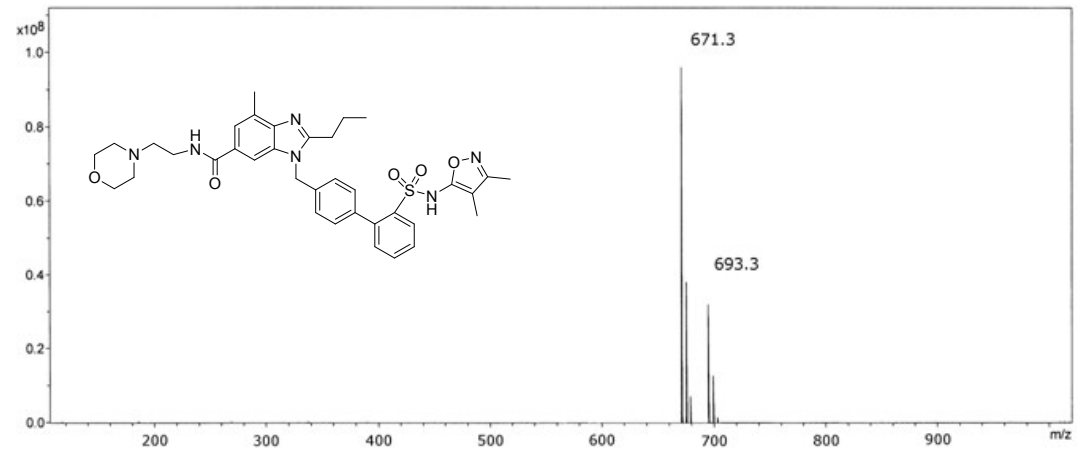

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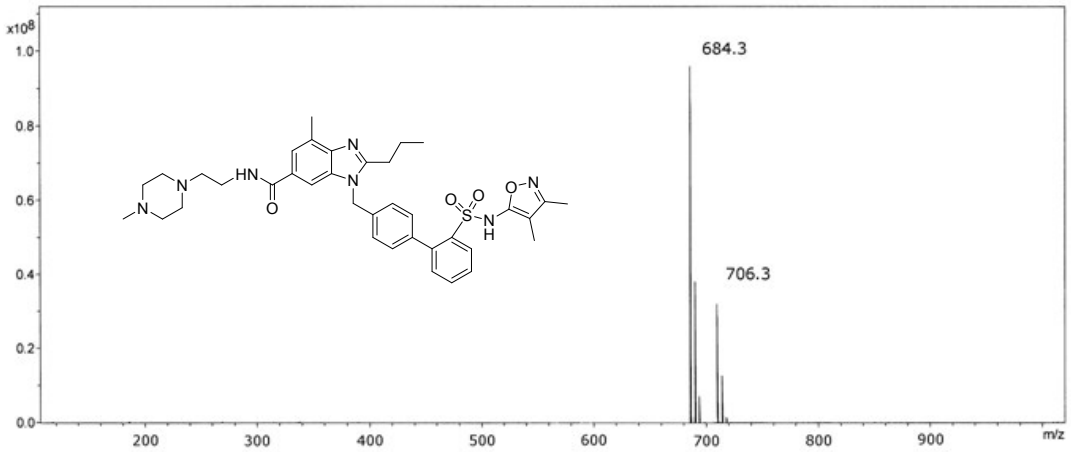

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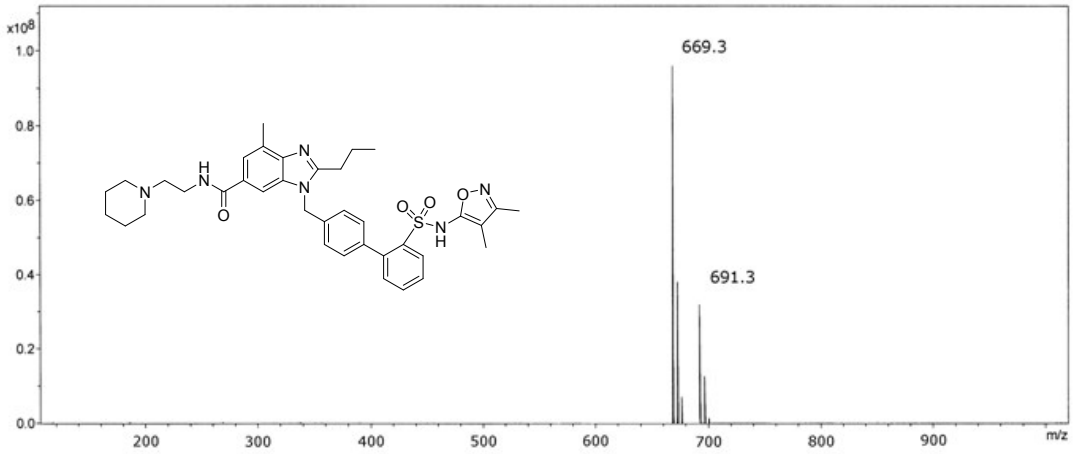

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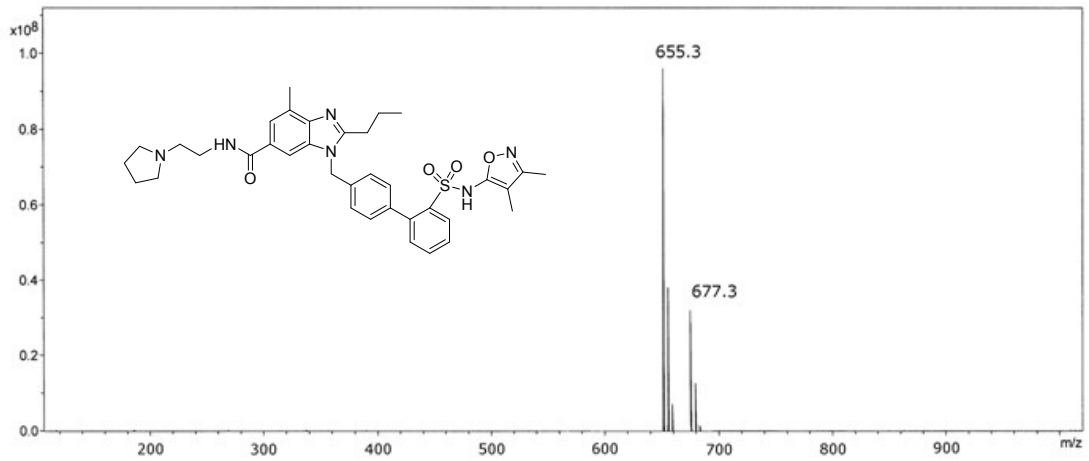

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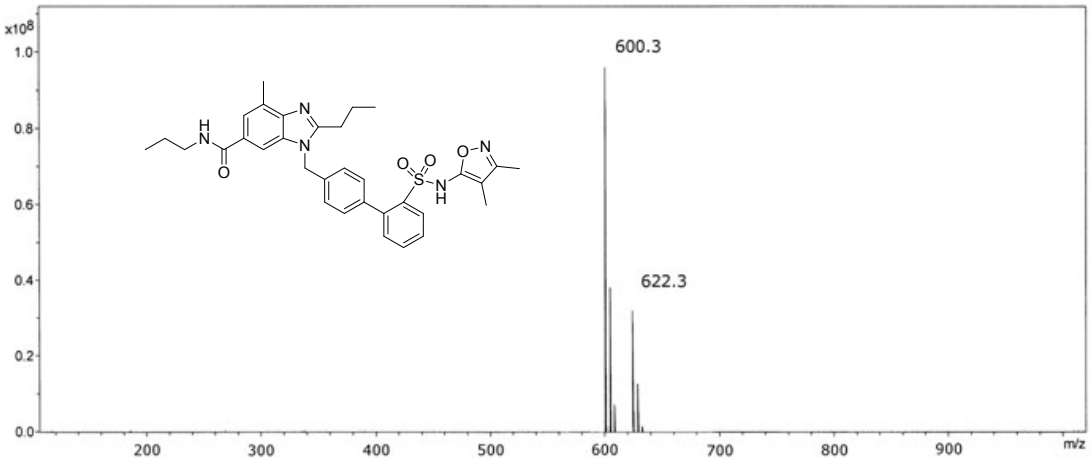

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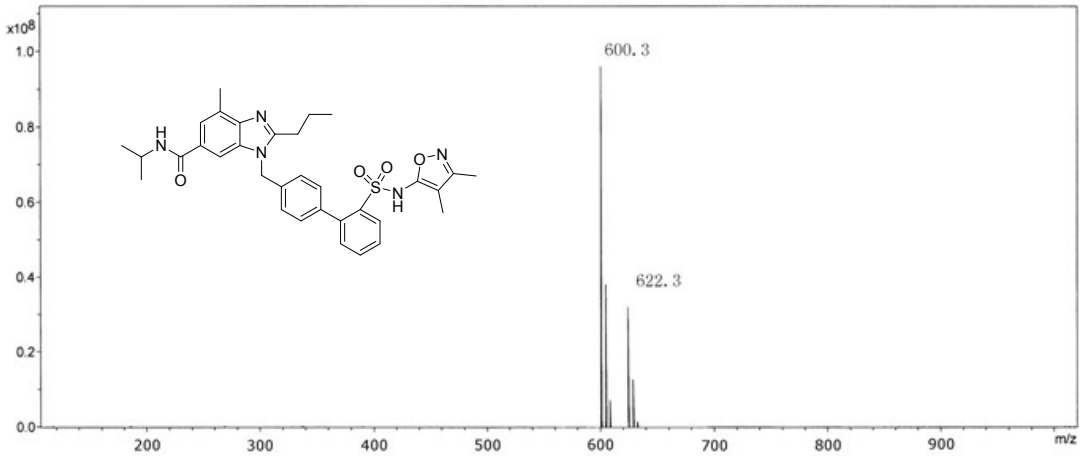

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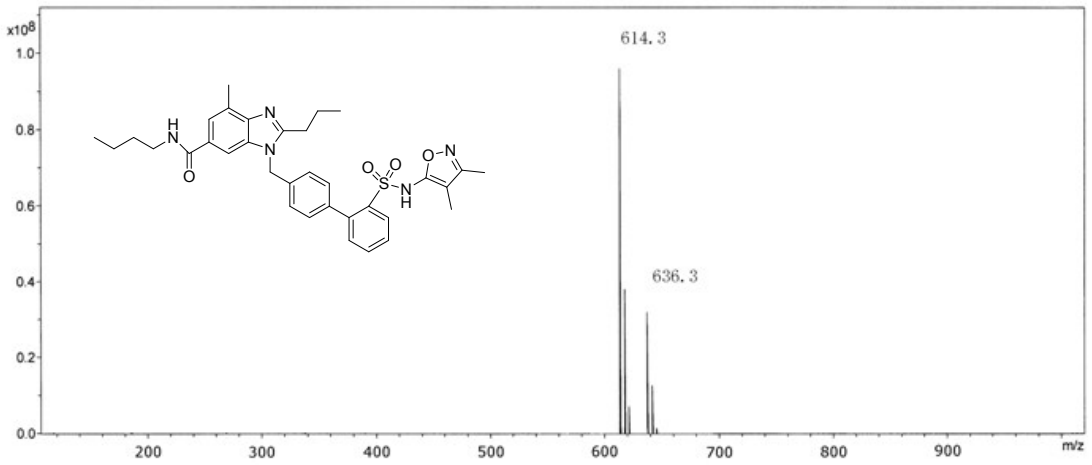
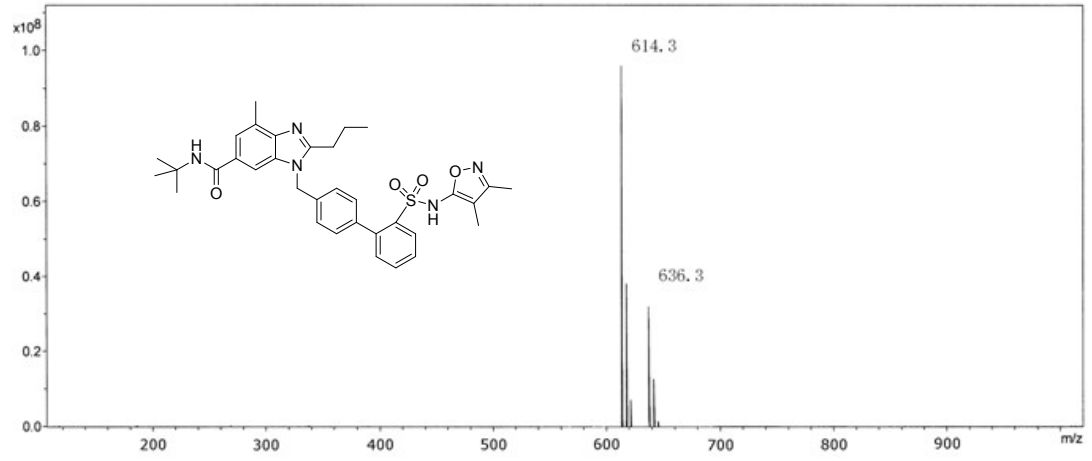
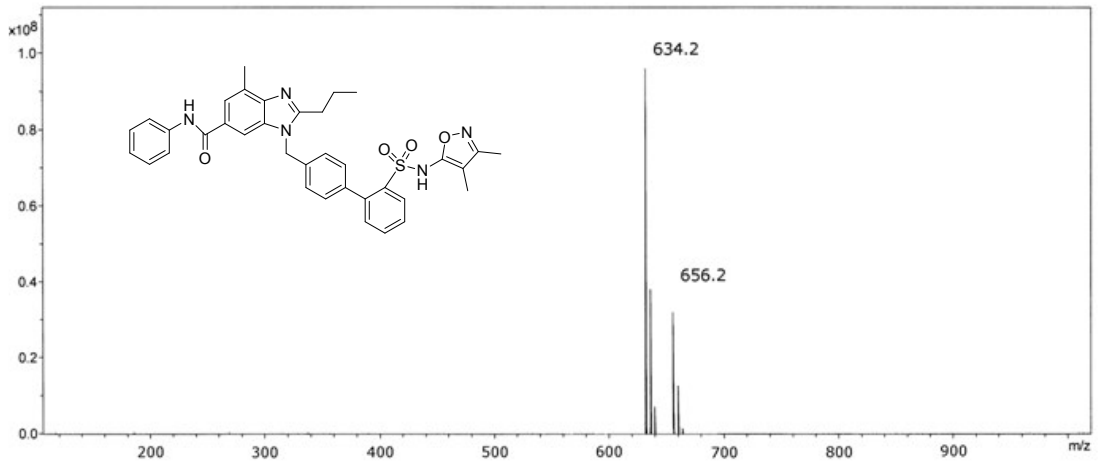


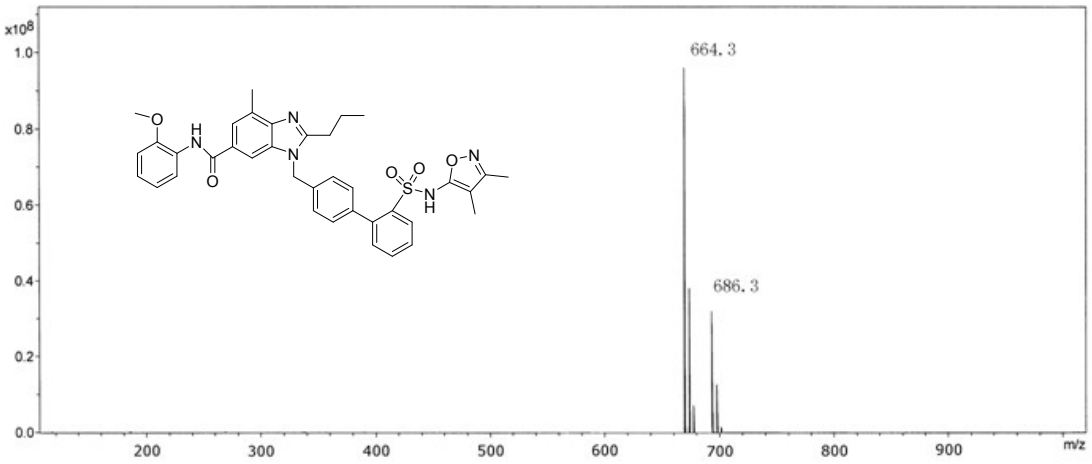
MS spetrum of Compound **7**



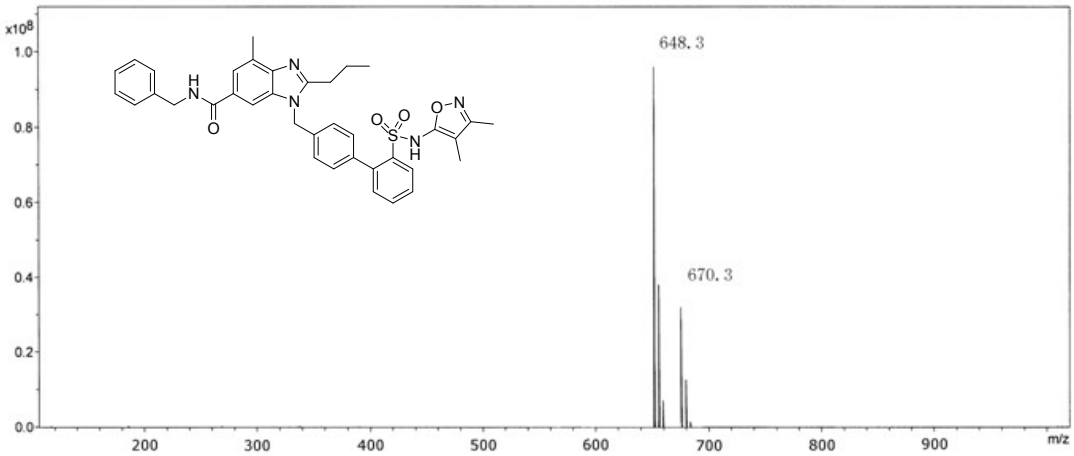
MS spetrum of Compound **8**



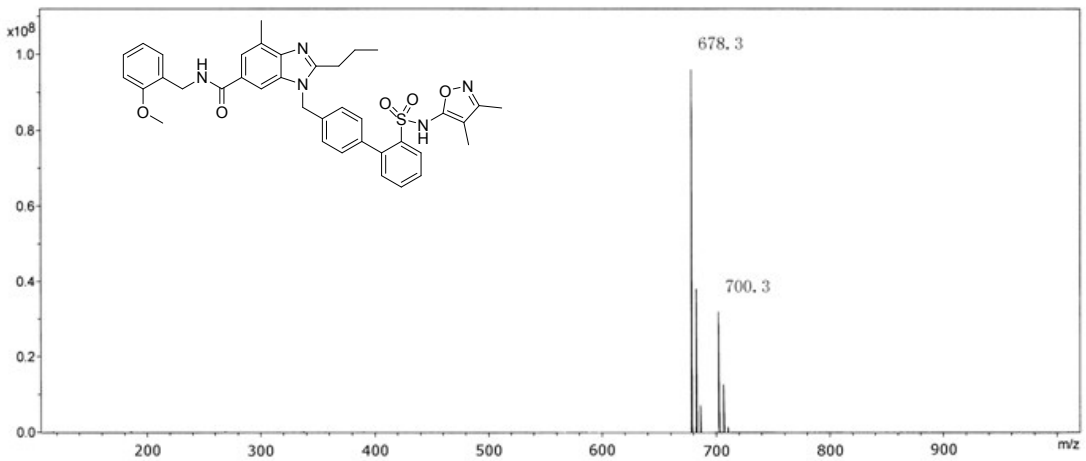
MS spetrum of Compound 9



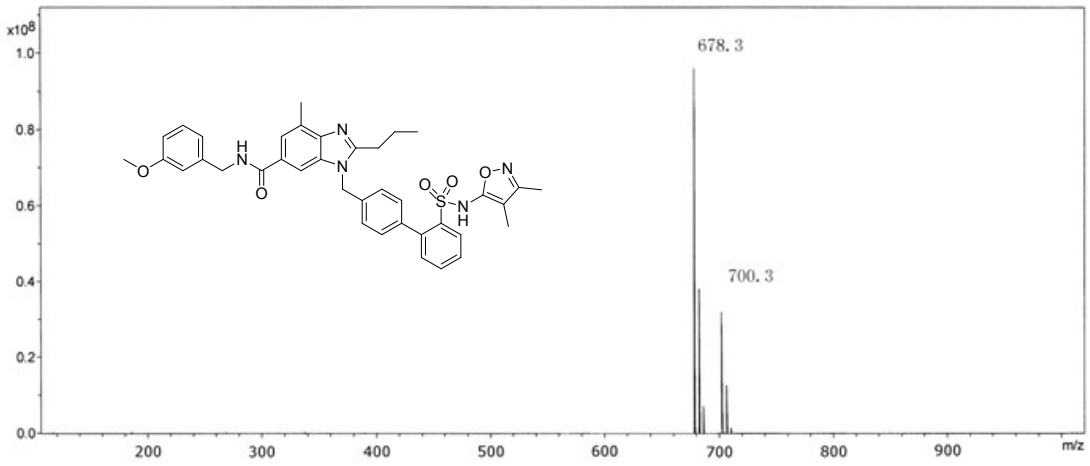
MS spetrum of Compound **10**



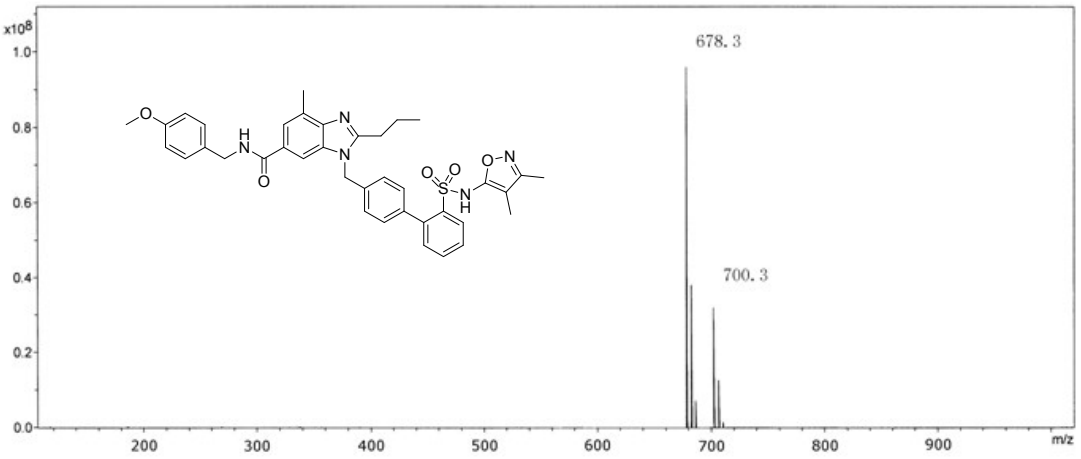
MS spetrum of Compound **11**



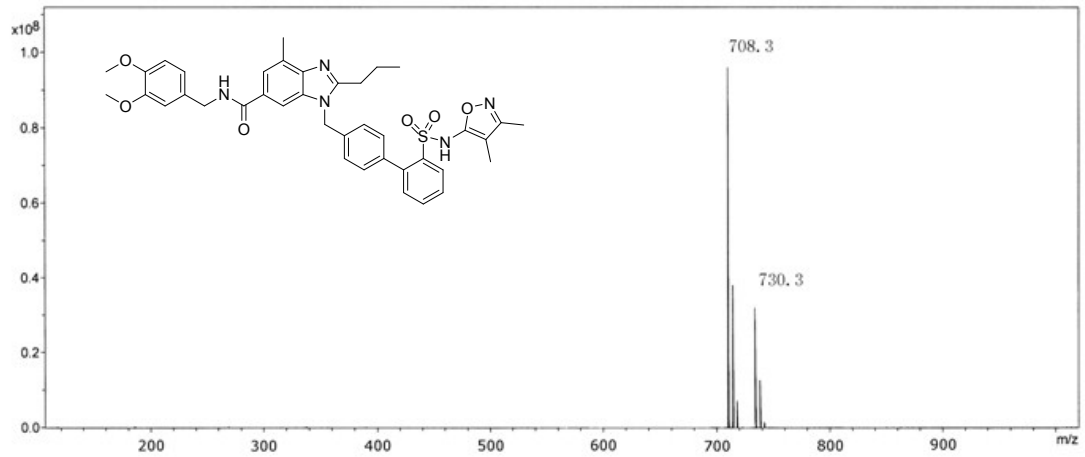
MS spetrum of Compound **12**



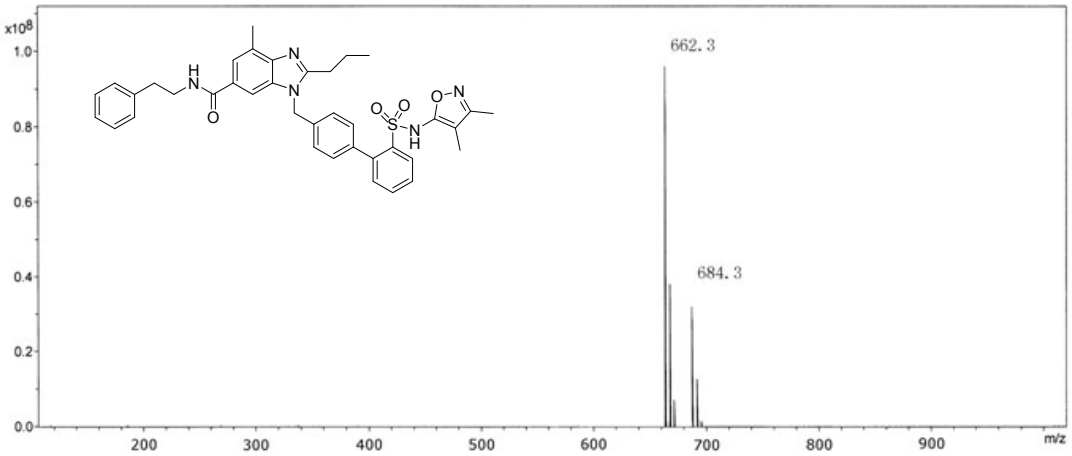
MS spetrum of Compound **13**



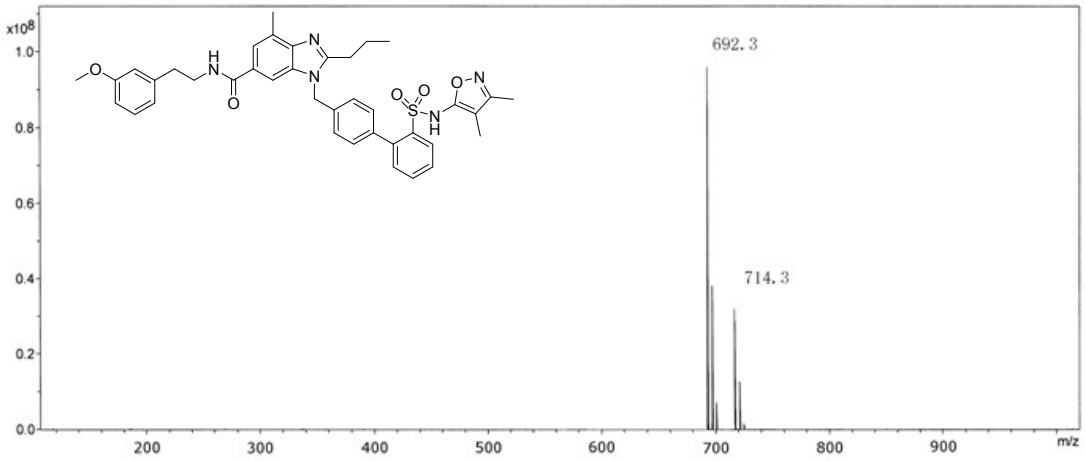
MS spetrum of Compound 14



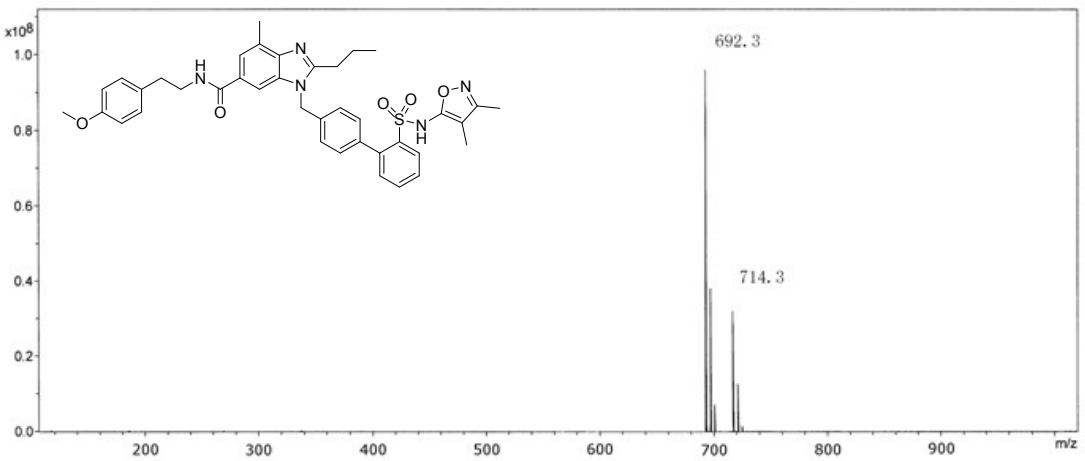
MS spetrum of Compound **15**



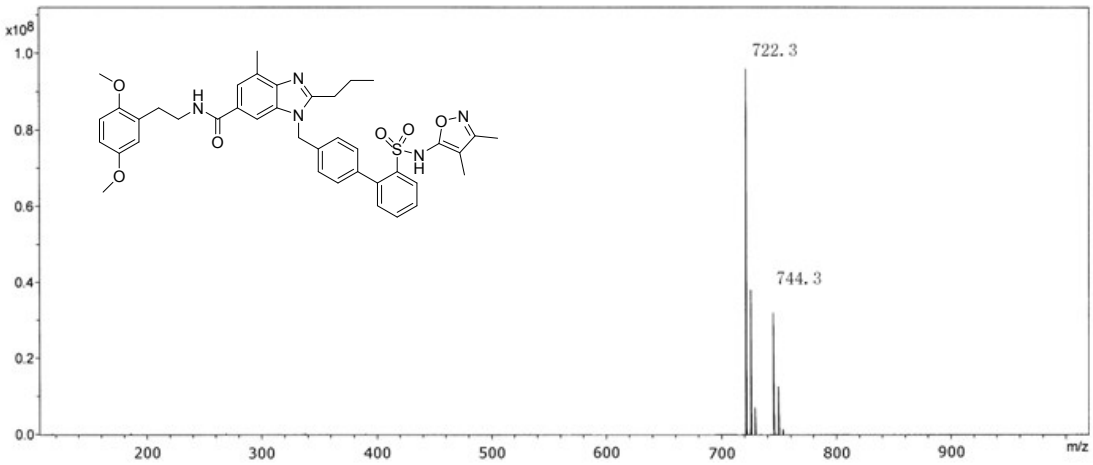
MS spetrum of Compound **16**



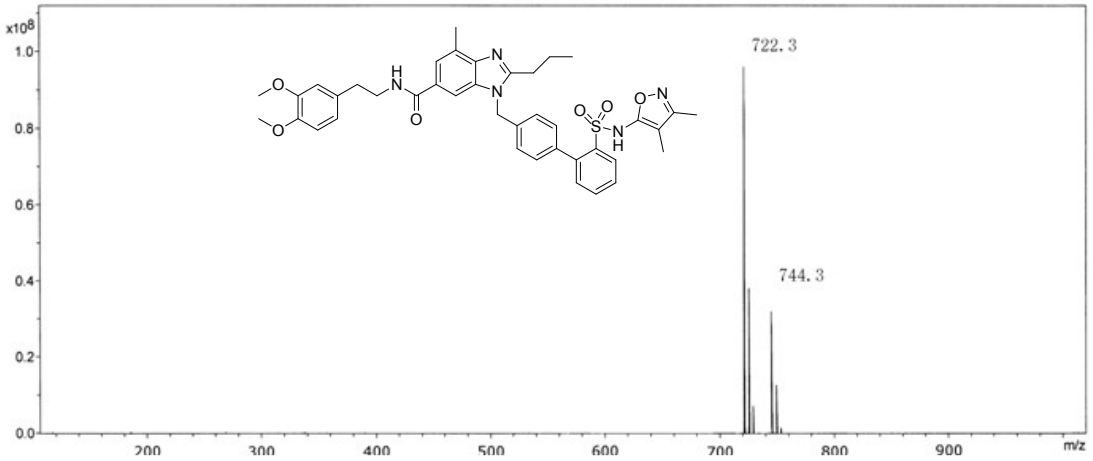
MS spetrum of Compound **17**



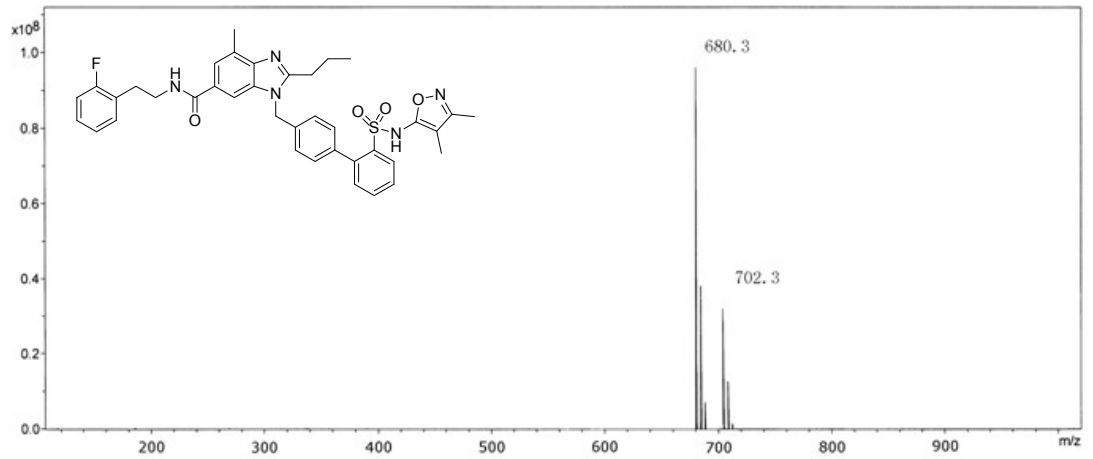
MS spetrum of Compound **18**



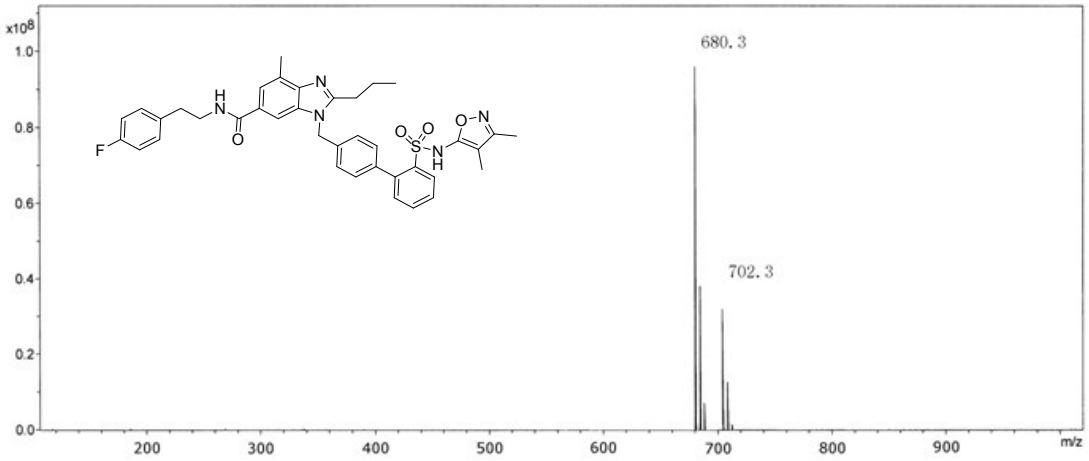
MS spetrum of Compound **19**



MS spetrum of Compound **20**



MS spetrum of Compound **21**



MS spetrum of Compound *22*