ChemistrySelect / Volume 6, Issue 14 / p. 3444-3452

Full Paper

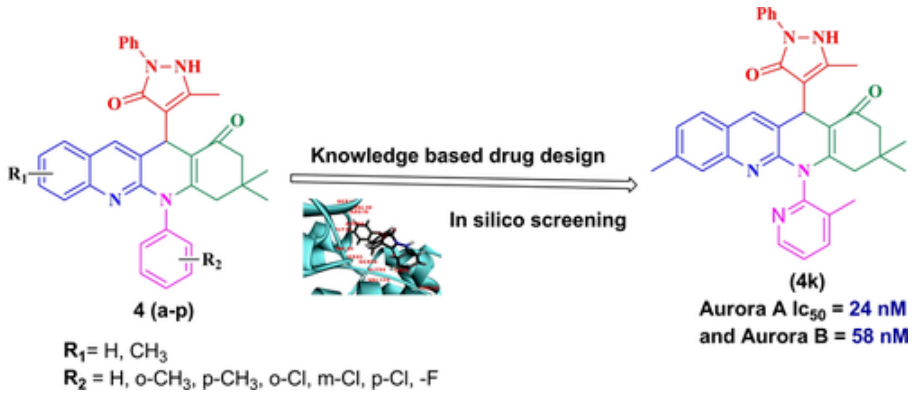
Design, Synthesis and Biological Evaluation of Tetrahydrodibenzo[b,g][1,8]napthyridinones as Potential Anticancer Agents and Novel Aurora Kinases Inhibitors

Dr. Asha V. Chate, Pramod A. Tagad, Dr. Giribala M. Bondle, Dr. Aniket P. Sarkate, Dr. Shailee V. Tiwari, Rajaram Azad

First published: 14 April 2021
https://doi.org/10.1002/slct.202004666

Graphical Abstract

We have designed and synthesized novel tetrahydrodibenzo[b,g] [1,8]naphthyridinone molecules by one-pot synthesis, The synthesized compounds were biologically evaluated for anticancer activity against three cancer cells A549, HepG2, and HeLa using MTT assay by VX-680 as standard drug, specifically inhibiting Aurora A and B kinases. The compound 4k was found to be the foremost potent anticancer compound among the all derivatives.



Abstract

Aurora kinases inhibitors A and B have elucidated a vital role within the carcinogenesis and metastases of assorted sort of cancer. Variety of novel methodologies of drug style and support of potential enzyme inhibitors square measure listed in clinical trials, probably there's no advanced clinical role for kinases because the key targets for developing drug than in cancer medical care until date. Therefore, we have designed and synthesized novel tetrahydrodibenzo[b,g] [1,8]naphthyridinone molecules victimisation L-Proline in ethanol as associate adept organocatalyst for one-pot synthesis. This methodology is delicate, competent, high yielding, and also the product was directly crystallized from hot ethanol, in addition to this synthesized compounds were biologically evaluated for anticancer activity against human respiratory organ cancer (A549), human hepatocellular liver cancer (HepG2) and human cervical cancer animal tissue (HeLa) cells victimisation MTT assay victimisation VX-680 as normal drug, specifically inhibiting Aurora A and Aurora B kinases. The compounds 4 f,4 h and 4k were found to be sensible anticancer agents against the complete selected cancer cell lines. The compound

4k was found to be the foremost potent anticancer compound among the synthesized derivatives with IC50 value 16.22 μM, 20.14 μM and 5.32 μM against A549, HepG2 and Hela cell lines. The potent compounds 4 f,4 h and 4k were specifically inhibiting Aurora A and Aurora B kinases. The compound 4k was found to be potent Aurora kinases substance with IC50 value 24 nM and 58 nM against Aurora A and Aurora B, respectively. The results of Aurora enzymes restrictive activities recommend that the synthesized compounds exert their anticancer activity by inhibiting aurora kinase inhibitors.

Conflict of interest

The authors declare no conflict of interest.

References

1 P. D. Andrews, *Oncogene* 2005, **24(33)**, 5005–5015.

Web of Science® | Google Scholar

2 M. Carmena, W. C. Earnshaw, *Nat. Rev. Mol. Cell Biol.* 2003, **4**, 842–854.

CAS | PubMed | Web of Science® | Google Scholar

3 P. D. Andrews, E. Knatko, W. J. Moore, J. R. Swedlow, *Curr. Opin. Cell Biol.* 2003, **15**, 672–683.

CAS | PubMed | Web of Science® | Google Scholar

4 D. Fancelli, J. Moll, M. Varasi, R. Bravo, R. Artico, D. Berta, S. Bindi, A. Cameron, I. Candiani, P. Cappella, P. Carpinelli, W. Croci, B. Forte, M. L. Giorgini, J. Klapwijk, A. Marsiglio, E. Pesenti, M. Rocchetti, F. Roletto, D. Severino, C. Soncini, P. Storici, R. Tonani, P. Zugnoni, P. Vianello, *J. Med. Chem.* 2006, **49**, 7247–7251.

CAS | PubMed | Web of Science® | Google Scholar

5 E. A. Harrington, D. Bebbington, J. Moore, R. K. Rasmussen, A. O. Ajose-Adeogunn, T. Nakayama, J. A. Graham, C. Demur, T. Hercend, A. Diu-Hercend, M. Su, J. M. C. Golec, K. M. Miller, *Nat. Med.* 2004, **10**, 262–267.

CAS | PubMed | Web of Science® | Google Scholar

6 S. Howard, V. Berdini, J. A. Boulstridge, M. G. Carr, D. M. Cross, J. Curry, L. A. Devine, T. R. Early, L. Fazal, A. L. Gill, M. Heathcote, S. Maman, J. E. Matthews, R. L. McMenamin, E. F. Navarro, M. A. O'Brien, M. O'Reilly, D. C. Rees, M. Reule, D. Tisi, G. Williams, M. Vinkovic, P. G. Wyatt, *J. Med. Chem.* 2009, **52**, 379–388.

CAS | PubMed | Web of Science® | Google Scholar

7 M. G. Manfredi, J. A. Exsedy, K. A. Meetze, S. K. Balani, O. Burenkova, W. Chen, K. M. Galvin, K. M. Hoar, J. J. Huck, P. J. LeRoy, E. T. Ray, T. B. Sells, B. Stringer, S. G. Stroud, T. J. Vos, G. S. Weatherhead, D. R. Wysong, M. Zhang, J. B. Bolen, C. F. Claiborne, *Proc. Natl. Acad. Sci. USA* 2007, **104**, 4106–4111.

CAS | PubMed | Web of Science® | Google Scholar

8 J. R. Pollard, M. Mortimore, *J. Med. Chem.* 2009, **52**, 2629–2651.

CAS | PubMed | Web of Science® | Google Scholar

9 A. H. Kishore, B. M. Vedamurthy, K. Mantelingu, S. Agrawal, B. A. A. Reddy, S. Roy, K. S. Rangappa, T. K. Kundu, *J. Med. Chem.* 2008, **51**, 792–797.

CAS | PubMed | Web of Science® | Google Scholar

10 H. Katayama, W. R. Brinkley, S. Sen, *Cancer Metast. Rev.* 2003, **22**, 451–464.

PubMed | Google Scholar

11 H. L. Gold, J. Wengrod, E. V. S. de Miera, D. Wang, N. Fleming, L. Sikkema, T. Kirchhoff, T. Hochman, J. D. Goldberg, I. Osman, *Mol. Cancer Res.* 2014, **12**, 433–439.

CAS | PubMed | Web of Science® | Google Scholar

12 R. Reiter, P. Gais, U. Jütting, M. K. Steuer-Vogt, A. Pickhard, K. Bink, S. Rauser, S. Lassmann, H. Höfler, M. Werner, A. Walch, *Clin. Cancer Res.* 2006, **12**, 5136–5141.

CAS | PubMed | Web of Science® | Google Scholar

13 J. Sun, K. Knickelbein, K. He, D. Chen, C. Dudgeon, Y. Shu, et al., *Mol. Cancer Ther.* 2014, **13**, 1298–1308.

CAS | PubMed | Web of Science® | Google Scholar

14 C. J. Morrow, A. Tighe, V. L. Johnson, M. I. F. Scott, C. Ditchfield, S. S. Taylor, *J. Cell Sci.* 2005, **118**, 3639–3652.

CAS | PubMed | Web of Science® | Google Scholar

15 A. Castro, Y. Arlot-Bonnemains, S. Vigneron, J. C. Labbe, C. Prigent, T. Lorca, *EMBO Rep.* 2002, **3**, 457–462.

CAS | PubMed | Web of Science® | Google Scholar

16 P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* 2008, **41**, 40–49.

CAS | PubMed | Web of Science® | Google Scholar

17 M. Shiri, M. Heydari, V. Zadsirjan, *Tetrahedron* 2017, **73**, 2116–2122.

CAS | Web of Science® | Google Scholar

18

18a A. S. Ivanov, N. Z. Tugusheva, V. G. Granik, *Russ. Chem. Rev.* 2005, **74**, 915–936;

CAS | Google Scholar

18b G. Roma, G. Grossi, M. D. Braccio, D. Piras, V. Ballabeni, M. Tognolini, S. Bertoni, E. Barocelli, *Eur. J. Med. Chem.* 2008, **43**, 1665–1680.

CAS | PubMed | Web of Science® | Google Scholar

19 G. Roma, M. D. Braccio, G. Grossi, F. Mattioli, M. Ghia, *Eur. J. Med. Chem.* 2000, **35**, 1021–1035.

CAS | PubMed | Web of Science® | Google Scholar

20 M. Atanasova, S. Ilieva, B. Galabov, *Eur. J. Med. Chem.* 2007, **42**, 1184–1192.

CAS | PubMed | Web of Science® | Google Scholar

21 Y. Kuramoto, Y. Ohshita, J. Yoshida, A. Yazaki, M. Shiro, T. Koike, *J. Med. Chem.* 2003, **46**, 1905–1917.

CAS | PubMed | Web of Science® | Google Scholar

22 K. Chen, S. C. Kuo, M. C. Hsieh, A. Mauger, C. M. Lin, E. Hamel, K. H. Lee, *J. Med. Chem.* 1997, **40**, 2266–2275.

CAS | PubMed | Web of Science® | Google Scholar

23 P. L. Ferrarini, C. Mori, M. Badawneh, V. Calderone, R. Greco, C. Manera, A. Martinelli, P. Nieri, G. Saccomanni, *Eur. J. Med. Chem.* 2000, **35**, 815–826.

CAS | PubMed | Web of Science® | Google Scholar

24 M. H. Sherlock, J. J. Kaminski, W. C. Tom, J. F. Lee, S. C. Wong, W. Kreutner, R. W. Bryant, A. T. Mcphail, *J. Med. Chem.* 1988, **31**, 2108–2121.

CAS | PubMed | Web of Science® | Google Scholar

25 G. Barlin, W. Tan, *Aust. J. Chem.* 1984, **37**, 1065–1073.

CAS | Web of Science® | Google Scholar

26 H. Li, W. Fu, L. Li, X. Gan, W. Mu, W. Chen, X Duan, H. Song, *Org. Lett.* 2010, **12**, 2924–2927.

CAS | PubMed | Web of Science® | Google Scholar

27

27a K. Ghosh, T. Sen, R. Froehlich, *Tetrahedron Lett.* 2007, **48**, 2935–2938;

CAS | Web of Science® | Google Scholar

27b Z. Li, M. Yu, L. Zhang, M. Yu, J. Liu, L. Wei, H. A. Zhang, *Chem. Commun.* 2010, **46**, 7169–7171.

CAS | PubMed | Web of Science® | Google Scholar

28

28a A. V. Chate, A. A. Redlawar, G. M. Bondle, A. P. Sarkate, S. V. Tiwari, D. K. Lokwani, *New J. Chem.* 2019, **43**, 9002–9011;

CAS | Web of Science® | Google Scholar

28b A. V. Chate, R. M. Dongre, M. K. Khaire, G. M. Bondle, J. N. Sangshetti, M. Damale, *Res. Chem. Intermed.* 2018, **44**, 6119–6136;

CAS | Web of Science® | Google Scholar

28c A. V. Chate, S. P. Kamdi, A. N. Bhagat, C. K. Jadhav, A. Nipte, A. P. Sarkate, S. V. Tiwari, C. H. Gill, *J. Heterocycl. Chem.* 2018, **55**, 2297–2302;

CAS | Web of Science® | Google Scholar

28d A. V. Chate, G. Y. Shinde, A. P. Sarkate, S. V. Tiwari, C. H. Gill, *Res. Chem. Intermed.* 2018, **44(7)**, 4029–4043.

Web of Science® | Google Scholar

29

29a B. Yan, Y. Liu, *Org. Lett.* 2007, **9**, 4323–4326;

CAS | PubMed | Web of Science® | Google Scholar

29b M. Misra, S. K. V. P. Pandey, V. P. Pandey, J. Pandey, R. Tripathi, R. P. Tripathi, *Bioorg. Med. Chem.* 2009, **17**, 625–633.

CAS | PubMed | Web of Science® | Google Scholar

30 B. Datta, M. B. Madhusudana Reddy, M. A. Pasha, *Synth. Commun.* 2011, **41**, 2331–2336.

CAS | Web of Science® | Google Scholar

31 L. Fu, W. Lin, M. H. Hu, X. C. Liu, Z. B. Huang, D. Q. Shi, *ACS Comb. Sci.* 2014, **16**, 238–243.

CAS | PubMed | Web of Science® | Google Scholar

32 R. A. Friesner, R. B. Murphy, M. P. Repasky, L. L. Frye, J. R. Greenwood, T. A. Halgren, P. C. Sanschagrin, D. T. Mainz, *J. Med. Chem.* 2006, **49**, 6177–6196.

CAS | PubMed | Web of Science® | Google Scholar

33 S. V. Tiwari, J. Seijas, M. P. Vazquez-Tato, A. P. Sarkate, D. K. Lokwani, A. G. Nikalje, *Molecules* 2016, 21, 894–916.

Google Scholar

34 M. A. Kashem, R. M. Nelson, J. D. Yingling, S. S. Pullen, A. S. Prokopowicz 3rd, J. W. Jones, J. P. Wolak, G. R. Rogers, M. M. Morelock, R. J. Snow, C. A. Homon, S. Jakes *J. Biomol. Screening* 2007, **12(1)**, 70–83.

Google Scholar