Bioorganic & Medicinal Chemistry Letters 25 (2015) 3120–3124

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Molecular modeling based approach, synthesis, and cytotoxic activity of novel benzoin derivatives targeting phosphoinostide 3-kinase (PI3Kα)

Dima A. Sabbah [a,*], Musaab Saada [a], Reema Abu Khalaf [a], Sanaa Bardaweel [b], Kamal Sweidan [c], Tariq Al-Qirim [a], Amani Al-Zughier [a], Heba Abdel Halim [d], Ghassan Abu Sheikha [a]

[a] Department of Pharmacy, Faculty of Pharmacy, Al-Zaytoonah University of Jordan, P.O. Box 130, Amman 11733, Jordan
[b] Department of Pharmaceutical Sciences, Faculty of Pharmacy, The University of Jordan, Amman 11942, Jordan
[c] Department of Chemistry, The University of Jordan, Amman 11942, Jordan
[d] Faculty of Pharmacy and Medical Sciences, University of Petra, P.O. Box 961343, Amman, Jordan

ARTICLE INFO

Article history:
Received 3 April 2015
Revised 24 May 2015
Accepted 2 June 2015
Available online 11 June 2015

Keywords:
PI3Kα
Cancer
Docking
HCT116
Benzoin

ABSTRACT

The oncogenic potential of phosphatidylinositol 3-kinase (PI3Kα) has made it an attractive target for anticancer drug design. In this work, we describe our efforts to optimize the lead PI3Kα inhibitor 2-hydroxy-1,2-diphenylethanone (benzoin). A series of 2-oxo-1,2-diphenylethyl benzoate analogs were identified as potential PI3Kα inhibitors. Docking studies confirmed that the aromatic interaction is mediating ligand/protein complex formation and identified Lys802 and Val851 as H-bonding key residues. Our biological data in human colon carcinoma HCT116 showed that the structure analogs inhibited cell proliferation and induced apoptosis.

Phosphatidylinositol 3-kinases (PI3Ks) are lipid kinases that phosphorylate phosphatidylinositol 4,5-biphosphate (PIP_2) generating 3,4,5-triphosphate (PIP_3).[1] PI3Ks are negatively regulated by the phosphatase and tensin homolog protein (PTEN), which dephosphorylates PIP_3.[2,3] PIP_3 is an important second messenger that regulates the activities of PI3K downstream effector protein kinase B (PKB), also known as AKT.[4]

The activation of PI3K/AKT signaling cascade induces cell proliferation, growth, angiogenesis, and metastasis. Aberrant PI3K/AKT pathway has been involved in a number of human cancers.[4] PI3Ks are grouped into three classes based on their primary structure and substrate specificity. Among them, class IA PI3Kα (coding gene PIK3CA) is amplified, overexpressed, and mutated in several human tumors.[5–9] PIK3CA mutations and amplification have been identified in an array of cancers. PI3Kα mutations have been detected in colon, breast, brain, and endometrial tumors.[10,11] Two major classes of mutations are located in the helical (E542K and E545K) and kinase (H1047R) domains. These 'hot-spot' mutations induce PI3Kα in vitro kinase activity resulting in 'gain-of-function'.[5,12]

Therefore, selective inhibitors targeting mutant PI3Kα might afford an effective therapeutic protocol.[11,13]

Due to the oncogenic potential of PI3Kα and its negative regulator PTEN, PI3Kα has emerged as an attractive target for anticancer drug design.[14,15]

Several chemical scaffolds have been designed and synthesized targeting PI3Kα[16–30] and some of these have been investigated in clinical trials.[31–34] We previously reported the pharmacophore features for PI3Kα inhibitors and identified potential inhibitors.[35] Novel *N*-Phenyl-4-hydroxy-2-quinolone-3-carboxamides were synthesized as selective H1047R PI3Kα inhibitors.[36] Recruiting ligand-based pharmacophore modeling for PI3Kα inhibitors and database searching against the National Cancer Institute (NCI) compound database[37] identified NSC 8082 (benzoin) (**1**) as a hit (Fig. 1).[35]

Fortunately, benzoin (**1**) and its structure analog 4,4′-dimethoxybenzoin (*p*-anisoin) (**2**) are commercially available. Both **1** and **2** fit the pharmacophore features of PI3Kα inhibitor as shown in Figure 2. Thus, we hypothesized that functionalization of the backbones of **1** and **2** would generate promising inhibitors targeting PI3Kα. This work describes our efforts to functionalize **1** and **2** employing structure-based drug design and molecular docking approach.

* Corresponding author. Tel.: +962 64291511x296; fax: +962 64291432.
E-mail address: dima_sabbah@yahoo.com (D.A. Sabbah).

http://dx.doi.org/10.1016/j.bmcl.2015.06.011
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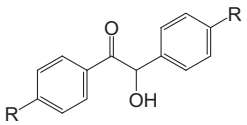


1, R = H
2, R = OCH_3

Figure 1. Chemical structures of **1** and **2**.

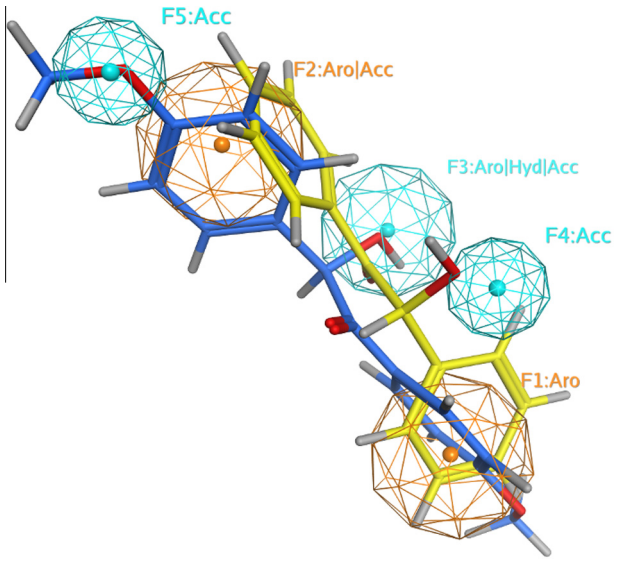
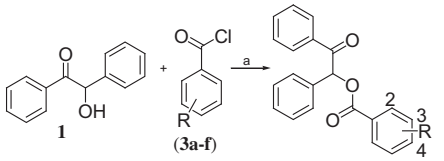
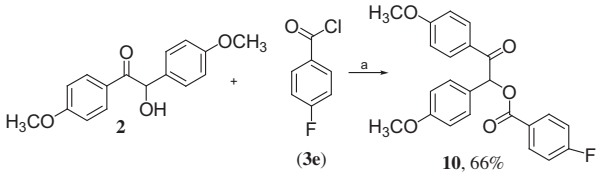


Figure 2. PI3Kα pharmacophore model with **1** (C atoms in yellow) and **2** (C atoms in blue). Aro stands for aromatic rings; Acc for H-bond acceptor; and Hyd for hydrophobic groups. Picture made by MOE.[38]



4, R = H, 65%
5, R = (*p*-NO_2), 4-NO_2, 73%
6, R = (*o*-F), 2-F, 60%
7, R = (*m*-F), 3-F, 52%
8, R = (*p*-F), 4-F, 76%
9, R = (*p*-Cl), 4-Cl, 71%



Scheme 1. Condition: (a) THF, Et_3N, 50 °C, 24 h.

Table 1
Growth inhibition IC_{50} (mM) of HCT116 cell line after 24 h exposure time

Compounds	HCT-116
1	2.12
2	1.17
4	2.66
5	0.88
6	0.91
7	0.97
8	1.29
9	0.73
10	2.82

Standard deviation (SD) never exceeded 5%.

The target products **4**–**9** were prepared by reacting benzoin (**1**) with substituted benzoyl chlorides (**3a**–**f**), in a one pot reaction, in a dry aprotic polar solvent (tetrahydrofuran) under heating condition via a nucleophilic substitution mechanism (Scheme 1). Triethylamine (Et_3N) was added to the reaction mixture as a catalyst and an acid scavenger; in a similar manner, 4-fluorobenzoyl chloride (**3e**) was reacted with *p*-anisoin (**2**) to produce **10**. The chemical structure of the prepared compounds was determined using spectroscopic approaches; FT-IR and NMR (^1H and ^{13}C).

In order to examine their antiproliferative activities, we assessed the growth inhibition in the colon cancer cell line (HCT-116) induced by **1**, **2** and **4**–**10** (Table 1).

HCT116 is a highly malignant colon carcinoma cell line harboring both wild-type and mutant (H1047R) PI3Kα that was created from a primary tumor tissue culture.[39]

The tested compounds inhibited PI3Kα activity in HCT-116 cell line. Interestingly, **5**, **6**, **7**, and **9** exerted a relatively high potency in HCT116 cell line (IC_{50} <1 mM). Additionally, **2** and **8** with IC_{50s} 1.17 and 1.29 mM showed comparable potency. A two-fold increase in IC_{50s} suggests a weak inhibitor such as **1**, **4**, and **10**.

This result suggests that derivative with *p*-substituent is more favored for –Cl and –NO_2 functionalities. This might infer that the size and electron-withdrawing effects of the *p*-substituent are significant to attain potent inhibition. The size of –Cl and –NO_2 is bigger compared to that of –F (H isostere). The electron-withdrawing effect of –NO_2 and –F is higher than that of –Cl. Substitution is favored for –F at *o*- or *m*-position. This implies that the size and electron-withdrawing effects of substituents at *p*-position should be considered to induce higher potency.

Compound **10** having *p*-methoxy groups on benzoin scaffold showed to be the least potent compound. This indicates that harboring two methoxy groups at *p*-position is not preferred due to steric clash as well as electron-donating effect. Surprisingly, the parent compound **2** showed similar potency to that of **8**. This implies that the steric effect (size, shape, and volume) of the verified molecules determines their potency. Also, the activity of **1**, **4**, and **10** confirms that both the steric and substituent effects should be balanced to attain higher potency. The fact that HCT116 contains both alleles (wild-type and mutant H1047R PI3Kα) has hindered our efforts to extrapolate more reasons for our results. Our future research will aim to knockout either allele to harvest only one specific gene in HCT116 cell line.

In order to determine possible pathways responsible for the observed growth inhibition, caspase-3 enzyme activity was measured via the caspase-3 colorimetric assay. Activation of the caspase-3 pathway is a hallmark of apoptosis[40,41] and can be utilized in cellular assays to appraise activators and inhibitors of the 'death cascade'. To determine the apoptotic effects of the examined compounds on HCT116 cells, cells were incubated with 700 μM of each compound for either 24 or 48 h and changes in caspase-3 enzyme activities were analyzed. The results demonstrate that there is a significant increase in caspase-3 activity in response to 24 h treatment for each compound. Indeed, lengthening of the treatment period results in further increase in caspase-3 activity relative to the untreated cells control (Fig. 3).

Interestingly, similar pattern of efficacy was exhibited in the apoptosis assay for *p*- (**5**, **8**, and **9**) as well as *o*- and *m*-substituents (**6** and **7**), and the parent structure **2**. The consistency of the results of both bioassays provides a clue for the significance of this scaffold as a potential antitumor agent.

In order to investigate the structural basis of binding of the verified inhibitors in the active domain of PI3Kα, we carried out docking studies employing Glide[42,43] dock approach against the

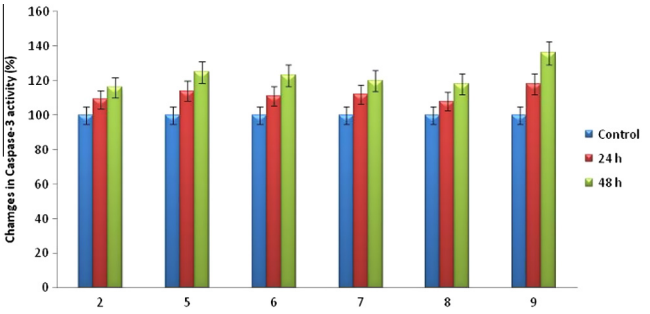


Figure 3. Effects of compounds treatment on caspase-3 activity in HCT cells after 24 and 48 h. The results are the means of two independent experiments. P <0.05 was considered significant.

wild-type PI3Kα (PDB ID: 2RD0).[7] Our Glide docking data show that these compounds occupy the kinase domain of PI3Kα (Fig. 4).

Most of these compounds tend to form H-bond with Lys802 (NH_2 side chain) and Val851 (NH backbone) (Table 2). The significance of these binding residues has been validated by other computational[35,36,44–46] and experimental studies.[12]

The low docking score of **5** might be due to ion-dipole or ion-induced dipole interaction with Tyr836 (Fig. 5). Contrary to structures having hydrophobic moiety attached on *p*-position (**2**, **9**, and **10**) exhibited comparable good binding affinity.

Notably, **8** tailored with *p*-F substituent showed comparable binding affinity to that of (**2**, **9**, and **10**). This might be contributed

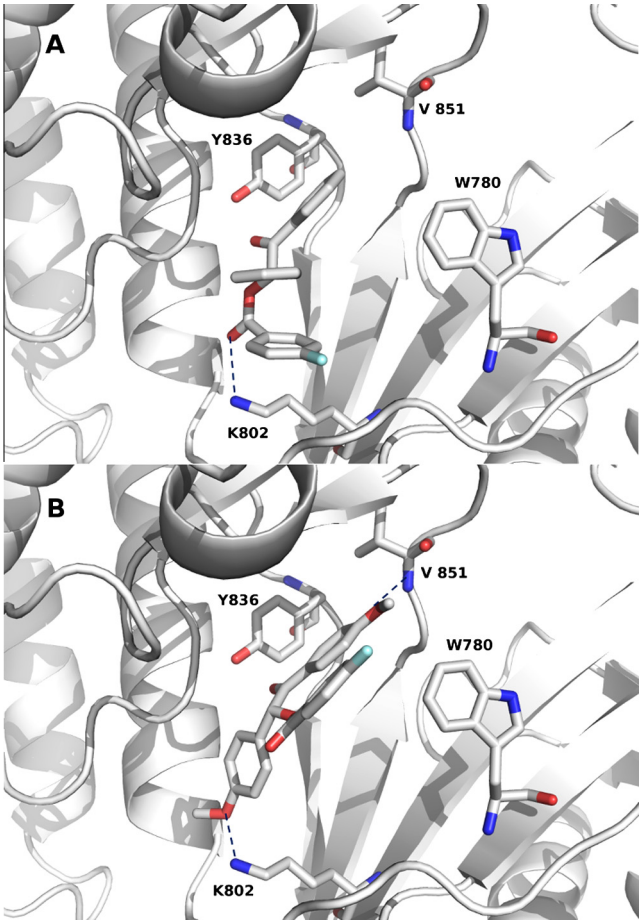


Fig. 4. Binding conformation of **8** (A) and **10** (B) in PI3Kα (PDB ID: 2RD0) kinase domain. H-Bond is depicted in blue dotted line. H-atoms are hidden for clarity. Picture made by PYMOL.

Table 2
Docking scores (kcal/mol) and H-bond interactions between compounds and PI3Kα (PDB ID: 2RD0)

Compounds	Docking score (kcal/mol)	Binding residues
1	−4.71	NA
2	−7.28	V851
4	−6.25	K802
5	−4.58	V851
6	−5.82	NA
7	−5.08	NA
8	−6.13	K802
9	−7.12	NA
10	−6.48	K802, V851

NA stands for not available.

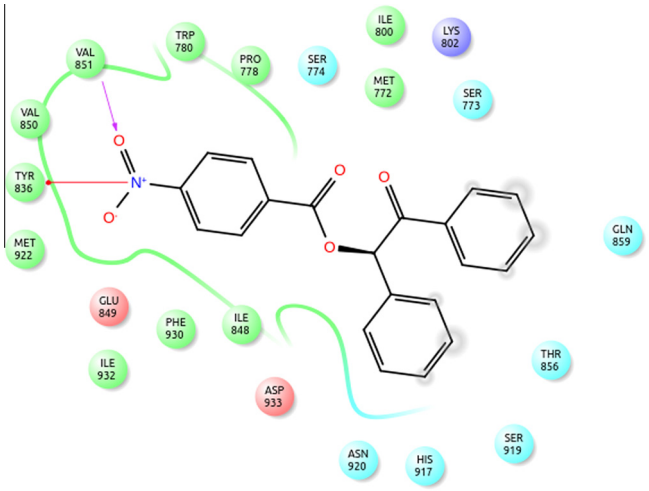


Figure 5. Protein/ligand interactions with **5**. Hydrophobic residues are colored green, acidic residues are red, basic residues are purple, and polar residues are light blue. Picture made by MAESTRO.

to the size of F (H isostere) and low hydrophobicity character of F compared to that of Cl (higher atomic weight). This finding suggests that *p*-substituent having hydrophobic and electron-withdrawing properties are essential to elicit an activity. Additionally, *p*-substituted derivatives adopt a planar pose in the binding domain (Figs. 1S and 2S), which explains the *o*- and *m*-substituents' corresponding binding affinity. Comparing the binding affinity of **1** and **4** infers that the ligand's size is critical to induce an activity. All together, *p*-attachment and ligand's size are both required to attain favorable binding affinity. Figure 3S (Supporting information) shows that the theoretical docking scores (kcal/mol) are positively correlated (R^2 = 0.76) with the experimentally verified IC_{50}s, rationalizing that docking scores could be recruited to predict ligand binding affinities.

The aromatic (π-stacking) and hydrophobic interactions were found to drive the ligand/receptor complex formation (Fig. 5). PI3Kα kinase domain is enclosed with hydrophobic and aromatic residues; particularly Met772, Trp780, Ile800, Leu807, Tyr836, Ile848, Val850, Val851, Met922, Phe930, Ile932, and Phe934.

To evaluate the performance of Glide dock program, we compared the docked pose of 1LT in PI3Kα (PDB ID: 4JPS)[29] to its native conformation in the crystal structure. Figure 6 shows the superposition of the Glide-generated 1LT pose and the native conformation in 4JPS. The RMSD for heavy atoms of 1LT between Glide-generated docked poses and the native poses was 0.55 Å. This indicates that Glide dock is capable to identify the native poses in crystal structures and can successfully predict the ligand binding conformation. Moreover, the verified compounds satisfy the same

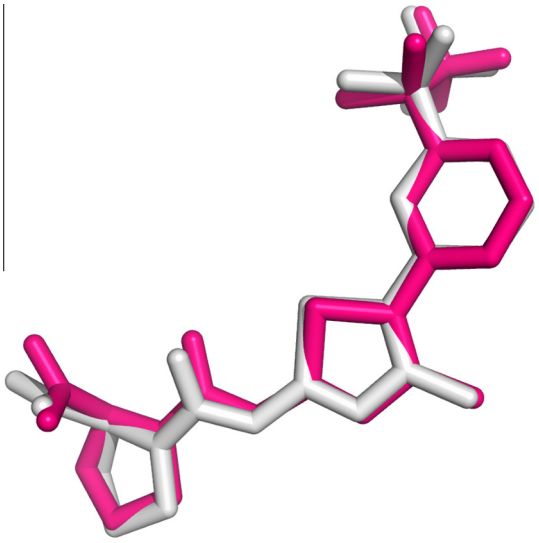


Figure 6. Superposition of the Glide-docked 1LT pose and its native conformation in 4JPS. The native coordinates are pink colored and the docked pose is grey colored. Picture made by PYMOL.

pharmacophoric features of PI3Kα inhibitors inferring that these compounds occupy the kinase domain in a similar manner to those of reported inhibitors (Fig. 7).

In conclusion, PI3Kα is a promising target for anticancer drug design. In our effort to develop novel PI3Kα inhibitors, we recruited structure-based design and molecular docking to optimize the lead PI3Kα inhibitor (NSC 8082) 2-hydroxy-1,2-diphenylethanone (benzoin). We identified a series of 2-oxo-1,2-diphenylethyl benzoate as potential PI3Kα inhibitors.

Glide docking approach identified Lys802 and Val851 as H-bonding key residues and confirmed that the aromatic interaction is the driving force for ligand/receptor complex formation. The biological testing data showed that the synthesized molecules inhibited PI3Kα activity in human colon adenocarcinoma HCT116 cell line. Substituted benzoate derivatives exhibited higher inhibitory activity compared to those of non-substituted core structures.

Potent inhibitory activity was exhibited for *p*-chloro and *p*-nitro substituent indicating that hydrophobic and/or hydrogen bond-acceptor mediate(s) drug-receptor interaction. Tailoring the benzoate with fluoro moiety at *o*-, *m*-, and *p*-position suggested that small size functionality is favored at *o*- or *m*-sites. Non-substituted benzoate showed lower activity implying that tailored benzoate is preferred for activity. Moreover, these derivatives induced apoptosis and cell cycle arrest through caspase-3.

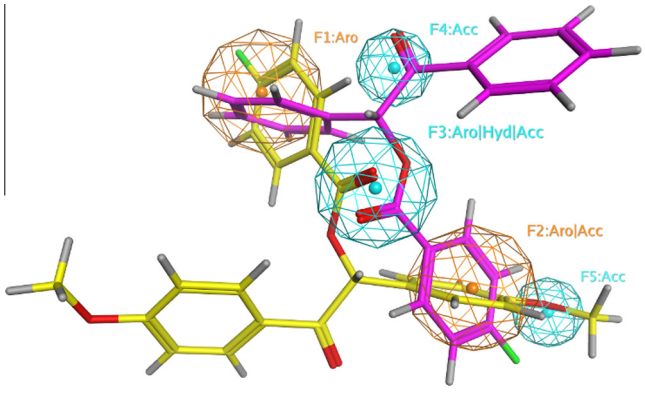


Figure 7. PI3Kα pharmacophore model with **8** (C atoms in purple) and **10** (C atoms in yellow).

Interestingly, compounds with benzoin core nucleus were previously reported as anticancer agent against Ehrlich ascites carcinoma (EAC) xenograft model in mice.[47,48] Attaching nitro at *o*- or *p*-position or hydroxyl group at *o*-position enhances the anticancer activity.[47] Also, these derivatives revitalized blood cells count toward normal, extended life-span, and decreased tumor size effectively.[47] Additionally, diversified derivatives of benzoin showed pronounced broad spectrum antimicrobial,[49–52] analgesic and anti-inflammatory,[53] and antidepressant activity in mice model.[54] Our future goal is to optimize this scaffold to enhance the antitumor activity and selectivity against an array of kinases.

Acknowledgements

This work was fully supported by the Deanship of Scientific Research and Graduate Studies at Al-Zaytoonah University of Jordan. The authors acknowledge the Chemistry Department at the University of Jordan for use of the NMR facility. We are grateful to the College of Pharmacy at the University of Jordan for use of cell culture laboratory and equipment. We thank Dr. Ma'mon Hatmal at the Faculty of Allied Health Sciences in Hashemite University for granting us the human colon carcinoma (HCT116) cell line.

Supplementary data

Supplementary data (detailed experimental methods, computational approaches, NMR and FT-IR characterization results, as well as additional figures) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.06.011.

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