In the present work, a novel series of B-RAF inhibitors having imidazo[2,1-b]oxazole scaffold was designed and synthesized based on the structures of the well-known BRAF inhibitors and on our previous work. The final compounds were tested over A375 and SKMEL28 cell lines to determine the primary cytotoxic activity of these compounds using sorafenib as standard. Compounds 11r, 11q, 11u, 11o, 11e and 11c exhibited higher cellular activity compared to sorafenib. In addition, the final target compounds were screened for their anticancer activity by the National Cancer Institute 60 cell lines assay. Compounds 11v and 11u were the most potent compounds with percent inhibition reached 95.99% for 11v and 87.03% for 11u over K562 cell line. Compound 11v was selected for 5 doses test mode. The RAF inhibitory activities of 11a, 11c, 11e, 11i, 11o, 11q, 11r, 11u, and 11v were determined. Moreover, the molecular docking simulation of the synthesized compounds was performed with the B-RAF protein kinase domain (PDB code: 4FK3) in order to investigate the binding modes of the tested compounds with the target enzyme active site.