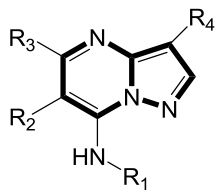


## Supporting information

**Table S1 Structure-activity relationship data related to the series of pyrazolo[1,5-a]pyrimidine analogues as CDK2/cyclin A inhibitor**

**Table S2 Observed and predicted CDK2 inhibitor activities (pIC<sub>50</sub> value, M)**

**Table S1 Structure-activity relationship data related to the series of pyrazolo[1,5-a]pyrimidine analogues as CDK2/cyclin A inhibitor**



| No.            | R <sub>1</sub> | R <sub>2</sub> | R <sub>3</sub> | R <sub>4</sub> | pIC <sub>50</sub> (M) |
|----------------|----------------|----------------|----------------|----------------|-----------------------|
| 1              |                | H              |                | Br             | 7.52                  |
| 2              |                | H              |                | Br             | 7.52                  |
| 3              |                | H              |                | Br             | 7.74                  |
| 4              |                | H              |                | Br             | 9.00                  |
| 5              |                | H              |                | Br             | 9.00                  |
| 6 <sup>s</sup> |                | H              |                | Br             | 9.00                  |
| 7              |                | H              |                | Br             | 7.74                  |
| 8              |                | H              |                | Et             | 9.00                  |
| 9              |                | H              |                | Et             | 9.00                  |
| 10             | H              | H              |                | H              | 5.11                  |
| 11             | H              | H              |                |                | 7.10                  |
| 12             | H              | H              |                |                | 6.09                  |
| 13             | H              | H              |                |                | 6.57                  |

To be continued

| No.             | R <sub>1</sub>                                                                      | R <sub>2</sub>                     | R <sub>3</sub>                                                                      | R <sub>4</sub>                                                                        | pIC <sub>50</sub> (M) |
|-----------------|-------------------------------------------------------------------------------------|------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------|
| 14              | H                                                                                   | H                                  |    |    | 6.15                  |
| 15              | H                                                                                   | H                                  |    |    | 5.34                  |
| 16              | H                                                                                   | H                                  |    |    | 6.19                  |
| 17 <sup>s</sup> | H                                                                                   | H                                  |    |    | 5.27                  |
| 18              | H                                                                                   | H                                  |    |    | 5.92                  |
| 19 <sup>s</sup> | H                                                                                   | H                                  |    |    | 6.23                  |
| 20              | H                                                                                   | H                                  |    |    | 6.16                  |
| 21              | H                                                                                   | H                                  |    |    | 5.66                  |
| 22 <sup>s</sup> | H                                                                                   | H                                  |  |   | 5.00                  |
| 23              | H                                                                                   | H                                  |  |  | 5.21                  |
| 24              | H                                                                                   | H                                  |  |  | 6.10                  |
| 25              |  | H                                  |  |  | 4.51                  |
| 26              |  | H                                  |  |  | 4.40                  |
| 27 <sup>s</sup> | H                                                                                   | H                                  |  | Br                                                                                    | 7.07                  |
| 28 <sup>s</sup> | H                                                                                   | Cl                                 |  |  | 6.51                  |
| 29              | H                                                                                   | Br                                 |  |  | 6.80                  |
| 30              | H                                                                                   | I                                  |  |  | 6.48                  |
| 31              | H                                                                                   | Et                                 |  |  | 6.48                  |
| 32              | H                                                                                   | Propynyl                           |  |  | 6.28                  |
| 33              | H                                                                                   | c-Pr                               |  |  | 6.77                  |
| 34              | H                                                                                   | (CH <sub>2</sub> ) <sub>2</sub> OH |  |  | 7.32                  |

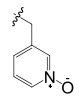
To be continued

| No.             | R <sub>1</sub> | R <sub>2</sub>           | R <sub>3</sub>                                                                      | R <sub>4</sub>                                                                        | pIC <sub>50</sub> (M) |
|-----------------|----------------|--------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------|
| 35 <sup>s</sup> | H              | CH=CHCH <sub>2</sub> OMe |    |    | 5.66                  |
| 36              | H              | CN                       |    |    | 5.77                  |
| 37              | H              | Ph                       |    |    | 5.08                  |
| 38              | H              | 2-Thienyl                |    |    | 6.00                  |
| 39 <sup>s</sup> | H              | 3-Thienyl                |    |    | 5.66                  |
| 40 <sup>s</sup> | H              | 3-Fural                  |    |    | 5.64                  |
| 41 <sup>s</sup> | H              | 3-Pyridyl                |    |    | 5.82                  |
| 42              | H              | 4-Pyridyl                |    |    | 4.96                  |
| 43 <sup>s</sup> | H              | 4-N-Methylpyrazolyl      |   |   | 4.66                  |
| 44 <sup>s</sup> | H              | Br                       |  |  | 6.77                  |
| 45              | H              | Br                       |  |  | 7.00                  |
| 46              | H              | Br                       |  |  | 6.70                  |
| 47 <sup>s</sup> | H              | Br                       |  |  | 5.89                  |
| 48              | H              | Br                       |  |  | 4.54                  |
| 49 <sup>s</sup> | H              | Br                       |  |  | 6.31                  |
| 50              | H              | Br                       |  |  | 5.92                  |
| 51              | H              | Br                       |  |  | 6.82                  |
| 52              | H              | Br                       |  |  | 6.29                  |
| 53              | H              | Br                       |  |  | 6.04                  |
| 54              | H              | Br                       |  |  | 5.55                  |

To be continued

| No.             | R <sub>1</sub>                                                                      | R <sub>2</sub> | R <sub>3</sub>                                                                    | R <sub>4</sub>                                                                      | pIC <sub>50</sub> (M) |
|-----------------|-------------------------------------------------------------------------------------|----------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------|
| 55              | H                                                                                   | Br             |  |  | 6.08                  |
| 56              | H                                                                                   | Br             |  |  | 5.62                  |
| 57              | H                                                                                   | Br             |  |  | 6.36                  |
| 58 <sup>§</sup> |    | H              | Ph                                                                                | H                                                                                   | 6.60                  |
| 59              |    | H              | Ph                                                                                | Br                                                                                  | 7.96                  |
| 60              |    | H              | Ph                                                                                | Me                                                                                  | 7.14                  |
| 61 <sup>§</sup> |    | H              | Ph                                                                                | Et                                                                                  | 8.10                  |
| 62              |    | H              | Ph                                                                                | Pr                                                                                  | 6.05                  |
| 63              |    | H              | Ph                                                                                | Bu                                                                                  | 5.92                  |
| 64              |  | H              | Ph                                                                                | Ethynyl                                                                             | 7.32                  |
| 65              |  | H              | Ph                                                                                | Vinyl                                                                               | 7.05                  |
| 66              |  | H              | Ph                                                                                | Propynyl                                                                            | 6.08                  |
| 67              |  | H              | Ph                                                                                | <i>c</i> -Pr                                                                        | 7.15                  |
| 68              |  | H              | Ph                                                                                | CF <sub>3</sub>                                                                     | 7.02                  |
| 69              |  | H              | Ph                                                                                | CH <sub>2</sub> CF <sub>3</sub>                                                     | 6.15                  |
| 70              |  | H              | Ph                                                                                | SCH <sub>3</sub>                                                                    | 8.15                  |
| 71 <sup>§</sup> |  | H              | Ph                                                                                | OCH <sub>3</sub>                                                                    | 5.96                  |
| 72              |  | H              | Ph                                                                                | CH <sub>2</sub> OH                                                                  | 5.66                  |
| 73              |  | H              | Ph                                                                                | CH(OH)CF <sub>3</sub>                                                               | 5.47                  |
| 74              |  | H              | Ph                                                                                | <i>i</i> -Pr                                                                        | 6.43                  |
| 75              |  | H              | Ph                                                                                | CH <sub>2</sub> Ph                                                                  | 4.80                  |

| To be continued |                                                                                     |                |                                                                                     |                                       |                       |
|-----------------|-------------------------------------------------------------------------------------|----------------|-------------------------------------------------------------------------------------|---------------------------------------|-----------------------|
| No.             | R <sub>1</sub>                                                                      | R <sub>2</sub> | R <sub>3</sub>                                                                      | R <sub>4</sub>                        | pIC <sub>50</sub> (M) |
| 76              |    | H              | Ph                                                                                  | CH <sub>2</sub> N(Me) <sub>2</sub>    | 4.47                  |
| 77              |    | H              | Ph                                                                                  | S(CH <sub>2</sub> ) <sub>2</sub> NHAc | 8.70                  |
| 78 <sup>s</sup> |    | H              | Ph                                                                                  | S(CH <sub>2</sub> ) <sub>2</sub> OH   | 7.52                  |
| 79              |    | H              | Ph                                                                                  | CH <sub>2</sub> CN                    | 7.31                  |
| 80              |    | H              | Me                                                                                  | Br                                    | 7.22                  |
| 81 <sup>s</sup> |    | H              | Et                                                                                  | Br                                    | 7.74                  |
| 82              |    | H              | <i>i</i> -Pr                                                                        | Br                                    | 7.77                  |
| 83              |    | H              | <i>c</i> -Pr                                                                        | Br                                    | 7.35                  |
| 84 <sup>s</sup> |   | H              | CH(CH <sub>3</sub> )OH                                                              | Br                                    | 7.42                  |
| 85              |  | H              | CO <sub>2</sub> Et                                                                  | Br                                    | 7.05                  |
| 86              |  | H              | NHCH <sub>3</sub>                                                                   | Br                                    | 7.37                  |
| 87              |  | H              | OCH <sub>3</sub>                                                                    | Br                                    | 7.46                  |
| 88              |  | H              | SCH <sub>3</sub>                                                                    | Br                                    | 7.42                  |
| 89              |  | H              | Ph-2-Cl                                                                             | Br                                    | 8.52                  |
| 90 <sup>s</sup> |  | H              | <i>c</i> -Hexyl                                                                     | Br                                    | 8.40                  |
| 91              |  | H              | 3-PiperidinyI                                                                       | Br                                    | 8.10                  |
| 92              |  | H              | 4-PiperidinyI                                                                       | Br                                    | 7.80                  |
| 93              |  | H              | Piperazine                                                                          | Br                                    | 6.68                  |
| 94              |  | H              | 2-FuryI                                                                             | Br                                    | 8.10                  |
| 95              |  | H              | 2-Thienyl                                                                           | Br                                    | 7.89                  |
| 96              | H                                                                                   | H              |  | Br                                    | 6.60                  |

| To be continued  |                                                                                     |                |                                                                                     |                |                       |
|------------------|-------------------------------------------------------------------------------------|----------------|-------------------------------------------------------------------------------------|----------------|-----------------------|
| No.              | R <sub>1</sub>                                                                      | R <sub>2</sub> | R <sub>3</sub>                                                                      | R <sub>4</sub> | pIC <sub>50</sub> (M) |
| 97               | Me                                                                                  | H              |    | Br             | 7.70                  |
| 98               | Pr                                                                                  | H              |    | Br             | 6.79                  |
| 99               | <i>c</i> -Pr                                                                        | H              |    | Br             | 6.08                  |
| 100              | Ph                                                                                  | H              |    | Br             | 6.39                  |
| 101              | Ph-4-SO <sub>2</sub> CH <sub>3</sub>                                                | H              |    | Br             | 6.46                  |
| 102              | Bn                                                                                  | H              |    | Br             | 6.52                  |
| 103              | CH <sub>2</sub> -3Pyr                                                               | H              |    | Br             | 8.40                  |
| 104              | CH <sub>2</sub> -3Pyr-O                                                             | H              |    | Br             | 7.96                  |
| 105 <sup>§</sup> | CH <sub>2</sub> -3Pyr-O                                                             | H              |   | Br             | 7.89                  |
| 106              | CH <sub>2</sub> -3Pyr-O                                                             | H              |  | Br             | 7.47                  |
| 107              | CH(Me)-3Pyr                                                                         | H              |  | Br             | 5.52                  |
| 108              |  | H              |  | H              | 6.30                  |
| 109              |  | H              |  | Br             | 7.31                  |
| 110              |  | H              | Ph                                                                                  | H              | 6.30                  |
| 111              |  | H              | Ph                                                                                  | Br             | 7.54                  |

<sup>§</sup> Test set

**Table S2 Observed and predicted CDK2 inhibitor activities (pIC<sub>50</sub> value, M)**

| No. | Observed<br>activity | CoMFA     |         | CoMSIA    |         |
|-----|----------------------|-----------|---------|-----------|---------|
|     |                      | Predicted | Residue | Predicted | Residue |
| 1   | 7.52                 | 7.318     | -0.202  | 7.410     | -0.110  |
| 2   | 7.52                 | 7.413     | -0.107  | 8.004     | 0.484   |
| 3   | 7.74                 | 7.784     | 0.044   | 7.636     | -0.104  |
| 4   | 9.00                 | 9.126     | 0.126   | 8.999     | -0.001  |
| 5   | 9.00                 | 8.915     | -0.085  | 9.279     | 0.279   |
| 6   | 9.00                 | 9.036     | 0.036   | 9.675     | 0.675   |
| 7   | 7.74                 | 7.563     | -0.177  | 7.512     | -0.228  |
| 8   | 9.00                 | 9.121     | 0.121   | 8.586     | -0.414  |
| 9   | 9.00                 | 9.125     | 0.125   | 8.934     | -0.066  |
| 10  | 5.11                 | 5.469     | 0.359   | 6.387     | 1.277   |
| 11  | 7.10                 | 6.408     | -0.692  | 5.997     | -1.103  |
| 12  | 6.09                 | 6.836     | 0.746   | 6.259     | 0.169   |
| 13  | 6.57                 | 5.934     | -0.636  | 5.990     | -0.580  |
| 14  | 6.15                 | 5.960     | -0.190  | 6.296     | 0.146   |
| 15  | 5.34                 | 5.202     | -0.138  | 5.641     | 0.301   |
| 16  | 6.19                 | 6.228     | 0.038   | 6.184     | -0.006  |
| 17  | 5.27                 | 5.923     | 0.653   | 5.438     | 0.168   |
| 18  | 5.92                 | 5.885     | -0.035  | 5.639     | -0.281  |
| 19  | 6.23                 | 5.830     | -0.400  | 6.194     | -0.036  |
| 20  | 6.16                 | 6.013     | -0.147  | 5.715     | -0.445  |
| 21  | 5.66                 | 5.587     | -0.073  | 5.635     | -0.025  |
| 22  | 5.00                 | 5.903     | 0.903   | 5.529     | 0.529   |
| 23  | 5.21                 | 5.351     | 0.141   | 5.585     | 0.375   |
| 24  | 6.10                 | 6.370     | 0.270   | 6.317     | 0.217   |
| 25  | 4.51                 | 4.665     | 0.155   | 4.320     | -0.190  |
| 26  | 4.40                 | 4.250     | -0.150  | 4.388     | -0.012  |
| 27  | 7.07                 | 6.733     | -0.337  | 7.095     | 0.025   |
| 28  | 6.51                 | 6.394     | -0.116  | 6.306     | -0.204  |
| 29  | 6.80                 | 6.420     | -0.380  | 6.520     | -0.28   |
| 30  | 6.48                 | 6.339     | -0.141  | 6.895     | 0.415   |
| 31  | 6.48                 | 6.843     | 0.363   | 6.638     | 0.158   |
| 32  | 6.28                 | 6.202     | -0.078  | 6.021     | -0.259  |
| 33  | 6.77                 | 6.789     | 0.019   | 6.906     | 0.136   |
| 34  | 7.32                 | 7.248     | -0.072  | 7.189     | -0.131  |
| 35  | 5.66                 | 5.605     | -0.055  | 5.707     | 0.047   |
| 36  | 5.77                 | 6.129     | 0.359   | 5.908     | 0.138   |
| 37  | 5.08                 | 5.070     | -0.010  | 5.429     | 0.349   |
| 38  | 6.00                 | 5.883     | -0.117  | 5.913     | -0.087  |
| 39  | 5.66                 | 5.808     | 0.148   | 5.722     | 0.062   |
| 40  | 5.64                 | 6.193     | 0.553   | 5.488     | -0.152  |
| 41  | 5.82                 | 5.682     | -0.138  | 5.611     | -0.209  |



**To be continued**

| No. | Observed activity | CoMFA     |         | CoMSIA    |         |
|-----|-------------------|-----------|---------|-----------|---------|
|     |                   | Predicted | Residue | Predicted | Residue |
| 42  | 4.96              | 5.079     | 0.119   | 4.964     | 0.004   |
| 43  | 4.66              | 5.812     | 1.152   | 5.491     | 0.831   |
| 44  | 6.77              | 7.057     | 0.287   | 6.802     | 0.032   |
| 45  | 7.00              | 7.111     | 0.111   | 7.066     | 0.066   |
| 46  | 6.70              | 6.692     | -0.008  | 6.067     | -0.633  |
| 47  | 5.89              | 7.284     | 1.394   | 6.305     | 0.415   |
| 48  | 4.54              | 5.148     | 0.608   | 4.395     | -0.145  |
| 49  | 6.31              | 6.058     | -0.252  | 6.307     | -0.003  |
| 50  | 5.92              | 5.989     | 0.069   | 5.977     | 0.057   |
| 51  | 6.82              | 6.792     | -0.028  | 7.000     | 0.180   |
| 52  | 6.29              | 6.186     | -0.104  | 6.234     | -0.056  |
| 53  | 6.04              | 5.939     | -0.101  | 6.013     | -0.027  |
| 54  | 5.55              | 5.582     | 0.032   | 5.378     | -0.172  |
| 55  | 6.08              | 6.018     | -0.062  | 6.251     | 0.171   |
| 56  | 5.62              | 5.799     | 0.179   | 5.757     | 0.137   |
| 57  | 6.36              | 5.827     | -0.533  | 6.196     | -0.164  |
| 58  | 6.60              | 5.345     | -1.255  | 6.846     | 0.246   |
| 59  | 7.96              | 7.357     | -0.603  | 7.828     | -0.132  |
| 60  | 7.14              | 7.415     | 0.275   | 7.264     | 0.124   |
| 61  | 8.10              | 9.062     | 0.962   | 7.853     | -0.247  |
| 62  | 6.05              | 6.185     | 0.135   | 6.568     | 0.518   |
| 63  | 5.92              | 5.575     | -0.345  | 6.008     | 0.088   |
| 64  | 7.32              | 7.059     | -0.261  | 7.003     | -0.317  |
| 65  | 7.05              | 6.869     | -0.181  | 7.192     | 0.142   |
| 66  | 6.08              | 6.54      | 0.46    | 6.729     | 0.649   |
| 67  | 7.15              | 7.238     | 0.088   | 6.783     | -0.367  |
| 68  | 7.02              | 7.301     | 0.281   | 7.229     | 0.209   |
| 69  | 6.15              | 6.297     | 0.147   | 6.303     | 0.153   |
| 70  | 8.15              | 7.484     | -0.666  | 7.172     | -0.978  |
| 71  | 5.96              | 6.316     | 0.356   | 6.622     | 0.662   |
| 72  | 5.66              | 5.746     | 0.086   | 5.607     | -0.053  |
| 73  | 5.47              | 5.982     | 0.512   | 5.690     | 0.220   |
| 74  | 6.43              | 6.561     | 0.131   | 6.489     | 0.059   |
| 75  | 4.80              | 4.666     | -0.134  | 4.533     | -0.267  |
| 76  | 4.47              | 4.538     | 0.068   | 4.987     | 0.517   |
| 77  | 8.70              | 8.945     | 0.245   | 8.627     | -0.073  |
| 78  | 7.52              | 6.564     | -0.956  | 7.130     | -0.390  |
| 79  | 7.31              | 7.125     | -0.185  | 6.789     | -0.521  |
| 80  | 7.22              | 7.466     | 0.246   | 7.563     | 0.343   |
| 81  | 7.74              | 7.299     | -0.441  | 7.643     | -0.097  |
| 82  | 7.77              | 7.996     | 0.226   | 7.925     | 0.155   |

| To be continued |                      |           |         |           |         |
|-----------------|----------------------|-----------|---------|-----------|---------|
| No.             | Observed<br>activity | CoMFA     |         | CoMSIA    |         |
|                 |                      | Predicted | Residue | Predicted | Residue |
| 83              | 7.35                 | 7.345     | -0.005  | 7.503     | 0.153   |
| 84              | 7.42                 | 7.848     | 0.428   | 7.432     | 0.012   |
| 85              | 7.05                 | 6.787     | -0.263  | 6.910     | -0.140  |
| 86              | 7.37                 | 7.281     | -0.089  | 7.331     | -0.039  |
| 87              | 7.46                 | 7.367     | -0.093  | 7.495     | 0.035   |
| 88              | 7.42                 | 7.278     | -0.142  | 7.478     | 0.058   |
| 89              | 8.52                 | 8.563     | 0.043   | 8.408     | -0.112  |
| 90              | 8.40                 | 7.574     | -0.826  | 8.345     | -0.055  |
| 91              | 8.10                 | 7.691     | -0.409  | 8.107     | 0.007   |
| 92              | 7.80                 | 7.898     | 0.098   | 7.603     | -0.197  |
| 93              | 6.68                 | 6.907     | 0.227   | 6.669     | -0.011  |
| 94              | 8.10                 | 7.931     | -0.169  | 7.509     | -0.591  |
| 95              | 7.89                 | 7.868     | -0.022  | 7.549     | -0.341  |
| 96              | 6.60                 | 6.607     | 0.007   | 6.856     | 0.256   |
| 97              | 7.70                 | 7.654     | -0.046  | 7.751     | 0.051   |
| 98              | 6.79                 | 6.783     | -0.007  | 6.955     | 0.165   |
| 99              | 6.08                 | 6.198     | 0.118   | 6.456     | 0.376   |
| 100             | 6.39                 | 6.318     | -0.072  | 6.376     | -0.014  |
| 101             | 6.46                 | 6.613     | 0.153   | 6.645     | 0.185   |
| 102             | 6.52                 | 6.961     | 0.441   | 6.639     | 0.119   |
| 103             | 8.40                 | 8.318     | -0.082  | 8.082     | -0.318  |
| 104             | 7.96                 | 8.015     | 0.055   | 7.965     | 0.005   |
| 105             | 7.89                 | 7.319     | -0.571  | 7.758     | -0.132  |
| 106             | 7.47                 | 7.230     | -0.240  | 7.694     | 0.224   |
| 107             | 5.52                 | 5.637     | 0.117   | 5.327     | -0.193  |
| 108             | 6.30                 | 6.085     | -0.215  | 6.453     | 0.153   |
| 109             | 7.31                 | 7.596     | 0.286   | 7.292     | -0.018  |
| 110             | 6.30                 | 6.490     | 0.190   | 6.476     | 0.176   |
| 111             | 7.54                 | 7.404     | -0.136  | 7.528     | -0.012  |