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SYNTHESIS, STRUCTURAL COMMENTARY, SUPRAMOLECULAR ARCHITECTURE AND MOLECULAR DOCKING INVESTIGATIONS OF A NOVEL THIOPHENE-FUSED 1,2,3,4-TETRAHYDROISOQUINOLINE DERIVATIVE AS A POTENT ANTI-CANCER AGENT*

S. Murugavel[1], N. Manikandan[2], C. Ravikumar[3], K. Naveen[4], and P. T. Perumal[4]**

The 1,2,3,4-tetrahydroisoquinoline derivative compound fused with thiophene (BDTTIQ) is synthesized by the slow evaporation solution growth method and characterized by SCXRD, ^{1}H and ^{13}C NMR techniques. In the synthesized compound, the tetrahydroisoquinoline fragment of BDTTIQ is almost in the *half-chair* conformation. A 3D supramolecular architecture is attained by intermolecular C–H…O and C–H…π interactions in the crystal structure. Molecular docking simulations are carried out to examine the inhibitory nature of the synthesized compound BDTTIQ against ARK1C3 protein.

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INTRODUCTION

Structures containing 1,2,3,4-tetrahydroisoquinoline display a wide spectrum of pharmacological activities, particularly, the anticancer activity [1-3]. Aldoketoreducatace 1C3(AKR1C3) not only catalyzes the conversion as less potent hormones to more potent ones, which can lead to a nuclear receptor activation and tumor progression, but it also seems to sense as a unique AR-selective co-activator that promotes prostate cancer cell growth [4, 5]. ARK1C3 is overexpressed in a number of cancers, particularly, in the prostate and mammary gland where it is responsible for the production of a series of growth stimulatory steroid hormones. Thus, ARK1C3 has recently been regarded as an attractive therapeutic target for treating various types of cancer. Doxorubicin is one of the standard drugs used for chemotherapy in curing breast cancer and other types of cancers [6, 7]. Doxorubicin is administrated by the intravenous mode that has regular side effects. However,

[1]Department of Physics, Thanthai Periyar Government Institute of Technology, Vellore, Tamilnadu, India; **smurugavel27@gmail.com. [2]Department of Physics, Bharathidasan Engineering College, Vellore, India. [3]Department of Physics, Thanthai Periyar EVR Government Polytechnic College, Vellore, India. [4]Organic Chemistry Division, CSIR – Central Leather Research Institute, Adyar, Chennai, India. Original article submitted February 4, 2019; revised February 4, 2019; accepted February 13, 2019.

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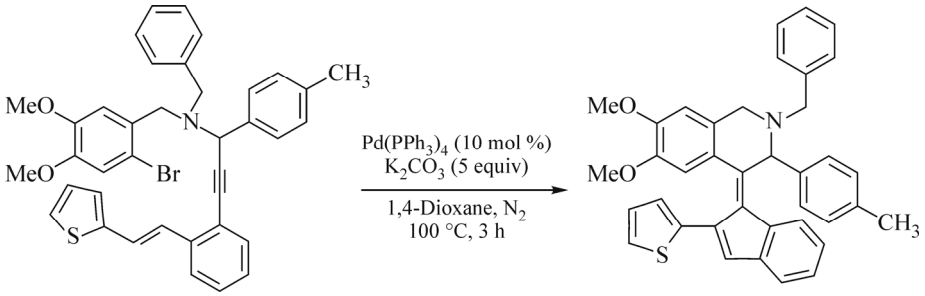
recently, a series of N-benzyl sulfonyl-1,2,3,4-tetrahydroisoquinoline-based triazoles and a series of 3-(3,4-dihydroisoquinoline-2(1H)-ylsulfonyl) benzoic acids were identified as novel inhibitors of AKR1C3 [8, 9]. In this paper, the compound (*E*)-2-benzyl-6,7-dimethoxy-4-(2-(thiophen-2-yl)-1*H*-inden-1-ylidene)-3-*p*-tolyl-1,2,3,4-tetrahydroisoquinoline (BDTTIQ) has been synthesized and its crystal structure has been investigated. Drug-likeness of the title molecule was estimated. Also, the binding affinity of BDTTIQ and doxorubicin into the active site of ARK1C3 Protein (PDB id: 4FAL) has been investigated by molecular docking.

EXPERIMENTAL AND COMPUTATIONAL

Synthesis of BDTTIQ. The title compound BDTTIQ was prepared following the procedure in Scheme 1. Into a clean, dry, two-necked round-bottomed flask, a solution of (*E*)-N-benzyl-N-(2-bromo-4,5-dimethoxybenzyl)-3-(2-(2-(thiophen-2-yl)vinyl)phenyl)-1-(*p*-tolyl)prop-2-yn-1-amine (0.3 mmol) in 1,4-dioxane (4 mL) was added to a mixture of $Pd(PPh_3)_4$ (10 mol%) and K_2CO_3 (5 equiv) under a N_2 atmosphere. The reaction mixture was stirred at 100 °C for 3 h. Ethyl acetate (15 mL) and water (3×10 mL) were mixed with the reaction mixture, after it was cooled to ordinary temperature. The segregated organic layer was dried with anhydrous Na_2SO_4 and concentrated under minimized pressure. The compound BDTTIQ was acquired by cleaning the crude mass by column chromatography (silica gel, 5-40% petroleum ether/ethyl acetate). Single crystals of BDTTIQ apt for SCXRD investigations have been prepared in an ethanolic solution by slow evaporation of the solvent at normal temperature (yield 80%, m.p. 114-116 °C).



Scheme 1. Synthesis scheme of the title BDTTIQ molecule.

The chemical shifts, recorded as δ values in parts per million (ppm) with respect to tetramethylsilane, with *J* values in Hertz were determined by NMR spectra (^{1}H NMR and ^{13}C NMR). The splitting patterns in ^{1}H NMR spectra are recorded as follows: s = singlet; d = doublet; br s = broad singlet; br d = broad doublet; m = multiplet. ^{13}C NMR data are accounted with the solvent peak ($CDCl_3$ = 100.0 MHz) as the internal standard. The obtained NMR data for the title compound are given in the Supplementary information.

X-ray crystallography. The X-ray analysis for an apt single crystal of the compound BDTTIQ was executed on a Bruker AXS Kappa Apex II single crystal X-ray diffractometer using graphite mono-chromated MoK_α (λ = 0.71073 Å) radiation and a CCD detector. Data collection was executed by the APEX2 software [10] whereas the cell refinement and data reduction were carried out by the SAINT software [11]. SHELXS-97 [12] implemented in the WinGX [13] software was employed to solve the crystal structure as BDTTIQ. SHELXL-97 [14] was utilized to perform the refinement. Empirical absorption correction (multi-scan) was applied to the crystal data utilizing the SADABS software [10]. The hydrogen atoms were constrained geometrically with C–H = 0.93 Å, 0.96 Å, and 0.97 Å for aryl, methyl, and methylene H atoms, respectively.

The thiophene ring S1/C34–C37 is positionally disordered over two sets of sites, with an occupancy ratio of 0.566(3):0.434(3). Thermal parameter (SIMU) and same distance (SADI) restraints were applied to the disordered thiophene ring. A low reflection (100) was omitted due to beam stop shading using the OMIT instruction in SHELX97-L. The

PLATON [15] program was used to compute geometrical parameters. ORTEP [16] and MERCURY [17] were used to draw molecular graphics.

Molecular docking. The molecular docking analysis was performed to know the ARK1C3 inhibition of the BDTTIQ compound using the 1-click docking web tool that uses AutoDock Vina as a backend program for docking simulations. The protein structure of the ARK1C3 receptor (PDB ID: 4FAL) was acquired from the RCSB–PDB website. The active site parameter of the protein AKR1C3 was defined using a resident ligand in the receptor (x = 7.616, y = 5.6316 and z = 11.0790) and recognized from the previous studies [8]. The docked result was analyzed with the help of BIOVIA Discovery studio Visualizer [18].

RESULTS AND DISCUSSION

Crystal structure description. The labelled displacement ellipsoid plot for the compound BDTTIQ is shown in Fig. 1. The detailed crystal and structure refinement data for BDTTIQ are listed in Table 1. The crystal parameters of the BDTTIQ molecule are given in Table S1 (Supplementary Materials).

The asymmetry parameter [19] ΔC_2[C2–C7] = 8.25(18)° and the puckering parameters [20] Q, θ, and φ are 0.4864(14) Å, 46.36 (18)°, and 319.1(2)°, respectively, confirm the existence of a *half-chair* conformation for the tetrahydroisoquinoline fragment. Here, the local two-fold axis travels across the centre of the (C2–C7) and (C9–N1) bonds.

The C22–C27 and (C28–C33) benzene rings are inclined at an angle of 77.9(1)° and (89.7(1)°, respectively, to the tetrahydroisoquinoline fragment. The indene ring (C12–C20) is almost planar (maximum deviation = 0.049(2) Å for the C13 atom) and is inclined at an angle of 47.8(1)° with respect to the tetrahydroisoquinoline fragment. The ratio of the refined site-occupancy factors of the major and minor parts of the disordered thiophene ring is 0.566(3):0.434(3). The indene ring forms dihedral angles of 38.9(5)° and 44.0(7)° with the major and minor parts of the disordered thiophene ring. The bond distances and angles of BDTTIQ are consistent with the previous reported values [21].

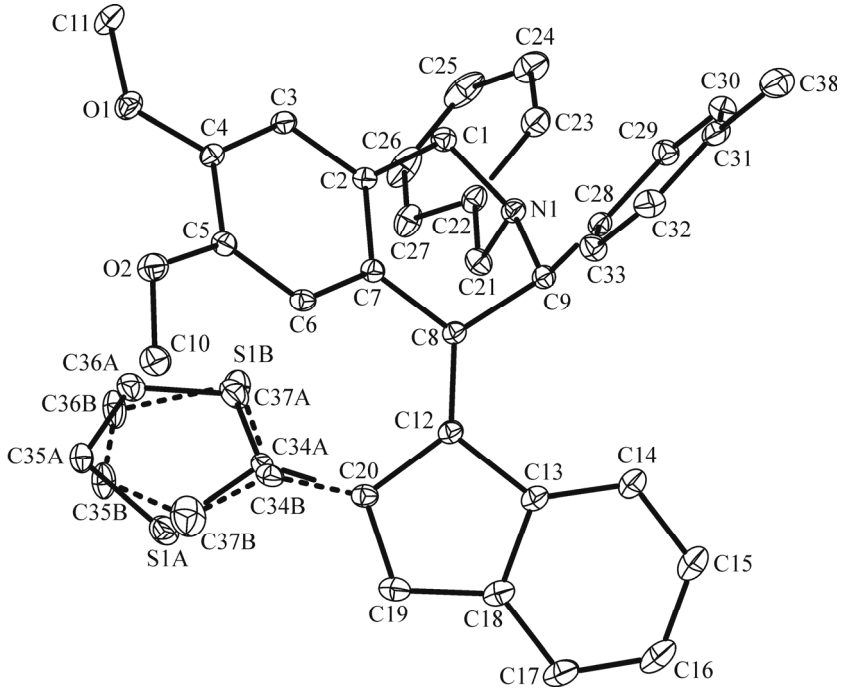


Fig. 1. ORTEP atom numbering scheme of the compound BDTTIQ.

TABLE 1. Crystal and Experimental Data for the Compound BDTTIQ

Empirical formula	$C_{38}H_{33}NO_2S$
Formula weight	567.71
Temperature, K	293(2)
Wavelength, Å	0.71073
Crystal system	Monoclinic
Space group	*P*21/*c*
Unit cell dimensions *a*, *b*, *c*, Å; β, deg.	16.3387(8), 10.0237(4), 19.6852(9); 110.7050(10)
V, Å^3	3015.7(2)
Z	4
Calculated density, mg/m^3	1.250
Absorption coefficient, mm^{-1}	0.142
F(000)	1200
Crystal dimensions, mm	0.30×0.25×0.19
θ range for data collection, deg.	2.14-26.00
Index ranges	$h = -20 \rightarrow 20$, $k = -12 \rightarrow 12$, $l = -24 \rightarrow 24$
Reflections collected	40755
Independent reflections	5926 [*R*(int) = 0.0259]
Completeness to θ = 26.00%	100.0
Absorption correction	Multi-scan
Max. and min. transmission	0.973 and 0.958
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5926 / 130 / 428
GOOF on F^2	1.044
*R*1 / *wR*2 [$I > 2\sigma(I)$]	0.0371 / 0.0925
*R*1 / *wR*2 (all data)	0.0527 / 0.1046
Largest diff. peak and hole, e/Å^3	0.19 and –0.14

The hydrogen bond geometrical parameters for BDTTIQ are given in Table 2. The crystal structure of BDTTIQ features C30–H30…O2^{i} (symmetry code: $^{i} = x, -1/2-y, -1/2+z$) hydrogen bonds forming zigzag C(10) chains propagating along (001). These zigzag chains are cross-linked by two intermolecular C25–H25…Cg1^{ii} and C35A–H35A…Cg2^{iii} (Cg1 and Cg2 are the centroids of C13–C18 and C22–C27 benzene rings, respectively, and symmetry codes: $^{ii} = 1-x, -1/2+y, 3/2-z$ and ^{iii} $1-x, -y, 2-z$) hydrogen bonds, and thus, a three-dimensional supramolecular network is achieved (Fig. 2).

Molecular docking. Since ARK1C3 is responsible for the production of series of growth stimulatory steroid hormones, it may be an ideal drug target. The ARK1C3 inhibition behavior of the title molecule was analyzed by a molecular docking procedure using the 1-click docking online web server. Hence, the compound BDTTIQ and standard drug doxorubicin were docked into the ARK1C3 protein active site. Out of the four poses obtained, the best pose was selected

TABLE 2. Hydrogen Bonding Geometry for the Compound BDTTIQ (Å, deg.)

D–H…A	D–H	*d*(HA)	*d*(D…A)	∠(DHA)
C30–H30…O2^{i}	0.93	2.56	3.277(2)	134
C25–H25…Cg1^{ii}	0.93	2.88	3.804(3)	175
C35A–H35A…Cg2^{iii}	0.97	3.00	3.692(6)	133

Cg1 is the centroid of the C13–C18 ring, Cg2 is the centroid of the C22–C27 ring.
Symmetry codes: ^{i} $x, -1/2-y, -1/2+z$; ^{ii} $1-x, -1/2+y, 3/2-z$; ^{iii} $1-x, -y, 2-z$.

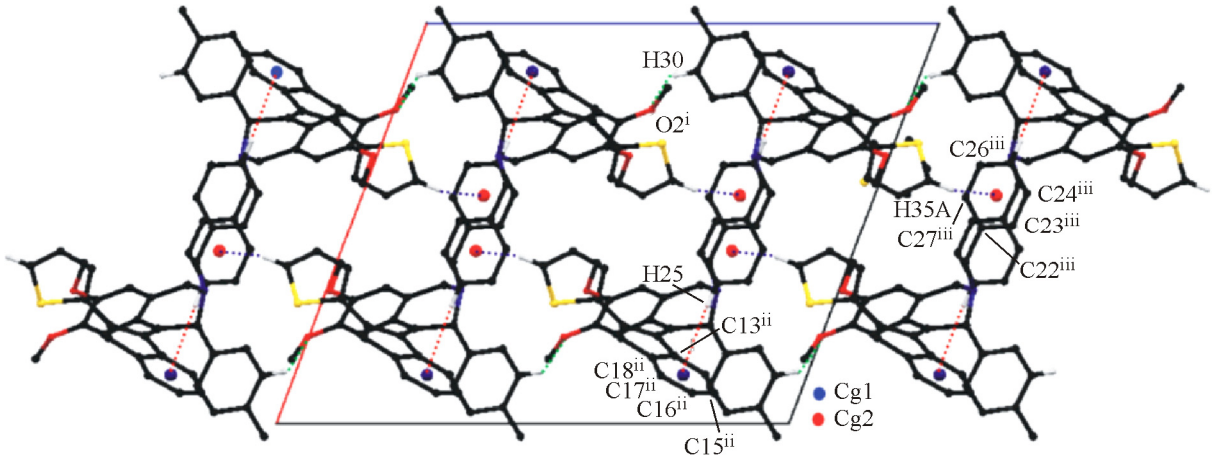


Fig. 2. Partial crystal packing of the compound BDTTIQ showing the performance of a three-dimensional supramolecular network through C–H…O and C–H…π hydrogen bonds. Cg1 and Cg2 are the centroids of C13–C18 and C22–C27 benzene rings, respectively, and symmetry codes are [i] *x*, –1/2–*y*, –1/2+*z*; [ii] 1–*x*, –1/2+*y*, 3/2–*z* and [iii] 1–*x*, –*y*, 2–*z*.

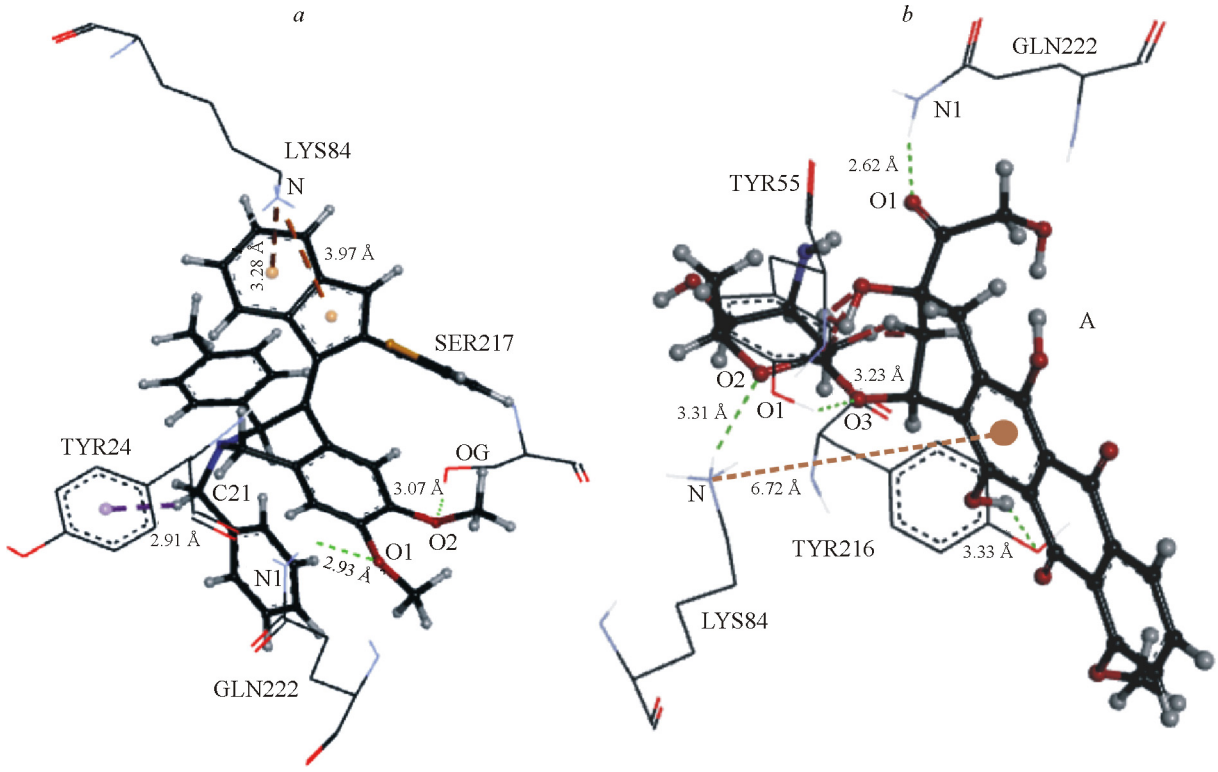


Fig. 3. Interaction of BDTTIQ (*a*) and doxorubicin (*b*) with Aldo ketoreducs 1C3 binding site.

based on the top dock score. The ligand–protein interaction of BDTTIQ and doxorubicin with the active site of ARK1C3 are shown in Fig. 3. The drug score and molecular interactions of the compound BDTTIQ and standard drug doxorubicin with ARK1C3 are listed in Table S2 (табл. S2 Supplementary Materials).

The docking score for BDTTIQ–4FAL and doxorubicin–4FAL complexes are –12.2 kcal/mol and –10.8 kcal/mol, respectively. Fig. 3*a* presents the docking mode between ARK1C3 and BDTTIQ in which two hydrogen bonds are formed: the first one between OG–HG of SER217 and the O2 atom of the BDTTIQ ligand (angle OG–HG…O2 = 150.81°, distance = 3.07 Å) and the second one between N1–H1 of GLN222 and the O1 atom of the BDTTIQ ligand (angle N1–H1…O1 = 117.81°, and distance = 2.930 Å). Also, the N atom of LYS84 interacts with six- (C13–C18) (distance = 3.28 Å)

and five-membered C12/C13/C18–C20 (distance = 3.97 Å) rings of the BDTTIQ ligand, generating two cation–π electrostatic interactions. Further, a σ–π hydrophobic interaction is observed between C21–H21 of the BDTTIQ ligand and the six-membered ring of TYR24 (distance = 2.91 Å).

Fig. 3*b* presents the docking mode between ARK1C3 and doxorubicin in which four hydrogen bonds are formed: the first between N1–H1 of GLN222 and the O1 atom of the doxorubicin ligand (angle N1–H1…O1 = 163.66°, distance = 2.61 Å), the second between N1–H1 = 3.31 Å, the third between O1–H1 of TYR55 and the O3 atom of the doxorubicin ligand (angle O1–H1…O3 = 121.19° and distance = 3.23 Å), and the fourth between O2–H2 of the doxorubicin ligand and the O atom of LYS84 and the O2 atom of the doxorubicin ligand (angle N1–H1…O2 = 132.91°) and TYR216 (angle O2–H2…O = 141.80°, and distance = 3.34 Å). Further, a cation–π hydrophobic interaction is observed between the N atom of LYS84 and the six-membered ring of doxorubicin (distance = 6.72 Å).

The significant part of the docking study is that two hydrogen bonds, two electrostatic interactions, and one hydrophobic interaction were noticed in the BDTTIQ–4FAL complex, and four hydrogen bond interactions and one hydrophobic interaction were noticed in the doxorubicin–4FAL complex. The presence of the hydrogen bond, cation–π and σ–π interactions in the BDTTIQ–4FAL complex determines the hike in the binding affinity and medicinal activity of the compound BDTTIQ. Moreover, the docking study illustrated the affinity of BDTTIQ towards its target protein ARK1C3 with a good docking score value of –12.2 kcal/mol when compared with a docking score of –10.8 kcal/mol of the doxorubicin–4FAL complex. These docking results point out that the compound BDTTIQ may reveal inhibitory against ARK1C3 and thus might act as a potent anti-cancer drug.

CONCLUSIONS

The compound BDTTIQ was synthesized and its structural characterization was performed using single crystal X-ray diffraction and ^{1}H, ^{13}C NMR techniques. In the crystal structure, a three-dimensional supramolecular network is achieved by intermolecular C–H…O and C–H…π hydrogen bonds. The molecular docking simulations indicate that the synthesized compound BDTTIQ has the inhibitory nature against ARK1C3 protein and may act as a capable anti-cancer drug.

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ADDITIONAL INFORMATION

Supplementary materials. The supplementary crystallographic data CCDC 1539107 could be downloaded from CCDC web server.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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