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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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 C₁-C₂

To a solution of compound B (0.24 mmol) in 1 mL DMF was added NaH (0.228 mmol, 60%) at 0 °C. After stirring for 0.5 h, compound A (0.24 mmol) was added at 0 °C, 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 Na₂SO₄ 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 (C₁)
Colorless oil, 122.1 mg, 60.5 %. ¹H NMR (400MHz, CDCl₃) 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 (C₂)
Colorless oil, 120.1 mg, 59.5 %. ¹H NMR (400MHz, CDCl₃) δ: 0.95 (t, J = 7.2 Hz, 3H), 1.74 (m, 2H), 1.88 (s, 3H), 2.15 (s, 3H), 2.30 (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 (C₃)
Colorless oil, 123.2 mg, 61.4 %. ¹H NMR (400MHz, CDCl₃) 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), 2.83 (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 %. 1H 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 %. 1H 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 %. 1H 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 %. 1H 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 %. 1H 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 %. 1H 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 (C10)
Colorless oil, 131.1 mg, 64.8 %. 1H NMR (400MHz, CDCl3) 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 (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 (C11)
Colorless oil, 129.2 mg, 63.9 %. 1H NMR (400MHz, CDCl3) 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 (C12)
Colorless oil, 132.3 mg, 65.1 %. 1H NMR (400MHz, CDCl3) δ: 0.97 (t, J = 7.2 Hz, 3H), 1.74 (m, 2H), 1.88 (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 (C13)
Colorless oil, 136.3 mg, 67.1 %. 1H NMR (400MHz, CDCl3) 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 (C14)
Colorless oil, 122.2 mg, 60.3 %. 1H NMR (400MHz, CDCl3) 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 (C15)
Colorless oil, 138.1 mg, 68.2 %. \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta: 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 (C16)
Colorless oil, 136.2 mg, 67.7 %. \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta: 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 (C17)
Colorless oil, 131.1 mg, 64.8 %. \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta: 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 (C18)
Colorless oil, 130.2 mg, 64.5 %. \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta: 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 (C19)
Colorless oil, 128.3 mg, 63.7 %. \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta: 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 (C20)
Colorless oil, 127.2 mg, 63.3 %. \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta: 0.94 (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).
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 (C21)

Colorless oil, 130.1 mg, 64.2 %.

1H NMR (400MHz, CDCl3) 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 (C22)

Colorless oil, 132.3 mg, 65.7 %.

1H NMR (400MHz, CDCl3) 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), 3.67 (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 NaHCO3, then acidified with AcOH to pH=5. The mixture was extract with EtOAc, the combined organic layers were washed with brine, dried over anhydrous Na2SO4 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 °C. 1H 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); 13C NMR (400MHz, CDCl3) 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 (C36H42N6O5S)(%): 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)
carboxamide (2)

Yellow solid, 58.3 mg, 47.8 %, m.p. 101-103 °C. 1H 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); 13C NMR (400MHz, CDCl3) 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 (C37H45N7O4S)(%): 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 °C. 1H 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, 1H); 13C NMR (400MHz, CDCl3) 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, 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 (C37H44N6O4S)(%): 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 °C. 1H 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); 13C NMR (400MHz, CDCl3) 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 (C36H42N6O4S)(%): 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-2-propyl-N,2-dipropyl-1H-benzo[d]imidazole-6-carboxamide (5)

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

S8
(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); 13C NMR (400MHz, CDCl3) 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 (C33H37N5O4S)(%): 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[4]imidazole-6-carboxamide (6)

Yellow solid, 66.8 mg, 54.8 %, m.p. 111-113 °C. 1H 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); 13C NMR (400MHz, CDCl3) 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, 130.2, 133.1, 133.4, 135.1, 135.8, 138.4, 141.8, 143.2, 154.8, 156.6, 162.2, 170.1; MS (ESI), m/z: 600.3 (M+H); Anal. Calcd. For (C33H37N5O4S)(%): 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[4]imidazole-6-carboxamide (7)

Yellow solid, 72.2 mg, 59.2 %, m.p. 116-118 °C. 1H 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), 8.44 (s, 1H); 13C NMR (400MHz, CDCl3) 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 (C34H39N5O4S)(%): 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[4]imidazole-6-carboxamide (8)

Yellow solid, 70.6 mg, 57.9 %, m.p. 114-116 °C. 1H 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); 13C NMR (400MHz, CDCl3) 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 (C34H39N5O4S)(%): 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 °C. \(^1\)H NMR (400MHz, DMSO) \(\delta\): 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\(_3\)) \(\delta\): 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\(_{5}\)O\(_{4}\)S) (%): 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 °C. \(^1\)H NMR (400MHz, DMSO) \(\delta\): 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\(_3\)) \(\delta\): 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, 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\(_{5}\)O\(_{5}\)S) (%): 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 °C. \(^1\)H NMR (400MHz, DMSO) \(\delta\): 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\(_3\)) \(\delta\): 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\(_{5}\)O\(_{4}\)S) (%): C, 66.80; 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 °C. \(^1\)H NMR (400MHz, DMSO) \(\delta\): 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);
13C NMR (400MHz, CDCl3) 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 (C38H39N5O5S) (%): 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 °C. 1H 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); 13C NMR (400MHz, CDCl3) 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 (C38H39N5O5S) (%): 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-(4-methoxybenzyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxamide (14)

Yellow solid, 65.4 mg, 53.6 %, m.p. 103-105 °C. 1H 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, CDCl3) 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 (C38H39N5O5S) (%): C, 67.34; H, 5.80; N, 10.33; Found (%): C, 67.29; H, 5.80; N, 11.31.

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 °C. 1H 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); 13C NMR (400MHz,CDCl3) 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 (C39H41N5O6S) (%): 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 °C. 1H NMR (400MHz, CDCl₃) 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);
13C NMR (400MHz, CDCl₃) 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, 141.2, 142.5, 154.1, 156.0, 161.6, 169.4; MS (ESI), m/z: 662.3 (M+H);
Anal. Calcd. For (C₃₈H₃₉N₅O₄S) (%): C, 68.96; 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 °C. 1H 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);
13C NMR (400MHz, CDCl₃) 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, 129.0, 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);

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 °C. 1H NMR (400MHz, DMSO) δ: 1.07 (t, J = 7.2 Hz, 3H), 1.77 (m, 2H), 1.88 (s, 3H), 2.15 (s, 3H), 2.83 (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), 7.07-7.90 (m, 14H), 8.45 (s, 1H);
13C NMR (400MHz, CDCl₃) 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, 130.4, 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);

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 °C. 1H 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);
13C NMR (400MHz, CDCl₃) 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, 128.1, 129.2, 130.0, 130.3, 133.5, 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_{5}O_{6}S) (%): 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 °C.

\(^1\)H NMR (400MHz, DMSO) \(\delta\): 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\(_3\)) \(\delta\): 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_{5}O_{6}S) (%): C, 66.55; H, 6.00; N, 9.70; Found (%): C, 66.54; 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 °C.

\(^1\)H NMR (400MHz, DMSO) \(\delta\): 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\(_3\)) \(\delta\): 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_{5}O_{4}S) (%): 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 °C.

\(^1\)H NMR (400MHz, DMSO) \(\delta\): 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\(_3\)) \(\delta\): 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_{5}O_{4}S)(%): 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 model

The DARAs pharmacophore model for AT₁ and ET₄ receptor antagonists was generated using the HipHop module of the CATALYST software. 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 models were selected according to their ranking scores in HipHop scores.

![Figure 1. Structures and observed activities of DARAs for the HipHop training set](image)

2.2. DARAs test set selection

Five DARAs (Figure 3) were selected as the training 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](image)

3. Procedure for Receptor Binding Assay

3.1. Angiotensin II. AT₁ receptor binding assay was carried out by competitive displacement of the binding of 0.2 nM ¹²⁵I-labeled Sar¹-Ile⁸-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 $^\circ$C 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.

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**


6. $^1$H NMR & MS Spectra Attached
$^1$HNMR spectrum of compound 1

$^1$HNMR spectrum of compound 2
$^1$HNMR spectrum of compound 3

$^1$HNMR spectrum of compound 4
$^1$HNMR spetrum of compound 5

$^1$HNMR spetrum of compound 6
$^1$HNMR spetrum of compound 7

$^1$HNMR spetrum of compound 8
$^1$HNMR spectrum of compound 9

$^1$HNMR spectrum of compound 10
$^1$HNMR spectrum of compound 11

$^1$HNMR spectrum of compound 12
$^1$HNMR spectrum of compound 13

$^1$HNMR spectrum of compound 14
$^1$HNMR spectrum of compound 15

$^1$HNMR spectrum of compound 16
$^1$HNMR spectrum of compound 17

$^1$HNMR spectrum of compound 18
$^1$HNMR spectrum of compound 19

$^1$HNMR spectrum of compound 20
$^1$HNMR spectrum of compound 21

$^1$HNMR spectrum of compound 22

S27
MS spectrum of Compound 1

MS spectrum of Compound 2

MS spectrum of Compound 3
MS spectrum of Compound 4

MS spectrum of Compound 5

MS spectrum of Compound 6
MS spectrum of Compound 7

MS spectrum of Compound 8

MS spectrum of Compound 9
MS spectrum of Compound 13

MS spectrum of Compound 14

MS spectrum of Compound 15
MS spectrum of Compound 19

MS spectrum of Compound 20

MS spectrum of Compound 21
MS spectrum of Compound 22