



**Design and Synthesis of Novel  
2-Substituted-Benzyl-5-(2-Methylbenzofuran-3-Yl)-2H-Tetrazoles:  
Anti-Proliferative Activity**

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**Abstract**—A new series of 2,5-regioselective benzofuran-tetrazole hybrids (**XIIIa–XIIIp**) were synthesised from 2H-chromene-3-carbonitriles (**IXa**), (**IXb**) in multi steps approach under mild reaction conditions in good yields and evaluated their anti-proliferative activity against HCT116 and Miapaca2 cell lines. Wherein compounds (**XIIIe**) ( $IC_{50}$ : 3.19  $\mu$ M) and (**XIIIm**) ( $IC_{50}$ : 2.25  $\mu$ M) were displayed highest anti-proliferative activity in both cell lines. Molecular docking and SAR studies revealed the *in vitro* results with target Proto-oncogene tyrosine kinase Src protein.

**Keywords:** benzofuran, tetrazoles, anti-proliferative activity, molecular docking, SAR studies

REFERENCES

1. Majid, M.H., Vahideh, Z., Hoda, H., Parvin, H.T.A., *RSC Adv.*, 2017, vol. 7, pp. 24470–24521. doi 10.1039/c7ra03551a
2. Dawson, P., Juffry, J.O., Moffatt, J.D., Daniju, Y., Dutta, N., Ramsey, J., Davidson, C., *Progress in neuro-psychopharmacology & biological psychiatry.*, 2014, vol. 48, pp. 57–63. doi 10.1016/j.pnpbp.2013.08.013
3. Hena, K., Shamsuzzaman., *Eur. J. Med. Chem.*, 2015, vol. 97, pp. 483–504. doi 10.1016/j.ejmech.2014.11.039
4. Koca, M., Servi, S., Kirilmis, C., Ahmedzade, M., Kazaz, C., Ozbek, B., Otuk, G., *Eur. J. Med. Chem.*, 2005, vol. 40, pp. 1351–1358. doi 10.1016/j.ejmech.2005.07.004
5. Rao, G.K., Venugopala, K. N., Pai, P. N. S., *J. Pharmacol. Toxicol.*, 2007, vol. 2, no. 5, pp. 481–488. doi 10.3923/jpt.2007.481.488
6. Dawood, K.M., Abdel, G.H., Rageb, E.A., Ellithy, M., Mohamed, H.A., *Bioorg. Med. Chem.*, 2006, vol. 14, pp. 3672–3680. doi 10.1016/j.bmc.2006.01.033
7. Tsujihara, K., Hongu, M., Saito, K., Kawanishi, H., Kuriyama, K., Matsumoto, M., Oku, A., Ueta, K., Tsuda, M., Saito, A., *J. Med. Chem.*, 1999, vol. 42, pp. 5311–5324. doi 10.1021/jm990175n
8. Navarro, E., Alonso, S.J., Trujillo, J., Jorge, E., Perez, C., *J. Nat. Prod.*, 2001, vol. 64, pp. 134–135. doi 10.1021/np9904861

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9. Ikeda, R., Nagao, T., Okabe, H., Nakano, Y., Matsunaga, H., Katano, M., Mori, M., *Chem. Pharm. Bull.*, 1998, vol. 46, no. 5, pp. 871–874. doi 10.1248/cpb.46.871
10. Liao, Y., Kozikowski, A.P., Guidotti, A., Costa, E., *Bioorg. Med. Chem. Lett.*, 1988, vol. 8, pp. 2099–2102. doi 10.1016/S0960-894X(98)00374-6
11. Banskota, A.H., Tezuka, Y., Midorikawa, K., Matsushige, K., Kadota, S., *J. Nat. Prod.*, 2000, vol. 63, pp. 1277–1279. doi 10.1021/np000143z
12. Radadiya, A., Shah, A., *Eur. J. Med. Chem.*, 2015, vol. 97, pp. 356–376. doi 10.1016/j.ejmech.2015.01.021
13. Delost, M.D., Smith, D.T., Anderson, B.J., Njardarson, J.T., *J. Med. Chem.*, 2018, vol. 61, pp. 10996–11020. doi 10.1021/acs.jmedchem.8b00876
14. Li, X.Y., He, B.F., Luo, H.J., Huang, N.Y., Deng, W.Q., *Bioorg. Med. Chem. Lett.*, 2013, vol. 23, pp. 4617–4621. doi 10.1016/j.bmcl.2013.06.022
15. Salome, C., Ribeiro, N., Chavagnan, T., Thuaud, F., Serova, M., Gramont, A., Faivre, S., Raymond, E., Desaubry, L., *Eur. J. Med. Chem.*, 2014, vol. 81, pp. 181–191. doi 10.1016/j.ejmech.2014.05.014
16. Wan, W.C., Chen, W., Liu, L.X., Li, Y., Yang, L.J., Deng, X.Y., Zhang, H.B., Yang, X.D., *Med. Chem. Res.*, 2014, vol. 23, pp. 1599–1611. doi 10.1007/s00044-013-0760-8
17. Hranjec, M., Sovic, I., Ratkaj, I., Pavlovic, G., Ilic, N., Valjalo, L., Pavelic, K., Pavelic, S.K., Zamola, G.K., *Eur. J. Med. Chem.*, 2013, vol. 59, pp. 111–119. doi 10.1016/j.ejmech.2012.11.009
18. Wei, C.X., Bian, M., Gong, G.H., *Molecules*, 2015, vol. 20, pp. 5528–5553. doi 10.3390/molecules20045528
19. Frija, L.M.T., Ismael, A., Cristiano, M.L.S., *Molecules*, 2010, vol. 15, , pp. 3757–3774. doi 10.3390/molecules15053757
20. Myznikov, L.V., Hrabalek, A., Koldobskii, G.I., *Chem. Heterocycl. Compd.*, 2007, vol. 43, pp. 1–9. doi 10.1007/s10593-007-0001-5
21. Feng, L., Liu, Y., Zou, J., Zhang, D., Yao, Z., *Dyes. Pigm.*, 2006, vol. 68, pp. 211–216. doi 10.1016/j.dyepig.2004.07.017
22. Song, W., Wang, Y., Qu, J., Madden, M.M., Lin, Q., *Angew. Chem. Int. Ed.*, 2008, vol. 47, pp. 2832–2835. doi 10.1002/anie.200705805
23. Shmatova, O.I., Nenajdenko, V.G., *J. Org. Chem.*, 2013, vol. 78, pp. 9214–9222. doi 10.1021/jo401428q
24. Staniszewska, M., Gizinska, M., Mikulak, E., Adamus, K., Koronkiewicz, M., Lukowska, E.C., *Eur. J. Med. Chem.*, 2018, vol. 145, pp. 124–139. doi 10.1016/j.ejmech.2017.11.089
25. Popova, E.A., Protas, A.V., Trifonov, P.E., *Anti-Cancer Agents Med. Chem.*, 2017, vol. 17, pp. 1856–1868. doi 10.2174/1871520617666170327143148
26. Qian, A.R., Zheng, Y.Z., Wang, R.L., Wei, J.H., Cui, Y.M., Cao, X.F., Yang, Y.S., *Bioorg. Med. Chem. Lett.*, 2018, vol. 28, pp. 344–350. doi 10.1016/j.bmcl.2017.12.040
27. Tukulula, M., Sharma, R.K., Meurillon, M., Mahajan, A., Naran, K., Warner, D., Huang, J., Mekonnen, B., Chibale, K., *ACS. Med. Chem. Lett.*, 2013, vol. 4, no. 1, pp. 128–131. doi 10.1021/ml300362a
28. Elavarasan, T., Sivakumar, D., Gopalakrishnan, M., *J. Pharm. Res.*, 2018, vol. 12, no. 5, pp. 749–757.
29. Yeung, K.S., Qiu, Z., Yang, Z., D'Arienzo, C.J., Browning, M.R., Hansel, S., Huang, X.S., Eggers, B.J., Riccardi, K., Lin, P.F., Meanwell, N.A., Kadow, J.F., *Bioorg. Med. Chem. Lett.*, 2013, vol. 23, no. 1, pp. 209–212. doi 10.1016/j.bmcl.2012.10.125
30. Lamie, P.F., Philoppe, J.N., Azouz, A.A., Safwat, N.M., *J. Enzym. Inhib. Med. Chem.*, 2017, vol. 32, pp. 805–820. doi 10.1080/14756366.2017.1326110
31. Romagnoli, R., Baraldi, P.G., Salvador, M.K., Preti, D., Tabrizi, M.A., Brancale, A., Fu, X. H., Li, J., Zhang, S.Z., Hamel, E., Bortolozzi, R., Basso, G., Viola, G., *J. Med. Chem.*, 2012, vol. 55, pp. 475–488. doi 10.1021/jm2013979
32. Neochoritis, C.G., Zhao, T., Dömling, A., *Chem. Rev.*, 2019, vol. 119, no. 3, pp. 1970–2042. doi 10.1021/acs.chemrev.8b00564

33. Kumar, K.S., Daniel, V., Shanker, S.K., Rao, C.P., Krupadanam, G.L.D., *Med. Chem. Res.*, 2016, vol. 25, no. 10, pp. 2179–2186. doi 10.1007/s00044-016-1651-6
34. Gawande, S.D., Raihan, M.J., Zanwar, M.R., Veerababurao, K., Janreddy, D., Kuo, C.W., Chen, M.L., Kuo, T.S., Yao, C.F., *Tetrahedron*, 2013, vol. 69, pp. 1841–1848. doi 10.1016/j.tet.2012.12.062
35. Yeatman, T.J., *Nat. Rev. Cancer.*, 2004, vol. 4, pp. 470–480. doi 10.1038/nrc1366
36. Dalgarno, D., Stehle, T., Narula, S., Schelling, P., Schravendijk, M.R., Adams, S., Andrade, L., Keats, J., Ram, M., Jin, L., Grossman, T., MacNeil, I., Metcalf, C., Shakespeare, W., Wang, Y., Keenan, T., Sundaramoorthi, R., Bohacek, R., Weigle, M., Sawyer, T., *Chem. Biol. Drug. Des.*, 2006, vol. 67, pp. 46–57. doi 10.1111/j.1747-0285.2005.00316.x
37. Robert, W.H., *Nature*, 1975, vol. 258, pp. 487–490. doi 10.1038/258487a0
38. Mosmann, T., *J. Immun. Methods*, 1983, vol. 65, no. 1–2, pp. 55–63. doi 10.1016/0022-1759(83)90303-4
39. CLCbio (2012) Molegro Virtual Docker User Manual. MVD (2012.5.5) for Windows, Linux, and Mac OS X, Molegro – A CLC Bio Company.