

Supporting Material

Synthesis, spectroscopic data and references of precursor chloroacetamides **1a-g**.

Compounds **1a-g** were synthesized as follows: In a dichloromethane solution (2-3 mL) of chloroacetylchloride (1.1 eq), a dichloromethane solution (8-10 mL) of the appropriate amine (1 eq) and triethylamine (1.1 eq) was added dropwise and the reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere. The reaction mixture was evaporated and the residue was extracted with ethyl acetate-brine. The organic layer was dried over Na₂SO₄ and upon rotary evaporation gave the desired product, which was pure in most cases (by TLC). In certain cases, chromatography was applied for further purification.

2-chloro-N-(4'-cyano-[1,1'-biphenyl]-4-yl)acetamide (1a): Yellow-orange powder (92 %): ¹H NMR [500 MHz, (CD₃)₂CO] δ: 9.44 (br s, 1H), 7.76-7.70 (m, 6H), 7.62 (d, *J*=8.5 Hz, 2H), 4.14 (s, 2H). HRESIMS calcd for C₁₅H₁₂ClN₂O and C₁₅H₁₁ClN₂NaO *m/z* [M+H]⁺ and [M+Na]⁺ 271.0633, 273.0607 and 293.0452, 295.0427 found 271.0645, 273.0615 and 293.0462, 295.0434.

2-chloro-N-(4-(4-chlorophenyl)thiazol-2-yl)acetamide (1b):^[1] White powder (93%): ¹H NMR [500 MHz, (CD₃)₂CO] δ: 11.41 (br s, 1H), 9.93 (d, *J*=8.5 Hz, 2H), 7.61 (s, 1H), 7.44 (d, *J*=8.5 Hz, 2H), 4.49 (s, 2H). HRESIMS calcd for C₁₁H₉Cl₂N₂OS *m/z* [M+H]⁺ 286.9807, 288.9778 found 286.9816, 288.9786.

2-chloro-N-(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)acetamide (1c):¹²¹ White powder (88%): ¹H NMR [500 MHz, (DMSO-6d)] δ: 13.09 (br s, 1H), 7.97 (d, *J*=8.0 Hz, 2H), 7.59 (d, *J*=8.5 Hz, 2H), 4.47 (s, 2H). HRESIMS calcd for C₁₀H₈Cl₂N₃OS *m/z* [M+H]⁺ 287.9760, 289.9730 found 287.9764, 289.9734.

2-chloro-N-(4'-chloro-[1,1'-biphenyl]-4-yl)acetamide (1d):¹³¹ Off white powder (87%): ¹H NMR [400 MHz, (CDCl₃)] δ: 8.27 (br s, 1H), 7.63 (d, *J*=8.4 Hz, 2H), 7.55 (d, *J*=8.4 Hz, 2H), 7.50 (d, *J*=8.4 Hz, 2H), 7.40 (d, *J*=8.4 Hz, 2H), 4.22 (s, 2H). HRESIMS calcd for C₁₄H₁₂Cl₂NO and C₁₄H₁₁Cl₂NNaO *m/z* [M+H]⁺ and [M+Na]⁺ 280.0290, 282.0263 and 302.0110, 304.0082 found 280.0290, 282.0251 and 302.0111, 304.0084.

2-chloro-N-(4-(3,4-difluorophenyl)thiazol-2-yl)acetamide (1e) (known, **no** ref): Light yellow crystals (72 %): ¹H NMR [500 MHz, (CDCl₃)] δ: 9.66 (br s, 1H), 7.58 (ddd, *J*=11.5, 7.5, 2.5 Hz, 1H), 7.55 (m, 1H), 7.20 (ddd, *J*=17.0, 8.0, 2.0 Hz, 1H), 7.15 (s, 1H), 4.31 (s, 2H). HRESIMS calcd for C₁₁H₈ClF₂N₂OS *m/z* [M+H]⁺ 289.0008, 290.9980 found 289.0013, 290.9988.

2-chloro-N-(3-(2-methylthiazol-4-yl)phenyl)acetamide (1f) (known, **no** ref): Off white crystals (86 %): mp 79-81 °C; ¹H NMR [500 MHz, (CDCl₃)] δ: 8.32 (br s, 1H), 7.97 (s, 1H), 7.69 (dd, *J*=8.5, 2.5 Hz, 1H), 7.65 (d, *J*=8.0 Hz, 1H), 7.41 (t, *J*=8.5 Hz, 1H), 7.36 (s, 1H), 4.21 (s, 2H), 2.78 (s, 3H). HRESIMS calcd for C₁₂H₁₂ClN₂OS *m/z* [M+H]⁺ 267.0353, 269.0325 found 267.0359, 269.0330.

2-chloro-N-(4-(piperidin-1-yl)phenyl)acetamide (**1g**)¹⁴¹ (Chinese pat.): Beige microcrystals (75%): ¹H NMR [500 MHz, (CDCl₃)] δ: 8.09 (br s, 1H), 7.39 (d, *J*=9.5 Hz, 2H), 6.91 (d, *J*=9.5 Hz, 2H), 4.17 (s, 2H), 3.13 (t, *J*=5.5 Hz, 4H), 1.71 (quintet, *J*=5.5 Hz, 4H), 1.57 (m, 2H). HRESIMS calcd for C₁₃H₁₈ClN₂O *m/z* [M+H]⁺ 253.1102, 255.1076 found 253.1108, 255.1082.

References of supporting information:

1. Wang, Y.; Wang, F.; Yu, J-P.; Jiang, F-C.; Guan, X-L.; Wang, C-M.; Li, L.; Cao, H.; Li, M-X.; Jian-Guo Chen, J-G. Novel multipotent phenylthiazole-tacrine hybrids for the inhibition of cholinesterase activity, b-amyloid aggregation and Ca²⁺ overload. *Bioorg. Med. Chem.* **2012**, *20*, 6513–6522.
2. Küçükgülzel, I.; Satılmış, G.; Gurukumar, K. R.; Basu, A.; Tatar, E.; Nichols, D. B.; Talele, T. T.; Kaushik-Basu, N. 2-Heteroarylimino-5-arylidene-4-thiazolidinones as a new class of non-nucleoside inhibitors of HCV NS5B polymerase. *Eur. J. Med. Chem.* **2013**, *69*, 931-941.
3. a) Eliel, E. L.; Mc Coy, J. W.; Price, C. C. Dehydration of cis- and trans-2-phenylcyclohexanols. *J. Org. Chem.* **1957**, *22*, 1533-1539; b) Hiroshi, N. Biphenyl derivatives. III. Dialkylamino-acylaminobiphenyl derivatives. From *Tohoku Yakka Daigaku Kiyō* **1957**, *4*, 31-60.
4. By Yinglan, Z.; Yuquan, W.; Li, Y.; Shengyong, Y. From Faming Zhuanli Shenqing (**2013**), CN 103102314 A 20130515. Language: Chinese